PSI 2026 - BELFAST

NOVEL BAYESIAN EVENT PREDICTION MODEL USING MIXTURE DISTRIBUTION FOR RANDOMIZED CONTROLLED TRIALS

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DISCLAIMER

- The numbers used in the slides are based on simulations.
- The views from the presentation reflect those of the authors and should not be construed as representing the views of their companies

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OUTLINE

BACKGROUND AND OBJECTIVE

PROPOSED BAYESPET METHOD

MOTIVATING CASE STUDY

SIMULATIONS & DISCUSSION

DRUG DEVELOPMENT IS A COMPLEX PROCESS MARKED BY LONG TIMELINES

Improve resource allocation

Make timely decisions

Accelerate Drug Development for Patients' Benefit

CONTEXT AND OBJECTIVE

- Randomised clinical trials
- Time to event endpoints*
- Blinded Trials

When Will the Target number of Event, will Be Reached?

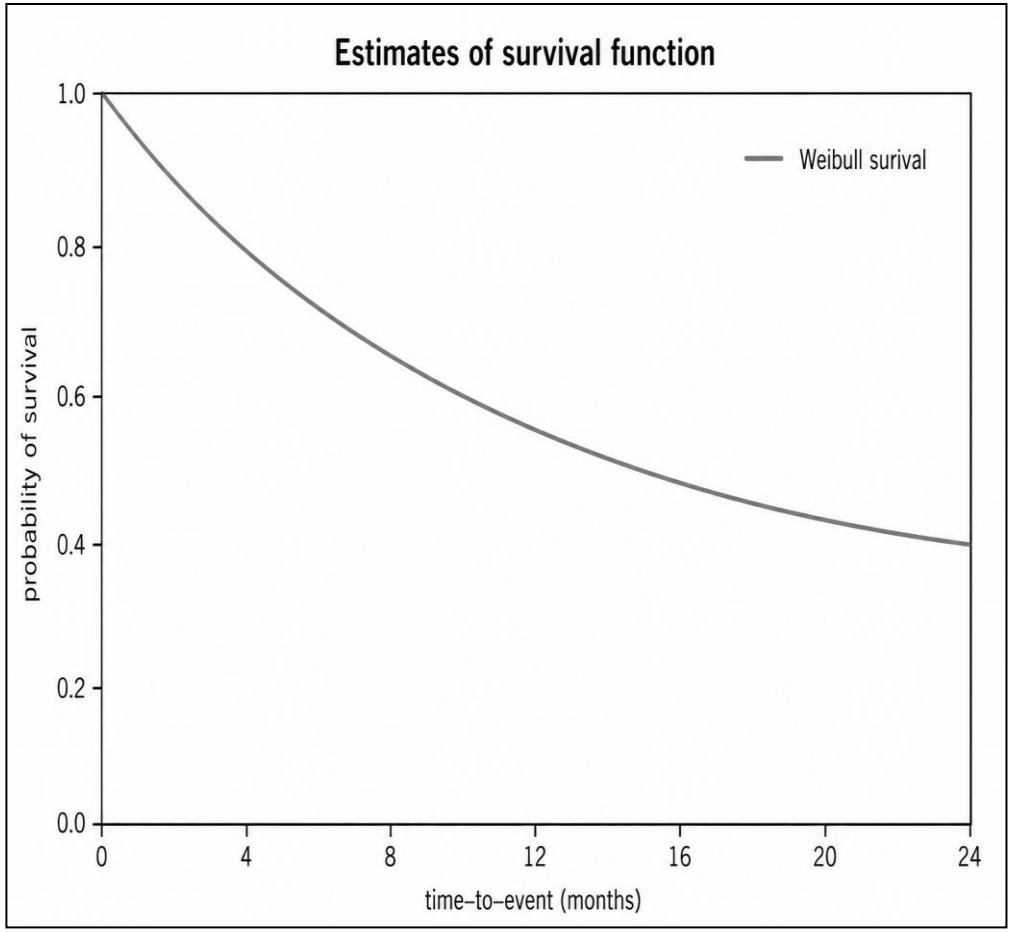
*Analyses are events driven

UNPACKING THE CHALLENGES OF TIMELINES PREDICTION

Most existing prediction methods for Blinded RCT:

- Use a **single pooled** survival curve
- Assume **identical event-time distribution**[(a)] for arms

➡ When a treatment effect exists, event projections lose accuracy



(a): no treatment effect
RCT: randomized Clinical Trial

KEY HIGHLIGHT

Even in Blinded RCTs, the data can be viewed as coming from a mixture of survival distributions while preserving blinding in a Bayesian framework

The novel **Bayes**ian **P**rediction of **E**vent **T**imes (**BayesPET**) method allows for different time-to-event distributions between arms in blinded RCTs

RCT: Randomised Clinical Trial

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METHODOLOGY

MODELING THE THREE ESSENTIAL PROCESSES

A- Enrollment Prediction

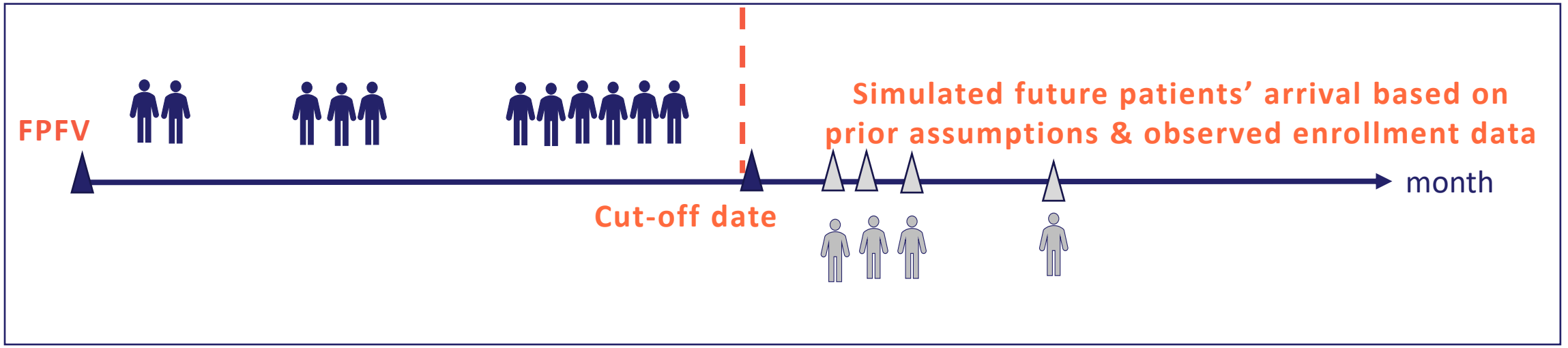
B- Time to Event Prediction

C- Time to Censor Prediction

USE OF A BAYESIAN FRAMEWORK CONSIDERING UNCERTAINTY AND OFFERING FLEXIBILITY

For time to event and censor, Weibull distributions will be used

ENROLLMENT PROJECTION:
WHEN WILL FUTURE PATIENTS ENTER THE TRIAL?



Enrollment is modeled as a random Poisson process

Multiple simulations generate possible future enrollment paths

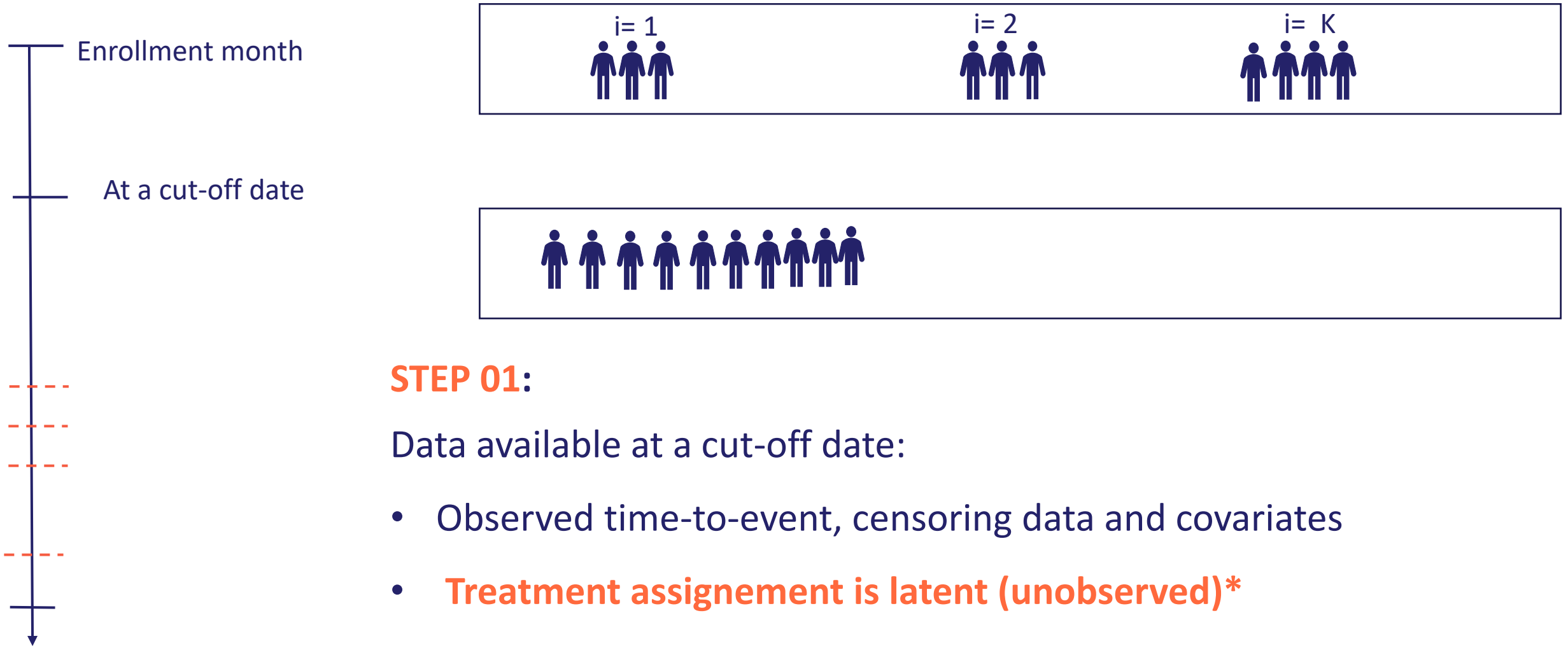
FPFV: First Patient First Visit

TIME TO EVENT PREDICTION
USING A MIXTURE WEIBULL MODEL

Instead of assuming a single survival pattern, the Weibull time-to-event model account for two possible survival behaviors; a mixture of survival distributions corresponding to experimental and control arms in a blinded setting.

TIME TO EVENT PREDICTION

OBSERVED DATA



STEP 01:

Data available at a cut-off date:

- Observed time-to-event, censoring data and covariates
- **Treatment assignement is latent (unobserved)***

*Arms will be inferred probabilistically in subsequent steps

Enrolled patients

TIME TO EVENT PREDICTION
DATA AUGMENTATION

STEP 02
Latent treatment imputation

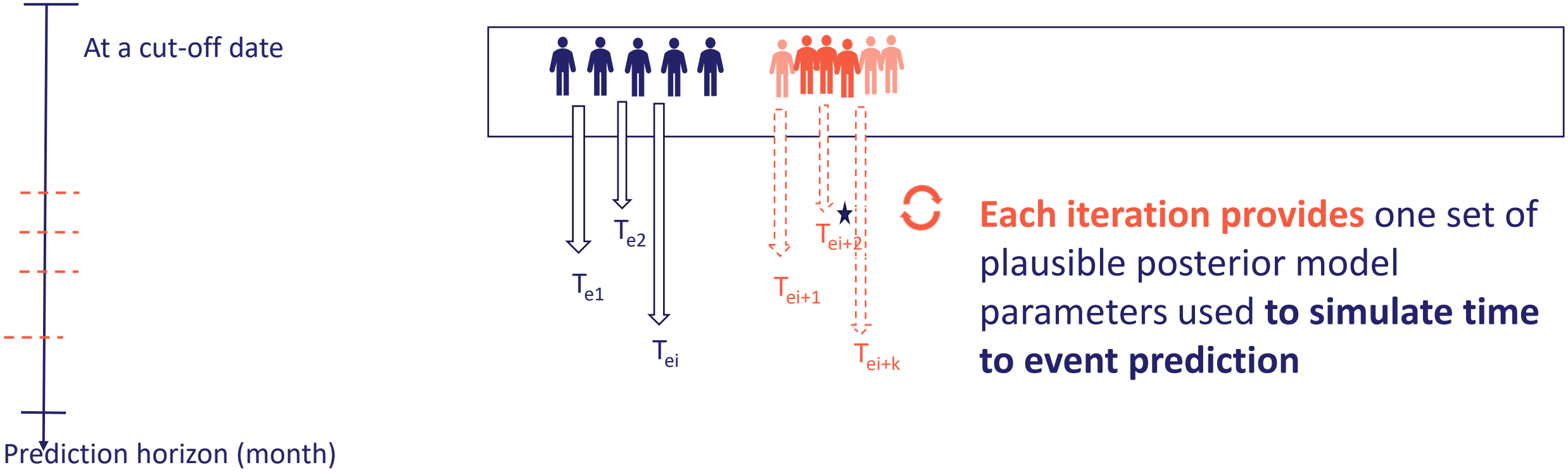
- Each patient is probablilistically associated with Experimental or Control* at each MCMC iteration, based on survival fit and model assumptions
- Assignement is updated at every iteration
- This results in a mixture of two possible survival behaviors (Experimental vs control)

* Each patient could belong to either arm with a probability updated at each iteration

TIME TO EVENT PREDICTION:
PARAMETERS'UPDATE

STEP 03:

- Given imputed latent treatment assignements, the survival model is updated



Each iteration provides one set of plausible posterior model parameters used **to simulate time to event prediction**

->T_{ei} observed time to event for patient i

->T_{ei+K} simulated event times using sampled parameters for patient i+k

Enrolled patients

Patients to be enrolled after cut-off date

Administrative censored patients

MODELING DROPOUT (TIME-TO-CENSOR)
USING A WEIBULL MODEL

- The censoring Weibull model refers to loss-of-follow-up (permanent censoring),rather than administrative censoring

- Modeled using a Weibull distribution, similar to the time-to-event model

- Unlike time-to-event, **censoring is assumed independent of treatment assignment***

* Both arms share the same censoring pattern

SUMMARY

For each iteration:

Observed time = min (Time to event , Time to censor)➡ Compute Time to reach target # events

Summary Statistics for Posterior Time to Target number of events

CASE STUDY

MOTIVATING CASE STUDY (1)

Equally Randomised

Phase III Trial

N~296

Patients with advanced anaplastic lymphoma kinase(ALK)-Positive non-small-cell lung cancer*

- **Primary endpoint:** Progression Free Survival (PFS)
- **Target Number of events:** 127 PFS events
- **FPI:** May 2017
- **LPI:** Feb 2019
- **Cut-off:** at 70% of the information fraction (89/127)

WHEN THE 127 EVENTS WILL BE REACHED ?

*First-Line Lorlatinib or Crizotinib in Advanced ALK-Positive Lung Cancer | New England Journal of Medicine

MOTIVATING CASE STUDY

WHEN THE 127 EVENTS WILL BE REACHED ?

Statistics in Medicine

RESEARCH ARTICLE OPEN ACCESS

Bayesian Prediction of Event Times Using Mixture Model for Blinded Randomized Controlled Trials

Jingyan Fu[1] | Dan Zhao[2] | Donia Skanji[3] | Hua Liu[2] | Rui (Sammi) Tang[4] | Ying Yuan[5]

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BAYESPET METHOD

MOTIVATING CASE STUDY

WHEN THE 127 EVENTS WILL BE REACHED ?

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BAYESPET METHOD

Statistics in Medicine

RESEARCH ARTICLE

A Bayesian approach for event predictions in clinical trials with time-to-event outcomes

Paul Aubel, Marine Antigny, Ronan Fougeray, Frédéric Dubois, Gaëlle Saint-Hilary

First published: 20 September 2021 | https://doi.org/10.1002/sim.9186 | VIEW METRICS

Funding information Institut de Recherches Internationales Servier, France

BEP METHOD

MOTIVATING CASE STUDY
PREDICTION RESULTS

% of times the median predicted date falls within 1 month of the True event time (March 2020)

Method	< 1 week	< 2 weeks	< 1 month	< 2 months
BayesPET	15%	32%	69%	98%
BEP	0%	1%	8%	20%

- BayesPET: 69% of simulations predict final analysis date within ±1 month
- BEP: 8%

The observed HR of 0.29 indicates a clear distinction between arms

➡ BayesPET, utilizing data augmentation, enables superior predictive accuracy

SIMULATIONS & DISCUSSION

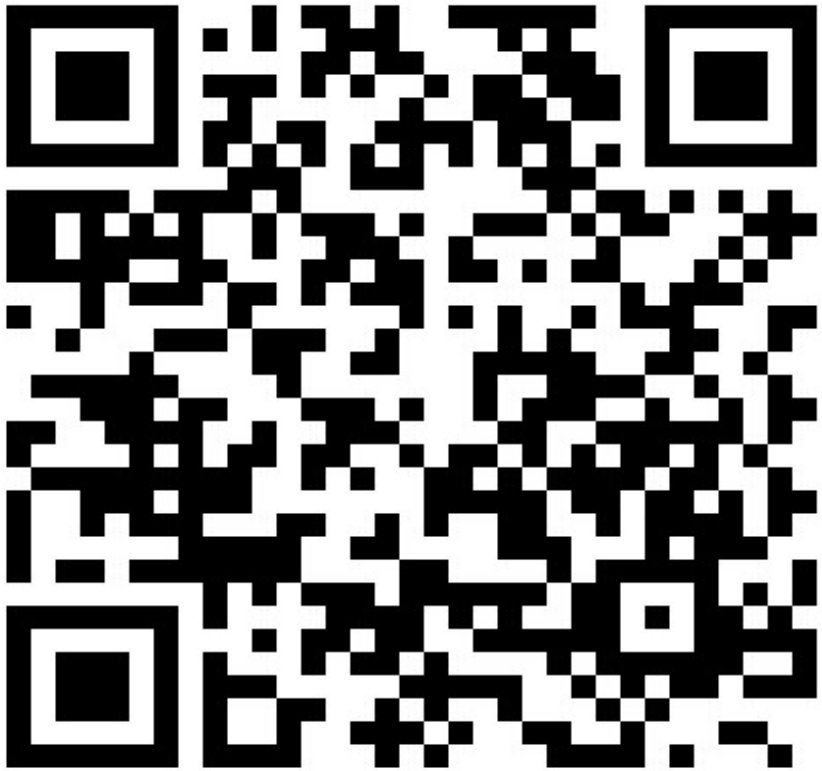
SIMULATIONS AND FINAL REMARKS

Based on simulations, as expected, BAYESPET prediction accuracy improves as the **information fraction increases**

Phase III trials generally provide more accurate predictions than Phase II trials due to **the larger number of events available for estimation and prediction**

Across all scenarios, including different trial phases and varying HR, BayesPET **consistently demonstrated optimal prediction accuracy**, highlighting the importance of **accounting for different time-to-event distributions**

BAYESPET PACKAGE



https://cran.r-project.org/web/packages/BayesPET/index.html

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Q & A

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