Global Biometrics
Team SERVIER

WHY ACCURATE TIME TO TARGET RESPONSE PREDICTION MATTERS?

Donia SKANJI
Sarah-Laure RINCOURT
Clément DANIEL

PSI CONFERENCE 2025

Wednesday, June 11th

London UK

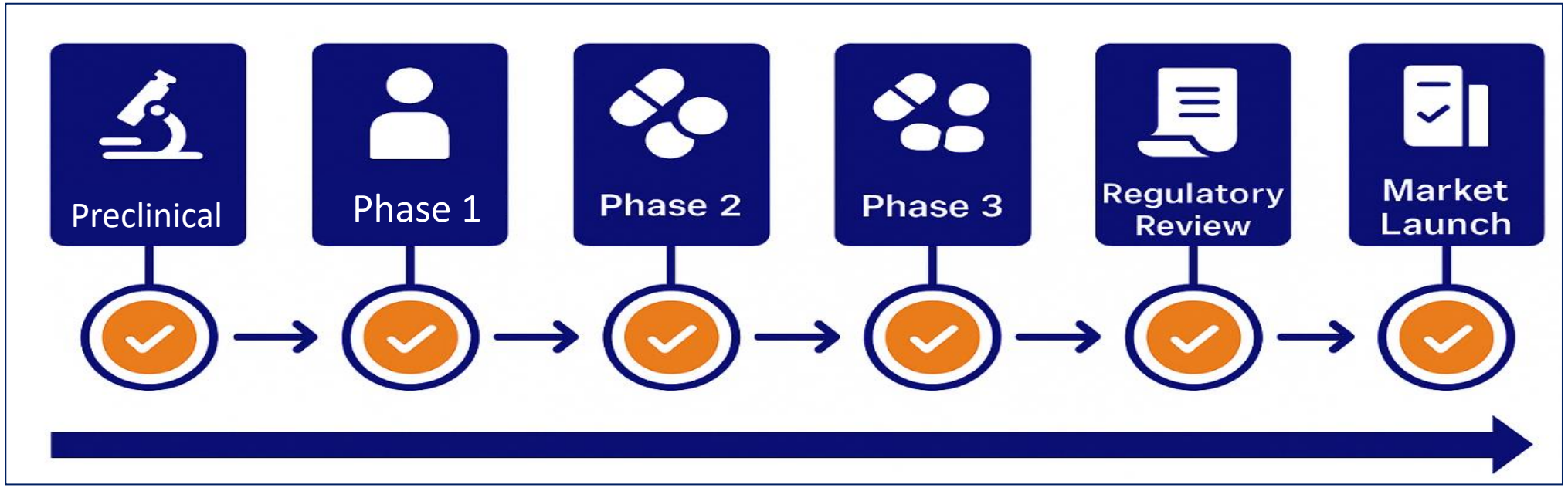
DISCLAIMERS

- 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

OUTLINE

- INTRODUCTION
- PREDICTION MODELS
- CASE STUDY
- DISCUSSION

DRUG DEVELOPMENT IS A COMPLEX PROCESS MARKED BY LONG TIMELINES



The entire process of clinical development requires **precise planning** for **strategic milestones**

TIMELINES PREDICTION: RESEARCH EMPHASIS

Extensive Research:
Time to event Endpoints
(e.g., OS, PFS..)

→

Limited Research:
Binary Endpoints
(e.g., ORR..)

Focus of this work

PREDICT WHEN THE TARGET NUMBER OF RESPONDERS WILL BE REACHED

ORR is the proportion of patients experiencing a predefined level of tumor shrinkage (In solid Tumors either a complete or partial response)
PFS: progression free survival defined as the time to progression or death, OS: overall survival defined as time to death

STATISTICIANS DRIVE INFORMED TIMELINES THROUGH ACTIVE ENGAGEMENT WITH STAKEHOLDERS

Proactive communication

Inefficient/suboptimal outcomes

Better outcomes

Accurate Timelines prediction ensures:

- **Timely decisions**
- Improves **resource allocation**
- Faster access to effective treatments for **Patients' Benefit**

PREDICTION MODELS

PREDICTION MODELS

Method 1

Based on historical data on Response rate and time to response from previous study

Method 2

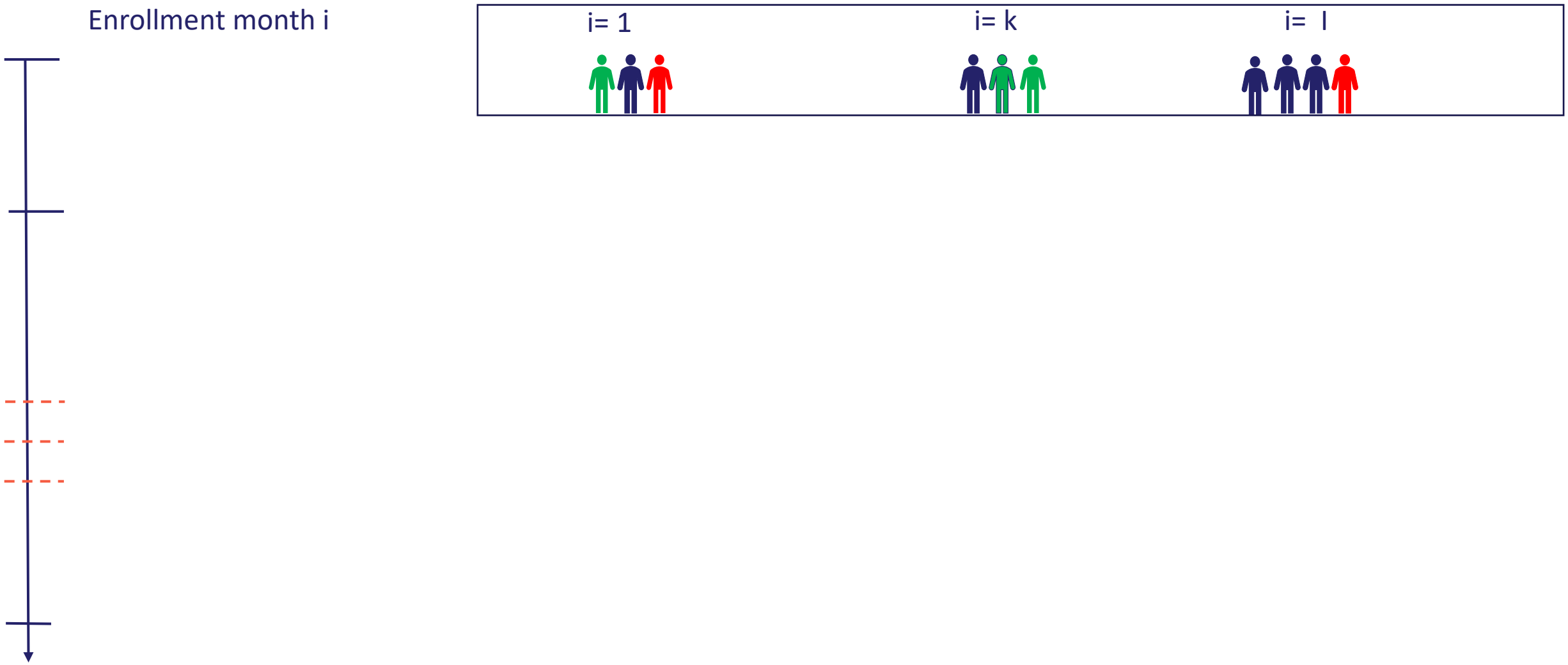
Based on a random sample of the expected response rate in the current study over a fixed period

Example for Method1 : data available from a global study to predict a bridging* study

Example for Method2 : No prior information on the response pattern over time, random sampling will be used

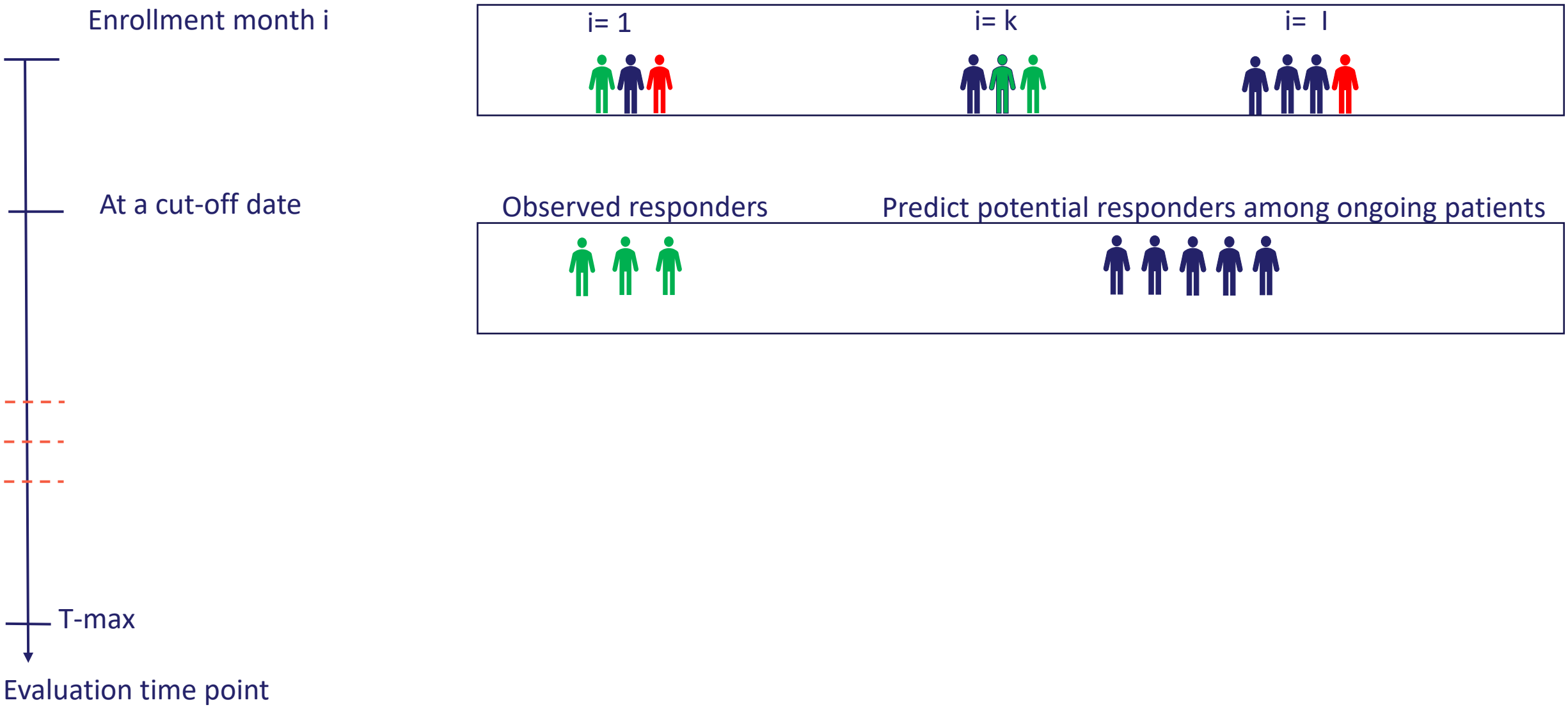
*Under the consistency hypothesis, the global study could be used to inform timelines for the local/ bridging study

PREDICTION MODELS: METHOD 1



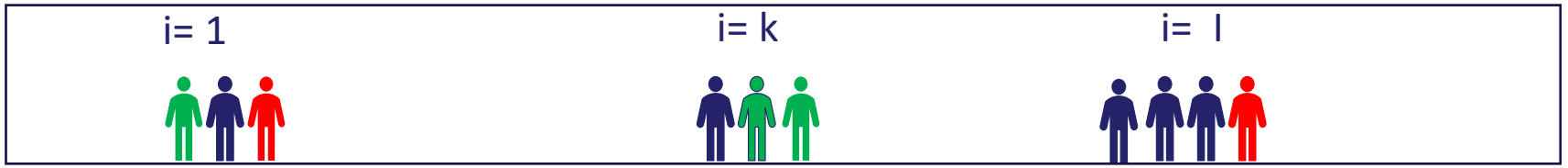
Responders Terminated Stable: eligible to respond

PREDICTION MODELS: METHOD 1



PREDICTION MODELS: METHOD 1

Enrollment month i



At a cut-off date ($t_{cut-off}$)

Observed responders

Predict potential responders among ongoing patients

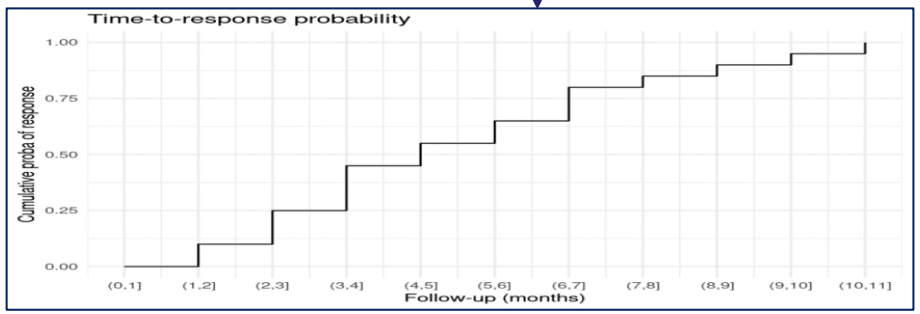
$N_{resp}\ (t_{cut-off} + j)$

$N_{resp}(t \leq t_{cut-off})$ + $\sum_{i=1}^{I} \sum_{j=1}^{n_i - xi} P_{resp}(t_{fu}(i, t_{cut-off}, j))$. ORR

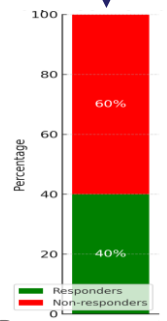
Increase j until reaching the target ORR or t_{max}

T-max

Evaluation time point (month)



Cumulative probability of response (using a parametric approximation)



Response rate: Random variable ~beta distribution

n_i *is the total number of patients enrolled the ith month* , xi is the number of patients enrolled the ith month who terminated the trial, j (in month)from 1 to T_{max} − cut_off

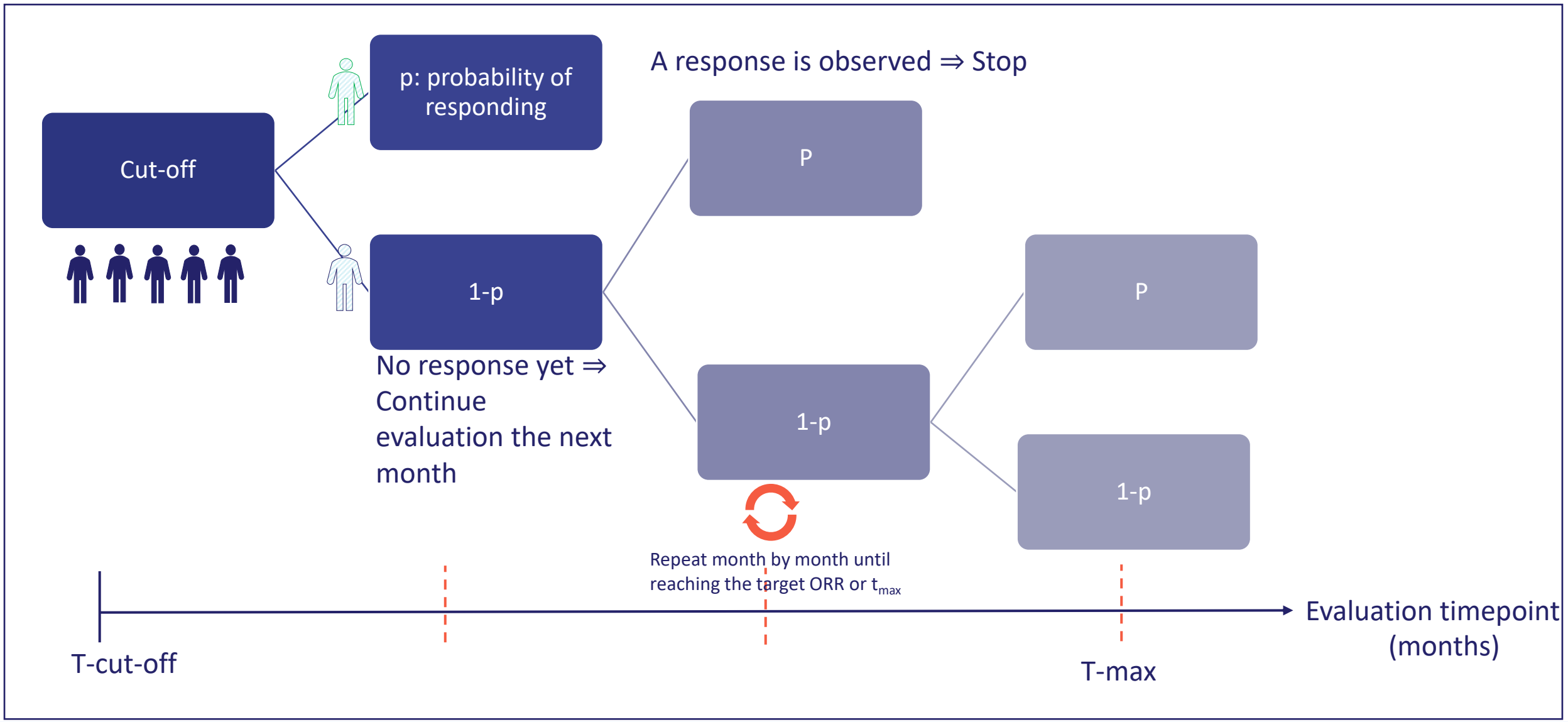
SERVIER

PREDICTION MODELS: METHOD 1

Method 1 assumes a reasonable understanding of the response pattern over time

PREDICTION MODELS: METHOD 2

Sequential decision tree



probability to respond depends on the remaning chances to success until $T - max$

SERVIER

CASE STUDY

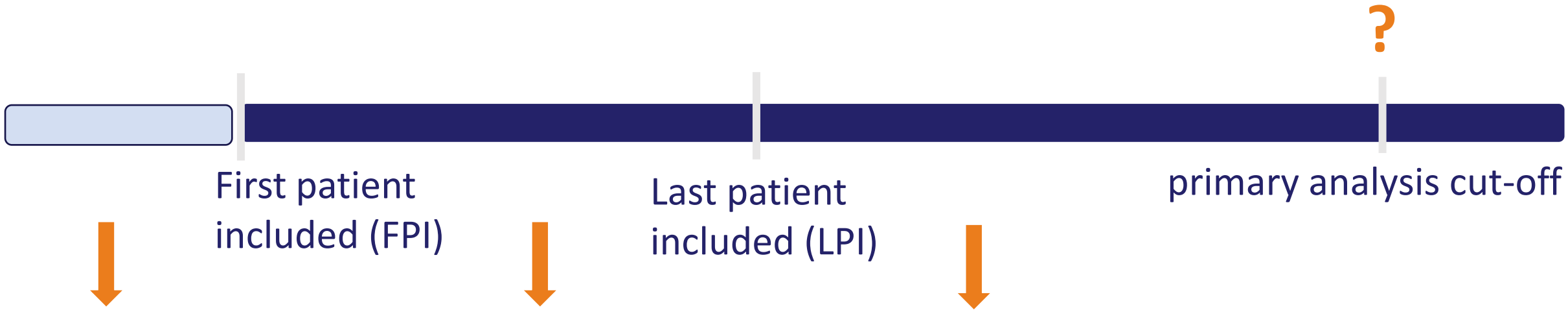
MOTIVATING CASE STUDY

Single arm

N~50

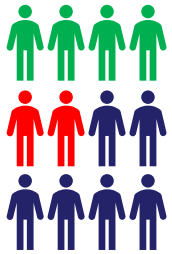
- ORR as a primary endpoint
- Success criteria: reach at least 40% ORR
- Target # responses: at least 20 responders out of 50 patients

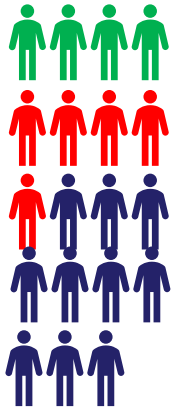
PATIENTS' ENROLLMENT

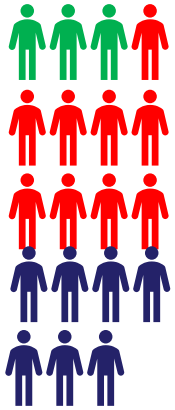


DATA DESCRIPTION- CUT-OFF DATE: JUNE 2024

Jan 2024 N = 12	Feb 2024 N = 19	Mar 2024 N = 19





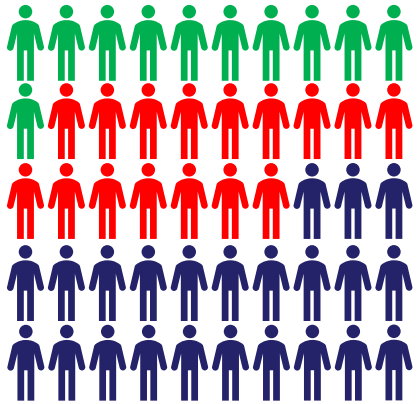


- 4 responses
- 2 terminated
- 6 still eligible

- 4 responses
- 5 terminated
- 10 still eligible

- 3 responses
- 9 terminated
- 7 still eligible

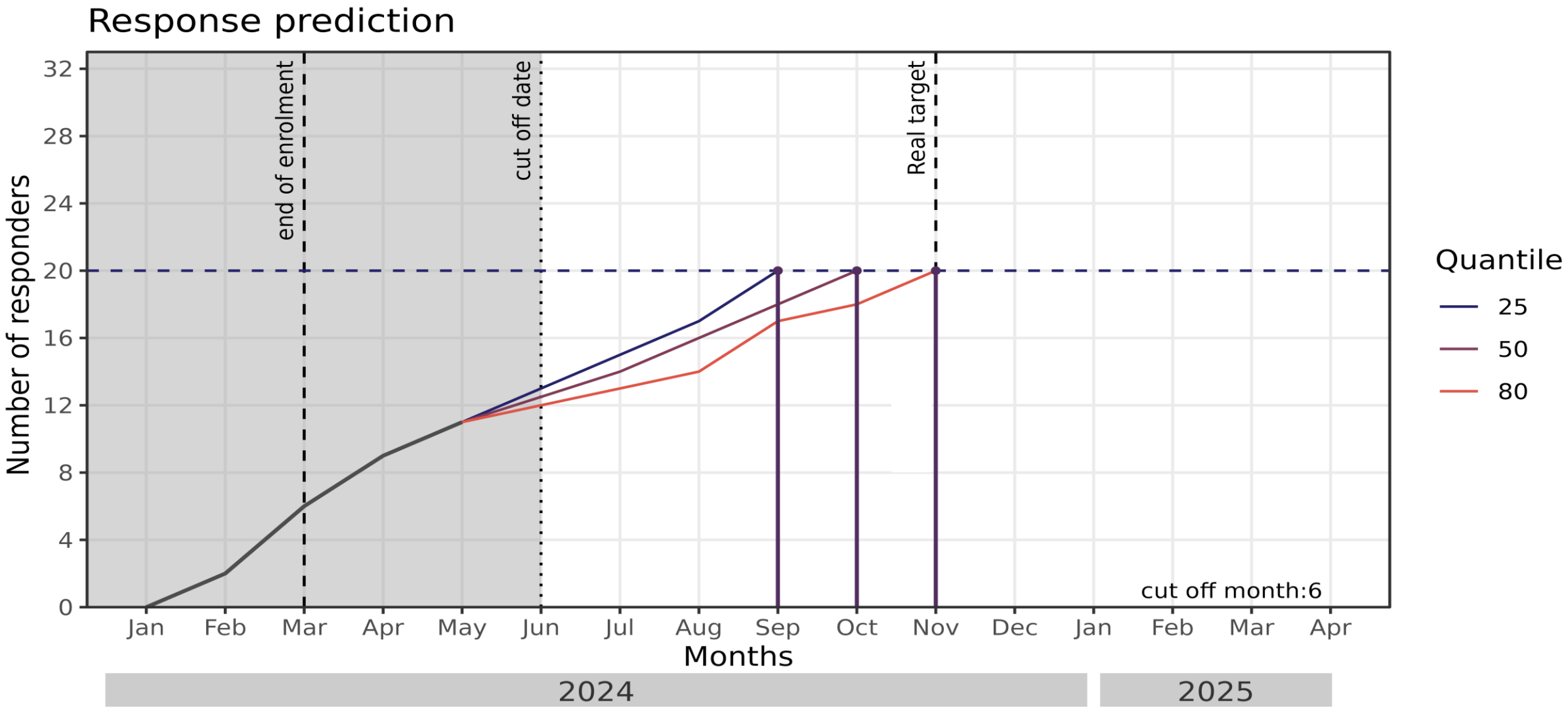
Total N = 50



- 11 responses
- 16 terminated
- 23 still eligible to respond

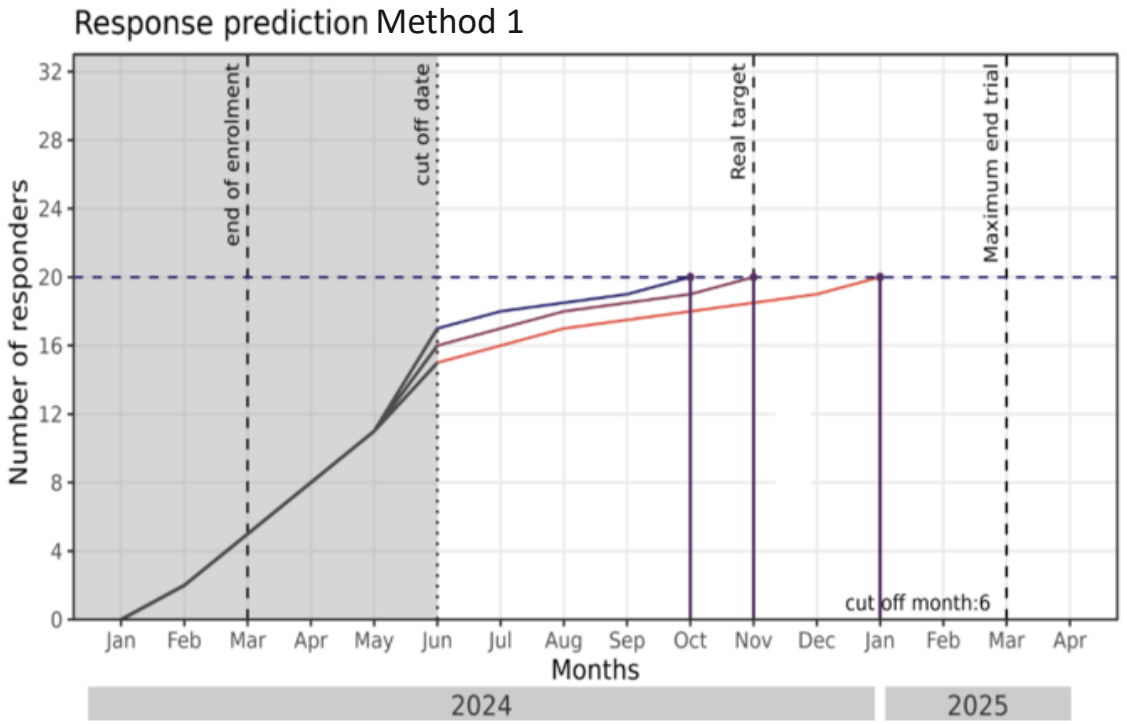
Responder Terminated Stable: eligible to respond

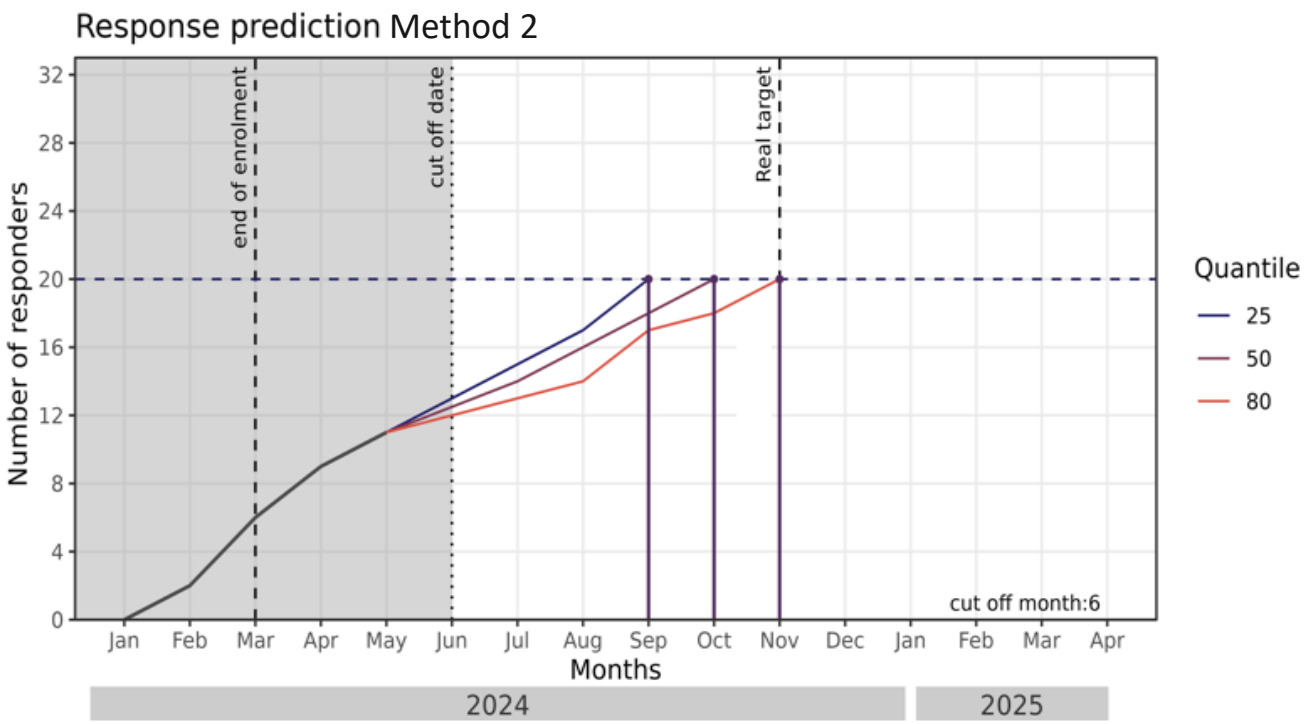
PREDICTION RESULTS



As more data continue to be gathered, the models are updated to improve projections

PROACTIVE PLANNING: ANTICIPATION AHEAD OF TIME





Probability	Method1	Method2
25%	October 2024	September 2024
50% (Median)	November 2024	October 2024
80%	January 2025	November 2024

DISCUSSION

FINAL REMARKS AND NEXT STEPS

Based on simulations, prediction accuracy improves for both methods as the **information fraction increases.**

When the probability of success **(PoS) is low**, neither method reliably reaches the target[(a)]

a-models predict a significantly extended duration

FINAL REMARKS AND NEXT STEPS

Method1: Historical data can enhance response prediction if it aligns well with current data. Further research will focus on Bayesian MAP, power prior or other methods.

Method2: Straightforward approach but the instantaneous probabilities depend on Tmax, which needs to be precisely defined

Collaboration between statisticians and cross-functional team becomes more frequent, supporting faster and more informed decision-making and activity planning.

MAP: meta-analytic predictive prior, Tmax: maximum follow-up time among responders

MAIN REFERENCES

[1] Proschan MA, Gordon Lan WJT K K. In: Statistical Monitoring of Clinical Trials: A Unified Approach Springer; 2006.

[2] Heitjan DF, Ge Z, Ying Gs. Real-time prediction of clinical trial enrollment and event counts: A review. Contemporary Clinical Trials 2015;45(Part A):26–33.

[3] Bakhshi A, Modelling and predicting patient recruitment in multi-centre clinical trials.; 2011.

[4] Bagiella E, Heitjan D. Predicting analysis times in randomized clinical trials. Statistics in Medicine 2001;20(14):2055– 2063.

[5] Ying GS, Heitjan D, Chen TT. Nonparametric prediction of event times in randomized clinical trials. Clinical Trials 2004;1(4):352–361.

[6] Ying GS, Daniel H. Weibull prediction of event times in clinical trials. Pharmaceutical Statistics 2008;7(2):107–120.

[7] Donovan JM, Elliott MR, Heitjan DF. Predicting Event Times in Clinical Trials When Treatment Arm Is Masked. Journal of Biopharmaceutical Statistics 2006;16(3).

[8] Lan Y, Daniel H. Adaptive parametric prediction of event times in clinical trials. Clinical Trials 2018;15(2):159–168.

[9] Ou FS, Heller M, Shi Q. Milestone prediction for time-to-event endpoint monitoring in clinical trials. Pharmaceutical Statistics 2019;18(4):433–446.

[10] Aubel P, Antigny M, Fougeray R, Dubois F, Saint-Hilary G. A Bayesian approach for event predictions in clinical trials with time-to-event outcomes. Statistics in Medicine 2021;40(28):6344–6359.