Enrollment and Event Projection in Oncology Trials

Jihong Chen and Jiang Qian

Abbott Laboratories

November 8, 2010

Why Enrollment and Event Projection?

- Forecasting enrollment during a clinical trial will help to ensure adequate drug supplies and monitoring resources, as well as to coordinate sites to avoid over-enrollment.
- In oncology trials, interim/final efficacy analyses are often scheduled when target number of events are observed. Projecting the event timing is the basis for planning of database lock, for phase 3 start up activities, potential regulatory submission, publication of the results and product launch, etc.
- To inform upper management with anticipated trial milestone dates and to enable portfolio review/plan.

Literature Review

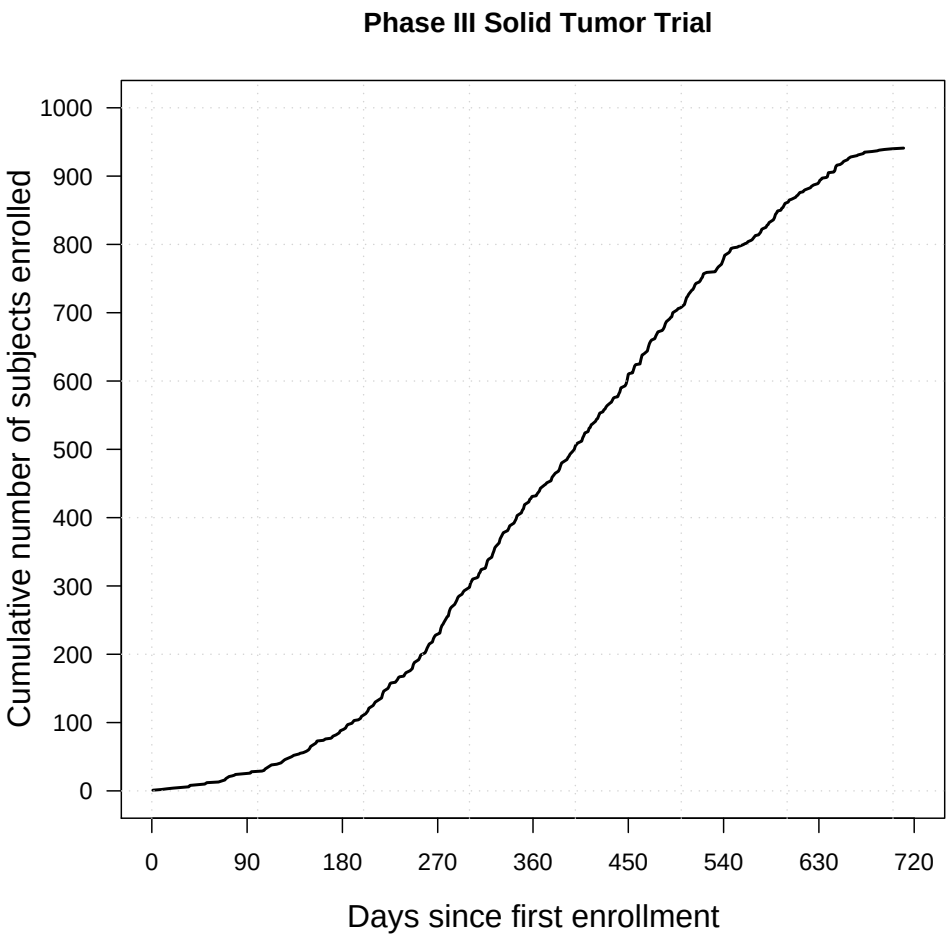
- Enrollment projection
  - Homogeneous Poisson process (Senn 1998)
  - Bayesian method (Gajewski et al, 2007)
  - Poisson-Gamma model (Anisimov and Fedorov, 2007)
- Event projection: most current work are based on homogeneous Poisson enrollment but consider different distributions for time to event
  - Exponential distribution (Bagiella & Heitjian 2001)
  - Nonparametric distribution (Ying, Heitjian & Chen 2004)
  - Weibull distribution (Ying & Heitjian 2008)

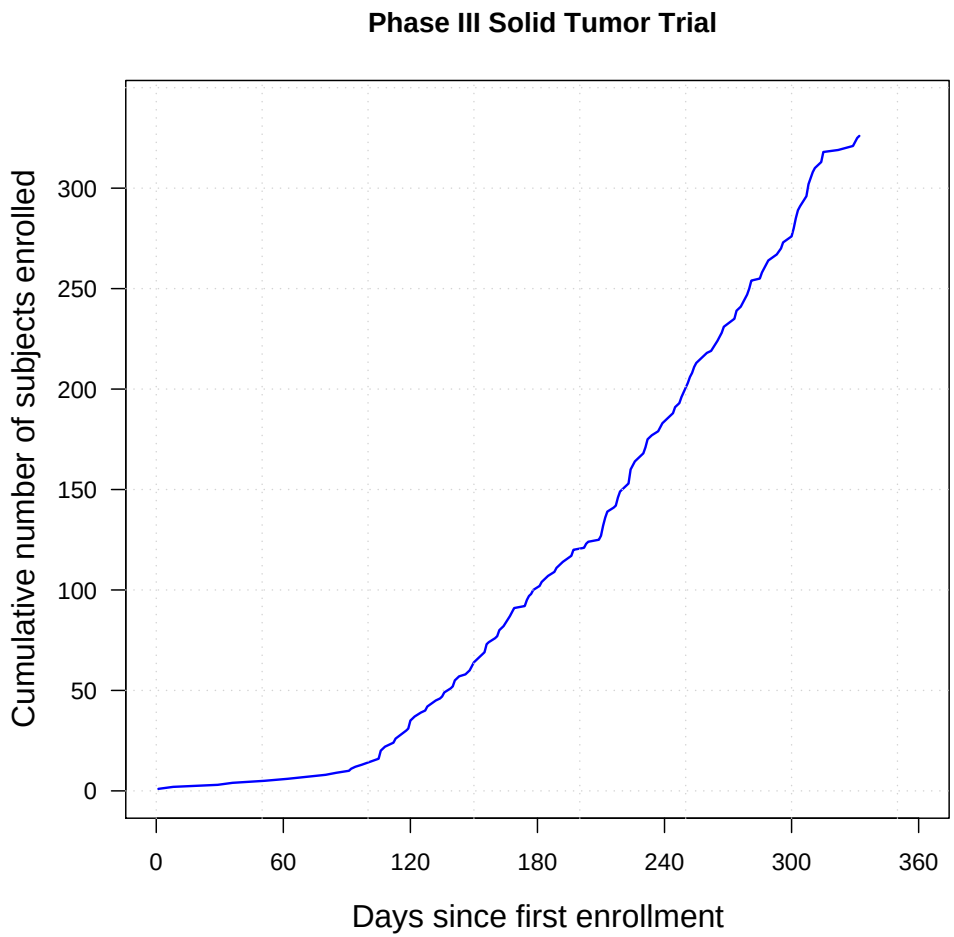
Overview

- Objective of projection
  - Number of enrollment/events at specified times
  - Timing of landmark enrollment/events
- Timing of projection
  - Pre-trial projection:
    - Purely based on prior assumption of enrollment, event and loss rates
  - Real-time projection:
    - Based on the data from ongoing trial itself
    - Can be updated frequently as data accumulate
    - Potentially more realistic and accurate

Outline

Enrollment Pattern in Real Oncology Trials





- Enrollment is slow at the beginning, speeds up, then slows down.
- Homogeneous Poisson arrival is not adequate to model the pattern.

Poisson-Gamma Enrollment Model (Anisimov and Fedorov, 2007)

- Enrollment process:

  protocol approval $\longrightarrow$ site activation $\longrightarrow$ subject enrollment

- The ith site is activated at time $u_i, i = 1, \ldots, N$. Subjects arrive at the ith site according to Poisson processes with time-constant rate λ_i.
- The overall enrollment follows a non-homogeneous Poisson process with rate at time t defined as

$$\Sigma(t) = \sum_{i=1}^{N} \lambda_i \cdot [t - u_i]_+$$

- Assume $\lambda_i \sim \Gamma(\alpha, \beta)$. Mean enrollment rate across sites is $\lambda = \alpha/\beta$.

Overall Enrollment

General Case (Fakinos, 1984)

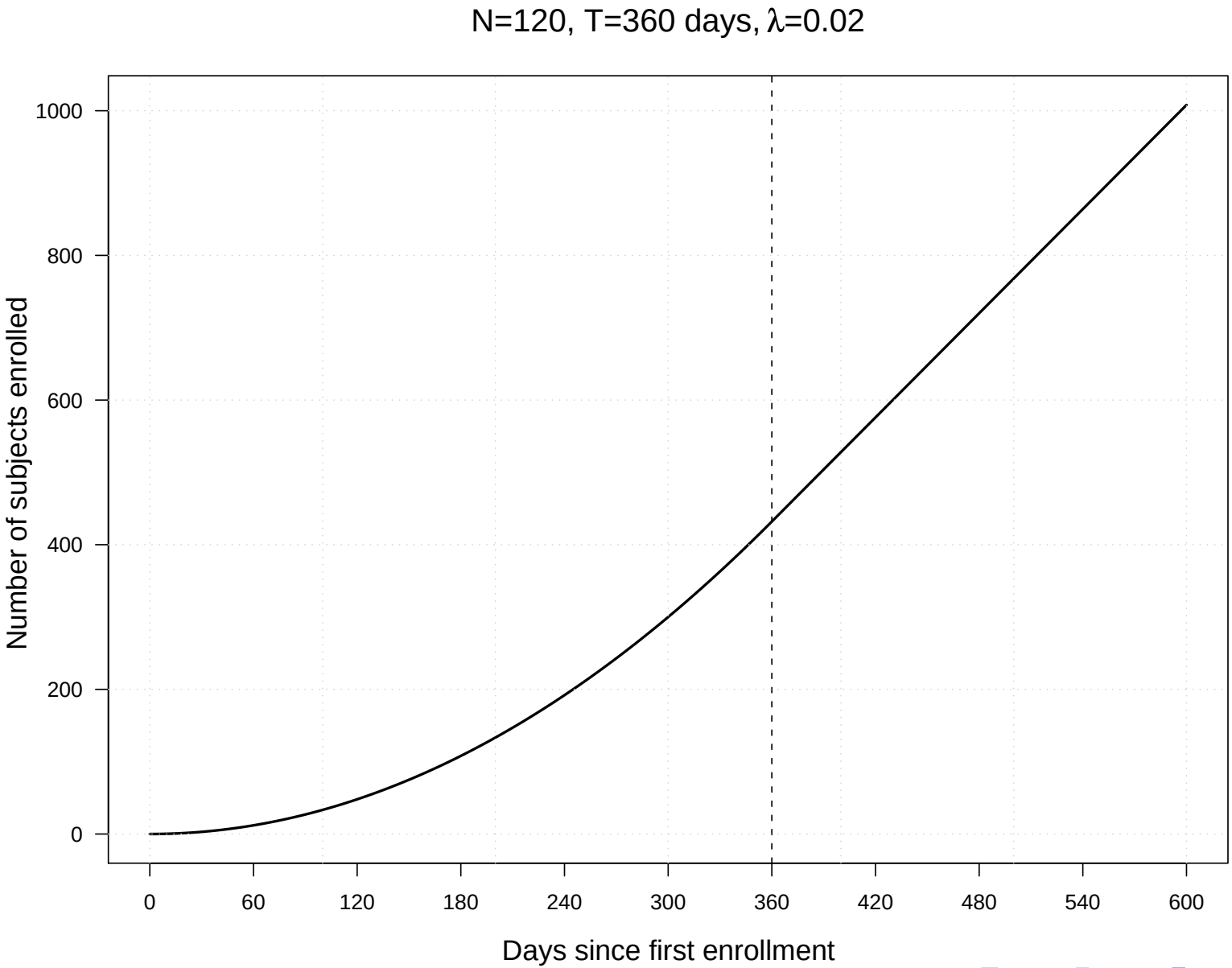
Assume time to site activation has density function $h(u), u \in [0, \infty)$. The number of subjects enrolled at time t follows Poisson distribution with mean

$$A(t) = \int_0^t \Sigma(u) h(t-u) du$$

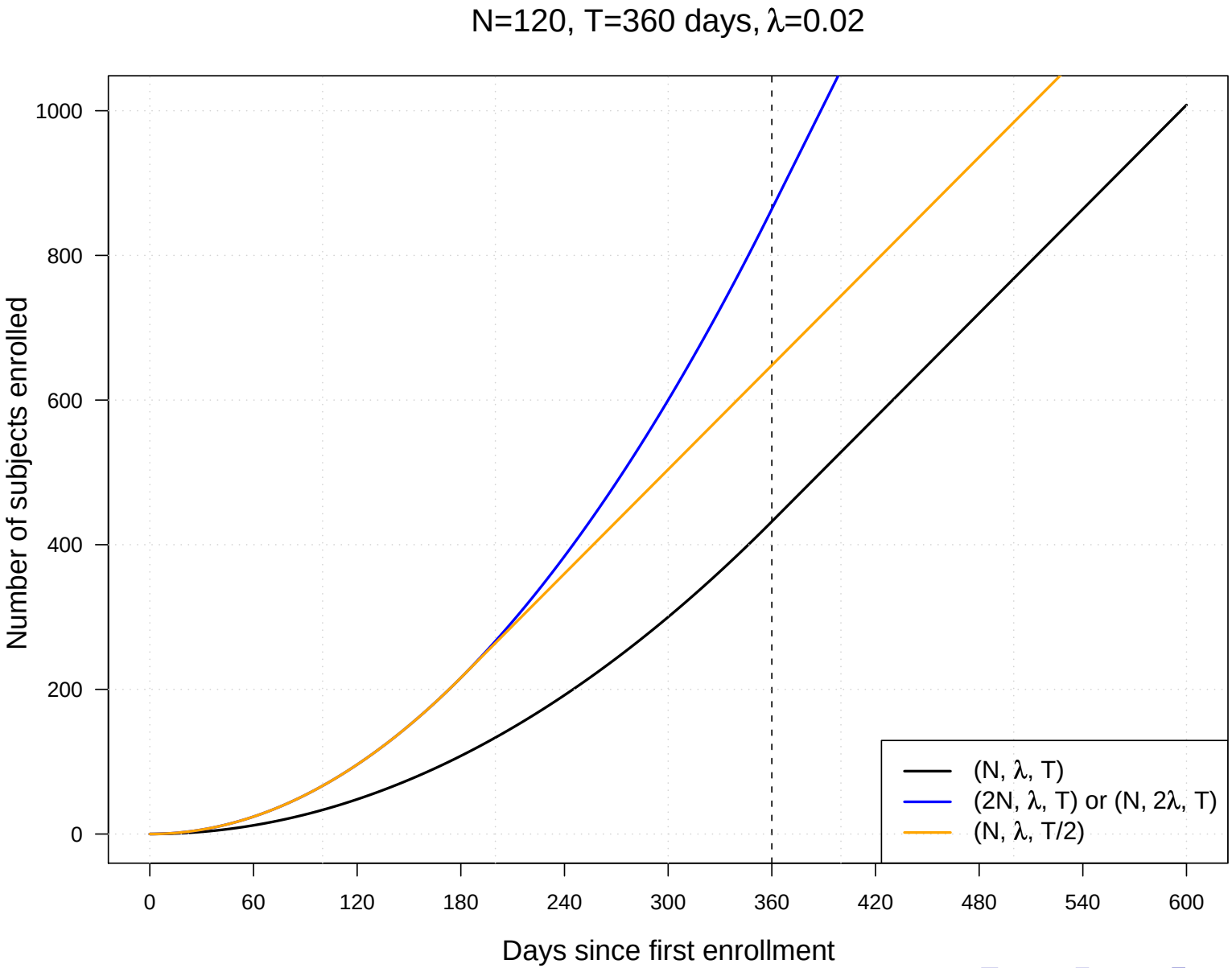
In particular, if $h(u)$ is the density function of an uniform distribution on $[0, T]$, then

$$A(t) = \begin{cases} N\lambda t^2/2T & t \leq T \\ N\lambda(t - \frac{T}{2}) & t > T \end{cases} \tag{1}$$

Overall Enrollment: Mean Enrollment Curve



Overall Enrollment: How to Speed up?



Factors that Determine the Enrollment

1. Number of planned sites: N.
2. Site activation times u_i:
   - Elicit opinions from clinical team regarding estimated time frame for each site.
   - According to past trials, it usually takes one year for all sites to be activated.
   - For most phase II oncology trials, enrollment is often finished before all sites are activated.
3. Enrollment rate at each site $\lambda_i \sim \Gamma(\alpha, \beta)$.
   - Pre-trial: estimate is based on past experience.
   - On-going trial: estimate is based on data collected.

Parameter Estimation for Gamma Distribution

At current time t_0, define

N_1: number of sites activated by time t_0.

k_i: number of subjects enrolled at the ith site by time t_0.

$K_1 = \sum_{i=1}^{N_1} k_i$: total number of subjects enrolled by time t_0.

$\tau_i = t_0 - u_i$: time elapsed since the ith site was activated by time t_0

- Maximum Likelihood Estimate

$$L(\alpha, \beta) = \sum_{i=1}^{N_1} \ln \Gamma(k_i+\alpha) - N_1 \ln \Gamma(\alpha) - K_1 \ln \beta - \sum_{i=1}^{N_1} (k_i+\alpha) \ln(1+\tau_i/\beta)$$

- Bayesian estimate: Given a prior $\lambda_i \sim \Gamma(\alpha_0, \beta_0)$, the posterior is

$$\lambda_i \sim \Gamma(\alpha_0 + K_1, \frac{\beta_0}{1 + N_1 \beta_0})$$

Enrollment Projection: Simulation Algorithm

1. At current time, estimate parameters for $\Gamma(\alpha, \beta)$.
2. For N_1 open sites, simulate Poisson arrivals with rate sampled from $\Gamma(N_1\alpha, \beta)$.
3. For sites not yet activated, simulate times of site activation according to uniform distribution and Poisson arrivals with rate sampled from $\Gamma(\alpha, \beta)$. The calendar enrollment date of each subject is the sum of site activation time and arrival time.
4. Rank the enrollment dates.
5. For a future date, calculate the number of subjects enrolled.
6. Find the landmark date when planned number of subjects are enrolled.
7. Repeat the simulations. Obtain the median and prediction interval.

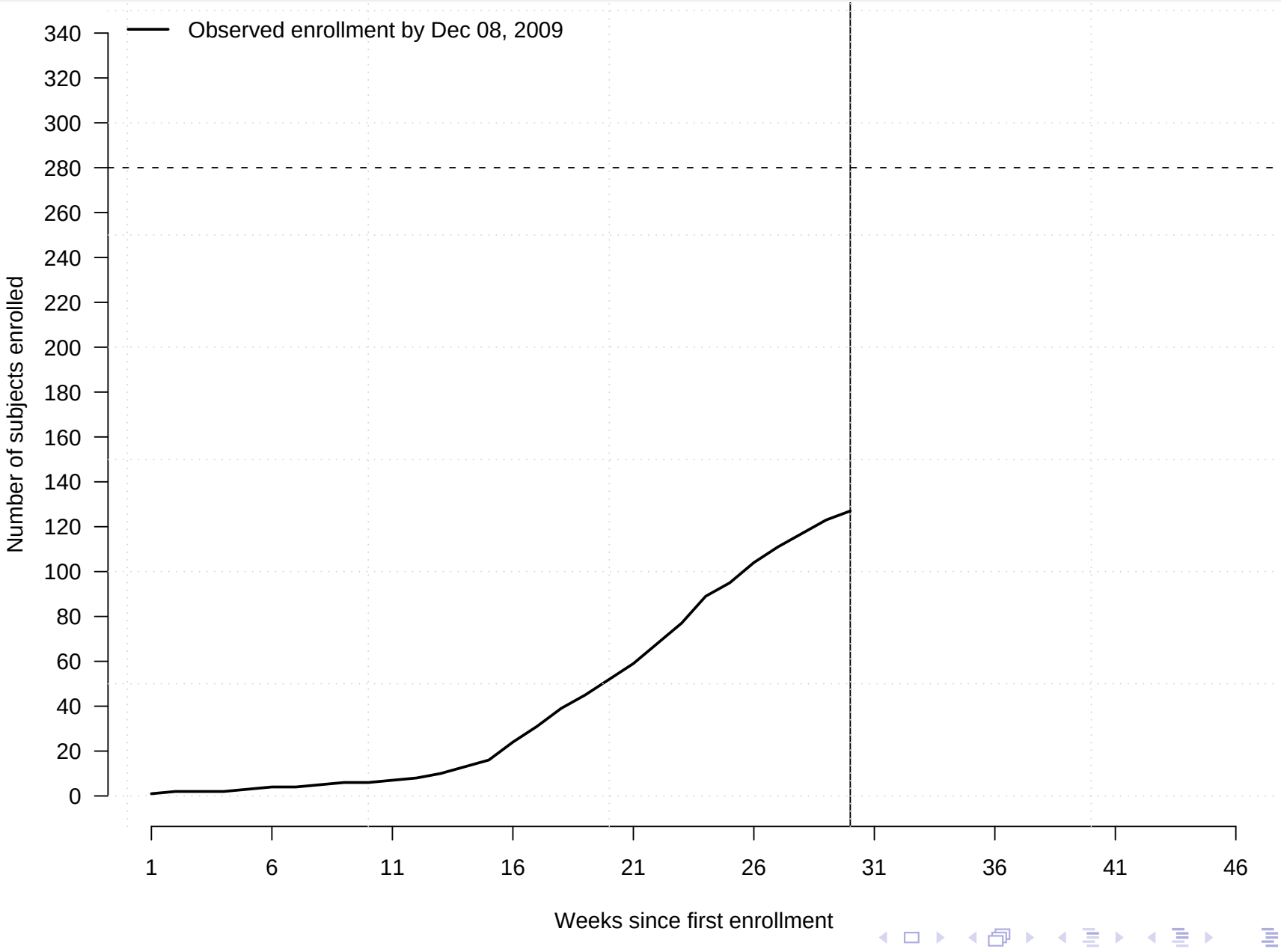
Phase III Solid Tumor Trial: Background

- Planned sample size: 280 subjects, 65 sites.
- Clinical team expected the enrollment to finish on Sep 30, 2010.
- First subject enrolled on May 12, 2009.
- Nine subjects enrolled by Aug 04, 2009.
- Projection of enrollment started in Nov, 2009.

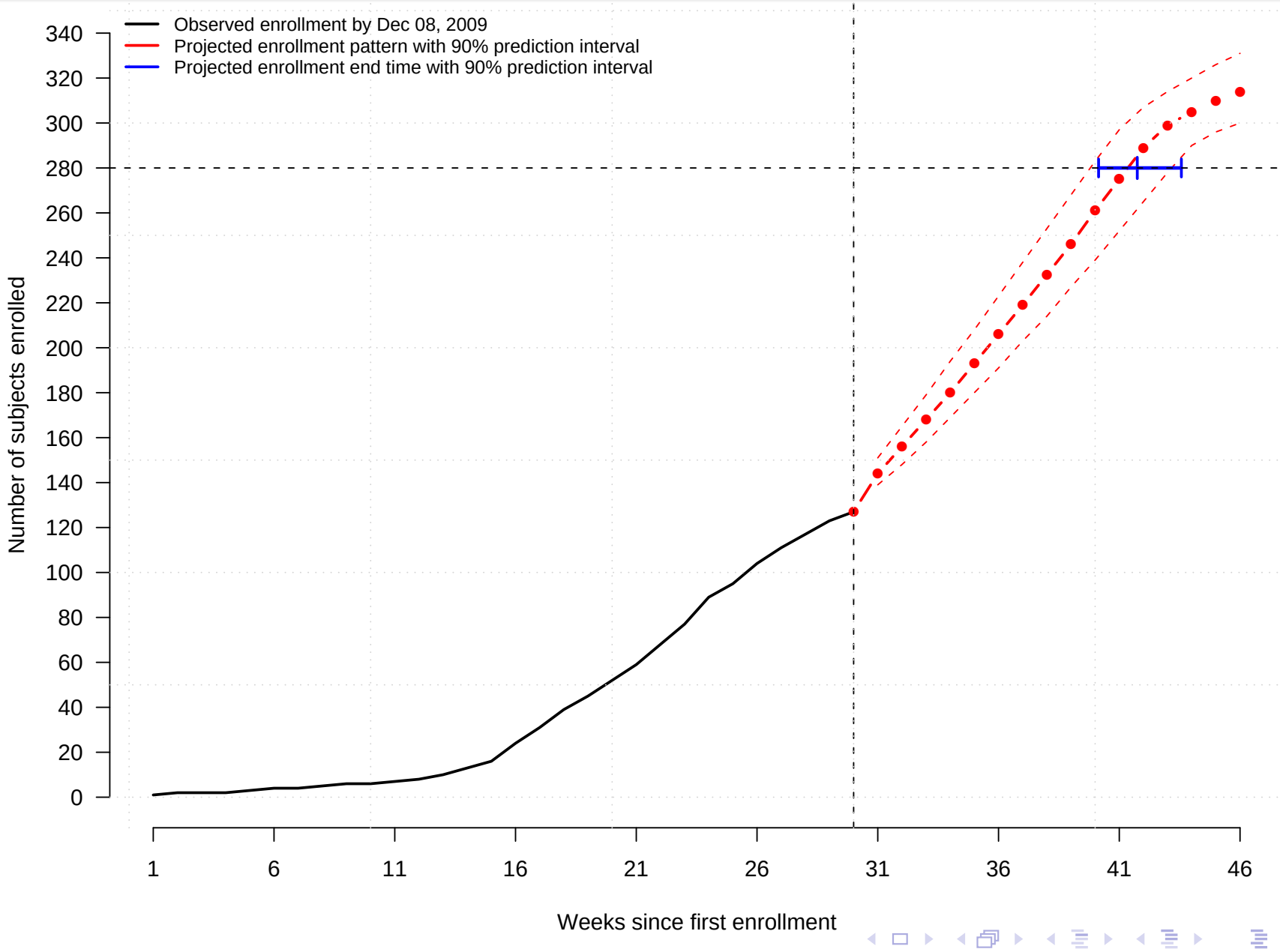
Date	#. Subjects Enrolled	Projected Enrollment End Date
11/03/09	95	02/11/10
11/22/09	114	03/04/10
12/10/09	139	03/09/10
12/23/09	164	03/05/10
01/04/10	181	03/05/10
01/14/10	192	03/07/10

- 280 subjects were enrolled on Mar 08, 2010.
- The actual enrollment is 326 subjects by Apr 08, 2010.

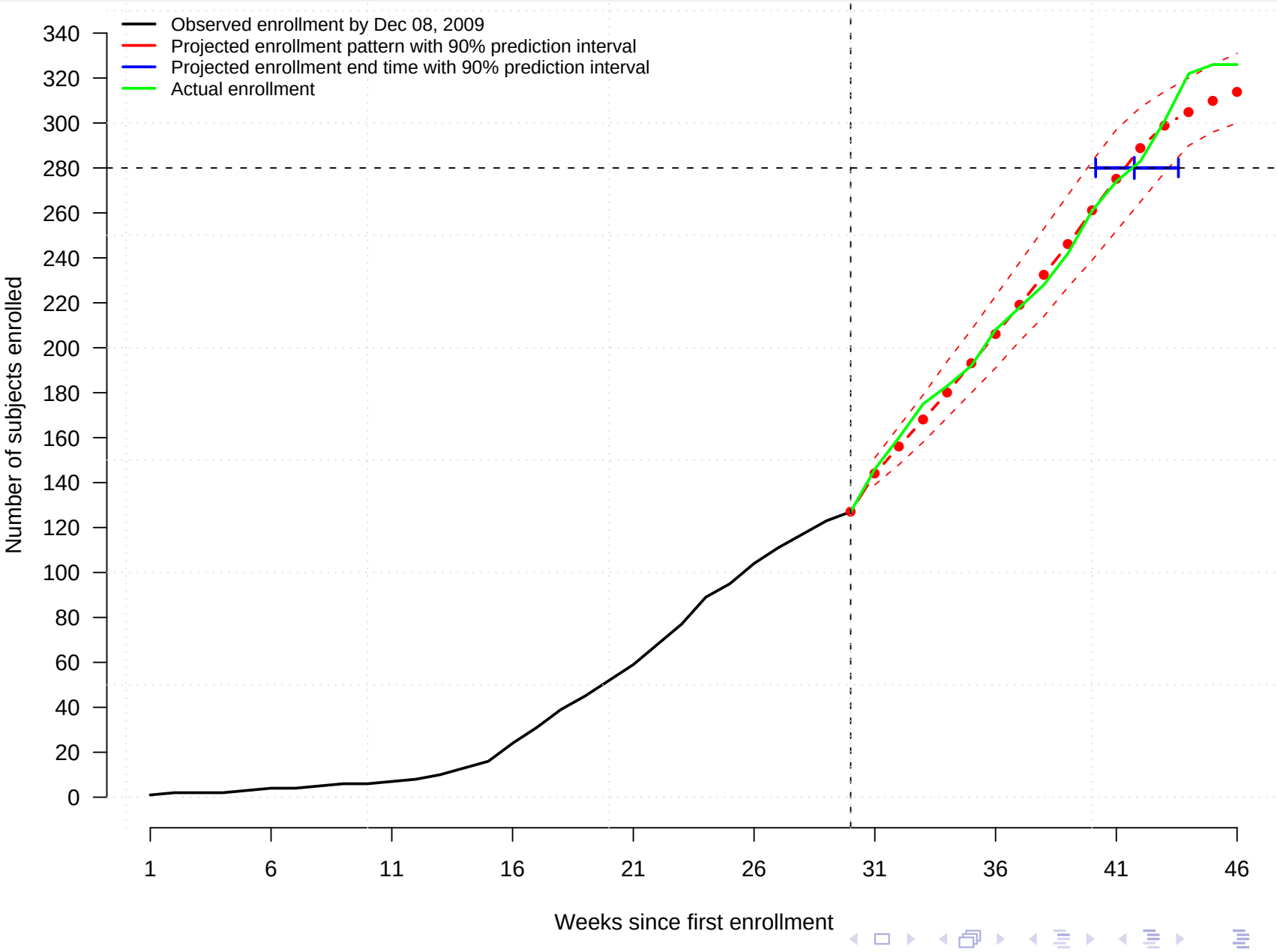
Phase III Solid Tumor Trial: Enrollment Projection



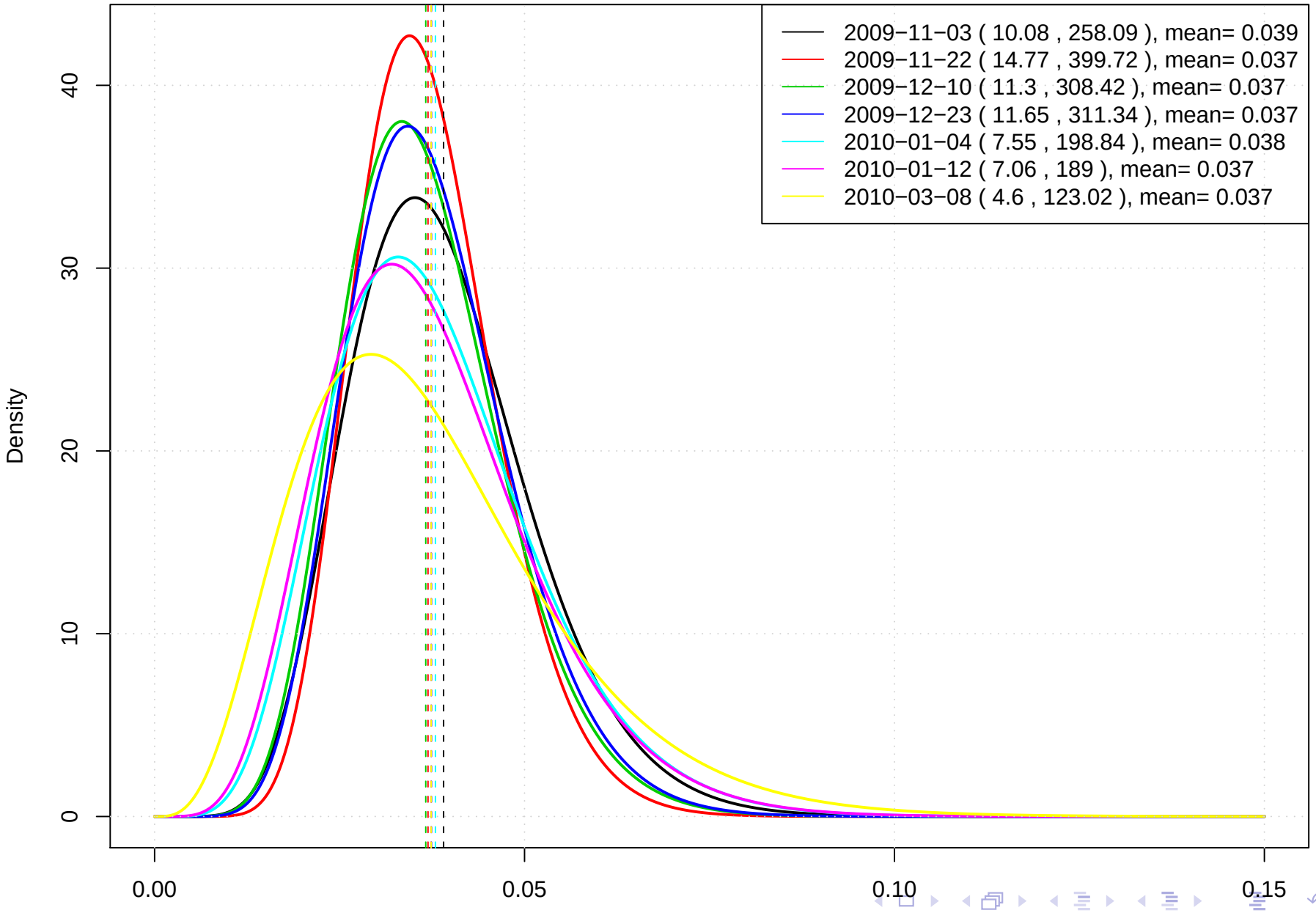
Phase III Solid Tumor Trial: Enrollment Projection



Phase III Solid Tumor Trial: Enrollment Projection



Phase III Solid Tumor Trial: Estimate of $\lambda_i \sim \Gamma(\alpha, \beta)$

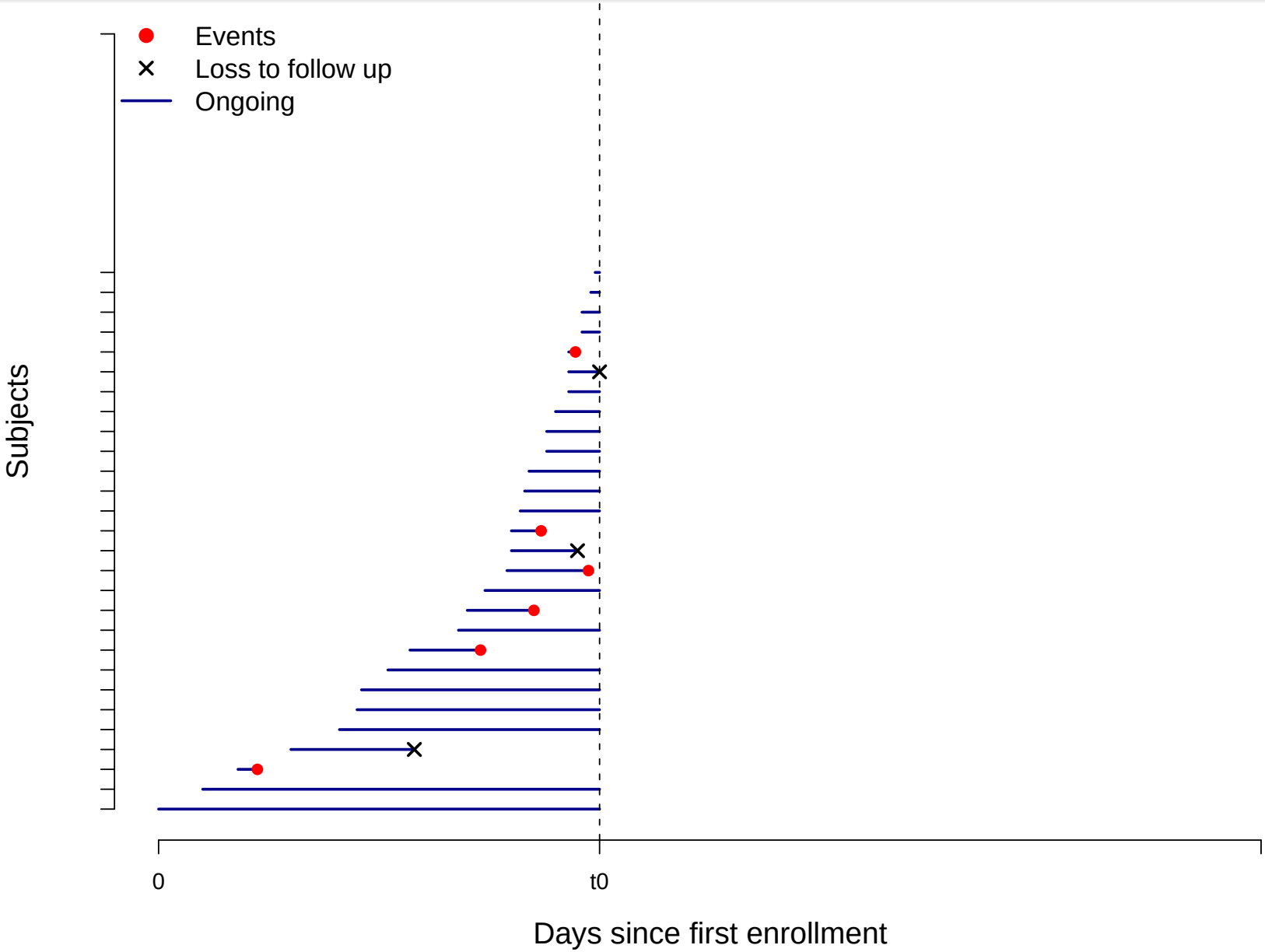


Outline

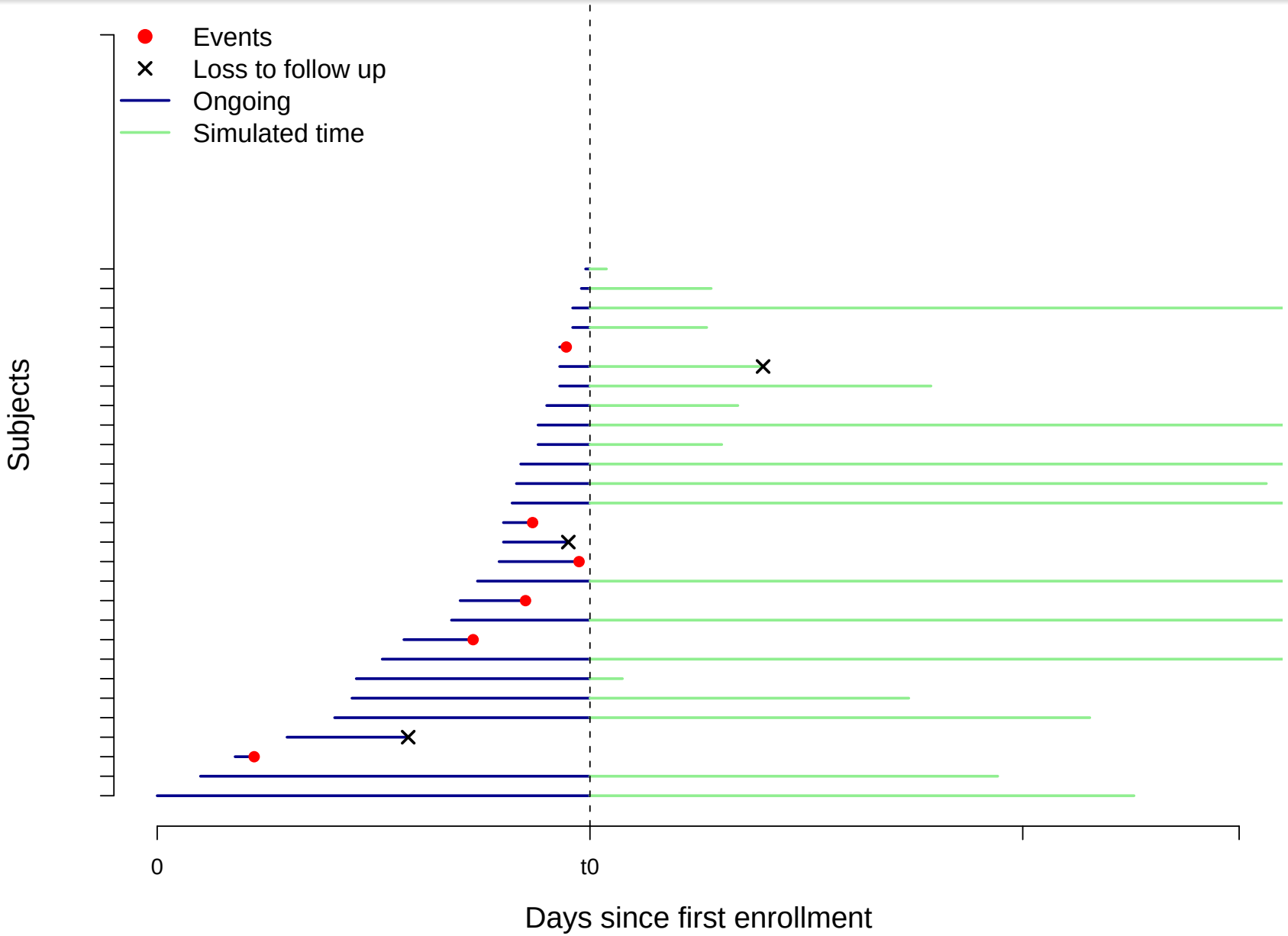
Introduction

- Time to event: The time from entry into a study until a subject has a particular event of interest. Examples: time to death, time to disease progression.
- Censored subject: During the period of observation, the subject does not have the event.
- Loss to follow-up: Subjects withdraw the study without events.
- Future number of events is the summation of:
  - Number of events observed so far;
  - Number of events among subjects enrolled and censored;
  - Number of events among subjects not yet enrolled.

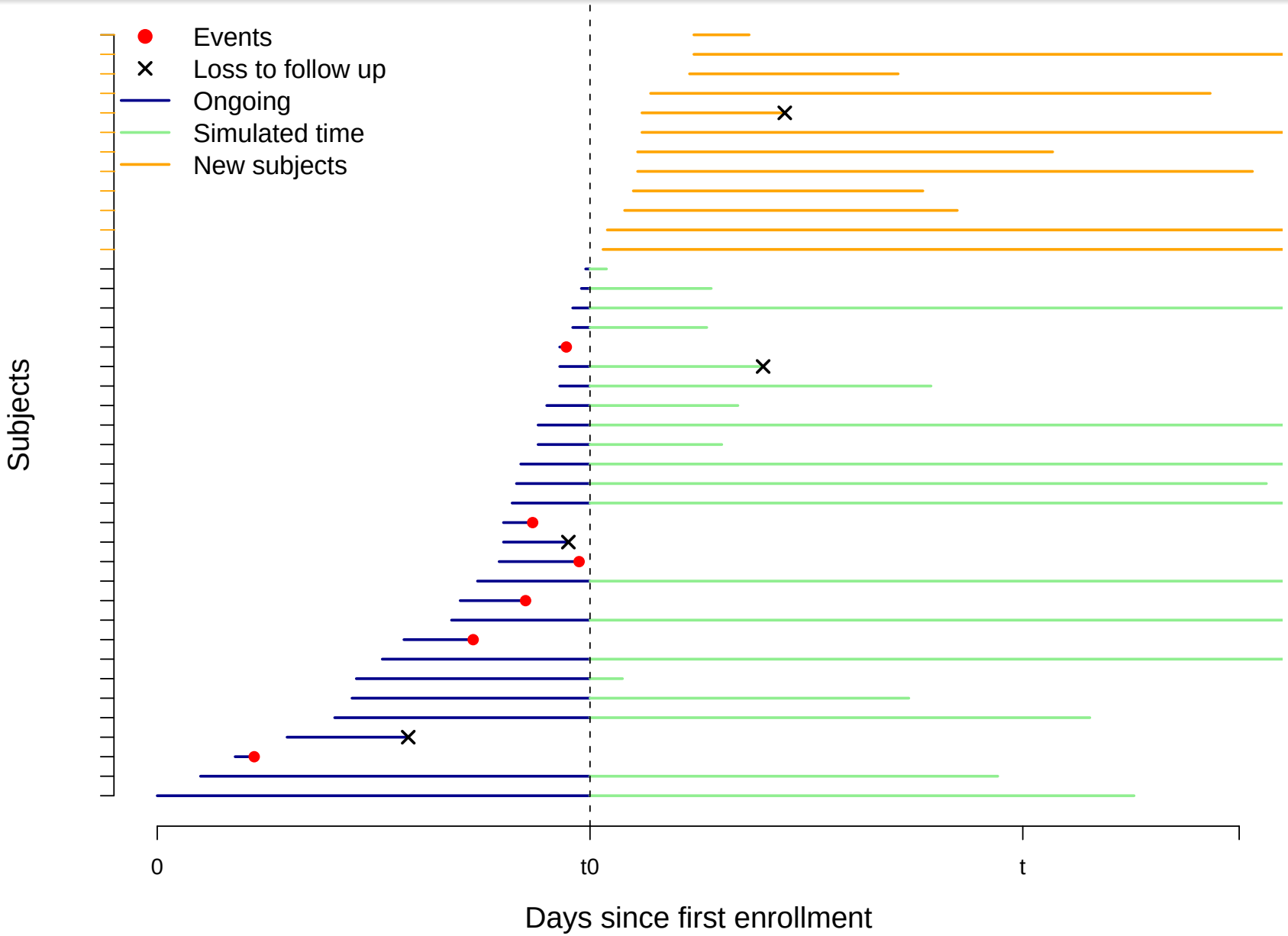
Event Projection: Illustration of Main Idea



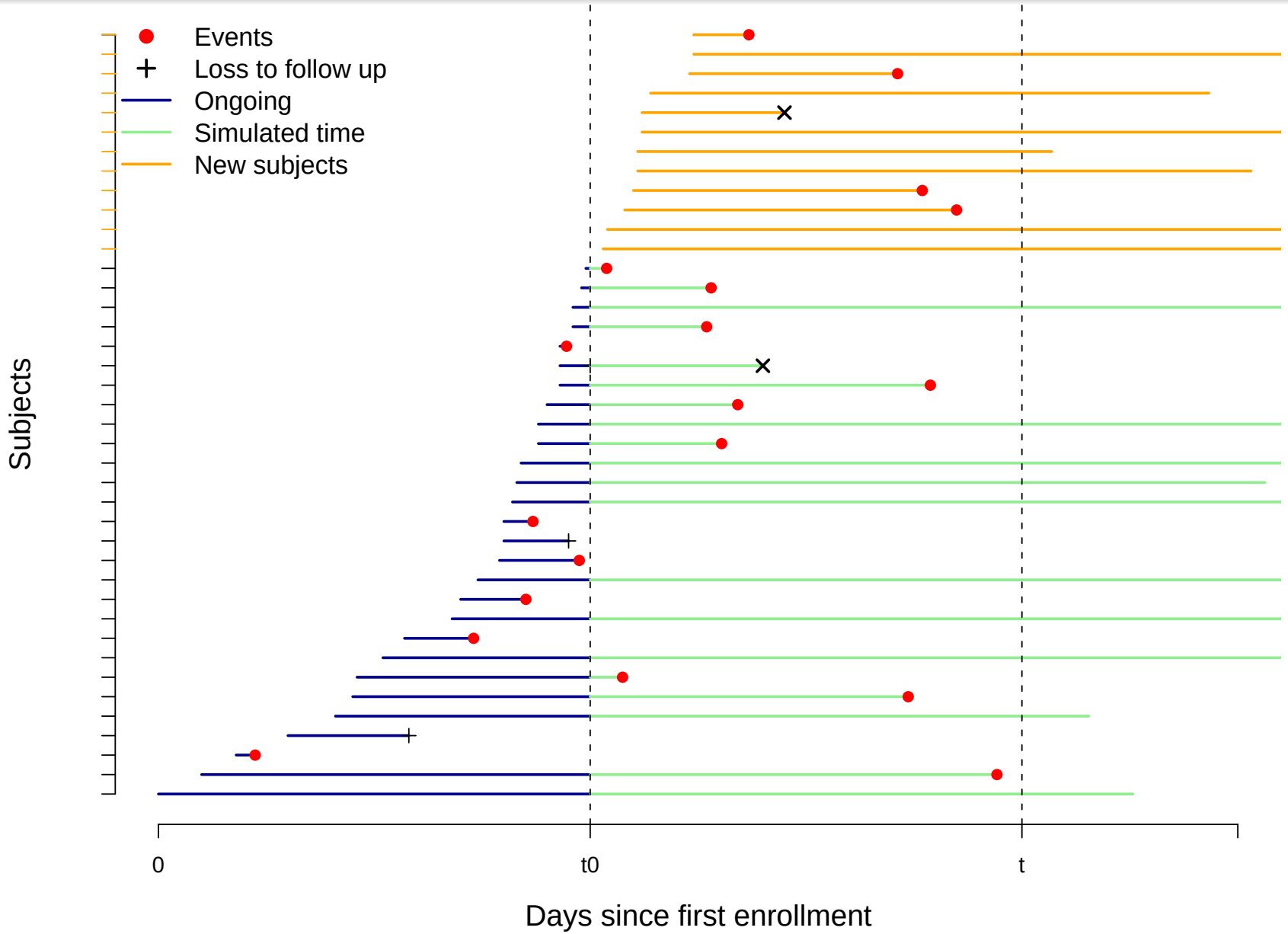
Event Projection: Illustration of Main Idea



Event Projection: Illustration of Main Idea



Event Projection: Illustration of Main Idea



Mean Number of Events by Time

General Case (Fakinos, 1984)

Let $\Sigma(u)$ denote the overall enrollment rate at time u. Assume time to event has CDF $F(u), u \in [0, \infty)$. The number of events at time t follows Poisson distribution with mean

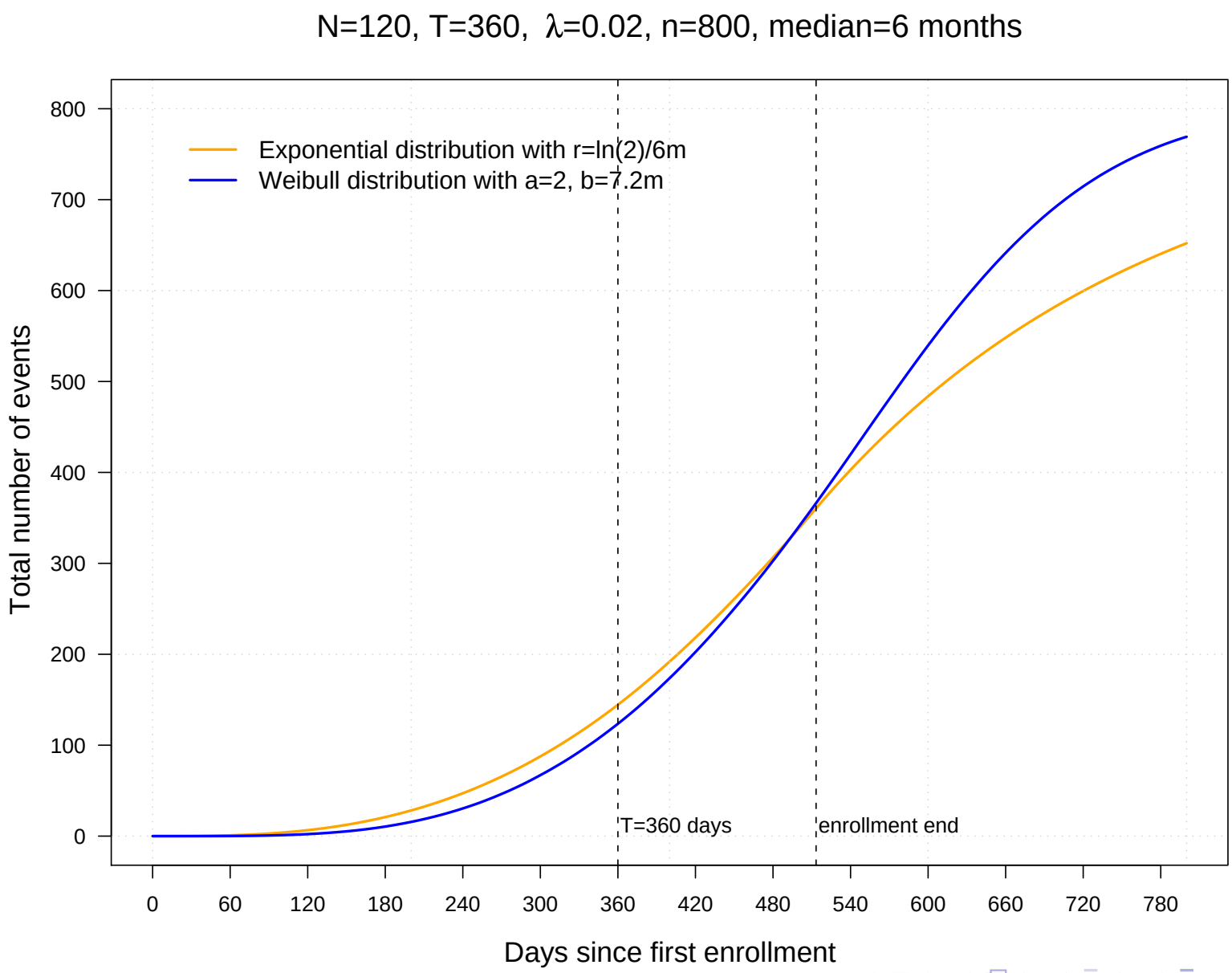
$$E(t) = \int_0^t F(t-u)\Sigma(u)du$$

In particular, when time to event follows exponential with rate r,

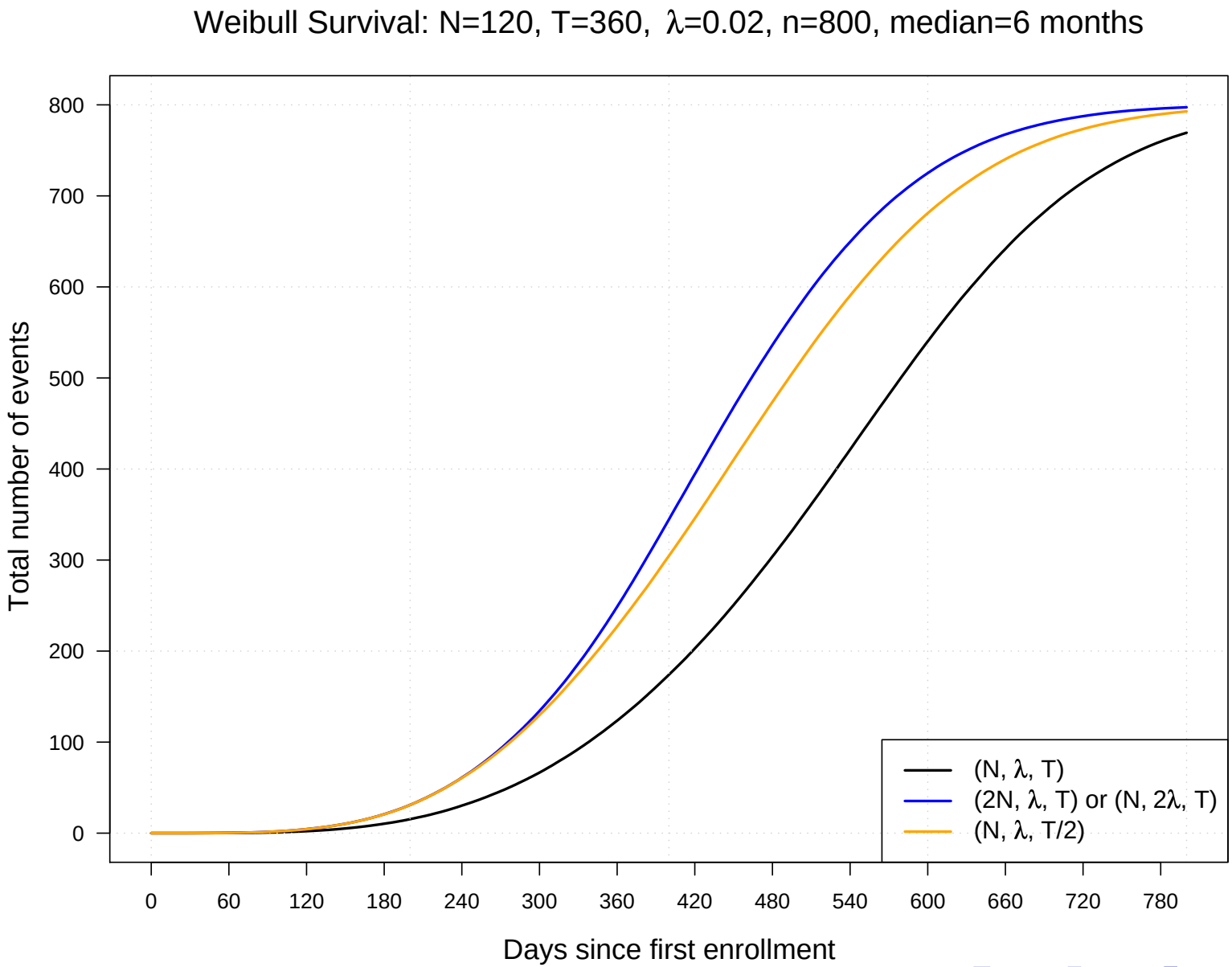
$$E(t) = \begin{cases} \frac{N\lambda}{T}\{\frac{t^2}{2} - \frac{t}{r} + \frac{1}{r^2}[1 - exp(-rt)]\} & t \leq T \\ \lambda N(t - \frac{T}{2} - \frac{1}{r}) - [\frac{\lambda NT}{2} - E(T) - \frac{\lambda N}{r}]e^{-r(t-T)} & T < t \leq t_E \\ n - [n - E(t_0)]e^{[-r(t-t_0)]} & t > t_E \end{cases} \quad (2)$$

where $t_E = \frac{n}{N\lambda} + \frac{T}{2}$, $\lambda = \alpha/\beta$, n is the total number of subjects.

Mean Number of Events: Illustration



Mean Number of Events: Illustration



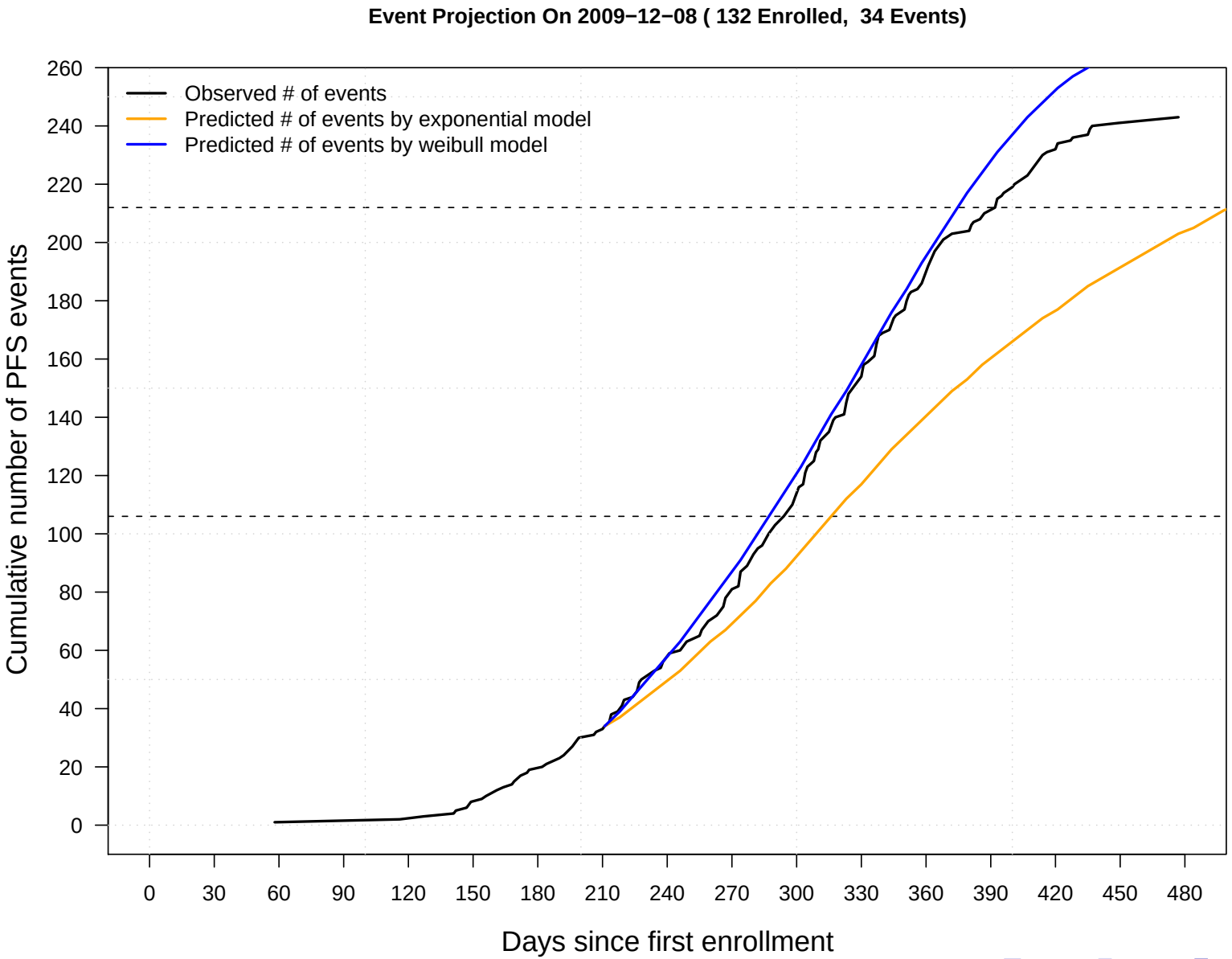
Event Projection: Simulation Algorithm

1. Based on current data (and historical information), estimate parameters for distributions of time to event.
2. For new subjects, simulate time to event data.
3. For enrolled and censored subjects, simulate time to event conditional on the times that subjects have spent in the study so far.
4. For each subject, calculate estimated date of event based on enrollment date and time to event.
5. Rank the event dates.
6. For a future date, calculate the number of events.
7. Find the landmark date corresponding to the target number of event.
8. Repeat the simulations. Obtain the median and prediction interval.

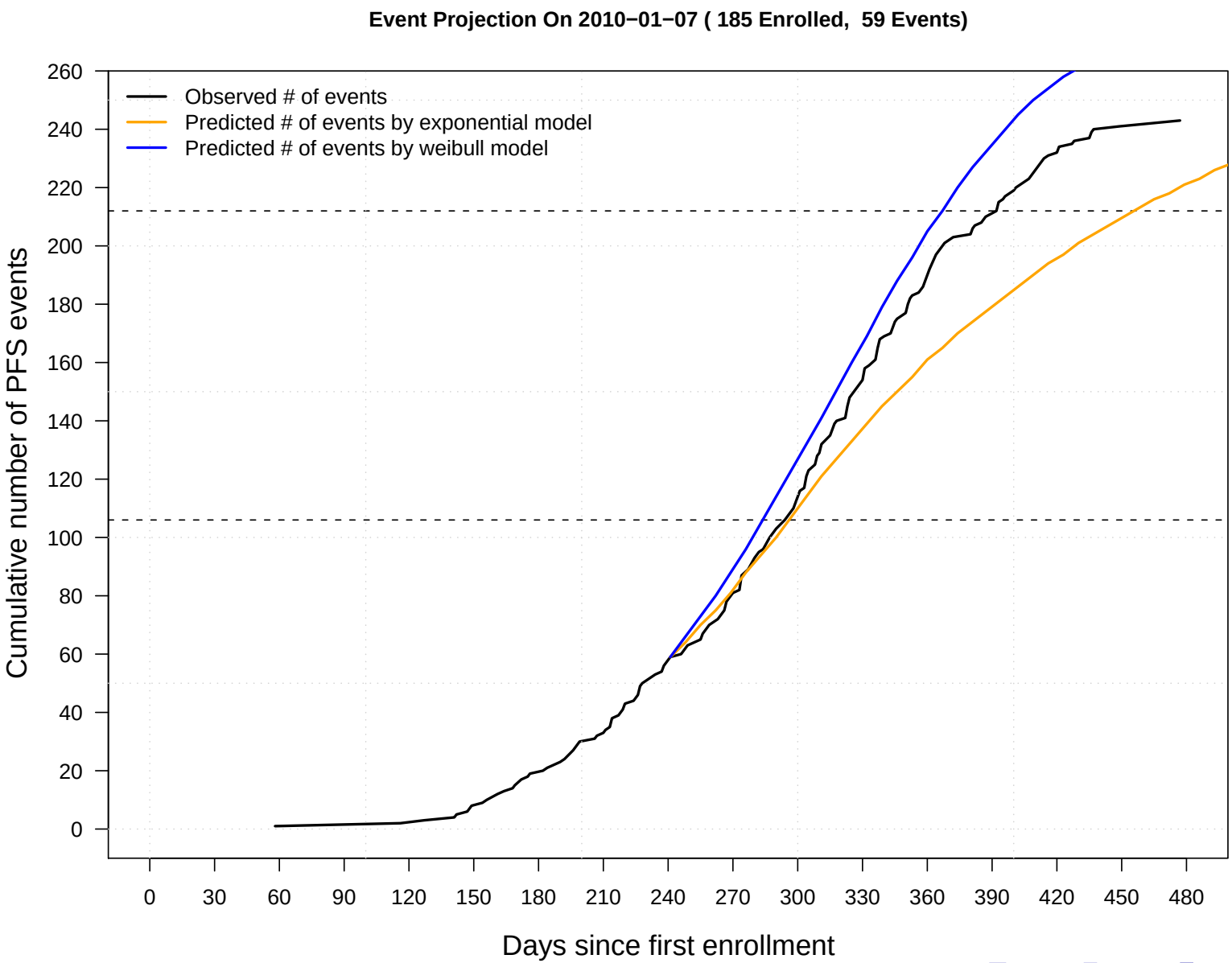
Phase III Solid Tumor Trial: Analysis Plan

- Randomized, double-blinded study.
- Primary endpoint was Progression Free Survival (PFS), defined as the time from randomization to disease progression or death.
- Interim analysis was planned at 106 PFS events.
- Final analysis: 212 PFS events.
- Considerable delay in reporting PFS events in the database.
- The projection was based on the excel tracking file provided by the clinical team.
- At projection times, the treatment code remained blinded. The median PFS for combined data is expected to be around 3 months.

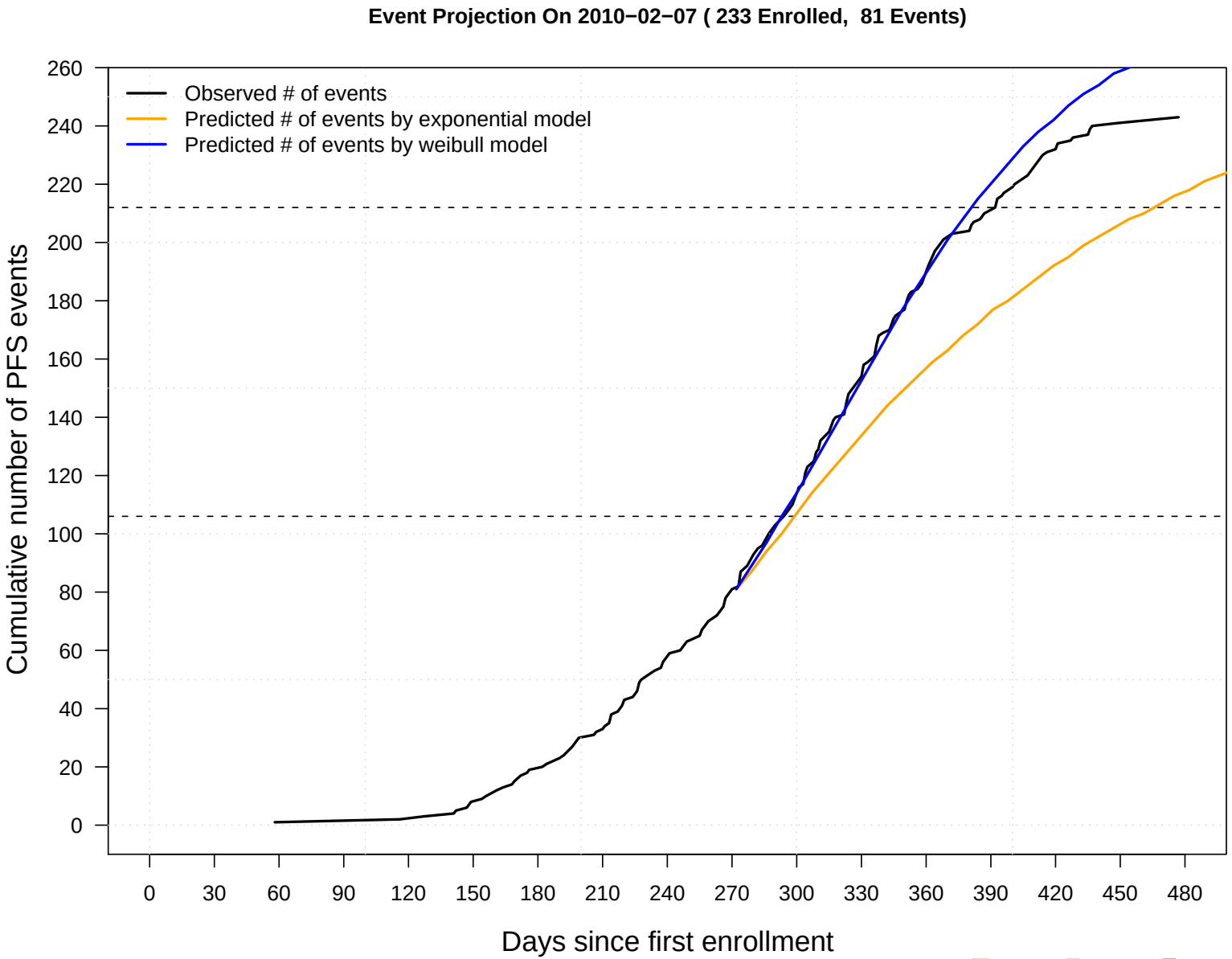
Phase III Solid Tumor Trial: Event Projection



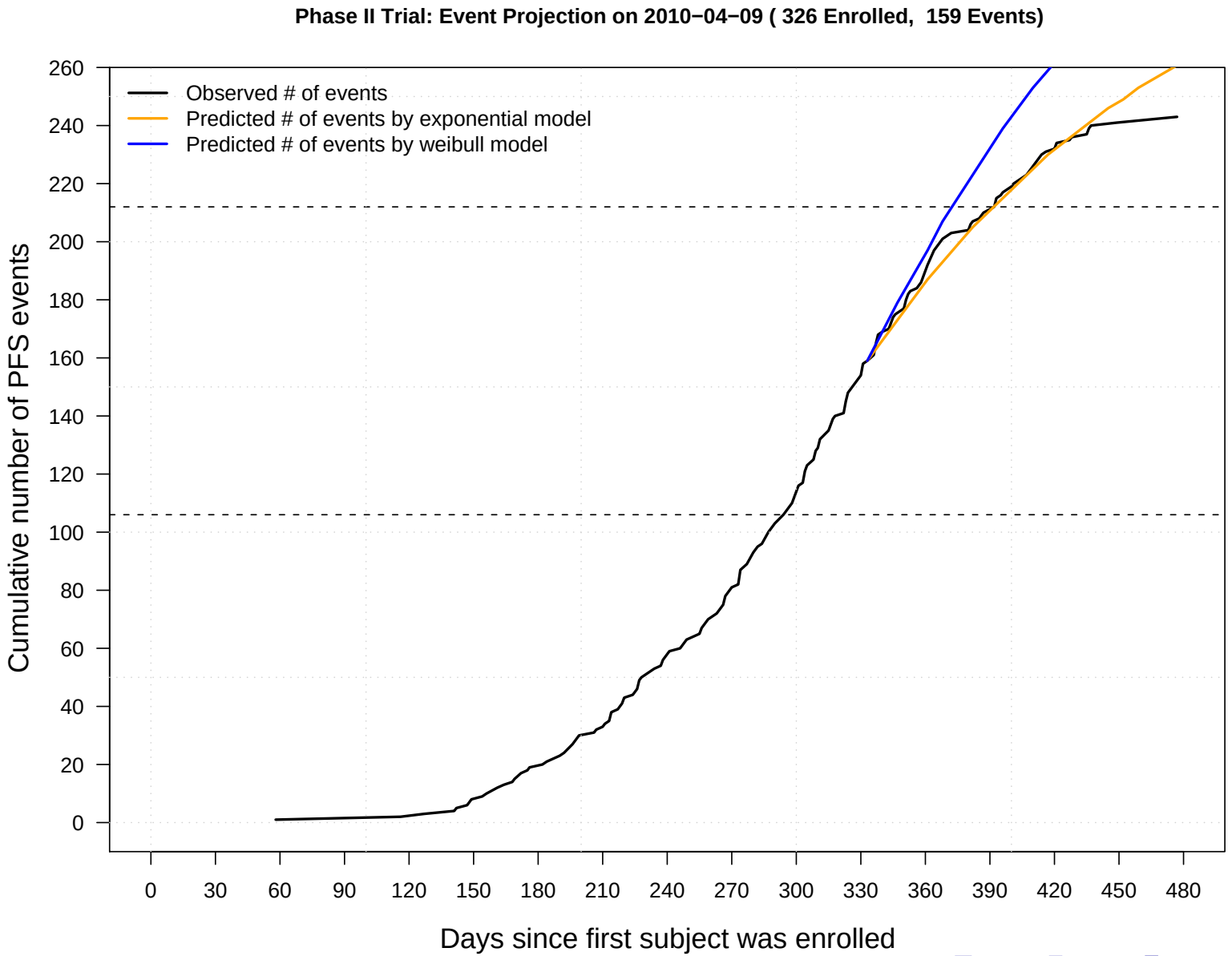
Phase III Solid Tumor Trial: Event Projection



Phase III Solid Tumor Trial: Event Projection



Phase III Solid Tumor Trial: Event Projection



Summary

- We proposed an integrated approach for enrollment and event projection in oncology clinical trials based on Poisson-Gamma enrollment model.
- We developed some theoretical results for trial planning purpose and designed a real-time projection algorithm.
- We have implemented the method for many of our past trials. The prediction accuracy may vary for different trials. It is important to add a time window on the projected analysis timing, and to update the projection as data are accumulating.
- The method is not restricted to oncology trials. It can be applied to all trials with time to event endpoints.

References

- Anisimov V., Fedorov V.. Modelling, prediction and adaptive adjustment of recruitment in multicentre trials. Statistics in Medicine. 2007;26(27):4958-4975.
- Bagiella E, Heitjan DF. Predicting analysis times in randomized clinical trials. Statistics in Medicine 2001; 20:2055C2063.
- Fakinos D.. The infinite server queue with arrivals generated by a non-homogeneous compound Poisson process. Journal of the Operational Research Society, 1984; Vol. 35, No. 5.
- Gajewski, BJ, Simon, SD, and Carlson, SE. Predicting accrual in clinical trials with Bayesian posterior predictive distributions. Statistics in Medicine, 2007; 27, 2328-2340.
- Senn, S. Some controversies in planning and analyzing multi-center trials. Statistics in Medicine, 1998; 17, 1753-1765.
- Ying GS, Heitjan DF. Weibull prediction of event times in clinical trials. Pharmaceutical Statistics, 2008 Apr-Jun;7(2):107-20.
- Ying GS, Heitjan DF, Chen TT. Nonparametric prediction of event times in randomized clinical trials. Clinical Trials 2004; 1:352C361.