Monitoring Accrual and Events in a Time-to-Event Endpoint Trial

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Introduction

- A number of things can go wrong in a survival study, especially if you have a fixed end of trial time. Potential issues (not exhaustive):
  - **Accrual starts off slowly**
  - **The events in each treatment arm do not occur according to pre-trial hazard rate assumptions**
  - **Sites initiated slowly**
- The consequences of these issues are a potentially underpowered trial and a significant delay in the end-of-trial analysis

Objectives of Accrual and Event Forecasting

1. **Patient Recruitment Forecasting**

   Classic Approach:

   Predictions are made from feasibility studies and produce deterministic curves.

   New Suggested Approach:

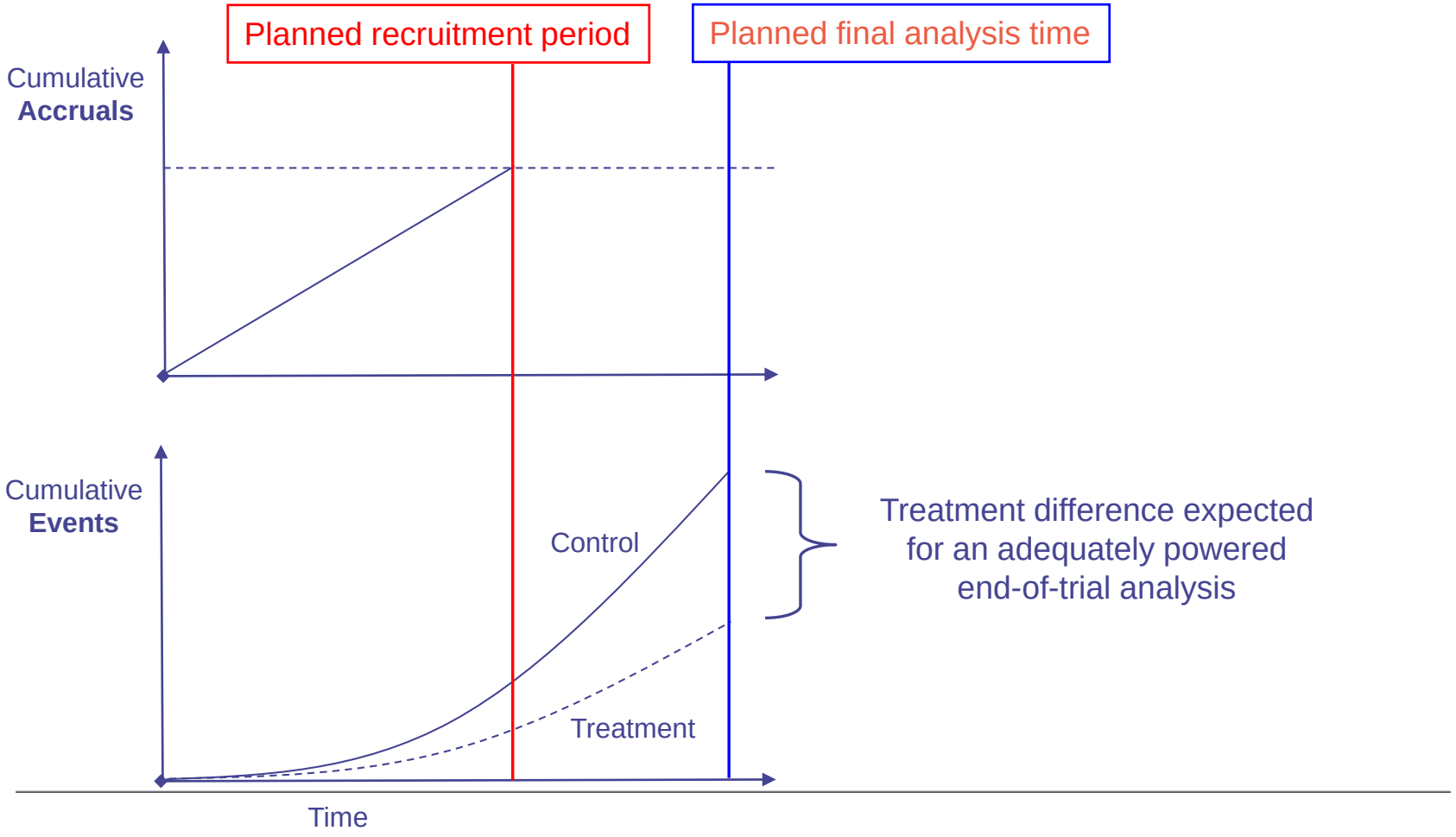
   Take into account the various sources of variability in our planning. Modeling the process of patient recruitment (site initiations, variability of the recruitment rates across sites) to improve the forecasting of the whole trial recruitment curve.

2. **Event monitoring and prediction**

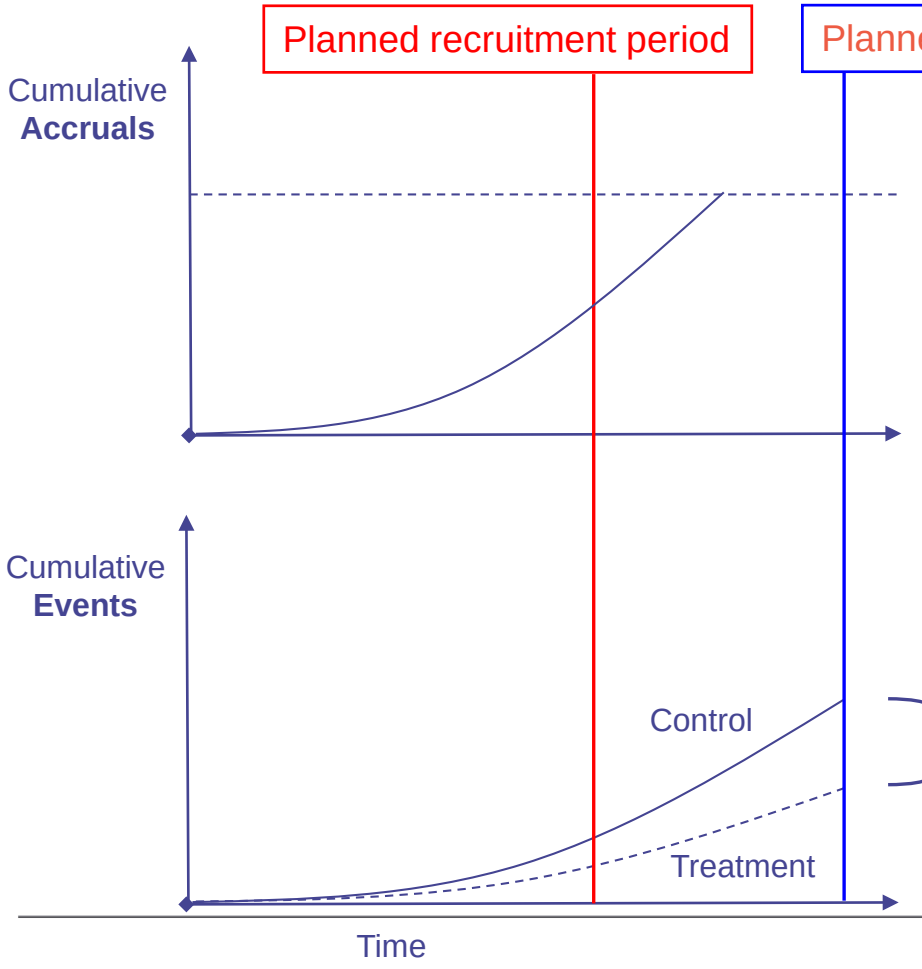
   Primary objective:

   At various times during the conduct of a study, summarize accumulated events and forecast the future number of events with a certain degree of precision

The Importance of Trial Monitoring: Expected Accrual and Survival Outcomes



The Importance of Trial Monitoring: Actual Accrual and Survival Outcomes



Actual, potentially under-powered, end-of-trial analysis

What could go wrong?

- Accrual starts off slowly
- Actual hazard rates different than expected
- Sites initiated slowly
- Etc.

Accrual monitoring and prediction

- **Primary objective:**
  - At various times during the conduct of a study, summarize accrual rates per site and forecast the duration of the remaining recruitment period with a certain degree of precision
- **Traditional accrual monitoring approaches**
  - Largely deterministic
  - Do not account for various sources of variability:
    - Site initiation times
    - Rate of accrual by site
- **Recent advances**
  - Model accrual rates by site using a probabilistic model
  - Naturally account for variability in accrual through the use of either ML or Bayesian techniques

Overview of Accrual Prediction Methodology
(1/3)

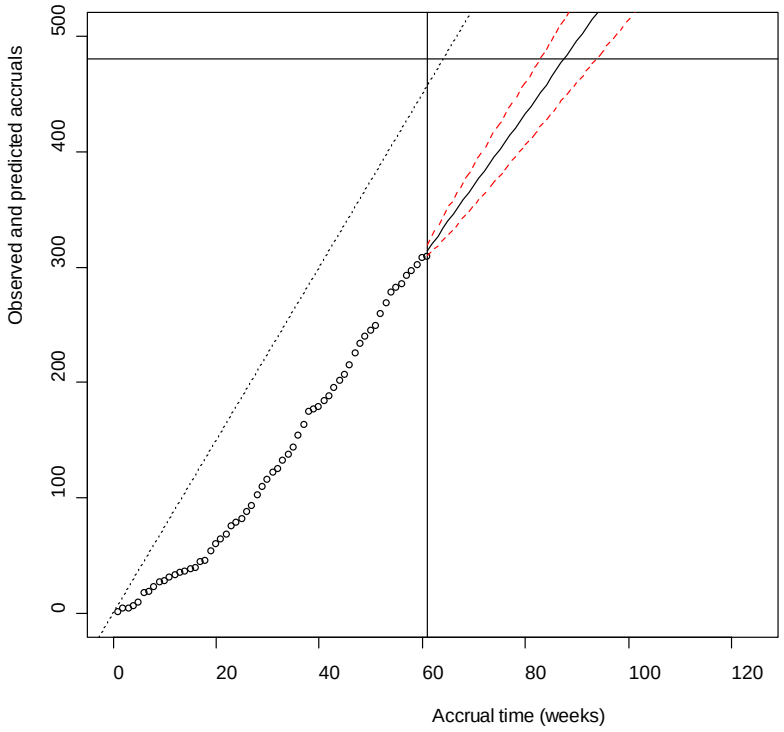
- Assume accrual at each site, i, occurs as a Poisson process with rate λ_i
  - **Gamma prior on rate at each site:** $\Gamma(\alpha_i, \beta_i)$
- Let
  - t_0 = **Current time**
  - T = **Time of future forecast**
  - a_i = **Site initiation time**
  - n_{0i} = **Number of current subjects at each site**
- Posterior predictive dist^n of number of subjects accrued at site i by time T:

$$NB\left(n_{0i} + \alpha_i, \frac{t_0 - a_i + \beta_i}{T - a_i + \beta_i}\right)$$

- Poisson accrual model has been shown to work well on a by **SITE** basis, however alternative accrual models can be applied as well

Overview of Accrual Prediction Methodology
(2/3)

- Total number of future accruals by time T distributed as the convolution of the negative binomial posterior predictive distribution from each site
  - Evaluated using simulation (Monte Carlo)



Overview of Accrual Prediction Methodology (3/3)

- Extensions of methodology
  - **Alternative accrual models to Poisson**
  - **Future site initiation dates can be random or fixed**
  - **Can incorporate random or fixed site closure dates**

- Prior elicitation of accrual rate parameters: $\Gamma(\alpha_i, \beta_i)$
  - **Incorporate accrual rate assumptions for a site by asking each investigator:**
    1. On average, how many patients do you expect to enroll each day/month/year?
    2. How many patients is your assessment in (1.) based on?
  - **Facilitates the prediction of accruals from sites that will be initiated in the future – *prior predictive* distribution will then be used.**

Event Monitoring and Prediction

- Primary objective:
  - **At various times during the conduct of a study, summarize accumulated events and forecast the future number of events with a certain degree of precision**

- Novel statistical methodology
  - **Bayesian statistical model for predicting future events accounting for various sources of variability**
  - **For a fully-enrolled study, forecasting future events can be based solely on currently observed accrual and event rates**
  - **For studies that are not fully enrolled, the task becomes more complex:**
    - We need to predict future events for future patients – the uncertainty in future accruals must be accounted for in the future event predictions
  - **In all cases, there are no "closed-form" mathematical solutions**
    - The currently proposed methodology employs Monte Carlo integration to simulate the posterior predictive distribution of the future number of events

Overview of Event Prediction Methodology

- Assume events occur according to an exponential distribution: $p(\tau_i|\theta) \sim \theta e^{-\theta\tau_i}$
  - Apply a Gamma prior which will yield a Gamma posterior distribution
- Let:
  - d_0 = Current number of events
  - d_1 = No. of future events from current subjects
  - d_2 = No. of future events from future subjects
  - n_0 = Current number of accruals
  - n = Number of future accruals (estimated from accrual model predictions)
- Future events from current subjects (with prob of event $\pi_1 = 1 - e^{\theta(T-t_0)}$):

$$p(d_1|\theta, X) \sim binomial(n_0 - d_0, \pi_1)$$

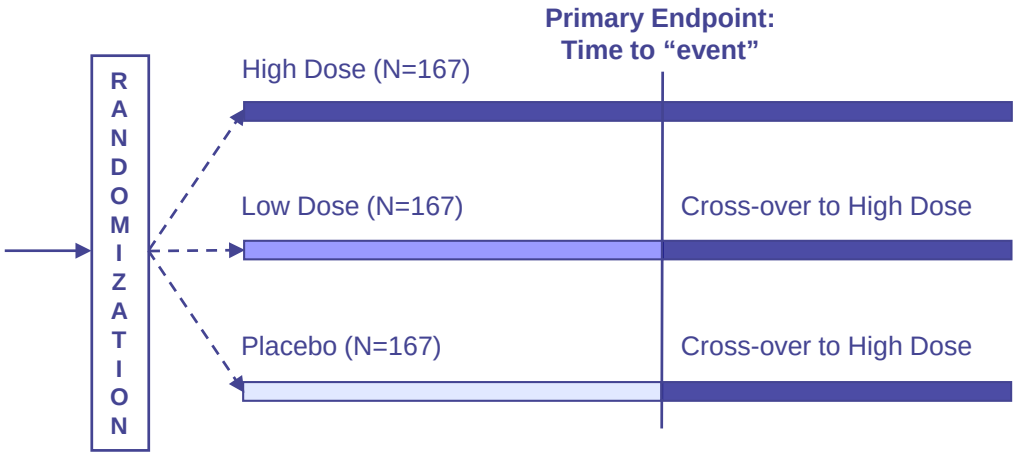
- Number of future events from future subjects:

$$p(d_2|\theta, n, X) \sim binomial(n, \pi_2) \qquad \pi_2 = 1 - \frac{e^{-\theta(t_e - t_a)} - e^{-\theta(t_e - t_c)}}{\theta(t_a - t_c)}$$

$$p(d_2|X) = \sum_k^{\infty} \left(\int_0^{\infty} p(d_2|\theta, n = k, X) p(\theta|X) d\theta \right) p(n = k|n_0)$$

Example:
Design of the ABC Trial

- Phase III, randomized, double-blind, placebo-controlled, multi-center (>100) trial
- Primary endpoint: Time-to-event
- End of trial primary analysis to compare high-dose vs. placebo
- Study design:

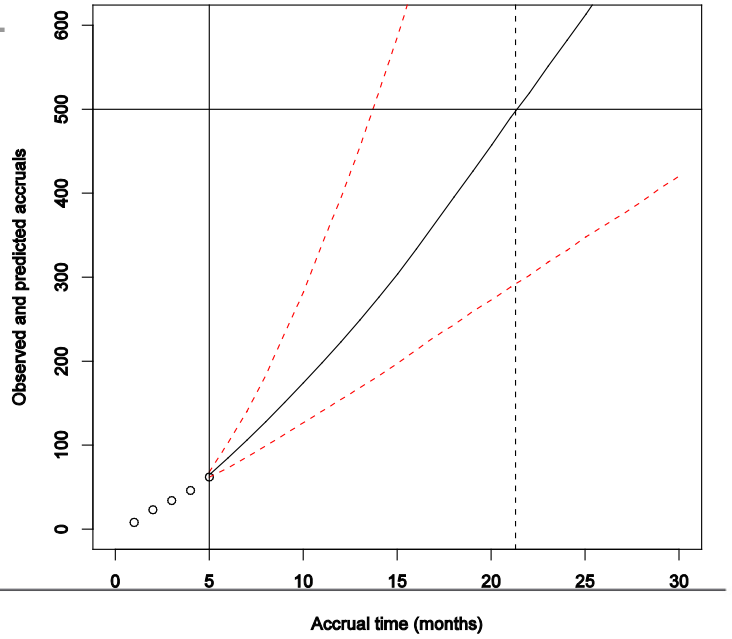


- **Power / sample size calculations yield requirement of 500 subjects**
- **Assumed (constant) recruitment rate of 30 subjects / month**
- **Assumed a 17-month recruitment period**
- **Expected 165 total events by month 21 (goal to beat competitor to market)**
  - With assumed hazard ratio, this would provide 90% power to detect tx effect

Monitoring of ABC Trial – Month 5

- First predictions took place at Month 5 of the trial
  - Accrual started very slowly – few sites initiated on time
  - Estimated >30 months to reach desired recruitment goal (500)
  - Too few events (<10) to accurately predict future events
- Recommendations to operations team:
  - Expedite site initiation process and add additional sites
  - Continue enrollment through Month 21

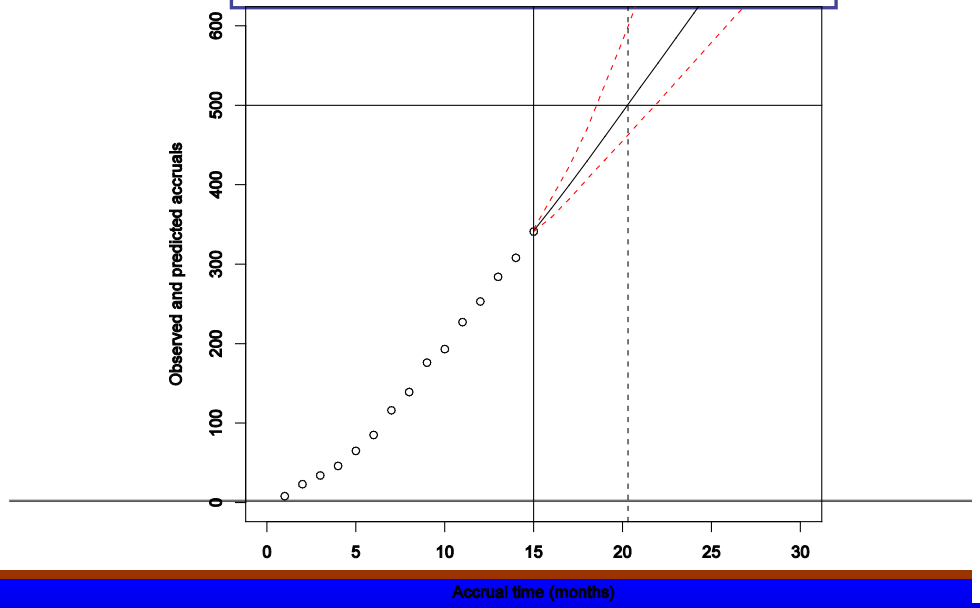
Accrual projection (and 95% credible envelope) based on recommended modifications to trial operational plan



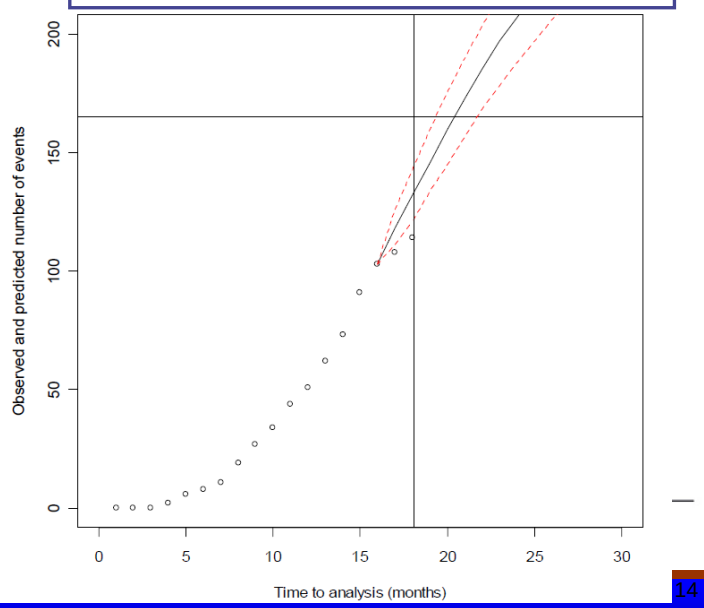
Monitoring of ABC Trial – Month 15

- At Month 15 of the trial
  - Accruals followed Month 5 projections very closely
  - Accrual goal predicted to occur at Month **21**
  - Event goal (165 events) predicted to occur at Month **21**
- Final analysis took place at Month 21
  - As a result of trial accrual and event monitoring, sponsor company was able to file application prior to their competitor

Accrual projection at Month 15



Event projection at Month 15



Operational Aspects of Monitoring

- Continual access to IVRS data
  - **Accrual data (randomization dates)**
  - **Adjudicated response data for event monitoring**
- SOPs in place to ensure that study data is not compromised