Planning and Monitoring Clinical Operations: Methodology and Implementation

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Innovative Medicine

Disclaimer and Acknowledgement

- Joint work
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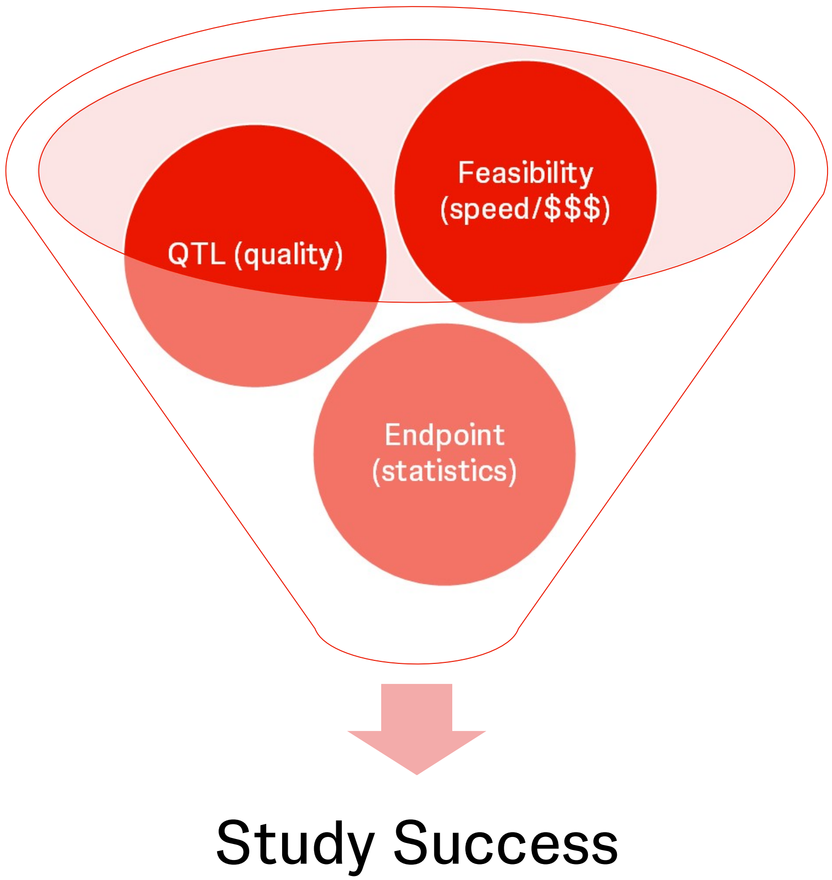
- Graphs and numerical values are all based on simulation

Empower Business with Probability of Operational Success

- Scientific and operational success is connected
  - Improve scientific success via operation
  - Guide operation based on scientific success
- Strategical decision reflects what we can achieve in operation and science via an optimal trade-off between multiple factors (e.g. footprint, landscape, time, cost)



Measuring Operational Success

- Clinical trial operations encompass the planning, execution, and monitoring of activities essential to deliver a successful trial
  - Timeline adherence
  - Supply chain management
  - Data integrity, completeness and quality
  - Cost control
  - Regulatory compliance

• Measuring Enrollment Success

- Enrollment progress impacts key financial milestones and study phases (e.g., recruitment completion, data lock).
- Aligns budget forecasts with updated timelines, ensuring financial plans remain accurate and relevant.
- Real-time enrollment data allows for dynamic demand forecasts, adjusting supply needs based on actual and projected patient numbers, minimizing shortages or surpluses
- Enrollment rates directly impact site costs (e.g., investigator fees, patient reimbursement) and resource needs (e.g., personnel, site maintenance).
- Ongoing enrollment monitoring allows for real-time budget adjustments, aligning spending with actual site activity.
- Supports cost-saving measures by identifying underperforming sites early, enabling redirection of funds to high-performing sites.

Agenda

- Enrollment modeling with Gamma-Poisson
  - Anisimov and Fedorov 2007/IQVIA StudyOptimizer
- Monitoring
- Planning
  - Justify with historical data
  - Optimize interim analysis
- Challenges in implementation
- Model extensions

Modeling Enrollment: Poisson vs Poisson Gamma Models

- Poisson Model
  - One enrollment rate across all sites

$$n_{study} \sim \text{Poisson}(\lambda_{study}, T_{study})$$

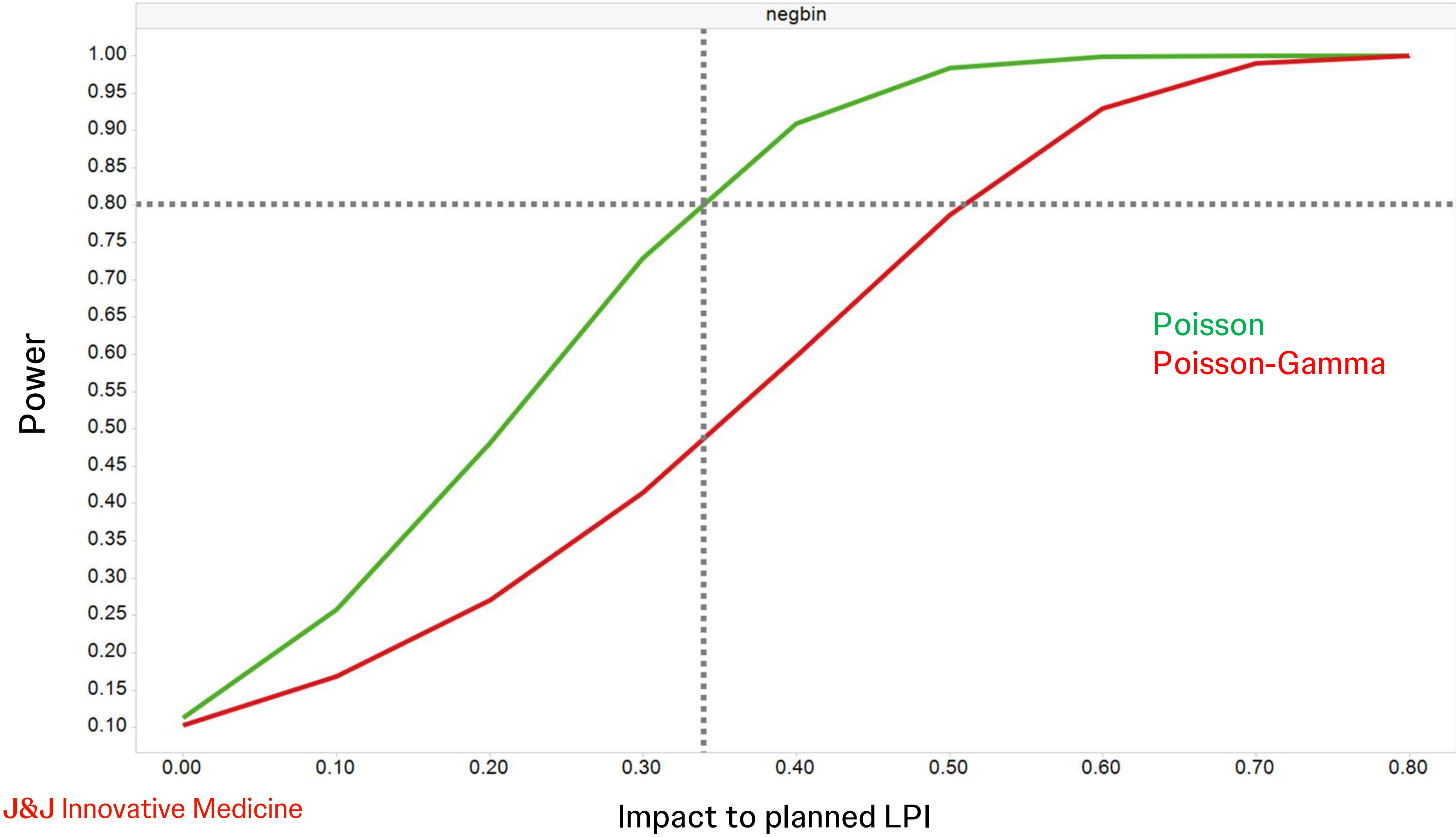
- Gamma-Poisson Model
  - Variability between sites, modeled with a Gamma distribution

$$\lambda_{site} \sim Gamma(\alpha, \beta)$$
$$n_{site} \sim \text{Poisson}(\lambda_{site}, T_{site})$$

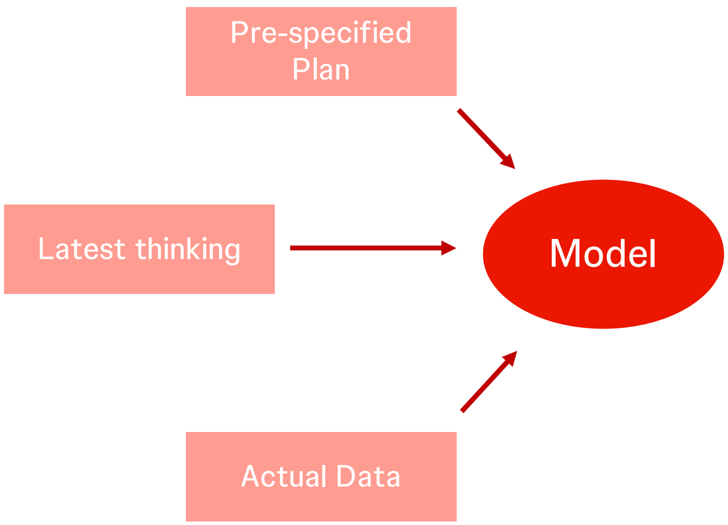
  - Or random effect

$$\log(\lambda_{site}) \sim Normal(\mu, \sigma)$$

Modeling Enrollment: Poisson vs Poisson Gamma Models



Data for Enrollment Monitoring



- Inputs
  - Actual opening and patient enrolled (date)
  - Planned number of sites/countries/patients
  - Latest thinking on the ground
- Model
  - Incorporates the information with a mixture distribution with dynamic weights based on trial progress
- Output
  - Visualization
  - Probabilistic statements about timelines, enrollment milestones, primary analysis event timing, QTL, inter-current events, etc.

Multi-Level Gamma Poisson Model with Mixture Prior

$$\alpha_1, \alpha_2, \beta_1, \beta_2 \sim \exp(1)$$

Country

$$\lambda_c \sim \text{Gamma}(\alpha_1, \beta_1)$$

$$m_c \sim \text{Poisson}(\lambda_c t_c)$$

→ Site opening

$$\lambda_{cj} \sim \text{Gamma}(\alpha_2, \beta_2)$$

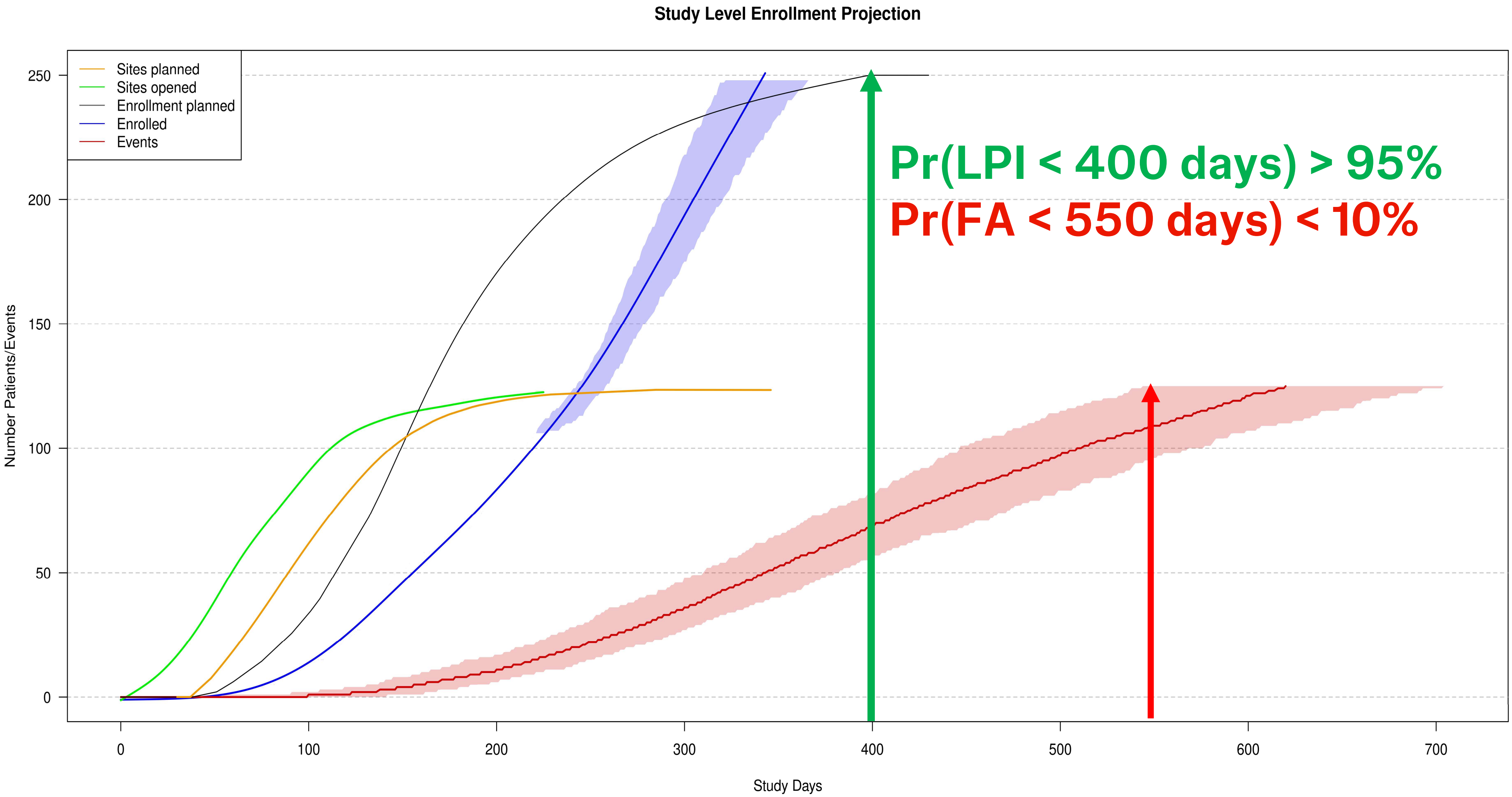
$$n_{cj} \sim \text{Poisson}(\lambda_{cj} t_{cj})$$

→ Patient enrollment

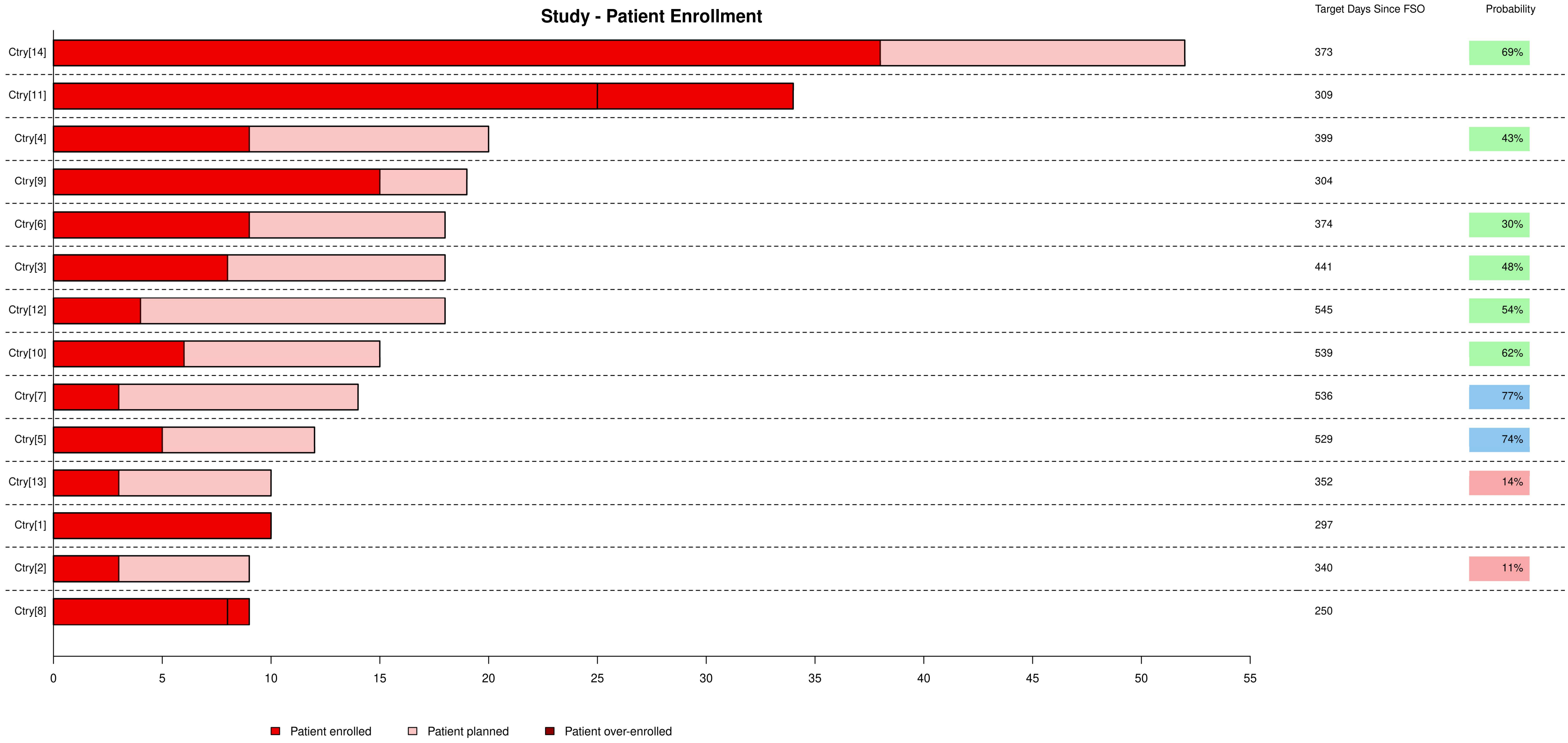
$r_{\text{siteactivate}}$ New site $\lambda_{\text{newsite}} \sim w\text{Gamma}(\alpha_1, \beta_1) + (1-w)\text{Gamma}(\alpha_{1,\text{plan}}, \beta_{1,\text{plan}})$

$r_{\text{screenfailure}}$ Patient enrollment $\lambda_{\text{newpatient}} \sim w\text{Gamma}(\alpha_2, \beta_2) + (1-w)\text{Gamma}(\alpha_{2,\text{plan}}, \beta_{2,\text{plan}})$

Continuous Enrollment and Event Projections



Country level forecast



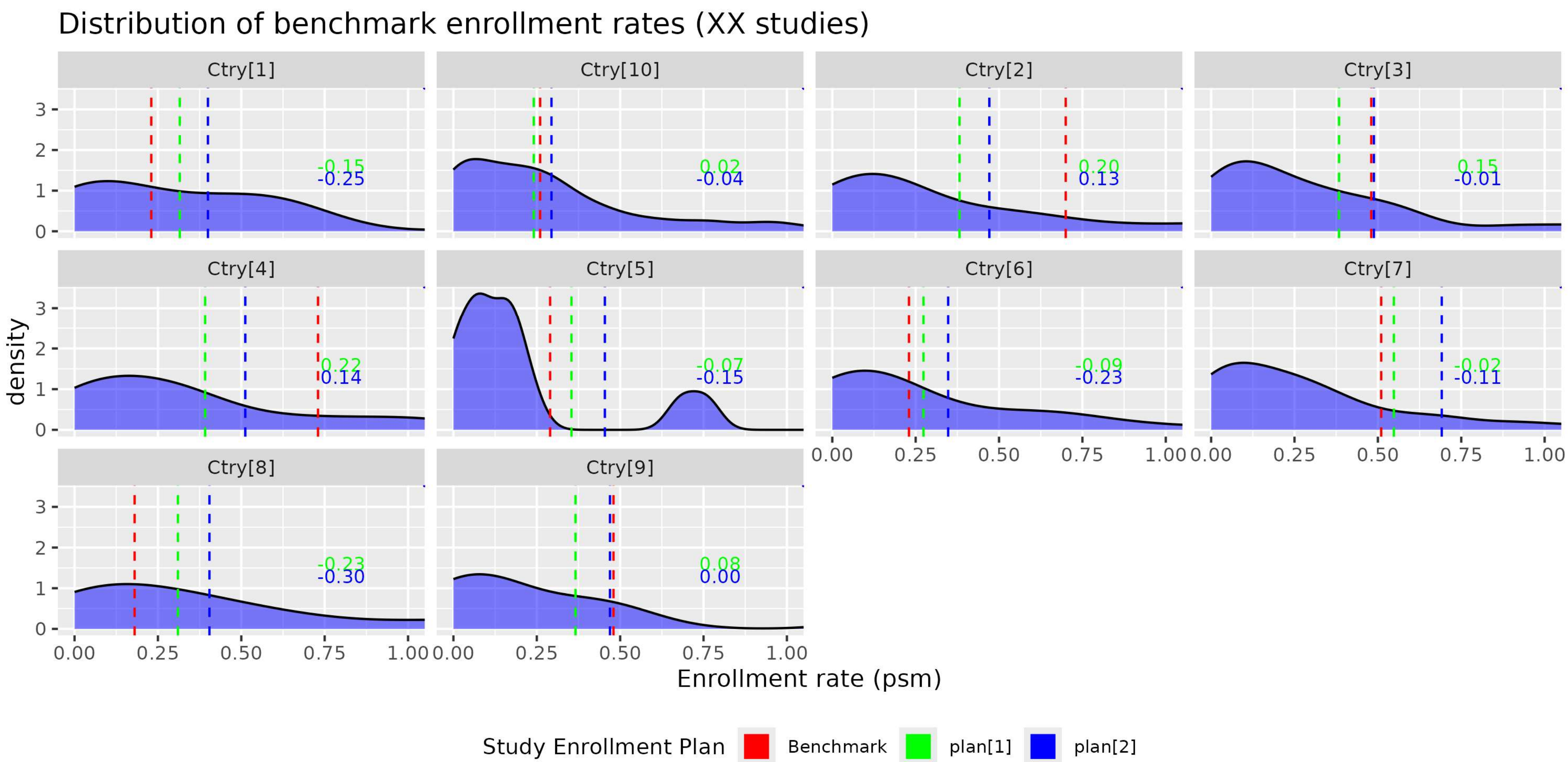
Planning a study

- Proper planning and active monitoring are essential to:
  - Mitigate risk and avoid costly delays.
  - Optimize resource allocation and maintain budget control.
  - Adapt to real-world variability in enrollment and operations, ensuring trial success.
- Budget and Operational Metrics
  - Monitor spending and resource allocation (patient costs, site costs, etc.) against the planned budget.
- Mitigating Risks
  - Identify slow enrollment and implement contingency plans (e.g., add new sites).
  - Rebaseline Plan: Adjust projections and timelines based on updated data, ensuring study goals are met.

Planning a study

- Properly setting assumptions and benchmarks ensures realistic and achievable goals
  - Quantitative assessment of various scenarios
- Country and Site Selection
  - Choose countries and sites with a track record
  - Consider regional regulatory requirements, operational capacity, and prior performance
- Expected Enrollment Rate
  - Set initial rates based on historical benchmarks for similar trials
  - Take into account country-specific variability and adjust assumptions accordingly.
- Importance of Regular Monitoring and Progress Checks
  - Continuous monitoring is crucial for identifying risks early and adjusting strategies to stay on track.
- Track enrollment at the site level to quickly spot and address underperforming sites.
- Use real-time data to identify trends and adapt assumptions dynamically.

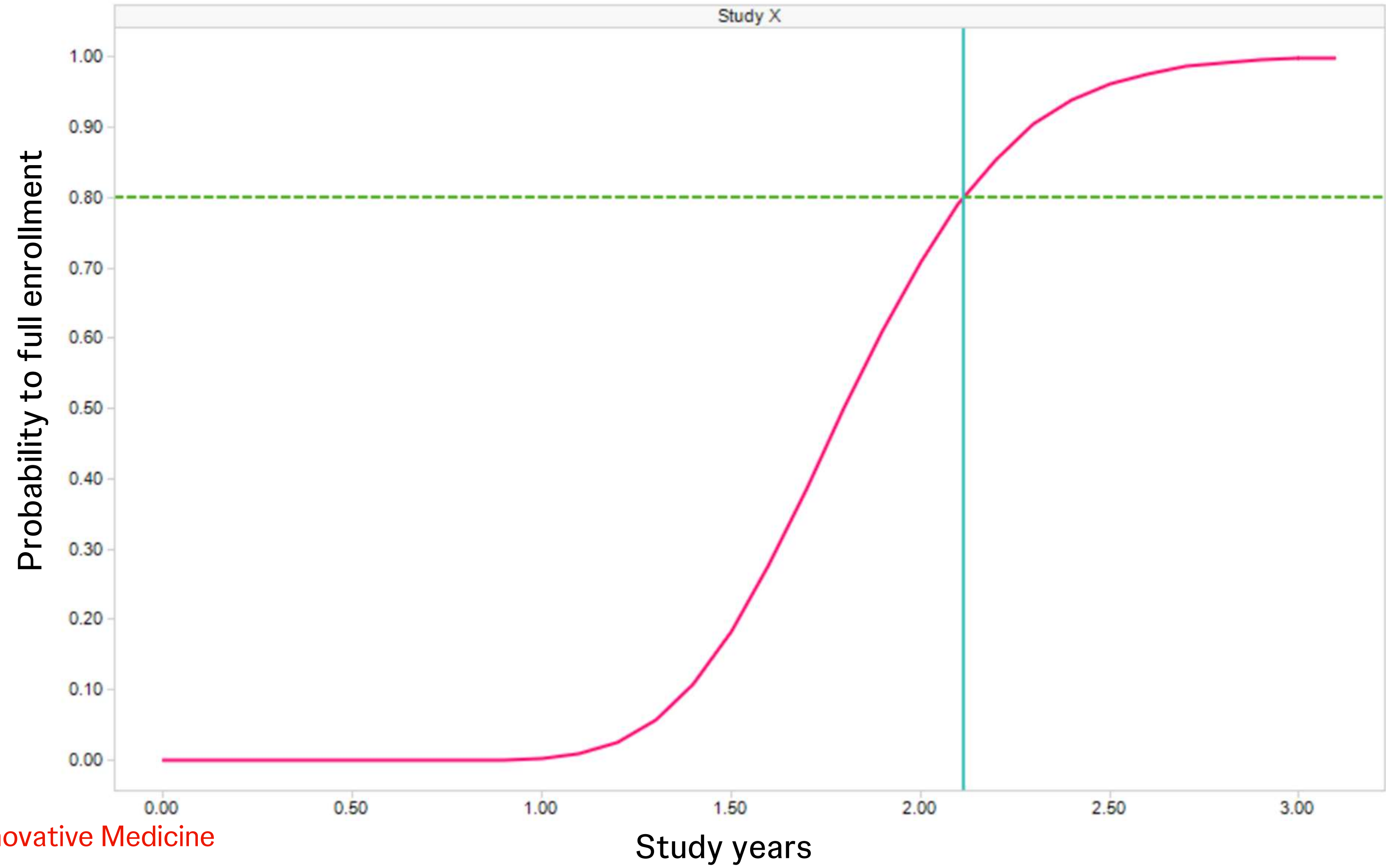
Enrollment assumptions based on historical benchmark



Assessing Enrollment Success Probability with the Gamma-Poisson Model

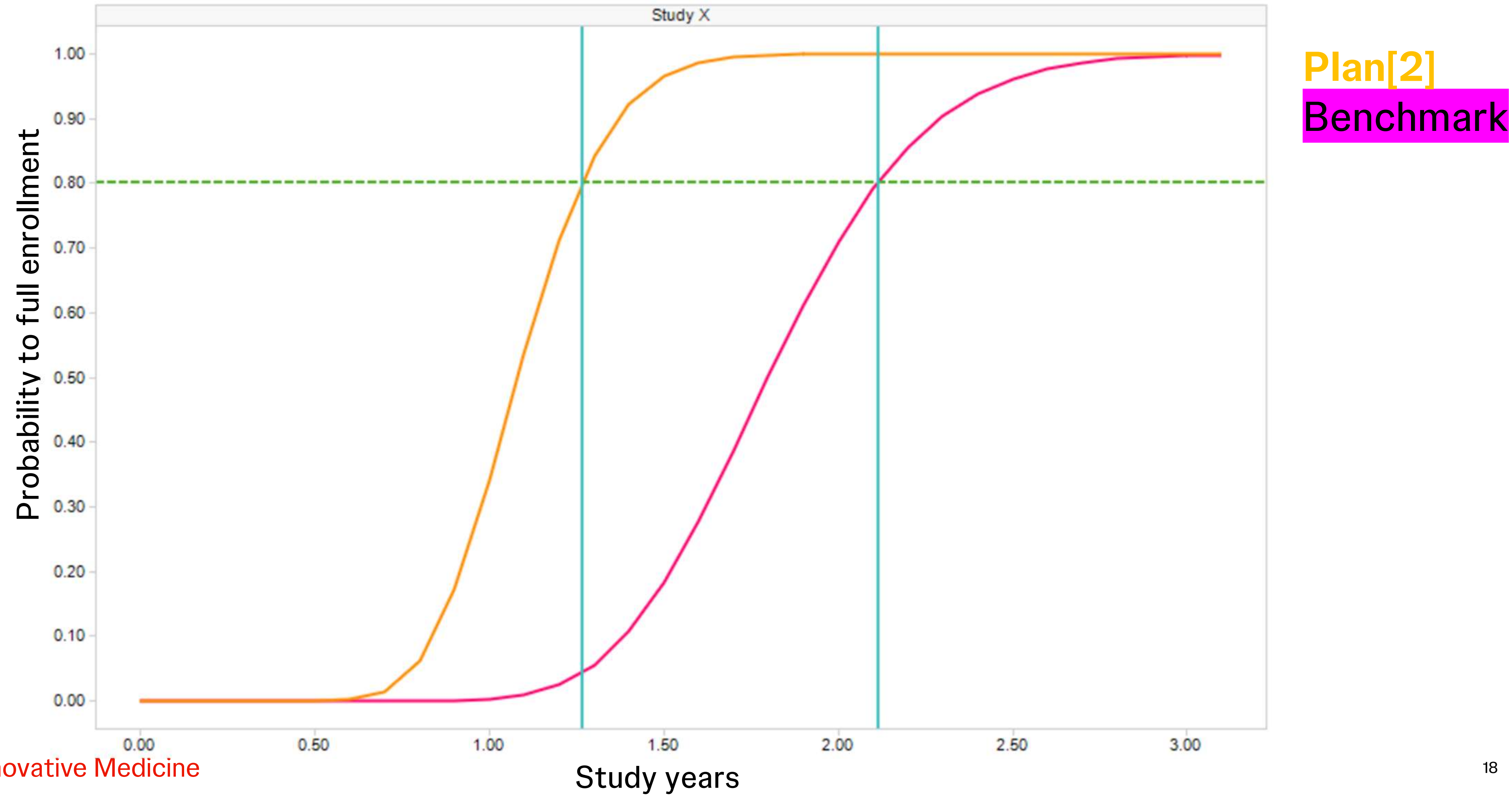
- Establish reasonable assumptions for randomization rates within each country, based on historical data and past trial performance.
  - Account for country-specific factors that influence enrollment (e.g., healthcare infrastructure, patient population).
- Randomization rates may vary across sites even within the same country.
  - With assumed randomization rates, country and site opening schedules, the Gamma-Poisson model allows us to simulate enrollment trajectories over time.
  - Using these simulations, we can calculate the Probability of achieving target enrollment within a given timeline.

Time to signal under benchmark plan

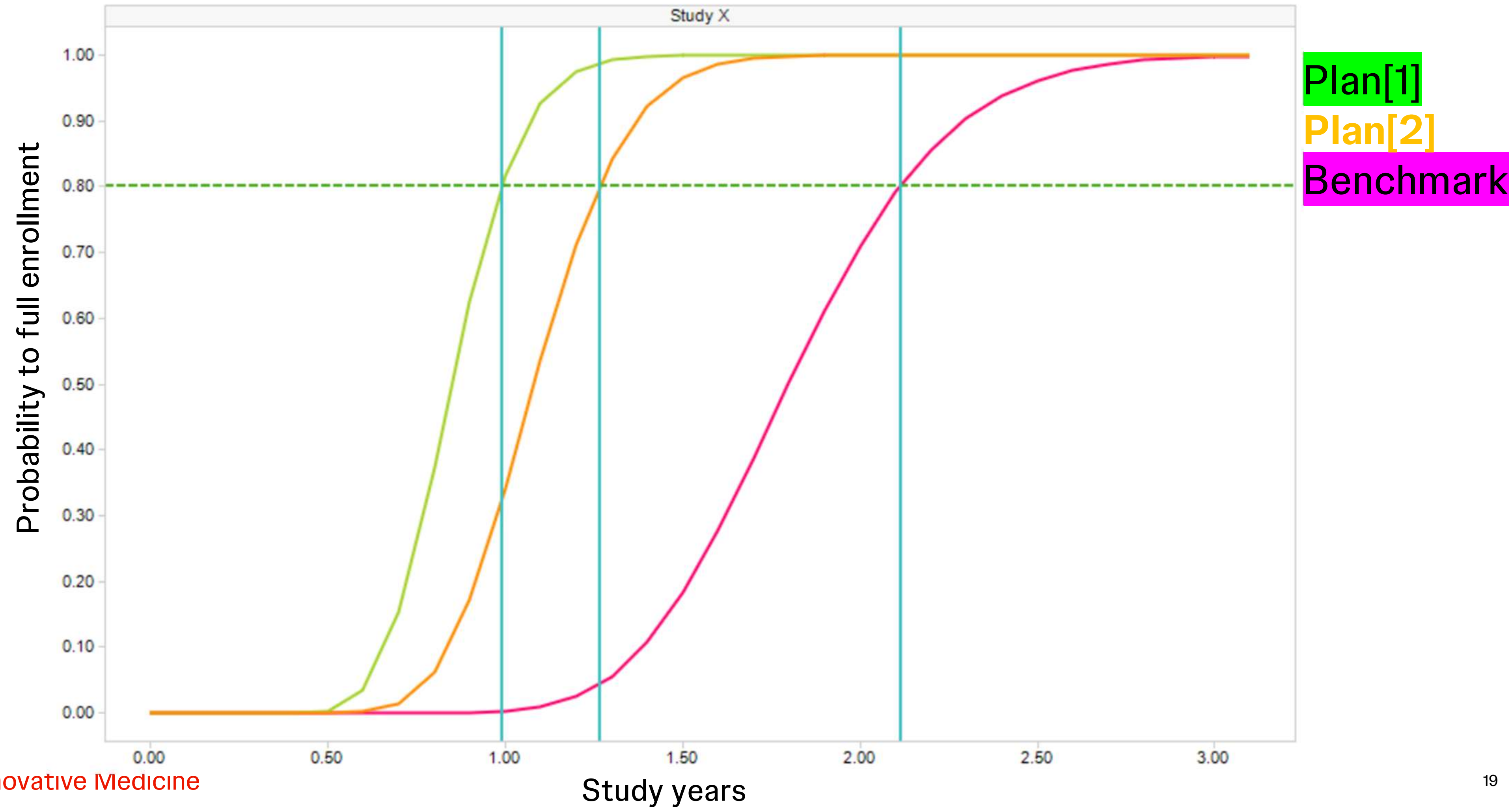


Benchmark

Time to signal under alternative plan



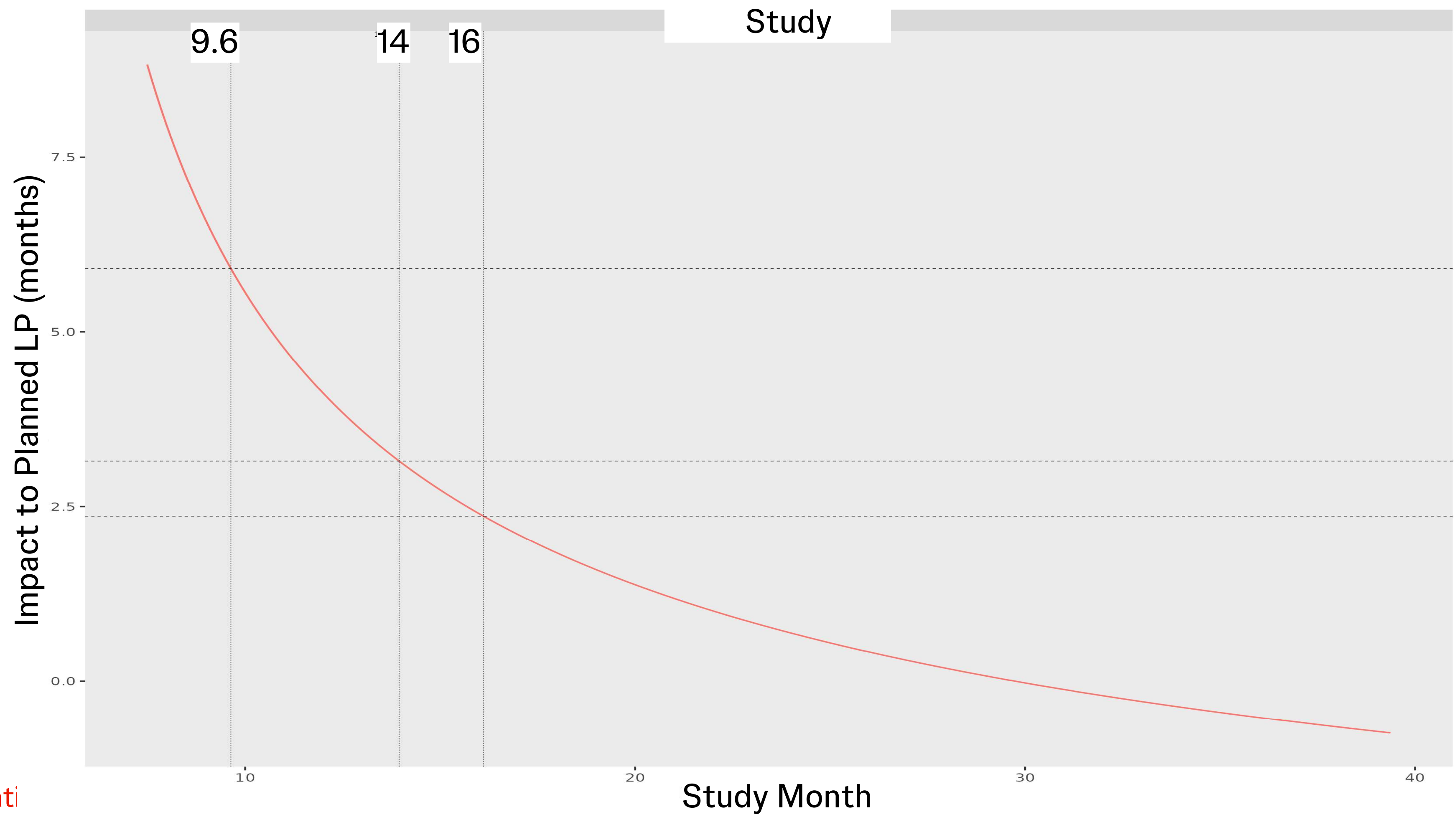
Time to signal under optimistic plan



Planning an interim analysis

- Find the earliest checkpoint, post FPI, that can detect deviations with a level of confidence that a project team is comfortable with
- Interim analysis points are
  - A set of timepoints, post FPI
  - To detect deviations from a plan
  - With a statistical level of confidence/power
    - e.g. a power calculation for an interim analysis

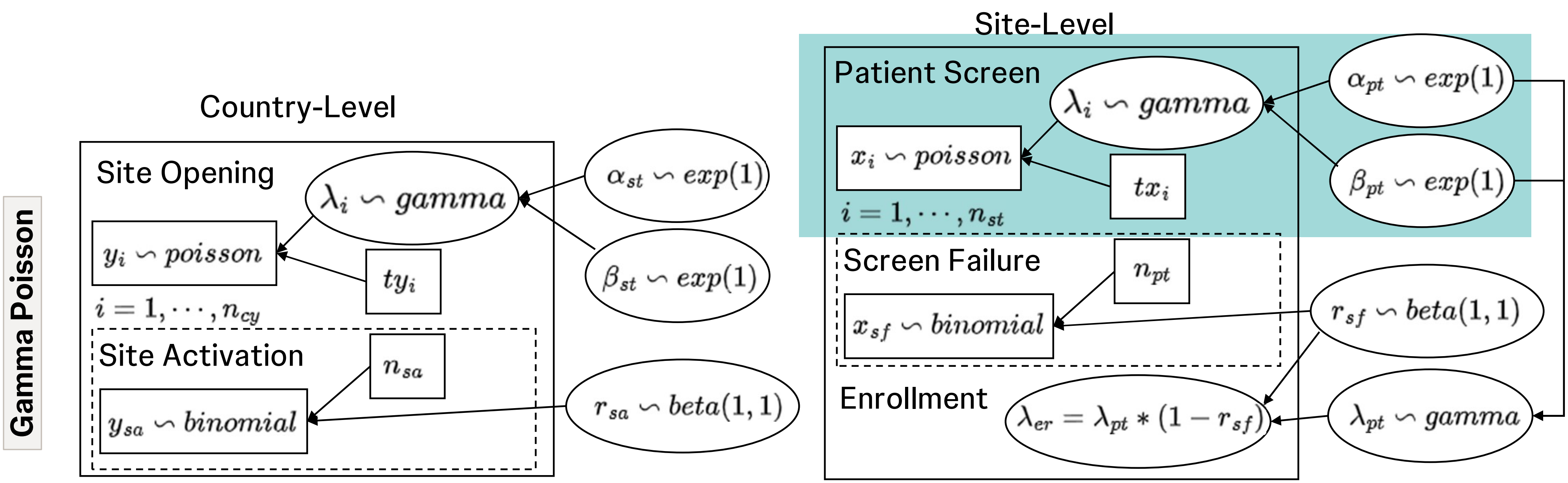
Timepoints at which to detect impact to LPI with 90% power



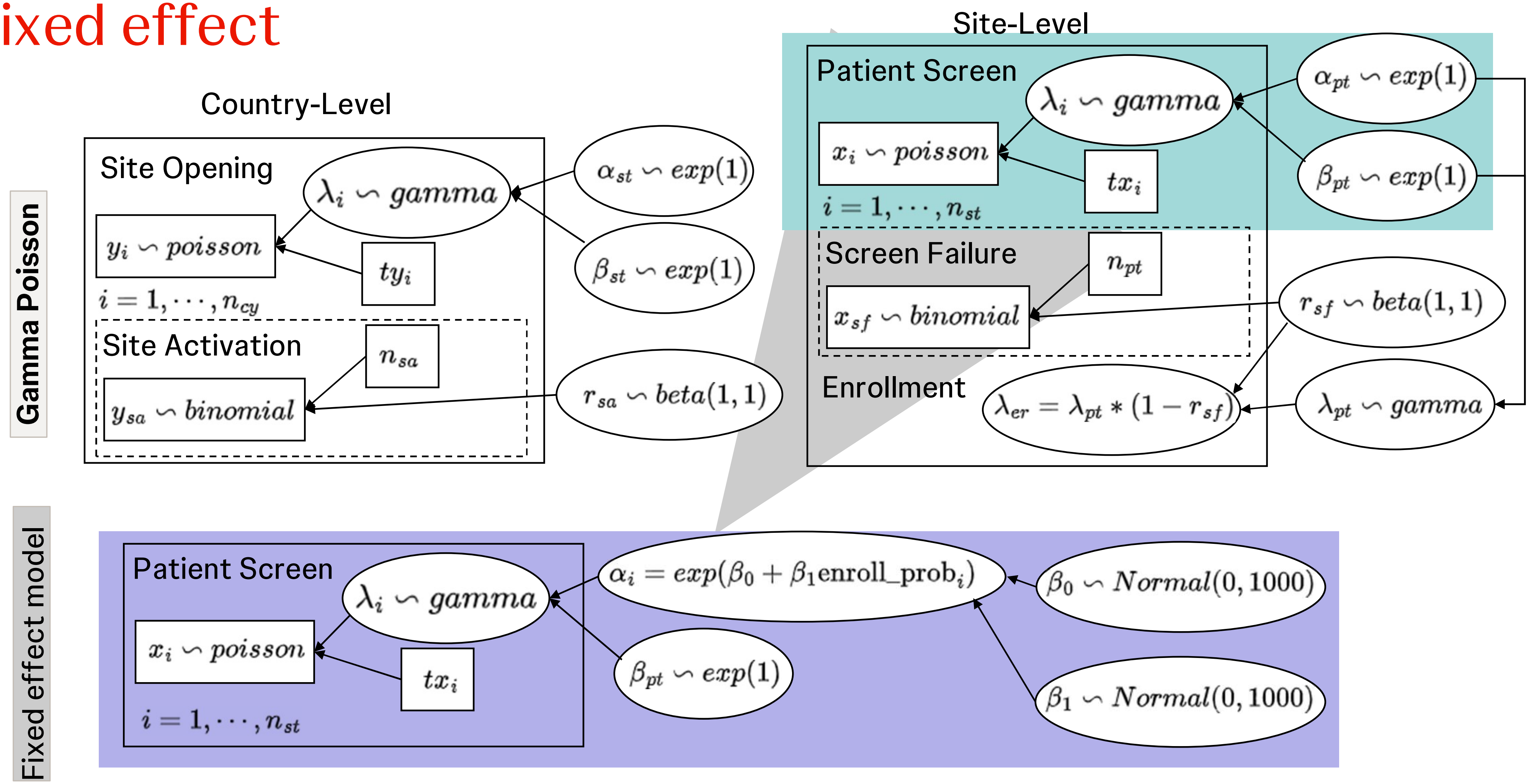
Model Extension

- Many areas to model
  - Country/site activation
  - Patient (pre-) screening/failure/randomization
  - Non-active sites
  - Discontinuation/intercurrent events
  - Event projection
- Fixed effect model
  - incorporate enrollment probabilities over specified time frame
- Mixed effect model: fixed effect model + site clustering
  - Incorporate site features into fixed effect model
  - Cluster sites based on benchmark performance
  - Cluster sites based on site level attributes

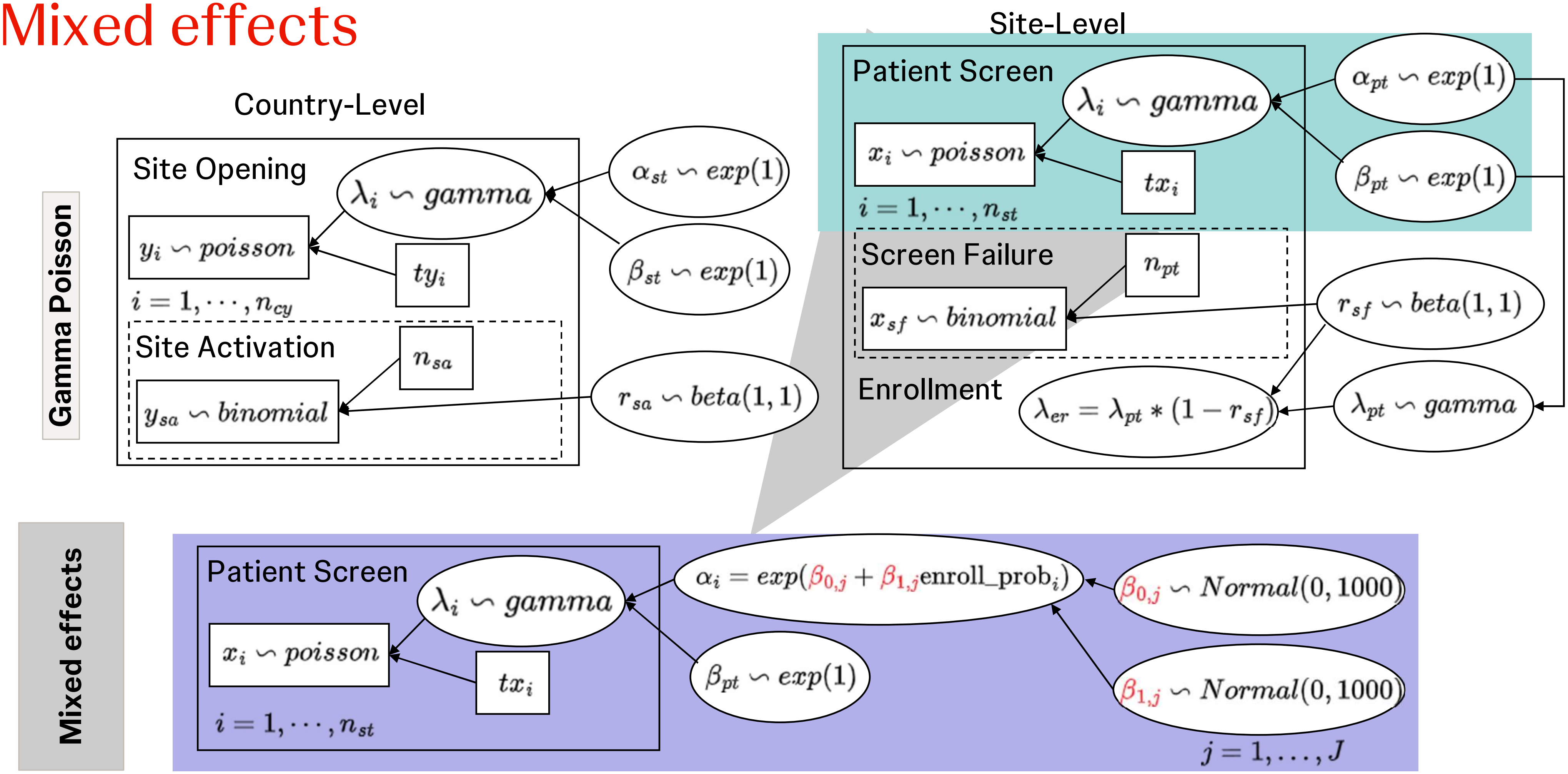
Gamm Poisson



Fixed effect



Mixed effects



Model Extension

- Regularization

  Cluster sites with similar characteristics, regularization to stabilize estimates, especially for smaller or underperforming sites

$$Penalty_{site} = \alpha * \sum_{site} (\lambda[site] - \lambda_{area})^2 \ \# \ local \ smoothing$$

$$Penalty_{site} = \beta * \sum_{site} \left(\lambda[site] - \lambda_{study}\right)^2 \ \# \ global \ smoothing$$

- Incorporate time-varying estimates

Challenges of Implementation

- Communication
  - How to explain ideas effectively to a different audience, who are used to existing systems/workflow
- Data Integration Across Multiple Systems
  - Enrollment data often resides in multiple databases (e.g., EDC, CTMS, external CRO systems)
- Standardization of Metrics and Definitions
  - Different teams may use varying definitions of metrics (e.g., “enrolled,” “randomized”, “last patient dosed”), leading to inconsistencies in reporting and interpretation.
- Change Management and Training
  - Introducing new monitoring tools requires alignment from multiple stakeholders and may face resistance due to established processes as well as new learnings.
  - Regular cross-functional team meeting to interpret outputs together with statisticians
- Data Privacy and Compliance
  - Monitoring requires handling sensitive patient level and clinical (most often blinded) data, strict access control must be put in place

Things we are working on

- Improving current models
- Primary event, intercurrent events, QTL events, etc.
- Subgroup Planning and Monitoring
  - Integrate subgroup-specific projections for diverse patient populations
  - Establish real-time monitoring of subgroups to identify early trends or discrepancies
- Site selection
- Budget Monitoring

Concluding Remarks

- What questions and gaps most important to stakeholders?
- Critical to understand current workflow
- How can new model fit into existing workflow?
- There is not one model that's better than all other models for all studies, but on average we can expect to develop models that are better by considering specifics of our data
- Interpreting results always hard, even for people developing these models, let alone non-statisticians
  - Especially when discrepancies arise from existing model vs new model
- Continually improving model performance by identifying aspects of data the model is not capturing
- Always do back-testing on retrospective data for any model modification
  - Computing resource critical as well