Driving Operational Excellence: The Power of Statistical Innovation in Clinical Development

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Outline

Motivation: increasing operational efficiency in drug development via statistical methods

Areas of opportunity: patient recruitment, event projection, clinical drug supply, managing OOP costs, resource allocation, etc.

ASA BIOP **Efficiency+** scientific working group

Closing remarks

Motivation

Statistics is a core discipline in drug development, being an integral part of trial design, as well efficacy and safety data analysis

Use of statistics in clinical trial operations is less prevalent in the pharma industry and provides great opportunities to improve efficiency and reduce costs of drug development

Overall costs of clinical operations are estimated to account for over half of drug development expenses: achieving meaningful, sustainable operational efficiencies is critical for the survival of the pharma industry

Statistics can, and should, play an integral part in that effort

Challenges

Operational ecosystem already populated by several other disciplines/functions: e.g., Data Science, Drug Supply, Clinical Operations, etc. – no history of sustained involvement from Statistics

Often statisticians do not see operations as part of their responsibilities, or even interest: "not my job"

Identifying opportunities to effectively use Statistics in operations require good understanding of the particular area of application, humility to learn from non-statisticians, and follow through to earn a place in the "operational team"

Potential areas of opportunity

Patient recruitment: accrual projections, site selection, feasibility assessment already part of operational groups remit; Statistics can play a value-added role in **monitoring** and **adaptative** approaches

Event projection: critical for event-driven studies (e.g., Oncology and CV trials) – challenging if based on blinded data

Drug supply: also under existing operational function(s), but Statistics can play important supporting role: leveraging recruitment projections at site level, estimating probability of no recruitment, etc.

 OOP costs and resource planning: monitoring and course correction based on accumulating information: adaptive operations

Patient recruitment

Entry-point for involvement in Operations: clinical study on a rare disease with recruitment slower than predicted by Feasibility group

Clinical Operations team wanted to have rationale to establish "recruitment futility" rule: when to pull the plug on study

Approached it as a Group Sequential Design, with endpoint being number of participants recruited and boundaries determined based on probability of making target sample size by recruitment deadline

Interim analysis evaluations determined based on calendar time, decoupled from IA for efficacy and safety endpoints in study

Patient recruitment: rare disease example

Goals of monitoring rule were to evaluate how soon was it possible to conclude recruitment deadline would/would not be met

Also of interest to evaluate how high recruitment rate would need to be to still meet target deadline, at some point during the study

Clinical operations team more concerned about false negative risk: keep going a study that would not meet recruitment deadline (patent expiry would make compound commercially unattractive)

Clinical team prioritized false positive rate, stopping a study that would complete recruitment in time, if continued
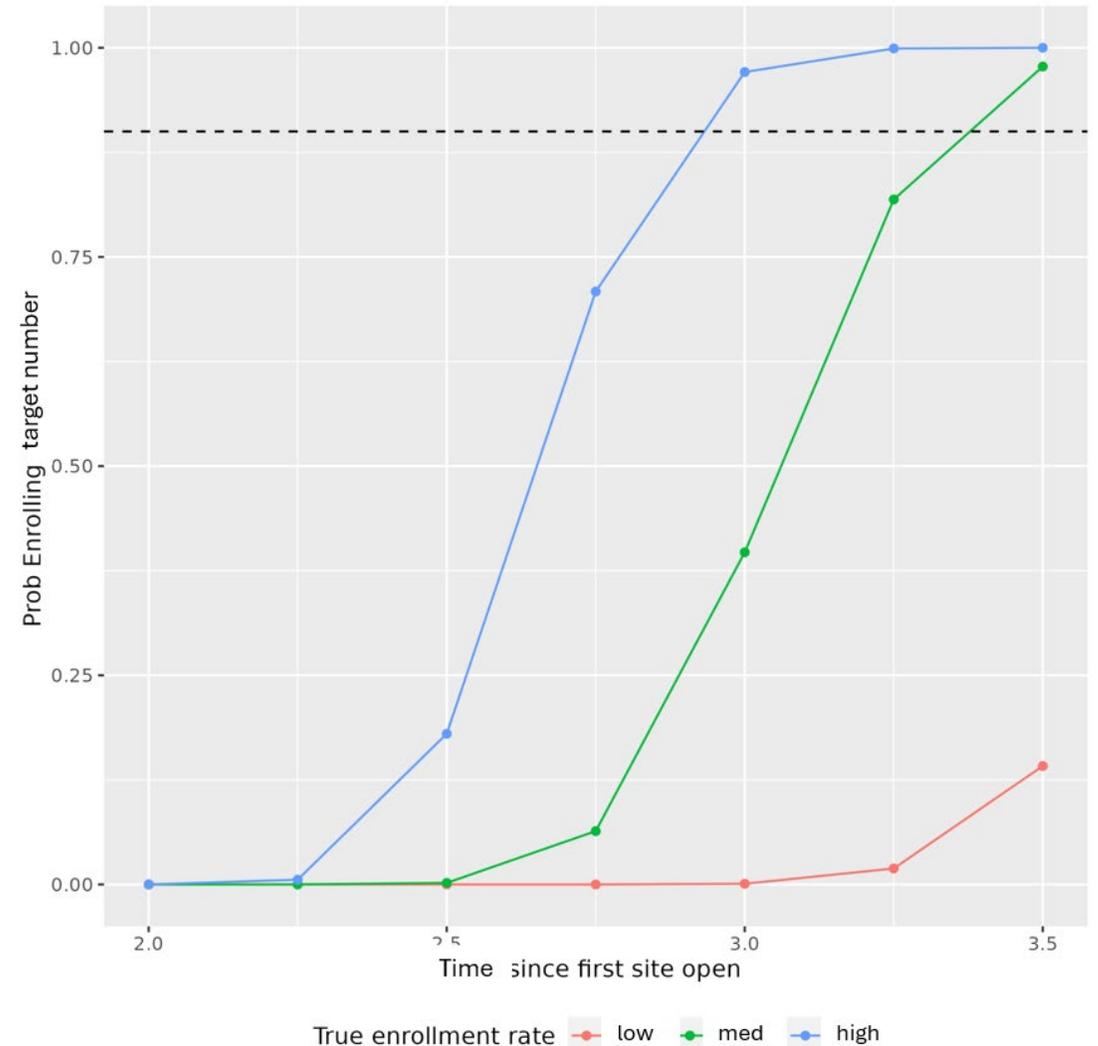
Rare disease example (cont.)

Less than 15% chance of meeting target recruitment date under observed (low) rate

Would need over 40% increase in rate to have about 90% confidence

Under a 60% higher rate near certainty of meeting recruitment timelines

Challenge: how to safely conclude which rate scenario is true and how early can it be done?
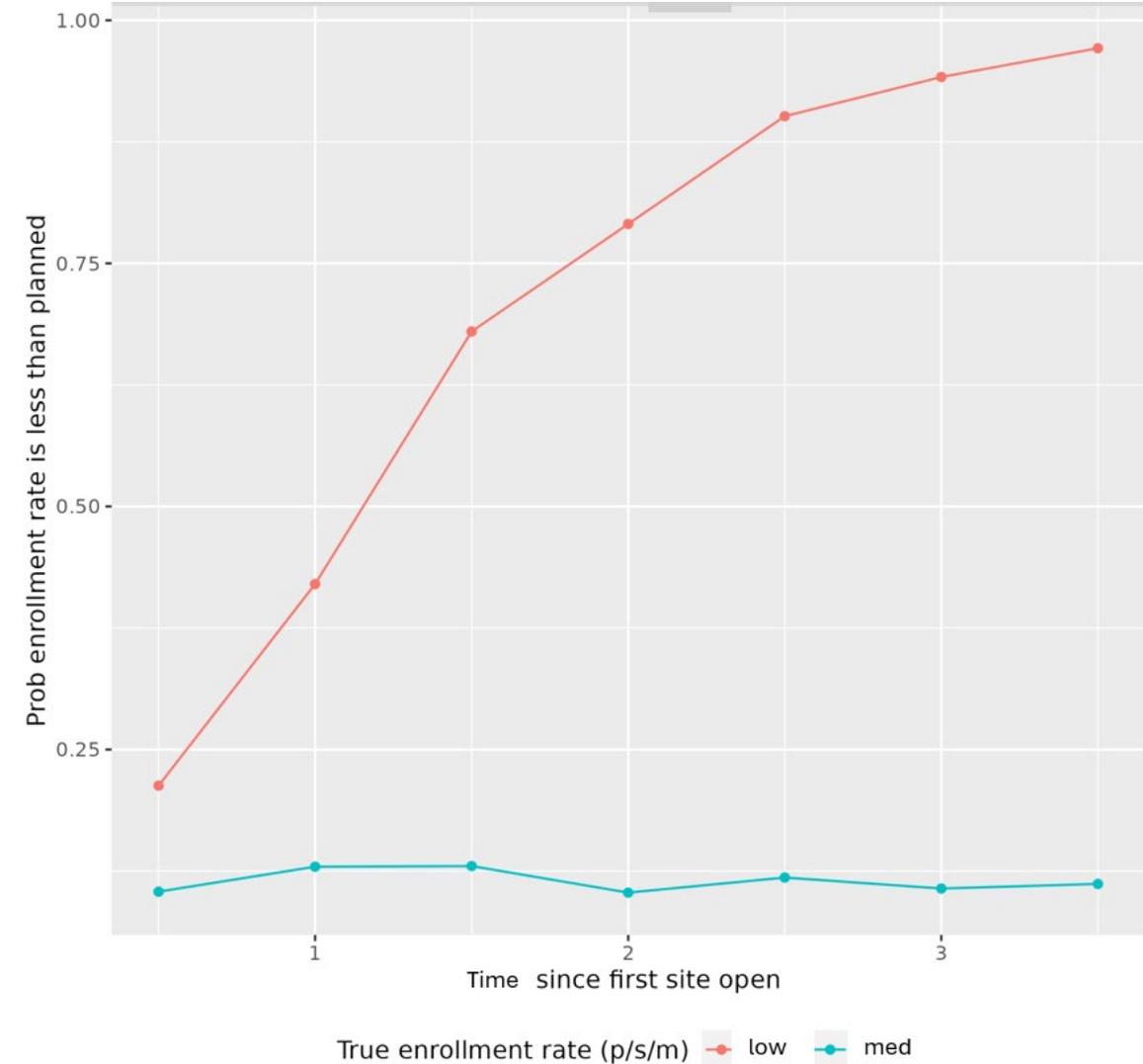
Rare disease example (cont.)

Would take at least two time units before lower than planned recruitment rate could be safely detected

Low chance of indicating lower than planned rate, when it's true rate

Can calibrate false positive rate to provide quicker detection of low rate

Design of operations tracks closely with trial design features

Enrollment monitoring

Optimizing Trial Design and Execution

- Accurately forecasting the patient recruitment is crucial. It directly impacts the timing of statistical analysis and ensures that the drug supply meets patient demand, both during the trial design phase and throughout its progression

Ensuring Operational Excellence

- Predicting the enrollment timeline allows for more efficient planning and allocation of resources. This foresight helps in optimizing staffing, site operations, and overall trial management, ensuring that the study runs smoothly

- A robust predictive model supports timely decision-making, which in turn protects the integrity and success of the trial

Challenges in Patient Enrollment Forecasting

- Patient enrollment involves sequential steps with variability in country initiation, site activation and patient screening

- Real-world patient recruitment often deviates from initial plans due to various uncertainties and stochastic fluctuations. Incorporating these factors into predictive models is essential to anticipate for potential variations

Classical Enrollment Model Framework for Multi-center Clinical Trials

Patient ← **Site** ← **Country**

Elements considered

- Patient screening in each site is a random process
- Screened ≠ Enrolled

- Number of sites is a random number
- Sites won't be activated simultaneously

- Protocol need to be approved by HA

Model options

- Poisson process for patient-arrival in each site
- Binomial distribution for screen failure rate

- Poisson process for site activation in each country (exponential waiting time between site activation

- Poisson process for country initiation

Hierachical model structrue to enable information sharing across sites and countries

Improved Model Options to Best Utilize Available Information

Clinical trial is a highly regulated, well managed, and time sensitive project

	Patient	Site	Country

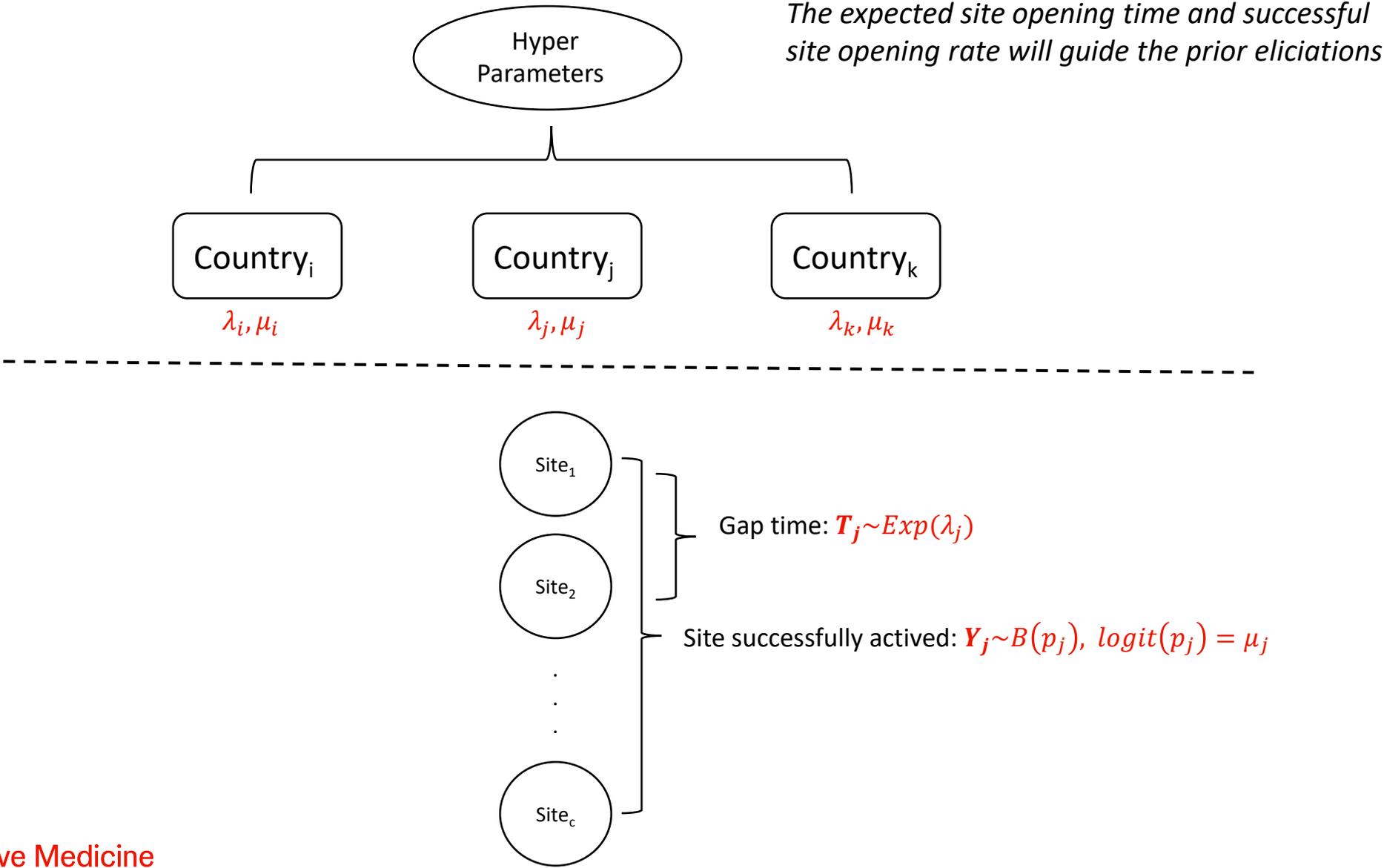**Information to be incorporated**

- Screening rate and screening failure rate can be estimated based on past experience and epidemiology evidence
- Sites participant the study and their possible time for initiation are thoroughly assessed
- Timeline for protocol submission, approval are often well tracked

Model Adaptation

- Informative prior elicitation for patient screening and rate of screening failure
- Sites all come from the pre-specified list
- Account for potential site activation failure
- **Cancel** the modeling for country initiation as the actual initiation date are often very close to the anticipated initiation date
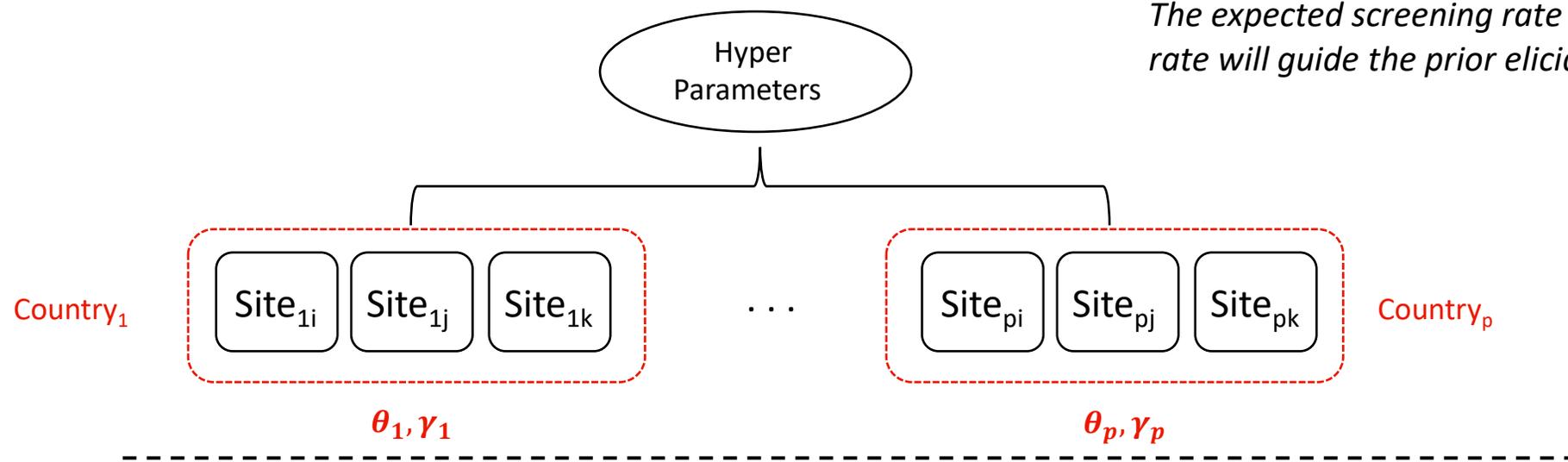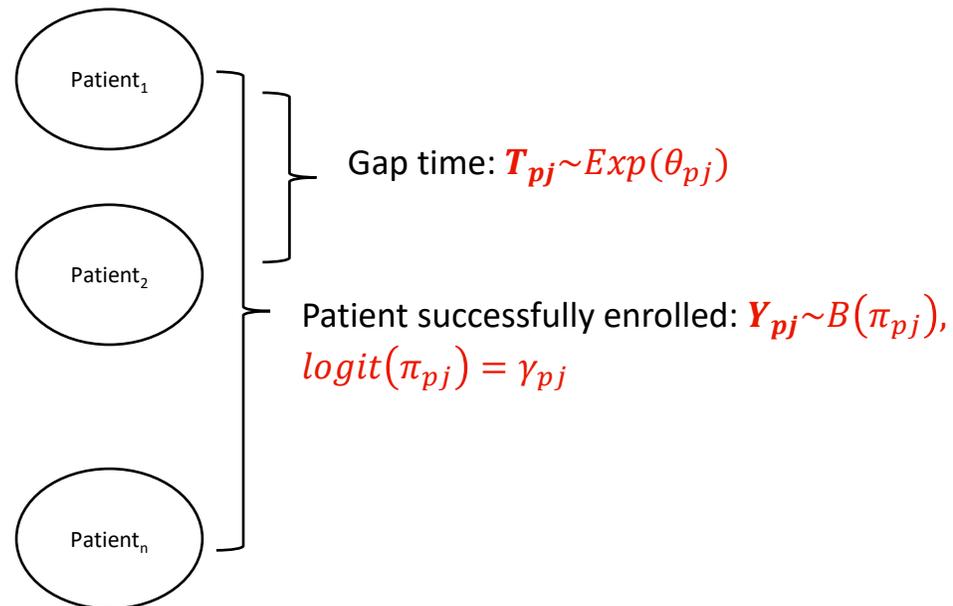
Model Specifics
Site Activation

The expected site opening time and successful site opening rate will guide the prior eliciations

Hyper Parameters

Country$_i$ Country$_j$ Country$_k$

λ_i, μ_i λ_j, μ_j λ_k, μ_k

Site$_1$

Site$_2$

Site$_c$

Gap time: $T_j \sim Exp(\lambda_j)$

Site successfully actived: $Y_j \sim B(p_j),\ logit(p_j) = \mu_j$

Model Specifics

Patient screening and enrollment

The expected screening rate and screening failure rate will guide the prior elicitations

Hyper Parameters

Country$_1$ Site$_{1i}$ Site$_{1j}$ Site$_{1k}$ . . .   Site$_{pi}$ Site$_{pj}$ Site$_{pk}$ Country$_p$

$\boldsymbol{\theta_1, \gamma_1}$ $\boldsymbol{\theta_p, \gamma_p}$

Patient$_1$

Patient$_2$

Patient$_n$

Gap time: $\boldsymbol{T_{pj}} \sim Exp(\theta_{pj})$

Patient successfully enrolled: $\boldsymbol{Y_{pj}} \sim B(\pi_{pj})$,
$logit(\pi_{pj}) = \gamma_{pj}$

Sythetic Prediction

The previous model framework is detailed down to each specific site. There are other source of predictions made down to the country level. We can find a way to combine these predictions together

| Predicted Enrollment Curve 1 (data detailed to sites) | Predicted Enrollment Curve 2 (data detailed to countries) |

w   1-w
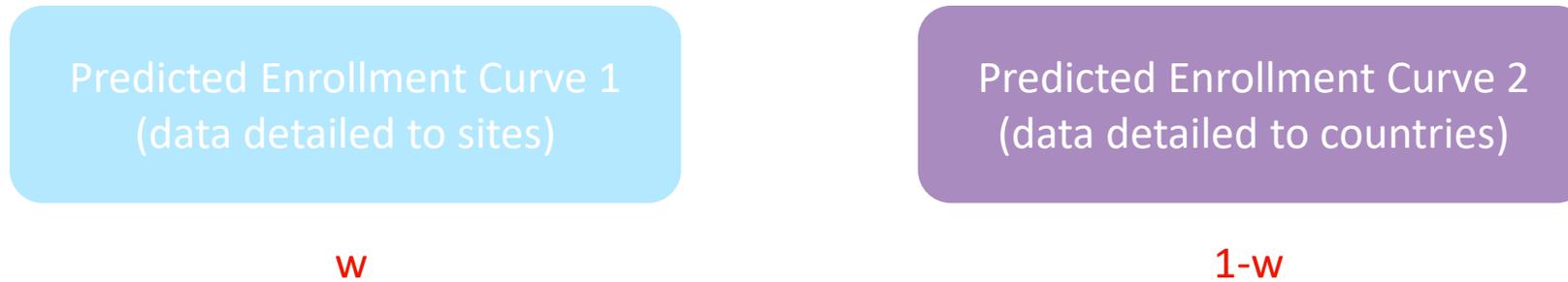
The key is how to determine the weight

- Artificially cut the existing data up to an earlier date (d_0)
- Train the model use data up to d_0
- Predict the enrollment from d_0 to current date (d_1)
- In the time period d_0 to d_1, numerically search for w which can minimze the prediction error
  - $[\text{observed} - (w * \text{prediction1} + (1 - w) * \text{prediction2})]^2$
  - Subject to $0 \leq w \leq 1$

Predicted Patient Screening on Multiple Studies Based on Observed Trend
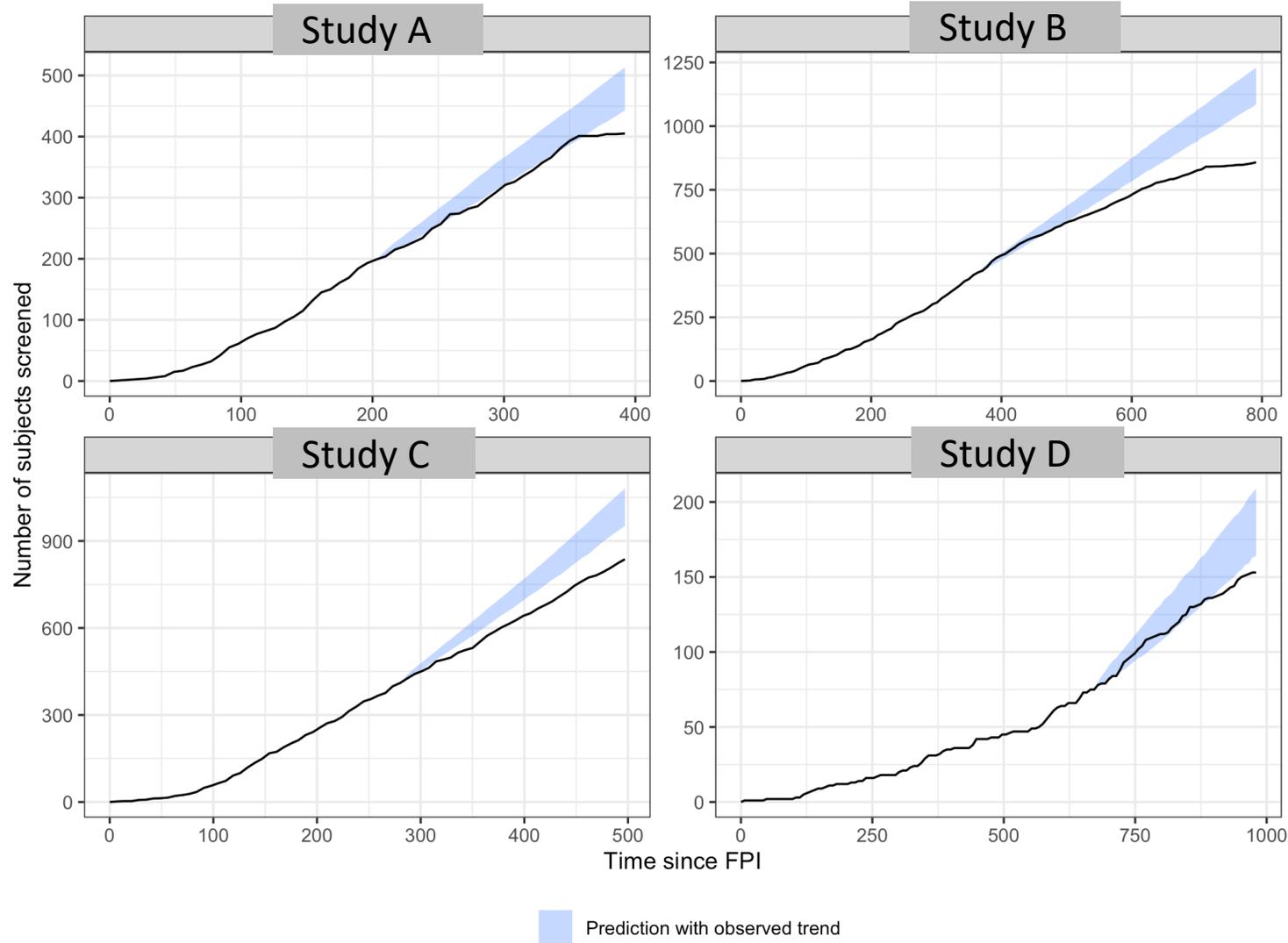
- For each study, we retrospectively cut the screening data at the median of the all screening time

- Use the first half of data to train the model parameters, then simulate new data to predict the patient screening of the second half

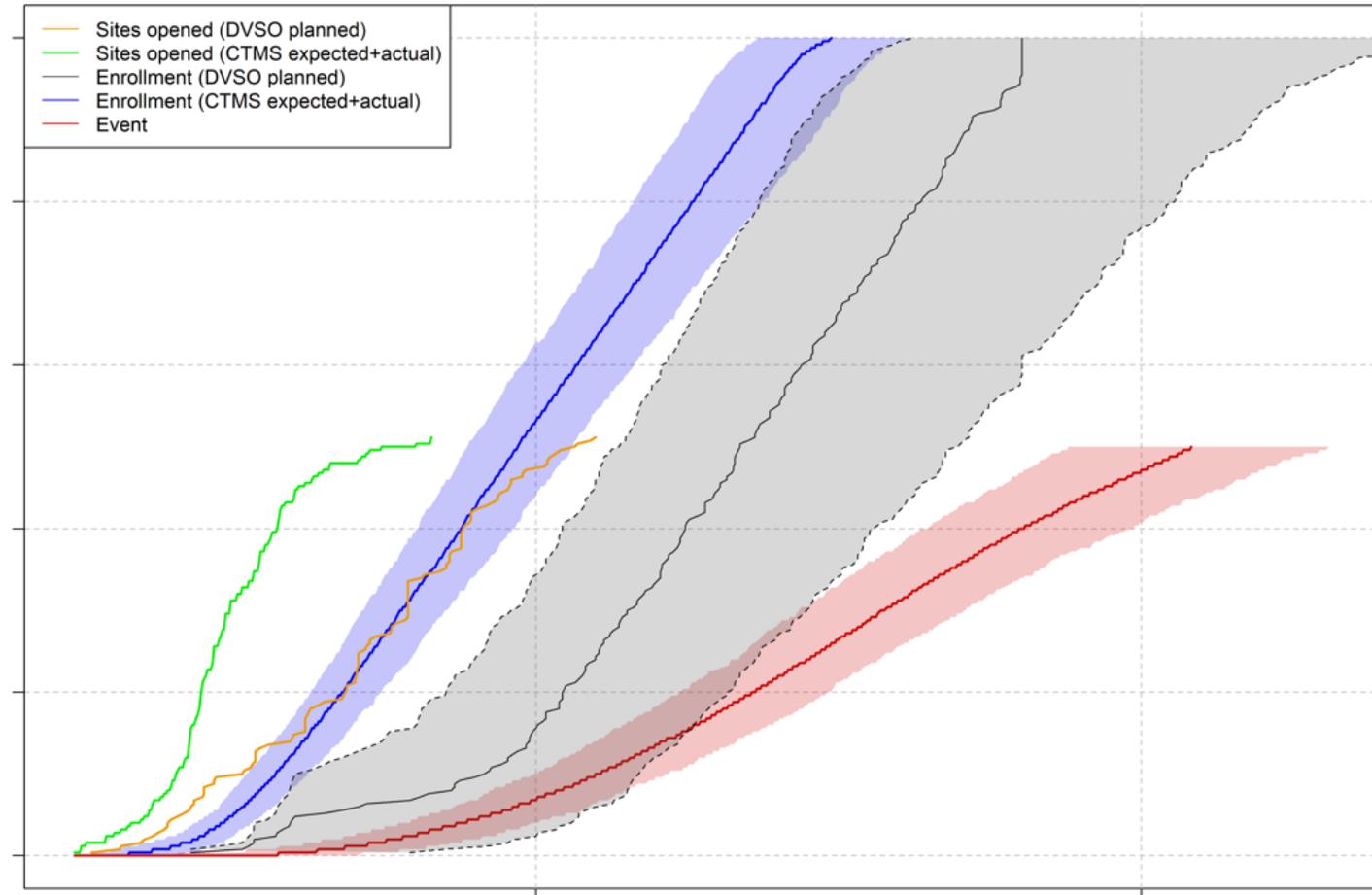# Synthetic Prediction Incorporating Country Plan Data
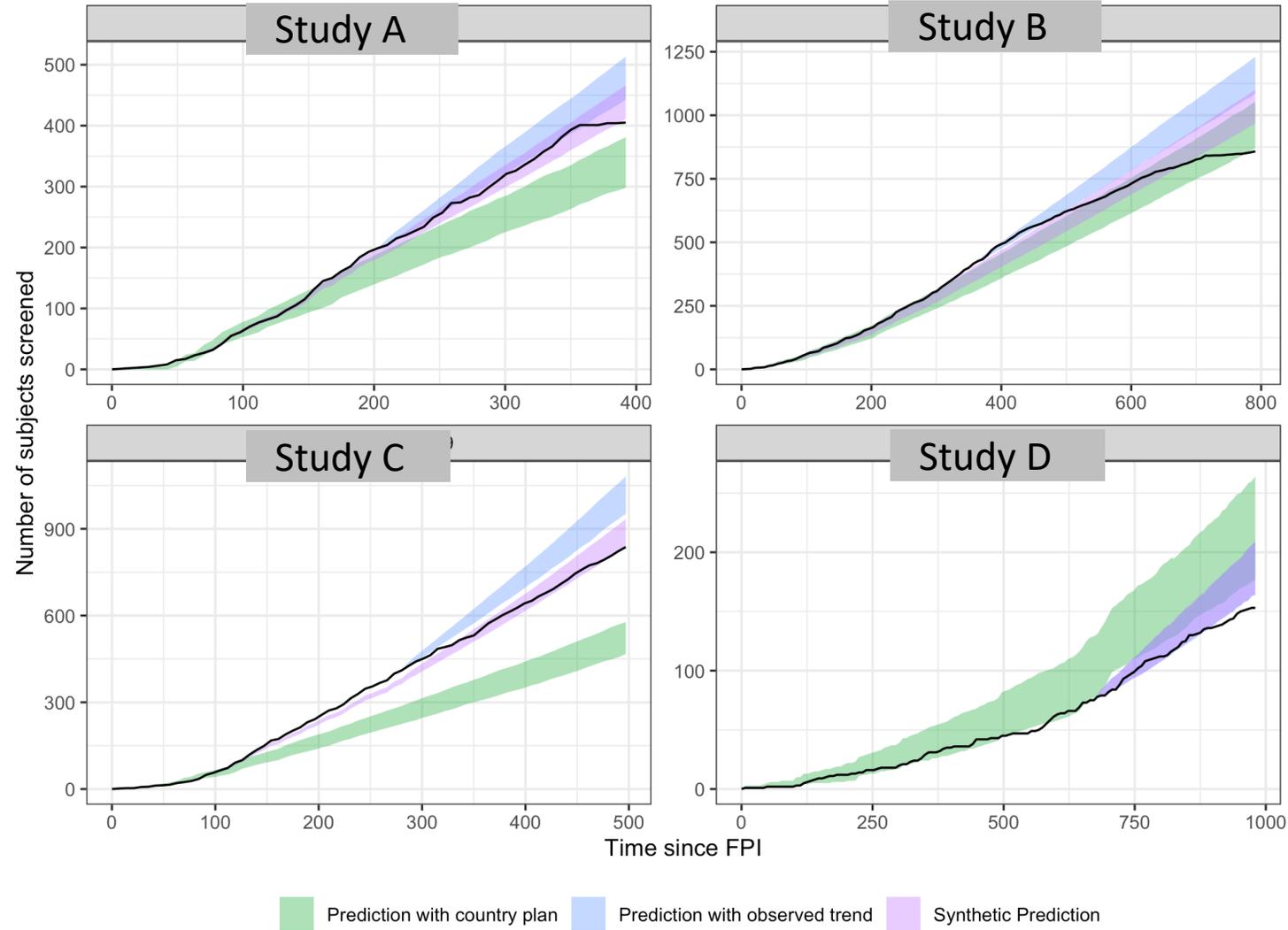
- We combine the previous prediction with the prediction from country plan data (which may be updated during trial on-going based on latest thinking)

- The predictions are substantially improved

Rare disease example (final)

Collaboration with operational functions eventually led to encompassing recruitment monitoring application used across studies

Statistics led development of methodology and prototyping – taken over by other functions for industrialization stage

Legend:
- Sites opened (DVSO planned)
- Sites opened (CTMS expected+actual)
- Enrollment (DVSO planned)
- Enrollment (CTMS expected+actual)
- Event

Event projection during study

Critically important for event-driven studies (e.g., Oncology, CV)

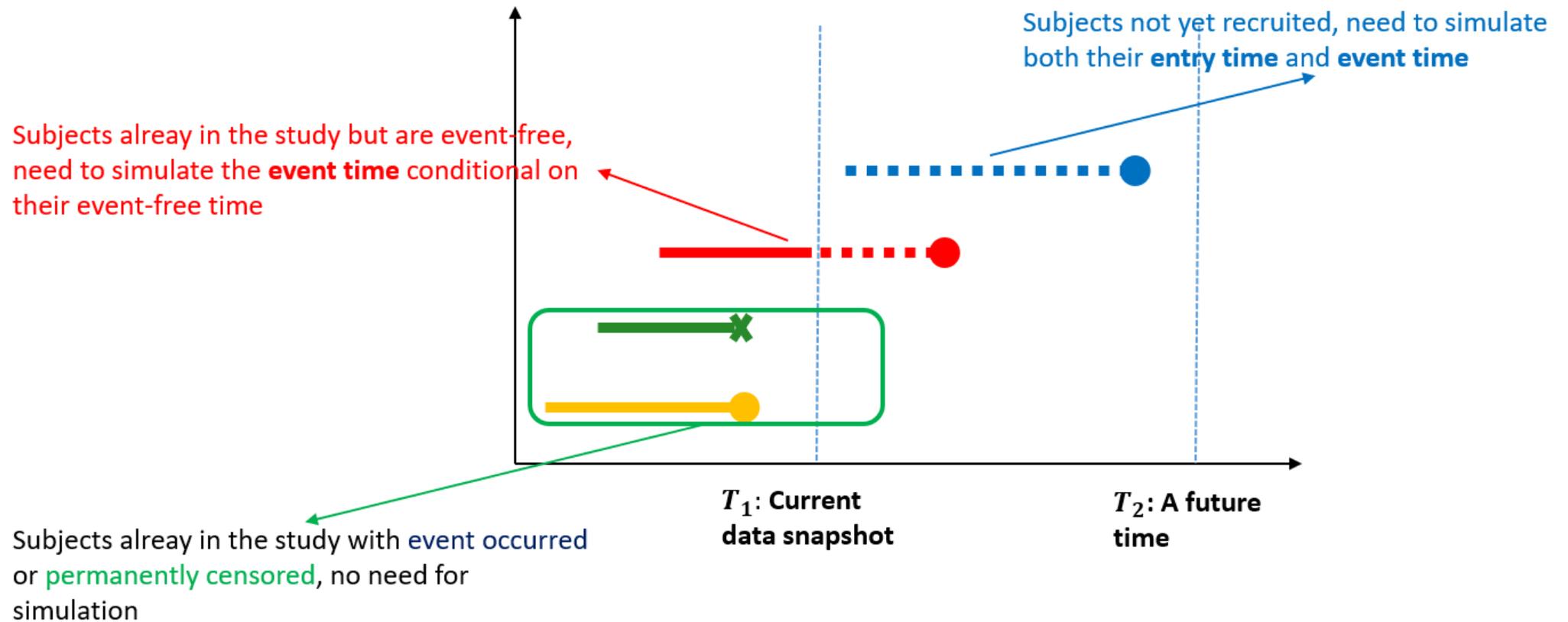Determine planning of interim analyses, database lock, submissions, etc.

Challenging to do with blinded data: need to rely on assumptions about hazard rates, hazard ratios, drop-out, etc. – often requires sensitivity analyses ("what if" scenarios)

Leveraging observed data can increase efficiency/reliability of estimation

Need to be careful with trying to infer too much from blinded observed data, to avoid risk to trial integrity (real or perceived)

Trial Lens: an R package for event prediction by simulation
by Jiajun Xu and Liangcai Zhang, J&J IM

Subjects not yet recruited, need to simulate both their **entry time** and **event time**

Subjects alreay in the study but are event-free, need to simulate the **event time** conditional on their event-free time

Subjects alreay in the study with event occurred or permanently censored, no need for simulation

T_1: Current data snapshot

T_2: A future time

Clinical drug supply

Learnings from patient recruitment monitoring motivated collaboration with drug supply function:

Drug supply planning driven by recruitment projections (initial and updated); main goal: reduce drug wastage due to inappropriate planning

Particularly important: predicting non-recruiting sites ahead of drug being shipped to them

Statistical models developed for recruitment monitoring (Bayesian Poisson-Gamma models) useful to provide site-level estimates (updated as information becomes available during study)

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Clinical drug supply - challenges

Well-established function with ingrained culture: needed to "break-in" to be able to learn more about processes and software; upper-management support helpful

Previous success in recruitment operations, including industrialization step driven by "owner function", has been quite helpful

Concerns about sharing historical data and being object of "auditing" evaluation – gaining trust takes time and constancy of purpose

Skill-set to be most impactful on planning and monitoring fronts goes beyond statistics: operations research, logistics inventory management, etc. can be close partner disciplines/functions

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ASA BIOP Efficiency+ Scientific WG

Group of pharma statisticians with experience/interest in applying statistical methods to improve operational efficiency in drug development

Co-leads:

Fei Chen, J&J IM, Inna Perevozskaya, BMS

Organized under the umbrella of ASA BIOP Section SWGs, focusing on:

- Site Selection and Performance Assessment
- Recruitment Monitoring and Forecasting
- Clinical Drug Supply Optimization
- Patient Representation
- Decentralized and Pragmatic Trial Settings
- Innovative Methodologies
- Patient-Centered Approaches

Efficiency+ SWG: Drive future of efficient clinical trials

- **Why?**
  - Clinical trials are increasingly operationally complex and costly.
  - Small incremental gains in efficiency, even at 1-2%, have the potential to bring substantial savings
  - Statistical innovation can unlock faster, more efficient trial execution.
  - Need for actionable methods in patient enrollment, monitoring and risk mitigation

- **Vision**
  - Establish a cross-pharma hub for statisticians, trial operations and regulatory professionals.
  - Advance practical solutions to improve trial efficiency, reduce costs, and accelerate timelines.
  - Influence industry practice and shape regulatory acceptance of statistical operational innovations

- **Impact**
  - Influence regulatory thinking on trial operational methods
  - Best practice and actionable methods for patient enrollment forecast, monitoring, and risk mitigation
  - Open-source toolkit

Efficiency+ SWG: Patient recruitment monitoring and forecasting, site selection

- 1 Junxiang Luo Abbvie
- 2 Xin Wang Abbvie
- 3 Vlad Anisimov Amgen
- 4 Clara Cali Mella Bayer
- 5 Xikun Wu Beonemed
- 6 Haoyu Wang BMS
- 7 Oleksandr Savenkov BMS
- 8 Palanikumar Ravindran BMS
- 9 Kyle Wathen Cytel
- 10 Bochao Jia Lilly
- 11 Guohui Wu Regeneron
- 12 CG Wang Regeneron

Efficiency+ SWG: Dynamic trial monitoring/data quality

- 1   Xikun Wu   Beonemed
- 2   Zhuoxin Yu   BMS
- 3   Oleksandr Savenkov   BMS
- 4   Palanikumar Ravindran   BMS
- 5   Bochao Jia   Lilly
- 6   Jun Xin   Sanofi

Efficiency+ SWG: Study design and operations impact

- 1   **Vlad Anisimov   Amgen**
- 2   **Angela Zhu   BI**
- 3   **Dooti Roy   BI**
- 4   **Haoyu Wang   BMS**
- 5   **Jessica Cannon-Hill   JNJ**

Efficiency+ SWG: Clinical supply chain

- 1 **Vlad Anisimov** Amgen
- 2 **Christi Kleoudis** AZ
- 3 **Kaifeng Lu** Beonemed
- 4 **Cunyi Wang** JNJ
- 5 **Allison Gray** JNJ
- 6 **Fei Chen** JNJ
- 7 **Guohui Wu** Regeneron
- 8 **CG Wang** Regeneron

Efficiency+ SWG: website

- https://efficiencyplustrials.github.io/#

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Concluding remarks

There is a great opportunity for increasing the scope and impact of Statistics within the drug development ecosystem, by leveraging advanced methods to improve operational efficiency

Potential for reducing development costs, improving decision making speed, and increasing meaningful cross-functional synergies

Achieving full potential will require: "showing up," having true humility to learn from and hear other functions, and constancy of purpose

Statisticians and quantitative scientists, more broadly, with different skillsets than typically expected from clinical biostatisticians will be needed and are yet to be fully established

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