Improving Operational Efficiency in Clinical Development through Statistical Innovation and Cross-functional Collaboration

José Pinheiro
J&J IM

Joint work with Fei Chen and Ken Cherasia, J&J IM

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

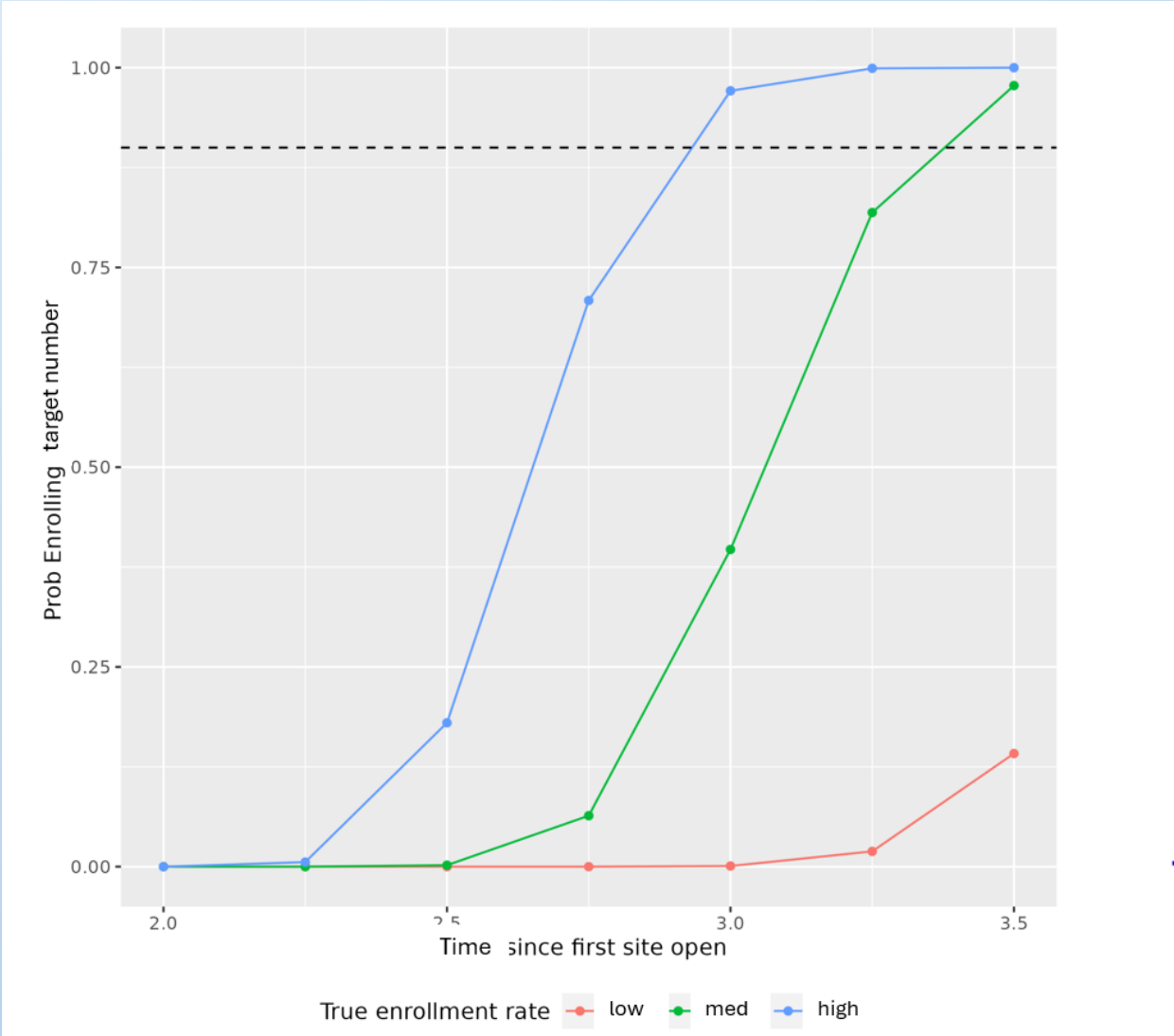
Patient recruitment: rare disease example

- 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

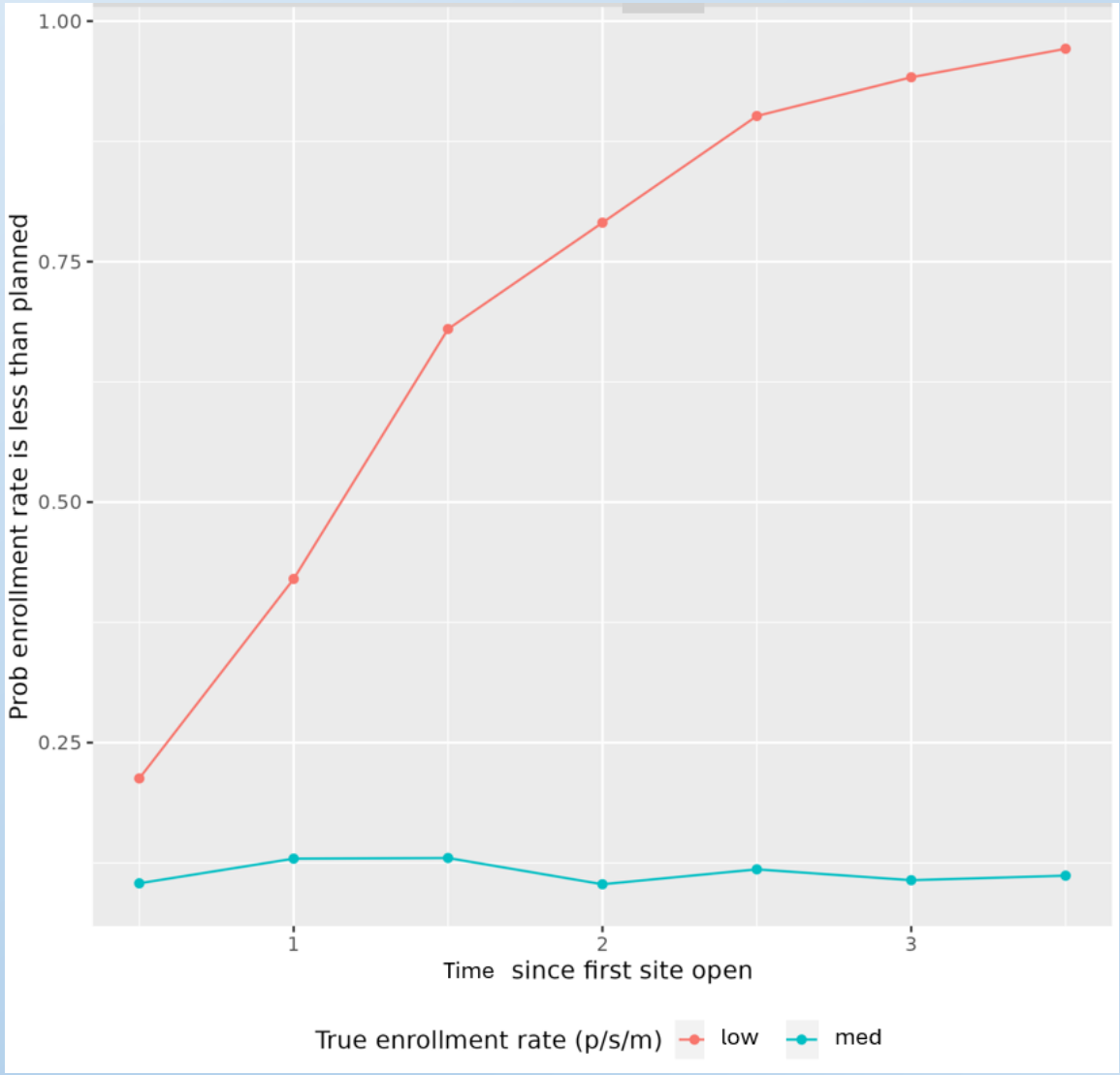
Challenge: how to safely conclude which rate scenario is true and how early can it be done?



Rare disease example (cont.)

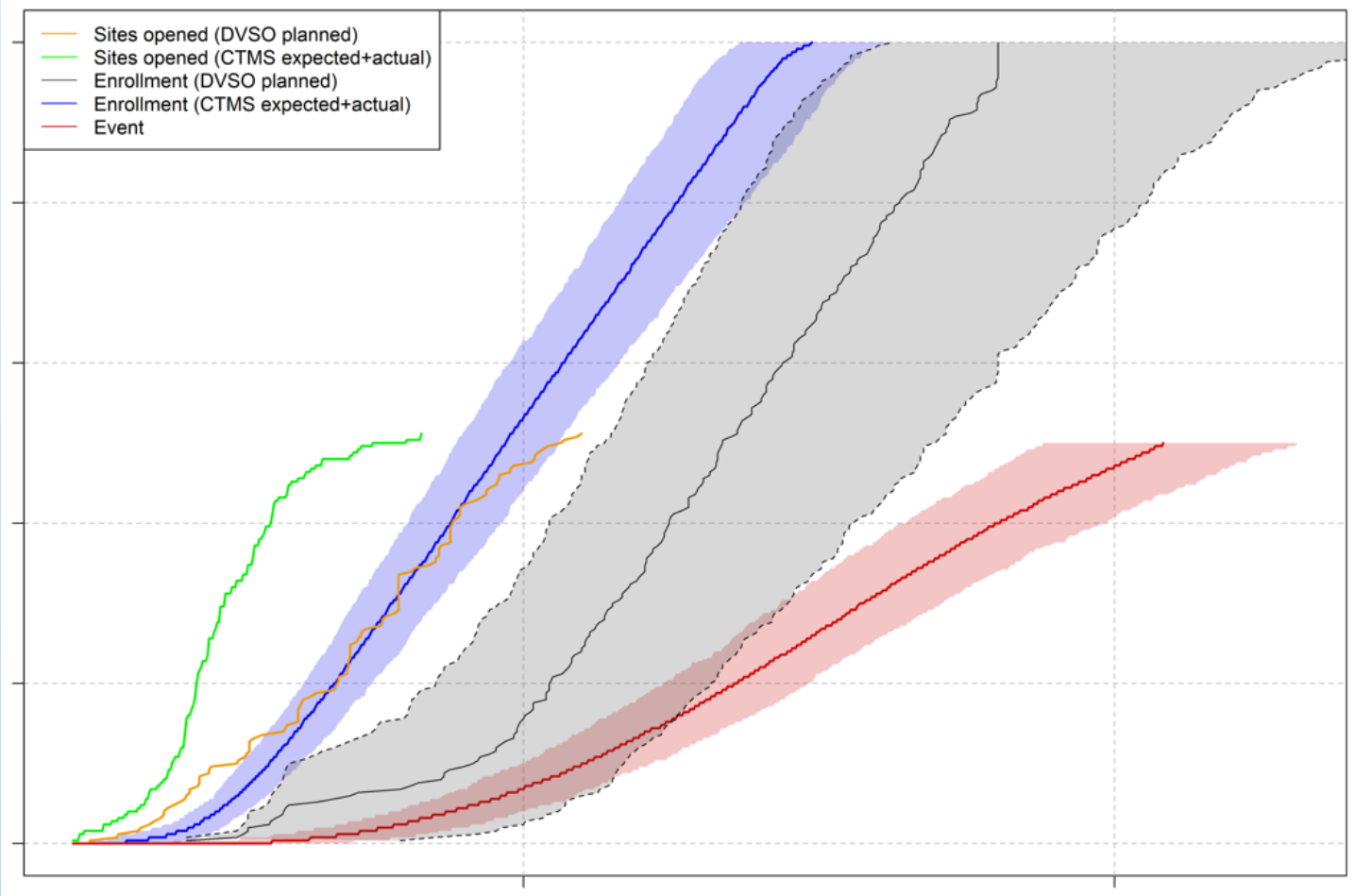
- Would take at least two time units before lower than planned recruitment rate could be safely detected
- Low chance of indicating lower than planned rate, when it's true rate
- Can calibrate false positive rate to provide quicker detection of low rate

Design of operations tracks closely with trial design features



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

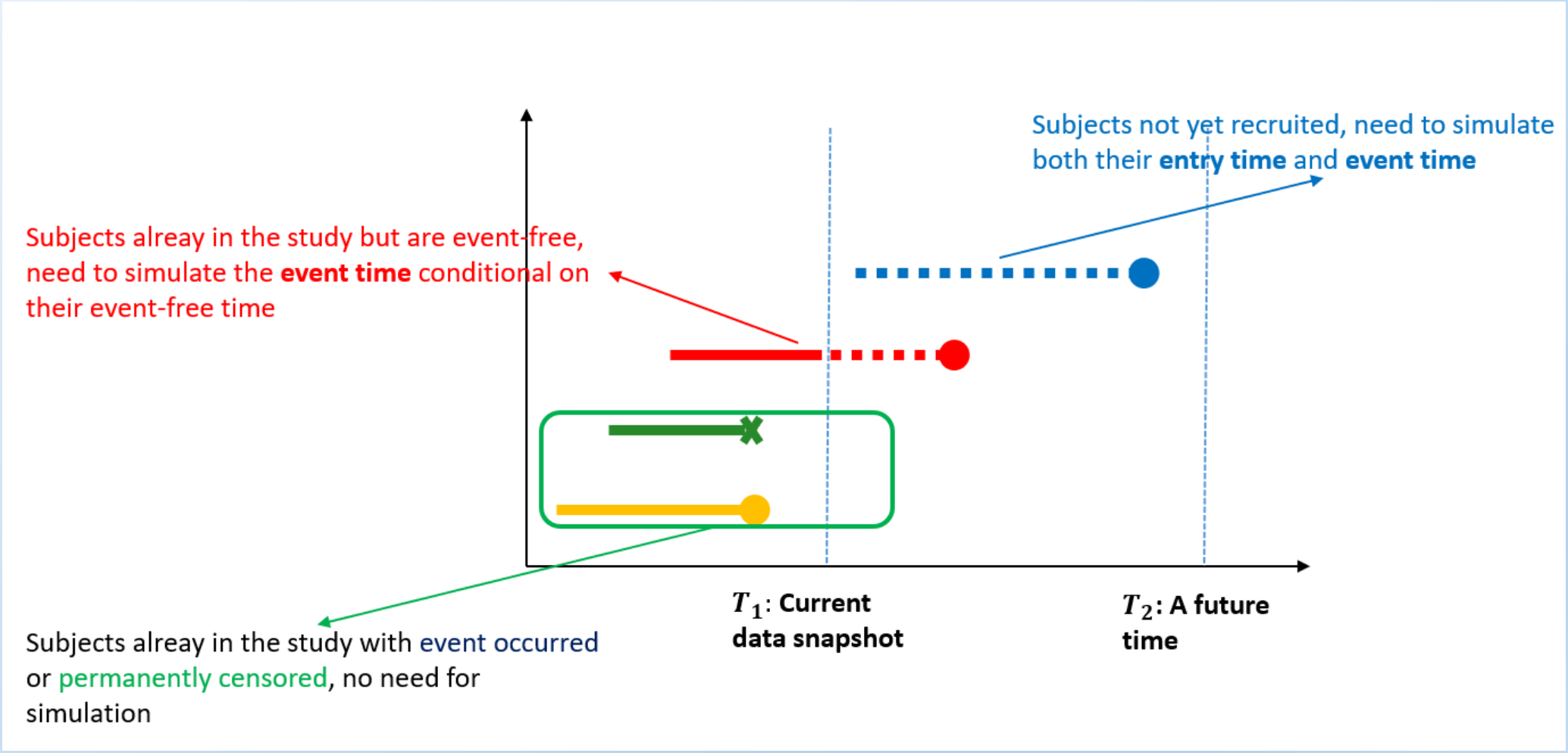


Event projection during study

- 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



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)

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

ASA BIOP Efficiency+ Scientific WG

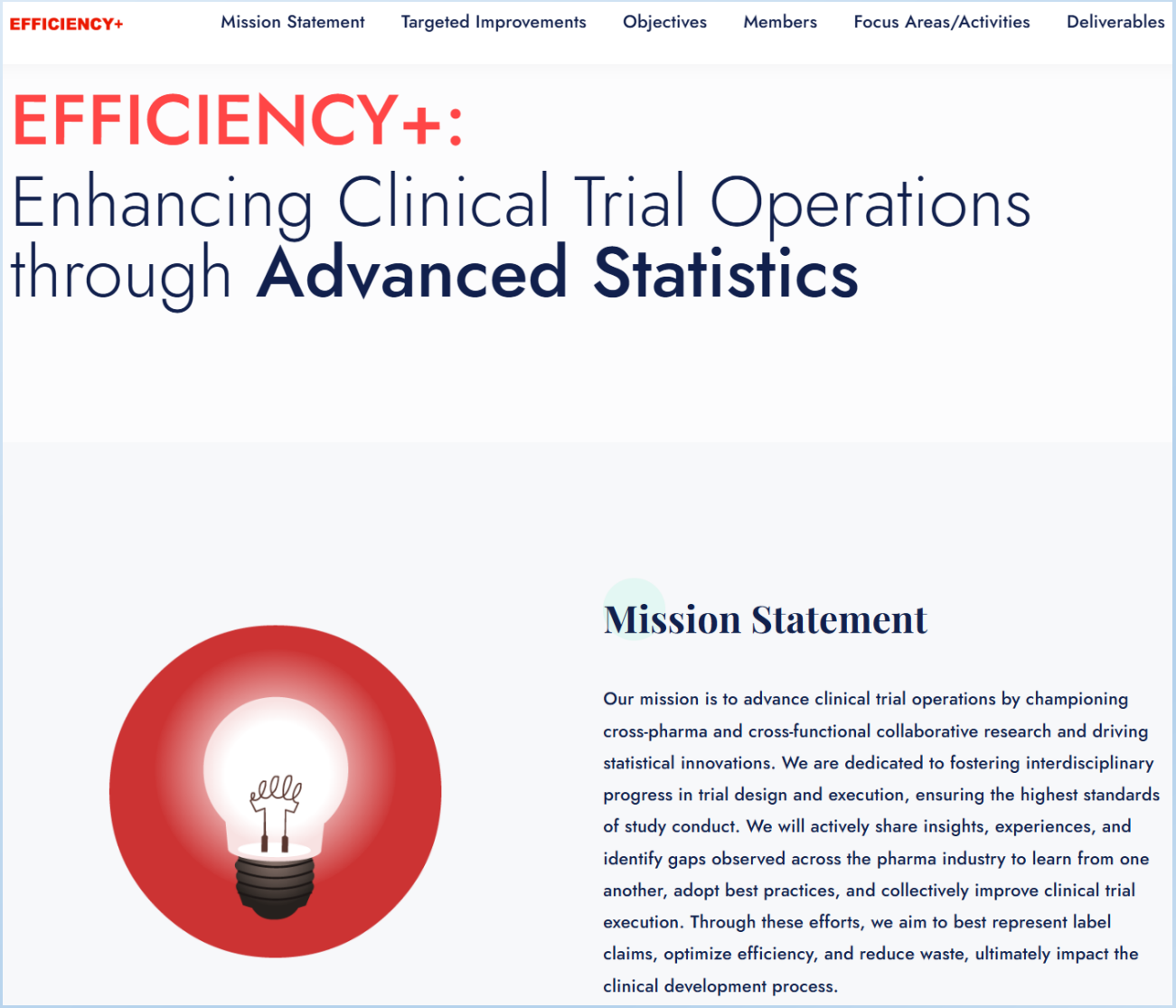
- Group of pharma statisticians with experience/interest in applying statistical methods to improve operational efficiency in drug development
- Co-leads: Fei Chen, J&J IM and Bohdana Ratitch, Bayer
- Organized under the umbrella of ASA BIOP Section SWGs, focusing on:
  - Site Selection and Performance 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: website

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



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