Re-imagining Clinical Trials

Leveraging Statistics & Cloud-Computing to Increase Development Productivity

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Research described at a recent DIA conference on Complex Innovative Design noted that the integration of innovative trial designs with other drug development tools and best available technology can save a program 20-30% in time and cost. Yet, despite the emergence of these more innovative trial designs, the average time it takes for a drug to reach the market has stagnated at 6 years, while the success of Phase 3 trials has hovered at about 30-35% for the past decade. The promise of adaptive designs that provide flexibility in the face of uncertainty remains largely unfulfilled.

We wondered if adoption of these efficient design methodologies was the issue. A recent survey conducted by Cytel found that only 42% of respondents reported using any complex or adaptive designs beyond the most widely adopted group sequential approach. While regulatory and operational barriers remain a cause for concern in the sphere of research and development, there is mounting evidence that regulators will accept well designed flexible studies that put patients first. There is even more evidence that clinical operations teams can rise to the challenge. There are a growing number of drug approvals, for example, which include adaptive designs for regulatory findings, even for pivotal studies.

So what has prevented the adoption of these new methodologies? Cytel's research uncovered that teams confronted with the need for innovative trials that employ advanced methodology often find difficulty exploring and communicating trade-offs in cost, time and probability of success. Whereas statisticians previously needed several days to make these calculations, the advent of cloud-computing has now made it possible to make these calculations rapidly. Cytel's trial simulation platform Solara™, for example, can calculate in fewer than 30 minutes what would have taken 500 hours only a year ago.

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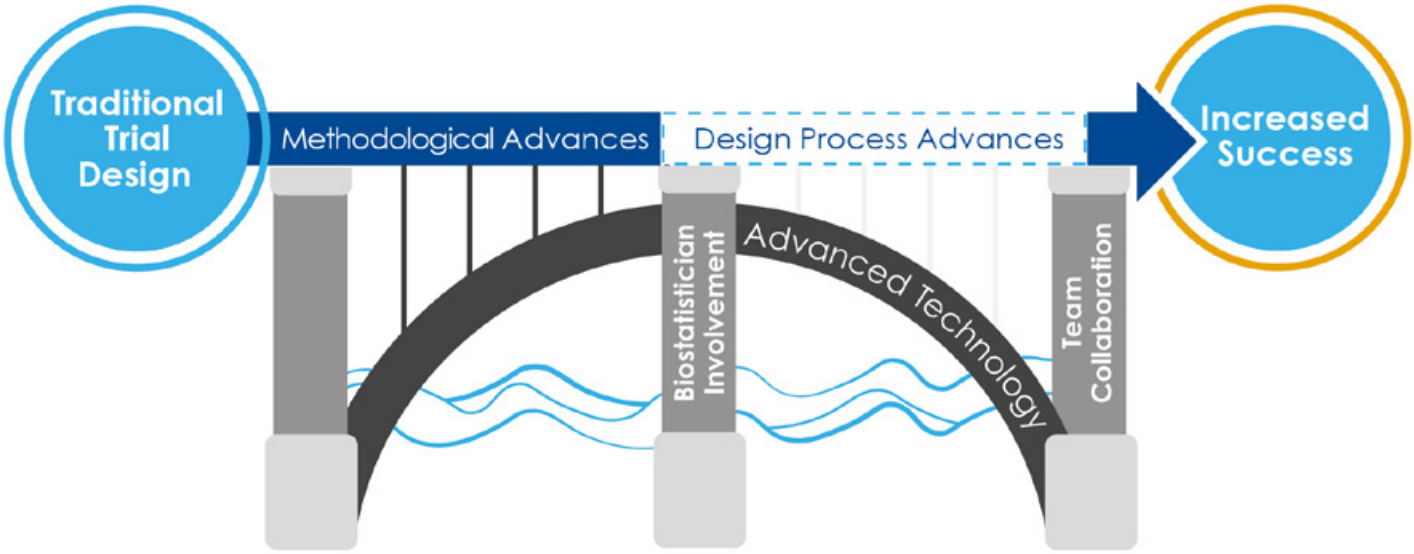

Leveraging advanced statistical methodologies to increase success requires advances in the end-to-end trial design process.

What Development teams now need in the Age of Cloud Computing is a process that allows new technology to explore more designs strategically. In response, Cytel's developed a new Advanced Design Framework for the Re-imagined Clinical Trial. This framework includes three steps:

- Thoroughly Explore the more expansive design spaces offered by cloud-computing;
- Decide Together using a quantitative evaluation approach that mitigates bias and generates data-driven decision-making at a collective level;
- Communicate Trade-offs in a way that translates statistical insight into cogent evidence that drives commercial decision-making.

As you will see throughout the paper, the framework works best when sponsors are able to improve collaboration across the disciplines of a development team, while also involving biostatisticians earlier in the design process. Cytel's early results suggest that when these two things are done in tandem, supported by technology that activities the full potential of biostatisticians, development teams improve R&D productivity by 10 – 20%. The process leads to superior outcomes due to its ability to identify optimal study designs given the commercial goals of a trial.

Advanced Design Framework

Cytel introduced a new Advanced Design Framework to address the need for improvements in the end-to-end trial design process.

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The Opportunity to Thoroughly Explore

The first step in this new Advanced Design Framework is to Thoroughly Explore. The use of cloud computing means access to exponentially more design options. The move from exploring five or six designs to several thousand results in new opportunities as well as challenges.

SATISFICING

Satisficing Leaves Design Space Mostly Unexplored
Organizations that employ satisficing are unlikely to find more than a local optimum.

OPTIMIZING

Thoroughly Exploring Reveals Global Optimum
Key changes needed to explore the full design space:
★**Expand Collaboration** ★**Biostatistician in Strategy** ★**Powerful Technology**

A conventional trial design approach can be thought of as a three step process. First an R&D team takes a few guesses about scenarios that might satisfy certain resource constraints, and then it consults a statistician about which of the designs in this smaller subset would yield the best expected results. The first two steps of this process would involve what economists call ***satisficing***, seeking a solution that is 'good-enough,' followed by a search for a ***local optimum***, which involves optimizing across a constrained subset of opportunities. The third step reflects an iteration at which point this process is repeated again, and again, for greater refinement of the study design. Each iteration can be translated into several days if not weeks of trial delay. Even when the process completes, trial designers have found the local optimum, not a global one.

Modern simulation techniques can increase the likelihood of finding a ***global optimum***, the option which serves as the actual best design for a trial. This is the objective of the Re-Imagined Clinical Trial.

As patients wait for promising treatments and sponsors for returns, many organizations look to stretch the impact of their budget. Leaders instituting

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a mindset shift can encourage the transition from satisficing to optimizing clinical trial design. Rather than beginning with a small subset of trial designs that account for a smaller set of requirements and resources, a well-resourced biostatistician who is strategically involved earlier in the design process and who is therefore informed by a wider range of cross-functional perspectives has the potential to explore a much broader set of options within the available timeframe than ever before. Biostatisticians wielding the latest technology, such as Cytel's Solara software platform, can apply massive cloud computing power to thoroughly map the entire relevant design space in minutes, thereby surfacing more promising opportunities to meet development goals.

Suddenly a trial sponsor can quickly determine the benefits of one or more interim looks, assess the benefits of placing those looks earlier or later during the course of a trial, the value of prospectively planning sample size re-estimations or arm drops, and multiple other variations of trial design. Perhaps a trial with three arms benefits from an earlier interim look, but an interim look on a two-armed trial that occurs later on will yield more information for decision-making. These detailed trade-offs can also be examined more explicitly once operating characteristics are available that showcase in detail what these options are.

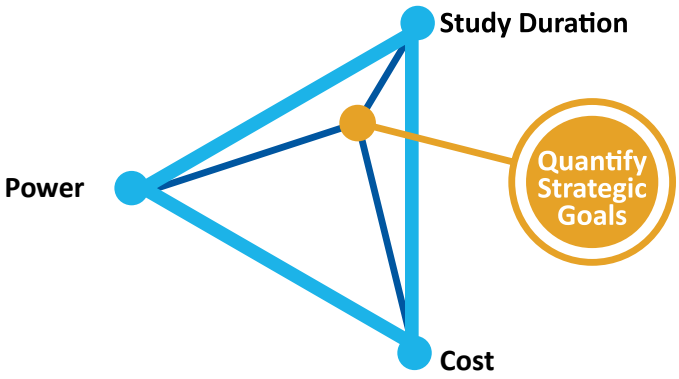
A biostatistician who is approached early enough in the strategic planning of a trial and afforded the context of a broader set of cross-functional perspectives can quickly help identify a promising set of opportunities for consideration that better support business goals, even helping development teams quantify returns on one design over another.

Decide Together

Has your organization ever completed the execution of a long, expensive Phase 3 clinical trial only to learn that the organization is unable to commercialize the therapy? Has a faster competitor ever locked your organization out of a market?

Historical processes for selecting statistical trial designs have several shortcomings. Some have not always been as inclusive of cross-functional perspectives as they ought to be. Others have relied heavily on qualitative comparison approaches. The emergence of cloud-powered trial optimization capabilities warrants an examination of the end-to-end approach to statistical trial design.

The second component of Cytel's new Advanced Design Framework, "Decide Together", helps trial sponsors select statistical designs that can successfully deliver greater value to patients and



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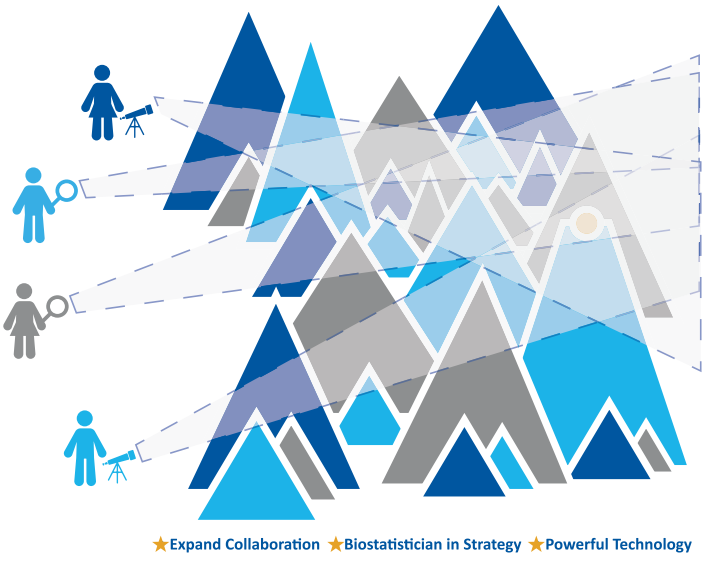
shareholders. Deciding together requires unifying team perspectives into a consistent quantitative evaluation approach, while also using computational power to ensure efficient evaluations of the entire design space. A well-resourced statistician is ideally suited to engage tactical as well as strategic opportunities for collective decisions.

A quantitative evaluation approach is one that mitigates bias caused by one or more stakeholders having undue influence over discussions about trial design. This ensures that decisions are evidence-based rather than "eminence-based" – that is, decisions are not influenced by the loudest or most senior voice in the room.

A decision framework is a set of rules that explicitly articulates how different evaluation criteria should be weighted. Some trials might need accelerated timelines due to a competitor nearing completion of a trial, and a slightly lower probability of success is worth the risk of completing a year early. Other trials might warrant higher probability of success and therefore need extra time to acquire time-to-event endpoints. A decision framework should stipulate how different trial parameters will be measured so that trade-offs are clearly and adequately prioritized. Agreeing to these priorities prior to evaluating the options helps further reduce bias.



The decision framework can then be used to aggregate the judgments and perspectives of multiple stakeholders. One way to achieve this is through a quantitative scoring rule, such as that employed by Cytel's Solara. The scoring rule asks members of the R&D team to explicitly place value on various trade-offs that inform decision-making. This allows the team to establish consistent, quantifiable decision criteria prior to evaluating the various options. These criteria might include speed of trial, the probability of success, and the expected commercial value. Once an R&D team agrees on how to weight these various criteria they must also ensure that all relevant stakeholders are involved in the decision-making process.

Traditionally, trial designs were compared by manual scoring, a process by which each trial design under consideration was compared to every other in a process of pairwise comparison. So, five potential designs would lead to 24 comparisons (i.e. 4x3x2x1 = 24). Given that statisticians now have to compare thousands of designs as opposed to 5 or 6, this is no longer tenable. Rules and processes for collective decision-making must find quantitative and objective ways to aggregate and streamline judgment formation. Note that this is nearly impossible if a statistician is not well-resourced with requisite technology.

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Communicate Trade-offs

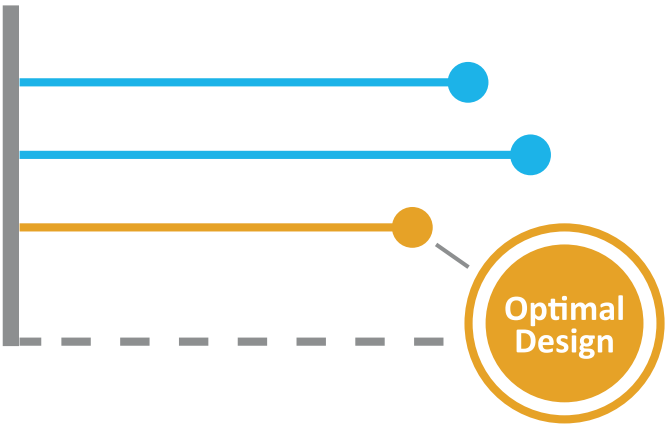
Statistical insights do not always translate into commercial implications in a straightforward way. Communicating the nuances of risk-quantification, optimization or cross-parameter trade-offs can lead to misunderstandings.

Using visual communication tools to graphically represent trade-offs and leveraging software that can give feedback in real time ensure that every member of the team understands the decision problem and the data being used to resolve challenges.

Data-driven decision-making means recognizing and confronting trial design outcomes that result from the improper quantification of operational characteristics like forecasted timelines, enrollment targets, trial sites and so forth.

The complex challenge of communicating statistical insights about trial risk and articulating the commercial implications of not pursuing sound risk-mitigation are often much easier to articulate graphically rather than mathematically.

Using the latest decision-support technology, the necessary intuitions about risk and reward can be captured through graphs and other representations. Having a biostatistician available to clarify trade-offs or guide discussions about uncertainty and opportunity has also helped facilitate discussions about aligning complex uncertainties with the focus on driving commercial value.



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Adopting the Advanced Design Framework can Drive Speed, Savings & Success

Advanced Design Framework

At base, there are three elements to improving the commercial return on any clinical trial.

There is the speed at which a trial can be completed, which affects time to market; the resources that can be saved during the course of a trial; and the likelihood of success. Together, these three elements can give a strategic development team a clear sense of the net present value of a trial.

The use of simulations and modeling predicts more accurate calculations across all three of these parameters and enables sponsors to quantify risks and understand trade-offs. None of these on their own will provide strategic direction, but the ability to compare them together, across millions of different possible eventualities, can be a powerful resource.

Allowing statistical expertise to guide strategic decisions by harnessing the potential and unlocking the full promise of these revelations can enable the development team to shorten trial duration, improve probability of success, secure power and reduce costs.

The next time managers have a stream of questions about when to schedule interim looks, and whether those looks can facilitate financial incentives, know that a million new possibilities can be available to a statistician.

Adopting Cytel's new framework can ensure your team finds the optimal one.

[1]Presentation at DIA Conference on CID by Richard Moscicki, MD, March 2020.
[2]PhRMA, http://phrma-docs.phrma.org/sites/default/files/pdf/rd_brochure_022307.pdf, accessed 29-Apr-2020.
[3]Bradley, Ben. "Against satisficing consequentialism." Utilitas 18.2 (2006): 97-108.

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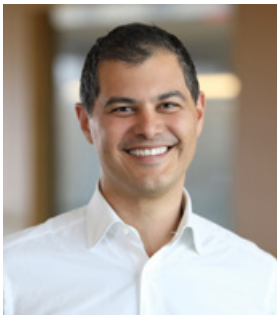

Chief Scientific Officer, Cytel, Inc.

Yannis Jemiai, PhD, is Chief Scientific Officer at Cytel Inc., a specialized provider of data-focused clinical research services and software solutions for the design and analysis of clinical trials, including industry standards East® and Xact®.

In his role as CSO, Dr. Jemiai leads scientific activities and product for the company, including product vision and strategy, product innovation and design, and product management and marketing. Cytel's products are intended to help clients design innovative studies and answer tough questions about their data. Dr. Jemiai's research interests include adaptive designs, modeling and simulation, quantitative decision-making, and causal inference.

Dr. Jemiai obtained his PhD in Biostatistics and AB in Molecular & Cellular Biology both at Harvard University.

Sue Feury, MBA

Associate Director, Product Marketing Management, Cytel, Inc.

Sue Feury has over twenty years of diverse experience in healthcare ranging from biotech and medical devices to software in marketing, product management, and biologics process engineering capacities.

Currently, Sue is responsible for product marketing at Cytel, where she is focused on helping to educate clients on the benefits of the company's existing products and future innovations.

Prior to Cytel, Sue was responsible for product marketing of GE Healthcare's electronic medical record and practice management software portfolio for ambulatory practices. There she launched population health and analytics capabilities to help practices transition to value-based care. She also has marketing and product management experience launching medical devices and analytical instrumentation products to both the European and US markets.

Sue began her career as a process engineer at Biogen, helping to build their first large-scale manufacturing facility. Sue earned undergraduate degrees in chemistry and chemical engineering from Dartmouth College and later earned her Master of Business Administration degree from the Tuck School of Business at Dartmouth.

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Esha Senchaudhuri, PhD

Senior Manager, Content Marketing, Cytel, Inc.

Esha Senchaudhuri is a research and communications specialist, committed to helping scholars and scientists translate their research findings to private and public sector executives. She has worked in education, philanthropy, arts policy and biomedicine, ensuring that the research findings of knowledgeable experts are channeled towards evidence-driven policies and decision-making.

At Cytel, Esha leads content strategy and content production across the company's five business units. Her team produces ebooks, whitepapers, webinars, case studies and podcasts, to broaden the reach of Cytel's numerous industry thought-leaders. She also provides content strategy for Cytel's product launches, services campaigns, mergers & acquisitions.

Esha received a doctorate in philosophy from the London School of Economics, examining challenges to democratic discourse and collective decision-making. She then went on to teach medical ethics and global health, social choice theory, and normative ethics, at institutions like York University and the TH Chan School of Public Health at Harvard University. She was also named an early career policy fellow of the American Academy of Arts and Sciences, where she contributed to national commissions on America's language policy, America's arts policy, the protection of cultural heritage in war zones, and a nuclear ethics working group.

Esha currently serves on the Steering Committee of the Society of Women in Philosophy's Eastern Division, the Division responsible for awarding the prestigious Distinguished Woman in Philosophy Award. She has served as a reviewer for the British Medical Journal and the American Journal of Public Health, and was a special rapporteur for the J Paul Getty Trust's global workshop on the Protection of Heritage in War Zones.

Joshua Schultz

Chief Executive Officer, Cytel, Inc.

Joshua Schultz is an accomplished leader with a 20-year track record of success in life sciences and clinical research organizations. Prior to joining Cytel he served as an Officer of PAREXEL and Senior Vice President for PAREXEL's Access business unit.

Joshua has built and led groups for services spanning the development lifecycle, including study-start up, late phase trials and market access. His achievements include the development of novel approaches to building high value strategic partnerships with life science companies and creating innovative operational models that leverage real world data and related technologies.

Prior to joining PAREXEL, he served as Vice President of Corporate Development at Veritas Medicine, which he co-founded. Previously, he worked at Mercer Management Consulting, where he developed growth strategies for Fortune 500 companies.

Joshua holds a B.S.E. in Finance from the Wharton School of Business, a B.A. in International Relations from the University of Pennsylvania, and a Masters of Philosophy in International Relations from the University of Cambridge, UK.

About Cytel

Cytel is the largest provider of statistical software and advanced analytics for clinical trial design and execution. Cytel's Solara™ is a patent-pending software platform that unifies statistics and strategy to optimize clinical trial design.

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