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BIOPHARMACEUTICAL REPORT

ASA BIOP Section Chairs: Ted Lystig(2024), Erik Bloomquist (2025), Steven Novick (2026)

Note from Editor:

This year has been filled with many great conferences that continue to inspire and connect our community. Notably, the **Joint Statistical Meetings** held recently in Nashville brought together brilliant minds and sparked meaningful discussions. Looking ahead, we're excited for the upcoming **FDA-Industry Statistics Workshop** at the end of September, which promises to be another valuable opportunity for collaboration and insight. I look forward to seeing some of you there and continuing these important conversations.

This Summer ASA Biop Report brings together a timely and thought-provoking collection of articles that reflect the shifting landscape of our profession. As AI and machine learning continue to reshape clinical research and regulatory science, statisticians are being called to evolve—not just in skillset, but in mindset. From strategic leadership to multidisciplinary collaboration, the role of the statistician is expanding in exciting and sometimes unexpected ways. We're proud to feature voices from across the community, including an insightful conversation with Xiao-Li Meng, practical career guidance for early-career statisticians, and updates from key regulatory discussions and events. We hope this issue sparks ideas, conversations, and perhaps even a bit of inspiration as we navigate this new era together.

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RESHAPING THE ROLE OF STATISTICIANS IN THE ERA OF EVOLVING AI/ML APPROACHES IN CLINICAL TRIALS

Abie Ekangaki (Premier Research)

Highlights

- Learn about the historical foundation of statistical modeling
- Understand the shift from traditional to algorithmic modeling
- Explore a conceptual framework for AI/ML-generated synthetic controls
- Learn about the role of statistician in driving innovative AI/ML approaches

Abie Ekangaki
Senior Vice President, Biometrics, Premier Research

Introduction

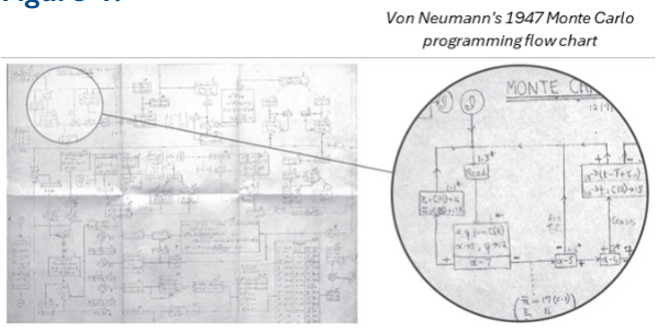
As artificial intelligence (AI) and machine learning (ML) technologies rapidly evolve, they are transforming the landscape of clinical trials, necessitating a redefinition of the traditional role of statisticians. No longer confined to data analysis and trial design, statisticians must now engage as interdisciplinary collaborators who bridge methodological rigor with the dynamic capabilities of AI/ML tools. This shift demands expanded competencies, including algorithmic literacy, a deep understanding of model interpretability and validation in the context of the regulatory environment around AI/ML, and of particular importance, a high aptitude for both strategic leadership and sound business acumen to help drive the value proposition for innovative AI/ML approaches. Statisticians are uniquely positioned to guide ethical AI integration, ensuring robustness, reproducibility and regulatory compliance in decision-making processes. By embracing these expanded responsibilities, statisticians can lead the development of hybrid analytical frameworks that leverage both classical statistical principles and modern innovative computational approaches, ultimately enhancing the efficiency, transparency, and integrity of clinical research.

Brief Historical Overview of Statistical Modeling

Today's experience with more sophisticated AI/ML algorithmic modeling approaches stems from a long and rich history of classical modeling and simulation techniques. This history offers insight into how statistical modeling has progressed over time.

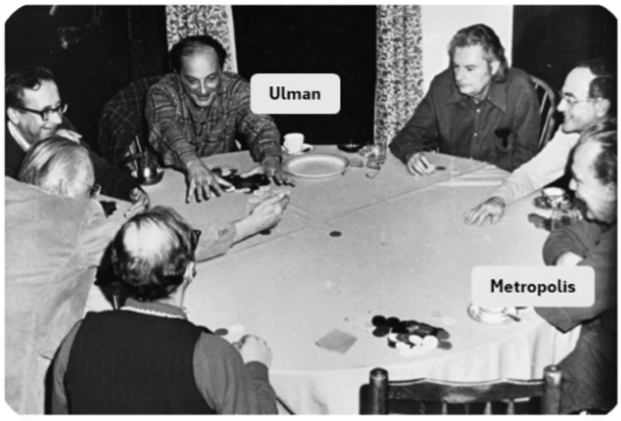
It began in the early 1940s with a game of solitaire, a case of insomnia, a chance meeting at a train station, and a penchant for gambling, which all contributed to the creation of one of the most influential computing tools in the world – the Monte Carlo method. This was conceived by Stanislaw Ulman, a physicist working on nuclear weapons during WWII. Ulman had a passion for card games that was spurred by his uncle, an avid gambler who frequented the Monte Carlo casino in Monaco, hence, the inspiration for the name. True to his passion, Ulman latched on the idea of calculating the probability of winning card games by applying combinatorial computation methods with repeated random sampling, using the ENAIC computer – the first known computer that was produced in February 1946. The idea was to use random sampling to solve problems that might be deterministic in principle but are complex in practice. His close friend, Jon Von Neumann, also a physicist, expanded Monte Carlo to develop accept/reject techniques in neutron diffusion. Early applications of the Monte Carlo method were in stochastic modeling of biological systems and have since evolved to simulated trial outcomes to evaluate designs and decision rules under uncertainty.

Figure 1:



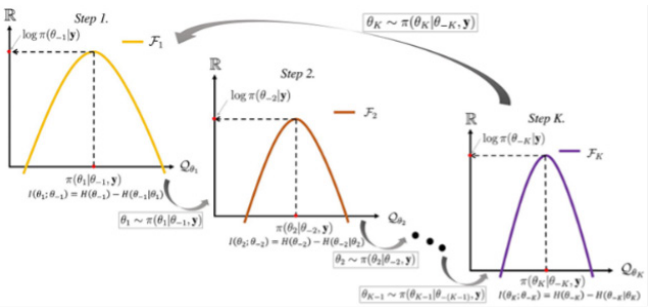
In 1953, Nicholas Metropolis introduced the Metropolis algorithm, the first MCMC algorithm initially used to simulate uniform distributions. Later in the 1970s, Karl Hastings extended the Metropolis Algorithm to simulate non-uniform distributions. This led to the well-known Metropolis-Hastings algorithm, an MCMC method for generating samples from complex probability distributions. Subsequently, the Metropolis-Hastings algorithm was extensively used in Bayesian analysis by providing a practical way to sample from high-dimensional posterior distributions. This facilitated Bayesian inference for complex models where analytical solutions are infeasible and for posterior estimation in hierarchical models, treatment effects, and adaptive designs.

Figure 2:



A few years later in 1984, Geman and Geman went a step further and introduced Gibbs Sampling, an MCMC method used to generate samples from complex, high-dimensional joint probability distributions, when direct sampling is difficult. The key idea was to break the problem down by sampling sequentially from conditional distributions instead. Gibbs sampling has been widely applied in Bayesian hierarchical models, mixed-effects models, and missing data imputation.

Figure 3: Gibbs Sampling



Through the 1980s-1990s, advancements in computer technologies and computational power, combined with the expanding applications of MCMC methods, further revolutionized Bayesian statistics by enabling the computation of posterior distributions in situations where closed-form solutions are unavailable.

This period also saw the emergence of population-based PK/PD modeling using nonlinear mixed-effects models (e.g., NONMEM software). The key concepts involved modeling drug concentration-time profiles and linking drug exposure to clinical outcomes. Statisticians used simulation for dose optimization, trial design simulations, power calculations, as well as personalized dosing strategies and regulatory decision support.

The 1990s-2000s saw increased use of simulation to explore trial operating characteristics under different assumptions, particularly as applied to adaptive designs (e.g., sample size re-estimation, dose escalation). Software tools like FACTS, ADDPLAN and Simulx enabled complex simulation-based design evaluations.

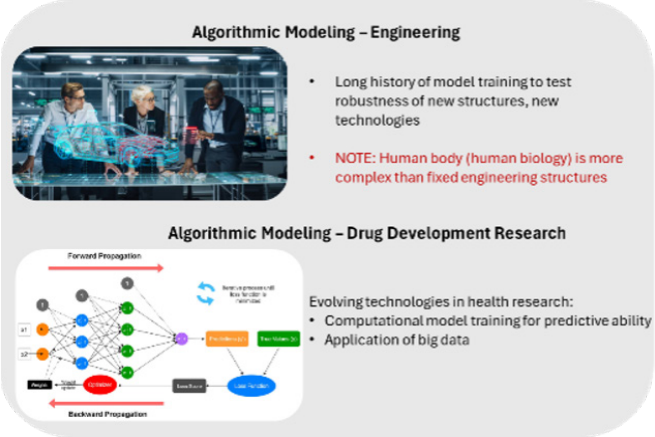
Shift from Traditional Data-based Modeling to Algorithmic-based Modeling

Since the early 2000s there have been increasing developments in big-data technologies and cloud-computing infrastructure, and these have led to more sophisticated AI/ML approaches. It has brought a notable shift in building statistical models from the traditional reliance on observed data for defining a model, to the more algorithm-driven approaches to modeling. Traditional modeling and simulation has always involved defining a simple representation of a real-world system (the *model*), then conducting experiments with the model (*simulations*) to characterize the system. In contrast, AI techniques more broadly enable complex computer algorithms to simulate human intelligence, which involves complex computer algorithms for human

learning, comprehension, problem solving, decision-making, creativity, and autonomy. Said otherwise, AI algorithms simulate the entire system behavior using algorithmic pattern recognition and learning routines for generating an array of AI-generated systemic pathways (or AI sub-models) which together characterize the full system behavior. On the other hand, ML is a branch of AI which for a given systemic pathway, trains the algorithm to create a model for making predictions and decisions based on actual data it has received and processed.

The superior power of algorithmic-based modeling has had a long history in engineering for designing and testing robustness of thermodynamic systems, e.g. design technologies for vehicles.

Figure 4:



More recently with the advent of big-data technologies and AI/ML methods, algorithmic-based modeling approaches are increasingly being applied in drug development research. For instance, since the 2010s, ML approaches have been used to generate synthetic control patients from historical data to reduce the need for placebo/control groups in rare diseases or trials with ethical constraints, thus, improving efficiency in single-arm or early-phase trials.

Statisticians have implemented approaches such as generative models (e.g., GANs, VAEs), propensity score matching or regression-based methods to simulate matched controls. Bayesian borrowing from historical data using dynamic borrowing (e.g., commensurate priors) has also been used.

Notably, it wasn't until the 2000s that regulatory agencies began releasing guidance documents that specifically accommodate innovative modeling and simulation approaches for the design, implementation, and statistical analysis of clinical trials. Examples include the 2020 FDA guidance on Complex Innovative Designs (CID), which established a framework for adequate implementation and model verification in complex adaptive designs using Bayesian adaptive modeling techniques. The 2021 FDA guidance on Assessing the Credibility of Computational Modeling and Simulation in Medical Device Submissions, was intended to inject trust in the predictive capability of computational models used for supporting pre-market approval of medical devices. Also, FDA's 2024 Model-Informed Drug Development (MIDD) guidance encourages the use of modeling and simulation in drug development with the view to improve efficiency, reduce uncertainty, and support more informed decisions in the drug development cycle.

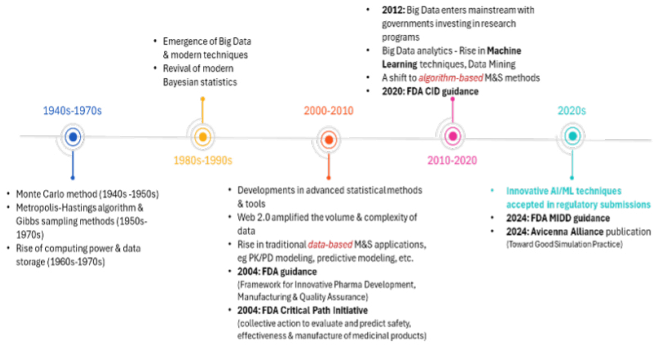
More recent efforts for leveraging modeling and simulation to advance adoption of AI/ML *in silico* modeling techniques in clinical trials, and in healthcare in general, have led to the release in 2024 of a best-practice publication, "*Toward Good Simulation Practices*," by the Avicenna Alliance – a global non-profit organization that brings together stakeholders from industry, academia, healthcare, and regulatory bodies, including FDA and EMA. This document identifies five critical elements of good simulation practice that establish a scientifically sound framework for the construction, validity and credibility of computational modeling and simulation – defining the theoretical interdisciplinary foundation for the clinical mechanism to be explored; development and credibility assessment of the models; outlining possible regulatory and health technology assessment pathways; framing the ethical review process; and clarifying the role of the sponsor and investigators. Until specific guidance documents are available from major regulatory agencies, this best-practice document may prove of value in the interim.

This transformation has real-world implications for how clinical trials are designed, conducted, and evaluated today. The expanding availability of complex data sources and regulatory openness to innovative methods are driving adoption of these AI/ML approaches across a range of therapeutic areas.

For example, availability of more complex, high-dimensional data allows models to learn patterns, trends and relationships that traditional methods cannot detect. Also, the increasing recognition of AI/ML approaches by regulatory agencies helps reduce institutional barriers thereby, overcoming the limitations of traditional statisti-

cal methods. Together, this creates a safe and high-value environment for drug development innovation.

Fig 5: Trajectory of Modeling & Simulation:



Conceptual Framework for AI/ML Algorithmic-based Approach for Generating *In Silico* Synthetic Control

Whereas traditional approaches for generating matched controls like propensity scores or regression-based methods are hinged on first defining a predictive model using observed data, machine learning algorithmic-based modeling relies on using AI algorithms to explore patterns in the data, then formulate those patterns into an algorithm-driven model and finally, apply what the model learns to generate new, unseen data. For any disease condition, the three main principles underlying AI/ML algorithmic approaches for generating *in silico* synthetic controls are firstly, understanding the disease pathophysiology (or disease model), which requires deep interdisciplinary collaboration; secondly, building a system of disease mechanistic models that characterize the disease; and thirdly, train the system of mechanistic models to predict key disease characteristics and use these in simulating synthetic (or virtual) patients.

As a conceptual example using Relapse-Remitting Multiple Sclerosis (RRMS), it is well known that the disease pathophysiology is described by three clinical pathways: disruption of the blood-brain barrier due to white matter lesions; migration of immune reactive T-cells from bloodstream to the brain; and damage incurred to CNS cells and myelin due to T-cell migration. AI algorithms for the disease model are run on those relevant biomarkers and/or PK parameters which define the disease pathways, along with other relevant demographic or real-world data, to develop algorithmic-based disease mechanistic models representing each clinical pathway; thus, characterizing the overall disease model. Simulations are then run using the set of disease mechanistic models to generate virtual patients that match the disease characteristics and overall profile of a typical RRMS patient.

By necessity, expanded expectations for intensive early collaboration with clinicians, PK scientists, data scientists, regulatory experts, and others, are cast on the statistician's role when implementing such AI/ML algorithmic-based modeling approaches in clinical trials. This is particularly true at the pre-implementation design stages for the disease model but continues throughout the process to ensure that selected algorithmic techniques are appropriate and adequately satisfy regulatory standards for scientific validity and robustness in the modeling approach.

While it is true that under the traditional data-based modeling paradigm, regulatory guidance documents have proven invaluable for providing visibility and coherence towards scientifically sound and robust innovative methods, when it comes to AI/ML algorithmic *in silico* modeling strategies, more work is needed to establish clear regulatory guidance and expectations of statisticians for adequate implementation and model credibility assessment.

Practical Applications in Clinical Research

The evolution of modeling and simulation - from Monte Carlo to mechanistic AI/ML models - has not been a purely academic exercise. In clinical research, these innovations are increasingly being operationalized to streamline trial execution, accelerate development timelines, and strengthen regulatory confidence in novel designs.

Modern clinical trials now often involve complex, high-dimensional datasets sourced from electronic health records (EHRs), wearable technologies, genomics, and imaging. Statisticians are needed to ensure these datasets are fit-for-purpose, harmonized, and appropriately used in training AI models for key applications, such as synthetic control arm development, dynamic Bayesian borrowing techniques or through predictive analytics for patient recruitment optimization or risk-based monitoring.

As the nature of clinical trials evolves, so too must the role of the statistician. This shift is not just about acquiring new tools, but about reimagining the impact statisticians can have across the drug development lifecycle.

Role of Statistician in Driving Innovative AI/ML Approaches

The historical trajectory of modeling & simulation described and illustrated above, offers a roadmap for exploring how statistician responsibilities have evolved. Although one could choose a much earlier starting point, the 1950s-1970s could arguably be credited for setting the foundational role of statisticians in trial design and analysis, with focus on classical statistical design with the randomized controlled trial. The main role of the statistician in that era centered on experimental design, sample size calculation, and analyzing data using simple frequentist methods, e.g. t-tests, ANOVA. The tools implored included simple mainframe computers and for the most part, hand calculations, where the statistician stayed mostly behind the scenes and was at best considered a ***consultant***, rather than a collaborator.

The 1980s-1990s leapt into the regulatory era with the emergence of ICH guidelines (e.g. ICH E9), where drug development and compliance hailed large and the statistician became more involved in clinical trials for regulatory approval. Statistician focus was with protocol development, data monitoring and interim analysis, as well as the procedural infrastructure around regulatory submission, e.g. statistical analysis plans and integrated summaries of efficacy and safety. SAS software was the norm for statistical analysis as e-data systems began to flourish. In that period the statistician was raised to an ***essential player*** on the drug development project team but still was mostly relegated to carrying out needed statistical tasks which contributed to the broader submission package.

The 2000s-2010s opened the era of Big Data and adaptive designs, where statistician focus began to shift towards innovation that yielded efficiencies. Greater methodological prowess was required of the statistician in designing adaptive, Bayesian, and seamless phase trials, as well as delving into surrogate endpoints and real-word evidence. More advanced statistical programming languages like R and other advanced simulation software came to bear. This unlocked channels that elevated the statistician to ***strategic collaborator*** status, working cross-functionally with clinicians and regulators.

Now in the 2020s-2025, we have entered the digital age, where AI/ML approaches extend traditional RWE and precision medicine techniques. Statistician focus is preeminently sought for evaluating complex data ecosystems and advising on possible implementation of AI/ML analytics. Responsibilities have now scaled up to integrating AI/ML into trial design and analysis, handling high-dimensional omics or imaging data, supporting decentralized trials with digital patients, and collaborating with a broader spectrum of inter-disciplinary experts, including data scientists, informaticians, regulatory experts, etc. The programming infrastructure for this digital age has grown in complexity, with cloud computing applications using R, Python, and other languages applied to more advanced Bayesian modeling and AI learning algorithms. By necessity, the statistician role in today's more complex digital age has expanded to be the ***data integrity steward, the innovator, the ethical advisor***. The statistician is accountable for ensuring credibility of data used in analysis, for verifying robustness of new innovative methods, and for providing guidance on the interpretability and appropriate use of the outcomes of data analysis.

Over the decades, the underlying constant associated with the statistician role remains unequivocally the technical expertise they bring to the table. Statistical methodological prowess coupled with computational expertise continues to be pivotal to growing the statistician's impact in drug development, through the introduction and implementation of innovative approaches. In today's digital age, AI algorithms are applied to high-dimensional, multivariate, multi-distributional, multi-source data for delivering actual innovative solutions that drive critical decision-making much sooner than may otherwise be possible under traditional methods. For the statistician, this conjures renewed pressure to develop innovative value-add "solutions," beyond just introducing innovative statistical "methods." Meeting this challenge requires of the statistician a new level of "strategic statistical leadership" which goes beyond, and compliments, methodological prowess alone.

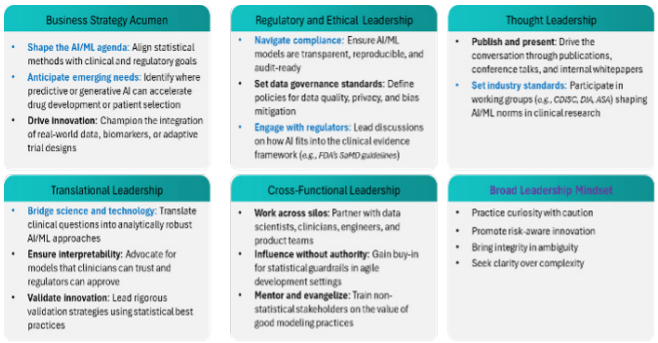
Vamping up business acumen is vital in this era, as the statistician should be savvy with big picture opportunities for AI implementation in their organization. Bolstering the skill of when, how, and for what purpose to engage cross-functionally and at higher levels within their organization would encourage the statistician to leverage data and analytics to promote, guide, and influence change and decision- making. Improved awareness of the broader business strategy enables statisticians to proactively raise awareness of how innovation could impact business strategy.

The responsibility for maximizing the potential for AI/ML innovation does not rest on the statistician alone. Organizations need to be more intentional about

establishing a business environment that embraces and enables innovation. Companies also need to show greater proactiveness in leveraging for strategic decision-making their top statisticians with demonstrated aptitude as technical advisors on drug development strategy.

Figure 6 offers a few additional influential roles the statistician should adopt for boosting their effectiveness, particularly in the digital era of AI/ML innovation in drug development.

Figure 6: Strategic Statistical Leadership



Conclusion

Statistical leadership is more critical than ever in shaping responsible, rigorous, and innovative data-driven decision-making. As AI/ML methodologies become integral to research and development across industries, particularly in healthcare, pharmaceuticals, and clinical trials, statistical leaders are uniquely positioned to ensure that these technologies are applied with scientific integrity, transparency, and accountability. This new paradigm calls for statisticians not only to master computational tools, but also to assert strategic influence in multidisciplinary teams, guiding the design, validation and interpretation of complex models. Statistical leadership involves championing reproducibility, fairness, and ethical considerations, while fostering a culture of critical thinking and continuous learning. By embracing this evolving role, statisticians can lead the integration of AI/ML in ways that uphold statistical principles and drive meaningful, trustworthy innovation.

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STATISTICIAN 2.0 — STATISTICS AND STATISTICIAN IN THE AI/ML ERA

Interview by Xun Chen (AbbVie) with Xiao-Li Meng (Harvard)

Highlights

- Learn how statisticians can leverage their rigorous training and critical thinking to carve out a distinctive edge in interdisciplinary teams and high-impact projects.
- Explore the deeper value of advanced statistical education—what skills truly matter, and how students can future-proof their careers by focusing on the right capabilities.
- Gain insights into how statisticians can proactively drive scientific innovation —and what the rise of AI means for traditional academic paths and tenure-track expectation

Xun Chen
Vice President, AbbVie

Xiao-Li Meng
Whipple V. N. Jones Professor of Statistics, Harvard

Xiao-Li Meng is the Founding Editor-in-Chief of *Harvard Data Science Review*, faculty co-director of LabXchange and the Whipple V. N. Jones Professor of Statistics. He is renowned for his extensive research, innovative teaching methods, visionary administration, and engaging speaking. Meng was recognized as the best statistician under 40 by Committee of Presidents of Statistical Societies (COPSS) in 2001 and has received numerous awards for his over 150 publications across various theoretical, methodological, pedagogical, and professional development areas.

In 2020, Xiao-Li Meng was elected to the American Academy of Arts and Sciences. He has delivered over 400 research presentations and public speeches. His writing, including the popular column "The XL-Files" in the Institute of Mathematical Statistics (IMS) Bulletin, is celebrated for its clarity, wit, and thoughtfulness.

Xiao-Li Meng's interests encompass the theoretical foundations of statistical inferences, including the interplay among Bayesian, Fiducial, and frequentist perspectives, and frameworks for multi-source inferences. He is also focused on statistical methods and computation, such as posterior predictive p-values, the EM algorithm, Markov chain Monte Carlo, and bridge and path sampling. Additionally, Meng applies complex statistical modeling across various fields, including among others astronomy, mental health services, and genetic studies.

Xiao-Li Meng earned his B.Sc. in mathematics from Fudan University (1982) and his Ph.D. in statistics from Harvard (1990). He began his academic career at the University of Chicago (1991 to 2001) before returning to Harvard, where he served as Chair of the Department of Statistics (2004–2012) and later as Dean of Graduate School of Arts and Sciences (2012–2017).

Xiao-Li Meng is widely recognized for his deep and wide-ranging contributions to statistics and data science. He has helped shape the field through both scholarship and leadership.

Xun Chen is the Vice President and a Global Head of Data and Statistical Sciences at Abbvie. In her current role at Abbvie, Xun Chen leads the statistical strategy and execution across all clinical development programs, supporting a diverse portfolio of successful therapies in oncology, immunology, rare diseases, diabetes, and cardiovascular disease.

Xun Chen, who received her PhD in Biostatistics from Columbia University, is a passionate advocate for statistical leadership in drug development. She led the successful buildout of a comprehensive clinical sciences and operations platform in China (2010–2015) and is widely recognized as an industry thought leader through her contributions to major biostatistics con-

sortia. Xun Chen served as President of the International Chinese Statistical Association (ICSA) in 2024. Her research spans key areas including multiplicity adjustment, missing data, adaptive design, multiregional trials, and Bayesian methods.

Building on her commitment to advancing the field, Dr. Chen recently sat down with Prof. Xiao-Li Meng for an in-depth conversation on the evolving role of statisticians in the pharmaceutical and biotech industries. In a time of rapid scientific and technological change, she emphasized the importance of fostering new mindsets and a data-driven culture to develop future leaders. We're grateful to share this insightful interview with *Biopharmaceutical Report* readers and invite you to explore the ideas it brings to light.

Xun CHEN: Thank you, Xiao-Li, for joining me today to discuss the future of Statistics and Statisticians in the era of data and digital transformation.

The pharmaceutical industry is undergoing a digital transformation driven by emerging technology, data proliferation, and artificial intelligence (AI). The role of advanced data science capability has significantly expanded within the biopharmaceutical industry. This shift brings forth unprecedented opportunity to improve insights and data-driven decisions. Statisticians in the pharmaceutical industry, however, once regarded as the 'stewards of sound thinking for good decision-making,' are now often perceived as 'obsolete' in the public eyes in the new data era. There have been increasing calls for statisticians in the pharmaceutical industry to evolve in recent years.

This imperative has also been recognized within academia. As highlighted in last year's fireside chat, a central theme among participating professors was the evolution of statistical training to effectively support and engage with diverse fields of practice

With the growing call for 'Statistician 2.0' in the AI/ML era, what's your take on it?

Xiao-Li MENG: Thank you, Xun! The fireside chat on AI that you mentioned will appear in the upcoming April issue of *HDSR*. Interestingly, there's also another article, written independently by a separate group of Statisticians, expressing very similar concerns. Both pieces are from academic perspectives, as you noted, and I can certainly relate to your observations about the pharmaceutical industry.

One thing probably is all clear is that few of us worry about statistics is going to be obsolete. Much of what practitioners in machine learning do is grounded in statistical thinking. They use statistics either in ways we don't commonly use, or sometimes without realizing they're applying well-established statistical methods. Take A/B testing, for example. It's widely used, but as statisticians, we've developed far more sophisticated approaches, like factorial designs. The real concern, which I completely understand, is what the future is for statisticians.

If we stay within our traditional role, which is typically analyzing data using standard statistical modeling techniques, we certainly have a very strong competitor, in this age of days. In fact, at the large scale, large language models (LLM) clearly have a far greater impact, whether we like it or not. The rise of AI has shown us something important and I'll admit to anyone that we statisticians probably would never come up with the idea of LLM. And even if we had, we probably never would be able to implement or popularize it on the same scale as computer scientists can. Therefore, we definitely need to reflect on the limitations of our field and consider how we might evolve.

At the same time, I also believe that every field has its own boundaries. That's why I often emphasize that science is not a single, unified discipline. For example, you can be a top physicist, but that doesn't mean you can solve complex problems in biology - you still need a biologist. Even though both are scientists, their expertise is domain specific. Similarly, as statisticians, we shouldn't claim that everything falls under statistics because that's clearly not true. And if we think that way, it's not going to be effective. The truth is, we're not trained to do everything others do, and frankly, some of us may not even enjoy it. For many statisticians, the idea of mindlessly searching for patterns without understanding them can feel beneath their training. But there are others who have no problem with that approach and embrace an engineer-like mentality. Engineers often operate with the belief that I can make it work, even if I don't fully understand why right now. They iterate, try things, and build solutions that may not be optimal, but they get things done and create something tangible that others can see and use.

As statisticians, we tend to think from the very fundamental point, which is that we like to understand the 'why' behind things. Even when we produce a result or a product, we want to evaluate it rigorously and understand what's working, what's not, and why. That mindset is incredibly valuable. At the same time, when it comes to our role in data science, I believe statisticians should be at the core, but not necessarily the sole leaders. Instead, we should view ourselves as co-leaders. It's like a center with two directors – one is a statistician, the other is a computer scientist. Each brings a complementary perspective, and together they provide joint leadership.

I've worked with a variety of people, including scientists and social scientists. Often, they come to me and say, "Xiao-Li, I don't need you to teach me the basics of statistics. I can handle that myself, and my students can too. What I really need from you is to help me understand when not to use certain methods. What are their limitations, and when can they be dangerous?" That's the usual thing that takes the most statistical insight.

So, one important role we can certainly play is by reviewing what's already been done, which is what I'm currently exploring with large language models. I'm trying to identify areas where people struggle, and as statisticians, we can step in to offer solutions. We don't always need to invent new methods. Sometimes, it's about applying what we already know. For example, Bayesian thinking and uncertainty quantification are core to our training – and they are certainly not new - but they may not be as familiar to those focused purely on algorithms.

I've seen people try to use a kind of pseudo-Bayesian approach. They know they need to combine prior information with data, but the way they do it by averaging, for instance, can be very problematic. As statisticians, we would look at that and say, "Wait, that's not the right way to do it." There's a whole framework like Bayes' Theorem that they might not be using properly. We know how to propagate and combine information in a more robust way.

So, I think statisticians can really help others save time by guiding them through these challenges, helping them avoid pitfalls, and applying proven methods to make their work more effective.

I believe there's one major area, one big direction, where we can now play an increasingly important role, and where people are more willing to listen to us. When we look at the current state of general AI and large language models, much of it is still driven by brute force. They are trained on massive datasets with enormous number of parameters, relying on extensive computing power and significant human labor. It's essentially a proof of concept that this kind of massive training and fitting approach can work.

But now, there's growing recognition that this brute-force method isn't sustainable. It consumes immense amounts of energy and resources. As a result, people start to ask - What's a better, more efficient way to make things more optimal?

That's where statistical thinking, especially Bayesian thinking, becomes essential. It's like the difference between doing targeted probabilistic calculations and running endless simulations. If you had infinite resources, you could simulate everything and hope to find the right answer. But in practice, that's inefficient. Instead, we can use theoretical calculation and probabilistic reasoning to narrow down the space to focus on what's most likely and avoid wasting time and energy on the improbable.

I think one good example we statisticians should reflect on is the DeepSeek model. Remember how shocked the market was - how could it perform so well with seemingly so little? To me, that wasn't surprising. The success wasn't necessarily about doing more with less - it was about doing better with thought. Prior approaches relied heavily on brute force: massive datasets, huge parameter spaces, and enormous computational resources. That kind of race tends to incentivize massive experimentations than deep contemplation.

When you have enough resources, you tend to rely on brute-force methods—running all kinds of powerful simulations. But then someone steps in and says, "Wait, we can do this more efficiently." And suddenly, you achieve substantial gains, not by scaling up, but by thinking differently. Now, what we're seeing is a shift. With the global race among companies and nations, people who understand models more deeply, who can reason about structure, penalization, trade-offs, etc, are becoming increasingly more valuable.

And this is where theoretical thinking matters. Not necessarily mathematical in the formal sense, but conceptual. As statisticians, we understand ideas like the bias-variance tradeoff. We know you can't minimize both simultaneously, so we don't waste time chasing the impossible. But someone without that training

might spend ages experimenting, only to arrive at that realization the hard way. We can help shorten that learning curve.

But to be effective, we need to speak their language, literally and conceptually. Otherwise, we'll be sharing valuable insights that no one can apply because they don't understand the framing. That's why I really appreciate seeing students today diving into machine learning. When they come back to classical statistics, they often realize ---Oh, this is just a formalization of what we've been doing intuitively. That connection is powerful.

I believe there's so much more we can contribute than we often realize. But to do so, we need to adapt. For example, I've been telling my department not to spend an entire semester teaching linear regression. There's so much more we could be teaching that it would better prepare students for the real-world challenges.

Xun CHEN: There are a lot of great points. I have several questions I'd love to discuss with you further.

Your insights on the value of statistical thinking truly resonated with me. **Could you elaborate on how statisticians can leverage such unique training and experience to distinguish themselves at work?**

Xiao-Li MENG: Let me give you a very concrete example which I may talk about during my visit to Maryland in September. There's a major area in machine learning known as 'divide and conquer' or, more generally, distributed learning. The idea is straightforward - when you have too much data to process at once, you break it into smaller chunks, analyze each part separately, and then combine the results.

Now, here's where the difference between deep statistical thinking and treating something as just an algorithm becomes evident. Many practitioners simply average the results from the different subsets. But a statistician, trained in concepts like likelihood and sufficiency, would immediately recognize the potential pitfalls of that approach. Averaging estimators can lead to a terrible, biased result. This has been seen in distributed regression to run regressions separately, average them, and you end up with a highly biased estimator.

A statistician would say: "Wait, you're combining the wrong things." Instead of averaging the estimators, you should be combining the sufficient statistics, like the cross-product terms in regression (i.e., the numerator and the denominator of the slope estimator). If you aggregate those, and then compute the estimator, you get the same result as if you had fit the full model on the entire dataset. Same computation, but much more efficient and statistically sound.

This is the power of statistical thinking. I've seen machine learning researchers go to great lengths to prove theoretically how to combine estimators, when in reality, the principle of sufficiency, something every statistician learns early on, already provides the answer. The concept of sufficiency may be a little foreign to some in the machine learning community, but it's not beyond their reach. They can learn it if we teach them. The issue is, we haven't been teaching it in a way that connects with the way they work or think.

Statistics has always been about extracting as much insight as possible from limited data. Historically, we didn't have the luxury of big data. That constraint forced us to think deeply and develop powerful, efficient methods. This is actually our strength. Imagine if computer science had been developed long before statistics - everything might have been brute-force computation, with little incentive to think critically about information and efficiency.

Now, ironically, even as we deal with massive datasets, the need for careful, efficient thinking is resurfacing. Companies are realizing how costly brute-force approaches are after investing heavily in building their data centers. Now, tools like DeepSeek are showing real promise, revealing just how much more we can achieve. As we face deeper and more complex problems, we're starting to lose clarity and even information. That's where statisticians can and should step in, because we know how to extract meaningful insights, even from limited or very noisy data.

But here's the challenge: when results are driven by brute-force methods, and shiny products are produced quickly, people assume that's where the value lies. They don't always see how inefficient or wasteful the process was. As the cost of data processing becomes more visible, people are beginning to ask, 'Can we do better?' That's our opportunity. We need to show that we have tools and thinking that can lead to more efficient and interpretable solutions.

However, it's not just about claiming territory. If we come in simply to say, 'This is our territory,' it will backfire. We need to collaborate in a way that adds

value. That's the hard part. People naturally ask, 'Why do we need statisticians? They don't build products.' But the truth is, we can make those products better, smarter, and more efficient. We just need to approach it with humility, clarity, and a spirit of partnership.

Xun Chen: The power of statistical thinking! That's truly fascinating, Xiao-Li. In practice, we know, however, it's not uncommon for statisticians with advanced degrees — those who excel in exams and complex problem-solving— to struggle with grasping the broader context and deeper implications of statistical thinking. I used to be one of them. It took me years at work to develop the ability of deeper, intuitive statistical thinking.

What do you believe to be the true value of additional years of advanced statistical training? Specifically, what knowledge and skills should students pursuing a Ph.D. in statistics consciously develop and enhance?

Xiao-Li MENG: You've pinpointed something very important, and I'd like to respond just as concretely. To me, the key difference between a master's degree and a PhD is this: at the master's level, you acquire practical skills and learn how to do things; with a PhD, of course you also learn how to do things, but more importantly, you learn why we do them, and when we shouldn't.

If you think about it in terms of business value from a startup's perspective - a Master can help you build a product and get something off the ground. A PhD, assuming they also have practical skills (and that's important - there's a common criticism that some PhDs focus too much on theory and not enough on application), can help make that product optimal and competitive.

Anyone can create something these days, whether it's using ChatGPT or building an app. But what makes one solution better than another? That's where deeper thinking and analytical rigor come in. That's the value a PhD can bring to elevate something from functional to exceptional.

And when I talk about being competitive, I mean more than just technical excellence. This is why I believe we need to think about data science very broadly. It's not just statistics or computer science. It also includes understanding people, communication, marketing and operations. Building something is just the start - developing it, deploying it, and making it impactful require a broader set of skills.

So if I had to put it in concrete terms – a Masters gets you started and a PhD helps you to optimize.

Lately, I've been reflecting on the broader landscape of General AI. Computer scientists have done an impressive job initiating the field, including demonstrating the possibilities, inspiring innovation, and getting society genuinely excited. As we move toward the next level of development, I believe we, as statisticians, should be co-pilots in this journey.

When you look closely at the deep thinking happening in computer science and machine learning, you'll find that much of it is grounded in statistical and probabilistic reasoning. These researchers may not always call it statistics, but they're using many of the core ideas we've developed by applying through their own lens. They have a key advantage: by starting with implementation, they quickly realized the need for optimization and deeper theoretical grounding. In doing so, they've become eager students of what we already know.

In contrast, statisticians often begin from a different place. We focus on understanding how to do things before we actually build them. While this gives us depth, it can put us at a disadvantage position when it comes to implementation, especially in areas like managing large-scale databases or deploying models at scale. Many of us, even or especially with strong theoretical training, lack hands-on experience in handling massive datasets or infrastructure-level work. That's where collaboration becomes essential.

We need stronger communication and partnerships with computer scientists. Realistically, when top-level AI researchers need help, they're unlikely to turn to entry-level statisticians or master's graduates for basic tasks, because those are skills computer scientists often possess themselves and may even execute more efficiently. But when they encounter deep statistical challenges - questions that require critical thinking, modeling expertise, and theoretical insight - that's where PhD-level statisticians can and should step in, at exactly the level where they add the most value.

Xun CHEN: You are spot on again, Xiao-Li. In today's rapidly evolving landscape, merely knowing how to apply statistical methods is no longer sufficient. With the proliferation of alternative digital tools and quantitative methodologies, and the continual emergence

of new ones, it's essential to move beyond traditional practices. Adhering to statistical methods solely out of tradition or regulatory mandates will not succeed. Statisticians in academia, industry, and regulatory bodies should collaborate to proactively advocate for the core value of statistical thinking and embrace new data sources and methodologies, ensuring that statistical insights remain integral and complementary within the broader data science ecosystem.

I remember a paper you featured early on in HDSR, comparing predictive models and inferential models (https://hdsr.mitpress.mit.edu/pub/a7gxkn0a/release/7). That duality is key. We need to help the broader community understand that it's not either/or. On the one hand, we must embrace the usefulness of black-box models when they perform well. On the other hand, we need to stay vigilant about the risks they pose and develop strategies to mitigate those risks.

So rather than waiting for something to go wrong and then fixing it, how can we more proactively navigate the advancement of science and technology?

Xiao-Li MENG: Yeah, that's a great question. I think there's an easy answer and a hard one.

The easy answer is humans are actually very good at using black boxes. We do it all the time. I use my computer every day without really understanding how all the hardware works. Most people drive cars without knowing exactly how the engine functions and that's fine, because we know enough not to do anything reckless. We don't pour water on a laptop. We don't put gasoline in the wrong part of the car. So, at a broad level, black boxes themselves aren't the issue. People often feel threatened by them, which I understand, I have my own concerns, but we shouldn't have fear for them just because we don't understand every part.

What we should be cautious about is the scale and speed at which these black-box systems can operate, especially things like general AI. In daily life, we learn through trial and error. You misuse an appliance, it might cost you money or cause a minor injury, but you learn from the experience. However, with powerful AI systems, we often don't get a second chance. Mistakes can happen instantly, at massive scale, and with consequences we can't reverse. That's the real risk.

So how do we address that? I think we need to take a cue from the lab sciences. Anyone who's worked in a chemistry or biology lab knows that one must follow strict safety protocols. Most of the time, those measures might seem excessive, but they exist to prevent rare, potentially catastrophic events. Over time, this becomes part of the lab culture. We need a similar cultural shift in how we handle large-scale, high-impact technology. That's where statisticians have a critical role to play in ensuring due diligence. We should be embedded in the process as quality control experts, not just after the fact, but from the beginning. I was once invited by the U.S. Census Bureau to serve as a quality control expert. At first, I thought I've never done anything like that. But then I realized that they were right about the role I can play. They've got economists building the models, but they need a Statistician to evaluate whether what they're doing is legitimate.

In fact, as we build powerful systems, we should also build defense systems in parallel. It's like developing missile technology. If you build offensive capabilities, you must also develop anti-missile defense systems. Otherwise, you're vulnerable. That same logic applies here. Alongside building black-box tools, we need to build counter-tools, mechanisms to detect, audit, interpret, and safeguard.

Statisticians are uniquely positioned for this. We bring more insight than simply relying on brute-force trial and error. We are the professionals entrusted with the role to do quantitative thinking with variations. Variability is not just noise, it's where information lives. Unfortunately, we're often viewed only as the people who talk about uncertainty, which gives us an image problem. People think of us as the ones who raise doubts and create complications.

But in reality, we are information experts. We understand signals and noises. We think about everything together, including how data behave, how to extract meaning, and how to build robust systems. Sadly, much of the credit for 'signal processing' has gone to engineers. The 'product building' is credited to computer scientists. And statisticians are seen as the ones who slow things down by worrying about uncertainty. That's a false narrative.

Our role should be present in all those areas - signal, noise, and everything in between -they're fundamentally part of our domain. So, I believe one

of our key responsibilities is not only helping to build the product, but also to build the counter-product alongside it.

This also brings us back to the issue of training. It may not be realistic to expect single individual to master everything. That's why I've always been cautious about the idea of defining data science as a single, standalone discipline, and building a department of data science, as I wrote in the inaugural editorial for HDSR, I don't think that model reflects the complexity of the field. Even within statistics, expecting a PhD student to be trained to do everything, from deep theory to full-stack implementation, isn't always feasible.

What this really points to is the need for building strong, interdisciplinary teams. A company, for example, should hire a mix of people: PhDs in statistics, master's-level statisticians, computer scientists, and others with complementary skills. But don't place them into separate teams. Instead, put them on the same team. Let them work together, build a language, and develop mutual understanding. That's how we learn from one another.

To me, that's what data science is all about - not everyone doing everything, but people with deep expertise in one area who also have working knowledge across others, all brought together by a shared focus on solving real problems by learning from data.

If a company wants to grow data science capability, I'd actually recommend not starting by hiring people just because they're labeled 'Data Scientists.' Often, they may not have the breadth or depth you expect. Instead, hire people with clearly defined, strong skill set in specific areas - statistics, computer science, domain knowledge - and form a unified team around real problems. Let them build and grow together.

Whether or not you call them 'Data Scientists' doesn't matter. What you'll have is a true data science team and that's far more powerful.

Xun CHEN: Yes, that's a great point. I've been thinking we might benefit from building a more hybrid talent pool. It could be valuable to bring together a mix of backgrounds, PhDs, master's-level professionals, and people with training in statistics, data science, and related fields. That diversity could really strengthen the team.

Xiao-Li MENG: Right, and really building a true data science team.

Xun CHEN: Exactly. Now that you've mentioned co-leadership, I'm curious about how this works in academia. In industry, for statisticians to stand out on a cross-disciplinary team, communication skills, the ability to influence, and the capacity to collaborate effectively are just as important as technical skills.

Does this shift in thinking imply something different for those pursuing academic careers, or are they still bound by the traditional tenure track expectations, where publishing papers is the primary focus?

Xiao-Li MENG: Right! You've touched on something really crucial and genuinely difficult. This issue has a long history. In academia, especially in the mathematical sciences, which includes people like me, we've been trained, valued, and rewarded based on our individual contributions. We're not typically trained or incentivized to think in terms of contributions to a team. That's a deep, systemic challenge, because the reward structures haven't evolved to support collaborative work.

One of the biggest challenges in promoting people was evaluating their contributions in massive, team-based projects. In our traditional model, especially in fields like Mathematics, papers are often single-authored or have just a few co-authors. We're not used to seeing names on papers with hundreds of contributors, like in physics where some publications list a thousand authors. So how do you assess individual value in that context? It really calls for a fundamental shift in academic culture.

But I do think that shift is already happening, especially when I look at my own students. Fifteen years ago, almost all my students would've followed a path similar to mine to become professors. They weren't thinking about industry. But today, the majority go into industry. That tells me something important that students are signaling that the landscape is changing.

When they go into industry, they're not expecting recognition in the form of academic fame. They're not thinking, "This is going to be Xiao-Li's paper" or "This product will have my name on it." Instead, the

reward systems are different. Of course, compensation is a factor obviously, but so is the opportunity to work on complex, high-impact problems. The mindset is entirely different.

I was just talking with the President of a French university this morning. He was visiting us to discuss AI. I told him, "You're in a position to make real change." Society now sees how much value and power the Tech industry can generate. Traditionally, major scientific and technological advances started in universities and were later translated into industry. But that's no longer the case. Deep learning, for instance, has largely emerged from industry, because academia simply can't compete on that scale. We don't have the data, the computational resources, or even the manpower.

So what we need now is a new kind of entity - a hybrid model that brings together the strengths of both academia and industry. Industry brings speed, scale, and resources. Academia brings rigor, deep thinking, and a vast knowledge base. There's so much potential in that kind of partnership. Maybe it's a think tank, maybe it's a new research institute, but it has to be something new, built for this era, where both sides contribute as equal partners.

And this is exactly where we're starting to train the next generation. In the end, the concept of a traditional degree will probably continue to exist, but I wouldn't be surprised if we eventually see the emergence of entirely new kinds of degrees. Right now, we have academic degrees like PhDs, as well as a range of professional degrees. But perhaps there should be a new kind of recognition, something that signals not just depth in a field, but a broader, integrative knowledge across disciplines.

We've been talking for years about interdisciplinary and multidisciplinary training. Some now use the term transdisciplinary. But I think we're heading toward something even more transformative, not just combining disciplines, but organizing around problems rather than fields.

Take climate change, for example. It's a massive, complex issue that spans science, technology, policy, economics, ethics, etc. And it's becoming increasingly political. You could imagine building an entire educational and research structure focused on that one grand challenge. Students, faculty, and professionals wouldn't be organized by department or discipline, but by the shared goal of solving that specific problem. It would be more than a think tank. It would be an action tank, with structure, collaboration, and implementation all built in.

The way we currently structure knowledge, whether in industry or academia, reflects an old model of division of labor, which made sense historically. But today, the increasing need for integration suggests that model no longer serves us well. We may be headed toward a reorganization by not just bringing disciplines together to create new disciplines but going beyond that. A model where disciplines dissolve into new ways of thinking and doing.

I don't know exactly what form this will take, but I believe it's already happening organically. What's emerging may be more fundamental than just merging fields - it's about reshaping how we define knowledge, contribution, and collaboration. That's the big picture I'm currently seeing.

Xun CHEN: That's really great, Xiao-Li. I'll summarize the key points you shared today and let's see how the discussion evolves in the next round.

Xiao-Li MENG: Absolutely, I'd love to work with you on this. Once you have a summary, please send it to me. I'd love to build on these notes and develop ideas further. There's a lot to learn here. What I aim is to bring in different voices. That way, we're not just sharing ideas, moreover we're gathering reactions and building momentum.

Xun CHEN: Fantastic! Thank you, Xiao-Li!

THE EVOLVING ROLE OF STATISTICIANS IN REGULATORY SCIENCE

Meijuan Li (Incyte)

Highlights

- Statisticians in Regulatory Science: Evolving from Technical Experts to Strategic Contributors
- Embracing Innovation: Regulatory Acceptance of Innovative Methods
- Cross-Sector Collaboration: A Catalyst for Innovation

Meijuan Li
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1. Introduction

In recent years, the role of statisticians in the pharmaceutical and biomedical fields has undergone a transformative shift. Traditionally responsible for designing clinical trials and performing data analyses, statisticians are now recognized as pivotal contributors to strategic planning, methodological innovation, and regulatory communication. This evolution reflects a response to the increasing complexity of drug development, the demand for innovative and efficient clinical trial designs, and the need for regulatory frameworks to evolve in parallel with scientific advancements.

2. From Technical Experts to Strategic Contributors

Statistical science has long underpinned clinical development, but its influence has broadened considerably. Statisticians are now involved earlier and more extensively in the drug development process, contributing to key elements such as the selection of clinical endpoints and the definition of estimands, in accordance with the International Council for Harmonisation (ICH) E9(R1) guidelines on estimands and sensitivity analyses [1]. Their role now extends well beyond traditional statistical analysis. Statisticians are at the forefront of designing and implementing innovative trial methodologies [2][3], including:

- Bayesian methods, which incorporate prior knowledge to enhance flexibility in decision-making.
- Adaptive designs, which allow for pre-specified interim modifications without compromising trial integrity.
- Synthetic and external control arms, which leverage real-world data (RWD) to augment or replace traditional control groups.
- Master protocols, which enable simultaneous investigation of multiple therapies or indications within a unified framework.
- Dose optimization strategies, which are aimed at identifying the most effective and safe dosing regimens through model-based or adaptive approaches.

These approaches not only enhance trial efficiency and minimize patient risk but also support the increasing emphasis on personalized, patient-centric drug development.

Statisticians are increasingly active participants in regulatory interactions, including FDA Type B and C meetings, EMA Scientific Advice sessions, and negotiations around drug labeling. Their responsibilities include defending statistical methodologies, interpreting interim and exploratory findings, and navigating benefit-risk assessments. Clear and persuasive communication of complex statistical concepts is vital; not only to meet regulatory expectations but also to align cross-functional stakeholders in clinical, regulatory, and commercial domains [4].

3. Regulatory Acceptance of Innovative Methods

Regulatory agencies have responded to the need for more flexible and patient-centered approaches by endorsing complex and adaptive trial methodologies. Key initiatives include FDA's Complex Innovative Trial Designs (CID) Pilot Program, Real-World Evidence (RWE) Framework, and Model-Informed Drug Development (MIDD) Program [5]. These frameworks provide statisticians with opportunities to implement and validate novel methods under formal regulatory oversight. Successfully navigating these pathways requires not only technical acumen but also the ability to communicate assumptions, limitations, and justifications in regulatory language.

4. Cross-Sector Collaboration: A Catalyst for Innovation

The increasing complexity of clinical research has encouraged robust collaboration between industry, regulators, and academia. These partnerships foster methodological innovation and accelerate the development of consensus-driven standards. Notable examples include Clinical Trials Transformation Initiative (CTTI), Innovative Medicines Initiative (IMI), and International Council for Harmonisation [1]. Statisticians act not only as analysts, but also as architects of standards, shaping the use of adaptive designs, RWE, and decentralized clinical trials.

5. Conclusion

The role of statisticians in regulatory science is more pivotal than ever. As the pharmaceutical landscape becomes increasingly intricate, statisticians are not merely adapting, and they are leading. Through expanded technical expertise, deeper engagement with regulators, and active collaboration across sectors, statisticians are poised to drive meaningful innovation while preserving scientific integrity throughout the lifecycle of clinical development.

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THE FUTURE OF STATISTICIANS IN THE PHARMACEUTICAL INDUSTRY: FROM DATA ANALYSTS TO STRATEGIC PARTNERS

Yannis Jemiai

Highlights

- **From Analysts to Strategists**: Statisticians now shape drug development strategy, not just support trials.
- **Driving Innovation:** They lead in real-world evidence, digital biomarkers, adaptive designs, and AI validation.
- **Regulatory & Precision Medicine Impact:** Statisticians are shaping guidelines and enabling personalized medicine while ensuring equity.
- **Future Skills & Outlook:** Strong programming, business acumen, and cross-functional collaboration will make statisticians indispensable as demand grows.

Yannis Jemiai

Introduction: The Evolving Landscape

Not long ago, pharmaceutical statisticians were considered technical experts who supported the conduct of clinical trials by ensuring proper randomization, calculating power and sample size, and producing the statistical analyses required for regulatory submissions. Consequential decisions about how to derisk clinical development and move assets forward were left to clinical and commercial teams.

Today, that narrow definition feels antiquated. Throughout the industry, statisticians are increasingly asked to participate in or even frame decision-making, shaping drug development strategies from the earliest stages of discovery through clinical regulatory and reimbursement hurdles and into post-market surveillance. They're not just analyzing data; they're helping to define what data should be collected, how trials should be designed to answer the team's questions, how to even ask the right questions, and presently, how artificial intelligence (AI) can be responsibly integrated into the drug development process.

This transformation reflects broader changes reshaping the pharmaceutical landscape. The explosion of real-world data, the integration of AI and machine learning, the push toward personalized medicine, and evolving regulatory expectations have created both unprecedented opportunities and complex challenges. Statisticians, with their unique combination of mathematical rigor and deep understanding of clinical research, are uniquely positioned to navigate this new terrain.

The Expanding Statistical Universe in Drug Development

Beyond Clinical Trials: New Frontiers

The traditional boundaries of pharmaceutical statistics are rapidly dissolving. While randomized controlled trials remain the gold standard for regulatory approval, statisticians are now working across a much broader spectrum of evidence generation. Real-world evidence (RWE) has emerged as a critical component of drug development, requiring statisticians to develop and apply new methodologies for analyzing observational data that can complement or augment traditional clinical trial findings.

Digital biomarkers represent another frontier where statisticians are pioneering new approaches. As wearable

devices, smartphone apps, and remote monitoring technologies generate continuous streams of patient data, statisticians are developing frameworks to extract meaningful clinical insights from these novel data sources. This work requires not only statistical innovation but also close collaboration with clinicians to ensure that digital endpoints truly capture patient experiences and outcomes.

Clinical operations have long been focused on strategies to boost site activation and trial enrollment followed by thorough monitoring practices to ensure site performance and data quality. Only in recent years have statisticians been recruited to integrate operational data sources and apply advanced modeling and optimization methods to detect signals and accurately forecast performance.

From Protocol to Strategy

Perhaps most significantly, statisticians are increasingly involved in strategic decision-making throughout the drug development lifecycle. During early phases of development, they're helping to design experiments that maximize the information content of limited resources. In program and portfolio management, they're developing probabilistic models that help executives decide which compounds to advance and which to terminate.

This strategic role extends to regulatory interactions, where statisticians are becoming key ambassadors between pharmaceutical companies and regulatory agencies. They're not just implementing regulatory requirements but actively participating in the development of new guidelines and standards. Their deep understanding of both statistical principles and regulatory expectations makes them invaluable in navigating the complex landscape of drug approval.

The AI Revolution: Collaboration, Not Competition

Statisticians as AI Validators

The rise of artificial intelligence in pharmaceutical research has generated significant discussion about the future role of statisticians. Rather than being displaced by AI, statisticians are emerging as essential partners in ensuring that AI systems are reliable, interpretable, and compliant with regulatory standards. They have an important role to play in developing validation frameworks that can assess the performance of machine learning models across different use cases.

This validation role is particularly critical in a regulated industry where the stakes of algorithmic bias or model failure are measured in patient lives. Statisticians bring a unique perspective to AI development, understanding both the mathematical foundations of machine learning and the clinical context in which these tools will be applied. They're helping to bridge the gap between data science innovation and regulatory acceptance.

Enhanced Analytical Capabilities

AI is also dramatically expanding the analytical capabilities available to statisticians. Machine learning algorithms can identify patterns in complex datasets that would be impossible to detect using traditional statistical methods. Statisticians have continuously looked to integrate these tools into their workflows, but the necessity of doing so is accelerating.

Predictive modeling has become particularly powerful when AI and traditional statistics are combined. Statisticians are developing hybrid approaches that leverage the pattern recognition capabilities of machine learning while maintaining the interpretability and uncertainty quantification that regulators and clinicians require.

Navigating the Data Deluge

Big Data Challenges

The pharmaceutical industry is experiencing an unprecedented explosion of data. Genomics studies now routinely generate terabytes of information, electronic health records contain detailed longitudinal patient histories, and wearable devices provide continuous monitoring of physiological parameters. This data richness creates enormous opportunities but also significant challenges for statisticians.

Traditional statistical methods, designed for smaller, more structured datasets, often struggle with the scale and complexity of modern pharmaceutical data. Statisticians are developing new approaches that can handle high-dimensional data while maintaining sta-

tistical rigor. They're also grappling with issues of data quality, integration, and privacy that are fundamental to responsible data use in healthcare.

Methodological Innovation

The complexity of modern pharmaceutical data has driven significant methodological innovation. Causal inference methods are becoming essential tools for statisticians working with observational data or looking to combine real-world data with clinical data. These methods help distinguish correlation from causation in situations where randomization isn't possible.

Federated learning approaches are gaining traction as a way to analyze data across multiple institutions without compromising patient privacy. Statisticians are being called to develop protocols that allow for collaborative analysis while ensuring that sensitive patient information never leaves its original location. This work is particularly important for rare disease research, where patient populations are distributed across multiple centers.

Adaptive trial designs continue to represent another area of innovation, allowing trials to modify their approach based on accumulating data. Adjusting sample size, modifying treatment arms, or even changing the study population while maintaining statistical validity is almost commonplace. More sophisticated methods – master protocols, Bayesian information-borrowing, and ML-driven designs – are among the latest approaches that promise to significantly reduce the time and cost of drug development while potentially improving patient outcomes.

Regulatory Evolution and Statistical Leadership

Shaping New Guidelines

Regulatory agencies worldwide are recognizing the need to modernize their approaches to drug evaluation. The FDA's embrace of innovative trial designs, including Bayesian designs, master protocols and platform trials, has created new opportunities for statisticians to influence regulatory thinking. Many of the agency's recent guidance on topics like real-world evidence and digital health technologies have been developed with significant input from pharmaceutical statisticians.

This regulatory evolution is creating a feedback loop where statisticians are not just implementing regulatory requirements but actively shaping them. By demonstrating the value of new statistical approaches through successful regulatory submissions, they're helping to establish new standards that benefit the entire industry. This influence extends beyond individual companies to industry-wide initiatives aimed at improving the efficiency and effectiveness of drug development.

Strategic Regulatory Partnerships

The relationship between pharmaceutical statisticians and regulatory agencies has become increasingly collaborative. Rather than the traditional adversarial model where companies submit analyses and regulators evaluate them, there's a growing trend toward early engagement and ongoing dialogue. Statisticians are playing a key role in these interactions, helping to align company strategies with regulatory expectations.

This collaborative approach is particularly important in emerging areas like personalized medicine and AI-driven drug development, where regulatory precedents are still being established. Statisticians who can effectively communicate both the potential benefits and limitations of new approaches are becoming invaluable assets to their organizations.

The Personalized Medicine Challenge

Statistical Complexities

The shift toward personalized medicine presents both enormous opportunities and significant challenges for pharmaceutical statisticians. Traditional clinical trials, designed to demonstrate efficacy in broad patient populations, are increasingly inadequate for evaluating treatments that may only work in specific patient subgroups. Statisticians are developing new approaches to biomarker-driven trial designs that can efficiently identify the patients most likely to benefit from a particular treatment.

Subgroup identification and validation represent particular challenges. With the ability to stratify patients based on genetic, molecular, or other biomarkers, the number of potential subgroups can quickly become overwhelming. Statisticians are developing sophisticated methods to identify clinically meaningful subgroups while controlling for multiple testing and ensuring that findings are reproducible.

Precision Healthcare Implementation

The translation of personalized medicine from research to clinical practice presents unique statistical challenges. Population-level predictions, the traditional focus of clinical trials, may not translate directly to individual patient care. Statisticians are developing frameworks for assessing the clinical utility of personalized treatments that go beyond traditional efficacy measures.

Health disparities and equity considerations are becoming increasingly important in personalized medicine. Statisticians are working to ensure that the benefits of precision healthcare are available to all patient populations, not just those who have been historically well-represented in clinical trials. This work requires careful attention to issues of generalizability and external validity.

Skills for the Future Statistician

Technical Evolution

The technical skills required for pharmaceutical statisticians are rapidly evolving. Programming proficiency, once optional, is now essential. Statisticians must be comfortable working with multiple programming languages and platforms, from traditional statistical software like SAS and R to more general-purpose tools like Python and SQL. Cloud computing platforms are becoming increasingly important as the computational demands of statistical algorithms increase dramatically and as companies move toward distributed computing environments.

Data visualization and communication skills are becoming as important as analytical capabilities. Statisticians must be able to translate complex statistical findings into clear, actionable insights for diverse audiences. This requires not only technical skills but also a deep understanding of how different stakeholders consume and use statistical information.

Strategic Competencies

Beyond technical skills, future pharmaceutical statisticians will need to develop strong business acumen. Understanding the commercial implications of statistical decisions is becoming increasingly important as statisticians take on more strategic roles. This includes knowledge of healthcare economics, market access considerations, and competitive dynamics.

Regulatory knowledge remains crucial, but it's no longer sufficient to simply understand current requirements. Statisticians must stay ahead of regulatory trends and participate in shaping future guidelines. This requires ongoing engagement with regulatory agencies, professional organizations, and industry working groups.

Cross-functional collaboration skills are perhaps most important of all. Modern drug development is inherently multidisciplinary, requiring close collaboration between statisticians, clinicians, regulatory experts, data scientists, and commercial teams. Statisticians who can effectively communicate across these different domains and contribute to integrated decision-making will be most successful.

Conclusion: The Statistical Advantage

Value Proposition

The future of pharmaceutical statistics is bright, but it will require adaptation and growth. Statisticians who thrive in this new environment will be those who can combine rigorous analytical skills with strategic thinking, regulatory knowledge, and strong communication abilities. They will be the bridge between innovation and implementation.

The unique value proposition of pharmaceutical statisticians lies in their ability to provide both technical expertise and strategic insight. While data scientists may be able to build sophisticated models and clinicians may understand patient needs, statisticians bring a unique combination of mathematical rigor, regulatory knowledge, and clinical understanding that is essential for successful drug development.

Future Outlook

The demand for skilled pharmaceutical statisticians is only expected to grow as the industry continues to evolve. The increasing complexity of drug development, the regulatory focus on evidence-based decision making, and the integration of new technologies all create opportunities for statisticians to contribute value. Those who embrace this evolution and develop the skills needed for the future will find themselves at the center of some of the most important work in modern medicine.

A MULTIDISCIPLINARY APPROACH FOR DEVELOPING TWO BESPOKE AI TOOLS TO SUPPORT REGULATORY ACTIVITIES WITHIN THE MHRA CLINICAL TRIALS UNIT

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Highlights

- Clinical trials are complex for several reasons, including scientific, regulatory, logistical, and ethical challenges.
- We have identified an opportunity to develop two bespoke AI-driven solutions to support regulatory assessments of clinical trials.
- The creation of these AI tools will support the assessment of the clinical trials, improving efficiency, accuracy, and consistency, during the analysis of the large volume of data, providing greater transparency, regulatory confidence and public trust.
- This paper presents the journey we went through with an incredible mix of extremely talented people, from the conceptualisation stage to the creation of two AI tools that the MHRA Clinical Trials Unit will utilise.

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1. Introduction

1.1 The Importance of Clinical Trials

Clinical trials are systematic research studies conducted in humans to evaluate the safety, efficacy, and optimal use of medicines and healthcare products. They represent a critical step in the development of evidence-based medicine, providing the rigorous data necessary to support regulatory approval and inform clinical practice. By adhering to predefined protocols and ethical standards, clinical trials help ensure that new treatments are both safe and effective before they are widely adopted. They are essential in advancing medical knowledge, protecting patient health, and maintaining public trust in healthcare systems.

1.2 The Assessment Process – Current Challenges and Future Demands

Clinical trials are generally regarded as the gold standard for evidence-based medicine, supported by a complex set of timelines and dependencies in the clinical development of medicines from discovery to authorisation.

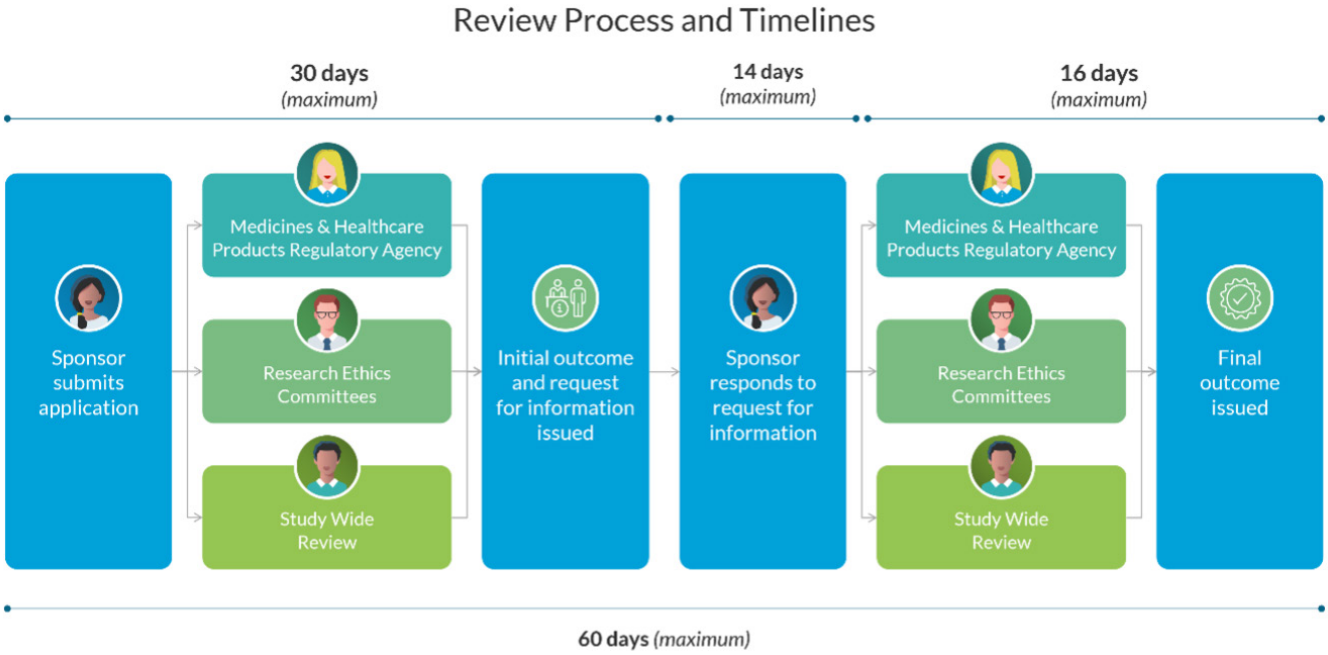
Sponsor organisations that submit applications to obtain authorisation to conduct clinical trials often face significant time pressures, driven by the benefits of being first to market and the imperative to improve patient outcomes through promising treatments keeping patient safety as the main priority. Clinical development can range from 5 to 20 years, with typical timescales of 10 to 15 years1.

Over the last five years (since the start of the pandemic), the median clinical development time for

innovative medicines for infectious diseases has been estimated at approximately 7.3 years, from first use in humans to market authorisation. This is supported by innovative new approaches to planning and conducting trials (e.g. adaptive protocol designs and decentralised trials).

Medicines regulators recognise the need for reliability and consistency in the assessment timelines for Clinical Trial Authorisation (CTA) to facilitate innovation. Last year, more than 5,000 applications were assessed by the UK's Medicines and Healthcare products Regulatory Agency (MHRA) Clinical Trials Unit. The work required to assess these applications is very time-consuming, and with the rise in adaptive and complex innovative clinical trial design, assessment times are set to increase further. Typically, assessment involves extensive re-reading of complex documentation to extract key information, reviewing responses to requests for information (RFIs), and cross-checking statements and justifications by subject matter experts. This process must occur within tight timescales, involving multiple organisations and stakeholders, as shown in Figure 1 below.

Figure 1 – Overview of the CT application process



Data from the MHRA indicates that most initial clinical trial applications will trigger questions from assessors - formally known as grounds for non-acceptance (GNAs), which sponsors must address before trial approval can be granted. This highlights a significant opportunity for assessors to provide scientific advice that could improve the quality of CTA applications. However, assessment teams currently spend much of their time reviewing these applications, many of which are not approved due to common GNAs, as well as meeting other demands across the Clinical Investigation and Trials (CIT) division.

This situation is expected to be compounded by new regulations coming into effect on 28th April 2026, which will shift critical time pressures away from sponsors and onto the regulator. In response, the MHRA needs to scale the capabilities of the CIT division, building the necessary capacity and flexibility to assess significantly greater volumes of work within demanding timescales, without compromising quality, ensuring patient safety as its priority.

1.3 The potential for AI

As quoted from the summary letter by Lord Darzi to the Secretary of State for Health and Social Care on 15th November 2024: "There is enormous potential in AI (Artificial Intelligence)2 to transform care and for life sciences breakthroughs to create new treatments". Since the popularisation of personalised AI, such as ChatGPT, in 20223, all stakeholders are looking to rapidly develop their own AI in various applications. Stakeholders have applied AI in many areas4,5 such as the process of drug discovery, predicting safety and efficacy, trial design, and recruitment and retention6.

The MHRA has adopted an innovative, industry-leading approach to exploring the potential of AI in a

responsible and risk-proportionate manner, which aligns with the MHRA Data Strategy published in September 20247. In 2024, MHRA's CIT division identified several potential partners to help develop an AI capability to support clinical trial assessments. However, initial discussions identified that the AI providers engaged did not understand the specific needs of MHRA's regulatory team, and existing tools didn't address the breadth and depth of MHRA's requirement or have proven capability working at scale in safety-critical environments.

Seeking a more collaborative approach, MHRA partnered with Informed Solutions, an organisation that provided a combination of AI expertise, User-Centred Design approaches and experience working with deep subject matter experts to deploy AI in demanding regulatory environments. The focus of the partnership was to deliver AI solutions to meet MHRA's specific regulatory needs.

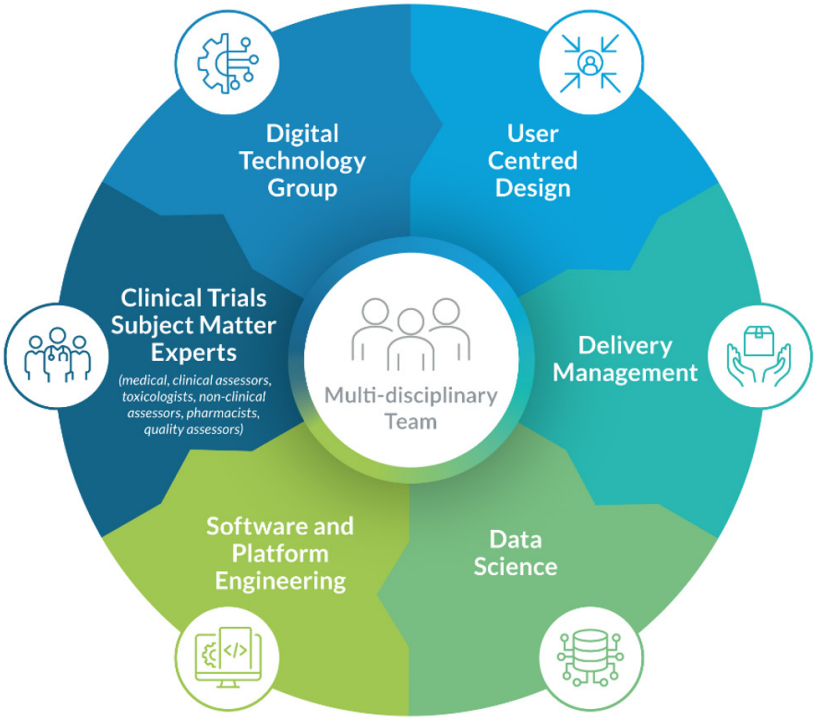
This paper outlines the recent work delivered by MHRA in partnership with Informed Solutions, which aimed to develop and deploy AI-enabled tools to support clinical trial assessors in managing increasing pressures, including higher workloads and shorter response times for CTAs. Informed Solutions applied a novel AI Readiness Assessment method to build a deep understanding of how MHRA's assessors work, mapping the data available and assessing its suitability for use by different AI techniques.

This approach rapidly developed an evidence-based view of how AI could be deployed responsibly to meet the needs of assessors and MHRA's wider business requirements. At critical milestones, key decisions on which potential solutions to prioritise were based on targeted proof-of-value exercises and insights from user research, maximising the return on investment that could be delivered within the limited time and funding available, resulting in the successful design, development and deployment of two novel AI-enabled tools to support the CIT division.

2. Methods

To deliver targeted AI innovation in a responsible manner, we drew upon a diverse team of experts from both MHRA and Informed Solutions. The MHRA contributed clinical trial subject matter expertise, as well as software engineering and architecture capabilities from their Digital Technology Group (DTG). These capabilities were complemented by Informed Solutions' strengths in software engineering, technical architecture, data science, delivery management and user-centred design skills. Together, this multi-disciplinary team (Figure 2) was able to rapidly identify and qualify opportunities for AI enablement and translate them into operational digital solutions.

Figure 2 – Key areas of expertise in the multi-disciplinary team



This work aimed to improve regulatory effectiveness by addressing four key domains: people, data, technology, and business. We assessed each domain to understand the existing landscape and develop targeted interventions to improve productivity, consistency and satisfaction, as set out below:

- The people domain focused on the tasks completed by expert clinical trials assessors, the pain points in their workflows, and maximising end-user value.
- The data domain assessed the quality, availability, governance structures, and compliance requirements of the data assets involved in clinical trial submissions, assessments and associated regulatory documents.
- The technology domain reviewed infrastructure capabilities, scalability, integration with existing systems, and security needs.
- The business domain explored practical AI solutions that could support decision-making, streamline processes and workflows, improve assessment consistency and boost user satisfaction.

We organised project delivery into two phases: discovery and productisation. The discovery phase built a strong, cross-domain understanding and pinpointed the most valuable opportunities for intervention. Then, the productisation phase applied a user-centred, iterative approach to turn those opportunities into operational solutions, securing user buy-in and keeping business value at the forefront of design.

2.1 Discovery Phase

During the discovery phase, our goal was to gain a comprehensive understanding of MHRA's clinical trial authorisation processes, data and technology landscape. To support this, we conducted an AI readiness assessment of the CTA process. This assessment unpacked the ambitions of the MHRA and developed our understanding of readiness across the four aforementioned domains.

We placed user-centred design at the heart of the discovery phase, drawing on extensive user research and business analysis. Working with key stakeholders, we mapped processes and pain points through targeted workshops, which revealed essential insights into workflows, roles, and interdependencies within the CTA process (Figure 3). We documented operational challenges, trust factors, and business priorities, alongside potential benefits, to inform solution design.

Figure 3 – A user-centred design approach to inform design of the Knowledge Hub

At the same time, our team probed the CTA process to gain a thorough understanding of the data involved across workflows. We clarified the scope, quality and structure of critical data assets, including CTA documents, internal guidance, and historical responses. In parallel, we unpacked existing data governance procedures to understand their structure. Given the regulatory environment and safety-critical nature of CTA, we paid particular attention to commercial and intellectual property, personally identifiable information, and compliance requirements.

Building on our understanding of the user and business contexts, we shifted focus to technical exploration and the evaluation of suitable AI techniques. This included the use of text embeddings for topic modelling (Figure 4) and natural language processing methods to identify patterns in regulatory documents. Specifically, we used text embeddings to analyse GNAs across both structural and

semantic dimensions. We also examined common CTA documents, including protocols, investigator brochures (IB), application forms, and good manufacturing practice (GMP) certificates. This analysis ultimately confirmed the suitability of existing data holdings to support process improvement and automation in live operations.

At the conclusion of our analysis, we identified a range of viable options utilising AI techniques, including intelligent document processing, predictive analytics, and generative AI. Engagement with clinical trial assessors helped us determine which options offered the most value and which were unlikely to be feasible within MHRA's operational constraints, timelines, and budget. We quickly ruled out fully generative approaches: the trial authorisation process requires critical scrutiny of detailed documents, and even the most advanced large language models (LLMs) cannot be relied on to generate accurate information consistently. We also found that predicting nuanced, context-specific GNAs in a fully automated way exceeded the scope of this initial project.

As we eliminated some options, others stood out as candidate deliverables to take forward to productisation. Specifically, we identified three solutions to develop into proofs-of-concept: data-driven guidance to trial sponsors, intelligent GNA search using natural language queries, and automating the validation of GMP compliance.

2.1.1 Data-driven Guidance for Trial Sponsors

Our first solution aimed to reduce rejections and delays in the CTA process by providing more insight into GNAs. We achieved this by converting free-text GNAs into text embeddings8, a modern natural language understanding technique pioneered by the transformer architecture9. Once transformed into this embedding vector space, GNAs were clustered into topics (Figure 4). The topics with many members and coherent themes were selected for further analysis. Our team then developed these candidates into updated guidance that is provided to sponsors ahead of the CTA process. This data-driven approach helped to aligned guidance with the most common issues prompting GNAs.

2.1.2 Intelligent GNA Search using Natural Language Queries

Our second solution addressed a common task in trial assessment: reviewing the rationale, structure, and language of GNAs raised in previous applications. A fundamental requirement for the MHRA is to provide consistency in trial assessment. This means that any two GNAs raised for the same reason should have uniform rationale and language. To achieve this, trial assessors must often spend significant time locating and reviewing historical GNAs to understand best practice and precedent.

Identifying and reviewing historical GNAs is a manual, time-consuming activity, complicated by multiple information sources. These can include tacit internal knowledge, business records and unstructured documentation spread across systems. To address this, we developed a domain-aware query tool which enables assessors to interrogate previously raised GNAs using natural language.

This tool is underpinned by the same text embedding methodology10 used to cluster the GNAs in topic analysis. First, GNAs are converted into fixed-length vector representations using an embedding model. These vectors are then stored in a vector database, which is optimised for vector comparison. This means an assessor can submit a query in plain language to the search engine, which is then converted into the same fixed-length vector representation as the GNAs already in the database. This query vector is then compared against the database to retrieve GNA vectors which are most similar. The results are inverted back to plain text using the embedding model and presented to assessors in a convenient interface we call the Knowledge Hub.

2.1.3 Automating the Validation of Good Manufacturing Practice Compliance

Our last solution streamlines the essential but laborious task of GMP validation. Any investigational medicinal product (IMP) or placebo being used in a clinical trial must satisfy the standards of good manufacturing practice. Sponsors submit relevant documentation with their application, which the MHRA must then validate. Verifying this information involves examination of manufacturing declarations made by the sponsors, which must be validated against the sites and activities approved by regulators.

To improve this process, our solution automates both the document review and verification processes using a set of fusion models that combine text and computer vision neural networks11. We fine-tuned these models by example, training them to extract the specific GMP content required for verification. In the case that our fine-tuned models fail to extract the required content, a

large language model is used to parse the text directly and return the desired content.

We then built a verification algorithm that matches the content extracted from application documents with regulatory certificates, proving that a given site is certified for GMP. This verification result is presented, alongside a confidence score, back to assessors for review in a tool we call the GMP Compliance Checker. This human-in-the-loop layer is essential and ensures that expert assessors are the decision makers.

2.2 Productisation Phase

To bring practical value to the clinical trials team, we converted each of our proofs-of-concept into production services. To scale up the GNA search and GMP validation solutions, we focussed on reliability and designed practical, repeatable workflows. These solutions were optimised for rapid processing, consistent performance, and effective management of the extensive historical GNA and GMP datasets.

Another key factor in moving from technical proofs-of-concept to production-grade solutions was ensuring effective user experience (UX). This involved designing intuitive interfaces that integrated seamlessly into assessors' day-to-day work to improve productivity. Our user-centred design experts developed and iterated designs based on UX best practices. We validated these designs through operational testing and refined them using evidence-based feedback to ensure they met user needs, business requirements and operational constraints.

To be deployed into the MHRA's live environment, each solution needed to meet DTG's technical, security, governance and architecture standards. During the productisation phase, we worked closely with DTG experts to assure technical design, complete formal testing, and conduct independent security reviews. Each solution was deployed in a secure, isolated environment using strict role-based access controls (RBAC), so that only clinical trial assessors could access data and service outputs. This approached maintained compliance with data protection and intellectual property requirements, reinforcing the trustworthiness of all solutions.

Overall, our methodology embedded AI-driven enhancements effectively within clinical trial authorisation process, combining technical innovation with user-centred design and responsible data practices. It was structured to uphold ethical standards, protect sensitive data and support assessors in working more productively ultimately contributing to a more effective and resilient regulatory process.

3. Results

Before the end of 2024, the CIT division, in collaboration with Informed Solutions, concluded a proof-of-concept study to support the assessors in their CTA activities. This study resulted in updated guidance to trial sponsors and the creation of two AI-enabled software solutions, which are presented below. These products were selected for initial development based on their potential to rapidly deliver return on investment and ability to build trust with end-users.

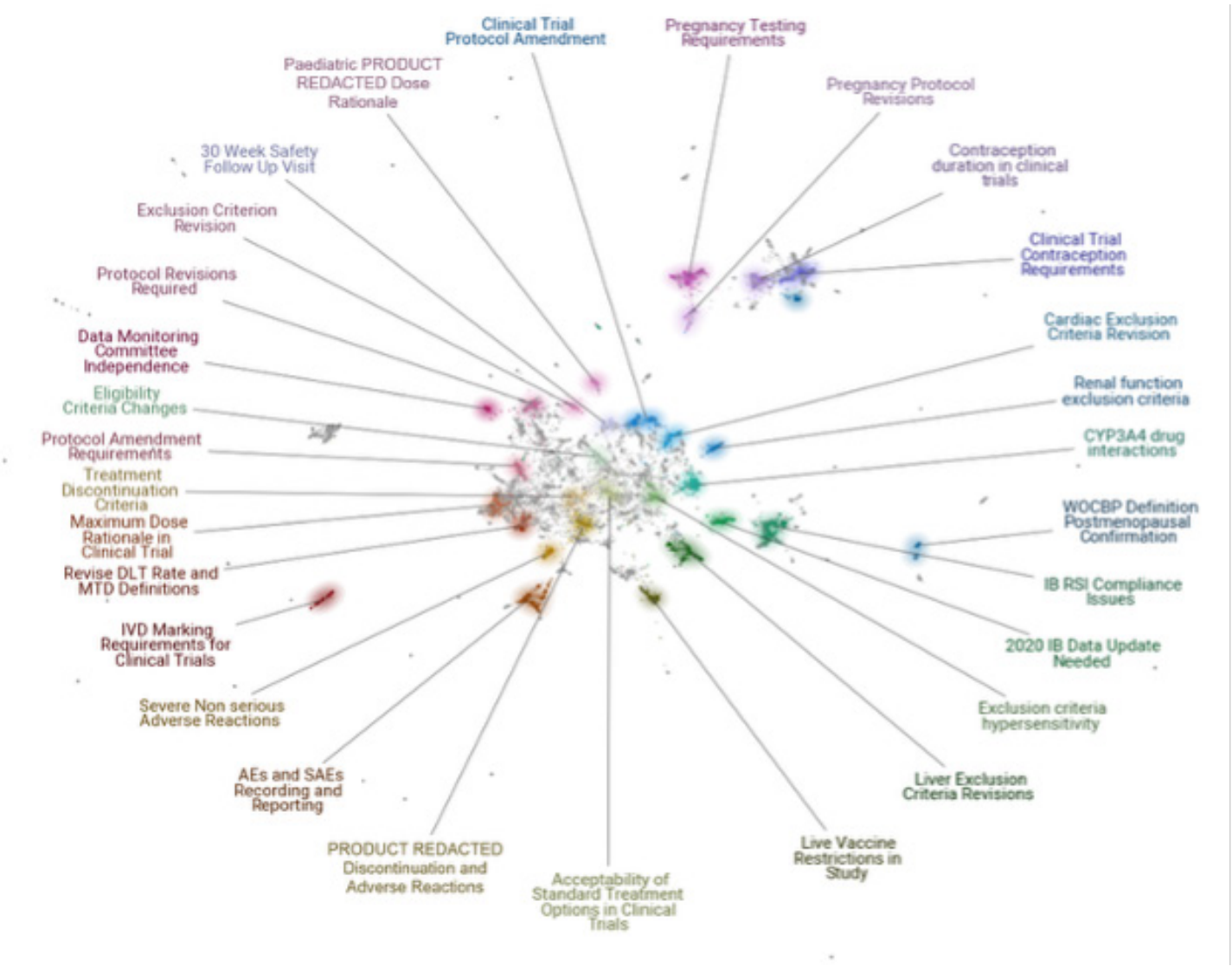
Our approach demonstrated that, with the correct method and expertise, it was possible to design, develop, and deploy an AI solution into a clinical trials environment. Moreover, our solution complied with DTG standards, considered all user needs, and delivered measurable improvements and efficiencies to the process. A user-centred design approach was central to this success. It helped build trust and confidence in the tools and supported adoption, dispelling the myths that AI is challenging for users and difficult to scale beyond proof-of-concept.

3.1 Data-driven Sponsor Guidance from Topic Modelling

During the discovery phase, topic modelling was initially used as an analytical tool to understand the nature of GNAs better. By evaluating its outputs, we identified two practical use-cases. The first informs the published sponsor guidance on common GNAs by deriving insights directly from the clustering of GNAs into topics. This approach enhances the existing, experience-based guidance with concrete, data-driven insights.

During this exercise of topic modelling, the CIT division took advantage of the opportunity to review the 110,000+ GNAs and compare them with the current website guidance (Common issues identified during clinical trial applications - GOV.UK). It confirmed that the majority of common issues listed were the same, thus validating the information. In addition, it highlighted several common issues not identified before. These are now being drafted for the next update to this MHRA webpage. This demonstrates the research benefits of developing AI, leading to a quantitative review and an enhancement of existing systems.

Figure 4 – GNAs embedded as vectors, clustered into similar groups, summarised into topics and projected into two dimensions for visualisation



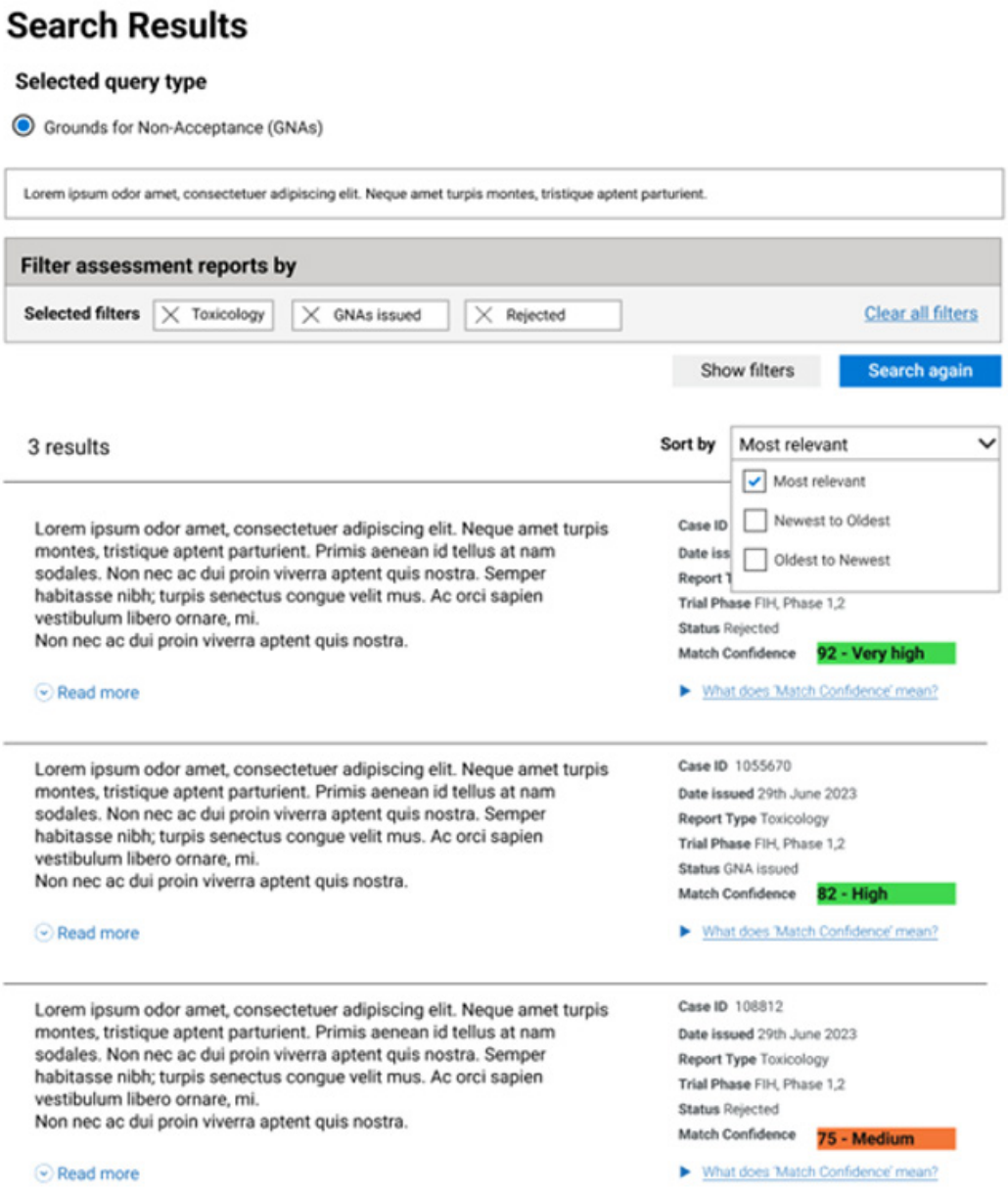
3.2 Knowledge Hub: Enhancing CTA Efficiency and Consistency

Assessors at the MHRA currently face challenges in efficiently accessing historical GNAs and prior clinical trial case data. This stems from the limited search functionality across existing records, which can delay decision-making and reduce consistency across assessments.

To address this, we developed our second use-case derived from the topic modelling work: a Knowledge Hub of historical application data, which represents our first AI tool. This idea emerged from recognising that the text embedding process used in topic modelling had standalone value. It encoded the structure and meaning of regulatory text, making it easily searchable. The resulting Knowledge Hub is a centralised, queryable database of historical GNAs and assessment reports from closed clinical trial applications.

The Knowledge Hub gives assessors access to actionable historical context, strengthening the quality, consistency, and replicability of regulatory oversight. By improving how prior decisions can be surfaced and referenced, it supports more informed and efficient clinical trial assessments. In providing an intuitive and efficient interface (Figure 5) the service offers an entirely new pathway for assessors to access and understand historical information.

Figure 5 – Knowledge Hub smart search results page; real data is not shown for data protection purposes

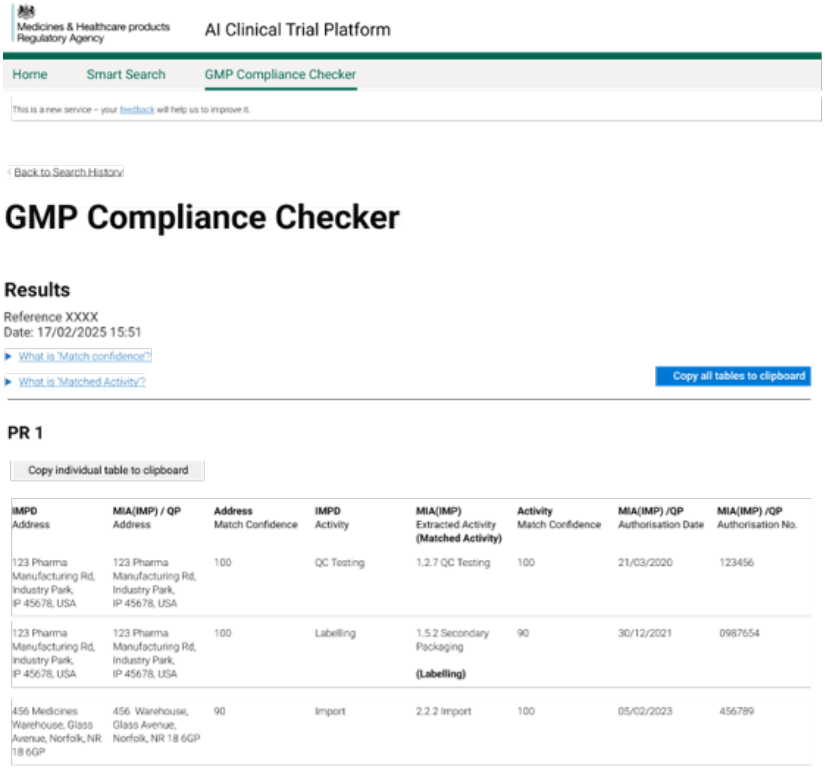


3.3 GMP Compliance Checker

As part of the CTA process, sponsors must submit mandatory documents detailing the manufacture of any investigational medicinal products (IMPs) included in the trial. These documents include both the sites involved in the manufacturing process and the activities each site has been approved for by regulators. Previously, pharmaceutical assessors at the MHRA had to manually review these documents to ensure compliance before authorisation of a trial.

With the introduction of our second tool, the GMP Compliance Checker, this verification process is streamlined. Instead of manually reviewing and cross-referencing what can be dozens of documents, assessors now submit the relevant documents to this solution. Our fine-tuned deep neural networks review and extract the relevant GMP information and collate it into a review interface (Figure 6).

Figure 6 – GMP Compliance Checker output page; real data is not shown for data protection purposes



The value of this tool is evident in a reduction of up to 60-fold in the time required for GMP validation. For human review, the time taken to verify GMP compliance scales with the number of IMPs involved in the trial, as each one requires manufacturing declarations. The GMP Compliance Checker dramatically reduces the time needed to validate each of these, meaning that efficiency gains scale proportionally to the number of documents needing review.

For a conventional trial application with numerous IMPs, the manual verification process can take up to two hours. Benchmark results from development of the GMP Compliance Checker indicate our automated solution can complete this verification step in less than 60 seconds, equating to more than 99% time-savings. This speed up allows assessors to concentrate their efforts on reviewing the results of the solution, reducing errors and improving consistency.

4. Discussion

The process of clinical trial authorisation requires attention to detail, deep subject-matter expertise, and the methodical application of regulations. These traits do not immediately seem to favour AI technologies, which are stochastic by design. Yet we have demonstrated that there are opportunities for AI to be applied judiciously, offering gains in productivity, consistency and satisfaction for the assessors charged with ensuring that new treatments are safe and effective.

Effectively introducing AI technologies to the CIT division required strict adherence to the governance procedures of the MHRA. Any solution also had to fit into the existing technology landscape and respect the organisation's security and data protection requirements. Critically, the needs of end-users had to be at the centre of design and development to ensure an effective solution with buy-in from users. All these factors mandated a multi-disciplinary team of clinical trial experts, user-centred designers, software developers, data scientists, and project managers to deliver valuable outcomes.

The new Knowledge Hub unlocks the value of years of experience and expertise by consolidating data into a shared tool that uses AI to organise and surface the most relevant information to experts. This allows experts to progress more quickly with cases and supports the upskilling of assessors by giving them access to a greater volume of high-quality knowledge. Our multidisciplinary team approach ensured that we developed effective products,

with buy-in from stakeholders and users (CIT team & the wider MHRA DTG). By focusing effort on what could realistically be delivered within the available time and budget, we maximised value and de-risked productization. This allowed us to progress beyond the proof-of-concept stage, where many initiatives stall.

Initial estimates indicate savings of up to 180 full-time equivalent (FTE) days per year in the clinical trial assessments. By rapidly realising these efficiencies, assessors can redirect time away from search activities to higher-value tasks, such as providing upstream advice to sponsors. In turn, this strengthens sponsors' applications, ultimately making them safer and faster to approve.

To address increasing case volumes and time-critical pressures at the MHRA, it was necessary to scale capability and adopt innovative, risk-controlled, user-centred AI approaches12. This did not come without challenges. For example, access to secure sandbox environments was initially limited, but MHRA's organisation-wide commitment to innovation allowed us to leverage investments in secure and prototype environments. Another challenge was restricted access to data: sourcing datasets and obtaining approvals took significant time, impeding some proof-of-concept work. Leadership support was critical in overcoming this barrier, by providing assurance and direction across teams. This leadership was also instrumental in overcoming domain and technical challenges, by providing backing to make use of the latest techniques and technologies[1].

4.1 Benefits of the two AI tools

Improved Efficiency: Rapid access to relevant historical decisions, reducing time spent searching fragmented records.

Consistency in Decision-Making: Aligns with past regulatory decisions to support harmonised and transparent assessments.

Enhanced Confidence: Equips assessors with data-driven insights to strengthen evaluations of new applications. This supports faster access to life-saving treatments, reinforces regulatory confidence, and demonstrates responsible AI design.

Skills Development: Accelerates the learning and development of new assessors by giving them immediate access to years of accumulated expertise.

Staff Satisfaction: Reduces repetitive manual work (e.g. GMP Compliance Checker), enabling highly skilled experts to focus on higher-value tasks.

Streamlined review: Increases efficiency in the review and approval process, cutting lead times, reducing costs and errors—for example, GMP assessment times were reduced from 120-180 minutes to under 5 minutes (a 95% efficiency gain).

4.2 Testimonials

> *"From an end user perspective, being involved in the development of AI required users to really focus on what tools would be beneficial to the assessment of clinical trial applications and how these could be applied."*

> *"We were able to collaborate with colleagues, across various disciplines, to identify processes/tools that would be helpful, and we were also heavily involved in the visual layout of the applications and performed extensive user end testing."*

> *"This allowed us to gain first-hand experience and provide feedback on the functions that worked well and others that still required development, which is critical to ensure end user functionality."*

4.3 Lessons Learned

This project was able to build trust with end-users through a heavily user-centred approach, leveraging AI in the most controlled and effective way to enable them to complete their tasks. A collaborative, multidisciplinary team approach allowed AI and Data Science skills transfer to MHRA staff, supplemented by the creation of written guidance and learning materials. The project ignited a passion for innovation within the CT team and across MHRA engineering and architecture (who were key enablers in achieving project success) and the desire to continue innovating.

4.4 Implications of The Knowledge Hub and GMP Compliance Checker for Future Practice, Policy and Research

Examining the Knowledge Hub specifically, we find a new tool that enables assessors to query the back catalogue of historical GNAs more quickly and easily. This empowers

[1]The rapid pace of AI research meant many of the most relevant advances were available only on arXiv, a moderated but non–peer-reviewed repository of research. While this limited the ability to cite recent peer-reviewed studies, the project's priority was on practical implementation and delivering a production-ready solution rather than academic publication.

assessors with actionable context, strengthening the quality and consistency of MHRA's regulatory oversight in clinical trials. The Hub serves as an indexed library of GNAs, continuously refreshed with new decisions. In doing so, it refines the consistency and reliability of new GNAs generated by assessors and may also support the development of case studies. This approach supports the standardisation of GNAs, ensuring that assessors adhere to a uniform review structure across all applications. It also provides structured guidance for issuing common GNAs, enhancing both consistency and replicability. Furthermore, regular updates offer ongoing training for both new and experienced assessors, allowing them to incorporate cutting-edge information more seamlessly into their assessments.

The GMP compliance checker represents a fundamental shift in the time required to validate GMP compliance. Compliance with GMP in clinical trials is crucial for ensuring the safety, quality, and integrity of investigational medicinal products (IMPs) used in human research. It minimises the risks of contamination, variability between batches, degradation or instability of active ingredients. This has a significant impact on regulatory activities because non-compliance may lead to a clinical trial hold or suspension, and eventually rejection of trial data, or legal or financial penalties.

Against this backdrop, the GMP compliance checker delivers significant value. By streamlining and structuring the validation procedure, it reinforces consistency in assessment while freeing up valuable expert time. Seen through this lens, we believe it could support the assessment of multi-centre or multi-national trials, which are extremely important because they can harmonise quality expectations across different countries, facilitate the import and export of IMPs, and increase stakeholder trust. If the results show promise, they might also impact the commercialisation of drugs. Additionally, GMP-compliant manufacturing further simplifies scaling to commercial production, reducing the need for re-validation and supporting faster global regulatory approval.

Our approach accelerated productisation by prioritising pathways that delivered the greatest value for the MHRA most quickly. Users were engaged throughout development, ensuring their needs were met at each stage of development and inspiring the CT team with a vision of what future AI solutions could achieve. The success of this project has built trust in new technology and established a roadmap for delivering further value through a collaborative, user-centred approach.

The outcomes of this project also have wider applicability. By enabling experts to access relevant information quickly and easily, the solutions developed here demonstrate how AI can support informed, timely decision-making across domains. This may help other regulators seeking to introduce AI into their processes. We have demonstrated that workflows that require greater consistency, or knowledge-intensive domains where experts spend substantial time reviewing complex, unstructured documentation stand to benefit.

5. Conclusion

This project led the teams through a challenging yet rewarding journey. The MHRA Clinical Trials Unit began by identifying a crucial problem: the need for assistance. Next, we searched for off-the-shelf products, only to realise that none were available. The collaboration between the DTG and the engineering team allowed us to unite additional groups, including assessors and external AI experts. This partnership transformed the work dynamic, fostering a shared purpose and enabling us to create customised tools that were not available on the market. The development of these two tools marks the beginning of a technological revolution that prioritises the individual, with technology designed to support and enhance our efficiency. We are establishing a new environment with a strong focus on patient safety, driven by the passion of our teams and integrated with AI technology. This innovative approach is creating an engaging regulatory framework that will facilitate the safe development and testing of new medications that have the potential to save lives.

This work has been conducted in full compliance with MHRA policy and governance, including assurance by the MHRA CIT team, as well as the MHRA DTG, and has been moved to live operation. The approach successfully identified products that would add the most value, doing so in a manner that built buy-in from expert end-users throughout. Also provided a forward view of other opportunities for adding value, which MHRA will pursue to benefit sponsors with topic model guidance directly.

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Conflict of Interest

There are no perceived or actual Conflicts of Interest relating to this work.

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THE ROLE OF LIPCOM IN ELEVATING LEADERSHIP IN STATISTICS

Petite Claude on behalf of the Leadership in Practice Committee (LiPCom)

The Leadership in Practice Committee (LiPCom) was introduced in the ASA BIOP Fall newsletter in 2022. To recap, LiPCom' s purpose is to serve as a bridge between BIOP and the broader ASA, drive efforts to establish, promote and maintain BIOP leadership development programs, and collaborate with other BIOP committees in raising visibility on mentor/mentee engagements across BIOP. It was formally established by the following founding members:

- Abie Ekangaki (Premier Research, Past Chair 2020)
- Lisa Lupinacci (Merck & Company, Past Chair 2021)
- Rakhi Kilaru (PPD, Past Chair 2022)
- Veronica Bubb (Altru Clinical Research, Past Chair 2023)
- Emily Butler (Prokidney)

Since then, LiPCom has expanded membership to include:

- Shanthi Sethuraman (Eli Lilly & Co.)
- Andy Chi (Takeda)
- Yabing Mai (Abbvie Inc., Chair-elect 2026)
- Claude Petit (Past Chair 2024)
- Vincent Tan (Vertex Pharmaceuticals)
- Hongwei Wang (Abbvie Inc.)
- Richard C. Zink (JMP Statistical Discovery LLC, Chair 2025)

What is the buzz around the concept of Leadership?

Leadership may seem like something unique or complex or something that is hard to achieve. Leadership starts from knowing and leading oneself and this can be done at any point of one's growth. Sometimes it is as simple as knowing "what makes one tick and what ticks one off".

LiPCom's passion lies in the growth of statisticians, data scientists, statistical analysts to be influencers, inspirers, and change agents through practical examples and real-world scenarios. In 2024, at select ASA chapter events, LiPCom focused on a leadership presentation series for three critical pillars of Leadership: leading oneself, leading others, and leading an organization. These concepts can be applied to any scientific discipline.

'Leading Oneself' is defined as the practice of intentionally influencing one's thinking, feelings, and actions towards having a meaningful, sustainable impact on people and in your profession.

The presentation emphasized the importance of self-awareness, understanding one's strengths, weaknesses, emotional reactions, and how others perceive you. It also talked about emotional intelligence.

"Leading others" starts with the very premise that it is a privilege and not a right. It is about empowering scientists to unleash their fullest potential, be it technical excellence, operational excellence and/or strategic excellence driven by a cause, by a purpose, and/or a belief that matters. Leading is about connecting with people, demonstrating care and authenticity, and creating a culture driven by trust, empathy and "radical candor."

These numerous activities were very successful, with great participation and renewed engagement from the broader statistical community.

In 2025, LiPCom proposes to expand this through continued standing workshops/panels at some ASA conferences like the Eastern North American Region (ENAR), Joint Statistical Meetings (JSM) or the Regulatory-In-Industry Statistics Workshop (RISW); hence the group started to reflect on the current perceived importance of leadership in statistics.

This year, the health industry experienced profound philosophical and technical changes. The mission, financial conditions and global mindset are being challenged at the FDA, in Academics and in the Pharma Industry. In addition, the emergence of artificial intelligence (AI) and machine learning (ML) has significantly reshaped the role and expectations of leadership.

The real question then becomes "Is statistical leadership still relevant or is it just a buzzword"?

Statistical Leadership in the era of ML/AI

In this fast-paced environment, most pharma companies and regulatory agencies are struggling to establish a clear AI strategy, not to mention a concrete implementation plan, and a culture change. In the age of AI and ML, the landscape of leadership is being redefined as high-tech AI products alone do not guarantee success, easy and quick adoption or productivity gain, Statistical leadership is more important than ever.

Continuously honing their technical skills, statisticians and data scientists are developing a profound understanding of AI and ML technologies, at the forefront of innovation. Combined with their unique skills of understanding, connecting and interpreting the data and their broad knowledge of drug development, their leadership role has become critical to:

1) Clarify AI's implication and ensure the company's success, as the C-suite may have an overly optimistic or unrealistic perspective on the benefits of AI
2) Design a customized and impactful AI map for the therapeutic area of interest or phase of development of the company's pipeline.
3) Be a change ambassador as the team members may push back due to fear of losing their job, lack of knowledge or miscommunication.

Statistical leaders have the opportunity to integrate AI and ML insights into strategic planning and decision-making processes to steer the organization towards data-driven success. By leveraging their knowledge of AI/ML and drug development, and their unique, profound understanding of data, they can further demonstrate leadership impacting trial designs, submission strategies, regulatory reviews and future guidance.

Leadership is an art which can always be perfected. Talking about leadership will ensure that statisticians and data scientists continue to be excellent communicators and undisputed collaborators all the while contributing to strategies and making an impact.

We are very interested in your opinion and your advice on how we can make statistical leadership more prominent at conferences. Please contact us at claude.petit2@att.net!

EVOLVING AND EMBRACING ML/AI AS A STATISTICIAN

Jingjing Chen (Takeda Pharmaceuticals)

Statisticians play a critical role at every stage of drug development from designing clinical trials, conducting data analysis, interpreting results to supporting regulatory submissions. More importantly, statisticians ensure the statistical rigor of the design and analysis, and help the team make informed and data-driven decisions.

Many may agree that the best statisticians are lifelong learners. As Herman Chernoff once noted "Years ago a statistician might have claimed that statistics deals with the processing of data…… to-days statistician will be more likely to say that statistics is concerned with decision making in the face of uncertainty." [1] It clearly shows that the field of statistics has never stopped evolving, from adaptive design, Bayesian methods, and estimands gaining popularity in the past decades to machine learning (ML) and artificial intelligence (AI) taking the center stage more recently. It naturally leads to a question: how can early-career statisticians position themselves for success in this ever-changing field, particularly in the new era of ML/AI? For those just starting this journey, I would encourage embracing a growth mindset, keep learning and keep evolving with the field.

- **Solid statistical training and a good understanding of regulatory guidance are the foundations.**

To excel in the pharmaceutical industry, early-career statisticians need a strong foundation of clinical trial design, modeling and simulations, and a good understanding of regulatory guidelines. With rapid development of ML/AL, statisticians now have more powerful tools than ever before. For example, ML can be leveraged to build predictive models for drug discovery, clinical outcome prediction, and patient identification. It can also help select high enrolling sites to accelerate trial recruitment. Additionally, many AI-assisted tools are available for use, particularly in AI-assisted literature review, programming, and meeting summaries.

While ML/AI offer exciting opportunities, foundational statistical thinking remains important. ML/AI models require careful statistical oversight to ensure they are correctly applied and yield meaningful results. I would not view ML/AI as a threat, nor underestimate their value. Instead, take ML/AI as a growth opportunity, experimenting with new AI-tools and looking for ways to apply them into daily work to gain efficiency. In fact, statisticians are needed more than ever to guide the appropriate and effective use of ML/AI technologies.

- **Strong communication skills are essential.**

Being a successful statistician also calls for strong communication skills, not only to explain complex statistical concepts with clarity but also to translate the data into meaningful narratives especially for non-statisticians. Effective storytelling with data would help greatly to build influence within the cross-functional team and help connect the dots between data and decision making. It becomes even more important when working with ML/AL, for instance, to interpret the "black box" nature of ML models.

- **Don't overlook the importance of operational excellence.**

Last but not least, don't overlook the importance of operational excellence, because our ultimate goal is to deliver safe and effective drug to patients. It is common for young statisticians to focus heavily on enhancing technical skills, but operational skills are equally important. Statisticians play a role in protecting data and study integrity, and overseeing the trial execution from data collection, database lock, unblinding management to risks monitoring.

In summary, the pharmaceutical industry offers an exciting career path for young statisticians that combines technical competency, effective communication, operational excellence, and cross-functional collaboration. The key to success goes to those who keep learning and aim to be a true partner in drug development.

Reference:

[1] Source: https://www.azquotes.com/author/42878-Herman_Chernoff

A LOOK BACK AT KEY TAKEAWAYS **FROM 8TH NONCLINICAL BIOSTATISTICS CONFERENCE: 2023**

Xin Huan (Abbvie), John Kolassa (Rutgers University)

The 2023 Nonclinical Biostatistics Conference took place from June 19-21, continuing a tradition of biennial gatherings since 2009. Organized by the ASA Biopharmaceutical Section's Nonclinical Working Group, the conference was co-chaired by Xin Huang (AbbVie Inc.) and John Kolassa (Rutgers). With 130 participants, the event featured a rich scientific program designed to foster discussion and collaboration in nonclinical biostatistics.

The conference opened with two engaging short courses: "Bayesian Methods for Nonclinical Statisticians" presented by Dr. Luwis Diya (Janssen) and Dr. Will Landau (Eli Lilly), and "Statistical Tolerance Intervals and Regions" by Dr. Thomas Mathew from UMBC.

Attendees benefited from a vibrant lineup of scientific presentations, including 12 invited talks, 27 contributed talks, and 11 poster sessions. These presentations spanned four key areas: Discovery/Biomarkers, Safety/Pharmacology, CMC, and Statistical Computing and Visualization.

Keynotes were delivered by distinguished speakers, including ASA President Dr. Madhumita (Bonnie) Ghosh Dastidar, who discussed the role of statistics in public policy with title "Statistics Is a Core Competency for Creating Effective Public Policy", and Dr. Ajaz S. Hussain, who emphasized statistical thinking in pharmaceutical professional development with title "Statistical Thinking and Pharmaceutical Professional Development for 21st-century Pharmaceutical Quality".

The conference also celebrated excellence in scholarly work by recognizing the top three nonclinical papers published over the years from 2021 to 2023.

- 1st Place: Faya P, et al. (2023) "Continuous Method Validation: Beyond One-Time Studies to Characterize Analytical Methods," Statistics in Biopharmaceutical Research.
- 2nd Place: Qiao, Z., et al. (2023) "Poisson hurdle model-based method for clustering microbiome features," Bioinformatics.
- 3rd Place: Mallick H, et al. (2021) "Multivariable association discovery in population-scale mIeta-omics studies," PLoS Comput Biol.

Additionally, graduate students were recognized for exceptional presentations:

- 1st Place: Yajie Duan (Rutgers University), "A Novel Two-stage Deming Regression Model with applications to Multiple Risks Assessment"
- 2nd Place: Sofia Prieto Leon (Hasselt University), "Covariate-driven dimensionality reduction methods for sc-RNA seq studies"

In addition, a special series of nonclinical biostatistics papers from NCB2023 are currently being published in the Journal of Biopharmaceutical Statistics:

[1] T. Zhang, B. Phillips, N. Karp, J. Wang, and S. Novick, "Whole-cage randomization for animal studies with unequal cage or group sizes," Journal of Biopharmaceutical Statistics, 2024. [2] W. Qiu, C. Wenren, T. Slavnic, E. Pattyn, and L. Essermeant, "An investigation to improve nonlinear mixed-effects approach for EC50 estimation based on multi-donor dose-response data," Journal of Biopharmaceutical Statistics, 2024.

[3] P. Faya, T. Zhang, S. Novick, and W. Walton, "Non-constant mean relative potency for antibody-dependent cellular cytotoxicity assays," Journal of Biopharmaceutical Statistics, 2024.

IISA 2025 ANNUAL CONFERENCE REPORT

JUNE 12–15, 2025 | UNIVERSITY OF NEBRASKA, LINCOLN

Hiya Banerjee (Eli Lilly)

The International Indian Statistical Association (IISA) held its flagship annual conference from June 12 to 15, 2025, at the University of Nebraska in Lincoln. This marked the second IISA conference in just six months and once again generated significant excitement and participation.

The conference brought together over 350 attendees from academia, industry, and government. The three-day program featured a variety of scientific activities, including keynote speeches, short courses, invited sessions, and student competitions in both paper and poster formats. The event aimed to highlight current developments and future directions in statistics, biostatistics, probability, artificial intelligence (AI), and machine learning.

Scientific Program Highlights

The scientific program was led by Dr. Bodhisattva Sen (Columbia University) with excellent support from Dr. Po-Ling Loh (Cambridge University) and Dr. Margaret Gamalo (Pfizer). Alongside a dedicated scientific committee, they designed a comprehensive agenda that showcased both foundational research and emerging trends in statistical science.

Key elements of the program included:

- Four keynote talks by distinguished scholars:
  - o Dr. Sourav Chatterjee (Stanford University)
  - o Dr. Linda Young (National Agricultural Statistical Service)
  - o Dr. Ryan J. Tibshirani (University of California, Berkeley)
  - o Dr. Debashis Ghosh (Colorado School of Public Health)
- Ten special invited presentations
- Around 80 invited sessions featuring top experts from diverse domains
- Two short courses aimed at graduate students and early-career researchers

This year's conference placed a strong emphasis on student engagement. Awards were given for outstanding student papers and posters, and the newly introduced STATBOWL competition provided a fun and interactive platform for students to test their statistical knowledge in a team-based format.

A special panel discussion titled "Women in Statistics: Breaking Barriers and Shaping the Future" was organized by the Committee on Women in Statistics (CWS). The panel brought together inspiring women leaders from across academia, industry, and government to share their experiences and insights.

IISA is grateful for the continued support from the National Science Foundation (NSF), which helped fund the participation of students and early-career researchers. Additional sponsors included Merck, Pfizer, Eli Lilly, the American Statistical Association (ASA), and the ASA Biopharmaceutical Section (ASA-BIOP).

Notably, the ASA Biopharmaceutical Section had a significant presence at the conference. IISA extends special thanks to ASA BIOP for their strong partnership and contribution to making this flagship event a success.

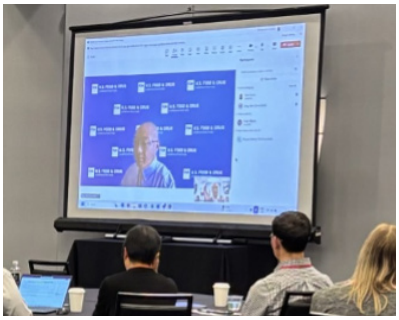
Looking Ahead

As always, IISA remains committed to advancing the statistical sciences while fostering community, collaboration, and inclusivity. The success of the 2025 conference reflects the organization's ongoing dedication to excellence and innovation in statistics and data science.

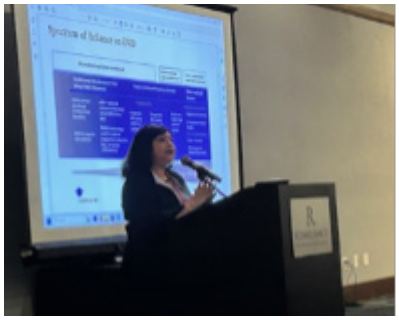
We are excited to announce that the IISA 2026 Annual Conference will be held in India, and we warmly invite you to join us next year for another enriching experience. Stay tuned for more details!

SOME REFLECTIONS FROM THE 48TH ANNUAL MIDWEST BIOPHARMACEUTICAL STATISTICS WORKSHOP (MBSW)

Melvin Munsaka (AbbVie)



Dr. Wen Zeng



Dr. Aloka Chakravarty

Dr. Abie Ekangaki

About MBSW

The 48th Annual Midwest Biopharmaceutical Statistics Workshop (MBSW) was held from the 19th to the 21st of May 2025 at the Renaissance Hotel in Carmel (Indianapolis), Indiana. The Workshop is co-sponsored by the ASA Biopharmaceutical Section. The 2025 workshop theme was Data and Beyond – A Deeper Dive. MBSW grew out of the Statistics Days Conference held at Ball State University in 1976. MBSW was co-founded by Dr. Charles B. Sampson and Dr. Mir Masoom Ali in 1978. MBSW, which was formally founded as a conference to meet the needs of U.S. pharmaceutical industry statisticians in the Midwest, welcomes attendees from across the United States and around the world.

Short Courses

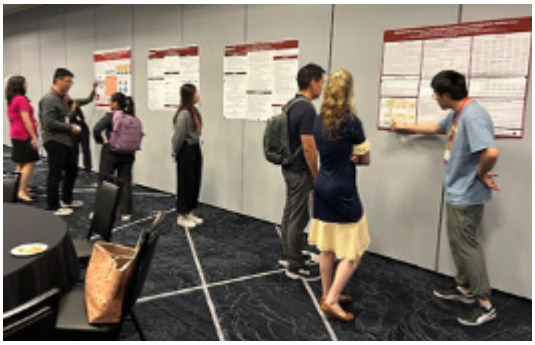
The 2025 workshop started off with two short courses on Monday morning. These included Causal inference and AI/ML in pharmaceutical statistics, by Dr. Yixin Fang (author of the book: Causal Inference in Pharmaceutical Statistics) from AbbVie and Hands-on Short Course on Enhancing the DMC Package Using Opensource Software, AI, and LLMs", by Dr. Melvin Munsaka, also from AbbVie.

Plenary Session

The short courses were followed by the Plenary Session on Monday afternoon which featured three speakers including Dr. Wen Zeng from the FDA who spoke on Immunobridging Approach for Recent COVID-19 Pre-exposure Prophylaxis (PrEP) EUA Application (virtual presentation), Dr. Aloka Chakravarty from Eli Lilly who discussed Clinical Data Insights and Advanced Analytics, and Dr. Abie Ekangaki from Premier Research who discussed Reshaping the Role of Statisticians in the Era of Evolving AI/ML Approaches in Clinical Trials.

Workshop Sessions

Between Tuesday and Wednesday, the workshop moved to its usual format of parallel tracks and sessions. The 2025 tracks included the Clinical, Real World Evidence and Health Technology Assessment, Chemical Manufacturing and Controls, Pre-clinical, Biomarker, and Discovery, Artificial Intelligence/Machine Learning, and Programming and Visualization.



Poster Session

Winner of the poster session

Dr. Lei Shen

Robert Rachford

The Clinical track included the following sessions: Applications of Simulation-Informed Trial Design, Advances in Statistical Methodologies for Dose Finding and Dose Response, and Borrowing Control Information from Historical Studies in Clinical Trials.

The Real World Evidence and Health Technology Assessment track sessions covered a variety of topics such as critical assessment of matching-adjusted indirect comparisons, decentralized clinical trials in the era of RWE generation, causal approaches for the design and long-term treatment effect estimations of hybrid randomized clinical trials, sensitivity analysis in driving real-world evidence from the analysis of real-world data, and leveraging large language models for rare disease named entity recognition.

The Chemical Manufacturing and Controls included sessions on Commercial Process and Quality and Advanced Nonlinear Modeling. Presentations included perspective on the use of Arrhenius model to predict drug shelf life, dissolution method specification risk assessment, and the role of acceptance sampling in pharmaceutical manufacturing to mention a few.

The Pre-clinical, Biomarker, and Discovery session included talks on robust multi-object tracking for home-cage behavioral phenotyping studies, robust multi-object tracking for home-cage behavioral phenotyping studies, additive Gaussian process models with applications in In Vivo digital biomarker studies, and harnessing artificial intelligence and large language models for discovery and preclinical science, and AI assistance for R session based data exploration and visualization.

Presentations in the artificial Intelligence/machine learning session included machine learning early warning system for diarrheal disease, knowledge extraction to facilitate phenotyping using drug records in real-world data, and bringing order to clinical data chaos with AI.

The Programming and Visualization included talks on interrogating data with a mouse, patient profiles, and open-source software in the analysis and reporting of clinical trials data.

Student Poster Session

MBSW also includes a dedicated Student Session with a focus on career development in the pharmaceutical industry and a student poster session. This year's posters included topics on decision-focused content selection from clinical notes, Bayesian optimal adaptive clinical trial design for integrated therapies, and multi-ancestry GWAS of neuroticism identifies novel

loci and enhances fine-mapping resolution, and estimation of heterogeneous causal mediation effects in the presence of high dimensional covariates. The Charlie Sampson poster award was given to Yining Li from Indiana University, Indianapolis for her work on "BIT: A Bayesian Optimal Adaptive Clinical Trial Design for Integrated Therapies."

Banquet Speakers

The Banquet speakers included Dr. Lei Shen from Eli Lilly and Robert Rachford, Founder, of Better Biostatistics who shared some insights on Biostatisticians in an AI-filled world: How to Ensure We Thrive in an Evolving Landscape.

This year's workshop was a great success as usual mainly due to the dedication and efforts of volunteers whose contributions were vital to the success of the workshop. They include, Cindy Wilson (Eli Lilly), Hongwei Wang (AbbVie), Bing Liu (Eli Lilly), Yanzhu Lin (Eli Lilly), Vipin Arora (Eli Lilly), David Manner (Eli Lilly), Melvin Munsaka (AbbVie), Ena Bromley (Oyanalytika), Yixin Fang (AbbVie), Richard Li (Eli Lilly), Jeff Gardner (DataPharm), Wanzhu Tu (IU-Indianapolis), Luna Sun (Eli Lilly). For additional details on the workshop, please visit the MBSW site online at: https://mbswonline.com.

MBSW would like to acknowledge the generous support for the workshop by Eli Lilly and Elsevier for providing student grants for students and academic participants.

LETTER FROM INTERNATIONAL BIOMETRIC SOCIETY

Peter Doherty, CAE, IBS Executive Director

Dear Members of the Biopharmaceutical Group,

First, I wish to share that the International Biometric Society sincerely appreciates your tangible support for the 500+ attendees who joined us in Atlanta for 100+ hours of education during the 2024 International Biometric Conference (IBC)! The conference was represented by attendees from 48 countries in 2024 and was a success in many respects!

I come to you with a message of hope and solidarity for 2025. Regardless of the challenges that we may have faced early in the year or the trials that lay ahead, remember that there are always positives that come with change (and interesting data sets, I suppose). It's how we meet these challenges and work together as a global community that will make a lasting difference.

The IBS remains committed to global collaboration and the sharing of perspectives and innovative techniques that serve our community and improve outcomes. As the BIOP group has shown, that collaboration can come in a variety of forms, to include conference support. And the Society itself continued to offer our support to attendees and the greater biometry community as 2025 began. You may not be aware that, due to travel and entry difficulties for some who had intended to join us in Atlanta, we continued to host IBC programming online following the conference and even into April! The conference has now formally concluded. Major award winners were announced during the IBC, including the Rob Kempton Award for Outstanding Contributions to the Development of Biometry in the Developing World, which was awarded to Girma Taye Aweke, of the Ethiopian Region, for his exceptional leadership and groundbreaking contributions to biometrics in Africa, inspiring future generations. Three of our members were recognized as new Honorary Life Members: Louise Ryan (Australasian Region), for fostering lasting connections between the Regions and the Society, and for promoting the advancement of women and future generations, Maria Grazia Valsecchi (Italian Region), for exceptional contributions to research in the field of medical statistics and her tireless dedication to advancing biostatistical research, and Geert Verbeke (Belgian Region), for scientific, educational, editorial, and administrative leadership to the biostatistics profession and to the International Biometric Society.

I thought it might be helpful to note BIOP-related content that was presented in Atlanta. Seven invited sessions were related to clinical trial analysis, innovative clinical trial design, (Bayesian) adaptive designs, and leveraging real-world data. There were also 27 oral sessions and six posters in clinical trials and related topics. Here is a sampling of the topics that were presented:

- Innovative Clinical Trial Designs: Enhancing Efficiency and Precision in Medical Research
- From Chaos to Clarity: Tackling Multiple Events in Clinical Trials
- Statistical Methods and Considerations in the Design and Analysis of Vaccine Clinical Trials
- Analyzing Survival or HER Data: Challenges, Estimation, and Deep Learning Approaches
- Bayesian Methods in the Design and Analysis of Clinical Trials
- Recent Advances in the Design and Analysis of Studies Reliant on Error-Prone Data

We also expect that many interested session presenters will submit abstracts supporting this area of focus during the Call for Short Courses, Invited Sessions, Contributed Sessions and Posters for IBC 2026, which is expected to launch no later than July 2025. Visit www.biometricsociety.org for the latest updates related to the Call for Abstract Submissions. As we set our sights on IBC 2026 in Seoul, Republic of Korea, we have launched a new "IBC News" communication to share conference-related details and opportunities for presenters and attendees. Those interested in receiving IBC News can reach out to ibs@biometricsociety.org to be added to our subscriber list free of charge.

In publications news, Biometric Bulletin Executive Editor Ajit Sahai (Indian Region) has stepped down and has been succeeded by Garth Tarr of the School of Mathematics and Statistics at the University of Sydney. Good luck to Garth! He will be overseeing a change to the look & feel for this newsletter, originally published for the first time in 1945. And we are currently concluding a search for the next Journal of Agricultural, Biological and Environmental Statistics (https://link.springer.com/journal/13253) Executive Editor. A joint ASA / IBS Editorial Management Committee has been evaluating applications, and we should be able to announce our selection shortly. Beyond this, several other Editor positions are in the midst of a search process, and we encourage those ASA members who are also members of the Society to consider involving themselves in Society publications activity.

Finally, and related to future programming, a fifth "Distinguished Lecture Series" online session will be held in June, with Caroline Brophy of Trinity College Dublin selected as our lecturer. Each session seeks to inspire the next generation of statisticians by focusing on current activities and lessons learned from each presenter, while also giving emerging professionals a chance to present as part of this prestigious series. Also, the IBS Journal Club has brought programming that focuses on high quality papers from Biometrics and JABES to our global audience. The series continues via Zoom in 2025, with 2025 representing our 9th year of programming, all of which has been captured on the IBS website and is available on demand free of charge to members. And in other membership-related news, the Society will unveil a refreshed website and several new services around the midpoint of 2025. Enhanced employment services, a new communications tool and new community-related boards are expected. The site will continue to use the current URL: www.biometricsociety.org. More information can be obtained by contacting ibs@biometricsociety.org. Thanks once again for your support!

With best wishes,
Peter Doherty, CAE, IBS Executive Director

SUMMARY OF ASA BIOP SECTION'S VIRTUAL DISCUSSION WITH REGULATORS ON

TOLERABILITY ENDPOINT CONSIDERATIONS TO GUIDE DOSAGE OPTIMIZATION IN ONCOLOGY CLINICAL TRIALS

Rajeshwari Sridhara (OCE, FDA), Olga Marchenko (Bayer), Qi Jiang (Pfizer), Yiyi Chen (Pfizer), Andrea Ferris (LUNGevity Foundation), Mirat Shah (FDA), Marc Theoret (FDA)

On September 10, 2024, the American Statistical Association (ASA) Biopharmaceutical Section (BIOP) and LUNGevity Foundation hosted a virtual forum to discuss Tolerability Endpoint Considerations to Guide Dosage Optimization in Oncology Clinical Trials. This forum was part of a series conducted under the guidance of the U.S. FDA Oncology Center of Excellence's Project SignifiCanT (Statistics in Cancer Trials). The goal of Project SignifiCanT is to advance cancer drug development through collaboration and engagement among various interested parties in the design and analysis of cancer clinical trials. The discussion was organized jointly by the ASA BIOP Statistical Methods in Oncology Scientific Working Group, the FDA Oncology Center of Excellence (OCE), and the LUNGevity Foundation.

This discussion is a continuation of four earlier discussions on pre- and post-market trial designs for dosage optimization. Typical oncology dose-finding studies focus on maximally tolerated dose (MTD) by assessing dose-limiting toxicities (DLT) in a small cohort of patients over a relatively short time period. Common assessments include clinician-assessed and graded adverse events, laboratory values, and dosage modifications. A more comprehensive assessment of tolerability may assist in better distinguishing between two or more candidate dosages. For example, in addition to clinician-reported assessments, patient-reported outcomes (PROs) based endpoints are important in evaluating symptomatic side effects and their impact on functioning, yet these data are not commonly used in dose-finding studies. This open forum discussion among multidisciplinary experts focused on the considerations for patient and clinician assessments and evaluating potential endpoints that may guide the determination of tolerability in dosage-optimization studies.

The speakers/panelists* for the discussion included members of the BIOP Statistical Methods in Oncology Scientific Working Group representing pharmaceutical companies, representatives from international regulatory agencies (Food and Drug Administration (FDA), Health Canada (HC), Medicines and Healthcare products Regulatory Agency (MHRA), and Brazilian Health Regulatory Agency (ANVISA)), clinicians, academicians, and expert statisticians. In addition, over 100 participants attended the virtual meeting, including representatives from other international regulatory agencies (European Medicines Agency (EMA), Therapeutic Goods Administration (TGA), Health Sciences Authority (HAS), Singapore; Ministry of Health, Israel; Pharmaceuticals and Medical Devices Agency (PMDA), Japan). The discussions were moderated by the BIOP Statistical Methods in Oncology Scientific Working Group co-chairs, Dr. Qi Jiang from Pfizer and Dr. Olga Marchenko from Bayer, and Dr. Rajeshwari Sridhara, a consultant from OCE, FDA.

In the introductory presentation, the OCE leadership presenter discussed the importance of dosage optimization studies in cancer clinical trials, pointing out the current limitations in dose-finding studies and emphasizing the need for a comprehensive assessment of pharmacology information, safety, tolerability and preliminary assessment of efficacy. Previous discussions highlighted the preference for determining optimized

dosages in pre-marketing settings while acknowledging the potential for post-marketing studies if further dosage optimization is necessary. The presenter noted the importance of including PROs as crucial for evaluating side effects and their impact on functioning. Recently, FDA has published a guidance on dosage optimization for oncology products (https://www.fda.gov/media/164555/download). This introduction set the stage for a deeper exploration of patient-reported outcomes in dosage optimization studies and their role in improving cancer drug development.

The speaker from academia discussed the importance of incorporating PROs in dose-finding clinical trials, highlighting the limitations of traditional methods that rely solely on clinician-reported toxicities. She introduced the Patient-Reported Outcome Continual Reassessment Method (PRO-CRM) and its extensions, which redefine the MTD to include both clinician and patient perspectives. The presenter emphasized the need for validated PRO instruments, such as PRO-CTCAE, and outlined key considerations for incorporating PROs in trials, including the proper definition of tolerability and establishing clear protocols for using PRO data in dosing decisions. She showcased practical applications of PRO-CRM, including R Shiny apps for simulations and trial conduct, and mentioned ongoing research to further refine these methods. The presentation concluded by stressing the importance of including PROs in dose-finding trials to ensure patient tolerability and calling for more research on defining tolerability from

the patient perspective.

The panelists from academia, industry, and regulatory agencies focused their discussion on the feasibility of incorporating both clinician and patient-reported tolerability outcomes, the potential for composite endpoints, preferred tolerability outcomes, minimum follow-up when measuring tolerability, and barriers to implementation in dose-finding and dosage-optimization cancer trials.

The key points raised in the panel discussion following the presentation were:

- PROs are crucial for evaluating tolerability and dosage optimization, but their implementation in early-phase trials is limited. There is a need to increase familiarity with PRO assessment among drug developers and improve their use in early-phase studies.
- Dosage optimization should consider safety, tolerability and early efficacy, focusing on benefit-risk trade-offs among multiple dosages. This requires a holistic approach throughout the entire clinical development process, from early-phase trials to post-market studies.
- Better tolerability endpoints are essential, including composite endpoints and quantitative scores that incorporate frequency, severity, and time components. PRO-CTCAE based scores and time-to-event models are valuable for assessing long-term tolerability.
- While PRO assessment are important, there are challenges in their implementation and interpretation, including sample size limitations, selecting appropriate PROs, ensuring adequate follow-up, and standardizing subjective patient-perspective data.
- The timing of PRO implementation is crucial. While their use in initial dose escalation may be premature (e.g. if the side effects of a drug are unknown), they could be more effectively incorporated in later phases, such as disease expansion cohorts or dosage optimization studies.
- There is a need to develop better methods for communicating safety, tolerability and efficacy information to patients, taking into account the duration and intensity of side effects, in order to facilitate informed decision-making.

This forum provided an opportunity for open scientific discussion among a multidisciplinary group of scientists, including clinicians, statisticians from academia and pharmaceutical companies, patient advocates, and international regulators, focused on emerging statistical issues in cancer drug development.

Acknowledgement: Authors thank Joan Todd (FDA) and Syed Shah (FDA) for technical support.

*** Speakers/ Panelists:**

Dr. Keaven Anderson (Merck), Dr. Vishal Bhatnagar (FDA), Ms. Rasika Bombatkar (LUNGevity), Dr. Ting-Yu (Jeff) Chen (FDA), Dr. Leonardo Costa (ANVISA, BR), Ms. Andrea Ferris (LUNGevity Foundation), Prof. Boris Freidlin (National Cancer Institute), Dr. Qi Jiang (Pfizer), Prof. Shing M. Lee (Columbia University), Dr. Olga Marchenko (Bayer), Prof. Sumithra Mandrekar (Mayo Clinic), Dr. Inna Perevozskaya (BMS), Dr. José Pinheiro (J&J), Dr. Khadija Rerhou Rantell (MHRA, UK), Dr. Gary Rosner (FDA, JHU), Dr. Mirat Shah (FDA), Dr. Suman Sen (Novartis), Dr. Rajeshwari Sridhara (FDA), Dr. Yinghua Su (Health Canada), Dr. Marc Theoret (FDA), Prof. Ying Yuan (MD Anderson Cancer Center)

SUMMARY OF ASA BIOP SECTION'S VIRTUAL DISCUSSION WITH REGULATORS ON CLINICAL TRIAL DESIGN AND ANALYSES CONSIDERATIONS IN EVALUATING TREATMENTS FOR ULTRA RARE CANCERS

Rajeshwari Sridhara (OCE, FDA), Olga Marchenko (Bayer), Qi Jiang (Pfizer), Yiyi Chen (Pfizer), Martha Donoghue (FDA), Marc Theoret (FDA)

On November 19, 2024, the American Statistical Association (ASA) Biopharmaceutical Section (BIOP) and LUNGevity Foundation hosted a virtual forum to discuss Clinical Trial Design and Analyses Considerations in Evaluating Treatments for Ultra Rare Cancers. This forum was part of a series conducted under the guidance of the U.S. FDA Oncology Center of Excellence's Project SignifiCanT (Statistics in Cancer Trials). The goal of Project SignifiCanT is to advance cancer drug development through collaboration and engagement among various interested parties in the design and analysis of cancer clinical trials. The discussion was organized jointly by the ASA BIOP Statistical Methods in Oncology Scientific Working Group, the FDA Oncology Center of Excellence (OCE), and the LUNGevity Foundation.

Patients with rare cancers, including ultra-rare cancers, have a significant unmet medical need for safe and effective treatments. For this discussion, the FDA OCE defined ultra-rare cancers as those with an annual incidence of approximately 300 people in the U.S. — a more stringent criterion than the rare disease threshold specified by the Orphan Drug Act (U.S. prevalence of <200,000 people). Drug development for such ultra-rare cancers is often considered economically unattractive and frequently infeasible with the use of traditional development paradigms. Compounding the challenges of drug development in ultra-rare cancers, evolving scientific understanding of the molecular biology of cancers has resulted in further subdivision of both common and rare cancers into small molecularly-defined subsets that may be eligible for clinical trials of targeted therapies.

This open forum discussion expanded upon prior Project SignifiCanT discussions on rare pediatric cancers (June 2021 and January 2022, https://doi.org/10.1080/19466315.2023.2238650), with a focus on innovative clinical trial designs, including Bayesian statistical design and analysis considerations for clinical trials evaluating new treatments for ultra-rare cancers where conventional randomized trials are deemed infeasible.

The speakers/panelists* for the discussion included members of the BIOP Statistical Methods in Oncology Scientific Working Group representing pharmaceutical companies, representatives from international regulatory agencies (Food and Drug Administration (FDA), Health Canada (HC), Medicines and Healthcare products Regulatory Agency (MHRA), Federal Institute for Drugs and Medical Devices (BfArM), and Therapeutic Goods Administration (TGA)), clinicians, academicians, and expert statisticians. In addition, over 100 participants attended the virtual meeting, including representatives from other international regulatory agencies (European Medicines Agency (EMA), Health Sciences Authority (HAS), Singapore; Brazilian Health Regulatory Agency (ANVIS), Ministry of Health, Israel; Pharmaceuticals and Medical Devices Agency (PMDA), Japan). The discussions were moderated by the BIOP Statistical Methods in Oncology Scientific Working Group co-chairs, Dr. Qi Jiang from Pfizer and Dr. Olga Marchenko from Bayer; and Dr. Rajeshwari Sridhara, consultant from OCE, FDA.

In the introductory presentation, the OCE leadership presenter reviewed key findings from previous discussions held in June 2021 and January 2022, building upon ongoing efforts to advance clinical trial designs for ultra-rare cancers. The presenter highlighted that while randomized clinical trials (RCTs) remain the gold standard, their feasibility in ultra-rare cancers requires careful consideration, particularly regarding the use of external data and Bayesian methodological approaches. She referenced two ongoing innovative trials, the CAMPFIRE platform trial and the NEOS trial, which demonstrate applications of Bayesian methods in rare disease settings. While acknowledging the limited regulatory experience with successful Bayesian trials to date, the presenter emphasized the FDA's support for Complex Innovative Designs (https://www.fda.gov/drugs/development-resources/complex-innovative-trial-design-meeting-program#case%20studies), particularly in ultra-rare cancers where traditional approaches may be infeasible.

The speaker from academia discussed innovative statistical approaches in ultra-rare disease trials through a case study of the Children's Oncology Group's ACNS 2321 trial, a single-arm phase II study in Central Nervous System Germinomas (CNSG). He presented the unique challenges of evaluating the efficacy of a reduced radiation dose in patients aged 3-30 with localized CNSG, where traditional non-inferiority testing is not feasible due to the disease's ultra-rare status. The presenter introduced a novel frequentist simulation-based futility design that leverages historical data to establish decision thresholds, particularly focusing on early futility assessment after observing four EFS events. Through 10,000 trial simulations, this method provided data-driven futility thresholds while acknowledging dependencies on the quality of historical data and model assumptions. The presentation concluded with an examination of alternative methodological approaches, emphasizing the need for continued exploration of improved methods for historical data integration in the ultra-rare disease setting.

The key points raised in the panel discussion following the presentations were:

- While Bayesian methods are frequently used in early-phase and exploratory settings, they have not yet been utilized in pivotal trials for regulatory approval in ultra-rare diseases.
- Although randomized controlled trials remain the preferred approach, they are often infeasible in ultra-rare settings, leading to predominantly single-arm trials or small randomized studies with overall response rate as the primary endpoint.
- Platform trials offer efficiency and improved data utilization but face challenges including unblinding, time effects, and implementation complexity.
- With few exceptions external data should primarily support rather than drive conclusions due to concerns about relevance, and quality of data. Careful assessment of similarity and exchangeability is crucial.
- There is a critical need for centralized institutions to capture and facilitate appropriate access to high-quality data for ultra-rare diseases, benefiting both academic and industry research.
- Successful trial design in ultra-rare diseases may require consideration of multiple endpoints and the integration of various data sources (biological, animal, and adult trials) while maintaining rigorous scientific standards.
- No single method is suitable for all ultra-rare disease studies; approaches must be tailored to specific disease settings, with early regulatory engagement and careful consideration of trade-offs between statistical rigor and practical constraints.

This forum provided an opportunity for open scientific discussion among a multidisciplinary scientific group, including clinicians, epidemiologists, and statisticians from academia and pharmaceutical companies, patient advocates, and international regulators, all focused on emerging statistical issues in cancer drug development.

Acknowledgement: Authors thank Joan Todd (FDA) and Syed Shah (FDA) for technical support.

*** Speakers/ Panelists:**

Dr. Alex Bliu (Health Canada), Dr. Diana Bradford (FDA), Dr. Andreas Brandt (Federal Institute for Drugs and Medical Devices (BfArM)), Dr. Michael Coory (TGA, AU), Dr. Martha Donoghue (FDA), Dr. Boris Freidlin (National Cancer Institute), Prof. Tim Friede (Medical University of Göttingen), Dr. Qi Jiang (Pfizer), Prof. Wendy London (Harvard Medical School), Ms. Stacie Lindsey (Cholangiocarcinoma Foundation), Dr. Olga Marchenko (Bayer), Dr. Gary Rosner (Johns Hopkins & FDA), Dr. Khadija Rerhou Rantell (MHRA, UK), Dr. Subodh Selukar (St. Jude Children's Research Hospital), Dr. Arup Sinha (FDA), Dr. Rajeshwari Sridhara (Oncology Center of Excellence, FDA), Dr. Marc Theoret (FDA), Dr. Zachary Thomas (Lily), Dr. Yevgen Tymofyeyev (JRUDS), Dr. Jonathon Vallejo (FDA), Dr. Jingjing Ye (Beigene), Prof. Ying Yuan (MD Anderson Cancer Center), Dr. Xin Zhao (Day One Biopharmaceuticals).