



## Note from Editor

Warm greetings, everyone! As the Year of the Dragon has been underway for quite some time, we wish you all a prosperous 2024. Now, we are excited to present you with the first issue of the BIOP report for the year. Several changes have been implemented in this issue, including a highlighted section and the addition of photos of authors at the beginning of most articles. In addition, we have categorized the articles into three sections:

- **Feature Articles on the Theme:** Gain valuable insights from the experts in regulatory and industry sectors on the theme "[Impact on Regulatory Policies to Drive Statistical Innovations](#)", exploring the connection between regulations and statistical advancements;
- **Leadership and Career Development:** Find guidance and inspiration for biopharmaceutical professionals to confidently navigate your careers;
- **Working Group and Conferences Update:** Get updates on recent developments and opportunities for collaboration within the statistical community.

We would like to extend our sincere thanks to our esteemed contributors for their invaluable insights and contributions to this issue. Additionally, a big thank you to our ASA colleagues Megan Murphy, Meg Ruyle, and Rick Peterson for their tremendous support in the production.



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## Editorial board



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# BIOPHARMACEUTICAL SECTION CHAIR TRANSITION REPORT

Brian A. Millen (BIOP Chair, 2023) and Ted Lystig (BIOP Chair, 2024)

Greetings, BIOP Members! We hope you are well, as 2024 quickly gets underway. In this report, we'd like to update you on BIOP happenings over the past year and introduce plans for 2024.

With 2023 as only the second year of the post-pandemic return to in-person meetings, it was great to see many members who were able to attend JSM or the Regulatory-Industry Statistics Workshop (RISW). Each of these meetings provided significant opportunity for our members to connect with one another while engaging in emerging scientific advancements in our field.

The BIOP Executive Committee is made up of 12 elected members and 6 appointed at-large members, all 18 of whom are voting members. The EC also has 12 subcommittees (each with its own chair and members) which execute important business of the Section. In addition, the Section supports 11 Scientific Working Groups which explore and conduct research of interest to our members. These numbers reflect significant growth in key bodies of the Section, as will be explained in more detail later in this report.

As usual, the Section held multiple meetings of the Executive Committee (EC) throughout the year. Our Spring and Fall 2023 EC meetings were each held virtually, while an in-person EC meeting and the annual BIOP mixer and business meeting were both held in-person at JSM.

A succinct operating philosophy for 2023 was "getting to Yes." Our members have many good ideas. While these ideas generally require refinement and tailoring, it's also generally easy to see the opportunity to benefit our profession and our BIOP membership. With this understanding, the pathway to growth in impact and innovation was rooted in finding "yes" throughout 2023.

In the subsequent sections, we address the activity and impact of the Section throughout 2023. We close

with a look at the 2024 plan and some final integrative thoughts.

## Awards

The designation of awards is a long-standing and significant way the Section provides service to the profession, encouraging leading-edge science by students and professional statisticians at all career levels. Our awards include the BIOP Student Scholarship Award and multiple presentation and paper awards associated with JSM and other conferences.

The BIOP Student Scholarship Award Committee fielded a record number of applications in 2023. Consideration for the awards is based primarily on notable academic achievement or applied project work related to the area of biopharmaceutical statistics, general academic performance, leadership, service/volunteering, and diversity. As a result of the large number of deserving, high-quality applicants, the committee awarded eight scholarships, rather than the traditional five scholarships. Recipients were recognized during the JSM Business Meeting and Mixer and via our social media channels. The 2023 recipients were:

- Ying Cui (Emory University)
- Robert Tumasian (Columbia University)
- Shanta Ghosh (University of Illinois Chicago)
- Emily Getzen (University of Pennsylvania)
- Jerry Chang (Harvard)
- Dominique McDaniel (Drexel University)
- Cole Manschot (North Carolina State University)
- MaryLena Bleile (Southern Methodist University)

Thank you to Jared Lunceford (2023 Chair of the Scholarship Award Committee), Wenting Cheng, and Bruce Binkowitz for stewarding the selection process.

Also recognized at the JSM Business Meeting and Mixer were the Student Paper Awards. The 2023 awardees were:

- First place: Rebecca B. Silva (Columbia University)
- Second place: Xiaohan Chi (The University of Texas, MD Anderson Cancer Center,)
- Third place: Jingyi Lin (Boston University)

Thank you to Lanju (Chair of the committee), Yang Chen, Jianchang Lin, Meijing Wu, Du Yu for their work in stewarding the award selection process.

We look forward to resuming recognition of the Best Contributed Paper Award and Best Contributed Poster Award in coming years.

## Scientific Working Groups

### *Summary of Scientific Working Groups (SWG)*

The process of establishing new SWG's is overseen by the Scientific Working Group proposal committee. Through the committee, section members may submit proposals for working groups to research topics that contribute to the goals of advancing science, enabling innovation, and leveraging membership expertise. New SWG's must be approved by the EC. All SWG's must provide annual reports to the EC, and the SWG proposal committee regularly monitors health of the existing SWG's.

In 2023 six new SWG's were established, bringing the total number of SWG's to 16. The new SWG's and their chairs are listed below:

- AI and Machine Learning – Meg Gamalo-Siebers and Yushi Liu
- Bayesian – Pritibha Singh and Melissa Spann
- Cell and Gene Therapy – Daniel Li and Alan Chiang
- Covariate Adjustment in Randomized Clinical Trials – Jingyi Liu and Ting Ye
- Health Technology Assessment – Weili He, Min-Hua Jen, and Cornelia Dunger-Baldauf

- Statistics in Pharmacometrics – Luke Fostvedt and Tim Waterhouse

Thank you to Brian Waterhouse (committee Chair) and LIST for their exemplary efforts in shepherding the SWG proposal process for BIOP.

## Committees

### *Membership Committee [Judy Li, 2023 Chair]*

The Membership Committee plays a crucial role in ensuring the engagement and satisfaction of BIOP members. The primary charge of the committee is to assess the demographics and interests of the Section through a triennial member survey. The committee also focuses on evaluating and implementing methods to increase BIOP membership involvement, particularly in underrepresented demographics. The committee also acts as a liaison with the ASA regarding association-wide membership efforts, bringing any relevant issues back to the BIOP EC for discussion and action.

In January, the Membership Committee launched the BIOP Membership survey. The results will be shared soon with the BIOP EC. This information provides insights and guides strategies for enhancing and sustaining the membership experience. Thank you to everyone who provided feedback in the survey. Your voice is instrumental in shaping our community!

### *Outreach and Collaboration Committee [Hrishikesh Kulkarni, Chair]*

The Outreach and Collaboration Committee aims to build bridges of collaboration with organizations that share the ideology of working together to promote the use and best practice of statistics in biopharmaceutical research. In 2023, there were multiple collaborations which grew out of the work of the OCC. One example is the collaboration with the ASA Boston Chapter in support of the Boston symposium. BIOP was a platinum sponsor of this event, with part of the sponsorship providing student poster awards. Another is collaboration with ISOP Statistics and Pharmacometrics (SXP), resulting in a joint webinar and a poster sharing BIOP at the ISOP Annual Meeting. SXP has now formed as an official SWG of BIOP, drawing a sustained tie between BIOP and ISOP!

### *Leadership in Practice Committee (LiPCom) [Veronica Bubb, Chair]*

BIOP's LiPcom had an active 2023, with presentations at ENAR, JSM, and RISW. They also held a webinar in conjunction with the ASA Committee on Career Development and initiated engagements with the Boston and Central Indiana Chapters of ASA.

Thank you to Veronica Bubb, Lisa Lupinacci, Abie Ekegaki, Emily Butler, Shanti Sethuraman, Claud-Petit, Hongwei Wang, Vincent Tan, and Andy Chi. Your efforts have brought practical, leadership-focused content to the BIOP community.

### *Funding Committee [Alan Hartford, Chair]*

The funding committee evaluates external requests for funding support or sponsorship from BIOP. The committee each year consists of the past Chair of the BIOP Section, the current BIOP treasurer and appointed member(s). Following the committee's work to clarify the requests, they evaluate the requests and bring a recommendation to the EC who then votes on funding each initiative. In 2023, the committee was quite busy. In total, nine deserving requests were granted.

Thank you to Alan Hartford, Emily Butler, and Sheela Kolluri for this important work on behalf of the Section.

### *Statisticians in Small Biotech committee [Mohamed Hamdani, chair]*

This recently formed committee is actively working to build a community to enable sharing of ideas, experiences, and best practices amongst statisticians in small biotech companies. In 2023, they progressed a website "community" to be a resource for statisticians in small biotech and beyond. They also offered a webinar in BIOP's webinar series, entitled, "Don't go it alone: Benefits of joining our community of statisticians in small biotechnology companies."

Thank you to Mohamed, Liang Fang, Alan Hartford, Sharon Murray, Jingtao Wu, Alan Chiang, Carmen Mak, Yujun Wu, and Junwu Shen.

## **Communications & Education**

BIOP has multiple communication-focused efforts for the benefit of our membership. These include our Biopharmaceutical Report, an active podcast, an active

social media presence, and an education-communication effort through our regular webinars. There are multiple people to thank for the success of these initiatives.

Thank you to Ling Wang and Meijing Wu, Donghui Zhang, who were the 2023 editor and co-editors of the Biopharmaceutical Report. They brought forward very rich content in the 3 editions of the Report throughout the year.

Thank you to Amy Lalonde, Christina Nurse, and Rebecca Wilson, cohosts of the ASA BIOP Podcast. The podcast offered engaging episodes on a wide variety of topics of interest to our community. These included podcasts on Estimands, Synthetic Data Integration, Communication Styles, and Imposter Syndrome. Podcasts for 2024 are already well underway, including a recently released podcast about industry-academia-government collaborations. Coming soon is a podcast on what it's like to be a working mom and statistician in the biopharma industry, in which Amy and Christina share from their personal experiences. All podcast episodes may be found here: <https://www.buzzsprout.com/16296>.

Thank you to Vivian Yuan for leading the active BIOP webinar series in 2023. These webinars cover a range of technical and non-technical topics of interest to our membership. Participation/viewing of webinars is free for all BIOP members. Herb Pang and So Young Park have begun to organize webinars for 2024, and you can view information on past webinars in 2024 here (<https://community.amstat.org/biop/home>) and in or before 2023 here (<https://community.amstat.org/biop/media-contents/webinararchive>). Upcoming webinars in the coming months include topics such as: Dose Escalation Trials, and Updates from Health Technology Assessment SWG. Further details will be announced on our discussion forums about a month ahead of the event time.

Finally, thank you to Hiya Banerjee who manages BIOP's social media presence. News of BIOP activities are actively shared on LinkedIn and X (formerly known as twitter). Traffic to these postings is strong and continues to grow, thanks to her continuous efforts to curate content in partnership with the EC and committee members.

## JSM

In 2023, BIOP sponsored 6 invited sessions. This includes our 4 allocated sessions plus two additional sessions earned through competition. In addition to the invited sessions, BIOP sponsored 16 topic-contributed sessions, 20 contributed paper sessions (containing 7 presentations each), 48 contributed poster presentations, and 19 contributed speed presentations. The short course, “Causal inference in Randomized Controlled Trials,” rounded out BIOP’s scientific offerings at JSM.

Thank you to Elena Polverejan (BIOP Program Chair) for driving the selection process for BIOP in 2023.

## RISW

The 2023 ASA Biopharmaceutical Section Regulatory-Industry Statistics Workshop (RISW) was held in North Bethesda, MD from September 27-29 and once again resulted in a highly successful event. The workshop had a theme of “Statistical Thinking and Innovation with Global Impact” and featured over 1,150 statisticians participating in 10 short courses, 49 parallel sessions, and 2 plenary sessions that focused on ICH harmonization and digital health technologies.

Thank you to 2023 RISW co-chairs Erik Bloomquist and Fanni Natanegara for your great efforts in making this happen.

## Finance

We are happy to report a strong end-of-year balance for BIOP of \$386,599. As a Section of a nonprofit organization, our goal is to deploy resources in service of our membership and the profession in a responsible and sustainable manner. Our current position provides an ideal opportunity to proactively evaluate financial standing going forward, in light of aggregate environmental changes over the past four years.

A task force, including the treasurer, past chair, current chair, and others will be engaging with ASA to ensure a strong financial future, as ASA as a whole evolves its fiscal approaches.

## BIOP Newly Elected Officers

BIOP welcomes four new elected officers for 2024 and two new at large members. Our section chair-elect in

2024 is Erik Bloomquist and Secretary Sabrina Wan are both at Merck. Jianchang Lin from Takeda will be program-chair elect in 2024 and Freda Cooner from Eli Lilly will be council of sections representative in 2024-2026. Our two new executive council at-large members are Li Chen from Amgen and Jim Rodgers from Metrum.

## Outgoing Officers at the end of 2023

At the end of 2023, we wish to thank Inna Perevozskaya for her service as BIOP secretary, Mark Levenson as council of sections representative and Alan Hartford as BIOP chair.

## 2024 Plan and Final Thoughts

Following a successful 2023, our Section is thriving with a healthily engaged membership, established programs that provide value to the members and our profession, and several recent, emerging initiatives, committees, and working groups aimed at further increasing our impact in the future. Our slate of officers and other volunteers bring a mindset of innovation and improvement to the business of the Section which is refreshing. From a financial perspective, we are in really strong standing with an end-of-year balance of \$386,599. The plan for 2024 builds on that success while addressing potential future threats or seizing needed future opportunities.

Our current position provides an ideal opportunity to proactively evaluate financial standing going forward, in light of aggregate environmental changes over the past four years. A task force, including the treasurer, past chair, current chair, and others will be engaging with ASA to ensure a strong financial future, as ASA as a whole evolves its fiscal approaches.

As we close this message, we want to thank all volunteers (officers and committee members and SWG members) who keep this very active session running. Your work is impactful and enormously appreciated. Lastly, we’d like to remind you that we want to hear your voice. We welcome ideas, suggestions, and all feedback which would help make BIOP a more relevant and impactful home for statisticians in our profession for years to come. Please reach out to us at any time!

**With Best Regards,**

*Brian and Ted*

# DEVELOPMENT OF STATISTICAL POLICY AND GUIDANCE IN THE FDA CENTER FOR DRUG EVALUATION AND RESEARCH

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## HIGHLIGHTS

- CDER's Office of Biostatistics (OB) leads the development and communication of statistical policy and guidance to help ensure the application of sound statistical principles in drug regulation and review.
- OB seeks to apply a flexible, transparent, and effective end-to-end process for statistical policy and guidance development that engages OB staff.
- There are many opportunities for engagement in the process by external stakeholders from industry, academia, and patient communities.
- Editor's Note – OB: Office of Biostatistic; OTS: Office of Translational Sciences; CDER: Center for Drug Evaluation and Research

## Introduction

The Federal Food, Drug, and Cosmetic (FD&C Act) and other federal laws and regulations establish the legal framework under which the FDA Center for Drug Evaluation and Research (CDER) helps ensure the safety and effectiveness of drugs. FDA uses guidance documents to explain the Agency's current thinking, or policy, on regulatory issues, including the application of scientific principles to meet regulatory standards. FDA also develops Manuals of Policies and Procedures (MAPPs) to document internal policies and procedures. Providing clarity on policy and guidance to regulated industry, FDA staff, and the public is important for ensuring the application of consistent and transparent scientific principles in regulatory review and for promoting the timely development of safe and effective drugs.

The application of sound statistical principles is critical to drug regulation and development. This is promoted through the development and communication of statistical policy and guidance, which is led by CDER's Office of Biostatistics (OB). OB provides statistical leadership and expertise and collaborates closely with other offices and disciplines in support of CDER's mission. In this article, we describe OB's approach to

developing statistical policy and guidance. We discuss the role of the Statistical Policy Council (SPC) and associated working groups and committees and outline the different steps of an end-to-end process for policy and guidance development. The description of this process highlights the many opportunities for engagement by external stakeholders from industry, academia, and patient communities.

### **Statistical Policy Council and Associated Working Groups and Committees**

The SPC provides leadership to CDER on statistical policy development, dissemination, and implementation. The SPC aims to ensure the conduct of high-quality reviews based on transparent, consistent, and sound statistical principles. The OB Immediate Office includes an Associate Director for Statistical Science and Policy, who provides statistical policy leadership for the office and serves as the Chair of the SPC. Members of the SPC currently also include the OB Director and Deputy Director, OB Division Directors, and clinicians from the CDER Office of New Drugs (OND) and Office of Medical Policy. The SPC generally meets twice monthly to provide input on statistical policy and review issues that are complex or precedent-setting. All OB staff are invited to attend and participate in these meetings. The SPC also determines when a policy issue merits the formation of a working group or committee. Working groups and committees generally have diverse representation from across OB divisions and play a critical role in policy and guidance development (e.g., by drafting guidances) and implementation (e.g., by providing training). They have been the primary drivers behind the drafting of many important statistical guidances, which are then reviewed by the SPC before being recommended. Additional details on the organization, membership, responsibilities, and procedures of the SPC and associated working groups and committees can be found in the CDER MAPP Statistical Policy Council.

### **End-to-end Process for Statistical Policy**

### **and Guidance Development**

OB seeks to apply a flexible, transparent, and effective end-to-end process for statistical policy and guidance development that engages OB staff and external stakeholders. In this section, we provide a high-level description of the different steps in the process.

#### *Identification and Selection of Topics*

An important initial step is the identification of critical and emerging topics that may warrant clarity in policy. Potential topics are identified based on many different sources, such as: reviews of submitted applications (e.g., discussed at meetings of the SPC, other CDER policy groups, Advisory Committees, OB divisions or teams, or with industry); internal and external research findings; surveys and focus groups; public workshops, meetings, and conferences; patient listening sessions; statutory and other commitments; public comments to the FDA docket; meetings with international regulatory agencies; and recommendations from OB working groups, committees, interest groups,<sup>1</sup> or review staff. It is often a combination of these information sources—for example, the identification of an emerging challenging statistical topic by both industry and FDA statisticians—that leads to OB and SPC consideration of policy and guidance development.

Once potential topics are identified, they need to be prioritized to facilitate selection of specific topics to dedicate resources (such as the creation of a new working group or committee) toward policy and guidance development. A list of potential topics is maintained and the SPC prioritizes and decides on new initiatives based on factors such as the following: the importance to the FDA mission of protecting public health, including the scope of impact (e.g., importance across different therapeutic areas); the degree to which clarity in policy would help sponsors and review staff; the degree of unexplained lack of consistency or clarity in approaches across units or areas; and the feasibility of developing sound policy and guidance in a timely manner.

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<sup>1</sup> See the CDER MAPP Policy and Procedures for Creating an Interest Group in the Office of Biostatistics <https://www.fda.gov/media/159390/download>

### *Development*

The approach for developing statistical policy and guidance is flexible and may take on different forms depending on the specific topic, the deliverable of interest (e.g., a guidance or another policy document such as a MAPP), and other factors. OB follows FDA regulations and best practices for initiation, prioritization, development, clearance, and issuance of guidance documents.<sup>2</sup> It is common for the development of policy and guidance deliverables to be led by a working group or committee formed through the SPC. These groups generally have a clear charge from the SPC and maintain a charter describing key objectives, roles and responsibilities, deliverables, and timelines. They provide regular updates to the SPC on progress and plans to help ensure the timely and effective development of important deliverables. Written documents should be clear, concise, and focused. Working groups and committees may also include representatives from other centers and offices, such as clinicians from OND and statisticians from the Center for Biologics Evaluation and Research (CBER). Members of other offices also often provide periodic feedback at key points during development. Cross-disciplinary collaboration is essential to the development of sound CDER policy and guidance. Understanding and acceptance of statistical policy by others in CDER is also critical for ensuring effective implementation. All OB staff are typically given an opportunity to comment on draft deliverables in writing and/or at office- or division-level meetings. The deliverables are then reviewed by the SPC before entering the preclearance and clearance process. Preclearance review is often utilized to provide key leaders an opportunity to confirm the content is substantively acceptable to their offices before formal clearance is initiated. After preclearance review and any necessary revisions are made, policy and guidance documents

undergo formal review and clearance by relevant FDA centers and offices.

OB members also contribute statistical leadership and expertise to the development of policy and guidance documents led by other offices and centers, including disease-specific guidances and guidances on emerging cross-disciplinary topics such as real-world evidence and digital health technologies. This may take the form of participating on working groups led by other offices and commenting on documents during preclearance and clearance review to ensure the consistent application of sound statistical principles. OB members also collaborate with global regulatory agencies by participating in joint regulatory efforts such as the development of International Council for Harmonisation (ICH) guidances. For example, OB members were key contributors to ICH working groups for the ICH E8(R1) guideline on general considerations for clinical studies, the ICH E9(R1) Addendum on estimands and sensitivity analyses, and the ICH E17 guideline on multi-regional clinical trials, and an OB member is currently serving as the Regulatory Chair of the working group developing the ICH E20 guideline on adaptive designs.

### *Implementation and Outreach*

After development of a policy or guidance document, multiple diverse approaches are used to ensure appropriate awareness, understanding, and adoption of the recommendations. Working groups and committees are encouraged to have communication and training plans. These typically include providing dedicated training for OB staff on newly developed statistical policy and guidance, and often also training for other relevant FDA offices and for external stakeholders. For example, the Estimands Working Group in OB has led several internal training sessions for OB and OND staff, as well as external training such as short courses at the 2022

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<sup>2</sup> See 21 CFR 10.115; see also, for example, <https://www.fda.gov/about-fda/reports/background-fda-good-guidance-practices> and the FDA Draft Report and Plan on Best Practices for Guidance <https://www.fda.gov/media/175121/download?attachment>

ASA Biopharmaceutical Section Regulatory-Industry Statistics Workshop and 2023 DIA/FDA Biostatistics Industry and Regulator Forum. Many different tools are used for internal and external outreach, such as email announcements, podcasts, social media posts, webinars, presentations and short courses at public meetings, press releases, and Guidance Snapshots. Guidance Snapshots are a communication tool to provide guidance highlights using visuals and plain language.<sup>3</sup> Multiple approaches are also taken to identify any gaps or concerns with the recommendations. FDA typically first publishes guidance documents as draft guidances with an opportunity for public comment. Guidances are posted on the FDA website and publicized with a Notice of Availability (NOA) in the Federal Register, and the public is usually provided 60 days to submit comments on drafts (though the public can comment on guidance at any time). External feedback is also obtained through forums such as public meetings, sponsor meetings, and listening sessions. Internal feedback is obtained during training sessions and potentially with other approaches such as surveys. We carefully review and consider public comments and other external and internal feedback in preparing final guidance documents and in any other revisions to policy and guidance documents.

### **An Example: Development of a Draft Guidance on Master Protocols**

The development of draft guidance on master protocols serves as one example of the end-to-end process described above. There has been increasing interest in the use of master protocols to efficiently evaluate one or more drugs in one or more diseases, and several umbrella and platform trials were initiated under master protocols to develop drugs for COVID-19. Based on both internal and external feedback, challenges were identified in ensuring appropriate design, conduct, and analysis of master protocols. This led to the creation of an OB working group in 2020 that was tasked with developing

statistical policy and guidance on master protocols, with an initial focus on umbrella and platform trials. The working group reviewed literature and case studies and formulated subteams to develop recommendations on specific statistical topics such as the use of nonconcurrent control data, handling multiplicity, and maintaining trial integrity. As an initial deliverable, members of the working group collaborated closely with clinical and administrative colleagues to develop the guidance COVID-19: Master Protocols Evaluating Drugs and Biological Products for Treatment or Prevention (May 2021). The OB working group also developed a more comprehensive written draft of some general statistical principles for umbrella and platform trials. This draft was reviewed by all OB staff and then reviewed and discussed by the SPC, with revisions made to address the feedback. These statistical principles were then leveraged in a cross-disciplinary collaboration to develop a guidance for industry. Statistical, clinical, regulatory, and administrative considerations were integrated into a draft, which went through preclearance and clearance review and editing, and resulted in the recent publication of the draft guidance Master Protocols for Drug and Biological Product Development (December 2023). Members of the working group have provided internal training through multiple presentations at different forums. There have also been multiple forms of outreach, such as presentations and panel discussions at several external conferences and release of a podcast and Guidance Snapshot.

### **Summary**

The development and communication of sound statistical policy and guidance is critical to CDER's mission. OB leads statistical policy and guidance development and seeks to apply a flexible, transparent, and effective end-to-end process that includes many opportunities for engagement by external stakeholders from industry, academia, and patient communities. ■

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<sup>3</sup> See <https://www.fda.gov/drugs/guidances-drugs/guidance-snapshot-pilot>

# COLLABORATION UNDER PROJECT SignifiCanT

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## HIGHLIGHTS

The article provides a brief overview of the collaboration under Project SignifiCanT. It addresses the following areas:

- How the partnership was initiated;
- How each forum is organized;
- What impact this partnership generates.

## Initiation of Partnership

The United States Food and Drug Administration (U.S. FDA) Oncology Center of Excellence (OCE) was authorized by the 21st Century Cures Act in 2016, and the OCE was established in January 2017. In addition to the review of medical products for oncologic and hematologic malignancies, OCE leads a variety of research, policy and educational outreach projects and programs designed to advance the OCE's mission of collaboration and innovation in cancer drug development. Project SignifiCanT (Statistics in Cancer Trials), for example, was created to promote collaboration and engagement among different stakeholders regarding the design and analysis of cancer clinical trials.

This partnership started with the Project SignifiCanT lead reaching out to the co-chairs of the American Statistical Association Biopharmaceutical Section (ASA BIOP) Statistical Methods in Oncology Scientific Working Group and chair of the ASA BIOP to co-organize a series of open discussions on various timely topics that would benefit from a collaborative understanding of the critical statistical issues different stakeholders face in oncology clinical trial design and analyses. Discussions were initiated in October of 2020, the first of which focused on Type I error considerations in master protocols with a common control and

featured expert panelists from pharmaceutical industry, international regulatory agencies, and academia. The meeting was so successful that it was decided to continue with the collaboration and expand this partnership further by inviting LUNGeivity Foundation to bring in the patient perspective in designing and analyzing cancer clinical trials.

Through Project SignifiCanT, the FDA OCE, with the ASA BIOP Statistical Methods in Oncology Scientific Working Group and LUNGeivity Foundation, have established a platform for discussion among diverse, multidisciplinary stakeholders in the oncology drug development ecosystem, including international regulators, professional organizations, industry, academicians, and patients and patient advocates. To date, 29 forums have been conducted with the goal of improving the design of cancer clinical trials through open discussion and dissemination of information to the stakeholders through publications.

### **Project SignifiCanT Forums**

The virtual forums all follow a similar format: introductory remarks by the OCE leadership on the selected topic that include the reasons for choosing the topic, brief overview of the current landscape, and some questions to guide the panel discussion; 2-3 short presentations; and a panel discussion. The speakers and panelists in these forums include members of the ASA BIOP Statistical Methods in Oncology Scientific Working Group (statisticians from industry, FDA, and academia), representatives from global regulatory agencies (including FDA, EMA, Health Canada, Australian Government Department of Health, Medicines and Healthcare products Regulatory Agency from the UK, Swissmedic from Switzerland, Pharmaceuticals and Medical Devices Agency from Japan, Health Sciences Authority from Singapore, Brazilian Health Regulatory Agency, Israel Ministry of Health), clinical investigators, patient advocacy groups, academicians, and other relevant experts. In addition, over 100

attendees join each of these forums, which take place roughly every other month.

Topics for the forums are brought primarily by regulators based on current critical statistical issues that arise in cancer clinical trials. There are no expectations for a consensus at these forums. It is important to hear and understand all stakeholders' points of view on the topic. Presentation slides are distributed to all forum attendees. Brief summaries of the discussions are printed in the Biopharmaceutical Report of the ASA BIOP Section and occasionally more detailed articles on prominent topics are published in *Statistics in Biopharmaceutical Research* journal. The full list of publications is available on the Project SignifiCanT website and on the ASA BIOP Statistical Methods in Oncology Scientific Working Group website.

### **Collaboration Impact**

These forums provide an opportunity for open, scientific discussion among a diverse, multidisciplinary group. Some topics are discussed over several meetings to more clearly understand the issues, share case studies, and come up with suggestions for improvement over the status quo. For example, four forums were dedicated to dose-optimization studies during which speakers and panelists shared novel designs and brainstormed ideas for improvement in selecting dose(s) in pre-approval and post-approval stages of drug development. Several topics have been discussed at two forums, including the evaluation of treatment effect in underrepresented populations, COVID learnings and use of elements from decentralized clinical trials, and statistical considerations for pediatric cancer clinical trials. The objectives of this collaboration are to assemble relevant stakeholders in a timely manner, to foster knowledge exchange, and to disseminate the proceedings to further promote broad understanding of the critical statistical issues. Points raised during the forums are taken into consideration by regulators and industry for addressing emerging statistical issues in cancer clinical trials and submissions. ■

# INFLUENCE ON REGULATORY GUIDANCE/POLICIES TO DRIVE STATISTICAL INNOVATION: INTERVIEW WITH IVAN CHAN AND BILL WANG

Meijing Wu(Sanofi), Di Zhang(Teva)

## HIGHLIGHTS

- Much progress has been made to harmonize the regulatory policies and implementation around the world for drug development, but we still sometimes encounter disparities between guidance and practice.
- There are good examples in broad collaboration to promote innovation in regulatory sciences, including public-private-partnership (PPP) and tripartite (regulatory-industry-academia) collaboration. More opportunities to broaden the collaboration.
- Industry can enhance collaboration and innovation by taking specific actions.

**Disclaimer:** *The opinions provided here are reflective of the viewpoints by the interviewees and interviewers and may not represent those of their employers.*

Drug development must adhere to a meticulously regulated environment, in which regulatory guidance and policies are crucial for providing structured and/or standardized approaches. There is a growing trend of collaboration among industry, academia, and regulators to implement and develop regulatory guidance and policies that promote innovative design and analysis methods. Positive strides have been made in this regard, and further advancements are anticipated.

The editors of the Biopharmaceutical report had the pleasure of interviewing Ivan Chan from BMS



**Ivan Chan**

Vice President, Head of Hematology Biostatistics BMS



**William (Bill) Wang**

Executive director, clinical safety statistics, Merck Research Laboratories

and Bill Wang from Merck to gather their insights on the impact of regulatory guidance/policies in driving statistical innovation.

**BIOP report: In your experience, do you observe any discrepancies between the recommendations outlined in current regulatory guidance and the actual practices within the industry? Could you provide specific examples to illustrate these disparities?**

**Ivan:** Much progress has been made to harmonize the regulatory policies and implementation around the world for drug development. However, we still sometimes encounter disparities between the regulatory guidance and actual practices. Managing these discrepancies can be complex and challenging, particularly when regulatory bodies from different countries have different requirements to meet their local needs. For example, for designing and analyzing time-to-event endpoints, FDA and EMA have different recommendations for censoring rules, leading to variations in our approach.

**Bill:** Indeed there have been broad collaboration in regulatory innovation in statistics. An illustrative example is the ICH E17 guidance, which establishes clear principles, on sample size allocation in a multiregional trial. Despite consensus on these principles, the implementation varies by country and region, due to local laws and regulations that may not align with ICH guidance.

Another scenario involves regional regulations providing their own guidance, making it difficult to bring regulators together even when the industry attempts to create unified ICH guidance. The FDA's IND safety reporting guidance serves as an example, where efforts to reduce reporting burden contradict with other agencies that insist on comprehensive data. This highlights the industry's struggle to align different regulators for mutual benefit, leading to divergent paths in regulatory approaches.

**BIOP report: What are the challenges in promoting statistical innovation within the constraints of regulatory guidance?**

**Bill:** There have been many noteworthy innovations being proposed by various entities, being it academia, industry, or regulatory agencies. These innovations sometimes find their way into regulatory practices and evolve into official guidance.

However, there are some obstacles. For example, many innovations, especially in statistical methods, often come with theoretical assumptions, whether model-based or not. These assumptions, when confronted with real-world scenarios, can be challenging to accommodate comprehensively. Consequently, guidance needs to strike a balance, being general enough to avoid specifying on every possible situation, yet specific enough for practical implementation. This creates a potential implementation challenge for the guidance.

**Ivan :** We're also dealing with regulatory requirements from different countries and various health agencies. Usually, sponsors aim to adopt the most conservative approach that would be accepted by all agencies because

the study will be run in multiple countries and data from the study will be used for global submissions. This conservative approach, however, tends to inhibit statistical innovation. Regulatory departments within companies are often very conservative. To ensure protocols pass every review body, this conservative practice may potentially impede innovation before reaching agencies. Educating regulatory liaisons in-house to be more willing to take risk is crucial, providing teams with the opportunity to engage with different agencies and experiment with novel approaches to trial design and analytical methods.

On the regulatory side, harmonizing policies across different regions and countries is essential for promoting innovation. A great example is the rollout of the Estimand Guidance, where every regulatory body aimed to adhere to common principles, showcasing the positive impact of unified approaches across regions.

**BIOP report: Did you have any experience/examples in successfully making an influence on a regulatory guidance?**

**Ivan:** There is a good example on adaptive designs that I was fortunate to be involved. A working group was initiated by a group of quantitative experts from industry in 2005, at a time when not many people besides the interested group would consider the potential for applying adaptive design to phase 3 trials. The industry working group developed a position paper on adaptive designs, and began collaborations with academics and regulatory agencies, primarily the FDA. This effort led to the draft guidance in 2010 developed by the FDA. Over the years, new methodologies and examples emerged from both academic and industry settings, culminating in the finalized guidance in 2019. This extensive process involved conversations, meetings, and workshops, creating a platform for the exchange of ideas and innovation, which laid the foundation for developing the guidance.

The ICH guidance, such as the E9(R1) and E17 documents, were recently finalized as well, with formal

industry participants contributing to its development. This model of industry involvement in guidance development is seen as a positive step forward.

Looking ahead, there's an opportunity for FDA to consider involving industry participants in the guidance development process, similar to the ICH model. This, I believe, would be a significant step forward in the development of guidance.

**Bill:** In the realm of statistics, we have numerous examples where statistics play a pivotal role in shaping regulatory guidelines. I can share two personal examples—one involving myself and the other related to Ivan.

The first example is Ivan's work in fundamental research on statistical methodology for vaccine trials. In vaccine trials, where outcomes are typically rare, Ivan and another former Merck colleague proposed an innovative method known as the "exact method" to design and analyze these rare endpoints. Ivan's method was specifically quoted in a recent draft NMPA guidance on vaccine clinical trials.

Another personal example involves my participation in the working group that drafted ICH E17. I was one of the few statisticians among almost a dozen cross disciplinary professionals, representing regulatory agencies and industry associations. In this case, we encountered an issue that, if each region required a specific sample size, it will make the multiregional clinical trial become unmanageably large. The challenge was to come up an approach that could achieve the global study objectives while still being implementable. In this context, a few statisticians, including myself, contemplated the idea of using pooling strategy, which is a statistical approach often applied but not necessarily as a major strategy in global collaborative trial design efforts. The idea received positive feedback and evolved into one of the seven principles finalized in ICH E17. This example illustrates how a statistical concept, originally just an analytical idea, can transform into a major strategic component in regulatory guidance.

**BIOP report: How would you assess the current efforts made by health authorities in fostering collaboration among health authorities, industry, and academia for the development of regulatory guidance? Are there any notable initiatives or strategies that you find particularly effective or lacking?**

**Ivan:** Bill's involvement in the ICH effort extends beyond the scope of a particular country. It aims to harmonize policies across different countries and regions, involving industry and developing guidance with participation from both industry and academia. The process invites not only industry representatives but also academic participants, creating an ideal forum for developing regulatory guidance. This approach fosters collaboration across the three different areas of expertise.

In the US, FDA has been collaborating with academic centers, and there may be opportunities to extend this collaboration to statistical experts from the industry.

Engaging industry partners in the development of guidance can be beneficial as they bring real-world examples, understand the challenges, and can help identify areas for innovation. This collaborative approach aligns well with the needs of the industry and can enhance the quality of regulatory guidance.

There is a good example of FDA involving the industry in initiatives like the Complex Innovative Trial Designs (CID) initiative. The FDA initiated several workshops where they invited academic experts as well as industry representatives. Participants presented ideas and commented on what they were thinking. Personally, I was fortunate to be involved from the pharma side, participating in these workshops invited by the FDA to discuss industry examples, potential gaps and challenges, and how to implement CID. These workshops foster open conversations between industry and regulators, addressing challenges and sharing experiences.

**Bill:** I can provide an example of a notable initiative that has proven to be effective. In the U.S., there is a Public-Private Partnership (PPP) initiated by the Center for Drug Evaluation and Research (CDER) and the

Center for Biologics Evaluation (CBER). The PPP promotes collaboration between industry and regulators.

Three years ago, I co-led the ASA safety working group and initiated a private-public partnership with the US FDA through a rigorous application process. Each task force under the working group has designated liaisons from different divisions of the FDA. This strategy of forming partnerships across industry, regulatory bodies, and academia has proven to be a successful and effective approach.

**BIOP report: What actions do you believe health authorities can take to enhance collaboration among health authorities, industry, and academia, specifically with the aim of driving statistical innovation in regulatory practices?**

**Bill:** Yes, there's an example of the tripartite effort in China, which is driven by regulators but closely involves partners from academia and industry experts. The goal is not only to develop innovative methodologies but also to apply them to regulatory practices. On the global scale, the ICH has involved industry and regulators, there are also academic professors from Europe who are part of the ICH working groups. These have enhanced collaboration among health authorities, industry, and academia, specifically with the aim of driving statistical innovation in regulatory practices.

**Ivan:** The private-public partnership is an excellent example, especially when working groups come together. I'm thinking that in addition to addressing issues and fostering innovation, we could take a step further in empowering different stakeholders during the process of writing the guidance. In the ICH, they usually have academic and industry experts participating in writing position papers and guidance documents. China

is attempting to follow the ICH model, which I believe is a good approach to emulate.

**BIOP report: In your opinion, what role can the industry play to strengthen collaboration in the development of regulatory guidance? Are there specific measures or initiatives that you think would be beneficial for enhancing industry participation in this collaborative process?**

**Bill:** I can identify a few aspects where industry can contribute. Pharmaceutical companies can leverage our implementation experiences to think about standardization and be part of the topic proposal for developing regulatory guidance. Collaborating with regulators, industry experts can identify areas that require practical innovations. Another area where industry can improve is sharing best practice and clinical trial examples. Sharing statistical methods isn't an issue, the difficulty increases when it comes to sharing specific data or detailed implementation, but it's still possible. In the CID case I participated in, several companies shared examples with the FDA. Around 4 or 5 companies shared their experiences on different aspects of CID, highlighting how methods were implemented in studies and the challenges faced. It's possible to share valuable insights without divulging proprietary information.

**Ivan:** Industry statisticians, with a wealth of trial experiences, understand the practical needs and challenges. They play a pivotal role in developing methodologies tailored to specific studies. By sharing results and experiences across the scientific community, industry experts contribute to a collective knowledge base. This collaboration enhances the voice of industry in shaping regulatory guidance, promoting standardization, and fostering innovation. ■

# A JOURNEY TOWARDS IMPACTING REGULATORY POLICY AND STATISTICAL INNOVATION THROUGH COLLABORATION AMONG HEALTH AUTHORITY, INDUSTRY, AND ACADEMIA

Margaret Gamalo (Pfizer)



**Margaret Gamalo**

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## HIGHLIGHTS

- My journey in impacting regulatory science and statistical innovation involves broadening reach and expanding networks. Key reflections include:
- Understand what is common interest or issues that strike accord from all parties.
- Implement a strategic approach to define drug development or statistical problems.
- Expect non-linear progress and embrace patience and persistence.

*“Real change, enduring change, happens one step at a time.” – Ruth Bader Ginsburg*

Given the requirement for medicines to undergo stringent testing and approval procedures mandated by health authorities, the operational process within the biopharmaceutical industry is methodically structured to guarantee the safety and effectiveness of medicines. This complexity is also reflected in the challenges confronting the industry which is multifaceted necessitating collective responsibility and a collaborative approach from health authorities, pharmaceutical companies, and academia. In this guest column, I will outline my trajectory in collaborative scientific pursuits, leveraging almost two decades of experience in the field. I'll explore the factors that promote collaboration and their role in driving statistical innovation and influencing regulatory science. While there are additional aspects to my journey that I won't cover here, I believe the learnings are likely to parallel those discussed.

A few years after I began working for the Center for Drug Evaluation and Research (CDER) at FDA, Dr. Ram Tiwari, then Associate Director of Statistical Policy at the Office of Biostatistics (OB) and whom I have been collaborating on a few statistical research, invited me to join the DIA Bayesian Scientific Working Group to represent and contribute to the topic on non-inferiority trials from a

regulatory perspective. This small group included industry statisticians such as Fanni Natanegara [Lilly], the late Frank Liu [Merck], Gouchen Song [Scholar Rock], and Heinz Schmidli [Novartis]. Our collaboration led to the publication of two manuscripts on Bayesian non-inferiority. Despite the time-consuming nature of the task due to our other commitments, I recognized the significance of assuming ownership and persisting in these voluntary efforts. Continuous progress on the project proved vital in sustaining motivation among all involved parties.

Two years later, that work became even more pertinent with the emergence of public health threats posed by infections from multi-drug resistant bacteria. In fall 2013 and a subsequent follow-up in 2014, then OB Director, Lisa Lavange, organized a think tank via the Clinical Trials Transformation Initiative to gather ideas on expediting clinical trials in areas with high unmet need. Dr. Tiwari and I were tasked with providing two proposals—one centered on hierarchical models using Bayesian methodology, and the other on augmented controls. The Bayesian hierarchical model aimed to aggregate patients with infections in different organs to ascertain overall efficacy of antibacterial drugs, a practice not commonly undertaken at that time. On the other

hand, augmented controls involved supplementing concurrent controls in a clinical trial with an external control. This marked the introduction of this methodology, offering feasibility and generalizability in clinical trials through a real-world application.

Recognizing the challenges facing the mainstream adoption of Bayesian methodology, including disagreement on priors and less understood operating characteristics, I redirected my focus towards diseases with high unmet medical need, such as pediatrics and orphan diseases. I took the initiative to lead a small pediatric subgroup within the Bayesian Scientific Working Group, aiming to raise awareness about the suitability of Bayesian methodology for efficient pediatric trial design. During that period, the concept of extrapolation was still in its infancy, and the biopharmaceutical industry lacked a comprehensive understanding of its principles and methodologies. Nevertheless, given that extrapolation involves transferring conclusions from one population to another, the Bayesian methodology held significant appeal. Its ability to incorporate prior knowledge from the reference adult population made it particularly well-suited for extrapolation. That subgroup, which included Mathangi Gopalakrishnan [Univ. Maryland], Laura Thompson [FDA CDRH], Amy Xia [Amgen], Karen Price [Lilly], Ram Tiwari [BMS], and Brad Carlin [Pharmalex], collaborated to publish a review paper on Bayesian methodologies and their applications in the design and analysis of pediatric trials – one of the most cited pediatric publications on extrapolation. My understanding of Bayesian methodology has evolved since then, leading me to a refined realization of its appropriate and scientifically sound utilization in pediatric trials.

The work on pediatrics propelled me into larger collaborative efforts with colleagues possessing diverse expertise beyond statistics. Upon joining Eli Lilly in 2016, I was introduced to Dr. AJ Allen, who led the Pediatric Center of Excellence (COE) at that time. His instrumental involvement led to my participation in advocating for numerous innovative pediatric trials in all therapeutic areas at Lilly. This collaboration also forged relationships with many individuals on the FDA Pediatric Review Committee who share a passion for advancing efficient pediatric trial designs and reducing the time lag for pediatric indication approval following initial adult approval. Furthermore, Dr. Allen involved me in the Biotechnology Innovation Organization (BIO) initiatives focusing on pediatric extrapolation, specifically in trials for pediatric Type II diabetes mellitus (T2DM). Between 2017 and 2018, there was mounting concern about the prolonged recruitment

timelines for many trials related to this disease. This engagement with BIO led to three significant contributions: (i) participation in an American Society for Clinical Pharmacology and Therapeutics panel on pediatric T2DM, where I led the discussion on insights from failed trials; (ii) presentation alongside Matt Rotelli at an FDA Workshop titled “Pediatric Trial Design and Modeling: Moving into the Next Decade,” focusing on the application of systems pharmacology into Bayesian approaches; and, (iii) involvement in a multi-sponsor (Lilly, Novartis, Novo Nordisk, Boehringer Ingelheim) dialogue with key FDA experts and policy makers regarding the utilization of augmented control designs for pediatric T2DM trials.

The collaboration within BIO opened my eyes to a vast network of efforts aimed at advancing appropriate regulatory science in pediatric drug development. At that time, I assumed the role of Co-Chair for the Innovation Taskforce in Pediatric Drug Development, where I spearheaded BIO’s Workshop on the Use of Innovative Analytic Tools and Study Designs for Efficient and Feasible Pediatric Drug Development. This endeavor resulted in the publication of the BIO white paper titled “Extrapolation as a Default Strategy in Pediatric Drug Development,” written in collaboration with key pediatric and drug development experts in the field, including Christina Bucci-Rechtweg [Novartis], Robert “Skip” Nelson [J&J], Helen Thackray [BioCryst], and Ronald Portman [Novartis]. The publication proved to be highly useful in the crafting of ICH E11A. In fact, many concepts from that publication were incorporated into the current draft of the ICH guidance. While this was certainly influential, I recognized that it was just one aspect of a broader collaboration involving initiatives such as iACT, IQ Consortium, Connect4Children (C4C), and the Children’s Medicine Working Party (CMWP) of the European Forum for Good Clinical Practice (EFGCP). Despite all these entities working towards the common goal of advancing medicines for children, interactions with stakeholders revealed divergent thoughts on implementation and perspectives.

Amidst all the collaborative efforts I participated in, a central theme persisted: improving the efficiency of pediatric trials and reducing redundant data generated to establish efficacy and safety in children. Acknowledging the crucial role of statistics in addressing this challenge, Mark Rothman [FDA], James Travis [FDA], and I collaborated to establish the Statistics in Pediatric Drug Development Scientific Working Group under the auspices the Biopharmaceutical Section of the American Statistical Association. It attracted numerous

individuals interested in pediatric drug development from the pharmaceutical industry, reviewers from multiple health authorities, and academia. This initiative focused on disseminating innovative trial designs used in pediatric drug development through multiple conference presentations, short courses, and publications. It emphasized that numerous complex innovative trial designs disclosed by the FDA have been mostly applied towards expediting the development of medicines in children. Furthermore, upon closer examination of these complex innovative designs, it becomes apparent that they rely on familiar methods such as Bayesian methods, hierarchical models, and external and augmented controls, which were introduced almost a decade earlier. Additionally, the workgroup elevated the issue of the extent of the pediatric safety database and pediatric safety analytics highlighting concerns that an excessively large safety database could hinder progress achieved by efficient trial designs. This focus has prompted other groups, including C4C, to adopt a multi-stakeholder approach to address the issue and propose potential solutions.

Christina Bucci-Rechtweg [Novartis], with whom I have collaborated previously, engaged me in another working group within the CMWP focused on age-inclusive trials. This diverse group includes EMA regulators, drug developers, researchers, ethicists, and patient advocates. Together, we examined the barriers to the inclusion of adolescents in adult research, delving into all the disease state guidance issued by the FDA and EMA—a comprehensive effort that yielded valuable insights. This endeavor culminated in the publication of “Strategies to Facilitate Adolescent Access to Medicines: Improving Regulatory Guidance,” which provided valuable recommendations to enhance regulatory guidance in this area. Following this initial effort, broader work commenced to explore additional dimensions for evaluating the inclusion of adolescents in adult research. This culminated in the creation of a tool titled “Considerations for Adolescent Inclusion in Adult Research – a Decision Tree,” which was adopted by EFGCP CMWP. This tool serves to facilitate conversations across the research ecosystem, promoting the broader incorporation of adolescent populations within appropriate drug development trials.

The inquiry into pediatric safety, mentioned earlier, spurred my recent focus on safety analytics and quantitative benefit-risk assessment, in general. Present methods for characterizing a drug’s safety profile are inadequate, as they primarily focus on the incidence of the first event without considering factors such as onset,

severity, duration, and recurrence. Moreover, there is a scarcity of methodology for incorporating correlations among events and for efficiently accounting for multiple testing in these outcomes. This research on safety also ventured on two divergent areas on novel methods on signal detection in spontaneous AE reporting as well as on less costly methods for quantitative benefit risk assessment. My partnership with academia and key technical experts in the industry on this endeavor became very helpful as they can provide novel solutions to these problems expediently. The remaining challenge is how to get this into mainstream analysis of medicinal safety profile and benefit risk.

Throughout my collaborative experiences, both during my tenure at the FDA and now within the industry, I have gleaned valuable insights on what it takes to impacting regulatory policy and statistical innovation. Below are some reflections based on my journey thus far.

### **1. Understand what is common interest or issues that strike accord from all parties.**

To drive progress in regulatory science and statistical innovation effectively, assembling a diverse group of stakeholders with requisite expertise is crucial. Academia’s leadership in fundamental research and cutting-edge statistical methodologies plays a pivotal role in advancing knowledge and cultivating skilled professionals. Leveraging the complementary roles of health authorities and industry, research findings and new statistical methodologies are translated into practical applications. Robust regulatory frameworks, on the other hand, provide the foundation for the development and sound implementation of emerging technologies, prioritizing public welfare. Industry serves as a crucial partner in driving scientific and statistical advancements by bringing innovation and domain expertise to the table. Operating within regulatory frameworks, industry drives progress while ensuring compliance with ethical and regulatory standards. Recognizing and leveraging these complementary roles between academia, industry and health authorities is essential for propelling responsible advancements forward, ensuring that technological innovations prioritize ethical standards and promote societal well-being.

With a diverse stakeholder group, it is important to understand that each will actively advocate for policies and objectives aligned with their individual interests. However, collaboration thrives when common ground is identified, allowing parties to align goals. This alignment enhances

willingness to engage in productive dialogue and collaboration. By acknowledging shared priorities, stakeholders increase the likelihood of achieving lasting outcomes, laying the foundation for enduring solutions to complex challenges. In any endeavor to improve regulatory science and statistical methodology, the guiding principle always remains the same and that is of the well-being and protection of patients. By prioritizing patient well-being, any group can navigate collaboration challenges effectively.

In think tanks focusing on establishing safety databases for investigational pediatric drugs that I have participated; tension often arises between academia and industry. Academics accuse industry of heavily influencing the agenda, while industry counters by accusing academics of lacking understanding of pre-market safety complexities. I realized that it is crucial to continuously test our assumptions and challenge our biases' accuracy. Progress can be hindered when we confine ourselves to the present context and perspective. Ultimately, our aim is to protect patients, which requires us to devise key principles that balance industry innovation with robust safety measures demanded by academics. Achieving this balance requires open dialogue and collaboration among the group to develop robust safety principles. Prioritizing patient well-being while also facilitating innovation in generating information and developing insights on pediatric safety profile helped the group move forward.

## **2. Implement a strategic approach to define drug development or statistical problems.**

Understanding the landscape surrounding a drug development or statistical problem is crucial as it provides context and accurate framing for collaborators, allowing them to grasp the broader public health or scientific issue. Moreover, knowing the landscape enables collaborators to assess the relevance and importance of the problem, ensuring alignment with their goals and priorities. This involves identifying specific aspects that require consideration to ensure a well-defined and manageable problem statement.

In the CMWP workgroup I participated in, which was composed of a diverse group of people, we meticulously dissected barriers to the inclusion of adolescents in adult research that also addressed our domains of expertise. This led to a comprehensive analysis encompassed understanding issues related to disease, product, statistical considerations, operational aspects, and legal and ethical dimensions. Additionally, the group examined the presence or absence of patient advocacy in various diseases, as a factor for age-inclusive

research. In examining the regulatory landscape, the group recognized that substantial scientific knowledge and regulatory precedence exist for the inclusion of adolescents within adult trials, which can inform research approaches. This led us to identify important opportunities for enhancing guidance. For instance, contextualizing developmental factors influencing adolescent disease progression provides valuable insights into the role of adolescent inclusion in research studies. Addressing these factors in guidance documents by health authorities can facilitate broader acceptance of age-inclusive trial methodologies and accelerate adolescent access to medicines. Indeed, conducting an exhaustive landscape search and questioning conventional wisdom and long-held assumptions enabled us to uncover new perspectives and alternative solutions to the problem.

In the domain of biostatistics, statistical methods must be clearly anchored in the landscape of science and practice. It requires meaningful translation of science. Furthermore, because most of the statistical methods attempt to solve real problems, it is essential to view the issue from a broader perspective, encompassing various stakeholders' concerns beyond just statistical considerations. By addressing most stakeholders' concerns, our solutions will be more comprehensive and applicable.

## **3. Expect non-linear progress and embrace patience and persistence.**

It is worth highlighting that pharmaceutical companies, often with help from academia, commit significant resources to research and development endeavors, with a dedicated emphasis on swiftly introducing pioneering solutions to address pressing drug development challenges. In the domain of statistics, innovation holds equal significance, as it equips us with the methodologies required to address inquiries that drive forward our comprehension of medicinal efficacy and safety. A wealth of innovation is currently underway; however, the critical question remains how best to effectively harness and leverage this progress within the confines of a structured regulatory science. Health authorities, on the other hand, actively fosters collaborative research partnerships with pharmaceutical companies and academia. These collaborations are geared towards advancing regulatory science, refining drug development methodologies, and deepening our insights into safety and efficacy assessments.

With every change in regulatory science of improvement of statistical methodology, it is important to acknowledge that their adoption often progresses in

a nonlinear manner. In my experience, my journey with utilizing Bayesian methodology and augmented controls was far from linear. I recall that publishing the seminal paper on augmented control with Junjing Lin [Takeda] and Ram Tiwari [BMS] was a prolonged process, marked by numerous rejections and lengthy journal review comments. At that time, the notion of combining an external control with a traditional randomized controlled trial seemed inconceivable as it is tantamount to adding noise to a pristine methodology to obtain causal inference. After a decade, that strategy is gaining ground as the best way to be able to benchmark external control given potential for unmeasured confounding and at the same time progress our understanding of real-world data.

As a reflection, in our contemporary landscape, characterized by a multitude of stakeholders, innovation, in general, demands adaptability and persistence to meet the diverse and evolving demands of our dynamic ecosystem. Innovative processes often involve iterations and feedback loops leading to necessary adjustments and shifts in direction rather than following a linear progression. The understanding of a problem may significantly transform over time, with phases of consensus and progress in method development, as well as periods of stagnation.

#### **4. Prioritize small wins while maintaining focus on long-term goals.**

“Think big, act small, learn fast.” It involves setting ambitious goals while systematically breaking down the process into manageable steps, fostering continuous learning, and adaptation. By prioritizing flexibility and adaptability, this approach facilitates the translation of ambitious goals into practical advancements, ultimately benefiting the development of innovative solutions. Prioritizing solvable problems and achieving measurable progress through small wins sustains motivation and momentum within research teams, contrasting with exhaustive efforts that can lead to burnout.

In the collaborative workgroups I have participated, the responsibilities usually start with modest goals that encompass promoting collaboration and knowledge-sharing. This involves sharing best practices, success stories, and facilitating access to analyses, studies, and research. Additionally, fostering discussions on overarching challenges, offering technical assistance, and maintaining open communication on relevant issues are crucial aspects. Furthermore, the role extends to

coalition building among stakeholders and providing valuable input and research to support informed decision-making and advancement within the field. Overall, these efforts aim to enhance cooperation, innovation, and progress in statistical endeavors. Some of these have led to statistical methodological work that was built through small coalitions with similar interests.

As I mentioned previously, it is important to take ownership in these volunteer efforts. Once the scope and stakeholders are defined, project planning is important. This involves outlining milestone steps, allocating resources, and establishing timelines to guide the problem-solving process systematically. This ensures alignment and progress towards common goals. Additionally, it facilitates benchmarking and evaluation by providing reference points for assessing the collaboration’s success.

#### **5. Foster mutual respect and assume good intent.**

Collaboration often involves encountering disagreements and necessitates compromise. Mutual respect is key, requiring active listening and understanding of others’ perspectives. It is crucial to consider players’ risks and incentives to foster effective collaboration. One also must be aware that excessive collaboration can lead to project stagnation, highlighting the importance of balancing divergent perspectives to maintain progress. Negotiation prioritizes win-win outcomes through common ground and creative problem-solving, yet strong perspectives or unwillingness to cooperate may lead some to quit participation. Maintaining positive relationships is crucial for sustaining collaboration and resolving conflicts amicably in such situations. Building trust, showing respect, and maintaining transparency contribute to enduring partnerships. Celebrating small wins along the way further reinforces progress and momentum towards mutually beneficial outcomes.

In summary, innovation in statistics and regulatory science involves incremental progress, requiring the engagement of various stakeholders and often unfolding in a nonlinear manner. Patience, respect, persistence, adaptability, and flexibility are essential virtues in this process. Collaborative efforts among stakeholders contribute multiplicatively to broader innovation, generating numerous ripples of progress. My journey in drug development has underscored the importance of these principles in driving meaningful advancements and provided valuable learning experiences. ■

# DECODING PROGRESSION-FREE SURVIVAL IN PHASE 3 CANCER CLINICAL TRIALS: A HISTORICAL PERSPECTIVE

Cong Chen (Merck)



**Cong Chen**

Scientific AVP, Biostatistics and Research Decision Science, Merck & Co., Inc.

## HIGHLIGHTS

- The issues raised at the sotorasib ODAC meeting related to PFS are well known, and the same issues have been frequently discussed in previous filings.
- A PhRMA PFS Working Group initiated in 2008 to address some of the key issues. The recommendations are still relevant today.
  - **Tumor assessment:** BICRs may not be necessary especially in truly blinded trials. A sampling based BICR may be used to determine whether to conduct a full BICR.
  - **Censoring rules:** Different censoring rules were generally consistent with the ITT approach in the analysis results. ITT approach may be considered for the primary PFS analysis.
  - **Statistical analysis:** PFS is intrinsically an interval-censored time-to-event variable. Simulation study has demonstrated the superior performance of a bona fide interval-censored data analysis method.

## CodeBreak 200

On December 26, 2023, the U.S. Food and Drug Administration (FDA) declined Amgen's request to secure full approval for its lung cancer therapy Lumakras (sotorasib). Sotorasib is a first-in-class, orally administered small molecule that selectively inhibits Kirsten rat sarcoma viral oncogene homolog protein (KRAS) with the G12C mutation, a target once considered "undruggable" for majority of the last four decades. As a major scientific breakthrough in recent years, the emergence of KRAS inhibitors has sparked immense enthusiasm within the oncology research and development community. On May 28, 2021, sotorasib was granted accelerated approval for the treatment of patients with KRAS G12C-mutated non-small cell lung cancer (NSCLC), who had received at least one prior systemic therapy. Subsequently, sotorasib has been approved in more than 52 countries.

As part of the Postmarketing Requirement (PMR) to verify the clinical benefit of sotorasib, Amgen conducted CodeBreak 200, an open-label Phase 3 clinical trial,

which randomized patients 1:1 to receive either single agent sotorasib or single agent docetaxel. The primary endpoint of CodeBreak 200 was progression-free survival (PFS) per blinded independent central review (BICR). The study showed that patients in the sotorasib arm (n = 171) experienced a median PFS of 5.6 months compared with 4.5 months for docetaxel (HR, 0.66; 95% CI, 0.51-0.86; p-value=0.002) [1]. The median overall survival (OS) was 10.6 months in the sotorasib arm and 11.3 months in the docetaxel arm (HR, 1.01; 95% CI, 0.77-1.33; p-value=0.53). The study allowed crossover of patients from the docetaxel arm to the sotorasib arm after 99% of the patients had been enrolled. Although the top-line results were favorable, the FDA's Oncologic Drugs Advisory Committee (ODAC) voted 10-2 on October 5, 2023, expressing concerns that the PFS data cannot be reliably interpreted. Setting time aside, the FDA's decision did not come as a surprise.

The issues raised at the ODAC are well known and the same issues have been frequently discussed in previ-

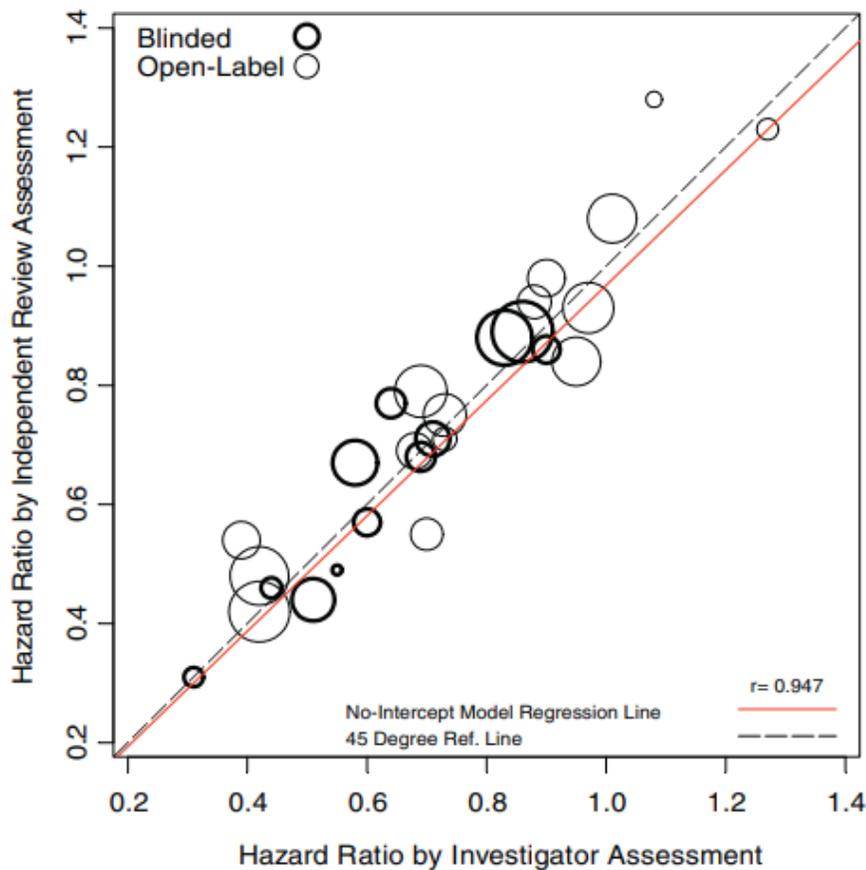


Figure 1: BICR versus LE HR by blinding status of trial (circle size proportional to sample size)

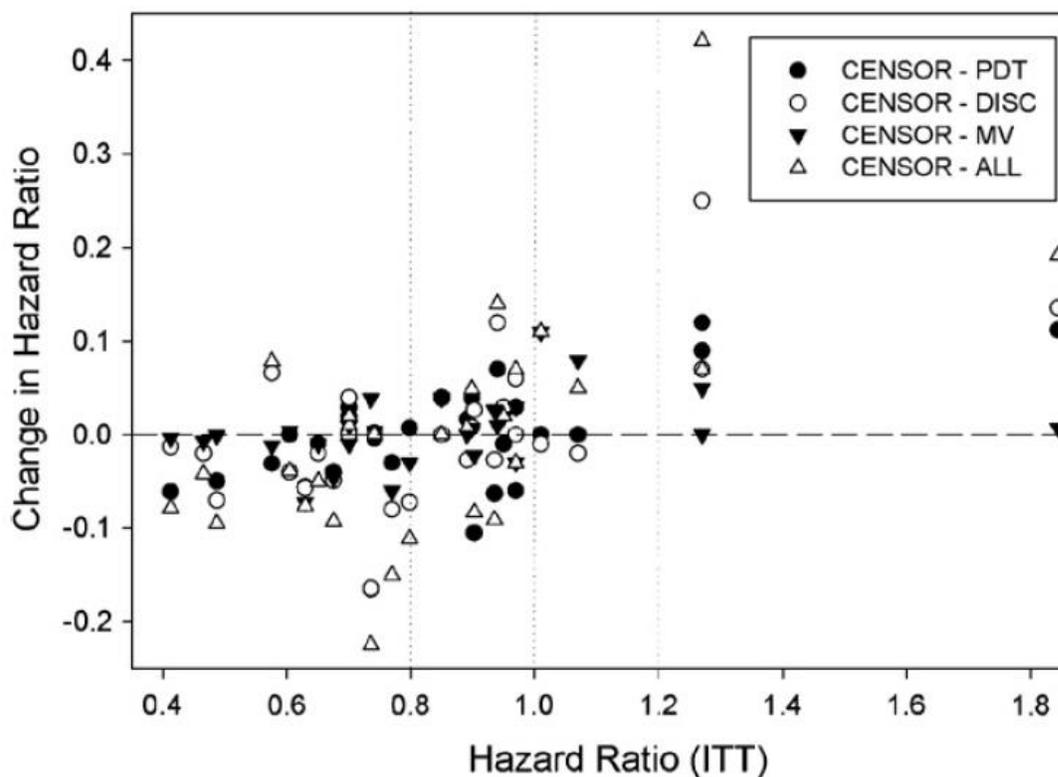
ous filings. A PhRMA Working Group initiated by the industry was formed in 2008 to address some of the key ones, namely, tumor assessment method, censoring rules, and statistical analysis method [2-3]. The working Group consisted of approximately 35 participants representing 17 pharmaceutical companies, the FDA, academic institutions, and imaging contract research organizations. The collaborative research concluded successfully in 2013 with three consensus recommendations. The emergence of immune checkpoint inhibitors, a new generation of antibody-drug conjugates, new kinase inhibitors such as sotorasib, and other novel drugs in the last decade have significantly transformed the field of oncology. However, there has been little methodological advancement in the design and analysis of clinical trials with PFS as the endpoint. The recommendations from the Working Group a decade ago are still relevant today. It is necessary to review them to shed light for the future.

### Recommendations from the PhRMA PFS Working Group

Tumor assessment method: The assessment of progression is not entirely objective, and different reviewers

of the same set of scans will not always agree when a patient has progressed. However, there is a critical distinction between measurement error resulting from random variation, which increased noise levels tend to attenuate treatment effects, and bias, which increases the probability of a false negative or false positive finding. While occasional disagreements in patient-level assessments between BICR and local evaluation (LE) are inevitable, a comprehensive meta-analysis by the Working Group [4] demonstrates that the hazard ratios in Phase 3 trials are consistent between the two assessment methods ( $R = 0.947$  (95% CI: 0.88, 0.97), Fig. 1). Similar findings were reported in [5-6]. Therefore, BICRs may not be necessary especially in truly blinded trials. Otherwise, a sampling based BICR may be used to detect the bias for deciding whether to conduct a full BICR.

In CodeBreak 200, as noted by the FDA, there were greater early calls of PFS by LE compared to BICR assessment for the docetaxel arm (early discordance) and there were also more late calls of PFS by LE compared to BICR assessments for the sotorasib arm (late discordance). Besides, there was early crossover to sotorasib treatment of patients in the docetaxel arm before BICR-assessed



**Figure 2: Change in ITT hazard ratio from applying censoring rules in analysis. Each point represents 1 of the 28 trials analyzed using one of the 4 censoring rules.**

progressive disease, which has confounded BICR assessment of progression with interference of the new therapy.

**Censoring rules:** There are various views on how censoring should be handled, which sensitivity analysis should be conducted, and which analysis should serve as primary. The variation in views includes guidance conflicting from regulatory agencies, where EMA favors an intend-to-treat (ITT) approach, while FDA prefers an alternative method [7-9]. The Working Group reanalyzed 28 oncology clinical trials to understand the impact of different conventions for handling censored observations. These conventions include: 1) ITT - includes all recorded PFS events, regardless of stopping randomized therapy or subsequent therapy; 2) PDT - same as ITT, but censors patients who receive subsequent anti-cancer therapy before progression at the latest prior assessment; 3) DISC - same as ITT, but censors patients who prematurely discontinue randomized therapy due to toxicity or other non-progression related reasons at the latest prior assessment; 4) MV – same as ITT, but censors patients who progress or die (in the absence of progression) after two or more missed visits, at the latest prior assessment; 5) ALL - same as ITT, but censors patients who are censored in either PDT, DISC, or MV at the earliest cen-

soring time. The hazard ratios from the analyses based on the four censoring rules were generally consistent with the ITT approach (Fig. 2). Importantly, although consistent, the ITT analysis generally resulted in smaller treatment effects (HRs closer to 1) than those obtained by applying the various censoring rules, a desirable feature for registration trials. Therefore, the ITT approach may be considered for the primary PFS analysis.

To adhere to the ITT principle, all patients should be assessed for disease progression even after early dropouts. However, in CodeBreaK 200, 13% of patients (n = 23) in the control arm withdrew consent and were censored at day 1 for not having a post-baseline assessment compared with 1% of patients (n = 2) in the sotorasib arm. Besides, patients in the docetaxel arm crossed over to sotorasib treatment before BICR-assessed progressive disease were censored at the last assessment prior to new therapy in the primary analysis. Incomplete information for the assessment of PFS per BICR was particularly concerning to FDA as this was the primary endpoint of CodeBreaK 200.

**Statistical analysis method:** The ‘true’ progression time for each patient is only known to have occurred at some point between the current and the previous clinical assessment. PFS is intrinsically an interval-censored

**Table 1. Comparison of log-rank test under the right-censored data approach and an interval-censored analysis method when the true HR = 0.6.**

Event rate	Log-rank		Interval censored		True <sup>a</sup>
	T1 error <sup>b</sup> (%)	HR	T1 error <sup>b</sup> (%)	HR	T1 error <sup>b</sup> (%)
<i>Equal assessment between arms<sup>c</sup></i>					
Constant	2.7	0.60	2.8	0.60	2.7
<i>Differential assessments between arms<sup>d</sup></i>					
Constant <sup>e</sup>	35.0	0.55	2.3	0.61	2.4
Increasing <sup>e</sup>	59.2	0.53	2.6	0.61	2.7
Decreasing <sup>e</sup>	32.3	0.55	2.8	0.60	2.5

<sup>a</sup> True is a benchmark assuming exact PFS time known.

<sup>b</sup> T1 Error: proportion of simulations where 1-sided  $p < 0.025$ .

<sup>c</sup> Equal assessment: patients assessed every 8 weeks in both groups.

<sup>d</sup> Differential assessment: patients are assessed every 8 weeks and 16 weeks in the control and experimental group respectively.

<sup>e</sup> Constant, increasing and decreasing event rates correspond to exponential, weibull 1.5 and weibull 0.67 distributions respectively.

**Table 2. Interval-censoring rules for primary and sensitivity analyses of PFS**

Situation	Primary analysis	Sensitivity analysis 1	Sensitivity analysis 2
No PD and no death; no treatment discontinuation without documentation of PD; no initiation of new anticancer therapy without documentation of PD	L= last non-PD assessment day R= infinity	L= last non-PD assessment day R= infinity	L= last non-PD assessment day R= infinity
No PD and no death; treatment is discontinued without documentation of PD; no initiation of new anticancer therapy without documentation of PD	L= last non-PD assessment day R=infinity	L= last non-PD assessment day before treatment discontinuation R=infinity	L= last non-PD assessment day before treatment discontinuation R= treatment discontinuation day
No PD and no death; new anticancer therapy is initiated	L= last non-PD assessment day R=infinity	L= last non-PD assessment day before initiation of new anticancer therapy R= infinity	L= last non-PD assessment day before initiation of new anticancer therapy R= new anticancer therapy initiation day
PD or death documented immediately after $\leq 1$ missed disease assessment	L= last non-PD assessment day R= documented PD or death day	L= last non-PD assessment day R= documented PD or death day	L= last non-PD assessment day R= documented PD or death day
PD or death documented immediately after $\geq 2$ missed disease assessments	L= last non-PD assessment day R= documented PD or death day	L= last non-PD assessment day R=infinity	L= last non-PD assessment day R= documented PD or death day

time-to-event variable. Despite the availability of multiple published techniques for conducting interval-censored data analyses [10-11], PFS data are routinely treated as right-censored, and the conventional log-rank test is used for the analysis. Using Finkelstein’s semiparametric method as an example, a comprehensive simulation study has successfully demonstrated the superior performance of a bona fide interval-censored data analysis method

[12]. Table 1 demonstrates its robustness [2].

To be consistent with the preceding recommendation, when PFS is analyzed as an interval-censored variable, it should also follow the ITT principle. Table 2 illustrates interval-censoring rules for both primary and sensitivity analyses [13].

Since the median PFS difference of approximately 5 weeks in CodeBreaK 200 was less than the 6-week scan

interval, the FDA considers the results unreliable. This is because it cannot be ruled out that the difference is not due to inherent measurement error. An interval-censored analysis was conducted by the FDA, resulting in a median difference of 5 days. It is important to note that this was not the first time the FDA conducted such an analysis. An earlier example occurred during the NDA review of the Phase 3 study of Genasense (G3139) in 2004. However, it raises questions as to why a method deemed more reliable is only used as a backup plan.

## Discussions

The potential for bias in investigator-based assessment of disease progression in open-label trials is well described and understood. In the case of CodeBreak 200, due to the difference in administration routes of sotorasib (oral) and docetaxel (IV), it is challenging to keep it double blinded. Besides, the investigator's enthusiasm over a potential breakthrough medicine may have led to a higher rate of discrepancy and potentially greater bias in the estimation of the treatment effect compared to a typical study. This is a major concern for the FDA. Unless the treatment effect is expected to be overwhelmingly evident, despite the potential challenges, it is advisable to keep a trial double blinded so that the PFS data would be more reliable even if they are based on LE. BICR takes time and has its fundamental limitations when a real time decision is required (e.g., crossover). In CodeBreak 200, Amgen implemented a procedure for crossover decisions that required an independent radiologist to review scans within three business days after an investigator made an assessment of disease progression. The effort was commendable; however, it didn't successfully achieve the desired outcome. The sampling-based method proposed by the Working Group and an audit method proposed by NCI [14] for reconciling the difference between LE and BICR were well accepted at the ODAC Meeting on "Evaluation of Radiologic Review of Progression-free Survival in Non-hematologic Malignancies" in July 2012. However, there are numerous challenges to implement either one in practice [15].

The imbalance in early withdrawal between the two groups in CodeBreak 200 would be preventable in a double-blinded trial. Continued follow-up of these patients would also be helpful. Ad-hoc sensitivity analyses on the impact of imbalance depend on the underlying assumptions and the results are often inconclusive. Censoring patients at the last assessment prior to new therapy is a common practice in submissions to the FDA.

Alternative censoring rules were also explored by Amgen in a sensitivity analysis: considering initiation of new anti-cancer therapy as an event; patients who were lost to follow-up or withdrew consent were treated as having an event at the next scheduled assessment; and using the closest scheduled visit date as progression or censoring date. The results are generally consistent with the primary analysis [16]. Moving forward, it is beneficial to have a consensus on the primary censoring rules, and the ITT approach seems to be the most natural choice. This aligns not only with the well-accepted statistical principles for clinical design (ICH E9) but also ensures consistency between the EMA and the FDA.

The interval-censored data analysis of PFS in CodeBreak 200 was mainly prompted by the underwhelming median improvement based on the right-censored analysis. It is debatable which parameter better captures the PFS effect, hazard ratio or median difference [18-19]. Nevertheless, as an intuitive measure of the PFS effect, median improvement is routinely cited in both medical publications and clinical practice. Unfortunately, the conventional right-censored approach is intrinsically biased (see Appendix for the properties of median PFS). In addition to taking an interval-censored data analysis approach, one may further improve it in trial design by randomizing patients to staggered assessment schedules (the idea was originally proposed by Keaven Anderson in a private communication). In a hypothetical example of a design with two staggered assessment schedules, the first assessment may be conducted at Week 9 in one schedule and Week 6 in the other, with subsequent assessments occurring at 6-week intervals under each schedule. As a result, there will be tumor assessments every 3 weeks in each arm starting from Week 6. A similar approach was successfully proposed for a Phase 3 chronic lymphocytic leukemia trial (unpublished). An extensive simulation study shows that the staggered assessment approach along with an interval-censored data analysis can substantially reduce the bias of median PFS estimation [19]. With software for interval-censored data analysis now widely available, the time is ripe for making it the primary analysis method.

There are issues that were not addressed by the Working Group, and additional simulation and research may be conducted to enhance the robustness of the recommendations regarding tumor assessment methods [20]. While the censoring rules need to be properly embedded in the emerging framework of estimand, the ITT principle should be followed. Interval-censored data analysis is a well-established statistical field. It is

our responsibility to make it a routine practice.

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## Appendix: Properties of median PFS based on the right-censored approach

Suppose that a time-to-event variable  $X$  has mean  $\mu$ , standard deviation  $\sigma$  and median  $\nu$ .

Denoting by  $f(\cdot)$  its density function, we have  $\mu = \int_{-\infty}^{\infty} xf(x)dx$ ,  $\sigma^2 = \int_{-\infty}^{\infty} (x - \mu)^2 f(x)dx$ ,

and  $\int_{-\infty}^{\nu} f(x)dx = 0.5$ . As an alternative definition of  $\nu$ , it is a value of  $d$  that minimizes

$\int_{-\infty}^{\infty} |x - d| f(x)dx$ . When  $X$  has an exponential distribution function with rate parameter

$\lambda$ ,  $\mu = 1/\lambda$  and  $\nu = \log(2)/\lambda$ . Let  $\{X_i, i=1, \dots, n\}$  be independent event times from  $f(\cdot)$ .

It is commonly known (e.g., <https://en.wikipedia.org/wiki/Median>) that the sample median

$X_{([n/2])}$  has an asymptotic normal distribution (denoted to be  $\Phi(\cdot)$ ) with mean  $\nu$  and

standard deviation  $(2\sqrt{n}f(\nu))^{-1}$ .

Let  $C_j$  be  $j$ -th assessment time for  $X$  ( $j=1, \dots, k$ ). Define  $C_0=0$  and  $C_{k+1}=\infty$  for ease of presentation. The empirical estimate of the median based on the right-censored approach is  $C_j$  if  $C_{j-1} < X_{([n/2])} \leq C_j$  for  $1 \leq j \leq k$ , and is not observable if  $X_{([n/2])} > C_k$ . Therefore, the probability is  $\Phi(C_j) - \Phi(C_{j-1})$  for the empirical median to be  $C_j$  ( $1 \leq j \leq k$ ), and  $1 - \Phi(C_k)$  for the empirical median to be not reached. Figure A provides asymptotic probabilities for empirical median estimates when true median ranges from 4 to 5 under the assessment schedule of  $C_j=j$  ( $j=1, \dots, 10$ ). Two sample sizes are considered ( $n=100$  and  $n=200$ ) and two values are considered for  $f(\nu)$  (0.2 and 0.4). It is easier to base upon a standard normal distribution to understand  $f(\nu)$ ;  $f(\nu)=0.4$  would approximately correspond to  $\sigma=1$  and  $f(\nu)=0.2$  would approximately correspond to  $\sigma=2$ . The two settings assume that 68% of the events fall within one or two assessment intervals of the median, respectively. The figure shows that 5 is the dominant estimate as expected. The estimate is either 4 or 5 when

the true median is between 4 and 4.5, and is either 5 or 6 when the true median is between 4.5 and 5. The uncertainty decreases as  $n$  or  $f(\nu)$  increases. For example, when  $n=200$ , the estimate will be most likely 5 unless the true median is very close to 4 or 5.

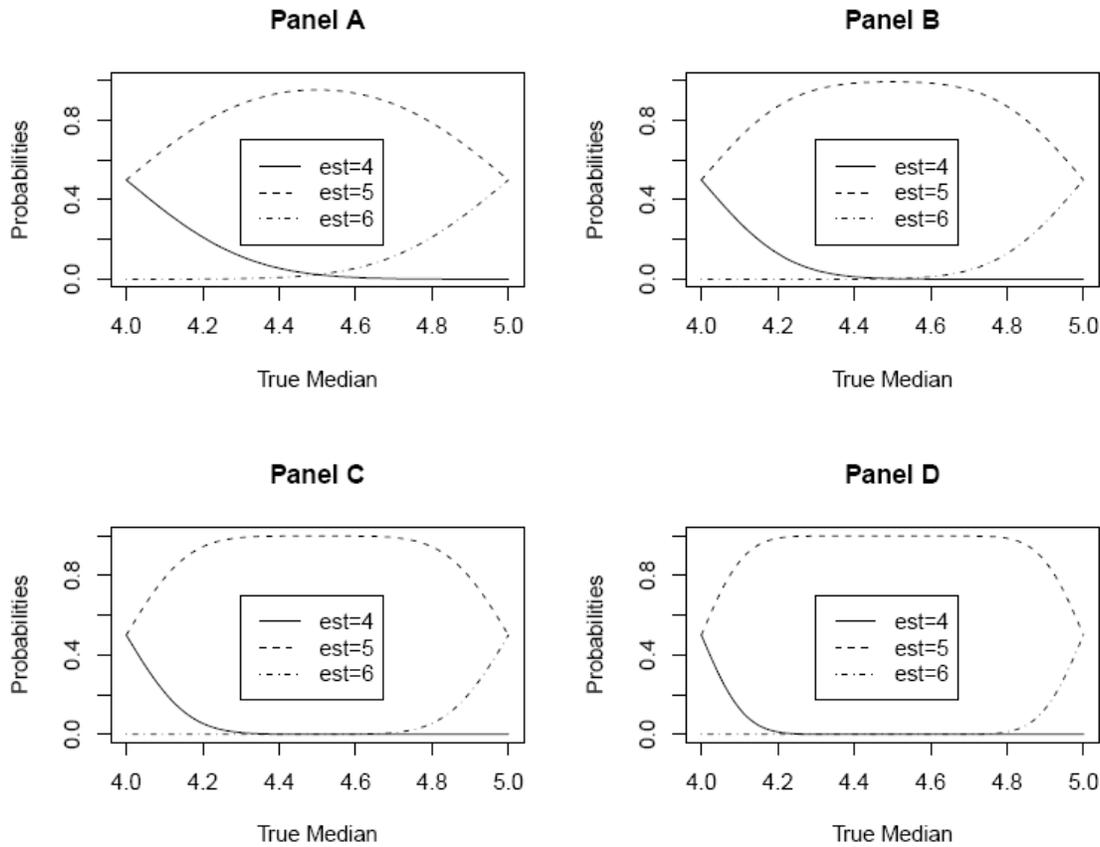


Figure A. Asymptotic probabilities for empirical median estimates to be 4 (est=4), 5 (est=5), or 6 (est=6) when true median ranges from 4 to 5 under the assessment schedule of  $C_j=j$  ( $j=1, \dots, 10$ ). **Panel A:**  $n=100$  and  $f(\nu)=0.2$ ; **Panel B:**  $n=200$  and  $f(\nu)=0.2$ ; **Panel C:**  $n=100$  and  $f(\nu)=0.4$ ; **Panel D:**  $n=200$  and  $f(\nu)=0.4$ . The probabilities of an estimate being less than 4 or greater than 6 is negligible and are not shown in the figure. ■

# A CALL FOR A REGULATORY GUIDANCE ON BAYESIAN METHODS IN THE STATISTICAL SUPPORT OF CMC DEVELOPMENT STUDIES

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## HIGHLIGHTS

- ASA Biopharmaceutical Nonclinical Biostatistics Bayesian CMC Scientific Working Group: Aiming to advance the use and acceptance of Bayesian methods in the nonclinical biopharmaceutical statistics.
- Bayesian methods in CMC: Bayesian methods are being increasingly applied to a wide array of CMC Studies including stability analysis, specification setting and assessment, validation of analytical procedures, process development, process validation, comparability studies.
- Calling for Regulatory Guidance on Bayesian Methods for CMC: Regulatory guidance similar to FDA Medical Devices guidance would enable improved statistical practice and enhance the statistical modeling of CMC studies.

## I. Introduction

### 1. The Nonclinical Biostatistics Bayesian Scientific Working Group

The Nonclinical Biostatistics Bayesian Scientific Working Group was established in 2019 by the American Statistical Association Biopharmaceutical Section's Nonclinical Working Group (<https://community.amstat.org/biop/workinggroups/nbcwg/index>). It was created to advance the use and acceptance of Bayesian methods within the nonclinical biopharmaceutical statistics space. Subsequently, the working group was split into two workstreams;

- The first workstream focuses on Chemistry, Manufacturing and Controls (CMC) applications.
- The second workstream focuses on Discovery/Preclinical applications.

This paper captures the thinking of the CMC working group, with the intention to advance the ideas articulated by Faya and Berry (2021) on the need for a Bayesian guidance focused on CMC applications. Our paper is intended to serve as a jumping off point for a more extensive collaborative effort to shine light on the increasing need for a CMC Bayesian guidance.

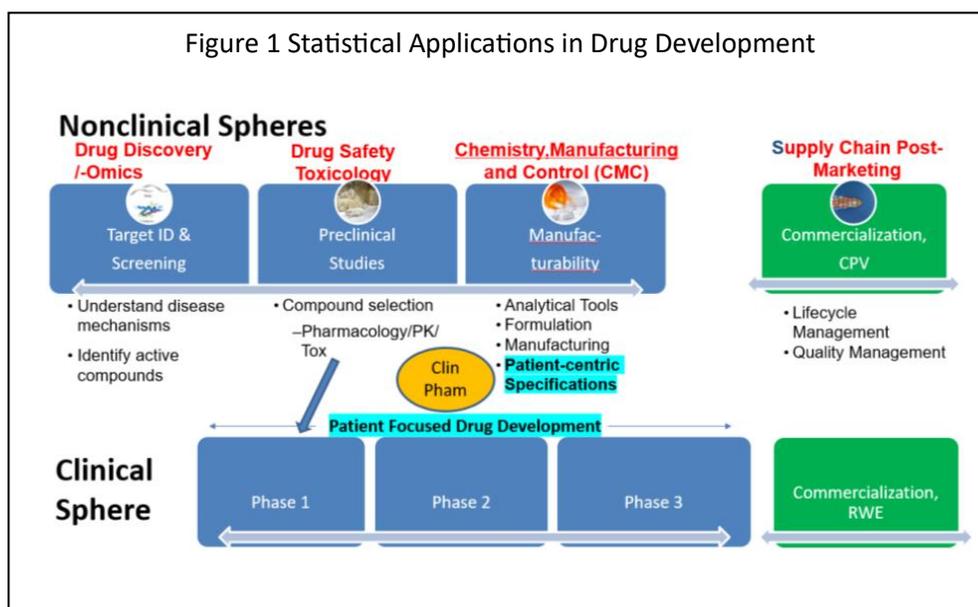
### 2. CMC studies are a critical part of the overall drug development process

Pharmaceutical development of a therapeutically important compound requires extensive biological, chemical/

physical, and engineering experimentation. Much of the development work is governed by regulatory rules and guidelines (see Chapter 2, Zhang, 2016). The drug development process begins with the discovery and chemical characterization phase, followed by toxicology and metabolism studies in animal models, concurrent CMC studies to formulate and manufacture a commercially viable dosage form, and ending with clinical studies that demonstrate the safety and efficacy of the compound in humans (Zhang, 2016). The general process is outlined in Figure 1 (Altan et al., 2023).

The ability to update current information with experience and knowledge makes Bayesian methods particularly useful in the face of rapid technological advances and data acquisition. This feature sets the stage for more efficient use of resources. As statistical analysis planning is an integral part of each phase of the drug development process, regulatory guidelines that pertain to the technical statistical work of nonclinical studies supporting regulatory applications are both helpful and necessary. A guidance would also improve their acceptance and use by harmonizing expectations for applications including Bayesian methods.

Recent publications in the CMC space have applied Bayesian approaches to stability studies, sample size estimation in process validation, equivalence/similarity testing and assay performance characterization (Sondag et al., 2016; Yang and Novick, 2019; Lesaffre et al, 2020; Faya and Pourmohamad, 2022; Altan et al, 2023). It is clear from these applications that the Bayesian paradigm has unique features arising from the



ability to use resources more efficiently and ultimately benefit patients and society. Section II reviews three FDA issued guidances as a basis for developing a CMC specific guidance. Section III reviews selected CMC Bayesian applications. Section IV presents a summary and Section V gives a set of recommended topics relevant to a CMC Bayesian guidance.

## II. Review of current FDA Bayesian guidances for industry

The following FDA guidances make substantive references to Bayesian methods:

- (1) Guidance for the use of Bayesian methods in the design and analysis of medical device trials (FDA-CDRH) (2010),

- (2) Adaptive Designs for Clinical Trials of Drugs and Biologics (2019),
- (3) Interacting with the FDA on Complex Innovative Trial Designs for Drugs and Biological Products (2019).

Guidance (1) provides an extensive discussion of Bayesian applications in Medical Device trials. In Guidance (2), Section IV.B offers a brief discussion on the topic of Bayesian Adaptive Designs with examples and points the reader to guidance (3) for information on FDA expectations in relation to methodology documentation. These three guidances apply to clinical trials. Our goal is to review these in relation to the specific needs of CMC studies. For that purpose, Table 1 lists a set of topics or questions we see as important for a regulatory guidance to address, and brief statements from the existing guidances that address these topics.

**Table 1. Key CMC regulatory topics addressed by three current guidances**

Topic	Devices Guidance (1)	Adaptive Clinical Trials (2) or Interacting with FDA Guidance (3)
1	When and how to leverage prior knowledge, e.g., platform or early development data?	
	Partial discussion <ol style="list-style-type: none"> <li>a. Section 4.6, page 25 - Borrowing strength from other studies: hierarchical models</li> <li>b. Section 2.8, page 10 - What software programs are available that can perform Bayesian analyses?</li> <li>c. Section 7.1, page 37 - Prior probability of the study claim</li> </ol>	Partial discussion <ol style="list-style-type: none"> <li>a. Section III.B, page 4, in Guidance (3) “If prior information is being formally borrowed, details about the source and choice of the prior information, its relevance to the proposed trial design, and an explanation of steps taken to ensure that all relevant prior information is accounted for, so that the prior information formally borrowed does not lead to misleading results.”</li> </ol>
2	Will the FDA advise and approve the use of prior knowledge, or the use of a specific Bayesian alternative, to established approaches (e.g., shelf life, product release, validations, transfers, similarity, equivalence studies)?	
	Not discussed but references to FDA consultation advisable for: <ol style="list-style-type: none"> <li>a. Section 2.8 page 10 - choice of software/computations,</li> <li>b. Section 4.9, page 30 - multiplicity adjustments</li> </ol>	Partial discussion <ol style="list-style-type: none"> <li>a. Section VI.B, page 20 in Guidance (2) – “...<b>when a sponsor and FDA have agreed</b> that a trial can explicitly borrow external information via informative prior distributions.”</li> </ol>

<b>3</b>	Should the impact of prior knowledge be characterized? If so, using what methods?	
	<p>Discussed</p> <p>a. Section 2.7, page 8-9 - What are potential challenges using the Bayesian approach. See paragraph on “Choices regarding prior information” - “perform sensitivity analysis to check the robustness of your models to different choices of prior distributions.”</p> <p>b. Section 5.7, page 36, Sensitivity Analysis</p>	Not discussed
<b>4</b>	If a current regulatory guidance requires 95% confidence, is a 95% credible interval an appropriate measure of uncertainty for decision making purposes?	
	<p>Discussed</p> <p>a. Section 5.2, page 32 Hypothesis Testing - “For Bayesian hypothesis testing, you may use the posterior distribution to calculate the probability that a particular hypothesis is true, given the observed data.”</p>	Not discussed
<b>5</b>	When should a sponsor present the operating characteristics of a Bayesian procedure?	
	<p>Discussed</p> <p>a. Section 4.8, page 28 Assessing the operating characteristics of a Bayesian design - “provide tables of the probability of satisfying the study claim, given various “true” parameter values.”</p> <p>b. Section 7.1, page 38 Suggested Information to Include in your proposal – see paragraph on Operating characteristics (power and type I error rate) - FDA recommends you provide tables of the probability of satisfying the study claim, given various “true” parameter values (e.g., event rates) and various sample sizes for the new trial.</p>	<p>Partially discussed</p> <p>a. Section VIII.B, page 27 in Guidance (2) Documentation Prior to Conducting an Adaptive Design – “it is good practice to evaluate the important operating characteristics of the proposed design”</p> <p>b. Section VI.A, page 17 in Guidance (2) Simulations in Adaptive Design Trials - “...estimate trial operating characteristics and to demonstrate that these operating characteristics meet desired levels.”</p>
<b>6</b>	What is expected in relation to the verification of convergence for Bayesian MCMC methods?	
	<p>Discussed</p> <p>a. Section 7.5 page 45 Calculations - “When MCMC techniques are used, FDA recommends you check that the chain of values generated has indeed converged”</p>	Not discussed
<b>7</b>	What is expected of the computer code for conducting Bayesian calculations in submissions?	
	<p>Partially discussed</p> <p>a. Section 7.1 page 40, see paragraph on “Program Code” - “FDA recommends you submit the program code”</p>	Not discussed

Our review of the existing clinical guidelines shows that the questions relevant to CMC were considered by the Medical Devices guidance and to a lesser extent by the Adaptive Designs guidance. Consequently, the Medical Device Bayesian Guidance may be more suitable to serve as a template for developing a specific guidance targeting CMC studies. We include the table of contents of the Devices guidance in Appendix 1 as a high-level overview of relevant topics. We seek acknowledgement that the Bayesian framework is an equally valid inferential methodology as conventional frequentist methodologies in CMC applications. Drawing from the structure of the Devices guidance, we propose the following key topics as a foundation for collaboration towards the goal of a CMC regulatory guidance:

1. Foreword /Introduction
2. Bayesian Statistics
3. Exchangeability/Borrowing Strength
4. Planning for a Bayesian CMC Study
5. Sources of Prior Knowledge
6. Assessing Operating Characteristics
7. Analyzing a Bayesian Model
8. References

The details of these topics will be elaborated on in future presentations and publications by the working group. Meanwhile, we seek input and comments from the readers of the Biopharmaceutical Report regarding their views and experiences with Bayesian applications and the need for a regulatory guidance in the CMC space.

### **III. Examples of CMC applications that would benefit from a guidance on Bayesian methods**

Bayesian methods have been applied to a wide array of studies in the CMC space. The following are examples of Bayesian applications that would benefit from regulatory guidance on the use of prior knowledge (whether informative or noninformative) in the modelling and analysis, as well as the other aspects of Bayesian modeling discussed in Section II. In addition, another important benefit to both regulators and industry would be the alignment of expectations with practice.

#### **I. Stability analysis**

Commercial pharmaceutical products are required to establish a shelf life or expiration date and specific storage condition instructions. Formal stability studies are conducted following requirements laid out in ICH guidances Q2, Q1D and Q1E. ICH Q1E lays out a frequentist fixed-effects model to describe stability profiles over time. ICH Q1D is a companion guideline that permits a reduced experimental design through bracketing and matrixing, where bracketing reduces the number of stability factors and matrixing permits selectively omitting time points for some batches. A Bayesian hierarchical model approach was published by Altan et al. (2023). When compared to traditional statistical approaches, Bayesian methods offer several advantages, such as direct assessment of hypotheses, a straight-forward framework for shelf-life estimation, and little or no need for large-sample approximations. The use of prior information could permit broader use of the hierarchical modeling approach to satisfy ICH Q1D and Q1E. Still, important questions relating to the nature and integration of prior knowledge would benefit from regulatory guidance. This is particularly important when the number of batches studied is small.

#### **2. Specification setting and assessment**

As defined in ICHQ6A, specification setting lies at the center of CMC studies establishing a framework for defining and controlling the quality of pharmaceutical products. Ideally, specifications and other manufacturing limits should be based on patient requirements, clinical experience, and scientific understanding to ensure a safe and efficacious product (Hermans et al., 2017). Although specification setting is not fundamentally a statistical activity, statistical modeling and analyses can help to inform the process of setting specifications. In circumstances where statistically derived ranges to inform specification setting are computed with limited data, the inclusion of prior knowledge, platform experience, and data from similar products has the potential to reduce the uncertainty in the estimates and consequently yields a narrower and more practical acceptance range. Regulatory guidance is therefore needed to clarify criteria for the inclusion of prior knowledge and historical information in setting manufacturing limits. In addition, given specification or control limits for a given quality attribute, the probability of observing results outside of the limits is a simple calculation from the posterior predictive distribution given a calibrated process model and valid assumptions.

### 3. Validation of analytical procedures

The revised version of ICH Q2/Q14 emphasizes the use of interval estimates for validation analyses. Bayesian methods would be particularly useful to generate appropriate and practical interval estimates, especially when working with limited sample sizes (Sondag et al., 2016). The Total Error approach (Dewé et al, 2007), which encompasses both accuracy and precision, would benefit from inclusion of prior knowledge with a Bayesian framework provided in Novick et al. (2021) and Faya et al. (2023). Regulatory guidance on analytical procedure validation would be helpful.

### 4. Process development

Process development refers to the systematic and progressive activities conducted to design, optimize, and establish a robust manufacturing process of a pharmaceutical product. It involves the exploration, evaluation, and refinement of various process parameters, equipment, and operating conditions to achieve the desired product quality, yield, and efficiency. These concepts are covered under ICH Q11 (Development and Manufacture of Drug Substance), which provides guidance in establishing the sets and ranges of input parameters (called the design space) that result in an acceptable-quality pharmaceutical product. Bayesian methods provide an excellent quality-by-design vehicle (Yu et al., 2014) because process parameter settings can be optimized through probabilistic definition of a manufacturing design space (Peterson, 2018, Mockus et al., 2019) where acceptable quality product can be manufactured with a high level of assurance. Relevant regulatory guidance on the use of prior knowledge in the context of limited experimental resources can be valuable to define a practical design space.

### 5. Process Validation

Process validation is conducted to ensure consistent and dependable performance of a manufacturing process. Bayesian sample size calculations can help to bring efficiencies to the validation studies, by integrating prior knowledge into the calculations from platform or historical information. The guidance would be useful to support appropriate choices of prior distributions.

Process validation, as defined by the FDA guidance “Process Validation: General Principles and Practices,” is conducted to ensure consistent and dependable performance of a manufacturing process. Validation-study sample sizes may be reduced using Bayesian priors to

supplement study data to improve efficiency. Regulatory guidance would be useful to support appropriate choices of prior distributions.

### 6. Comparability studies

ICH Q5E provides regulatory guidance for comparability studies, which serve to evaluate the potential impact of changes in a manufacturing process or product on critical quality attributes. A sound comparability protocol involves establishing well-defined acceptance criteria (Yu et al., 2017). However, in certain instances, comparability studies may encounter limited data, particularly when examining new products, which can entail complex model specifications. A Bayesian framework can effectively manage such scenarios by leveraging prior information to lead to more reliable criteria and inferences; for example, see Yu et al. (2017). Regulatory CMC guidance addressing this topic would be useful to the industry.

## IV. Summary

Given its ability to incorporate prior data and its straight-forward interpretation, the Bayesian statistical framework is particularly well suited for the design and analysis of CMC study data. Work in the CMC space is often built upon data collected from previous phases of development or experience with related drug products, producing a trove of prior information. In addition, the clinical and Devices Bayesian guidances have drawn greater attention to the use of Bayesian methods in pharmaceutical experimental studies in general, including CMC.

Despite these practical benefits, without a regulatory guidance, there can be reluctance to apply Bayesian methods to regulated CMC studies. In that light, we expanded on the issue raised by Faya and Berry (2021) on the importance of establishing regulatory guidance specific to Bayesian applications in CMC studies. Such a guidance would provide an analogue to the Bayesian regulatory guidance for medical devices. Several examples were provided to illustrate the types of CMC studies where Bayesian modeling could be applied, but with room for regulatory questions and guidance. Increased focus on incorporating prior knowledge and its potential to enhance the statistical modeling of CMC development studies further reinforces the need for a CMC guidance.

Based on our review of industry practices, three guidances, and the Faya and Berry article, we provide

some general recommendations in Section V.

## V. Recommendations

1. CMC studies are often built upon previous knowledge, and would naturally benefit from the incorporation of prior information. Currently, regulatory guidance is aimed at users of frequentist methods with descriptions of confidence intervals and p-values. Regulatory acknowledgment of the Bayesian approach and details on types of information that can form the basis for prior distributions, the limitations on prior distributions, and the usage of credible intervals and probabilities for making inferences should be covered.
2. Guidance on the supporting evidence to be provided (prior justification, model convergence, operating characteristics) would simplify the submission and review process and align expectations between industry and regulatory bodies. The Devices Guidance addresses these issues and contains reasonable language that gives helpful information. The use of similar language would ensure consistency.
3. A general baseline for considerations expected to be addressed in studies using Bayesian methods would be helpful. Future guidance should provide a comprehensive discussion on this topic.
4. The adaptive designs guidance suggests consultation with the regulatory authorities to discuss incorporation of Bayesian statistical methods prior to the conduct of the study. Unlike clinical trials where large numbers of human subjects are recruited, most CMC studies are small in scale and have shorter durations involving non-human subjects. Imposing a requirement for consultation prior to study initiation could impose undue burdens on companies and impede the progress of the development process. Guidelines regarding situations where prior-to-study consultation is recommended would be helpful.

### Authors' Note

*The views expressed in this article represent the personal opinions of the authors, and not those of their employers.*

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## Appendix I : Devices Guidance

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# STATISTICAL LEADERSHIP IN THE ERA OF AI/ML

ASA BIOP Leadership-in-Practice Committee (LiPCom)

## HIGHLIGHTS

- AI/ML technologies are increasingly prevalent across industries like drug development, finance, aeronautics, transportation, and retail.
- Statisticians and data scientists drive these innovative design methodologies in clinical trials.
- Broader adoption in drug development depends on experts' ability to address unease among key opinion leaders, sponsors, and investigators.
- Requires unique strategic leadership and engagement skills of statisticians and data scientists.
- This article explores crucial leadership and business acumen behaviors for those implementing AI/ML technologies.

Since the advent of big-data and cloud-computing, the concepts of artificial intelligence (AI) and machine learning (ML) have gained increasing prominence. Artificial intelligence has been defined as a set of technologies operating as a system designed with the ability to mimic cognitive functions associated with human intelligence, such as being able to see, understand and respond to spoken or written language or learn and act to solve complex problems. In contrast, machine learning is considered a subset of artificial intelligence, which uses algorithms to analyze large amounts of data, learn from the insights, make predictions, and enable informed decisions.

There is extensive published literature on the history and evolution of AI/ML and its broad applications across various industries and technology areas, including healthcare, drug development, finance, aeronautics, engineering, construction, transportation, and retail. However, within many organizations there remains a gap in understanding of when, for what and how these technologies can be implemented, as well as inherent skepticism around the acceptability of such techniques and the inferences drawn from them. Closing this gap requires proactive leadership across disciplines. Leadership is needed for raising awareness of the value proposition for organizations to invest in AI/ML, for building a strategic vision that leverages AI/ML and for sensitizing the organization to the required skill sets, technologies and the broader infrastructure and organizational culture that are critical for maximizing the value that AI/ML could bring.

The need for statistical leadership in the AI/ML space is easily appreciated within the context of research and

development, particularly given the expertise that statisticians and data scientists bring to data evaluation, starting from formulating the research question to constructing the study design, crafting the methodological approach to analysis and driving interpretation of results. For example, in clinical trial drug development there is existing broad consensus that statistical leadership is needed at the technical, operations and strategic levels. Such leadership exerts direct impact on shaping the array of complex technical aspects of trial design and innovative analytic methods. It also influences broader scientific, regulatory, and trial operation strategies associated with drug development programs. One major challenge of clinical trials is lack of enough participants in the disease population, from which to draw valid inference about the true treatment effect. This challenge, particularly prominent with rare diseases having low population prevalences, can be circumvented today with the implementation of AI/ML approaches including, for example, disease progression modeling or in silico modeling & simulation for generating synthetic or virtual control arms. These approaches place greater demands on statistical leadership and compel statisticians or data scientists to play important leading roles within their organizations that drive strategic alignment among key stakeholders on the added value of complex AI/ML methods, while continuing to exert influence on technical aspects of trial design and operations. These pressures in today's AI/ML era, require statisticians and data scientists to demonstrate a higher level of leadership influence in their organizations, beyond their naturally expected technical skills.

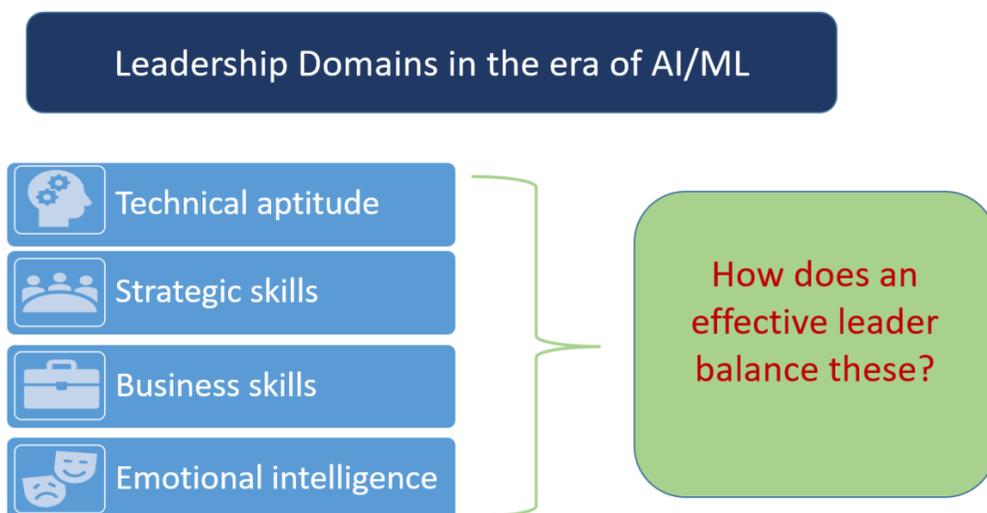


Figure 1

In her published opinions on leadership gaps in the AI world, Cindy Gordon<sup>1</sup> formulates the concept of the AI Brain Trust for organizations to consider at the macro level, and she identifies up to 40 general leadership skills categorized into 4 domains: strategic skills, business skills, emotional intelligence/social skills, and technical skills. This construct seems logical and can be useful in serving as a roadmap for organizations whose business strategy aims to develop and establish their capability in the AI space. In addition, the Berkeley Executive Education consortium in an article in Insights<sup>2</sup> discusses how to adjust leadership skills to address the disruptive potential of AI in the workplace. The article stresses the importance of adaptability in ensuring that work culture recognizes and balances the strengths of humans and machines. The vast body of published literature and opinion blogs on leadership skills in the era of AI is overwhelmingly tilted in the direction of big-data AI innovation using high-dimensional neural networks – an area less common to statisticians.

In clinical trial drug development, where statistical input is more visible, three common areas of application of AI/ML techniques are: (i) establishing proof-of-concept of a new chemical entity at the drug discovery stage for further clinical development into a potentially efficacious compound, (ii) precision medicine (also known as targeted therapeutics) applications for optimizing expected benefits of treatment or treatment sequence based on patients' characteristics from large real-world data (RWD) and (iii) construction of in silico synthetic control options for enriching clinical trials in confirming

efficacy. The proof-of-concept example relies heavily on deep-learning AI algorithms and requires knowledge well beyond statistics, such as expertise in molecular biology and chemoinformatics. The RWD example is a data driven approach that leverages both structured and unstructured data and holds the potential to improve healthcare quality and productivity. On the other hand, the in-silico example involves largely machine learning algorithms for modeling disease mechanism and predicting disease progression – an area far more wanting of statistical prowess. It is increasingly necessary to consider the types of leadership attributes and strategic impact behaviors needed of statisticians and data scientists in bridging the awareness gap for implementing AI/ML technologies in drug development.

Referring to Gordon's leadership categorization framework mentioned earlier, each domain highlights a broad class of leadership attributes or behaviors needed for effectively influencing acceptance and application of AI/ML approaches. When applied to clinical trial drug development, these leadership skills can help enhance the ability of statisticians and data scientists to impact the adoption and implementation of these technologies in their organizations.

We highlight the four leadership domains (Figure 1) according to Gordon's framework and encourage statisticians and data scientists to consider the individual leadership skills and behaviors pertaining to each domain.

The default expectation for statistical leadership in AI/ML is having the fundamental technical knowledge and expertise, which statisticians or data scientists possess.

Friedrich et al.<sup>3</sup> emphasize this point and claim that these experts play a pivotal role in the theoretical and practical understanding of AI/ML through their contributions in methodological development, planning and design of studies, assessment of data quality and data collection, differentiation between causality and association and assessment of uncertainty in results. Harnessing these relevant technical leadership skills in the AI/ML space requires sound literacy in mathematics, statistics, computer science, research methods, data analytics, computational modeling & simulation and most of all, aptitude in artificial intelligence and machine learning algorithms.

### Strategic skills

By virtue of their technical expertise in modeling and data analytics, statisticians or data scientists should be well positioned to lead development of the business case to build organizational capability in AI/ML and secure executive buy-in. This requires thinking at a strategic level and includes identifying a range of questions that might help construct key elements of the business case. For instance, where is the fit and vision for AI/ML in the organization? Would an external-facing strategic partnership model help to minimize disruption to the organization's business model? What expertise is needed and how to attract, develop and retain it? What's the value realization from such investment in talent? How would new AI/ML capability impact the cross-functional governance model and scientific and process alignment across disciplines? It is important to come up with the right types of higher-level questions that help bring together those key elements that define the big picture for making the case. Given their penchant for extracting meaningful insights from data, statisticians in general have the potential to be formidable strategic thinkers.

### Business skills

Recognizing that organizational success in AI/ML implementation requires multiple players and high-quality standards, statisticians or data scientists leading this implementation need to demonstrate ability to effectively handle key business drivers of success. These include relationship building with both internal and external customers, solution-oriented problem solving, attention to analytical and research rigor with strong ethical robustness, as well as program, project and process management skills. In addition,

it is important to maintain good awareness of key performance metrics and retain astute business and financial awareness associated with expansion of AI/ML activities.

### Emotional intelligence & Social skills:

The general gap in understanding around AI/ML techniques along with lack of established regulatory standards for their implementation, spurs a degree of concern and skepticism around their adoption in some areas of application. In the clinical trial drug development space, it is incumbent on statisticians and data scientists who are leading the way in pushing acceptance of such techniques, to adopt behaviors that enable positive engagement and that promote open collaboration. As pointed out by Gordon, behaviors such as curiosity to explore, listening to diverse opinions, flexibility to work under changing business conditions, adaptability, and resilience, as well as the ability to coach others and be an effective consultant, are critical skills for building trust in this new AI era. These behavioral skills set the stage for effective communication, a strong sense of teamwork and help guide collective efforts towards data driven decisions that contribute significantly to advancements in drug development. They also help with forging a fruitful environment for creativity, enthusiasm, and a common passion for success.

In summary, statistical leadership is critical to driving forward the adoption and implementation of AI/ML techniques. This is particularly true in drug development R&D, where recent publications from regulatory agencies such as FDA and EMA have opened the doors to implementation of these techniques. Statisticians and data scientists with strong technical expertise in this area, coupled with sound leadership ability are well placed to induce a paradigm shift in applying AI/ML techniques in drug development R&D.

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# REFLECTIONS ON MY TIME VOLUNTEERING WITH THE BIOPHARMACEUTICAL SECTION

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## HIGHLIGHTS

- A personal journey volunteering with the Biopharmaceutical Section
- Major activities of the Steering Committee during the years 2016-2020
- Ways for individuals to contribute their talents to the Biopharmaceutical Section

It's hard to believe that nearly five years have passed since serving as the 2019 Chair of the Biopharmaceutical Section (BIOP), and I'm happy to see that the Section is thriving and as busy as ever educating our members and providing them opportunities to collaborate with their peers. Chair was a role I served towards the end of a very active 10-plus-year period with BIOP. Like many journeys, things began small and became large over time as I took on more responsibility. To begin, I was a frequent member, starting in 2012, of the Organizing Committee (OC) of the then-called FDA-Industry Statistics Workshop. In other words, I submitted session proposals and worked to convince other OC members, including members of the Workshop Steering Committee (SC), that my proposals were worthwhile and should be selected for the final program. Despite not being a member of the SC, these journeys to Rockville to participate in the OC Meeting gave me a basic understanding of the inner workings of the Workshop. I found it fascinating. Responding to a call for volunteers at one of the OC meetings, I began my involvement with the Section podcast (which is detailed elsewhere) that would last until 2022. These initial footholds with the Workshop OC meetings and Podcast led to other opportunities, and these opportunities generally started off with "We need a volunteer to..."

Eventually, participating in OC meetings allowed me to meet numerous SC members which, in turn,

gave me the opportunity to join the Workshop SC in 2014. I guess I must have done a reasonable job on the SC, as I was recommended to serve as Industry Co-chair for the 2015 Workshop. I continued to serve on the OC and SC of the Workshop until 2018, though I took more of a supporting role over time. Podcasting was a wonderful opportunity to engage the larger BIOP community, and it provided me an opportunity to engage a significant portion of the BIOP SC – the Publications Committee. This committee, run by the Publications Officer, helped organize and lead activities surrounding the Biopharmaceutical Report, Webinars, Podcasts, webpage, and social media. Because I co-lead a key effort of Publications Committee, I was able to attend BIOP SC meetings to provide updates on podcasts. I enjoyed SC Meetings, as I had an opportunity to hear about ongoing and upcoming activities within BIOP. For example, there was a push in 2013-2014 to organize Scientific Working Groups (SWG). Given my research areas at the time, I became one of the charter members of the Safety SWG in 2014, the first in a long line of SWGs for BIOP. As time moved on, I started thinking about potential opportunities to serve as a BIOP officer. In 2016, I volunteered to become one of the two candidates for Publications officer. When the call came again two years later, I offered to become a candidate for Section Chair. (And somehow, I was elected twice – thank you for that!).

Section Chair is an enormous three-year role that is shared by three individuals; each year the nature of the role changes, with the second year being the most visible and what is considered “Chair”. During the first year as Chair-Elect, you learn the responsibilities of becoming Chair in the following year. In the second year as a Chair, you are responsible for organizing and leading the three BIOP SC meetings. In the final year as Past-Chair, your focus shifts to clean-up and documentation, most notably reviewing the Manual of Operations (MoO) for accuracy and identifying a list of candidates for the upcoming year. All of the details for Chair and other BIOP roles are listed in the MoO, posted to the BIOP website.

My time on the Steering Committee as Chair and Publication Officer (I only served two of three years) lasted from 2016-2020, and I witnessed a lot of important initiatives and growth within the Section during these years. The SC continued to review and approve requests for new SWGs which quickly grew in number. In turn, these SWGs generated valuable outputs such as manuscripts, webinars, short courses, and eventually books. Notably, BIOP extended its reach by producing content for YouTube. A Workshop Taskforce was convened to address many of the operational challenges that began to plague the Workshop, now called the Regulatory-Industry Statistics Workshop (RISW). I commend the BIOP SC for making this difficult decision, since a lot of thought and investigation were undertaken by the Taskforce, and there was insufficient time for thorough discussion during BIOP SC meetings. In addition, we formed a 40th Anniversary Committee to begin preparation to celebrate our longevity in 2021. The establishment of the Leadership in Practice Committee (LipCom) aims to offer training in practical leadership to members of the BIOP community. While all of these initiatives were extremely important, I think the most notable undertaking of the BIOP SC in those years was instituting the Scholarship Award. To date, more than two dozen students have been awarded for their research and leadership. The extremely generous cash award allows students to attend JSM to engage with other statisticians and data scientists about their research and, in turn, exposes them to new ideas.

As my term as Chair came to a close, the world underwent drastic changes due to the onset of COVID-19. While we had some preliminary preparations in place, none of us could anticipate how extensive or how

long our virtual existence would become. For example, in the spring of 2019 we held the first fully virtual meeting of the BIOP SC due to some logistical challenges that BIOP was experiencing with the ENAR meeting. There were some hiccups, but no one could have imagined that one year later we would be holding all of our SC meetings virtually, as well as entire conferences. Further, due to the economic pressures of COVID, the owners of the Marriott Wardman Park building would go bankrupt in late 2020, robbing the Section and RISW of its home for many years. In some ways, BIOP was prepared for this outcome. One of the Taskforce’s responsibilities was to identify larger space for RISW since the meeting had sold out for several years in a row with no space to grow in attendance or offerings. And slowly, over the next two years, I completed responsibilities for podcasting and the Safety SWG and took a much needed break. The times I spent contributing to BIOP and RISW were some of the greatest moments of my professional career, and I am grateful for the opportunities I had to serve the community and the trust others placed in me to serve it. I’m not totally retired; I am hoping to participate on the LipCom committee in the near future.

I am occasionally asked how to get involved with BIOP. It may seem extremely challenging to find a way to participate. Even hitting the volunteer button on the website can result in a waiting period as SC members figure out how volunteers can contribute. What follows is a short list: chairing a session at JSM or RISW, discussing your research for a podcast, or recording a short course video for the BIOP YouTube page, forming or actively contributing to a SWG, teaching a webinar, or writing an article for the Biopharmaceutical Report. Don’t know how to make this happen? Write to the individuals on the BIOP SC leading or chairing the individual activities - their contact information is on the BIOP website(<https://community.amstat.org/biop/home>)! Offer up your talents! These activities in turn will provide you visibility which can lead to additional responsibilities.

And if anyone asks, “We need a volunteer to...”, be the first individual to raise your hand and enthusiastically say “I can do it”, even if you have no idea on how to do it. I promise that there will be time to figure it out. Twelve years ago, I had no idea how to plan or produce a podcast, but what an amazing journey that turned out to be. Where will new opportunities lead you? ■

# STRATEGIES FOR ADVANCING YOUR CAREER: AN INTERVIEW WITH YINGWEN DONG

Jun Xing (Sanofi), Louise Traylor (Sanofi)



**Yingwen Dong**

Global Head Biostatistics,  
Rare Disease & Rare Blood  
Disorders, Sanofi



**Jun Xing**

Biostatistics Team Leader,  
Global Medical Affairs and  
Diabetes/Cardiovascular  
Development, Sanofi



**Louise Traylor**

Global Head of Functional  
Excellence, Biostatistics &  
Programming, Sanofi

## HIGHLIGHTS

- Know yourself: Be aware of your own interests, strengths, and weakness, and understand your own passions and skills.
- Be prepared: Prepare yourself by continually learning and acquiring new skills. The more adaptable you are, the better you will be able to seize opportunities in different areas.
- Build a strong network: Find a diverse and extensive network of contacts in the field that will help you to identify new opportunities.

## Yingwen Dong's Bio

**Yingwen Dong is the Global Head of Biostatistics in Rare Disease and Rare Blood Disorders at Sanofi. Prior to this role, she served as the Deputy Global Head of Oncology Biostatistics in late phase at Sanofi. She received her Ph.D in Statistics from University of Minnesota and has 15 years of experience in the pharmaceutical industry. She currently serves as an ICSA representative on**

**the 2024 JSM programming committee, and as a steering committee member for the 2024 ASA biopharmaceutical section regulatory-industry statistical workshop. She served as the vice chair of the ASA committee on membership retention and recruitment in 2023. She was recently elected as the 2025 industry co-chair for ASA Biopharmaceutical Section Regulatory-Industry Statistics Workshop.**

In the summer issue of the 2023 BIOP report, there was an enlightening interview with Anne Heatherington on Leadership. We continue this journey with a conversation with Yingwen Dong, the newly-appointed Global Head Biostatistics, Rare Disease & Rare Blood Disorders (RD&RBD), at Sanofi. In this role, Yingwen is responsible for providing strategic inputs into the overall strategy and development program, leading a team of statisticians to work cross-functionally to achieve its goals. The role requires a balance of technical and business acumen, alongside demanded soft skills to communicate and influence effectively.

In a recent Statistical Leadership Forum at Sanofi, I had the chance to explore Yingwen's experiences, challenges, and strategies that have prepared her well for success in this role. Without further ado, let's dive into the conversation and discover the insights that Yingwen has to offer.

**Jun: Congratulations once again to our esteemed guest, Yingwen! We would love to start by hearing about your background and journey leading up to this point. Can you please tell us about some key moments in your career that have prepared you for this new role?**

**Yingwen:** Thank you, Jun. I really appreciate the opportunities I've been given and want to thank all my colleagues, managers, and mentors who guided me to excel in my career. Reflecting on my journey, I believe the key moments that prepared me for this new role were the times when my responsibilities and the scope of work evolved, providing me with essential experiences.

I started my career as a clinical statistician in early clinical development, where three years of experience facilitated my transition from a fresh graduate student to an industry statistician. This position offered me a comprehensive understanding of the statistician's role in a pharmaceutical company from both technical and operational perspectives.

Subsequently, I transitioned to late-phase clinical development, assuming the role of a study lead statistician for a pivotal phase 3 study in neurology. This shift expanded my experience from early to late-phase development, allowing me to understand and contribute to the study design, conduct, and reporting in a confirmatory trial setting. Despite the unfavorable results from the phase 3 study, I was presented with the opportunity to serve as the submission lead for a Hemophilia project. This provided me with the chance to continue my journey in drug development and gain valuable experience in regulatory interactions, submission, and project management.

Another milestone was joining Sanofi in the oncology area. This move broadened my knowledge in a new therapeutic area and exposed me to innovative designs and ideas in this area. Additionally, taking on the role of a people manager marked an important milestone, allowing me to acquire people management skills and organizational experience.

The entire career journey equipped me with the essential experience and afforded me the chance to cultivate and enhance the leadership skills essential for the new role.

**Jun: Thank you. I see very clear steps in your career path. Transitioning to a different position and moving to a different therapeutic area can be a demanding endeavor. How did you manage to get the opportunity? What strategies did you use to quickly learn and adapt to new knowledge and dynamics?**

**Yingwen:** That's a great question. I think you're asking me how I managed to convince the hiring manager to bring me on board, even when I lacked the desired experience for the role at that time. First, I consider myself lucky. The hiring managers I engaged with were all open-minded and willing to have an initial conversation. Having an apparent weakness sometimes turned out to be advantageous, especially when addressing questions about weaknesses during the interview. I used it as an opportunity to acknowledge my lack of experience and transformed it into motivation for applying for the new role. In the conversation, I outlined a plan on how I intended to bridge the experience gap and bring myself up to speed, and leveraged experience and past achievements, emphasizing my potential to quickly acquire new skills necessary for the new role. For internal job transfers, having advocates, such as previous managers, collaborators, or stakeholders, proved invaluable. One of my internal transfers, for instance, was facilitated by my previous manager who convinced the new manager to give me a chance. Having someone speak for you and your potential is immensely beneficial.

In terms of how to quickly learn and adapt to new knowledge, recognizing the gaps and pinpointing the aspects that require additional learning is crucial. Engaging with people who are experienced in the area can provide valuable insights. When you are new to a company or a group, establishing a go-to person who is familiar with company processes, seeking out peers who can act as a sounding board for bouncing ideas, and connecting with mentors who can share their wealth of experience and offer guidance on navigating the new environment are extremely helpful. These strategies were proven valuable in my journey of transitioning into new areas and adapting to new work environments.

**Jun:** That was an impressive strategy of being transparent on your strengths and weakness, along with a motivated mindset, in order to convince the hiring manager. As you take on the role of the Global Head Biostatistics, RD & RBD, what do you perceive as the most significant challenges you will face? And how do you plan to approach those?

**Yingwen:** I plan to concentrate on three key areas: acquiring disease area knowledge, getting to know the RD&RBD statistics team, and establishing partnerships with cross-functional stakeholders. Despite having experience in Hemophilia projects, providing strategic input into the overall strategy and development program in RD&RBD poses a new challenge. I started with conducting a thorough portfolio review, engaging in conversations with colleagues well-versed in this area, and seizing every opportunity to comprehend the unique challenges in this disease area. Considering my recent integration into a new group, it is essential to acquaint myself with the team and gain a comprehensive understanding of the challenges they currently face. Engaging in one-on-one meetings and group discussions provides excellent opportunities to connect with team members and gather valuable insights. Lastly, building partnerships with cross-functional stakeholders is a priority. Moving from oncology to RD&RBD involves interacting with different stakeholders. Setting up introductory meetings and actively participating in various forum discussions will facilitate a smooth transition.

**Jun:** It's evident that embracing emerging opportunities requires diligent preparations while employing a proactive mindset. To help those in our audience who aspire to take the next big opportunity that comes their way, can you provide your choice of top 3 take-home advices to help them get ready?

**Yingwen:** Happy to share my thoughts. First, know yourself. Be aware of your own interests, strengths, weaknesses, and understand your own passions and skills. This self-awareness will help you identify opportunities that align with your abilities and goals. Second, be prepared. Prepare yourself by continually learning and acquiring new skills. The more adaptable you are, the better you will be able to seize opportunities in different areas. Last, but not least, build a strong network, find a diverse and extensive network of contacts in the field that will help you to identify new opportunities. Network not only offers valuable insights but also pave the way for possibilities.

**Jun:** Thank you, Yingwen. Know yourself, be prepared and build a strong network. Well said. As we conclude this insightful interview, I want to extend our sincere gratitude to you for sharing your incredible journey, wisdom, and valuable advice with us. Your experience and insights have undoubtedly inspired us to strive for greatness in our careers.

**Yingwen:** You are very welcome, Jun. ■

# UNDERSTANDING HEALTH TECHNOLOGY ASSESSMENT: AN OVERVIEW AND ESSENTIAL COMPONENTS

Weili He(Abbvie), Hongwei Wang(Abbvie), Julia Ma (Abbvie)



**Weili He**

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**Hongwei Wang**

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**Julia Ma**

Neuroscience TA Head, MA&HTA Statistics AbbVie

## HIGHLIGHTS

- Introduces the framework for Health Technology Assessment (HTA)
- Provides overview of key markets for HTA
- Discusses guidance and different requirements for HTA
- Introduces frequently used statistical methodologies for HTA

## 1. Introduction of conceptual framework of Health Technology Assessment

Health technology assessment (HTA) is a systematic evaluation process that assesses the clinical, economic, social, and ethical implications of medical technologies. The objective of HTA is to provide evidence-based information to healthcare decision-makers to ensure that patients have access to safe, effective, and affordable treatments. HTA evaluates the clinical effectiveness of medical technologies by reviewing available evidence from clinical trials and other sources to

determine whether a technology is safe and effective for its intended use. It also assesses the economic impact of medical technologies by analyzing their cost-effectiveness and budget impact to determine whether they represent value for money. Additionally, HTA considers the ethical and social implications of medical technologies, including their impact on patient autonomy, equity, and social values.

The field of HTA has evolved over the past few decades, reflecting a growing recognition of the importance of evidence-based decision-making in healthcare. HTA has become an essential tool for healthcare policymakers and decision-makers, as well as for patients and healthcare providers. HTA involves various stakeholders, including patients, healthcare providers, payers, industry, and government agencies and health authorities, each with a unique perspective and role in the HTA process. The involvement of these stakeholders ensures that HTA considers various perspectives and factors in the evaluation of medical technologies.

## 2. Major Markets for HTA

In order for any treatment or medical technology (in this article, we use the terms interchangeably) to reach patients, sponsors must undergo a “two-

step” process involving regulatory agency approval and subsequent market access and reimbursement applications to health authorities. These steps are crucial in ensuring the safety, efficacy, quality, and affordability of pharmaceuticals and medical devices. The specific agencies involved in this process vary by country. Regulatory agencies are responsible for evaluating the safety and efficacy of treatments. They review data provided by sponsors and assess the scientific evidence to determine whether the treatment meets the necessary standards. Examples of regulatory agencies include the Food and Drug Administration (FDA) in the United States (US), the European Medicines Agency (EMA) in Europe, and the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan. Following regulatory approval, sponsors need to seek market access and reimbursement from health authorities so that patient access to the licensed pharmaceuticals can be secured. These authorities evaluate the clinical and economic value of the treatment to determine its appropriate use and reimbursement coverage. In countries such as UK, Australia, and Canada, where the pricing and reimbursement processes depend on recommendations from HTA agencies, regulatory approval is just the first step in patient access to a licensed medicine. HTA agencies are responsible for evaluating the clinical effectiveness, cost-effectiveness, an overall value of health technologies and medical interventions. Their primary goal is to inform healthcare decision-making by providing evidence-based recommendations and assessments. Examples of HTA agencies include the National Institute for Health and Care Excellence (NICE) in the UK, the Pharmaceutical Benefits Advisory Committee (PBAC) in Australia, and Canadian Agency for Drugs and Technologies in Health (CADTH) in Canada. Together, regulatory agencies and health authorities ensure that treatments meet the necessary standards for safety, efficacy, and quality, while also considering their value and affordability. This comprehensive approach, from pre-market approval to post-marketing surveillance, is essential in safeguarding patient health and facilitating access to effective treatments.

In the United States, after the regulatory approval by FDA, CMS administers are responsible for health-care coverage programs for Medicare and Medicaid patients. The recent US Inflation Reduction Act (IRA) allows Medicare to negotiate drug pricing starting in 2026. Since the healthcare system in US include multiple payers, the Institute for Clinical and Economic Review (ICER), an independent non-profit research organization, evaluates the value of medical technologies and make recommendations to payers.

In Europe, the EMA is in charge of approving new drugs and conducting post-market surveillance to ensure their safety and effectiveness. The European Network for Health Technology Assessment (EUnetHTA) is a collaboration of HTA agencies across Europe. EUnetHTA facilitates the assessment of medical technologies by promoting cooperation among member agencies. In 2021, EUnetHTA released mandatory guidance on joint clinical assessments (JCA) specifically for advanced therapies, effective from 2025 onwards. In addition to EUnetHTA, each EU member state has its own national HTA agency. These national agencies are responsible for conducting HTA and advising policymakers on the appropriate use of medical technologies within their respective countries.

In Canada, the Canadian Agency for Drugs and Technologies in Health (CADTH) conducts HTA, and Health Canada regulates medical devices and pharmaceuticals. In Australia, the Therapeutic Goods Administration (TGA) regulates medical devices and pharmaceuticals, and the Pharmaceutical Benefits Advisory Committee (PBAC) conducts HTA.

### **3. Guidance Documents in Health Technology Assessment**

Health authorities worldwide release guidance documents that establish a framework for evaluating evidence on medical technologies, encompassing clinical trial data, observational studies, and other relevant sources. These documents also provide guidance on economic evaluation methods, such as cost-effectiveness and budget impact analysis. Additionally, they address the ethical and social implications of medical technologies and their integration into the HTA process.

Guidance documents not only outline the criteria and processes employed in healthcare decision-making based on HTA findings but also exhibit variations across major markets. These differences can be attributed to variances in healthcare priorities, cultural norms, and other related factors. Moreover, stakeholder involvement may vary, reflecting dissimilarities in healthcare systems and preferences among stakeholders. Furthermore, cultural and societal factors exert influence on guidance documents, as they reflect disparities in healthcare priorities and values across various regions and markets.

Guidance documents play a crucial role in providing a framework for conducting HTA and establishing the methods and criteria used to evaluate medical technologies. They promote consistency and transparency in the HTA process. However, there is currently a lack of harmonization among major markets, leading to variations in guidance documents. This highlights the importance of collaboration and harmonization in HTA to ensure equitable access to safe, effective, and affordable treatments for patients, regardless of their location.

#### 4. Methodology of HTA

HTA is a systematic and multidisciplinary process that involves a comprehensive evaluation of new healthcare technologies and their impact on the healthcare system. It requires the collaboration of professionals and researchers from various disciplines to ensure a comprehensive assessment. Statisticians play a critical role in this multidisciplinary approach, and several statistical methodologies commonly used in HTA can further enhance the evaluation of health technologies:

- **Use of Real-world evidence (RWE) to generate evidence:** RWE plays a critical role in quantifying disease prevalence and incidence, natural history of disease, unmet medical needs under standard of care, comparative effectiveness of medical interventions, and more effective randomized clinical trial design. The fit-for-purpose

selection of real-world data (RWD) sources, appropriate study design and analytic framework to minimize confounding and bias all demand statistical expertise.

- **Cost-effectiveness analysis (CEA):** CEA compares the costs and benefits of alternative interventions to determine their relative value. Incremental cost-effectiveness ratios (ICERs) are used to assess the additional cost per unit of quality adjusted life-years gained by an intervention, offering insights into cost-effectiveness.
- **Survival extrapolation:** The statistical methods for survival extrapolation aim to predict the long-term survival of a medical technology beyond the available follow-up period of clinical trials. It is crucial for assessing the cost-effectiveness of the technology and informing reimbursement decisions.
- **Treatment switching:** Treatment switching occurs when patients assigned to one treatment arm switch to another during a clinical trial. Statistical methods with treatment switching adjustment account for this phenomenon to mitigate its potential impact on estimated treatment effects.
- **Network meta-analysis:** This method allows for simultaneous comparison of multiple interventions by combining both direct and indirect evidence. It enables estimation of relative treatment effects between interventions that have not been directly compared in clinical trials.
- **Sensitivity analysis:** The analysis assesses the robustness of HTA results by changing key assumptions or the input parameter. It helps evaluate the uncertainty and variability of estimates, providing insights into the reliability of findings.
- **Subgroup analyses:** It is an analytical strategy used for investigating the effects of an intervention or treatment on a subset of participants within a large study population.

By employing these statistical methods, HTA synthesizes evidence, compares interventions, assesses cost-effectiveness, and ultimately informs healthcare decision-making.

## 5. Conclusion

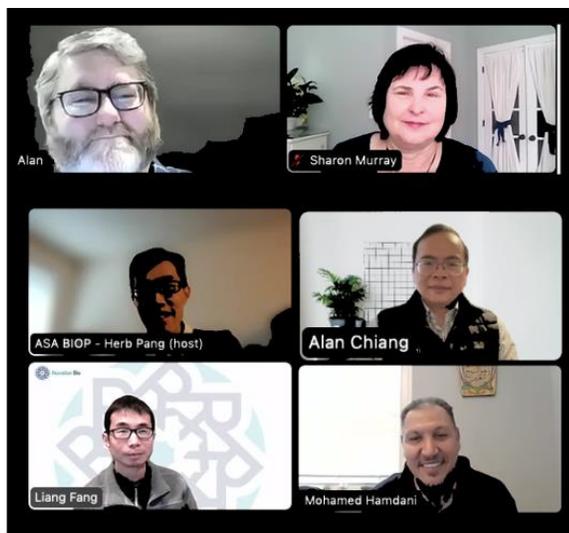
Health Technology Assessment (HTA) is a systematic evaluation process that considers the clinical, economic, social, and ethical implications of medical technologies. It involves a comprehensive review of available evidence, economic analysis, engagement with stakeholders, and decision-making processes. Statisticians as quantitative scientists play important roles in HTA evaluation. We are instrumental in guaranteeing the implementation of rigorous and credible methods. Our contribution ensures that the evaluation of medical technologies adheres to sound statistical principles and results in evidence-based and reliable recommendations.

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# SUMMARY OF ASA BIOP SECTION'S WEBINAR SERIES: DON'T GO IT ALONE: BENEFITS OF JOINING OUR COMMUNITY OF STATISTICIANS IN SMALL BIOTECHNOLOGY COMPANIES

Alan Y. Chiang(Lyell Immunopharma), Liang Fang(Nuvation Bio), Mohamed Hamdani(Larimar Therapeutics), Alan Hartford(Clene Nanomedicine), Sharon C. Murray(BioCryst Pharmaceuticals), Jingtao Wu(Carmot Therapeutics), Herb Pang(Genentech)



- Alan Y. Chiang, PhD, Vice President, Biometrics, Lyell Immunopharma
- Liang Fang, PhD, Vice President, Data Sciences, Nuvation Bio
- Mohamed Hamdani, Vice President, Statistics and Quantitative Sciences, Larimar Therapeutics
- Alan Hartford, PhD, Vice President, Biometrics, Clene Nanomedicine, Inc
- Sharon C. Murray, PhD, Vice President, Biometrics, BioCryst Pharmaceuticals
- Jingtao Wu, PhD, Senior Director, Biostatistics, Carmot Therapeutics
- Herb Pang, PhD, Expert Statistical Scientist (technical Senior Director level equivalent), Genentech/Roche

## HIGHLIGHTS

- A growing number of small biotech companies have now employed statisticians. The Biopharmaceutical Section (BIOP) Distance Learning Committee hosted a webinar to share learning on the benefits of joining the Community of Statisticians in Small Biotech.
- The panel discussion connected statisticians who either work, or want to work, for a small biotech company to share strategies, experiences, and ideas. The panelists shared what they see as unique career opportunities in joining a small biotech company, the main challenges they have faced, and the benefits of joining the community.

On December 1, 2023, the American Statistical Association (ASA) Biopharmaceutical Section (BIOP) Distance Learning Committee hosted a webinar to share learning on the benefits of joining the Community of Statisticians in Small Biotech. See the community web site at: <https://amstat.connectedcommunity.org/statisticiansinsmallbiotech/home>. This report summarizes the panel discussion.

With the rapid growth of biotechnology in the last half century, new drug discovery and development have now reached an inflection point where hundreds of emerging small biotech companies are progressing into the clinical development stage. These small biotech companies employ a growing number of statisticians. We are also seeing an increasing number of statisticians taking the leap into the small biotech world. The panel discussion aimed to connect statisticians who either work, or want to work, for a small biotech company so that they can share strategies, experiences, and ideas.

There are several challenges and opportunities when working in a small biotech. For example, there may be only one or a few statisticians/programmers working at the company, which means that there is heavy reliance on CROs for statistics and programming work. Consultants may be required for advice or to review documents. On the other hand, the statistician will have many opportunities for growth while making an impact on advancing human health through innovation. They will need to wear many hats, perhaps working on multiple phases of clinical trials, preparing for audits, answering analyst questions related to statistics, developing departmental SOPs and working instructions, participating in regulatory discussions and/or advisory committee meetings, and overseeing outsourcing. Resources are limited and forming a partnership strategy is key. Part of that strategy involves determining the level of CRO oversight, selecting preferred vendors, deciding what work to do in-house versus outsourcing, acquiring statistical software, and liaising with other departments as the company grows. The strategy will need to be revisited on a regular basis as the company evolves.

The panel discussion focused on four key questions:

- Considering the many ways in which the field of statistics adds value in drug development, what are the unique career opportunities in a small biotech company?
- What are the main challenges one needs to overcome in interdisciplinary collaboration?
- How has the application of statistics played a key role in innovation, decision making, and clinical advances in a small biotech company?
- How could members benefit from being part of the ASA community for statisticians working in small biotech companies?

The panel discussion was hosted by Herbert Pang (Genentech), moderated by Alan Y. Chiang (Lyell Immunopharma) with panelists Liang Fang (Nuvation Bio), Mohamed Hamdani (Larimar Therapeutics), Alan Hartford (Clene Nanomedicine), and

Sharon C. Murray (BioCryst Pharmaceuticals).

**Chiang: Thank you all for being here online with us today. Mohamed and Alan, could you give a brief background introduction of the statisticians in small biotech community?**

**Hamdani:** Thanks Alan and thank you for the opportunity to introduce our community. I was asked by Alan Hartford to join the community of statisticians in small biotech. I didn't hesitate because I saw the need for this kind of initiative as there is a growing number of small biotechs and startups. Often time statisticians who make the transition from mid to large companies into a small biotech find themselves isolated and confront many challenges that we don't want them to navigate alone. We identified a gap in the topics discussed in the ASA BIOP events and we would like to grow this supporting community.

**Hartford:** We started our community to battle all the challenges of working isolated from other statisticians. We all need someone to talk through problems. We all bring something to the table but can't be expected to know everything. The main areas we designed all this for are processes, insights into regulatory practices, and statistical methods. These are areas we can discuss without fear of sharing corporate secrets.

**Chiang: Many of you have worked in large pharmaceutical companies previously, could you tell us what drove you to join a small biotech company, and the unique career opportunities the company has provided for you?**

**Murray:** I spent the bulk of my career at GlaxoSmithKline (GSK), a large pharmaceutical company. However, I had opportunities while I was there to see what it was like to work at a small biopharmaceutical company. I worked on a project which was a partnership with a small company. We had a joint development committee and met once per month. The partnership was to proceed this way until the

company achieved the Proof-of-Concept Milestone, at which point GSK had the option to acquire the product. In addition, I participated on several due diligence teams, where GSK was considering purchasing a product from a small company. This gave me the opportunity to go on-site. In addition, I've been interested in small biotech companies for a while, and I saw some small companies have tremendous success while others failed. It wasn't until I was laid off from GSK that I made the leap, and I haven't looked back. Some of the opportunities in working at a small biopharmaceutical company are the chance to work on all phases of drug development and on multiple disease types as well as interacting with regulatory agencies like the FDA. I feel like I make a big contribution to the bottom line by working at a small company.

**Fang:** I jumped into the small biotech world almost 6 years ago and have loved it since then.

What motivated me was the opportunity to take on a broader role with many more responsibilities and also the small and intimate working environment. After 12 years of working for three large multinational pharmaceutical companies, it was clear to me that what I enjoyed most in my job was problem solving and what stressed me most in my job was that I had to navigate through complex organization structures to get things done in large pharma. So, naturally, small biotech is where I can spend most of my time doing what I enjoy the most while limiting my time spent on the things that I don't enjoy as much. This has been my experience in the last six years.

**Hartford:** For me, it's the desire to have a seat at the decision makers' table without giving up working directly on the science. I still enjoy working on protocols and calculating power. In Big Pharma, the higher you get, the more removed you are from the science and projects. Also, my work location is very important to me. For years I've wanted to work from my hometown in the Midwest, but the jobs have been on the east or

west coasts. Small Biotech seems more open for senior leaders to work remotely.

**Hamdani:** After spending almost 20 years in mid to large companies, I was approached to build a biometrics group in a small biotech, which is an opportunity that I would otherwise not have a chance to realize. I liked the challenges of building teams, processes, and also being a hands-on statistician. It is a rewarding chance to be involved in decision making and get to see the journey of product from pre-clinical to clinical stages. You have opportunities for impact like providing input for analyst calls, press releases, and interacting with top KOLs especially in rare diseases.

**Chiang:** **Small biotech companies have been responsible for a significant portion of newly approved medicines, especially for rare diseases. The success lies in part in their focus: innovative therapies for niche indications. Could you give an example of how you applied novel or lesser-known statistical applications in your organization's decision making and clinical advances, and how did it go?**

**Hartford:** We're at the end of the phase 2 stage and are working through many prespecified and ad hoc analyses. One fun analysis was using the rank-preserving structural failure time model to estimate the treatment effect if the control arm had not switched to active at the end of our phase 2 double-blind period. We included this work in our briefing but we're not sure the FDA will lend much credence to it. We also work with ordinal response variables. I've had the pleasure of working with a consultant to learn about the adjusted win ratio and U statistics. We've calculated power for a phase 3 study using this as a primary analysis. We haven't finalized anything yet. Both efforts were new to me and interesting. I'm glad I had access to external statisticians to discuss them.

**Murray:** I agree that innovative methods can be very helpful, especially for rare diseases. I will say that

for Orladeyo, our primary product, we had a very traditional development program with dose ranging in the proof of concept (POC) study and a pivotal trial with 2 doses and placebo without an interim analysis. Where I think innovation can be very helpful is in making the POC decision. We are using Bayesian posterior probabilities to help us determine when the POC milestone has been met. In addition, for an ultra-rare disease where we can't spare any patients, we are considering an adaptive Phase 2/3 design where we can drop a dose at an interim analysis. We won't be able to have a traditional dose-ranging study due to the rarity of the disease.

**Fang:** In one of the companies I worked for, we had a Phase 3 trial for a rare cardiovascular disease. It's a serious disease and very hard to treat. Our trial was the first phase 3 trial in the space. My manager, who was the only statistician before I joined the company, came up with this new composite endpoint, which ended up being accepted by the FDA as the primary endpoint for the phase 3 trial. Because of that endpoint, we were able to design a trial with 200 patients and ran a phase 3 trial in 2 years to gain FDA's approval. The company was acquired after the success of this phase 3 trial.

**Hamdani:** in my previous small biotech position as the head of biometrics, I started as the sole statistician and helped with the design of 2 phase 3 studies in a therapy with unmet need and a phase 2 in rare disease using a non-inferiority trial, which was a bold move. Both indications got the drug approved and we hired 19 staff members. In my current role, we are in Ph2 for a rare disease indication using RWD to supplement the control group.

**Chiang:** **Small biotech companies by design have a lean organizational structure. They also face many challenges, including limited resources and budget constraints. Could you share an example of how and what you had to overcome the hurdles to stay productive and effective?**

**Fang:** Budget is always a constraint for small biotech. That's the reality we have to live with. We

have to understand how finance works in a small biotech and plan our growth according to it. For example, if you work for an oncology company that is still in Phase 1, you will soon realize that you won't get any headcount before the drug has shown a promising response rate, but at the same time, upper management demands reviewing data almost in real time, for example, for an open label oncology trial, every tumor response in phase 1 could lead to a different business decision. So, what do you do? You don't have the budget to license an expensive software platform like Spotfire or Tableau. You don't have the headcount to hire SAS programmers and even if you do, can they turn around results in real time? So, what I ended up doing was to develop a set of R code myself or with my statistician (when I was lucky enough to have one) and produced a set of plots, such as swimmer plots, waterfall plots, and so on, to keep our management updated on a weekly basis. The code took data from EDC and transferred lab data directly and didn't rely on CDISC data resulting in skipping a step in the process to save time and resources. The key here is that we must understand the priorities of the company and be creative to overcome the resource constraint.

**Murray:** Yes, this is one of the most challenging aspects of working at a small biopharmaceutical company. Prior to approval for Orladeyo, we did not have enough money to support R&D. The company raised money through sale of stock and by getting investment from mutual fund holders. In addition, BioCryst had a bank loan. I would have liked to hire more people soon after I started, but it was not possible. My strategy was to partner closely with a CRO and to engage consultants who could help with study design and do things like review responses to regulatory requests. One thing I'll say is that you have to prioritize. I had to make choices on what I could do.

**Hamdani:** Yes, budget is a constraint but educating management about the need for resources and the benefit gained is always helpful. You always want to lay down the consequences of lack of resources. The emphasis should be on quality and timelines.

**Hartford:** I was lucky to be able to hire a contractor for a limited time to help with the overflow work with for an impending deadline. We have to know when to ask for help and be clear about reasonable timelines. In some companies it could be difficult to get this extra help, so you need to have this discussion at the time you're interviewing to align expectations regarding hiring contractors. You might not want to work at a company that won't be able to provide contract support from time to time.

**Chiang: Small biotech is a vital part of the broader health care ecosystem, and we just discussed its lean biometrics and biostatistics organizational structures. Forming a great partnership is key to efficiency. Could you tell us what you see as the biggest benefits of joining BIOP's community for statisticians working in small biotech?**

**Hamdani:** There are many benefits of being in this community. As I mentioned before, there is a growing number of biotech companies as this is the new way to bring therapies to market. Some large companies are cutting down on their discovery business units. This community will be there to support an incoming statistician to small biotech from processes, SOPs, and even having someone to check with regarding design and methodology issues and/or questions.

**Hartford:** Being connected with other statisticians is the most important benefit. We must have people we trust to ask questions and share problems with. Discussing FDA and ICH guidance documents with others is much better than reading them all on your own. This can lead to a better prioritization of SOP development and sharing of which papers to read for specific topics. For those of us already in our Statisticians in Small Biotech, we have several examples where someone has sent out an email asking if

anyone has experience with a particular method or process. Others have responded and it's been great to get more than one response for a better view and to get solutions under different circumstances.

**Murray:** It can be very isolating to work as the only statistician at a biopharmaceutical company. It's important to reach out to others in similar situations. I was fortunate that I knew some other people previously from GSK who are now also working at small companies. We were able to bounce ideas off of each other a bit. Participating in conferences like JSM or the Regulatory-industry Statistics Workshop can be very helpful. In fact, I met Mohammed at the RISW in September and that's how I got involved with this committee. It's important to build a network.

**Fang:** When I decided to join small biotech 6 years ago, I asked myself what I would be missing the most. It's the people. In large companies, I had hundreds of statisticians whom I could turn to and learn from. When you are in small biotech, you are likely there alone and expected to know everything. So, when you don't know everything, when you need a sounding board, when you need a thinking partner, what do you do? This is why I initiated the idea of forming this community a couple of years ago. We don't have to go alone. We can help each other and leverage each other's expertise, experience, on this journey. I found this group has been extremely helpful.

**Chiang: I would like to thank all panelists and participants for the fruitful discussion today. There is a lot of uncertainty out there, but I think we can be certain that for those who are running clinicals trials with limited resources, please join the community. You may not have to do everything yourself. Reach out to one of us on the call and thank you all for joining the webinar. ■**

# HOW TO WRITE AND PUBLISH A BOOK: BEST PRACTICES FROM PUBLISHER'S PERSPECTIVE

Lara Spieker (Taylor & Francis Group), David Grubbs, Rob Calver



**Lara Spieker**

Editor – *Biostatistics, Computational Statistics, Environmental Statistics, Statistics*, Chapman & Hall/CRC, Taylor & Francis Group



**David Grubbs**

Senior Editor – *Data Science, Statistics*, Chapman & Hall/CRC, Taylor & Francis Group



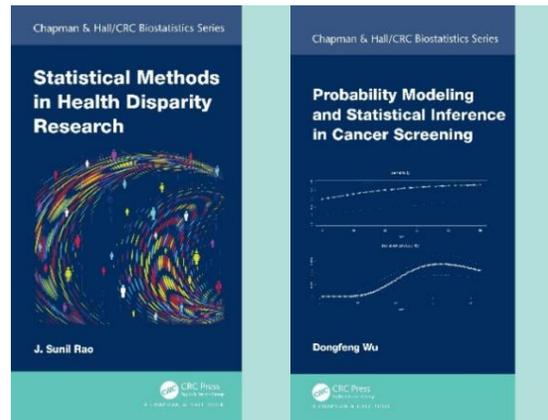
**Rob Calver**

Senior Publisher – *Mathematics, Statistics and Physics*, Chapman & Hall/CRC, Taylor & Francis Group

Many thanks to editors of BIOP report, who got in touch with us to ask for more information about the publishing process with Chapman & Hall/CRC. The idea of writing and publishing a book may seem overwhelming at first, but we will do our best in this article to cover the process and best practices.

Some of you might be familiar with the books from our Chapman & Hall/CRC Biostatistics series, which provides useful references for researchers and scientists in academia, industry, and government, as well as textbooks for undergraduate and graduate courses in the areas of biostatistics and bioinformatics. The scope of the series is wide, including applications of statistical methodology in biology, epidemiology, genetics, pharmaceutical science and clinical trials, public health, and medicine. It is committed to providing easy-to-understand, state-of-the-art references and textbooks. In each volume, statistical concepts and methodologies are illustrated through real world examples whenever possible. Some of the recent titles in the series are included to the right:

There are many reasons why someone might consider writing a book: it can provide significant exposure for your research, serve as a teaching tool for others and can be a useful vehicle to share your ideas that go beyond a journal article. Important things to





think about when considering writing a book include carefully selecting the topic, identifying the primary audience, and determining the appropriate level of engagement. Additionally, it is crucial to assess existing books on the same topic and explore ways in which the new book can distinguish itself from others in the field. Some other things to consider are the format, such as LaTeX or Microsoft Word and the proposed length of the manuscript.

Once all these questions have been considered, the next step is to submit a book proposal for our consideration; your editor can provide a form for this process. This brief form gives you the opportunity to provide a synopsis of your book, an overview of the audience, the competing books, as well as a draft of the proposed table of contents. The proposal should highlight your idea and your voice, and your editor would be happy to help with any questions you might have during the process. Sample chapters are welcome, but not required. Once you submit your proposal, your editor will then send it to peer reviewers, as well as possibly the series editors for the Biostatistics Series. The review process can take a few weeks, but it helps us to make a decision as to whether to move forward or not with your book project, and can also generate a lot of useful feedback for you regarding the project. Assuming a positive response from the reviewers, we would offer a publishing contract, which includes the approximate number of pages and figures, the agreed-

upon due date, who owns the copyright (in most cases, the authors), the royalty structure, number of author copies, and any other special terms. Once the contract has been signed, you will continue to work with a dedicated editor throughout the writing process, who will be on hand to answer any questions you may have and can offer feedback on the manuscript along the way. Our dedicated LaTeX helpdesk is also available to lend a hand with any issues should you choose to write in LaTeX.

Once the manuscript is completed and has been submitted, we handle the production process of the book (this includes things like typesetting, copyediting the text, designing the cover etc.), and publication in print and ebook format. Afterwards, we take care of the world-wide distribution and marketing of your book with the help of our dedicated global marketing and sales teams.

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Find more information about how to get in touch with us, and the Biostatistics Series, here: <https://bit.ly/CRCBiostatistics>. ■

# SUMMARY OF ASA BIOP SECTION'S VIRTUAL DISCUSSION WITH REGULATORS ON DESIGN CONSIDERATIONS IN THE EVALUATION OF CONTRIBUTION OF EFFECT OF COMBINATION OF TWO NEW INVESTIGATIONAL DRUGS IN RANDOMIZED CANCER CLINICAL TRIALS

Rajeshwari Sridhara (FDA), Olga Marchenko (Bayer), Qi Jiang (Seagen), Elizabeth Barksdale (LUNGevity Foundation), Nicole Li (Beigene), Marc Theoret (FDA)

## HIGHLIGHTS

- On August 10, 2023, ASA BIOP and LUNGevity Foundation hosted a virtual open forum to discuss design considerations in the evaluation of contribution of components of novel combination regimens in randomized cancer clinical trials, with participation from biostatisticians, clinicians, and regulators.
- OCE leadership highlighted the need for a trial design and analysis related to evaluation of contribution of components (CoC), three speakers gave presentations, followed by a panel discussion.
- Main takeaways from the panel discussion:
  - \* Determining the contribution of components is critical for combination therapies ;
  - \* Data from early stages may be used to inform phase 3 trial design evaluating contribution of components;
  - \* Use of historical/external data to include both monotherapy arms should be evaluated case by case.

On August 10, 2023, the American Statistical Association (ASA) Biopharmaceutical Section (BIOP) and LUNGevity Foundation hosted a virtual open forum to discuss design considerations in the evaluation of contribution of components of novel combination regimens in randomized cancer clinical trials, with participation from biostatisticians, clinicians, and regulators. This discussion was part of a series of discussions conducted under the United States Food and Drug Administration (US FDA) Oncology Center of Excellence (OCE) initiative, Project SignifiCanT (Statistics in Cancer Trials). The goal of Project SignifiCanT is to advance cancer drug development through collaboration and engagement among various stakeholders 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 OCE, and LUNGevity Foundation. This forum focused on trial designs and analysis methods in a randomized trial setting that can provide the requisite information to establish safety and efficacy of new drug combinations while exposing the least number of patients to a potentially less effective monotherapy.

The FDA Guidance for Industry on co-development of two or more new investigational drugs for use in combination was released in June of 2013. It includes examples of phase 3 study design considerations based on what has been previously demonstrated about the effects of the combination and the individual new investigational drugs, the feasibility of monotherapy and standard of care (SOC) alone treatment arms, and other factors ( <https://www.fda.gov/media/80100/download> ). An ideal design to evaluate the contribution of each of



**BIOP Section's Virtual Discussion with Regulators** on Design Considerations in the Evaluation of Contribution of Effect of Combination of Two New Investigational Drugs in Randomized Cancer Clinical Trials

the components of the combination therapy would be a four-arm study comparing the combination with each of the individual components (monotherapies) and SOC. Because this design is not always viable and practical in drug development, presenters and panelists were asked to explore different design options that could evaluate the contribution of effect from individual components.

The speakers/panelists\* for the discussion included members of the BIOP Statistical Methods in Oncology Scientific Working Group, representatives from international regulatory agencies including US FDA, Health Canada (HC), Medicines and Healthcare products Regulatory Agency (MHRA) from the United Kingdom, Swissmedic (SMC) from Switzerland, Australian Government Department of Health, and Brazilian Health Regulatory Agency (ANVISA), clinical investigators,

academicians, patient advocacy groups, and expert statisticians in industry. In addition, over 100 participants attended the virtual meeting, including representatives from other international regulatory agencies such as European Medicinal Agency (EMA), Health Sciences Authority (HAS) from Singapore, and Pharmaceutical Division Israel Ministry of Health. The discussions were moderated by the BIOP Statistical Methods in Oncology Scientific Working Group co-chairs, Dr. Qi Jiang from Seagen and Dr. Olga Marchenko from Bayer; Dr. Elizabeth Barksdale from LUNGevity Foundation; and Dr. Rajeshwari Sridhara, consultant from OCE, FDA.

After introductory remarks by the OCE leadership highlighting the need for a trial design and analysis related to evaluation of contribution of components (CoC), three speakers gave presentations. The first

speaker, from academia, focused on statistical methodology to make reliable and unbiased inferences on individual components' contributions based on whether it is feasible to include monotherapy arm(s) in the trial. Thoughts on how to leverage external data to make an early, unbiased determination of individual components' contributions to treatment effect were also presented.

The second speaker, from industry, presented a case study in relapsed/refractory multiple myeloma that involved a novel-novel drug combination to show how contribution of components could be demonstrated without using the factorial "ideal" design described above, and provided some insights on how to use data from different stages of drug development. The presenter also talked about considerations of the contribution of sequencing, using KEYNOTE-522, a peri-operative study in breast cancer, as an example to highlight the challenges of evaluating contribution of components of sequential treatments.

The third speaker, an academician, presented an example of an adaptive design with an early interim analysis to determine whether it is appropriate to drop the combination or one/ both monotherapy arms using different futility boundaries. Different scenarios were considered including a case of combining both monotherapy arms for a joint analysis at interim analysis. It was noted that if more than the effect of the combination is of interest (e.g., one of the monotherapies is also of interest), then when a certain order is assumed (for example, assuming that combination therapy treatment effect is at least as large as that for monotherapy), the sample size saving can be achieved when conducting this type of ordered analysis compared to using Bonferroni criteria for multiplicity control.

The main takeaways from the panel discussion following these presentations were:

- Determining the contribution of components is critical for combination therapies to understand 1) what is driving treatment effect and 2) potential additional toxicity from the combination on top of either monotherapy.
- Data from early stages of drug development may be used to inform the design of phase 3

trials evaluating contribution of components. For example, data from thoughtfully designed dose-optimization and signal-detection and/or single arm studies can provide necessary safety and efficacy data to guide the choice of phase 3 designs.

- Use of historical/external data for inference-making when it is infeasible to include both monotherapy arms in a randomized trial should be evaluated on a case-by-case basis. Such cases might require randomized data eventually, even if not available at the time of initial approval.

This forum provided an opportunity to have open scientific discussion among a diverse multidisciplinary stakeholder group - clinicians, statisticians, patient advocates, international regulators, and representatives from pharmaceutical companies - focused on emerging statistical issues in cancer drug development. We plan to continue with similar multi-disciplinary open forum discussions on a variety of important topics that include statistical aspects in cancer drug development with participation from various stakeholders.

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

\* *Speakers/ Panelists: Dr. Elizabeth Barksdale (LUNGevity Foundation), Dr. Michael Coory (TGA, AU), Dr. Leonardo Filho (ANVISA, BR), Dr. Boris Freidlin (NCI/NIH), Prof. Anastasia Ivanova (University North Carolina, Chapel Hill), Dr. Qi Jiang (Seagen), Dr. Xiaoxue Li (FDA), Dr. Rong Liu (BMS), Dr. Olga Marchenko (Bayer), Dr. Richard Pazdur (FDA), Dr. Khadija Rerhou Rantell (MHRA, UK), Mr. Andrew Raven (Health Canada), Dr. Nicholas Richardson (FDA), Dr. Satrajit Roychoudhury (Pfizer), Dr. Suman Sen (Novartis), Dr. Yuan Li Shen (FDA), Dr. Rajeshwari Sridhara (FDA), Dr. Garth Strohbahn (University Michigan), Dr. Marc Theoret (FDA), Dr. Hong Tian (Beigene), Dr. Anita Wolfer (Swissmedic), Prof. Ying Yuan (MD Anderson Cancer Center).* ■

# ADAPTIVE 2-IN-1 DESIGN IN ACTION

Cong Chen (Merck)



**Cong Chen**

Scientific AVP, Biostatistics  
and Research Decision  
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## HIGHLIGHTS

- Upon identifying an initial efficacy signal in a tumor indication, four potential courses of action typically follow. It is challenging to decide on the optimal path in practice.
- A decision matrix based on three key factors (scientific merit, strategic fit, and commercial value) can help make the decision-making process transparent and objective.
- A 2-in-1 adaptive Phase 2/3 design was proposed to mitigate the risk of a false No-Go decision to Phase 3.
- A dedicated collaborative working group was formed in 2022, consisting of over 40 statisticians and other professionals from industry and academia.

## The 2-in-1 adaptive Phase 2/3 design in oncology

In clinical oncology drug development, upon identifying an initial efficacy signal in a tumor indication, four potential courses of action typically follow:

1. The development program may be paused or terminated due to insufficient signal strength, as well as other factors such as strategic alignment with the pipeline and the commercial value of the indication.
2. The program may advance to a standard randomized-controlled Phase 2 study to establish formal proof-of-concept and to optimize dosage and/or population as necessary. A successful Phase 2 outcome will lead to a Phase 3 study, in a sequential Phase 2/3 approach. The transition from Phase 2 to Phase 3 may either take time or be expedited (e.g., operationally seamless).
3. The program may advance to an adaptive Phase 2/3 study, where data from Phase 2 and Phase 3 will be combined for making the final inference (i.e., inferentially seamless). The transition from Phase 2 to Phase 3 not only includes

a Go-No Go decision but may also include a dose/population selection, sample size re-estimation or other adaptive decisions.

4. The program may proceed directly to a Phase 3 study. In this case, a mid-trial futility analysis is routinely implemented to mitigate the risk. This analysis is typically carried out after majority of the patients are enrolled, and the futility bar is set low to reduce the risk of mistakenly terminating the study (i.e., “disaster check”).

It is challenging to decide on the optimal path in practice. Table 1 provides a decision matrix based on three key factors (scientific merit, strategic fit, and commercial value) that help make the decision-making process transparent and objective. The scientific merit of a study drug in a tumor indication measures the likelihood of the study drug having the target effect as determined by the strength of preliminary clinical data. Data from other tumor indications or from drugs with the same mechanism of action may also be consulted. The strategic fit of a study drug is determined by its strategic value relevant to the drug developer (i.e., complementary to drugs in the pipeline, emerging promising platform). The commercial

**Table 1. Recommended decisions (NG: No-Go; Ph2: Go to Phase 2; Ph2/3: Go to adaptive Phase 2/3; Ph3: Go to Phase 3) based on scientific merit, strategic fit and commercial value.**

Commercial value	Scientific merit (High strategic fit case)			Scientific merit (Low strategic fit case)		
	Low	Medium	High	Low	Medium	High
Low	NG	Ph2	Ph2/3	NG	NG	Ph2
Medium	Ph2	Ph2/3	Ph3	NG	Ph2	Ph2/3
High	Ph2/3	Ph3	Ph3	Ph2	Ph2/3	Ph3

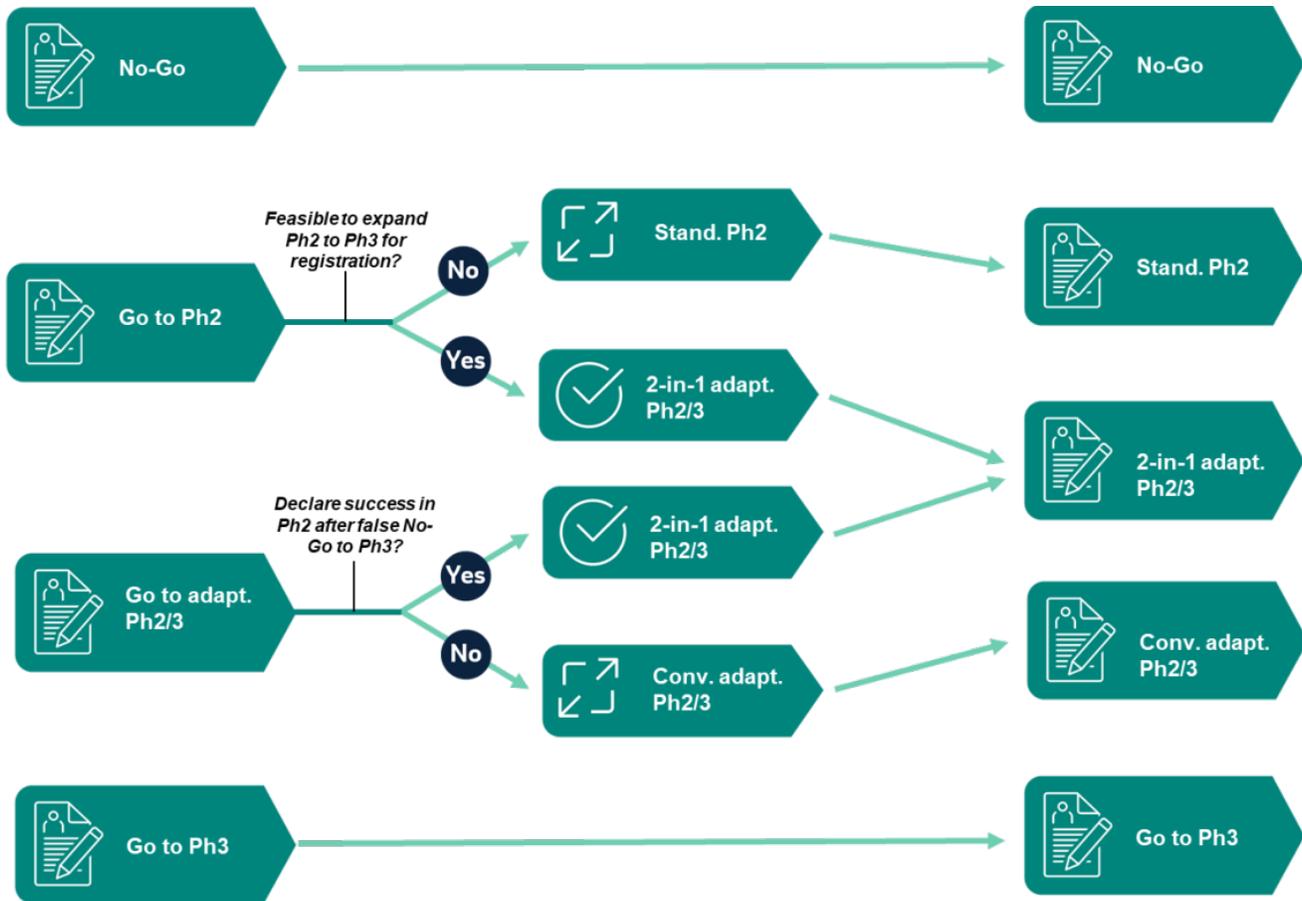
value of a tumor indication is determined not only by the size of the patient population but also by the competitive landscape, patent life, and various other considerations. Based on the decision matrix, when the tumor indication has high commercial value, a program with low scientific merit may still end up with a Go-decision to Phase 2 or even adaptive Phase 2/3, depending on its strategic fit. A program with medium scientific merit may have to be discontinued due to its low commercial value and low strategic fit. In addition to these three, other factors such as ethics and equality, regulatory policy, and operational challenges are also considered whenever applicable.

While an adaptive Phase 2/3 design can reduce the risk of a false Go-decision to Phase 3, it may increase the risk of a false No-Go decision to Phase 3. Unbeknown to biostatisticians until more recently, a 2-in-1 adaptive Phase 2/3 design was proposed to mitigate such risk [1-4]. In this design, without inflating the overall Type I error, Phase 2 data can be not only included in Phase 3 analysis but also legitimately declared positive after making a false No-Go decision to Phase 3. Unlike futility stopping in a Phase 3 study, a No-Go decision to Phase 3 in an adaptive Phase 2/3 design does not automatically mean that the study has failed. With the statistical rigor preserved, a positive outcome at the end of the Phase 2 component of an adaptive Phase 2/3 study has the same merit as a standalone Phase 2 study. INDUCE-3

was the first published study that explicitly implemented the 2-in-1 adaptive Phase 2/3 design [5]. When the 2-in-1 design option is incorporated into the planning of a Phase 2 study, it adds an upside scenario to expedite the transition to Phase 3; When it is incorporated into the planning of an adaptive Phase 2/3 study, it provides protection in case of a false No-Go decision to Phase 3. With the same flexibility as a conventional adaptive Phase 2/3 design for dose/population optimization, the 2-in-1 design improves the equilibrium of cost, risk, and benefit in clinical oncology development programs and naturally expands the design options following preliminary signal detection from four to five (Figure 1).

### The collaborative working group

Since its introduction six years ago, the 2-in-1 design has captured significant attention and generated substantial interest within the oncology drug development community. This innovative design was prominently showcased at the 2022 Society for Immunotherapy of Cancer (SITC) Annual Meeting. The overwhelming interest it received at the 2022 ASA Biopharmaceutical Section Regulatory-Industry Statistics Workshop (ASA BIOP RISW) led to the formation of a dedicated collaborative working group, consisting of over 40 statisticians and other professionals from industry and academia. The working group comprises four subteams with a common objective of conducting extensive



**Figure 1: Incorporation of the 2-in-1 design into a clinical oncology development program increases the design options from four categories on the left to five on the right (Stand. Ph2: standard Phase 2 design; Conv. adapt. Ph2/3: conventional adaptive Phase 2/3 design).**

research and promoting wider applications of this design. They are led by Jianchang Lin and Rachel Liu from Takeda (sample size re-estimation), Eric Zhang from Gilead (dose-election), Heng Zhou from Merck (biomarker subpopulation selection) and Mandy Jin from Abbvie (practical issues), respectively. This collective effort has resulted in multiple publications [6-10] and a range of informative presentations, solidifying knowledge surrounding the 2-in-1 design and its practical implementation. Notably, at the 2023 ASA BIOP RISW, a presentation titled “An Adaptive Seamless 2-in-1 Design with Biomarker-Driven Subgroup Enrichment” delivered by Liwen Wu and Jianchang Lin from the collaborative team, received the Excellence Award in the poster competition.

Statisticians interested in joining the working group may contact Cong Chen ([cong\\_chen@merck.com](mailto:cong_chen@merck.com)). References related to the 2-in-1 design and archived presentations at the previous team meetings may be requested from Eric Zhang ([pingye.zhang6@gilead.com](mailto:pingye.zhang6@gilead.com)).

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# ASA BIOPHARMACEUTICAL SECTION STUDENT PAPER REVIEW COMMITTEE

Lanju Zhang (Vertex), Meijing Wu (Sanofi)



**Lanju Zhang**  
Senior director  
Vertex

The ASA Biopharmaceutical (BIOP) section Student Paper Review Committee plays a crucial role in recognizing and promoting excellence of biopharmaceutical research and attracting top statistical talents to join the industry. The section provides generous cash reward and prominent recognition to the award winners. The committee comprises 8 members from various leading organizations, including Yang Chen from Vertex, Yu Du from Eli Lilly, Siddhesh Kulkarni from BMS, Ruitao Lin & Yunlong Yang from MD Anderson, Jimin Wu from Merck, Meijing Wu from Sanofi, and Lanju Zhang from Vertex, who serves as the chair of the committee. Together, these members bring a wealth of expertise and experience to the evaluation process.

For the 2023 - 2024 student paper competition, the submission process commenced with the announcement on the BIOP website in late July 2023. All submissions were directed to Bo Huang, the BIOP section Program Chair, with December 1, 2023 as the deadline. The announcement was then strategically promoted by a collaborative team effort. Bo Huang and Meijing Wu shared the details within the Biopharm Section community, focusing on BIOP section members. Lanju Zhang and

Yunlong Yang targeted academia networks for broader outreach. Erik Bloomquist and Hiya Banerjee crafted an attention-grabbing promotion poster and video, shared via LinkedIn, extending the announcement's visibility across diverse audiences. The promotion resulted in a record submission of 42 excellent papers.

The review and selection process demonstrated a commitment to thorough and unbiased evaluation. The committee received blinded papers from the Program Chair, Bo Huang, and conducted a 2-stage systematic review. In the first stage, all submissions were divided into three batches. Each batch was meticulously examined by 2-3 committee members, with any potential conflicts of interest prompting a switch of reviewers. Each member ranked their assigned papers after scoring papers (1-10) based on the social impact of methods, innovation in theory and methods, and the soundness of presentation. Twelve finalists, comprising top 4 papers from each batch, were progressed to the next stage. In the second stage, the 8 committee members collectively reviewed all 12 finalists to determine the top 8 papers, with three winners and five honorable mentions. Thanks a lot to BIOP section for the generous support.

This blinded and objective review process ensures that the selected papers represent the pinnacle of achievement in biopharmaceutical research, promoting papers with innovation, sound methodology, and social impact. The ASA BIOP section Student Paper Review Committee's dedication to excellence underscores its commitment to advancing the field and recognizing the outstanding contributions of emerging talent. If anyone is interested in joining this committee, please reach out to the chair. ■

# ASA BIOPHARMACEUTICAL SECTION STUDENT PAPER AWARDS

Theo Koulis (Genentech)

The Biopharmaceutical Section announced the winners of the 2024 American Statistical Association Student Paper Awards from a pool of 42 submissions. The award-winning students will present their papers in one of the contributed paper sessions at the Joint Statistical Meetings (JSM) 2024 in Portland, Oregon. And the awards will be presented at the Biopharmaceutical Section open business meeting at JSM. The students will also receive a cash award. For information on the upcoming student paper competition, please visit <https://community.amstat.org/biop/awards/studentpapercompetition> after JSM for updated information.



**Kai Chen**  
University of Texas

**FIRST PRIZE:** Kai Chen, University of Texas

**TITLE:** *BOP2-TE: Bayesian Optimal Phase 2 Design for Jointly Monitoring Efficacy and Toxicity with Application to Dose Optimization*

## What is your paper about?

Our paper introduces a Bayesian optimal phase 2 design for jointly monitoring efficacy and toxicity, referred to as BOP2-TE, to enhance patient safety and benefits. BOP2-TE rigorously controls multiple type I errors in cases where the treatment is toxic and futile, effective but toxic, or safe but futile, while optimizing power when the treatment is effective and safe. We provide a derivation of closed-form type I error, facilitating the rapid optimization of stopping boundaries. Furthermore,

our paper investigates the application of BOP2-TE in multiple-dose randomized trials for dose optimization, making it a promising tool for future clinical research

## What are your plans after graduation?

Following graduation, my aim is to pursue a career as a researcher and statistician specializing in oncology drug development. I am particularly interested in the prospect of joining the FDA, as it presents an extraordinary opportunity to engage deeply in this field.



**Chang Wang**  
University of Michigan

**SECOND PRIZE:** Chang Wang, University of Michigan

**TITLE:** *Non-greedy Tree-based Learning for Estimating Global Optimal Individualized Treatment Regime with Continuous Treatment Dosage*

## What is your paper about?

My work is about the integration of non-greedy tree learning and optimal dose finding, in the scenario of causal inference. During the algorithm development, the main theoretical innovation is that we developed a new estimator for individualized causal effect with continuous treatment and double robustness.

## What are your plans after graduation?

I plan to pursue an academic career.



**Edward Bi**

University of Chicago

### **THIRD PRIZE:** Edward Bi, University of Chicago

**TITLE:** *PAM-HC: A Bayesian Nonparametric Construction of Hybrid Control for Randomized Clinical Trials Using External Data*

#### **What is your paper about?**

My paper aims to construct a hybrid control by borrowing information from “similar patients” (those with similar baseline characteristics) in external data to augment the control arm of a current randomized clinical trial. We capture those “similar patients” through a novel clustering method called PAM, which is based on Bayesian nonparametric modeling.

#### **What are your plans after graduation?**

My plan after graduation is to seek a job in academia. I am currently applying for various post-doctoral positions and will be searching for a faculty position afterwards.

### **HONORABLE MENTIONS**

**Jack Wolf, University of Minnesota**

**Title:** *Leveraging Information from Secondary Endpoints to Enhance Dynamic Borrowing Across Subpopulations*

**Summary:** Randomized trials aim for efficient treatment effect estimation within target populations, yet interest often extends to subpopulations. Subgroup treatment effects are challenging to estimate due to limited subjects, but efficiency can be improved by borrowing strength across subpopulations, as in basket trials. A proposed multisource exchangeability model (MEM) incorporating secondary endpoints was used to assess subpopulation exchangeability.

**James Willard, McGill University**

**Title:** *Bayesian Optimization for Personalized Dose-Finding Trials with Combination Therapies*

**Summary:** Identifying optimal dose combinations in early phase trials presents challenges due to the trade-off

between parameter estimation and small sample sizes. This is exacerbated in personalized dose-finding, where patient characteristics are considered. To address this, Bayesian optimization was employed for finding optimal dose combinations in both standard and personalized trials.

**Qingzhi Liu, University of Michigan**

**Title:** *Pan-Cancer Drug Response Prediction Using Integrative Principal Component Regression*

**Summary:** Precision oncology relies on genomic and pharmacological data from preclinical cancer models like cell lines. Despite their utility, cell lines are not fully representative of patient tumors. Integrative methods like Integrative Principal Component Regression (iPCR) bridge this gap, uncovering joint and model-specific variations in genomic data. iPCR predicts patient drug responses using preclinical model data, identifying key driver genes and pathways.

**Marlena Bannick, University of Washington**

**Title:** *Joint calibration in randomized clinical trials: a general covariate-adjustment method with guaranteed efficiency gain and universal applicability to covariate-adaptive randomization schemes*

**Summary:** In randomized clinical trials, adjusting for baseline covariates enhances credibility and efficiency in demonstrating treatment effects. An augmented inverse propensity weighted (AIPW) estimator was explored, accommodating various models. Under covariate-adaptive randomization, conditions were established for AIPW estimators to gain efficiency. Motivated by these conditions, a Joint Calibration strategy was introduced to ensure efficiency gains and universal applicability across different randomization schemes.

**Xue Yang, University of Pittsburgh**

**Title:** *GO-SMART: Generalized Outcome-Adaptive Sequential Multiple Assignment Randomized Trial*

**Summary:** A dynamic treatment regime (DTR) is crucial for guiding multistage decision processes, particularly in medical contexts like chronic disease treatment selection. Sequential multiple assignment randomized trials (SMARTs) offer a framework for constructing DTRs, yet they may overlook valuable data from past patients, potentially impacting treatment adherence. To address this, a generalized outcome-adaptive (GO) SMART design was proposed that adaptively adjusts randomization probabilities based on past treatment effectiveness. ■

# UPCOMING CONFERENCES

Di Zhang (Teva)

## 2024 ASA Biopharmaceutical Section Regulatory-Industry Statistics Workshop

The ASA Biopharmaceutical Section Regulatory- Industry Statistics Workshop is sponsored by the ASA Biopharmaceutical Section in cooperation with the FDA Statistical Association. The conference will be held from September 25-27, 2024 in Rockville Maryland, with invited sessions co-chaired by statisticians from industry, academia, and the FDA. Short courses will be offered on the first day of the workshop. To register, please visit: <https://ww2.amstat.org/meetings/biop/2024>.

- Early Registration Opens: June 13, 2024
- Early Registration Closes: August 14, 2024

## 2024 WNAR of IBS

The WNAR 2024 will be held in Fort Collins, Colorado from June 9-12, 2024. To register, please visit: <https://www.wnar.org/wnar2024>.

## 2024 Symposium on Data Science & Statistics (SDSS)

The ASA's seventh annual SDSS will be held in Richmond, VA from June 4-7, 2024. SDSS provides a unique opportunity for data scientists, computer scientists, and statisticians to come together and exchange ideas. To register, please visit: <https://ww2.amstat.org/meetings/sdss/2024>.

- Early Registration Closes: April 30, 2024

## JSM 2024

Joint Statistical Meetings (JSM) will be held in Portland, Oregon from August 3-8, 2024. It is one of the largest statistical events and the broadest, with topics ranging from statistical applications to methodology and theory to the expanding boundaries of statistics, such as analytics and data science. JSM also offers a



unique opportunity for statisticians in academia, industry, and government to exchange ideas and explore opportunities for collaboration. To register, please visit: <https://ww2.amstat.org/meetings/jsm/2024>.

- Early Registration Opens: May 1, 2024
- Early Registration Closes: June 3, 2024

## DIA 2024

The DIA 2024 Global Annual Meeting will be held in San Diego, CA from June 16-20, 2024. It invites industry, regulators, governments, academics, innovators, and patients to network, problem-solve, and discuss global and local challenges facing the life sciences community. DIA 2024 will amplify different perspectives while highlighting expertise across the globe to reimagine current processes that better enhance health and well-being. To register, please visit: <https://www.diaglobal.org/Flagship/DIA-2024>.

- Standard Registration Closes: May 15, 2024