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BIOPHARMACEUTICAL REPORT

CONTENTS

Notes from the editors

Time flies as we are more than half way through 2021, we continue to reflect on the impact that we have made as statisticians not only during the global pandemic; but also, over the last 40 years as part of the Biopharmaceuticals (BIOP) Section of the American Statistical Association (ASA).

In the third issue of 2021, we open with a general article by **Meijing Wu** (AbbVie) talking about the third decade of BIOP after the turn of the millennium and highlighting the major achievements, which included the birth of one of our journals, *Statistics in Biopharmaceutical Research*. This is followed by reflections from three of the BIOP Section Chairs from the 2000s, **Nancy D. Smith** (2003), **Stacy Lindborg** (2006, and **Katherine Monti** 2010).

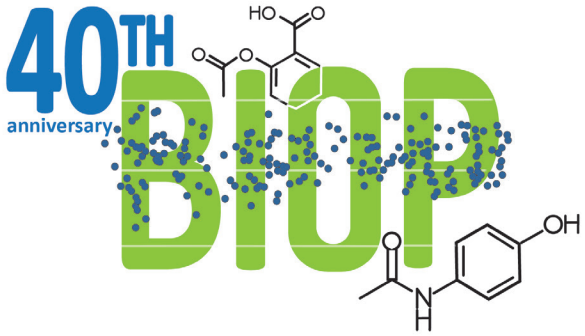
In this issue, you will find an article on Bayesian Methods in Chemistry, Manufacturing, and Controls that has been put together by **Paul Faya** (Eli Lilly), and **Donald Berry** (Berry Consultants), an example of contributions from non-clinical biostatistics that has become a regular feature of the BIOP report. This is followed by the non-clinical biostatistics conference report by **John Kolassa** (Rutgers) and **Richard Baumgartner** (Merck). Following this, we have two articles under the theme of Complex Innovative Trial Designs. The first one by **Yichen Lu** (Genentech, University of Washington), **Aijing Lin** (Genentech), **Herbert Pang** (Genentech), and **Jiawen Zhu** (Genentech), presents an R Tool for Bayesian Dynamic Borrowing. The second article by **Karen Price** (Eli Lilly), **JonDavid Sparks** (Eli Lilly), and **Fanni Natanegara** (Eli Lilly), gives us an industry perspective on FDA's Complex Innovative Trial Designs Pilot. In this issue, you will also find three summary reports from the meeting organized by the ASA BIOP Statistical Methods in Oncology Scientific Working Group, the FDA Oncology Center of Excellence, and LUNGevity Foundation's COVID and Clinical Trials Statistical Analysis Working Group that discussed the statistical considerations in oncology trials in the COVID era, the design of dose-optimization studies, and the evaluation of treatment effect in underrepresented population. This is followed by an update from the BIOP Fellows nomination committee.

Congratulations to the 8 BIOP members who were elected ASA Fellows in 2021. We also share an update of upcoming conferences which may be of interest to the BIOP community.

CELEBRATING THE 40TH ANNIVERSARY OF THE BIOPHARMACEUTICAL SECTION: THE THIRD DECADE (2001-2010)

Meijing Wu (AbbVie)

Following the success of ASA Biopharmaceutical Section Regulatory-Industry Statistics Workshop in late 1990s, the Biopharmaceutical Section (BIOP) continued to expand and grow with several milestones achieved during the third decade.



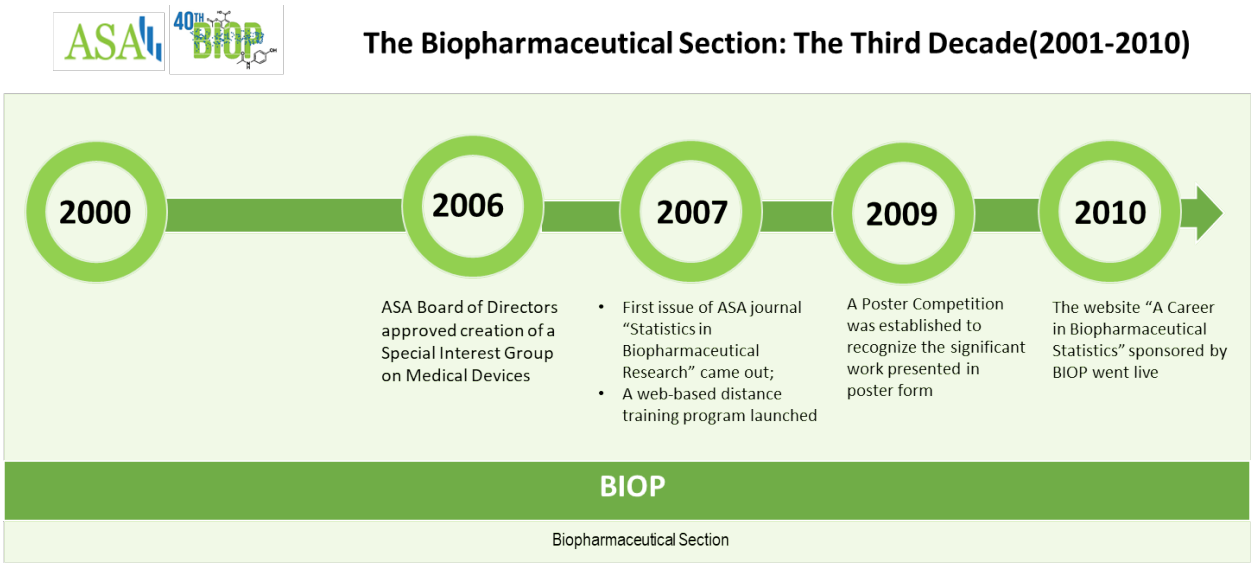
A New Group: Special Interest Group on Medical Devices (2006)

Since the early 2000s, the medical devices had been revolutionizing medicine with extraordinary advances not only in detecting and treating disease but also in mitigating the ravages of injury and age. Medical devices differ fundamentally from pharmaceutical drugs and biological products in their mechanisms of action, usage, laws for regulation, development, statistical issues and Post-Market Issues. However, despite the greater prevalence of medical devices than drugs, at that time, statisticians in the medical device industry did not have the same kind of statistical environment as the pharmaceutical statisticians. The associations of medical devices rarely had meetings, statistical courses, programs, workshops and sessions that the pharmaceutical statisticians frequently had from the support of their organizations. With advancement of the medical devices, more and more statisticians in the Biopharmaceutical Section were getting involved in research, development and evaluation of breakthrough medical products. At the Joint Statistical Meetings in August 2005, there were nine well-attended Topic Contributed Sessions on medical devices, all of which were sponsored by the Biopharmaceutical Section and six of which the section was the primary (first) sponsor. In addition, over 70 people attended an organizational meeting for statisticians interested in statistics for medical devices. It was pointed out at this meeting that the charter for the Biopharmaceutical Section explicitly includes not only pharmaceutical drugs and biologicals but also medical devices.

In 2006, through the leadership of Greg Campbell, the ASA Board of directors approved the creation of a Special Interest Group on Medical Devices, under the Biopharmaceutical Section. The Section had seen the continued strong presence of topics related to devices on Biopharmaceutical programs.

A New Journal: *Statistics in Biopharmaceutical Research* (2007)

In December 2005, the ASA Board of Directors approved the establishment of a new journal, Statistics in Biopharmaceutical Research (SBR). Bradley Efron originally proposed the idea for the new journal during his term as President of ASA. His intention was to provide a journal that would specifically address the growing needs of the biopharmaceutical sciences. Karen Kafadar led a task force to construct the business case for SBR and Joe Heyse was selected to be the first editor. Joe introduced the SBR in the Fall 2006 Biopharmaceutical Report. According to the report, "SBR will publish articles that focus on the needs of researchers and applied statisticians from academia, government, and industry. This includes papers discussing appropriate statistical methodology and information regarding the use of statistics in all phases of research, development, and practice in the pharmaceutical, biopharmaceutical, device and diagnostics industries. Articles will focus on the development of novel statistical methods,



novel applications of current methods, or the innovative application of statistical principles that can be used by statistical practitioners in these disciplines."

The journal was opened on July 1, 2006 to begin accepting papers online. In late 2007, the first issue of SBR was published. The establishment of SBR marked a tremendous commitment by the ASA to the biopharmaceutical sciences, with many people contributed to birth of the journal. Although the SBR was initiated by the ASA, it was fully supported by the executive committee. This new initiative provided an opportunity for the Biopharmaceutical Section members to increase their visibility as well as the support to the continually evolving area of research.

A New Program: Web-Based Distance Training Program (2007)

Web-based training was becoming increasingly popular across a variety of industries due to its flexibility and low cost: participants can learn from their own offices and the cost is much less as compared to a living training course. In 2007, the Biopharmaceutical Section launched a web-based distance training program on topics of interest to pharmaceutical statisticians. Alex Dmitrienko volunteered to lead this initiative, and worked with Rick Peterson of the ASA and others to develop this program. Alex Dmitrienko inaugurated this event with a webinar "Multiple Comparisons in Clinical Trials" taught by himself on March 21, following by a series of four webinars by Geert Verbeke and Geert Mohlenberghs in April – June. The Section had subsidized this training program to allow members to participate at the lowest possible rate. In addition, departments were encouraged to have multiple participants share a single session (for example, by projecting the webinar in a conference room).

A New Competition: Poster Competition (2009)

In early 2008, the Biopharmaceutical Section established a Poster Competition to recognize the significant work presented in poster form, increase the number of posters, and improve the quality of the posters at JSM. Yongming Qu spearheaded this initiative and served as the first chair of the Biopharmaceutical Section Poster Award Committee. The other two members in this committee were Jingli Song and Junyuan Wang. The charter was finalized and approved by the Biopharmaceutical Executive Committee in August 2008. Monica Clark, Daniel Christen and Neal Thomas helped advertise the poster competition by sending an email to Biopharmaceutical Section members, posting an announcement at *http://www.amstat.org* and publishing an announcement in the October 2008 issue of *Amstat News*. Twelve qualified posters were received before the submission deadline on May 1, 2009. Each poster was reviewed by two referees, and the evaluation was based on four criteria: innovation, genera applicability in pharmaceutical

research, appropriate example(s), and effectiveness of presentation (well written, well organized, etc). The three winning posters were submitted by Kelly Zou, Arminda Siqueira and William Coar. The poster titles and names of co-authors were as follows:

- **Kelly Zou, Martin Carlsson**."Beta-mapping and beta-regression for changes of ordinal-rating measures on Likert scales".

- **Arminda Siqueira, Daniela Braga** and **Paula Chellini.** "Clinical trials, drug discovery, making decisions in bioequivalence studies: A statistical contribution".

- **William Coar, Darrin Despain** and **Brian Wiens.** "Estimation of treatment retention: The peak-trough ratio".

A New Website: A Career in Biopharmaceutical Statistics (2010)

In 2010, the Biopharmaceutical Section sponsored website "A Career in Biopharmaceutical Statistics" went live. Steve Gulyas and Jeremy Jokinen had worked with the Creative Street Media Group on the Web Outreach Project to build the website. It was designed to entice high school and undergraduates to join our profession. The first documented success actually happened before the formal launch of the website. An Advance Placement (AP) teacher showed an early version of the site to her students, one of whom decided only to apply to biostatistics programs in colleges, based on the video clips of statisticians that were filmed at JSM in 2009. ■

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MEMORIES FROM PAST BIOPHARMACEUTICAL SECTION CHAIRS

IN COMMEMORATION OF THE 40TH ANNIVERSARY OF THE ASA BIOPHARMACEUTICAL SECTION PART 2 (2001-2000)

Throughout 2021, to remember all of the achievements of the Biopharmaceutical Section over the last 40 years, in each of the issues this year of the Biopharm Report, we plan to share reflections from past Section Chairs over this period.

The Section Chairs during this third decade were the following:

- 2001 Jeff Meeker
- 2002 Robert Small
- 2003 Nancy D. Smith
- 2004 Keith Soper
- 2005 Len Oppenheimer
- 2006 Stacy Lindborg
- 2007 Brian Wiens
- 2008 Kannan Nataranjan
- 2009 Anna Nevius
- 2010 Katherine Monti

In this issue, we share remembrances from Nancy D. Smith, Stacy Lindborg, and Katherine Monti.

Nancy D. Smith (Section Chair 2003)

In the summer of 2003, our section newsletter "Biopharmaceutical Reports" became electronic in line with modern technology. This led to substantial savings on postage and printing costs. The Section also continued to expand our new Corporate Sponsorship program and by the end of the year we had almost 20 sponsors! We organized invited sessions and contributed sessions for ENAR and JSM, along with several successful short courses and roundtables. We sponsored a very successful FDA/Industry Workshop in the fall, with over 350 attendees, despite the fact that hurricane Isabel chose to pass almost directly over Bethesda while we were meeting! These events provided many opportunities for our members to network with other statisticians from regulatory, academia, and the pharmaceutical industry.

Stacy Lindborg (Section Chair 2006)

As the American Statistical Association grows over time and the discipline of statistics has become more popular, we must continue to evaluate if the way we are structured as a professional society and how we allocate space on the program and at the annual meeting meets our needs or should evolve. Anyone who has been involved in section leadership knows this is a delicate topic. One of the ways this played out in 2006 focused on the desire to create a Special Interest Group on Devices. As a backdrop to this discussion, we decided it was important to document the history of the Biopharm section from 1966-1988, bringing to light a time when the Biopharm Section was first created as an interest group called the Pharmaceutical Steering Committee, emerging out of the Biometrics Section. During my tenure as Biopharm Chair, we produced a detailed historical document of the Biopharm section and took another step in our evolution as an ASA Section by recognizing the Device Industry through the creation of a Special Interest Group on Devices under the Biopharm Section, a decision that was approved by the ASA Board of Directors.

Katherine Monti (Section Chair 2010)

I was most involved with the section during the decade 2001-2011. During this time, the section was growing its tech wings, leading the ASA in developing webinars and working with Creative Streets Media on a website and a video aimed at encouraging students to consider careers in the biopharmaceutical industry; Steve Gulyas (2012 Chair) led the charge on these issues. Also afoot were the challenges that came with change as the Special Interest Group in Medical Devices and Diagnostics was formed (it later became a section) and talk began regarding another offshoot, now the Statistics and Pharmacokinetics Interest Group. In 2010, Kannan Natarajan (2008 chair), Anna Nevius (2009 chair), and I completed a major overhaul of the Manual of Operations. On the horizon for the section? I imagine that the sequelae of COVID-19 will result in a wide range of changes in the pharmaceutical industry. ■

BAYESIAN METHODS IN CMC – HAS THE TIME COME FOR A REGULATORY GUIDANCE?

Paul Faya (Eli Lilly) Donald Berry (Berry Consultants)

The field of biostatistics is commonly associated with clinical trial statistics. An under-emphasized and at times under-appreciated area in this field is the application of statistics to biopharmaceutical product and process development. This area is often referred to as Chemistry, Manufacturing, and Controls (CMC) statistics. CMC results are "preclinical" in the strongest sense of the word as they directly impact clinical outcomes. Good science and sound statistics are critical in the design and analysis of CMC studies.

Regulatory reviewers of new drug and biologic applications insist that CMC studies for new molecular entities and biosimilars meet the highest of standards. These studies ensure that a drug's manufacture and distribution provide patients with predictable safety, quality, and efficacy. Guidance documents are provided by the Food and Drug Administration (FDA), European Medicines Agency (EMA), and other regulatory bodies for a large number of CMC areas; but guidelines for CMC submissions that include Bayesian statistical methods do not exist. Before discussing some reasons for the absence of guidance for Bayesian methods, a short explanation of CMC applications is provided.

CMC data not only describe the manufacturing process and associated control measures, but also detail the capability of measurement systems to adequately characterize the critical quality attributes of the drug substance and drug product. For example, CMC scientists must propose and justify lot release and shelf-life specifications for the quality attributes of future manufactured lots. They must demonstrate the robustness, precision, and accuracy of analytical methods used to measure the quality attributes as well as describe and justify process control measures. They must also demonstrate the long-term chemical and biological stability of the molecule throughout the supply-chain and proposed shelf-life. And they must provide evidence of comparability of the drug throughout its various stages of process and product development.

For biosimilar development, CMC scientists must demonstrate analytical similarity between the proposed and reference products. Analytical similarity is foundational for providing totality-of-the-evidence of biosimilarity to regulatory agencies. Comparative analytical data influence decisions about the type and amount of animal and clinical data needed to support a demonstration of biosimilarity.

The new millennium has seen growing evidence of the benefits of Bayesian methods in biostatistical applications, especially in clinical trials, but also in CMC. Recent peer-reviewed journal publications and conference presentations have galvanized CMC statisticians into organizing industry groups aimed at promoting the understanding and use of Bayesian methods. Such groups are linked to the American Statistical Association (ASA), Drug Information Association (DIA), and the IQ Consortium. In the 2021 ASA Nonclinical Biostatistics Conference, five out of the six CMC invited speakers proposed innovative Bayesian applications, while two special sessions addressed the need for Bayesian methods to improve decision-making.

CMC studies are ideally suited for applying Bayesian methodologies. Knowledge regarding the product, process, and measurement systems accumulates and improves as molecules move from early to late-phase development. For example, early screening studies of critical manufacturing process parameters evolve into process characterization and optimization studies in late phase. Moreover, it is common for biopharmaceutical manufactures to adopt "first-to-try" or "platform" manufacturing processes and analytical methods, particularly for proteins of similar structure (e.g., monoclonal antibodies). Therefore, high quality and carefully collected prior information is available across similar molecules as well as from the current project. And the Bayesian approach is inherently synthetic in combining various sources of information. Despite the recent push from industry groups, statistical practice in CMC remains predominantly frequentist, with statistical significance driving most decisions.

The road to the increasing adoption of the Bayesian approach in clinical trials has been long and bumpy. One barrier is the lack of suitable training among statisticians. Another is the lack of understanding of the approach and its measures on the part of stakeholders. Education is essential. The same issues are present in CMC. But relative to CMC biostatisticians, Bayesian clinical trialists have several advantages over their fellow CMC biostatisticians.

There are at least three reasons why the hurdles seem higher in CMC studies than in clinical trials. First, CMC studies are seldom on the critical path to drug approval. While they are necessary, their timelines are set by clinical performance of the drug. Moreover, resources allocated for CMC development are typically triggered by clinical outcomes. Bayesian methods are widely touted as being efficient and minimizing time and expense of drug development. Clinical trials are voracious consumers of both. In contrast, CMC statisticians have difficulty arguing that Bayesian methods will help shorten the development timeline and so deliver effective therapies to patients sooner. In the clinical space, the least burdensome principle, mandated in Section 513(a)(3) of the Federal Food, Drug, and Cosmetic Act, was a key driver that paved the way for the 2010 Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials published by the Center for Devices and Radiological Health (CDRH). According to the CDRH, the Bayesian approach, when correctly employed, can be less burdensome than a frequentist approach in terms of evaluating effectiveness of a device. Similar reasoning has helped to advance innovative and adaptive clinical trial designs, which rely heavily on Bayesian methodology. There are analogous incentives for using a Bayesian approach within the CMC space but they are not as obvious or as powerful.

Second, one of the primary advantages of the Bayesian approach is the potential for sample size reduction through the use of prior information. In terms of clinical studies, the prospect of smaller-sized or shorter-duration trials is highly desirable from the perspective of regulators, drug sponsors, the medical community, and patients. Because the sampling unit for a clinical trial is a human being, regulators are incentivized to minimize testing on subjects. In CMC studies, sample size reduction is primarily a goal of the drug sponsor. The sampling units for CMC studies are typically batches or individual samples of a batch, and testing is performed at the expense of the manufacturer, without impact to a human patient. Therefore, in contrast to clinical trials, CMC studies can be perceived by regulators as being carried out strictly at producer's risk or cost. However, the incentives for sample size reduction in CMC extend beyond cost-reduction. For example, smaller CMC studies can free up limited manufacturing resources to supply medicines to patients. Smaller studies can also reduce the sample testing burden for scientists and laboratories, affording more time and resources for scientific and process innovation.

Finally, regulatory bodies commit far fewer statistical resources and infrastructure for the review of CMC studies than they do for clinical trials. For example, chemists and biologists in the FDA review the CMC sections of biologics license applications. A small group of CMC statisticians serve as consultants on an "as-needed" basis (Rahman et al., 2016). In contrast, the statistical infrastructure within regulatory bodies supporting the review of clinical trials is vast. Clinical trial statisticians are primary reviewers and have substantial influence on regulatory decisions. The Bayesian movement within the clinical trial space has benefited immensely from the leadership of and collaborations with regulatory statisticians. Joint industry and regulatory workshops, meetings, working groups, and publications have been major catalysts in the Bayesian movement over the years.

In particular, Gregory Campbell, former Director of the Division of Biostatistics in the Office of Surveillance and Biometrics of the CDRH, played a key role in overcoming resistance to Bayesian submissions for clinical device trials. He notes that achieving support from all levels of CDRH leadership and a concerted effort to educate staff were key success factors, culminating in the publishing of the Bayesian guidance document in 2010 (Campbell, 2021). Given the limited scale of CMC regulatory statistics, building momentum for Bayesian CMC submissions among regulatory bodies is much more challenging. Moreover, a common feature of many Bayesian approaches is the use of simulations and extensive modeling and computations. This will inevitably increase the review burden of CMC regulatory staff.

It is clear that some of the key factors spurring regulators to embrace Bayesian methods for clinical trials

do not extend to the CMC space. Despite this fact, it is important for CMC statistics to lead the effort towards risk-based, least-burdensome decision-making in biopharmaceutical development and manufacturing. This requires that CMC statisticians, scientists, and regulators understand Bayesian methods. And it requires that use of Bayesian methods increase in CMC studies. A regulatory document providing guidance to CMC statisticians on the application of Bayesian methods would be of great benefit in this regard. Statistical innovation in CMC submissions can be risky. That CMC regulatory reviewers are not statisticians means that unfamiliar approaches to study design and analysis could delay the approval of a drug. An FDA guidance document would help to reduce either perceived or real regulatory resistance to innovative Bayesian approaches. Indeed, in a recent survey of nonclinical statisticians conducted by the DIA-ASA Nonclinical Bayesian Working Group, two of the main hurdles to the adoption of Bayesian methods identified by responders were (1) lack of clarity and (2) perceived resistance from regulatory bodies (Faya et al., 2021).

The current guidance documents governing CMC practice (FDA and ICH) are silent on the use of Bayesian methods, not even mentioning them as alternatives to traditional approaches. This is curious given the enormous emphasis on risk control in pharmaceutical development and quality metrics (see ICH Q8 and Q9). In contrast, as far back as 1998, ICH E9, which governs statistical principles for clinical trials, noted that "the use of Bayesian and other approaches may be considered when the reasons for their use are clear and when resulting conclusions are sufficiently robust".

Demonstrating equivalence of biosimilars is similarly bereft of Bayesian guidance. This is despite the natural suitability of Bayesian approaches for such studies. Bayesian posterior and predictive distributions can be used to make probabilistic (risk-based) conclusions regarding the similarity of the physiochemical and functional properties of the two products. However, in the most recent FDA draft guidance (2019) for the development of therapeutic protein biosimilars, only frequentist equivalence testing is proposed, with no mention of the potential for Bayesian methods.

The time has come to update guidance documents governing CMC practices and for new guidances to be issued. The shift in the industry towards risk quantification and risk-based decision-making is inherently Bayesian. And computational limitations no longer pose barriers to the application of Bayes theorem and the associated methodologies. In a recent cover article of the American Institute of Chemical Engineers Journal, Tabora et al. (2019) called for chemical engineers to adopt Bayesian-based approaches, which quantify risk more effectively and meet the FDA's vision for robust pharmaceutical manufacturing. They argued that Bayesian methods are exceptionally effective at characterizing variability from limited data and anticipate a much wider adoption across the pharmaceutical industry. However, the authors also noted that regulatory agencies need to encourage the use of probabilistic risk-based methods and to move beyond the use of traditional statistical approaches.

At a broader level, the FDA's vision for *Pharmaceutical Quality for the 21st Century – A Risk Based Approach* has been around for nearly 20 years. One of the key pillars of the initiative was the concept of "Quality by Design" (QbD). QbD involves developing a thorough understanding of the product and process along with a knowledge of the risks involved in manufacturing the product. Extensive research has been published by industry (see for example, Peterson 2008, Peterson and Yahyah 2009, Peterson and Lief 2010, Rozet et al. 2013) on how Bayesian methods are ideally suited for QbD applications. Yet, in the years since the launch of the FDA QbD initiative, no regulatory document has been revised to reflect this fact.

We can also learn from the "least burdensome" provisions of the CDRH, which are linked to the FDA Modernization Act of 1997. Although written from the perspective of medical device clinical trials, the spirit of the provisions is completely relevant to other spheres such as CMC. Principles such as using only necessary (minimum required) information, acceptance of alternative approaches, the efficient use of resources, the use of alternative sources of data, leveraging existing data, and considering the "most efficient means" of obtaining scientific evidence are important in CMC, and in many ways, can be realized through Bayesian statistics.

In sum, adopting Bayesian methods in CMC has the potential to enhance decision-making and improve the quality, safety, and efficacy of biopharmaceutical products. Modernizing CMC regulatory guidance will open new paths for CMC scientists, engineers, and

statisticians to properly and fruitfully apply Bayesian principles throughout the product development and manufacturing life-cycle. The clinical space has already paved the way with guidance documents and examples of industry-regulatory collaborative efforts that the non-clinical community can learn from and leverage. Now we need initiative, clarity, and collaboration from the CMC regulatory community on both the industry and government sides. ■

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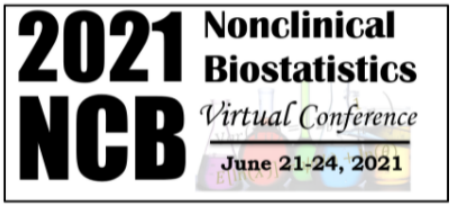
2021 NONCLINICAL BIOSTATISTICS CONFERENCE REPORT

John Kolassa (Rutgers) and Richard Baumgartner (Merck)

Don Berry, Berry Consultants, as discussant in special session: Bayesian methods in CMC – has the time come for a regulatory guidance?

Nassim Nicholas Taleb, Distinguished Professor, NYU, delivered keynote speech titled Statistical Consequences of Fat Tails

Ronald L. Wasserstein, American Statistical Association, joint discussant in roundtable: P-values in Nonclinical Studies



The 2021 Nonclinical Biostatistics Conference was held virtually June 21-24, 2021. The conference was the 7th such conference since 2009, meeting biennially. It was organized by the ASA biopharm section's nonclinical working group, co-chaired by Xin Huang (Abbvie) and John Kolassa (Rutgers). One-hundred-forty attendees participated in a program that kicked off with two short courses:

- Bayesian Regression Trees, Dr. Jason Roy (Rutgers University, NJ)
- Bayesian Survival and Joint Models using Rstanarm, Jacqueline Buros Novik (Generable Inc., NY)

Followed by 28 technical presentations and 14 posters related to the 4 main areas of nonclinical biostatistics (Discovery/Biomarkers, Safety/Pharmacology, CMC, Statistical Computing and Visualization). Keynote addresses were given by ASA incoming president Wendy Martinez, on data ethics, and author Nassim Nicholas Taleb, on statistical consequences of fat tails. The conference also recognized 3 awardees for the best nonclinical papers published over the preceding 3 years as follows:

- **1st Place:** Burdick, R. K., Thomas, N., & Cheng, A. (2017). Statistical considerations in demonstrating CMC analytical similarity for a biosimilar product. Statistics in Biopharmaceutical Research, 9(3), 249-257.
- **2nd Place:** Novick, S. J., Christian, E., Farmer, E., & Tejada, M. (2021). A Bayesian statistical approach to continuous qualification of a bioassay. PDA Journal of Pharmaceutical Science and Technology, 75(1), 8-23.
- **3rd Place:** Sondag, P., & Lebrun, P. (2020). Risk-based similarity testing for potency assays using MCMC simulations. Statistics in Biopharmaceutical Research, 1-10.

Two graduate students received best poster awards, with first prize ($250) going to Louise Leonard and second prize ($150) going to Jinghang Lin.

The 2021 NCB conference oral presentations and posters are available electronically at 2021 Nonclinical Biostatistics Conference: App Home (pathable.com). For a more detailed information about the conference presentations and proceedings please see the daily digest compiled at (NCB-Main - Biopharmaceutical Section (*amstat.org*) *https://community.amstat.org/biop/events/ncb/index*) ■

PSBORROW: BAYESIAN DYNAMIC BORROWING R TOOL FOR COMPLEX INNOVATIVE TRIAL DESIGNS

Yichen Lu (Genentech, University of Washington), Aijing Lin (Genentech), Herbert Pang (Genentech), Jiawen Zhu (Genentech)

Introduction

In disease areas with unmet medical need, clinical scientists and trial designers are constantly looking for ways to increase the chance for patients to be enrolled into the experimental arm from a randomized controlled trial (RCT), which remains a gold standard for confirmatory studies. In such situations, borrowing information from external controls can potentially help reduce the number of control arm patients that need to be enrolled in the RCTs, improve the statistical power or shorten the study duration of clinical trials. In this article, we focus on a type of design to best incorporate external controls in RCTs. Such trials are known as hybrid control trials. Viele et. al. (2014) conducted a review on approaches to combine concurrent and external control information from hybrid control trials, such as pooling, test-and-pool, down-weighting external control information through a fixed weighted prior or dynamic borrowing, which allows adaptive down-weighting of the external control information. Despite the advantage of leveraging external data to supplement the concurrent control arm, there are risks of Type 1 error inflation or bias in estimated treatment effect if the historical control arm differs from the concurrent one. Dynamic borrowing approaches have been developed for this type of design and have shown favorable trial operating characteristics (Ibrahim et al., 2000; Hobbs et al., 2012; Schmidli et al., 2014; Lewis, et al., 2019). However, the implementation of the dynamic borrowing method and trial design is relatively complicated compared to the traditional trial design and computationally intensive. Without efficient statistical tools, they can be key hurdles of wider applications.

We have developed the *psborrow* R package to provide an efficient framework for users to conduct dynamic borrowing analysis, simulate trial data under different trial operation and external control assumptions, and summarize the trial characteristics (e.g. type 1 error, power, bias, MSE, etc) with different prior options compared to full borrowing, which pools all control data together, and no borrowing, which discard external control data completely. Covariate simulation and propensity score calculation are incorporated in the R package for users to evaluate the impact from the baseline characteristics. The R package currently implements the commensurate prior approach while the framework is flexible to adapt other approaches. A part of the work has been leveraged in the Complex Innovation Trial Designs (CID) Pilot Meeting Program collaboration with the FDA on the design of a phase 3 study in hematology, incorporating a hybrid external control arm using Bayesian dynamic borrowing for the analysis of overall survival.

Framework - R package structure

The *psborrow* R package consists of three parts: trial data simulation, performing different borrowing methods using Bayesian models, and summarizing statistical characteristics of the trial design associated with each borrowing method (Figure 1). Each of the three parts in the

psborrow R package can be used separately as long as user-supplied data follows the required dataset formula.

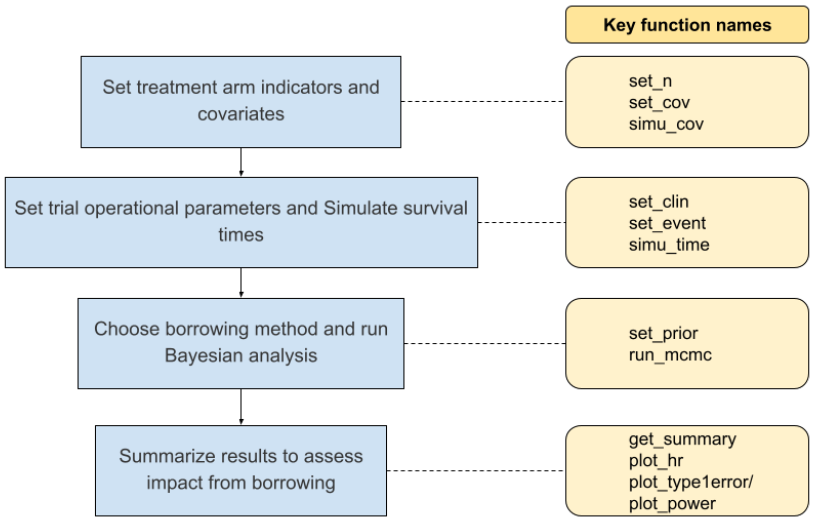


FIGURE 1. Analysis flow of the R package and key function names.

Trial simulation

Motivated by oncology examples, currently the *psborrow* R package focuses on trials with time to event endpoints, such as overall survival (OS) or progression free survival (PFS). The trial simulation includes assigning treatment arms to patients (concurrent treatment vs. concurrent control vs. external control) and an option to add binary or continuous covariates. The continuous covariates are generated following multivariate normal distribution where users need to specify (1) the mean for each variable (2) the covariance between each pair of covariates. The mean and variance for those covariates can be set differently to introduce heterogeneity between concurrent and external trials. The binary covariates are converted from the continuous covariates based on a user-specified probability. More details can be found in the *Illustration* section.

After simulating arm indicators (external control, concurrent control, concurrent treatment arms) and covariates (if desired) for each patient, the R package then assigns survival time and censoring status after accounting for enrollment rate and drop-out patterns. The survival time can be simulated through a piecewise exponential distribution (exponential distribution is a special case) or a Weibull distribution. Users start by specifying the hazard ratio (HR) between concurrent treatment vs. concurrent control arms, and the HR between the external control and concurrent control arms (called drift HR). For both HR and drift HR, the concurrent control arm is the reference arm.

By setting the drift HR not equal to one, the survival time of patients in the external control cohort will diverge from the survival time of patients in the concurrent control arm. It's also

possible to have covariate impact time-to-event by adding the covariates to the calculation of the scale parameter in the Weibull distribution and rate in the piecewise-exponential distribution.

For enrollment pattern and drop out pattern, the R package assumes that the inter-arrival times follow a piecewise exponential distribution. Users can also set the analysis start time such that patients recruited after the cutoff will be excluded from the analysis. Analysis can start after a fixed period of time from the first or last patient in, or be driven by the number of events observed.

Data analysis

The second element of the R package uses Markov chain Monte Carlo (MCMC) through *Jags* to obtain posterior distribution for hazard ratio between treatment and control arms. Bayesian commensurate prior approach is implemented (Lewis, et al., 2019). The probability density function for the survival time of patient i following a Weibull model is as below:

$$t_i \sim weibull(v, \lambda_i)$$

for $i = 1, 2, \ldots n$, where v is the shape parameter, λ_i is the rate, and n is the total sample size of the analysis population. The probability density function is:

$$f(t_i, x_i) = v\,\lambda_i\, t^{v-1} e^{-\lambda_i t^v}$$

with the rate taking the format:

$$\lambda_i = exp(\alpha_i + \beta_{trt} * I_{trt} + \beta_i * x_i)$$

where $\alpha_i = \alpha_{CC}$ if patient i is in the concurrent control arm, and $\alpha_i = \alpha_{EC}$ if patient i is in the external control arm. α_{CC} and α_{EC} correspond to the log of baseline hazard rate for concurrent control arm and external control arm, respectively.

$\beta = \{\beta_{trt}, \beta_i\}$ is the vector of regression coefficients and $\boldsymbol{x_i}$ is the corresponding covariate vector including the additional parameters to adjust for (e.g. propensity score). I_{trt} is the treatment indicators (value equals to 0 or 1). A hyperprior τ is set based on $\alpha_{cc}|\alpha_{EC} \sim N(\alpha_{EC}, \tau)$, an informative prior for concurrent control coefficient, with mean equal to the log of the external control effect.

Four borrowing methods have been implemented: (1) not borrowing any external control information (2) fully incorporate external control arm patients to the concurrent control group (3) dynamic borrowing with hierarchical Bayesian models with the commensurability hyperparameter τ following a Gamma distribution (4) dynamic borrowing with a half-Cauchy hyperprior distribution. For methods (1) and (2), a conventional Bayesian model is deployed with all relevant parameters assigned a non-informative prior. The concurrent and external control groups share the same prior for the log of the baseline hazard rate: $\alpha_{CC} \sim N(0, 0.0001)$ and $\alpha_{EC} \sim N(0, 0.0001)$.

In comparison, the latter two methods have the additional hyper-parameter τ, which acts as the precision variable assessing the similarity between the concurrent and external control groups. While the log of the baseline hazard rate of the external control group α_{EC} has a normal prior N(0, 0.0001), the prior for the log of the baseline hazard rate of the concurrent group is $\alpha_{CC} \sim$

$N(\alpha_{EC}, 1/\tau)$. The prior of τ follows a Gamma distribution (default: shape = 1, rate = 0.001) and a half-Cauchy distribution (default: location = 0, scale = 0.2), respectively. Users can update the default values for the parameter if they wish to customize the hyper-prior.

After users state the prior choices and the simulated data is ready for use, the Markov chain Monte Carlo (MCMC) algorithm is deployed to obtain samples from the posterior distribution.

Result summary

Lastly, a few tools are available for generating summary plots from posterior distributions. Summary statistics include estimated hazard ratio between treatment and control arms, Type 1 error, power, bias, and mean squared error (MSE) grouped by pre-specified hazard ratios between the arms.

For scenarios where pre-specified hazard ratio between concurrent treatment and control arms is set to 1, *psborrow* assesses type 1 error which is the percentage of time that the 97.5% quantile of the estimated range of HR between the treatment and control group from the posterior distribution falls below 1. This percentage translates to power when the pre-specified HR is below 1. Bias is calculated as the difference between the pre-specified HR and the average of the estimated hazard ratio from the posterior distributions. MSE is the sum of variance and bias squared.

In the next section, we illustrate the R package with a use case adapted from a real-world oncology trial design with the intent to borrow from a historical control arm. The posterior results for treatment effect are compared between full borrowing, no borrowing and dynamic borrowing with two different priors.

Use *psborrow* - illustration

The most recent version of *psborrow* can be installed from CRAN directly by running the following:

```
install.packages("psborrow")
```

After loading the library, the use case includes a concurrent trial with 140 patients on the treatment arm and 275 patients on the control arm, and an external control arm of 100 patients.

```
library(psborrow)
ss = set_n(ssC = 140, ssE = 275, ssExt = 100)
```

We assume that both trials collect data on patients' age, gender, and smoking history (ever smoked). *Psborrow* simulates a continuous variable for age from a normal distribution with a variance of 11^2, while the mean differs between concurrent and external trials (62 vs 65 years old).

```
age = set_cov(n_cat = 0, n_cont = 1, mu_int = 62, mu_ext = 65, var =
11^2)
```

For gender and smoking, the program generates two correlated continuous variables, and then dichotomizes them based on the user-specified probability threshold. In particular, 80% of the patients on the concurrent trial are randomized to be male patients while the percentage decreased to 70% for those on the external control arm. Similarly, 60% and 50% of patients from the concurrent trial and external trial are randomly selected to have a smoking history, respectively.

```
gender_smoking = set_cov(n_cat = 2, n_cont = 0, mu_int = 0, mu_ext = 0,
var = 1, cov = 0.5, prob_int = c(0.8, 0.6), prob_ext = c(0.7, 0.5))
```

We further add a few more covariates and combine all covariate information into one object.

```
covset3 = set_cov(n_cat = 2, n_cont = 0, mu_int = 0, mu_ext = 0, var =
1, cov = 0.3, prob_int = c(0.4, 0.5), prob_ext = c(0.3, 0.6))
covset4 = set_cov(n_cat = 3, n_cont = 0, mu_int = 0, mu_ext = 0, var =
1, cov = 0.2, prob_int = c(0.9, 0.3, 0.1), prob_ext = c(0.8, 0.4, 0.1))
cov_list = c(age, gender_smoking, covset3, covset4)
```

By using different distribution parameters for the covariates, we introduce some heterogeneity between patient populations from concurrent and external trials. We now prepare for survival time simulation by first specifying the hazard ratio between concurrent treatment and concurrent control arms (HR = 0.67 or 1 since users can test multiple hazard ratios at the same time), and the hazard ratio between the external and concurrent control arms (drift HR = 1).

For both trials, time-to-death followed an exponential distribution. The median overall survival time for patients on the concurrent control arm is set to be 51 months, translating to a rate of 0.0135 patients per month. Additionally, the survival time for each patient also depends on the baseline covariate values and the coefficients assigned by the users.

```
sample_cov <- simu_cov(ssObj = ss, covObj = cov_list, HR = c(0.67, 1),
driftHR = 1, seed = 47, nsim = 2)
evt <- set_event(event = "pwexp", lambdaC = 0.0135, beta = c(1, 1, 0.5,
rep(0.001, 5)))
```

The *psborrow* package can simulate survival time following a piecewise exponential distribution or the Weibull distribution as well. For different distributions, users are expected to set values for relevant parameters, otherwise default values will be used.

Users may set the accrual time and exit pattern that both follow an exponential distribution, with flexible settings of different exponential rates for external and concurrent trials. The analysis start time is 64 months after the first patient in and any patients with simulated recruitment time after the cut-off were excluded from the analysis. **Figure 2** shows the Kaplan-Meier curves of survival time for patients in the concurrent and external trials.

```
c_int = set_clin(gamma = 10, e_itv = 415/10, etaC = 0.04/12, CCOD =
"fixed-first", CCOD_t = 64)
```

```
c_ext = set_clin(gamma = 100/18, e_itv = 18, etaC = 0.01/12,  CCOD =
"fixed-first", CCOD_t = 64)
sample_time <- simu_time(dt = sample_cov, eventObj = evt, clinInt =
c_int, clinExt = c_ext, seed = 47)
```

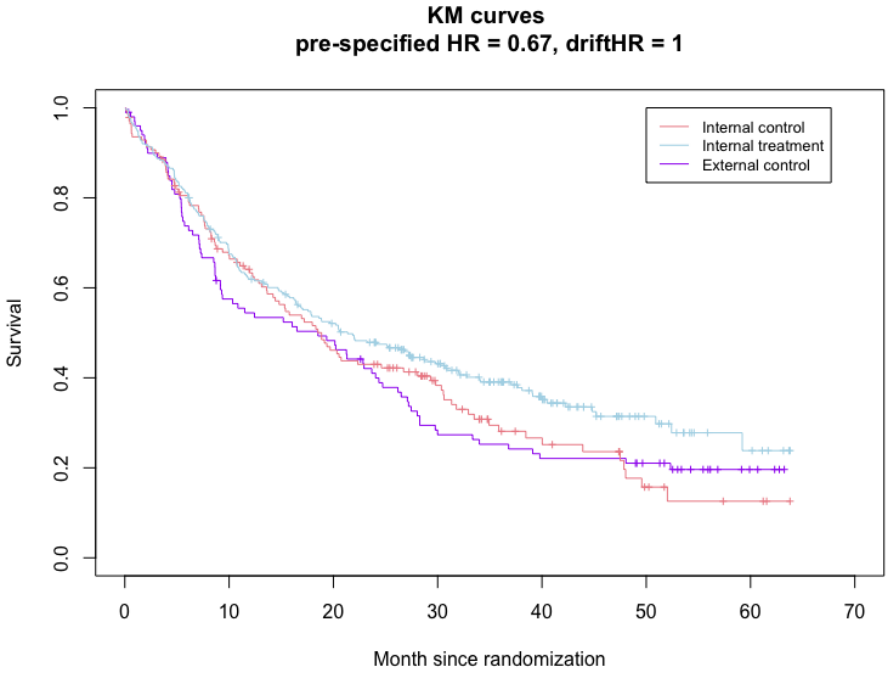


FIGURE 2. Kaplan-Meier curves of survival time for patients on the concurrent treatment, concurrent control and external control arms. Hazard ratio for time-to-events between concurrent treatment and concurrent control is 0.67, between external control and concurrent control is 1.

Once we complete trial data simulation, we proceed to analyze different borrowing methods with Bayesian models. We start with specifying the prior and the likelihood of the observed trial data. The current R package assumes that time-to-event can be modeled by a Weibull distribution and users can decide whether they want to use any covariate for the survival time.

In this example, we are generating posterior distributions with four borrowing methods available in *psborrow*. For the two dynamic borrowing methods using Bayesian commensurate prior approach, the precision hyper-parameter τ for controlling the variation between concurrent and external control information follows a Gamma distribution and a half-Cauchy distribution. The other two settings use conventional Bayesian models to assess the impact of borrowing all information from the external trial or not using any external information.

For priors of parameters including the shape parameter for the Weibull distribution, hazard ratio between the three arms, coefficient for the covariates if applicable, *psborrow* concurrently assigns vague priors to all of them.

```
pr1 <- set_prior(pred = "none", prior = "cauchy", r0 = 1, alpha = c(0,
0), sigma = 0.03)
pr2 <- set_prior(pred = "none", prior = "gamma", r0 = 1, alpha = c(0,
0))
pr3 <- set_prior(pred = "none", prior = "no_ext", alpha = 0)
pr4 <- set_prior(pred = "none", prior = "full_ext", alpha = 0)
pr_list <- c(pr1, pr2, pr3, pr4)
```

Lastly, we enter the initial values for these parameters for the MCMC process, and determine the number of chains, number of iterations for adaptation, number of iterations discarded as burn-in, and number of iterations to monitor. After calling the execution function, *psborrow* output the summary statistics from the posterior distributions for each simulation

```
res <- run_mcmc(dt = sample_time, pr_list, n.chains = 2, n.adapt =
1000, n.burn = 3000, n.iter = 6000)
```

For a clearer comparison among different borrowing methods, *psborrow* built in some plotting functions that showcase the posterior hazard ratio, power, type 1 error, bias, or MSE results averaged among all simulations for different borrowing methods.

```
summ <- get_summary(res_rbind)
plot_type1error(summ, driftHR = 1, pred = "none")
plot_power(summ, HR = 0.67, driftHR = 1, pred = "none")
```

To summarize, full borrowing using a simple Bayesian model is associated with the largest inflation in type 1 error. Dynamic borrowing using Bayesian commensurate approach with the precision parameter following a Gamma distribution encouraged borrowing more than half-Cauchy did, and it inflated type 1 error to a smaller extent compared to the full borrowing approach. On the other hand, dynamic borrowing with Gamma hyperprior boosted power almost as much as full borrowing. When comparing the two priors, Gamma vs half-Cauchy, for dynamic borrowing, the latter one is more conservative with power improvement, but it led to a smaller inflation in type 1 error (**Figure 3**).

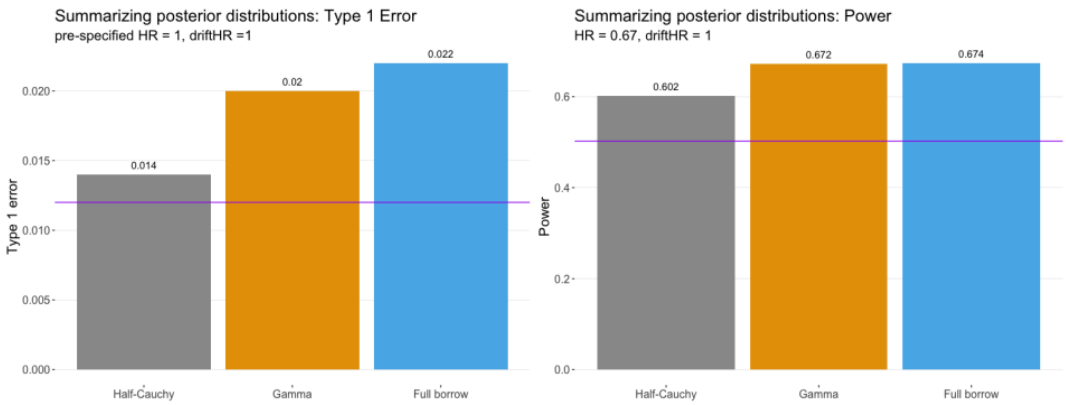


FIGURE 3. Left: The bars represent the type 1 error summarized from posterior distributions using three different borrowing methods: dynamic borrowing with Half-Cauchy hyper-prior, dynamic borrowing with Gamma hyper-prior and full borrowing. The purple line indicates the type 1 error from the no borrowing approach. Right: The bars represent the power summarized from posterior distributions using three different borrowing methods as labeled in the x-axis. The purple line indicates the power from the no borrowing approach.

Discussion

In conclusion, the objective of *psborrow* is to provide a tool for easy-to-conduct simulations and inform the users about the method's operating characteristics, especially the drifting impact on treatment effect estimates through different borrowing methods (full borrowing, dynamic borrowing vs no borrowing) in the hybrid control setting. The users can use *psborrow* to determine which borrowing setting suits their need the most with regard to the trade off between type 1 error, power, and bias in the treatment effect estimate.

If users want to use different distributions for hyper-priors in the Bayesian hierarchical model for dynamic borrowing, users can follow the format of the existing script for half-Cauchy or Gamma hyper-distribution to create their own, and adapt the new method through functions `set_prior`. Users can also use *psborrow* for trial data generation purposes, and we welcome them to incorporate their own borrowing method, Bayesian or non-Bayesian, on the trial datasets generated. Additionally, we encourage users to explore the supplementary functions included in *psborrow* (e.g. simulate survival time based on selected covariates, allow for a non-linear relationship between covariates and log of hazard ratios, use propensity score matching to balance the concurrent and external cohorts before running the Bayesian analysis).

Availability

The *psborrow* R package is published and actively maintained on The Comprehensive R Archive Network CRAN and can also be found at https://github.com/Genentech/psborrow. The repository includes a user guide and a vignette showing a few examples of using *psborrow* to quantify the benefits and limitations of different borrowing methods.

Recommended citation: Lu, Y., Lin, A., Pang, H., & Zhu, J. (2021). Bayesian Dynamic Borrowing Tool for Complex Innovative Trial Designs. *ASA Biopharmaceutical Report, Summer 2021, Volume 28, Issue 3*,11-19

Acknowledgements

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A BRIEF OVERVIEW OF COMPLEX INNOVATIVE TRIAL DESIGNS: AN INDUSTRY PERSPECTIVE

Karen Price (Eli Lilly), JonDavid Sparks (Eli Lilly), and Fanni Natanegara (Eli Lilly)

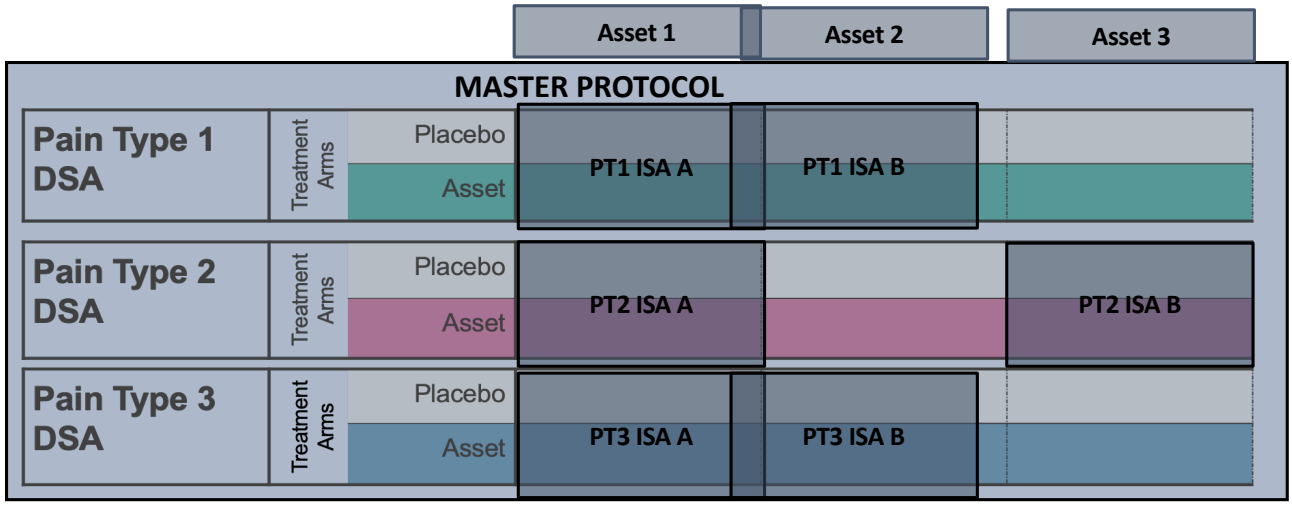
Introduction

Complex Innovative Trial Designs (CID) have received significant attention as part of broad efforts to further modernize the drug development process. It is well-recognized that CID have great potential to speed medicines to patients more efficiently and at lower cost relative to traditional designs. Close partnership and communication between drug developers in Academia, Industry, and Regulatory Agencies is key to enable broader and more appropriate use of CID.

There are important initiatives that have accelerated efforts to enable broader use of CID particularly in late-stage development. These efforts seek to facilitate the needed partnership and communication across stakeholders. For example, the 21st Century Cures Act included provisions related to advancing CID. Further, as part of PDUFA VI, a CID Pilot Meeting Program was launched by FDA in 2018. Specifically, as seen in the FDA announcement of the CID Pilot Meeting Program "As displayed in the Federal Register notice on August 29, 2018, FDA is conducting a Complex Innovative Trial Design (CID) Pilot Meeting Program to support the goal of facilitating and advancing the use of complex adaptive, Bayesian, and other novel clinical trial designs." (1)

The CID Pilot Meeting Program is led by FDA statisticians, with cross-functional representatives involved, and provides sponsors the opportunity to interact closely with FDA on the proposed CID via two meetings specifically structured to focus on the proposed design. Additionally, as part of the CID Pilot Meeting Program, FDA is permitted to publicly discuss the CID to share learnings and promote innovation.

Complex innovative designs encompass a range of study designs, acknowledging that the definition of CID will evolve over time. Examples of CID include (but not limited to) complex adaptive designs, Bayesian designs, and other innovative clinical trials such as master protocols that require the use of computer simulation to evaluate the trial's statistical operating characteristics. Hence, we must continue to establish best practices that enable interactions between Sponsors and FDA on technical aspects associated with Bayesian methods, simulation plans, and simulation results to occur more efficiently. Therefore, it is important that we continue to grow our experiences together and find sustainable ways to submit and achieve alignment (between Sponsors and FDA) on trials that require simulations to evaluate statistical properties.



DSA = Disease State Addendum
ISA = Intervention-Specific Appendix

Figure 1: Schematic of Chronic Pain Master Protocol

Lilly's CID Pilot Meeting Program Experience

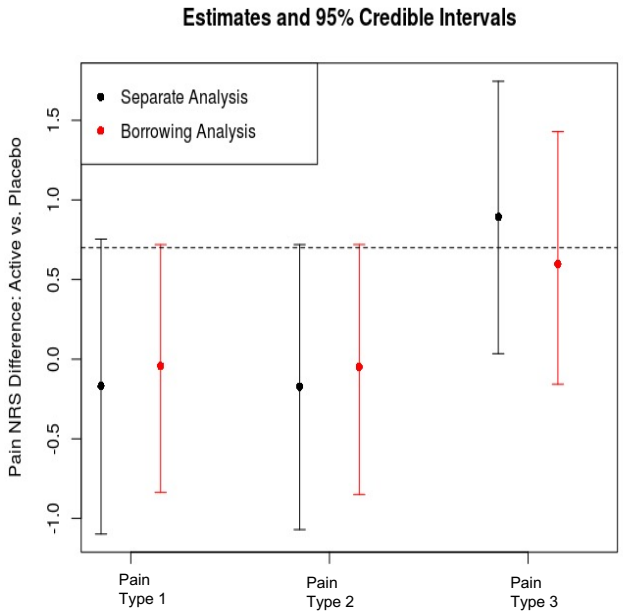
In September 2019, Lilly announced acceptance into CID pilot meeting program. The proposed program involved a master protocol for the development of novel approaches to the treatment of multiple types of chronic pain, one of the largest unmet medical needs in the United States.

As has been communicated in a variety of public forums, the Chronic Pain Master Protocol is a Phase 2 trial which evaluates multiple assets and multiple pain types simultaneously, with flexibility to allow new assets to come into the master protocol over time. This CID will speed evaluation of potential new treatments for patients suffering with chronic pain. An example schematic of the trial is shown in Figure 1, noting that assets need not come in at the same time and each asset may study the drug in 1, 2, or 3 pain types (PTs). Additional PTs can be added in the future if deemed necessary.

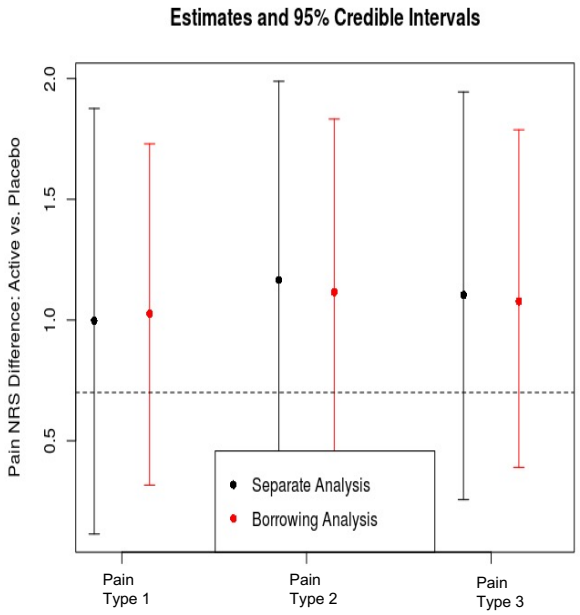
There are several operational and statistical efficiencies realized with this type of design. For example, standardized data collection across the intervention-specific appendices (ISAs), similar visit schedules, less site burden, and higher confidence in decisions regarding which assets to carry forward. It also allows for direct comparisons of assets within and between pain types and yields reductions in sample size of both active and placebo arms. All analyses are Bayesian enabling borrowing of information internally and externally to the study as deemed appropriate. Additionally, with this master protocol we enable the ability to create centralized oversight of the trial to analyze efficacy analysis data and to establish key decision rules for more accurate, consistent, and efficient portfolio-level decisions. We anticipate that this type of design and potential for centralized oversight of all assets coming into the master protocol will translate into higher probability of later-stage success relative to a traditional design.

As part of the CID Pilot Meeting Program process, Lilly submitted 2 briefing documents summarizing simulation plans and extensive simulation results. Lilly/FDA completed both meetings as part of the CID pilot meeting program and the key aspects of the design were improved because of the interactions. There were several important statistical and medical discussions as part of the CID meetings.

One example of a topic that was discussed extensively was the borrowing approach to be utilized for the primary Bayesian analyses. We utilized computer trial simulation, as well as exploring example trial results, to better understand the performance of various Bayesian models. There are a variety of sources for borrowing within the master protocol framework, in this case including historical controls, borrowing of placebo information from other ISAs within a pain type, and borrowing of treatment effect information for a given asset between pain types. A simulation plan was created that clearly described the simulation scenarios (i.e., data generation assumptions), borrowing methods that would be explored (ranging from no borrowing/partial borrowing/pooling), and trial options to be compared (e.g., individual trials vs master protocol for varying sample sizes and durations). Additionally, example simulated trials were explored to better understand the impact of each Bayesian model once the data is observed. Two example trials for an asset in each pain



No effect in Pain Types 1 and 2, but a good effect in Pain Type 3. The Pain Type 3 estimate is pulled down based on the Pain Type 1 and 2 estimates.



Good effect in all 3 pain types. The estimates are very similar between modeling approaches, but the credible intervals are shorter in all cases.

Figure 2: Two example outcomes from trials in Chronic Pain Master Protocol.

type are shown in Figure 2. For this assessment, two models were considered for each data set:

- Separate analysis (ISA only)
- Borrowing analysis (borrow treatment effect information between pain types) for a given intervention

Each simulated trial includes 80 drug and 40 placebo patients.

As can be seen in Figure 2, treatment effect borrowing reduces the length of the credible interval in all cases and the estimated means are adjusted based on the performance in other pain types, demonstrating the impact of the Bayesian analysis for two example outcomes from the master protocol. These types of visual displays which can be fully explored prior to the start of the study are very useful in cross-functional design discussions and to determine the analysis models to be used.

Other examples of key topics discussed included estimands, considerations for ensuring the appropriate blinding of key data outcomes, alignment on the document structure for the overall master protocol, and understanding the potential relationships between pain types.

Currently, the trial is ongoing and is improving the way we efficiently seek to identify new treatments for patients suffering from chronic pain.

Discussion

There is a great deal of excitement about the potential for CID to increase efficiency, lower cost, and enhance innovation to better deliver life-saving treatments to patients. We have briefly described one example, the Chronic Pain Master Protocol. There was value in being involved with the CID Pilot Meeting Program and the trial was improved because of the interactions. Note, it was recently published that the program will continue as part of PDUFA VII (2) and Lilly is excited for this program to continue as a way for us to jointly learn.

Involvement in the CID Pilot Meeting Program was a positive experience, and it would be beneficial to have ongoing interaction with the FDA for this CID (inside or outside of the pilot program process). In the case of Lilly's master protocol, there are valuable learnings that will emerge as assets complete the trial and new assets come in. Additionally, it is important to note that involvement in the program can be time-consuming, both from the standpoint of conducting simulations/preparation of briefing documents but also in terms of calendar time prior to a study's start to accommodate the meeting times. In terms of calendar time: as per the announcement (1), there are quarterly submission deadlines and applicants will be notified of eligibility to proceed to disclosure discussions approximately 45 days after submission deadlines. For each application granted as part of the pilot meeting program, FDA will conduct the 2 meetings within a span of approximately 120 days. Therefore, it is important that sponsors engage early in this program whenever possible.

Statisticians in industry play an important leadership role in identifying opportunities to leverage the CID

Pilot Meeting Program and engaging cross-functionally early and often to contribute to improving our ability to implement CID and speed medicines to patients. Furthermore, the extensive simulations we conducted were useful, regardless of whether the trial was considered "CID" or was part of the CID Pilot Meeting Program. That is, all trials benefit greatly from evaluation via simulation. It is, therefore, a leadership opportunity for statisticians to engage with cross-functional teams and facilitate a full simulation exercise to evaluate trial designs, as there are numerous benefits to the trial and ultimately to patients enrolling in the trial whenever this type of exercise is conducted.

Progress is being made; however, we have additional work ahead to enable routine utilization of CID. For example, whenever an innovative trial is proposed, there may be need for iterative engagement with FDA reviewers and hence we must efficiently and effectively communicate simulation results to ensure alignment is obtained. As part of achieving this, we need to utilize best practices for developing simulation plans and summarizing results in a more consistent way. We also need to fully leverage modern computational infrastructure to ease review of simulation results and permit interactive evaluation of simulation results. Additionally, we need to continue to educate our cross-functional colleagues, including medical, to ensure that sponsors and FDA can communicate effectively across key stakeholders.

While CID have received significant attention to modernize the drug development process, decentralization of clinical trials can bring these trials closer and more convenient to the patients. Decentralized clinical trial (DCT) makes use of digital health technologies, remote health services and processes to reduce patient burden, enable remote visits, and increase diversity of clinical trial participants. DCTs have gained substantial attention due to the global pandemic where alternative modalities of data collection to allow remote visits are necessary to continue collecting data. Regulatory guidance on DCT has been limited and therefore careful planning and receiving regulatory input early on would be necessary to implement decentralized capabilities into a clinical trial.

Finally, there are several resources available to learn more about these types of designs. For master protocols, there are numerous references with Woodcock and LaVange (3) as a great starting point. For more information on the CID Pilot Meeting Program, consider the FDA announcement (1) and CID Brochure (4). There are also several regulatory guidances available to date related to CID topics (e.g., references 5-9). If you are interested in engaging more on this topic, consider becoming involved in the DIA Bayesian Scientific Working Group and/or the DIA Innovative Design Scientific Working Group, formerly known as the DIA Adaptive Design Working Group. Additionally, there is a DIA Master Protocol and CID workshop in November 2021: *https://www.diaglobal.org/en/conference-listing/meetings/2021/11/master-protocols-and-complex-innovative-design.* ■

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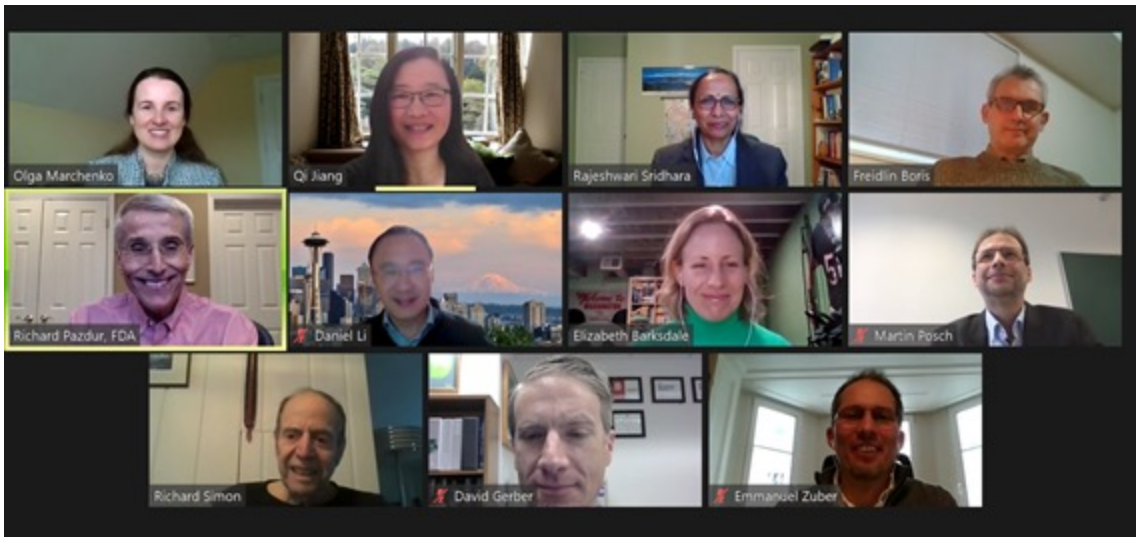
SUMMARY OF AMERICAN STATISTICAL ASSOCIATION BIOPHARMACEUTICAL SECTION'S VIRTUAL DISCUSSION WITH REGULATORS ON STATISTICAL CONSIDERATIONS IN ONCOLOGY TRIALS IN THE COVID-19 ERA

Elizabeth Barksdale (LUNGevity Foundation), Rajeshwari Sridhara (FDA), Olga Marchenko (Bayer), Qi Jiang (Seagen), Richard Pazdur (FDA)



On January 14 and February 8, 2021, the American Statistical Association (ASA) Biopharmaceutical Section (BIOP) hosted biostatisticians, clinicians, and regulators for the third and fourth meetings, respectively, in a series conducted under the aegis of the US FDA Oncology Center of Excellence's Project SignifiCanT (Statistics in Cancer Trials). The goal of Project Significant is to advance cancer drug development through collaboration and engagement among stakeholders in the design and analysis of cancer clinical trials. Organized jointly by the ASA BIOP Statistical Methods in Oncology Scientific Working Group, the FDA Oncology Center of Excellence, and LUNGevity Foundation's COVID and Clinical Trials Statistical Analysis Working Group, the overarching theme for these meetings was how best to incorporate lessons learned during the COVID-19 pandemic into the design of future oncology trials.

The speakers/panelists* for the discussion included members of the BIOP Statistical Methods in Oncology Scientific Working Group representing pharmaceutical companies, representatives from International Regulatory Agencies (FDA, EMA, HC, MHRA, SMC, PMDA, and TGA), academicians, patients and expert statistical consultants. In addition, over 100 members attended the virtual meeting including representatives from other International Regulatory Agencies (e.g., from Brazil, Israel, Singapore). 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, contractor from Oncology Center of Excellence, FDA.

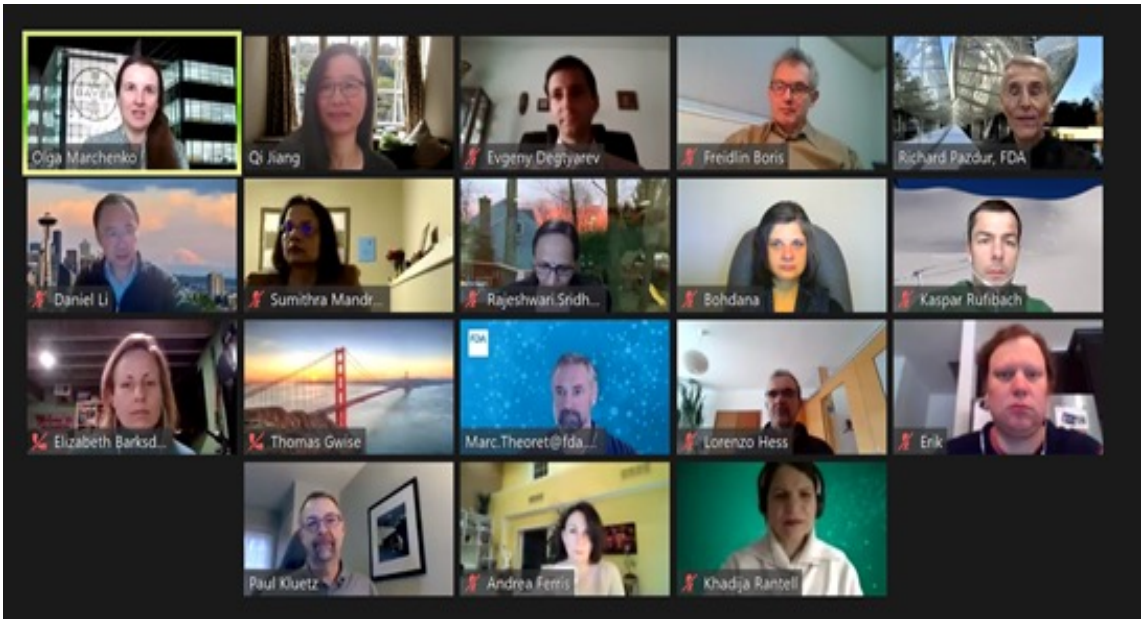
The January forum featured perspectives from a clinician and a lung cancer patient, who each addressed how the pandemic was impacting their respective involvement with clinical trials. Per the clinician/investigator perspective, the guidances issued by FDA, NIH

Central IRB (CIRB), and NCI Cancer Therapy Evaluation Program (CTEP), helped in adjusting the ongoing trials to include more virtual/remote elements such as remote consent, remote monitoring, off-site diagnostic testing, shipping of therapies, and telehealth visits. Surveys of clinical research staff showed that most viewed the trial modifications positively. The patient, a cancer survivor, shared how the clinical trial in which she is currently participating has adopted virtual elements since the onset of COVID-19. She receives her medication in the mail, has scans and blood work performed at local facilities, receives results through a patient portal, and consults with her oncologist and medical staff via video chat. She described the overall experience as positive and noted that in her personal experience she has not encountered any negative or unusual outcome.

The subsequent discussion among US and international regulators, academics, and industry biostatisticians focused largely on risks and benefits of fully decentralized/hybrid clinical trials and how to handle heterogeneity in future clinical trial populations stemming from COVID-19. Unlike fully decentralized clinical trials, decentralized elements can be adopted in hybrid trials while allowing participants to attend the clinical study site. US regulators from Oncology Center of Excellence pointed out the FDA's long-standing support of decentralized trials, and how they will be using the opportunity presented by the pandemic to assess the effect of unplanned decentralization on trial and data integrity. In addition, they noted that electronic patient consent and routine blood chemistry tests conducted in local laboratories are unlikely to affect the trial integrity, efficacy, or safety outcomes. International regulators reported increasing use of telehealth and openness to remote monitoring in some countries. However, the introduction of decentralized elements in clinical trials is assessed on a case by case basis taking into consideration the study population, the disease setting and proposed treatment, as well as stage of development. There were differing opinions among panelists on the risks of remote monitoring in decentralized trials, with one view being that remote monitoring more closely emulated a real-world setting while another held that it could introduce biases (e.g., if an imbalance in decentralized features of the trial exists between treatment and control arms). Many pointed to the increased flexibility of decentralized or hybrid trials being attractive to patients, however there will need to be further evaluation of data quality, adherence to study schedule, and how reliably and accurately these types of trials address study questions.

The February forum built on discussions started in January. There were four presentations by academic and industry perspectives. The academic statistician presented results from an ongoing study of the impact of COVID-19 Pandemic Study and the initial analysis suggests that protocol deviations were common, with switching from in-person to virtual visits and late/missed study procedures being the most prevalent. The speakers from the industry pointed out that the impact of exchangeability of data collected via different modalities needs to be assessed, and sensitivity analysis regarding alternative modalities of data collections are necessary. In terms of COVID-19-era trials, additional analyses may be needed to assess sub-groups, missing data, and safety. The Estimand framework (ICH E9 (R1)) can be useful for characterizing and assessing impacts of COVID-19 on ongoing clinical trials and for supporting the design of future trials to accommodate needed flexibilities during and after the pandemic. Results from a survey of industry conducted by OCE on COVID's impacts on cancer clinical trials and implications for increased use of decentralized trials in August of 2020 suggested that most had not made "major" adjustments to their statistical analysis plans, and about half had made "minor" adjustments, despite not altering follow-up schedules or the number of required tests. Most companies have not had major statistical issues. Hybrid oncology trials may become more common even after the pandemic subsides. It is anticipated that statisticians will have a major role in designing trials with planned flexibilities that will facilitate the clinical trials conduct in case of unplanned disruptions (e.g. pandemic) and introduce remote aspects in a safe manner while preserving data and trial integrity , as well as minimizing the introduction of biases that will affect trial conclusions.

The discussion highlighted that there is a tradeoff between variability and bias with multiple aspects of decentralized trials that have been implemented out of necessity during the pandemic, but likely to continue beyond the pandemic. Decentralized clinical trials



have the potential to include broader, more representative patient populations, which is one of the sources of higher variability. The other source of variability is associated with a higher measurement error and a higher potential for bias. Some thought the increased flexibility, and thus variability, presented by decentralized trials might unacceptably increase bias between treatment arms such that the trials would no longer have internal validity. As much as broader population is a desirable feature, it might also be achieved with minimal error/bias inflation by having conventional trials using broader eligibility criteria. The opposite view was that using broader eligibility criteria might allow slightly broader population enter a trial, but it will not address current issues with minorities or elderly population while decentralized clinical trials might. Also planning and accounting for flexibilities from the outset will help minimize potential bias. Increased adoption of decentralization in oncology trials will also depend on the extent to which heterogeneity—of populations, treatment modalities, endpoints, frequency of assessments, etc.—is accounted for in the planning of the trial. One would have to weigh the advantages and disadvantages of the approaches in the specific clinical setting context, including the ability to accurately capture both the relevant benefits and short/long term toxicities. Finally, putting patients and patient safety at the center of all trials, whether conventional, fully decentralized, or hybrid, is paramount. Engagement with patients and patient representatives earlier in the development is key to promoting patient-centricity in future trials. Allowing for flexibility to decrease patient burden has the potential to increase access and retention in cancer clinical trials, which will in turn promote a wider representation of trial participants.

This forum provided an opportunity to have open scientific discussions among diverse stakeholder group – academicians, patient advocates, international regulators, and pharmaceutical companies focused on emerging statistical issues in cancer drug development. We plan to continue with similar open forum discussions in the future on a variety of important topics that include statistical aspects in cancer drug development involving different stakeholders and a multi-disciplinary approach.

*Speakers/Panelists: Dr. Erik Bloomquist (FDA), Melissa Crouse (Patient Representative), Dr. Evgeny Degtyarev, Theodor Framke (EMA), Dr. Boris Freidlin (NCI), Dr. David Gerber (Harold C. Simmons Comprehensive Cancer Center at UT Southwestern), Lorenzo Hess (SMC, Switzerland), Dr. Filip Josephson (Medical Products Agency Sweden), Dr. Paul Kluetz (FDA), Dr. Daniel Li (BMS), Dr. Sumithra Mandrekar (Mayo Clinic), Prof. Martin Posch (Center for Medical Statistics, Informatics, and Intelligent Systems at the Medical University of Vienna, Austria), Dr. Khadija Rantell (MHRA, UK), Dr. Bohdana Ratitch (Bayer, Canada), Andrew Raven (Health Canada), Prof. Christian (Kit) Roes (Radboud University Medical Center & Dutch Medicines Evaluation Board), Dr. Kasper Rufibach (Roche), Sinan B Sarac (Danish Medicines Agency), Dr. Richard Simon (Simon Consulting), Dr. Harpreet Singh (FDA), Dr. Marc Theoret (FDA), Dr. Andrew Thomson (EMA), Dr. Emmanuel Zuber (Novartis). ■

SUMMARY OF ASA VIRTUAL DISCUSSION WITH REGULATORS ON DESIGNING DOSE-OPTIMIZATION STUDIES IN CANCER DRUG DEVELOPMENT

Olga Marchenko (Bayer), Rajeshwari Sridhara (FDA), Qi Jiang (Seagen), Elizabeth Barksdale (LUNGevity Foundation), Richard Pazdur (FDA)

On March 18th of 2021, American Statistical Association (ASA) Biopharmaceutical Section (BIOP) and LUNGevity Foundation organized an open forum in coordination with the US FDA Oncology Center of Excellence. The topic of this forum was "Designing dose-optimization studies in cancer drug development". The series of the forums was introduced by the ASA BIOP and the FDA as a part of the US FDA Oncology Center of Excellence Project SignifiCanT (Statistics in Cancer Trials), the goal of which is to promote collaboration and engagement among different stakeholders in design and analysis of cancer clinical trials to advance cancer drug development.

The accelerated cancer drug development in recent times particularly with targeted therapies in rare populations may have resulted in less than optimal doses studied in confirmatory clinical trials. The time from a typical dose-finding study to confirmatory Phase III clinical trial is shortened when high response rates are observed in early clinical development, which has resulted in regulatory applications with a limited safety and efficacy database. Nowadays, little data on dose finding are provided while submitting pivotal data based on Phase II trials (often designed as small, single-arm, open label studies). Higher toxicity than in other severe indications are often accepted in oncology trials. The dose-finding studies typically assess dose-limiting toxicity (DLT) in small cohorts of patients and thus may not provide good estimates of the maximum tolerated dose (MTD). Robust identification of MTD is important in oncology. The number of patients with DLTs in each dose level is used to determine the MTD; assuming toxicity and efficacy increase monotonically with dose (common approach used for cytotoxic agents). Furthermore, dose decisions in these studies are usually based on patients treated in the first cycle and not in subsequent cycles, and therefore do not adequately assess safety and tolerability to fully inform dose selection. This leads to selection of a higher dose often resulting in a high proportion of patients with dose modifications/ reductions, dose interruptions, and discontinuation of the drug in later phase trials intended to support regulatory approval, and therefore, results in less than optimal risk-benefit evaluation. The discussions of this forum focused on statistical considerations in designing dose-optimization studies of products for treatment of cancer patients.

The speakers/panelists* for the discussion included members of the BIOP Statistical Methods in Oncology Scientific Working Group representing pharmaceutical companies, representatives from International Regulatory Agencies (FDA, EMA, HC, MHRA and SMC), academicians and expert statistical consultants. In addition, over 100 members attended the virtual meeting including representatives from other International Regulatory Agencies (e.g., from Australia, Brazil, Israel, Japan, Singapore). 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, contractor from Oncology Center of Excellence, FDA.

The two-hour discussion was productive and covered different aspects of study designs in early and late development of cancer treatments. The meeting started with two questions: 1) How can we arrive at an optimal dose, and 2) What clinical trial designs should be considered and are feasible? The first presentation was focused on current industry experience and summarized common dose-escalation designs, including challenges and opportunities for dose-combination trials. Suggestions to improve included to look beyond DLTs in early dose-finding studies, consider additional adverse events that can lead to dose reductions and interruptions, and also a possibility to include more than one dose levels in

Phase II and Phase III studies. The presenter acknowledged that it is not common practice yet but provided some successful examples that included more than one dose levels in Phase II and Phase III studies. The second presentation was delivered by the FDA statistician and raised a need for addressing dose optimization earlier in drug development with a focus on benefit-risk. Scope for improvement included to study two or more dose levels at phase II before initiating Phase III trial, to use safety and efficacy endpoints guided by PK/PD for proper dose selection, and to capture safety in terms of a tolerability endpoint. Panelists discussed issues brought by the presenters. Suggestions were made to evaluate more patients in the therapeutic window in Phase I study to do a better dose estimation, continue to evaluate doses in Phase II study and characterize dose- and exposure- response by including more doses over a wide range in the Phase II study. It was noted that model-based dose escalation designs that allow variable cohort sizes and intermediate dose levels to be explored in a safe manner can be used as an effective tool for this purpose. There was an agreement to move away from the MTD approach and consider dose optimization approaches based on short-term efficacy, possibly guided by PK/PD, and longer-term safety. Over-dosing of patients in oncology trials is an important issue that needs to be considered carefully in terms of study design since the toxicities at the higher doses can be very harmful to patients. Panelists also acknowledged a need to use other endpoints for the decision making, for example, patient reported outcomes (PRO) could be useful to evaluate patient experience. Possibilities to take more than one dose for further development beyond Phase I trial were also discussed. The regulators emphasized that better studies are necessary to find optimal doses for cancer patients and this effort will require a close collaboration between industry, regulatory agencies, and patients/patient representatives

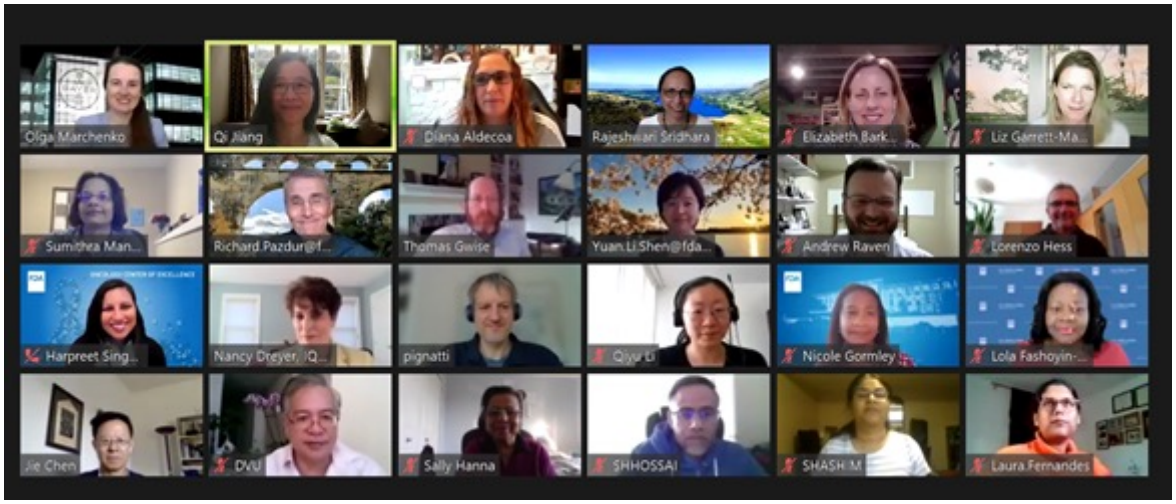
This forum provided an opportunity to have open scientific discussions among diverse stakeholder group – academicians, international regulators, and pharmaceutical companies. We plan to continue with similar open forum discussions on this topic specifically in the post-market and pre-market settings on June 10 and July 8 of 2021.

Acknowledgement: Authors thank Joan Todd (FDA) and Rick Peterson (ASA) for supporting the forum and Dr. Jianchang Lin (Takeda) for taking the meeting minutes.

* Speakers/ Panelists: Dr. Elizabeth Barksdale (LUNGevity Foundation), Katie Brown (LUNGevity Foundation), Dr. Laura Fernandes (FDA), Lorenzo Hess (SMC, Switzerland), Dr. Qi Jiang (Seagen), Dr. Rong Liu (BMS), Dr. Sumithra Mandrekar (Mayo Clinic), Dr. Olga Marchenko (Bayer), Dr. Daniele Ouellet (J&J), Dr. Richard Pazdur (FDA), Prof. Martin Posch (Center for Medical Statistics, Informatics, and Intelligent Systems at the Medical University of Vienna, Austria), Dr. Nam Atiqur Rahman (FDA), Dr. Khadija Rantell (MHRA, UK), Andrew Raven (Health Canada), Dr. Suman Sen (Novartis), Dr. Mirat Shah (FDA), Dr. Yuan-Li Shen (FDA), Dr. Richard Simon (Simon Consulting), Rajeshwari Sridhara (Contractor, Oncology Center of Excellence, FDA), Dr. Marc Theoret (FDA), Prof. Ying Yuan (MD Anderson Cancer Center). ■

SUMMARY OF AMERICAN STATISTICAL ASSOCIATION BIOPHARMACEUTICAL SECTION'S VIRTUAL DISCUSSIONS WITH REGULATORS ON EVALUATION OF TREATMENT EFFECT IN UNDERREPRESENTED POPULATION IN ONCOLOGY CLINICAL TRIALS

Rajeshwari Sridhara (FDA), Olga Marchenko (Bayer), Qi Jiang (Seagen), Elizabeth Barksdale (LUNGevity Foundation), Richard Pazdur (FDA)



The American Statistical Association (ASA) Biopharmaceutical Section (BIOP) and LUNGevity Foundation hosted open forum virtual discussions on April 8, 2021 and May 13, 2021 with participation from biostatisticians, clinicians, and regulators for the sixth and seventh meetings, respectively, in a series conducted under the aegis of the US FDA Oncology Center of Excellence's Project **S**ignifi**CanT** (**S**tatistics in **Can**cer **T**rials). The goal of Project **S**ignifi**CanT** is to advance cancer drug development through collaboration and engagement among stakeholders in the design and analysis of cancer clinical trials. These discussions were organized jointly by the ASA BIOP Statistical Methods in Oncology Scientific Working Group, the FDA Oncology Center of Excellence (OCE), and LUNGevity Foundation.

Despite a high incidence of malignancies in older adults and certain racial/ethnic minority groups, disproportionately low proportions of these populations participate in clinical trials. While efforts to broaden eligibility criteria have been ongoing (1,2), the data continue to suggest that there is still a participation gap. This results in a lack of information on the efficacy and safety of new treatments in such patient populations, which often leads to suboptimal management of patients in clinical practice. These virtual open forum discussions focused on how we can design pre- and post-marketing studies to fill the gap and evaluate treatment effects in underrepresented cancer populations by collecting and analyzing relevant data.

The speakers/panelists* for the discussion included members of the BIOP Statistical Methods in Oncology Scientific Working Group representing pharmaceutical companies, representatives from International Regulatory Agencies (FDA, HC, MHRA, SMC, and EMA),

academicians, patients and expert statistical consultants. In addition, over 100 members attended the virtual meeting, including representatives from other International Regulatory Agencies (TGA, PMDA, Brazil, Israel, Singapore). 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, contractor from OCE, FDA.

The April forum started with an introduction to the topic presentation followed by 3 short presentations. The first presentation was by a LUNGevity Foundation staff member who shared the results of a survey and multi-stakeholder discussion that led to recommendations (3) on the need for clinical justification on the inclusion and exclusion criteria that particularly affect older patients and racial/ethnic minorities in pre-market lung cancer clinical trials. Two OCE staff members presented examples from two retrospective analyses of oncology clinical trials submitted to FDA for regulatory action, highlighting the lack of adequate inclusion of racial/ethnic minority patients and older patients that limit the evaluation of treatment effect in these underrepresented groups.

The discussion that followed these presentations among US and international regulators, academics, and industry biostatisticians considered post-market studies and use of real world data (e.g., use of electronic health record data, registry data and observational studies). The panelists stated that currently the number of racial/ethnic minority and older patients in pre-marketing clinical trials are too small to infer the risk-benefit in these groups. However, there have been examples of successful post-marketing studies including real world data, for example in specific cases when a safety signal was observed in an underrepresented population. Including a broader population in the pre-marketing clinical trials is the best and most efficient way to determine the treatment effect in such subgroups. However, even when the eligibility criteria are broad, access to trials for some patients may be challenging. Decentralization may help in reaching underrepresented populations and enabling them to participate in cancer clinical trials. While real world data (RWD) can provide relevant information for a broader population, because of the data quality, selection bias, informative missing data and other limitations of RWD, currently it is commonly used only as complementary information in regulatory decision making.

The May open forum built on discussions started in April. After an introductory presentation, there were two presentations by representatives from industry and American Society of Clinical Oncology (ASCO). The industry statistician presented on why some populations are underrepresented in cancer clinical trials and possible solutions, including the use of adaptive clinical trials and pragmatic trials. The ASCO statistician presented results from a pilot study (4), conducted in collaboration with Friends of Cancer Research (FOCR), which examined whether a common protocol and endpoints could be implemented in several data sources (i.e., EHRs and claims dataset). The ASCO statistician also touched on the use of prospective cohort studies, pragmatic randomized trials and hybrid control arms as potential options to collect and analyze data and to evaluate treatment effect in underrepresented populations.

The discussion that followed the presentations highlighted that in the current paradigm, using homogeneous data which yields robust results limits the will to work towards diversity in clinical trial patient populations. The pharmaceutical industry needs to make changes by relaxing inclusion/exclusion criteria, expanding the trial enrollment to sites where underrepresented populations are cared for, and educating the investigators and patient population for better representation of a diverse population in the clinical trials (5). There are also potential clinical trial design solutions and statistical methods that can help to improve the current situation.

This forum provided an opportunity to have open scientific discussions among a diverse stakeholder group – academicians, patient advocates, international regulators, and pharmaceutical companies focused on emerging statistical issues in cancer drug development. We plan to continue with similar open forum discussions in the future on a variety of important topics that include statistical aspects in cancer drug development involving different stakeholders and a multi-disciplinary approach.

Acknowledgement: Authors thank Joan Todd (FDA) and Rick Peterson (ASA) for supporting the forum, and Dr. Rong Liu (BMS) and Dr. Jing Zhao (Merck) for taking the meeting minutes.

* Speakers/ Panelists: Dr. Elizabeth Barksdale (LUNGevity Foundation), Dr. Jie Chen (Overland Pharmaceuticals), Dr. Nancy Dreyer (IQVIA, Real World Solutions), Dr. Lola Fashoyin-Aje (FDA), Dr. Liz Garrett-Mayer (ASCO), Dr. Nicole Gormley (FDA),

Dr. Thomas Gwise (FDA), Lorenzo Hess (SMC, Switzerland), Dr. Qi Jiang (Seagen), Dr. Sumithra Mandrekar (Mayo Clinic), Dr. Olga Marchenko (Bayer), Dr. Richard Pazdur (OCE, FDA), Dr. Francesco Pignatti (EMA), Dr. Khadija Rantell (MHRA, UK), Andrew Raven (Health Canada), Dr. Yuan-Li Shen (FDA), Dr. Harpreet Singh (FDA), Rajeshwari Sridhara (Contractor, OCE, FDA), Dr. Marc Theoret (FDA), Dr. Craig L. Tendler (Janssen Pharmaceutical Company of Johnson & Johnson). ■

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UPDATE: BIOP FELLOWS NOMINATION COMMITTEE

Paul Gallo, Brenda J Crowe, Bruce Binkowitz, Ilya Lipkovich, and Amy Xia

Selection as a Fellow of the American Statistical Association is a high honor to which many members of the ASA aspire. Each year, new Fellows are chosen based upon their record of achievements and contributions to the field, summarized in nomination packages submitted to the ASA Committee on Fellows, announced in the spring, and recognized in ceremonies at the Joint Statistical Meetings. Biopharmaceutical Section (BIOP) members have been well represented among those honored, and there has been a trend towards increased BIOP representation among those selected. This year, 8 current BIOP members were among those honored.

To help BIOP members who are considering being put forth for selection, or would like to assist others in achieving this honor, a Fellows Nomination Committee has been operating within the section. Its members are ASA Fellows experienced in successfully supporting others in the nomination process. This year the committee is chaired by Brenda Crowe, and additionally includes Bruce Binkowitz, Paul Gallo, Ilya Lipkovich, and Amy Xia. The committee does not prepare packages for potential nominees, but can offer general advice and, importantly, send a proposed nomination package to an independent expert reviewer for comments and suggestions for improvements. Nominators who would like to take advantage of this service should send their draft packages to the committee chair (currently Brenda Crowe at bjcrowe@lilly.com) at least 2-3 weeks in advance of the planned submission date in order for feedback to be received and potentially acted upon (the submission deadline each year is March 1).

There are already a number of good sources of information readily available to prospective candidates and nominators. Certainly, those planning a nomination should thoroughly familiarize themselves with the process, along with suggestions for an effective nomination, described on the ASA website:

ASA Fellows (amstat.org)

In addition, a helpful article with perspectives and tips from a number of BIOP ASA Fellows, entitled "Nomination for ASA Fellowship" (Dmitrienko et al), appeared in the Spring 2020 Biopharmaceutical Report:

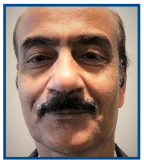
BIOPSpring2020_FINAL.pdf (higherlogicdownload.s3.amazonaws.com)

and an ASA-sponsored webinar was presented last fall, "Biopharmaceutical Section Offers Advice on Strategic Planning for ASA Fellow Nomination", containing presentations and panel discussions featuring a large group of BIOP members with experience in the Fellows process, and can be viewed at: *https://www.youtube.com/watch?v=YLkXund_p7I*

Good luck! ■

8 BIOP MEMBERS WERE ELECTED AS ASA FELLOWS IN 2021

NAME	AFFILIATION	NAME	AFFILIATION
Vipin Arora	Eli Lilly and Company	David Ohlssen	Novartis Pharmaceuticals
Amit Bhattacharyya	Alexion Pharmaceuticals	Olga Vitek	Northeastern University
Jie Chen	Overland Pharma	Xiaofei Wang	Duke University Medical Center
Martin Ho	Google	Yichuan Zhao	Georgia State University



Vipin Arora

Eli Lilly and Company

For important statistical contributions to major drug development projects; extensive service to the profession through impactful ASA section activity and numerous conference organization efforts; and influential educational outreach fostering academia-industry interactions.

Amit Bhattacharyya

Alexion Pharmaceuticals

For extensive service to the profession through numerous leadership positions in ASA sections and committees, and international statistical communities; and for his contributions to statistical leadership, collaborations and research in drug development and public health.

Jie Chen

Overland Pharma

For extraordinary contributions to and impact on the best practice of statistics and regulatory science; for innovative applications of statistics in medical product development and safety evaluation; and for dedicated service to the biopharmaceutical statistics profession.

Martin Ho

Google

For excellence in using statistics to quantify patient preferences for design and analysis of clinical trials to regulate medical products, for outstanding services to ASA and the statistical community, and for leadership to advance statistical methods in Real-World Evidence.

David Ohlssen

Novartis Pharmaceuticals

For outstanding development of innovative clinical trial methods; for advancing the role of statistical and data sciences in the pharmaceutical industry, including exceptional academia-industry partnerships; and for excellence in mentorship of young statisticians.

Olga Vitek

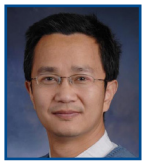
Northeastern University

For outstanding contributions of statistical methodology and open-source software to the bioinformatics and proteomics research communities; for furthering statistics education among experimental scientists; and for service to the profession.

Xiaofei Wang

Duke University

For original methodology development in clinical trials, biomarker validation, and comparative effectiveness research, for impactful collaboration in oncology, for dedication to the dissemination of statistical knowledge, and for outstanding service to the profession.



Yichuan Zhao

Georgia State University

For contributions in the areas of survival analysis, nonparametric statistics, and empirical likelihood-based methods; for applications in biomedical research; for service to the profession, including organizing conferences, editorial service, and mentoring graduate students.

CONFERENCES 2021

WSDS CONFERENCE

KEY DATES:

May 27, 2021– August 19, 2021
EARLY REGISTRATION OPENS

July 16, 2021
SPEAKER REGISTRATION DEADLINE

August 20, 2021 – October 9, 2021
REGULAR REGISTRATION
(increased fees apply)

October 6, 2021 – October 8, 2021
WSDS 2021 VIRTUAL

The 2021 Women in Statistics and Data Science Conference (WSDS) aims to bring together hundreds of statistical practitioners and data scientists. WSDS 2021 will highlight the achievements and career interests of women in statistics and data science. Senior, mid-level, and junior stars representing industrial, academic, and government communities will unite to present their life's work and share their perspectives on the role of women in today's statistics and data science fields. Through formal sessions and informal networking opportunities, the conference will empower and challenge women statisticians and biostatisticians to do the following:

- Share knowledge by offering technical talks about important, modern, and cutting-edge research
- Build community by encouraging discussions establishing fruitful multi-disciplinary collaborations, supporting mentoring relationships, and sharing strategies for resolving problems
- Grow influence by providing advice for establishing and sustaining successful careers, showcasing the accomplishments of successful women professionals, and supporting the development of leadership skills

77TH ANNUAL DEMING CONFERENCE ON APPLIED STATISTICS

The 77th Annual Deming Conference on Applied Statistics will be held from Monday, Dec. 6 to Wednesday, Dec. 8, 2021, followed by two parallel 2-day short courses on Thursday, Dec. 9, and Friday, Dec. 10 at the Tropicana Casino and Resort, Havana Tower, Atlantic City, NJ.

The purpose of the 3-day Deming Conference on Applied Statistics is to provide a learning experience on recent developments in statistical methodologies in biopharmaceutical applications. For more information: *https://demingconference.org/programs/2021-program/*

Registration is now open. Deadline for poster abstract submission and for student scholar is Oct. 15, 2021.

RISW

The ASA Biopharmaceutical Section Regulatory-Industry Statistics Workshop will be held online September 21-24, 2021. There will be many exciting events commemorating the 40th anniversary of the Biopharmaceutical Section of the ASA.

For those who have not already attended and would still like to attend it is not too late. Registration is $325 for general registration, $240 for academic non-students, $250 for Biopharmaceutical Section members, $160 for government employees, and $35 for students. The time has been adjusted due to the virtual nature of the meeting and sessions most days will start at around 10 am EDT.

BASS

BASS XXVIII will be held online on October 25-27, 2021. The virtual symposium is being held for two and one-half days. There will be a half-day "Historical Borrowing From RWE and Historical Trials" short course on Wednesday beginning at 1:00 PM EDT. General attendance registration is $225 for the symposium and is $50 for the short course

The Biopharmaceutical Applied Statistics Symposium (BASS), founded by Karl E. Peace, Ph.D., Fellow of the American Statistical Association, provides (1) a forum for pharmaceutical and medical researchers and regulators to share timely information concerning the application of biostatistics in pharmaceutical environments; and (2) funding to support graduate studies in Biostatistics.

Please visit BASS XXVIII-28th Annual Biopharmaceutical Applied Statistics Symposium to view the program and to register. ■