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BIOPHARMACEUTICAL REPORT

CONTENTS

Note from the editors

Time flies as we finish 2021 and the wonderful celebration of the 40th anniversary of the Biopharmaceuticals Section of ASA. 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), with focus on the accomplishments of the last decade. As we have learned throughout the last 21 months of the pandemic, quite often nothing happens exactly as we would have expected. We had hoped that this last issue of 2021 would allow us to share some stories and articles that would allow a broader audience to learn how biostatisticians have had an amazing impact on the development of many effective vaccines for COVID-19. However, as we are currently experiencing the fifth wave of increases in the daily cases of the virus in the US, the work of dedicated statisticians is never done for those who are involved with adapting the existing vaccines to be able to handle the new variants that have emerged. Thus, we are hopeful that articles on the COVID-19 vaccines can be shared as part of the BIOP report in 2022.

In the last issue of 2021, we open with a general article from **Jianchang Lin** (Takeda) talking about the major achievements of the most recent decade in BIOP followed by reflections from four of the BIOP section chairs of the past decade: **Amit Bhattacharyya** (2013) **Alex Dmitrienko** (2017), **Heather Thomas** (2018), **Richard Zink** (2019), **Bruce Binkowitz** (2020). This is followed by our regular non-clinical statistics article from **Stan Altan** (Janssen) and **Don Bennett** (Pfizer) reflecting on the history of the Nonclinical Biostatistics Leaders' Forum and the evolution of the Nonclinical Biostatistics Conference. We are proud of all of the knowledge we have gained from the non-clinical statistics community in 2021 and hope that we have all learned something new from a key segment of the BIOP community. Continuing the theme of Complex Innovative Designs from the summer issue, we provide to you the results of a survey from the ASA BIOP Oncology Methodology Working Group on Master Protocols which provides insights into where we are as an industry in the design and execution of such trials. This is followed by a summary from **Olga Marchenko** (Bayer) and others of two workshops that BIOP participated in with the FDA on the design of dose optimization studies oncology drug development. The last short article provides an update on upcoming BIOP conferences in 2022.

CELEBRATING THE 40TH ANNIVERSARY OF THE BIOPHARMACEUTICAL SECTION: THE FORTH DECADE (2011-2020)

Jianchang Lin (Takeda), Richard C. Zink (Lexitas Pharma Services) and Peter Mesenbrink (Novartis)

Over the past decade, the data science and digital have become breakthrough technology most anticipated to have a transformative impact on the pharmaceutical research and development. The demand and need for statisticians across different quantitative science disciplines continue to grow extensively and exponentially with many new challenges and opportunities. In 2021, the Biopharmaceutical (BIOP) Section of the American Statistical Association (ASA) has celebrated its 40th Anniversary and continues to play a critical leading role to promote the practice of our profession in medical product development in 21st century. The following paragraphs highlights some of major activities and milestones between 2011-2020.

Starting in 2012, podcasting was promoted as part of Continuing Education Initiative to enhance educational material with audio and video content. In addition, The YouTube channel for BIOP section was set up in early 2019 to create a new online platform to benefit the section members in addition to the sharing of webinar series, podcast series and online training program. The channel also helps expand the BIOP Section's digital capability for efficient communication and provide educational opportunities and training. Videos are being recorded on several important biostatistical topics such as adaptive designs and clinical trial simulations as well as other topics, including leadership and history of biostatistics. This platform will also allow chairs to provide information and key updates to BIOP section members, as well as grant Joint Statistical Meeting (JSM) session organizers the opportunity to create awareness of their sessions and related initiatives.

In 2014, thru the leadership of Matilde Sanchez-Kam, the Biopharmaceutical Section initiated the formation of Scientific Working Groups to encourage broad collaboration and scientific discussions of key statistical issues in drug development among industry, regulatory and academic statisticians. The number of working groups continued to expand after initiation, which also allowed for an increase in a statistician's leadership role in cross-function collaboration as well as communication in larger clinical trial communities. Currently, there are the following working groups to address a wide spectrum of topics in drug development:

- Alzheimer's Disease Working Group
- Biopharmaceutical Software Working Group
- Nonclinical Biostatistics Working Group
- Real World Evidence Working Group
- Safety Scientific Working Group
- Statistical Methods in Oncology Working Group
- Estimands in Oncology Scientific Working Group
- Pediatric Drug Development Working Group

Also in 2014, the Biopharmaceutical Section initiated a Mentoring Program spearheaded by Jennifer Gauvin and Amarjot Kaur. The goal of this initiative is to help members further enrich and enhance their professional experience through achieving personal and professional goals. This could commonly occur through sharing of knowledge and experience between a seasoned professional practitioner and someone newly entering the profession of biostatistics.

Figure 1: new BIOP section logo

A new BIOP section logo (Figure 1 above) as well as new format for Biopharmaceutical report were unveiled in 2016. This was the first major change to the Report format since its first issue in 1992. These changes

occurred with many people's effort, in particular, 2015 editor Paul Gallo playing an instrumental role in advocating for a facelift for the BIOP report.

To further support students, under the leadership of Richard C. Zink, BIOP section developed Biopharmaceutical Section Scholarship Award as part of the ASA awards program (*http://www.amstat.org/ ASA/Your-Career/Awards-and-Scholarships.aspx*) in 2018. The goal of this award is to recognize notable research, academic achievement, and applied project work related to the area of biopharmaceutical statistics. Three recipients for the first ever Biopharmaceutical Section Scholarship Award were granted in 2018. The deserving recipients were:

- Christopher R. Barbour, Montana State University
- Theyaa Chandereng, University of Wisconsin
- Will A. Eagan, Purdue University

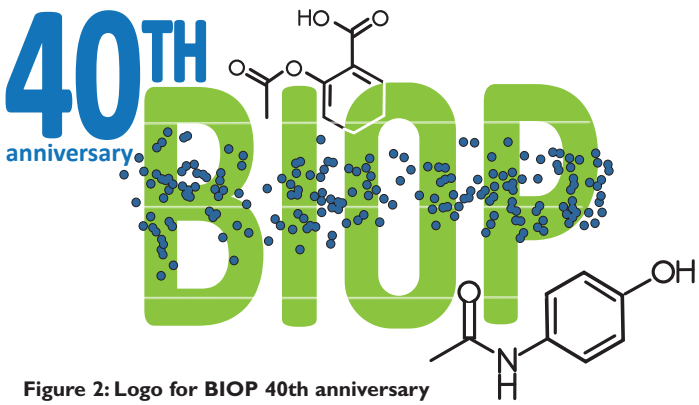

Figure 2: Logo for BIOP 40th anniversary

Due to the COVID-19 pandemic in 2020, our annual Regulatory-Industry Statistics Workshop (RISW) moved into a virtual meting format first time in the history. Although under such unprecedented challenges, The ASA, the workshop co-chairs and organizing committee did an outstanding work to put the workshop running smoothly with a record setting attendance of approximately 1200!

To begin planning for celebratory activities in 2021, a 40th anniversary committee was established in 2019. The Committee has done tremendous work with a panel session with past BIOP chairs at both the 2021 JSM and the RISW to celebrate the anniversary. Recent issues of the Biopharmaceutical Report have included articles from long time members on the importance of the Section both personally and professionally. In addition, a contest was run in 2020 for a logo – the winning logo (Figure 2), is also displayed on the web page and now on all communications about the 40th Anniversary. As we are celebrating the 40th Anniversary of the Biopharmaceutical Section in 2021, a list of BIOP section chairs during the fourth decade (2011-2021) is provided in Table 1, and a timeline of major events is summarized in Figure 3.

References

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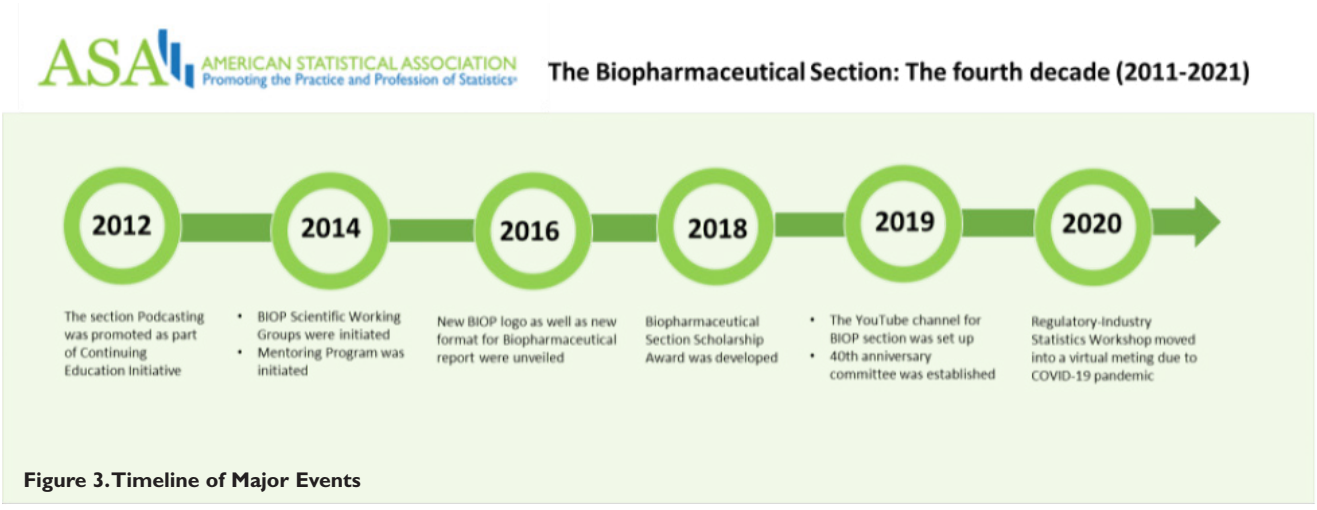

Figure 3. Timeline of Major Events

MEMORIES FROM PAST BIOPHARMACEUTICAL SECTION CHAIRS IN COMMEMORATION OF THE 40TH ANNIVERSARY OF THE ASA BIOPHARMACEUTICAL SECTION PART 4 (2011-2020)

Amit Bhattacharyya (Section Chair 2013)

I was privileged and honored to serve as the Chair of the Biopharm section in 2013. During the time, the section focused on new initiatives to foster collaborations with relevant ASA sections and committees, as well as statistical associations external to ASA. These resulted in supporting mentoring initiative with CAS (ASA Committee on Applied Statisticians), joint sponsorship in conferences with ASA Health Policy sections, and students' travel awards at the ICSA (International Chinese Statistical Association) conference during the year and beyond. The proposal for ASA Biopharm Safety working group was proposed and implemented during the same year. I am happy to see section's effort in supporting more scientific working groups over the years. I look forward to the section's continuous success in bringing ideas across members in solving statistical problems in the emerging areas like imaging, wearable devices in collaboration with data scientist colleagues and healthcare professionals.

Category 2011-2020	Year	Name
	2020	Bruce Binkowitz
	2019	Richard C. Zink
	2018	Heather Thomas
	2017	Alex Dmitrienko
	2016	B. Christine Clark
	2015	Dionne Price
	2014	Matilde Sanchez-Kam
	2013	Amit Bhattacharyya
	2012	Steve Gulyas
	2011	Stephen Wilson

Alex Dmitrienko (Section Chair 2017)

I have had the honor of serving in multiple roles on the BIOP Executive Committee and, as the Section's chair, I pursued several projects that built on the earlier initiatives. For example, as an extension of my work on the BIOP webinar program back in 2007-2010, I helped create an online training program and subsequently a YouTube channel aimed at a broad biostatistical community. We also made a few changes aimed at streamlining the EC's work, e.g., the last EC meeting was moved forward to be held during the Regulatory-Industry Statistics Workshop. It has been a real pleasure to contribute to BIOP and I am glad the Section continues to develop live and online forums to help biostatisticians come up to speed with new directions in healthcare research, e.g., virtual and hybrid clinical trials.

Heather Thomas (Section Chair 2018)

During my tenure, four scientific working groups were established, a YouTube channel was started, and an outreach committee was formed to liaise with other sections and outside groups. I truly enjoyed my time on the Executive Committee and I am humbled to have been given the opportunity to serve with so many incredible statisticians. I look forward to seeing how the Section advances in the coming years!

Richard C. Zink
(Section Chair 2019)

During my time on the Executive Committee, we developed ways to modernize the Regulatory-Industry Statistics Workshop. To further support students, we developed an annual scholarship award to recognize notable research, academic achievement, and applied project work related to the area of biopharmaceutical statistics. I am grateful for my time as chair, and look forward to seeing how we address tomorrow's challenges using wearable devices and other technologies.

Bruce Binkowitz
(Section Chair 2020)

My time as Chair of the section involved the usual rotation of 12 months as Chair-Elect, 12 months as Chair, and 12 months as past-Chair. I enjoyed all those roles, but certainly my term was bifurcated in March 2020 by the COVID-19 pandemic. With little warning the BIOP Section had to figure out how to keep the section business moving forward while still serving section members, in an unanticipated strange new environment. "Serving the members" was my mantra and my primary measure of any initiative and objective the section undertook. How are we, as the Executive Committee, serving the membership, was always question 1. Given the stay at home shift to a virtual working environment that a large majority of the BIOP members experienced, the immediate question was how do we continue to serve the members needs? What needs to change? How do we keep the BIOP committees moving forward? I quickly learned that different aspects suffered from different levels of impact. Committee work, driven mostly by conference calls and often little face to face interaction, moved forward smoothly. Immense credit goes to all the BIOP committee chairs for keeping the many committees on track, rarely skipping a beat. Executive Committee new objectives needed to also move forward. I wanted to continue the excellent support of recent past chairs to engage students, to support diversity, and to emphasize the need to develop the leadership skills of statisticians. I also wanted to drive harder to serve the membership. By the time I was Chair of the BIOP, the section was very fortunate to be in a monetary surplus, and I initiated a committee that has as its goal to develop ways to give that surplus back to the membership through more monetary awards, increasing the amount of the awards, and creating new opportunities for funding. The most obvious aspect of the BIOP section activities that were impacted by the pandemic were the in person meetings: JSM and the ASA Biopharmaceutical Section Regulatory Industry Workshop. Those could not be held in person, and we worked with ASA to move into unknown territory to put on virtual meetings. We also made sure the open business meeting was still held by taking a virtual approach. It was important to me to not default to a newsletter or email to report the section business, because I believe it is important for the Executive Committee to be as transparent as possible regarding section activities to the membership. Canceling the open business meeting and turning it into a written report was not an option in my mind, although the section guidelines would have allowed for that. Was the transition to virtual platforms an immediate success? If success is defined as actually still holding the meetings, then absolutely. Did everything go as planned? Was the technology glitch-free? No. But the efforts of our BIOP members to create the programs and hold the meetings, and the effort of those at the ASA, was extraordinary given the short runaway to prepare. Further benefits were then seen in 2021, with 2020 learnings as a basis to provide much more smooth virtual platforms. In 2020, we all adapted on the fly to achieve accomplishments no one could have guessed when I started my 12 months as Chair.

Serving my term as Chair is one of the great honors of my career, and I look forward to seeing how the statistical community adapts to the emerging capabilities of attending workshops and conferences in a virtual manner simultaneously with in person attendance options. We need to continue as a Statistical Community and connect with each other, network with each other, collaborate and learn from each other. We now have more ways to do this, and need to take advantage of them. ■

A BRIEF AND BIASED HISTORY OF THE **NONCLINICAL BIOSTATISTICS LEADERS' FORUM** AND THE **EVOLUTION OF THE NONCLINICAL BIOSTATISTICS CONFERENCE**

Stan Altan (Janssen) and Don Bennett (Pfizer)

During the 1990s, the increasing importance and regulatory requirement of Statistics in drug development and the pharmaceutical industry created wonderful and well attended conferences for statisticians. Those forums focused on clinical statistics, with spotty coverage of statistical innovation and emerging methodology in the areas of CMC, safety and toxicity, in vitro and in vivo experiments in early discovery, emerging -omics and genetics assays, and cell-based bioassays. ASA sponsored meetings and the FDA-Industry Statistics Workshop (now the ASA Biopharmaceutical section Regulatory-Industry Statistics Workshop) had dedicated, but sparsely attended sessions for nonclinical statisticians. The best nonclinical statistics venue at the time was the Midwest Biopharmaceutical Statistics Workshop (the Muncie conference) where there was a nonclinical statistics session parallel to a clinical session on the second day of the meeting.

There was a palpable sense at that time among the nonclinical statistics community of second class citizenship, and a feeling of isolation. To counter this, an important initiative was started by Ersen Arseven at Schering-Plough, who proposed an informal venue for nonclinical statisticians to meet and communicate on common issues. Ersen's proposal was widely supported, and the nonclinical statistics managers' group was born with its first meeting on October 10, 2003. Over the next few years, the group met somewhat irregularly, although at least once a year. Early meetings were hosted by participating pharmaceutical companies on a rotating basis, providing a great medium for sharing information and networking, and often touching on technical issues that were of broad interest. The fall 2007 meeting at Pfizer in Groton, CT departed from the usual meeting format to include several technical talks that were well-received and the decision was made to start a new venue dedicated exclusively to the technical aspects of nonclinical statistics, open to all statisticians.

The spring 2008 meeting was held at Biogen in Cambridge, MA on April 15th, and more technical presentations were added, which relegated our usual high-level interactions to late in the day. This meeting also marked a major shift in the direction of the managers' meeting. The group formally adopted the name "Nonclinical Biostatistics Leaders' Forum" (NCBLF), a name proposed by Wherly Hoffman (Lilly), and enthusiastically accepted by the attendees. A steering committee was also appointed to provide focus and direction to the group. The members of the first steering committee were Jim Colaianne (chair, J&J), Stan Altan (J&J), Don Bennett (Biogen), Ferdous Gheyas (Schering), Wherly Hoffman (Lilly), and Keith Soper (Merck). A mission statement and governance charter were written and approved shortly afterwards. The decision was made to formally organize the Nonclinical Biostatistics Conference as a venue for discussing the interesting new technical methods emerging from nonclinical statisticians to complement our NCBLF meetings. Because there was a European nonclinical biostatistics conference held every other year that many of our members attended, we decided that our conference should be held every other year to fill the gap between the European meetings.

Following the 2008 Spring meeting, the NCBLF has met in the spring and fall every year with the main remit of providing nonclinical statistics management

Table 1 Comparison of topics 1st NCBLF meeting (2003) with 34th meeting (2021)

Nonclinical Area	1st Meeting April 10, 2003	34th Meeting April 16, 2021
Drug Discovery	1. High throughput screening of drug candidates 2. Mass screening vs. enrichment strategies - Validation & Quality Control 3. Data Mining of HTS data sets	
Drug Metabolism/ Safety/ Toxicology/ Pathology	1. Modeling and Inference issues for assessment of QT liability from in-vivo and in-vitro studies using QTc (and its surrogates such as APD) 2. Adjustment of p-values for Peto Test in oncogenicity studies	1. Randomization and Blinding in Research Studies: Implementation Successes and Challenges
CMC/ Operations	1.Technology Validation & Transfer	1. Clinically Relevant Specifications 2. Interface of CMC Statistics and Data Science
Steering Committee		1. NCBLF Steering Committee Report, NCB2021, NCBWG, JSM session through ASA-BIOP 2. Update on conferences Biennial NCB conference Bayesian Leadership Forum Update from committee chairs 3. Nonclinical Column in the Biopharm Report and the NCBLF's Role 4. Increasing Nonclinical Statistics Topics in Forums/Workshops with Regulators

opportunities to discuss at a high level, statistical issues, regulatory concerns, emerging technologies, resources, and industry trends. In the fall of 2021, we held our 35th meeting (virtually) hosted by Steve Novick and Binbing Yu, at AstraZeneca. Just by way of historical comparison, to give some indication of how the focus of the NCBLF has shifted over the past 18 years, Table 1 shows the topics discussed in 2003 compared with 2021. The role of the steering committee is seen clearly in the table, and the topics show what was of current interest in 2003 compared with 2021.

In the intervening years of 2008 – 2021, the most significant achievement of the NCBLF has been the biennial Nonclinical Biostatistics (NCB) Conferences. Table 2 provides a historical overview of the conferences held over the period 2009 - 2021, with theme, number of attendees, the ASA Presidential address speaker and keynote speaker in separate columns.

The division of responsibilities for promoting different aspects of nonclinical statistics between the NCBLF meetings and the NCB conference was a game changer. The NCBLF was a forum where nonclinical statisticians became increasingly aware of each other and shared challenges across pharmaceutical and biotech companies. We discussed regulatory hurdles to our nonclinical submissions, improving industries' ability to address regulatory concerns and expedite submissions. Yi Tsong, at the FDA, as a member and driving force of the NCB conference organizing committee, opened a meaningful discussion on the perspectives and needs of regulatory statisticians paving future directions of research and debate for nonclinical regulatory submissions.

Group photo of attendees at first NCB conference 2009 Harvard University School of Public Health

2015 NCB Core Organizing Committee with David Morgenstein, Villanova University

The NCBLF meetings also provided ideas for methodological innovation, new publications, and avenues to greater recognition of the value that nonclinical statisticians bring to drug development. The NCB conferences rapidly became a premier venue for sharing nonclinical research and discovery. One of the NCB conference goals was to provide a network to bring academic, regulatory, and industry statisticians together to discuss better ways to collaborate. It provided a platform for nonclinical statisticians with new ideas, methodology, and areas of research to address a larger audience. The conferences also enticed some of our European counterparts to travel across the pond, bringing new ideas, collaborations, and integration with our European nonclinical statistical colleagues. From our biased perspective it was an avenue to make the statistical community and leadership aware of our increasingly important role in statistics and drug development. The NCB conferences have been intellectually, economically, collegially, and scientifically successful.

The 3rd and 4th NCB conferences, held respectively, in 2013 and 2015, were both hosted by Villanova University, in Valley Forge, PA. The relationship did not last and, in 2016, NCBLF formally severed its ties with Villanova. Simultaneously, it began the task of planning for the 2017 conference; but this required finding a new venue and some way to handle the administrative aspects of the conference, collecting registration fees, paying for expenses, and other conference functions. The NCBLF steering committee, led by Tony Lonardo, and the NCB conference chair, Steven Novick, then entered into discussions with the chair of the ASA-Biopharmaceutical Section (ASA-BIOP) at that time, B. Christine Clark, to consider forming a nonclinical working group within ASA-BIOP. With Christie's strong support, the intention to establish a formal connection between the NCBLF and the ASA was achieved, and thereby provided the needed infrastructure for the next NCB conference. In addition, a parallel effort was being pursued by Steven Novick and others to identify an academic partner for the next conference. Happily, NCB found a host partner in Rutgers University, with John Kolassa as the academic representative agreeing to serve as co-chair of the next conference in 2017. In addition, as a new working group within the ASA-BIOP section, it was agreed that the NCBLF chair and the NCB conference chair would sit on the Section's Executive Committee (EC). Those roles were filled by Mandy Bergquist, who had assumed the NCBLF chair, and Steven Novick, the NCB conference chair. In addition, Tony Lonardo was appointed to an ad-hoc position on the ASA-BIOP EC. Currently, the two BIOP-EC members representing NCB are Steven Novick and Xin Huang, as the NCBLF chair and NCB conference chair, respectively.

Table 2 – Historical overview of Nonclinical Biostatistics Conferences 2009 – 2021

Year	Venue	Chairs	Theme	Attendees	ASA Presidential Address	Keynote Speakers	Important Additions
2009	Harvard	Mathis Thoma, Don Bennett	"Statistical Methodologies: Key to Discovery and Development"	149		Dr. ShaAvhree Buckman (FDA), Dr. Steve Ruberg (Lilly)	
2011	Harvard	Mathis Thoma, Don Bennett	Advancing Discovery, Preclinical and CM&C Drug Development through Statistical Science	91	Bob Rodriguez 'Business Analytics and Big Data: Are Statisticians Prepared?'	Dr. Bob O'Neill (FDA) 'Advancing Regulatory Science at FDA: The Role of Nonclinical Regulatory Statistics.	ASA Presidential Address
2013	Villanova	Paul McCallister, Paul Lupinacci	Nonclinical Statistics – Improving Pharmaceutical Discovery, Development & Manufacturing	115	Marie Davidian 'The Present and Future of Statistics: Challenges and Opportunities'	Dr. Stan Young (NISS) 'A Tale of Two Matrix Factorizations.'	International Year of Statistics
2015	Villanova	Paul McCallister, Paul Lupinacci	Nonclinical Statistics – Building Continuity from Discovery through Manufacturing	116	David Morganstein, 'Communication is a Two-way Street: Its Importance in our Profession'.	Dr. Christian Airiau (GlaxoSmithKline) 'Advanced Analytics to Support Business Decision Making"	2015 nonclinical best paper award initiated
2017	Rutgers	Steve Novick, John Kolassa	Statistics accelerating the pharmaceutical sciences	150	Lisa Lavange, "Nonclinical Biostatistics at FDA"	John Storey, Cancelled due to a personal issue	Under auspices of ASA-BIOP
2019	Rutgers	Steve Novick, John Kolassa	Advancing drug development from discovery to commercialization	130	Karen Kafadar, "To Screen or Not to Screen? Evaluating Risks & Biases in Cancer Screening Trials"	Jose Pinheiro, "MCP-Mod overview and extensions"	
2021	Rutgers	Xin Huang, John Kolassa	Nonclinical Statistics in the age of Data Science	135	Wendy Martinez "A Conversation About Data Ethics"	Nassim Nicholas Taleb, "Statistical Consequences of Fat Tails"	Virtual

Each of the NCB conferences over the period 2009-2019 have led to a special nonclinical issue of the Statistics in Biopharmaceutical Research journal, an official journal of the ASA. The 2021 conference will be no exception, and the special issue will be edited by John Kolassa (Rutgers) and Eve Pickering (Pfizer). The best nonclinical statistics paper award was initiated in 2015 and has continued in subsequent years, recognizing one or more papers that have made a significant technical contribution to the practice of nonclinical statistics. The paper is chosen through a special award committee appointed each year to collect nominations and make a selection. The 2021 committee was led by Jason Zhang (Astrazeneca).

There were 3 awards presented at the 2021 conference :

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.

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 link to the daily digest at (NCB-Main - Biopharmaceutical Section (amstat.org) *https://bit.ly/3E0jiwn*)

The connection to ASA-BIOP accelerated NCBLF's ability to address technical and related issues by forming working groups within ASA-BIOP. The first working group was formed In 2019, to promote the use of Bayesian approaches in CMC and preclinical areas, led by Paul Faya. The Bayesian working group conducted a survey in 2020 and published one paper documenting their work. The Bayesian working group is currently engaged in discussions on ways to achieve either a regulatory guidance or industry best practices guide on the application of Bayesian methods in CMC studies (see *https://bit.ly/33lXmPpf* for more information). In 2020, the second working group was formed on p-values in nonclinical applications, led by Stan Altan. The p-value working group followed on the heels of the 2019 editorial on p-values (Wasserstein et al, 2019), to assess the use of p-values in driving decisions in nonclinical studies, and to harmonize with the ASA position paper on the same topic published earlier in 2016 (Wasserstein et al.). The p-value working group completed its discussions in 2021 and a white paper has been issued. A version of it has been accepted for publication and is under final refereeing as we write this article. Finally, NCBLF created a scholarship fund (John Kolassa, Rutgers, chairs the scholarship initiative) to attract graduate students to study problems in nonclinical biostatistics with both an academic and industry advisor. The first NCB scholar will be selected in 2022.

In summary, the NCBLF has, since its early beginnings in 2003, served as an effective and active advocate of nonclinical statistics, raising its visibility through journal publications, conferences, and encouragement of the science. Its crown jewel has been the biennial NCB conference. The NCBLF is led by a dedicated steering committee, headed today by Steven Novick (AstraZeneca), and members Mandy Bergquist (past-chair, GSK), Chi-Hse Teng (Novartis), Eve Pickering (Pfizer), Mariusz Lubomirski (Amgen), Scott Clark (Lilly), and Xin Huang (AbbVie), with advisers Don Bennett (Pfizer), Stan Altan (Janssen), and Tony Lonardo. In addition to the NCB conference, with the infrastructure provided by ASA-BIOP, a Bayesian working group and a p-value working group were formed with the goal of improving the practice of statistics in the nonclinical space. Recently, the steering committee formed a separate Communications and Public Outreach committee, chaired by Scott Clark, Lilly, to further sharpen the focus of the group's connections to the larger statistical community, to students and industry organizations and regulators. Through all of these initiatives, the NCBLF has promoted the value and importance of nonclinical statistics in the drug development process, and looks forward to continuing engagement and representing the nonclinical statistics community to the larger statistical constituencies.

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2. Wasserstein, R.L., Schirm, A.L., & Lazar, N.A. (2019) Moving to a World Beyond "p < 0.05", The American Statistician, 73:sup1, 1-19, DOI: 10.1080/00031305.2019.1583913 ■

CURRENT USAGE AND CHALLENGES OF MASTER PROTOCOLS

- A SURVEY REPORT BY ASA BIOP ONCOLOGY METHODOLOGY WORKING GROUP MASTER PROTOCOL SUBTEAM

Xiaoyun (Nicole) Li (BeiGene), Chengxing (Cindy) Lu (Biogen), Kristine Broglio (AstraZeneca), Paul Bycott (Pfizer), Jie Chen (Overland), Qi Jiang (Seagen), Jianchang Lin (Takeda), Jingjing Ye (BeiGene), Jun (Vivien) Yin (Mayo Clinic)

Introduction

The traditional drug development paradigm, where each clinical trial is used to evaluate one single experimental treatment in a single disease population, has rapidly become more expensive and suboptimal in terms of patient resource and development timeline, especially in the era of personalized medicines. Master protocol trial that could simultaneously evaluate more than one investigational drug and/or more than one disease population within the same overall trial structure (1, 2, 3) has the potential of increasing efficiency of drug development and saving patient resource. Although rising in popularity as summarized in multiple systematic review papers (4,5), there still exist many hindrances and challenges in real-life applications of master protocols (6,7). ASA BIOP Oncology Methods Scientific Working Group Master Protocol Subteam conducted a survey with the goal of understanding the current status of master protocol usage, and more importantly, the challenges and roadblocks in designing and implementing such trials. This would be valuable information for the community to identify and address the roadblocks.

Survey Designs and Distribution

Three key aspects were included in the survey: 1) current usage of master protocols across different organizations and the clinical phases of the usage of such designs, 2) statistical features including usage of randomization, adaptations, adjusting for multiplicity, and inclusion of non-concurrent control, and 3) challenges of designing, implementing and engaging stakeholders for such trials. A total of 19 questions were included in the survey.

Nineteen (19) questions were included in the survey on SurveyPlatnet.com and was active between April and May 2021 for participants to fill out. To avoid potential duplication of reports from the same organization, the ASA BIOP Master Protocol sub-team members reached out to contacts on a pre-determined list with 37 organizations covering major pharmaceutical companies, biotechnology companies, academic centers and non-profit organizations. One response from one organization is generally collected except that some larger global companies with multiple therapeutic areas (TAs), one response from oncology and another one from non-oncology TAs are surveyed. With this setting, results presented in this report are typically based on the number of responders as denominators with the exception that for multiple choice questions, number of selections are considered as denominators.

Survey Results

A total of 39 responses were received from the 37 organizations contacted with a few large organizations providing more than one response. It is not required to specify the name of each organization on the response; hence we do not have a complete list of the organizations that responded.

A total of 32 (82%) responses are from pharmaceutical or biotechnology companies, while the remaining 7 (18%) are from non-profit organizations such as academic centers, government agency etc.. Thirty-one (79%) respondents indicated that their organizations have had at least one master protocol trial either in planning or in implementation. Among the 8 respondents who indicated that their organization did not have a master protocol planned, 6 indicated they did not encounter such a need for having a master protocol in their drug development endeavor; 1 indicated a master protocol was considered but it was too complex and therefore not worth planning for in that specific situation; and 1 respondent did not specify why no master protocol was conducted.

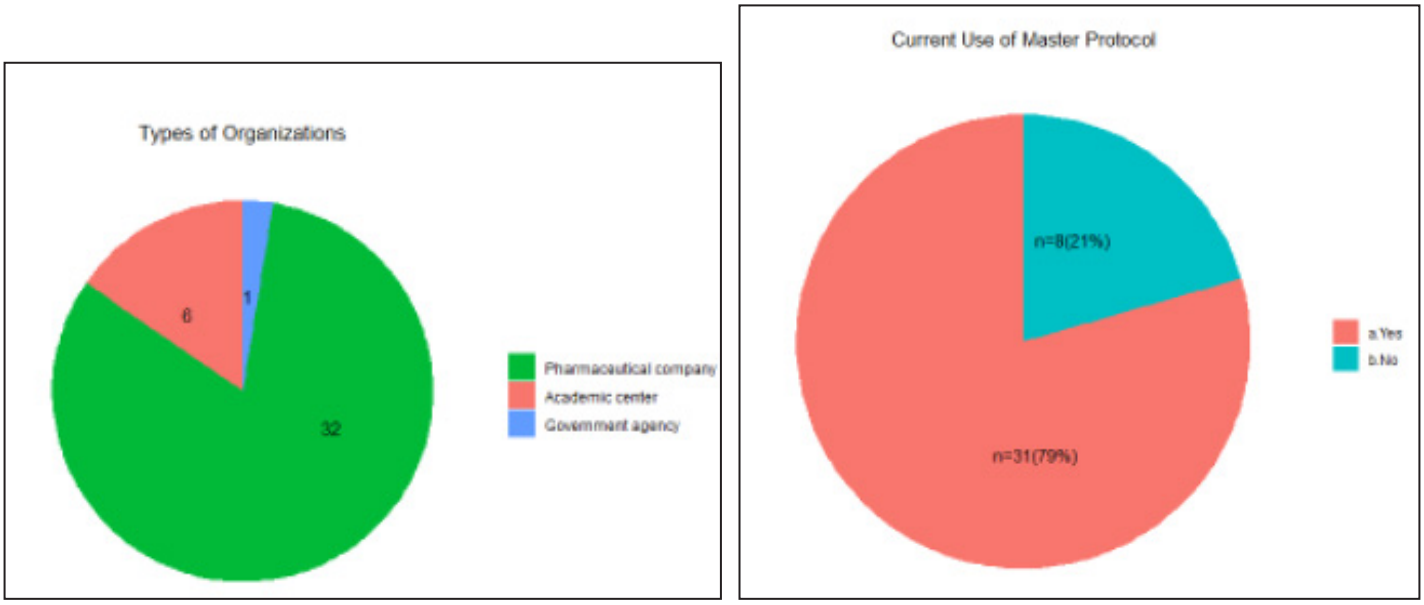

Figure 1: Type of organizations in the survey and current use of master protocols

Across 31 organizations that have master protocol trials planned or implemented, a total of 48 distinct choices were made in terms of therapeutic areas for the master protocols (one organization may have multiple master protocols in different therapeutic areas). Consistent with other published review articles (5,6), the majority (54%, 26 out of 48) are in oncology, followed by 19% (9 out of 48) in infectious diseases (including COVID-19 related treatments/vaccines), 13% (6 out of 48) in neurosciences, 8% (4 out of 48) in rare diseases, and 6% (3 out of 48) in immunology.

Survey results showed that the proportions of utilization of basket trials and platform trials are similar, with 24 responders indicating at least one basket trial planned in their organizations, and 23 responders indicating at least one platform trial planned in their organizations, while 15 responders having at least one umbrella trial planned in their organizations. Per the survey results on the phases of the master protocol trials, the majority of the master protocols are not confirmative trials (i.e., phase I or phase II): a total of 26 organizations had phase II master protocol trials, 18 had phase 1, and 17 had phase I/II. On the other hand, only 6 organizations had at least one phase II/III master protocol trial, and 6 had a phase III master protocol trial. All the phase III studies and two organizations with only phase II master protocols indicated their master protocol trials had registrational intent.

Overall, 24 organizations indicated they have solely sponsored master protocol trials, while 18 indicated they have cross-industry collaborative master protocol trials. A total of 11 organizations indicated they have both cross-industry collaborative master protocol trials and solely sponsored master protocol trials. Though we were not able to link each answer at the trial level, all the organizations that checked the box of phase III master protocols also indicated they had industry collaborative master protocol trials. It is difficult for us to know if all the phase III master protocols are indeed cross-industry collaborations as this survey is not conducted at the trial-level, but experiences from the working group members do indicate single company sponsored master protocol trials are currently mostly conducted in the early phase exploratory setting.

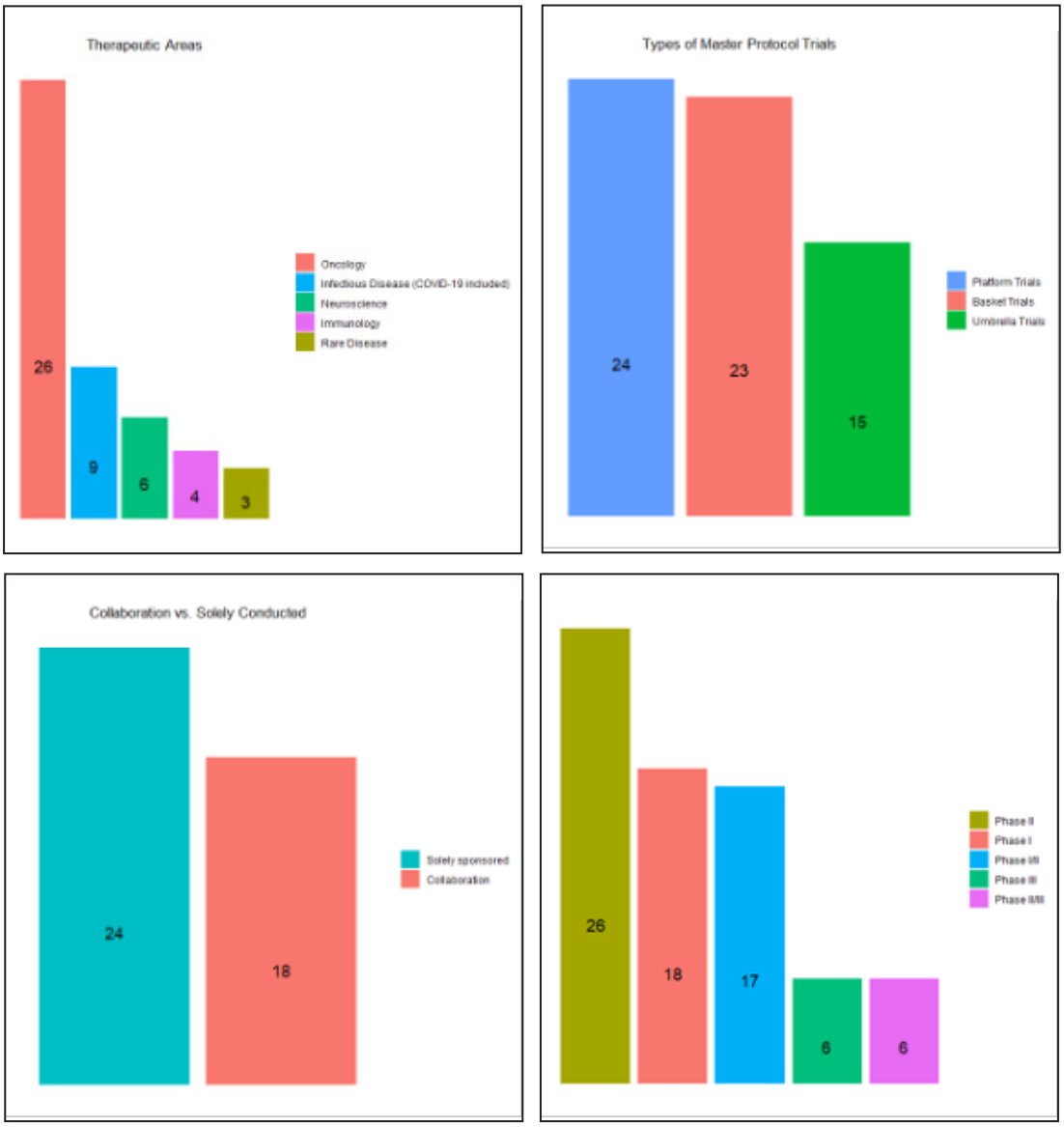

Figure 2: Master protocols use by therapeutic areas, types, cross-industry collaboration or no, and phases.

Different regulatory perspectives globally were experienced by some members in the working group. Therefore, one of the questions in the survey asked if the feedback is supportive and consistent from different regulatory agencies for trials with registrational intent. Among the 8 organizations with master protocol trials that have registrational intent, 50% (4 out of 8) indicated that the regulatory feedback was generally supportive and consistent, while 25% (2 out of 8) indicated they received inconsistent feedback from different regulatory agencies where some were supportive, and some were less supportive. The remaining two had missing data.

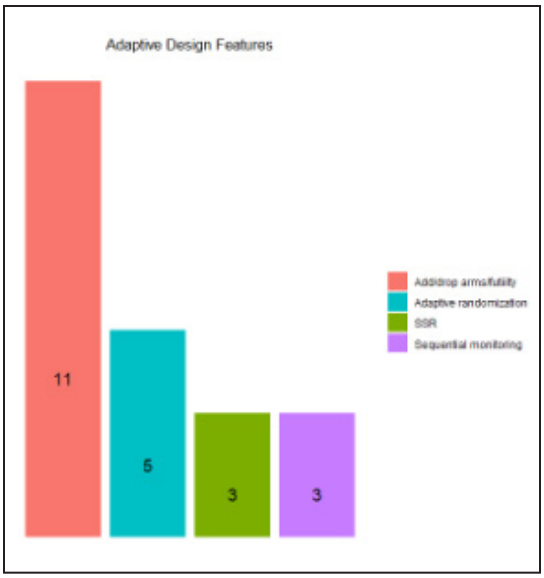

Figure 3: Adaptive design features for master protocols in the survey

Statistical features of the master protocol studies are further collected in the survey. Among the 31 organizations that had master protocol trials planned or implemented, 20 (65%) indicated they have adaptive design features included in the master protocols. The most commonly used adaptive design feature is treatment arm or population adding or dropping that accounted for more than 50% percent among the 20 responses with adaptive designs features, followed by response adaptive randomization from 5 responders, sample size re-estimation from 3 responders, sequential monitoring from 3 responders, and Simon's two-stage design from 1 responder. In terms of the role of a data monitoring committee for the trial adaptations the survey results indicated that although most confirmatory master protocol trials use an independent data monitoring committee (IDMC) that are external to the sponsor, the choices of monitoring exploratory master protocols can be quite different depending on the organization's internal processes and the disease setting of the trial. All 5 phase III studies indicated they used an IDMC. For phase I and II trials: 5 organizations indicated they used an IDMC, 4 indicated they used an internal team that is not associated with the study, and 4 indicated they used the study team for the interim analyses, and the remaining two had missing data.

A total of 26 (84%) of the organizations indicated that randomization was utilized in at least one master protocol. Out of these 26, 22 (85%) indicated their master protocol had randomized control. Among these, the majority 60% (13 out of 22) of the organizations used a common control group, 18% (4 out of 22) used separate controls, 18% (4 out of 22) indicated they had a mix of trials with common controls or separate controls, and 1 indicated "not-decided" as it is still in planning stage and this design feature is not yet determined. In terms of the primary analysis, there is an equal split on the use of concurrent control only data for the primary analysis and using all the control data including the non-concurrently randomized control for the primary analysis, 11 organizations for each. Out of the 31 responses with master protocol trials, 65% (20 out of 31) indicated they did not attempt to control the study level FWER, 29% (9 out of 31) indicated they did attempt to control the study level FWER. Out of those 9 that attempted to control the study level FWER, 2 used analytical methods to show the study level FWER control, and 7 used simulations to demonstrate the study level FWER.

The last question of the survey collected the main challenges in designing and conducting master protocol trials. Answer was allowed as free text. Based on the responses, challenges are summarized in the following four major categories:

- **Protocol documents:** For example, it is not clear how to organize multiple documents (master protocol, intervention-specific appendix etc.) and what goes where, as well as which sections goes to which document to reduce the redundancy in protocol documents.
- **Statistical challenges**: Lack of available software for evaluating the operating characteristics of the design, as well as lack of guidance on non-concurrent control use and multiplicity.
- **Operational hurdles:** How to overcome the operational complexities, as well as difficulties randomizing across multiple sub-studies; Since master protocol trials are quite different form the traditional trials, there are also difficulties in database setup. The longer initial setup time for the master protocol also poses a challenge especially for the initial study and the team working on it.
- **Challenges from stakeholders and regulatory:** There is difficulty achieving alignment on features of the master protocol with all stakeholders or participating companies, as well as potential inconsistent regulatory feedback and pushback.

Limitations and Future Work

With limited resources in the working group, the survey was designed with some limitations. First, as mentioned in the design section, the survey did not drill down to the level of each individual trial but rather focused on the overall usage and experience from each participant. Therefore, the survey results are based on the number of responding organizations rather than on the number of individual trials. In other words, a participant from a large organization may respond to the survey with multiple master protocol trials in mind while another participant from a small organization may respond to the survey with only one trial experience in mind. While organizational-based survey results are reasonably acceptable for some of the questions, for other questions such as master protocol trials usage by phases (phase I, II, III etc.) or the specific statistical features included in the master protocol, it may be more desirable to obtain an answer at the trial level. Secondly, the survey distribution is dependent on the working group members' network coverage. Therefore, a certain level of bias may exist as a higher percentage of pharmaceutical companies were contacted than academic, government, or other non-profit organizations, which may or may not reflect the distribution in the community who may conduct master protocol trials. However, since the major organizations that may conduct master protocol trials are mostly covered, we consider the bias due to the organizational coverage to be limited. Thirdly, we thought through options to avoid duplicate reporting within each organization. However, for cross-industry collaborative trials, such as I-SPY2, duplicate reporting may not be avoidable. A potential solution for this limitation is to request names or national clinical trials (NCT) numbers for each master protocol trial in the survey. However, for trials yet to be registered or openly published, there will be confidentiality considerations for the participants to reveal such details. Therefore, with the considerations of relieving confidentiality concerns from the survey participants, the subteam decided not to include the question of requesting trial identifications. Lastly, the survey included participants' email addresses as optional, which makes post-hoc query of survey results difficult. To systematically improve the survey from these limitations, an alternative approach that may be considered in the future is to meet and interview representatives from various organizations to deepen the understanding of master protocol usage from both the organizational level as well as at the trial level. This approach would be more resource intensive.

The master protocol framework is a highly evolving topic. The applications of master protocols are increasing exponentially in the past two decades (5). Part of the intention of our survey is to serve as a landmark on the usage of master protocols. We plan to repeat a survey in a few years and observe the applications, practical considerations, design features and the associated shift in mindset, if any, in this field. On the other hand, the survey we conducted mostly focused on statistical considerations. However, a successful application of master protocol framework requires not only statistical excellence but also awareness and effective collaborations from all related functions including clinical, regulatory, operations and many more. With that in mind, the plan is to conduct another survey focusing on multidisciplinary aspects to identify roadblocks and challenges more broadly in the near future.

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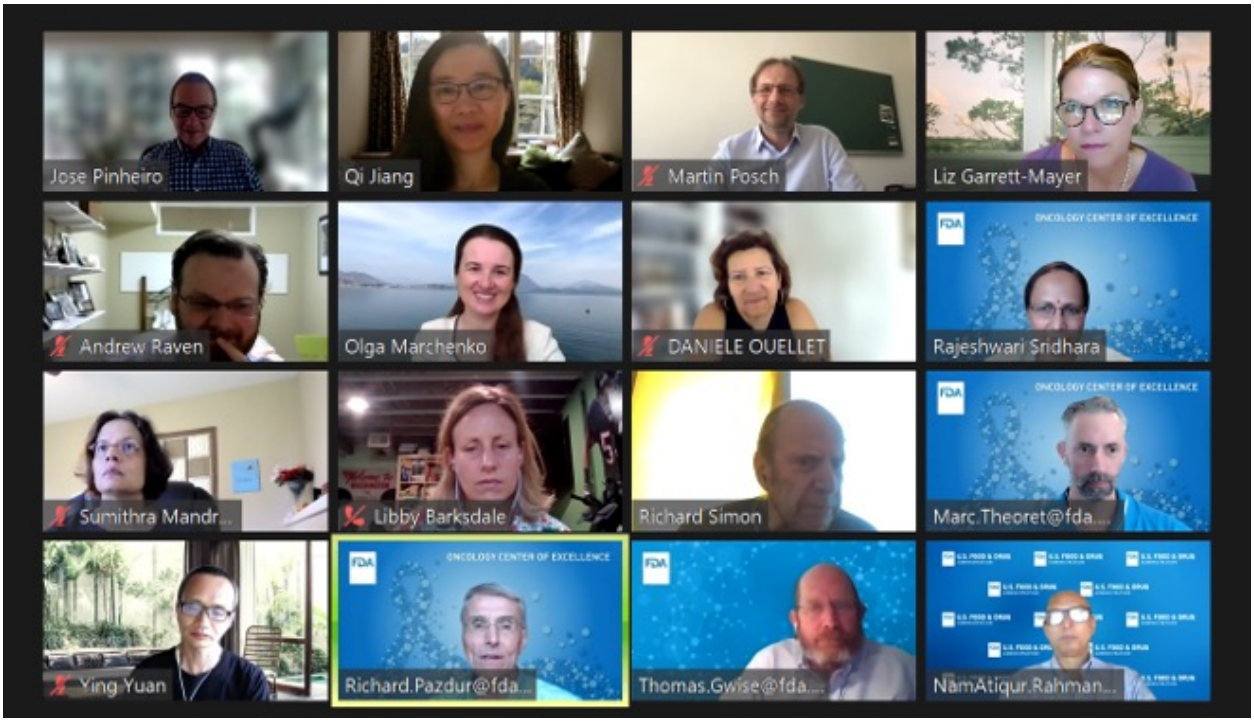
SUMMARY OF ASA VIRTUAL DISCUSSION WITH **REGULATORS ON DESIGNING DOSE-OPTIMIZATION STUDIES IN CANCER DRUG DEVELOPMENT**

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



On June 10th and July 8th of 2021, the American Statistical Association (ASA) Biopharmaceutical Section (BIOP) and the LUNGevity Foundation organized open forums in coordination with the US FDA Oncology Center of Excellence on dose-optimization studies in cancer drug development. This two-part discussion was a continuation of the open forum discussion held on March 18, 2021. The forum in June was mainly focused on design options for post-market studies and the forum in July was focused on different designs options for preapproval studies. These series of forums were introduced by the ASA BIOP and the FDA as 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.

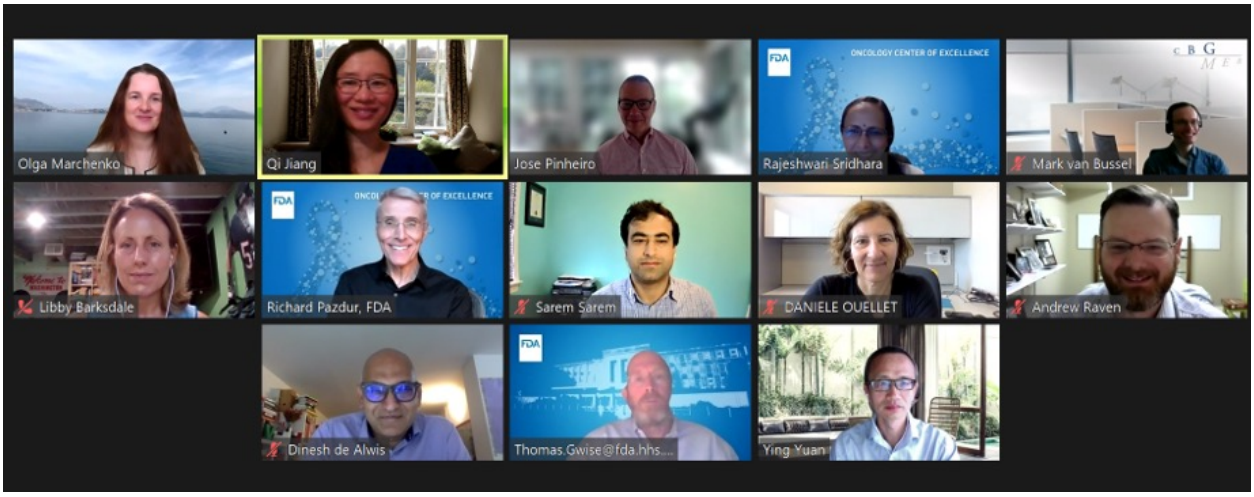
The accelerated cancer drug development in recent years, particularly with targeted therapies in rare populations, has resulted in sub-optimal doses studied in confirmatory clinical trials (Shah et al. 2021). The time from a typical first in human dose escalation study to a confirmatory Phase III clinical trial is shortened, particularly, when high response rates are observed in early clinical development, which has resulted in regulatory applications with limited safety and efficacy data. It is more common now to submit for regulatory decision-making minimal data on dose finding based on Phase

II trials (often designed as small, single-arm, open label studies). A new strategy is needed for oncology drug development that includes dose optimization but does not unnecessarily delay patient access to potentially efficacious new treatments.

The discussions of these two forums were focused on statistical considerations in designing dose-optimization studies of products for treatment of cancer patients in preapproval and post-marketing phases. The speakers and panelists* for the sessions included members of the ASA BIOP Statistical Methods in Oncology Scientific Working Group representing pharmaceutical companies, representatives from International Regulatory Agencies (FDA, EMA, Health Canada, Department of Health from Australia, MHRA from UK, SMC from Switzerland, HSA from Singapore), academicians and expert statistical consultants. In addition, over 100 participants attended these virtual meetings including representatives from other International Regulatory Agencies (e.g., from Brazil, Israel, Japan). The discussions were moderated by the ASA 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 the LUNGevity Foundation; and Dr. Rajeshwari Sridhara, contractor from the Oncology Center of Excellence, FDA.

The June meeting started with an introduction from the FDA followed by two presentations. Two questions were raised: 1) How can we arrive at an optimal dose, and 2) What clinical trial designs should be considered and are feasible in post-market studies? Discussion points included consideration of appropriate endpoints, types of hypotheses (superiority and non-inferiority), and study design features. The first presentation was delivered by Prof. Sumithra Mandrekar from the Mayo Clinic. She provided an overview of a trial design that uses joint modeling based on safety and efficacy data to find a dose that is considered to be safe and has an optimal clinical or biological effect. The dose finding algorithm utilized a total toxicity profile (TTP), a score between 0 and 1, that incorporates multiple adverse event (AE) types and grades over multiple cycles for each patient (Ezzalfani et al. 2013; Yin et al. 2017; Du et al. 2019). The concept of an AE burden score was introduced as an alternative and more comprehensive measure of treatment toxicity than the currently used summary of maximum grade and was discussed using a clinical trial example (Le-Rademacher et al, 2020). The second presentation was delivered by a statistician from the American Society of Clinical Oncology (ASCO), Dr. Liz Garrett-Mayer. The presentation brought out the need for a broader outlook on dose optimization (e.g., dose, schedule, delivery) and population (include older patients, minority and other underrepresented populations), and cautioned against a "one-size-fits-all" design in the post-marketing stage. Types of endpoints to consider included toxicity burden scores, dose interruptions/changes, and time to discontinuation of treatment, in addition to standard efficacy measures (e.g., survival, progression-free survival, event-free survival). A large post-market randomized study with non-inferiority tests for efficacy and superiority tests for toxicity that includes a broader and more diverse population was presented as a possible solution to address the question about dose selection in a post-marketing setting, but some limitations such as cost and challenges with "de-escalation" were also mentioned. A small non-comparative trial was proposed as an option for the population in question. Hybrid designs that leverage real world data (RWD) were also considered and briefly discussed (Hobbs et al. 2013; Normington et al. 2020). The panelists discussed issues brought up by the presenters and raised additional points for consideration. Several panelists mentioned that there is a historical paradigm in oncology drug development that the higher the dose, the better the efficacy – combined with this, the rush to bring a new treatment to patients leads to sub-optimal dose selection. It was noted that generally there is a lack of motivation to conduct dose optimization studies after drug approval (even if provisional). However, it is very important to find the optimal dose and dose schedule that yields the best treatment effect with acceptable toxicity. It was also noted that it is difficult to justify to patients to take lower dose levels when efficacy has been established and a higher dose has been approved by health authorities. In addition, the post-market studies evaluating two or more doses most likely need to be planned as non-inferiority trials that require a large sample size. Some panelists also emphasized the importance of considering multiple endpoints including Pharmacokinetics (PK) and Pharmacodynamics (PD) as well as learning from non-clinical data. Panelists had different opinions on whether using composite endpoints may improve the efficiency.

The July forum built upon discussions held in March and June. It started with an introduction from the FDA



followed by three presentations. Three questions were raised in the beginning: 1) What clinical trial designs should be considered and are feasible in pre-market studies, 2) How can we arrive at an optimal dose, and 3) What criteria can be used? Points for discussion included consideration of appropriate endpoints, whether to use estimation or hypotheses testing for dose selection, and study design features. The first presentation was delivered by Dr. Sarem Sarem from Health Canada on using PK Modeling and Simulation (M&S) to improve dosing of anticancer drugs. The role of M&S for initial dose selection and to provide evidence to update dosing recommendations was demonstrated using KEYTRUDA trials and publications (R de Greef et al. 2017; Freshwater et al. 2017; Lala et al. 2020). The second presenter was Prof. Ying Yuan from the University of Texas MD Anderson Cancer Center who spoke on trial design options in dose-optimization studies in cancer drug development, more specifically, designs that incorporate toxicity grade or delayed toxicity into decision making (e.g., Bekele and Thall, 2004; Ezzalfaniet al., 2013; Mu et al., 2019; Cheung and Chappell, 2000; Liu et al., 2013; Yuan et al., 2018) and seamless Phase I/II designs (e.g., Thall and Cook, 2004; Jin et al., 2014; Zhou et al., 2019; Lin et al., 2020; Zhou et al., 2021). Dr. Yuan's recommendations included: (1) use a larger sample size for early phases, (2) incorporate all relevant data into decision making, and (3) use novel adaptive designs to continuously learn and optimize the dose and regimen. The third presenter was Dr. José Pinheiro from Janssen R&D who spoke about the MCP-Mod method and its extension to exposure-response modeling for dose selection under model uncertainty (Bretz et al. 2005; Bornkamp et al. 2006; Pinheiro et al. 2014). The idea was demonstrated in a Phase II study in patients with Depression. While the MCP-Mod method is commonly used in therapeutic areas outside oncology and has been endorsed by regulators, it is not a common method in Oncology drug development. Perhaps exposure-response modeling (combined with strategies like MCP-Mod) can provide a feasible approach for more efficient dose selection in Oncology also. Panelists discussed points brought up by the presenters and raised additional ones for consideration. Suggestions were made to evaluate more patients in the therapeutic window in Phase I studies to do a better dose estimation and to use more innovative methods and tools that account for both efficacy and toxicity. Over-dosing of patients in oncology trials is an important issue that needs to be considered carefully in terms of study design, since toxicities observed at higher doses can be harmful to patients. It was noted that submissions relying on PK M&S need to demonstrate their reliability in the context of high impact application such as dose selection and optimization (i.e., satisfy high expectations regarding model development and performance) and to provide adequate transparency of model assumptions and the rationale of the model choice. There was an agreement that a change in paradigm is needed which may require bringing awareness and agreement from different stakeholders. Oncology drug development needs to move away from the MTD approach and consider dose optimization. Some panelists suggested using longer term endpoints and accounting for heterogeneity of population. The regulators emphasized that better study designs need to be implemented to find optimal doses for cancer patients and this effort will require a close collaboration among industry, regulatory agencies, aca-

demia, and patient representatives. Although a consensus was not achieved on every point, agreement was reached that we could and should do better.

These forums provided an opportunity to have open scientific discussions among a diverse stakeholder group – academicians, international regulators, and pharmaceutical companies.

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* Speakers/ Panelists: Dr. Dinesh De Alwis (Merck), Dr. Elizabeth Barksdale (LUNGevity Foundation), Katie Brown (LUNGevity Foundation), Dr. Mark van Bussel (EMA), Dr. Qiuyi Choo (HSA, Singapore), Dr. Michael Coory (Department of Health, Australia), Dr. Laura Fernandes (FDA), Dr. Liz Garrett-Mayer (ASCO), Dr. Thomas Gwise (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), Dr. José Pinheiro (J&J), 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. Sarem Sarem (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).

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