Bayesian Scientific Working Group

BSWG Newsletter
Q1 2021 Issue

The DIA Bayesian Scientific Working Group (BSWG) was formed in 2011 with the vision to ensure that Bayesian methods are well understood and broadly utilized for design and analysis throughout the medical product development process and to improve industrial, regulatory and economic decision-making. The group is comprised of individuals from academia, industry and regulatory authorities.

Guest Column

ADVOCATING FOR BAYES

Thomas A. Louis, Professor Emeritus,
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Application of Bayesian methods burgeons, with some approaches explicitly Bayes and some implicit or Bayes-like (e.g., regularization). And yet, "Bayes" still triggers nervous tremors, some resulting from lack of familiarity or trust, some because change, even acknowledged for the better, is nervous-making.

Brad Efron, in his 1986 classic, Why isn't everyone a Bayesian? *The American Statistician*, 40: 1-11 states, "A prime requirement for any statistical theory intended for scientific use is that it reassures oneself and others that the data have been interpreted fairly.'' Of course, that should be a requirement for any procedure, but the burden of proof for Bayes can be especially heavy in the regulatory context. It's understandable that there is resistance to change, especially when the current approaches appear to have served reasonably well. But, there are opportunity costs to holding on to current approaches too tenaciously.

Bayesian practice and culture in the FDA's CDRH, and pleasing progress in CDER and CBER generate optimism. Collaboration amongst industry, government and academe is the central to additional progress. We need to encourage and facilitate broad participation in statistical issues by all stakeholders, avoid signaling that we statisticians are the anointed ones, avoid communicating the analogue of, "Only historians are allowed to reminisce."

One example of the need for a culture change pertains to adherence to strict type I error control. It's a major stumbling block to adopting the Bayesian approach, because an optimistic prior will produce a high type I error (the null hypothesis is *a priori* unlikely, but type I error is computed by conditioning on it), and relatively high power. Similarly, a pessimistic prior will produce a low type I error, and relatively low power. However, if the prior is trusted, it should be used; if it isn't trusted, it needs to be replaced by one that is. It's good practice to compute frequentist properties, but rigid adherence to them will substantially attenuate or eliminate the advantages of a Bayesian approach.

Against this background, a trusted protocol/process for developing prior distributions, evaluating designs, and decision making is the key to increasing the role of Bayesian methods and embedding its culture. The particulars will differ from frequentist criteria, but the goals are the same: Valid design, conduct and analysis; fair decision-making.

At the FDA and elsewhere, transformation shouldn't be to wholesale adoption of Bayesian approaches. Rather, Bayesian designs and analyses should be used when they confer a sufficient advantage. For me,

> Pure Bayes, pure frequentist, pure any statistical philosophy, pairs nicely with Port, but when you leave port for the high seas of applications, some degree of impurity is usually necessary. Consequently, statisticians who engage in important

studies use their philosophy as an aid to navigation, not a straightjacket. The goal is to do a good job, and one can't be (too) doctrinaire.

Summary of BSWG 2020 Activities

- Bayesian Key Opinion Leader (KOL) lecture series: We have held monthly Bayesian KOL series since 2018 and the lectures for Q4/2020 are:
  30 Oct 2020, Dr. Lanju Zhang (Abbvie), **Incorporate External Control Data in New Clinical Trial Design and Analysis**
  20 Nov 2020, Dr. Ram Tiwari (FDA), **Leveraging External Evidence in Medical Device Decision-Making**
  18 Dec 2020, Dr. Brian Hobbs (U of Texas); Dr. Alex Kaizer (U of Colorado); Dr. Emily Zabor (Cleveland Clinic), **Statistical considerations for trials that study multiple indications**
  Slides are stored in our website.
- Book: Bayesian Applications in Pharmaceutical Development (2019), Mani Lakshimanarayanan and Fanni Natanegara (Editors), CRC Press
- Book Chapter in Bayesian Benefit-Risk Evaluation in Pharmaceutical Research (2020), Taylor and Francis: Bayesian methods in pharmaceutical research, Carl Di Casoli, Yueqin Zhao, Yannis Jemiai, Pritibha Singh, Maria Costa
- Manuscripts:
  - Statistical Opportunities to Accelerate Development for COVID-19 Therapeutics (Fanni Natanegara, Névine Zariffa, Joan Buenconsejo, Ran Liao, Freda Cooner, Divya Lakshminarayanan, Samiran Ghosh, Jerald S. Schindler, and Margaret Gamalo), *SBR*
  - The current state of Bayesian methods in nonclinical pharmaceutical statistics: survey results and recommendations from the DIA/ASA-BIOP Nonclinical Bayesian Working Group, (Paul Faya, Perceval Sondag, Steven Novick, Dwaine Banton, John W. Seaman, Jr., James D. Stamey, Bruno Boulanger), *Pharmaceutical Statistics*
- Conference Sponsorships: March 2-3, 2020 (co-sponsorships with IDSWG, FDA, DIA, BIO, PhRMA): DIA/FDA Advancing Complex Innovative Clinical Trial Designs to Efficiently Deliver Medicines to Patients
- Conference sessions
  - "How to Gain Alignment on Your Bayesian Clinical Trial Design and Analysis: Lessons Learned from Communicating with Clinicians, Statisticians, and Regulators" at ASA BIOP Section Regulatory-Industry Statistics Workshop
  - " Informative Prior Applications in Nonclinical CMC Statistics" at JSM
  - " Utilization of historical data for confirmatory trials" at JSM
- Assessing impact of accelerated approval: Manuscript submitted to PLOS one in December. Awaiting review comments. Authors: A. Lawrence Gould, Robert K. Campbell, John W. Loewy, Robert A. Beckman, Jyotirmoy Dey, Anja Schiel, Carl-Fredrik Burman, Joey Zhou , Zoran Antonijevic, Eva R. Miller, Rui Tang.
- Bayesian Approaches for Handling Hypothetical Estimands in Longitudinal Clinical Trials with Missing Data. Manuscript is revised and submitted to the Statistics in Biopharmaceutical Research. Authors: G. Frank Liu, Jiajun Liu, Fang Chen, Roee Gutman and Kaifeng Lu.

Upcoming Conferences

DIA 2021 Annual Meeting

June 27 – July 1, 2021
Virtual

Poster Submission here by **February 11, 2021**
For more information, please contact Freda Cooner

DIA/FDA Biostatistics Industry and Regulatory Forum

April 14–16, 2021
Virtual

Register here
For more information, please contact Brenda Crowe

Duke Industry Statistics Symposium 2021

Emerging Clinical Initiatives in Pharmaceutical Development: Methodology and Regulatory Perspectives

April 21–23, 2021

Virtual

Register here

For more information, please contact Freda Cooner

2021 Joint Statistical Meetings (JSM)

Statistics, Data and the Stories They Tell

August 7–12, 2021

Washington State Convention Center, Seattle, Washington

Topic-Contributed, Roundtable and Invited Poster Abstracts submission here by **February 2, 2021**

For more information, please contact Freda Cooner

2021 ASA Biopharmaceutical Section Regulatory-Industry Workshop

Statistical Innovation in Healthcare: Celebrating the Past 40 Years and Looking toward the Future

September 21–23, 2021

Bethesda North Marriott Hotel & Conference Center, Rockville, Maryland

Roundtable Discussion Topic Proposal Submission here **January 21 – March 30, 2021**

Poster Proposal Submission here **January 21 - April 14, 2021**

For more information, please contact Freda Cooner

Opportunities

- Please see the last page of the newsletter for a summary of our 16 sub-teams and join a sub-team. Each sub-team operates independently under the direction of sub-team leaders with its own objectives, goals, and deliverables and we welcome new members!
- **Master Protocol** sub-team is forming in collaboration with IDSWG and ASA Biopharm WG
- Potential topics for new sub-teams: Decentralized Clinical Trials, Novel-novel combination therapy, Vaccination development. Please contact Fanni Natanegara or Freda Cooner if you are interested.

Meet the BSWG Officers

Chair:	Fanni Natanegara
Vice-Chair:	Freda Cooner
Advisors:	Karen Price, Amy Xia
Secretary:	Pritibha Singh
Publication Chair:	Samiran Ghosh
KOL Organizers:	Haijun Ma, Fanni Natanegara, Freda Cooner, Mathangi Gopalakrishnan
Webmaster:	Frank Liu

If you have information for future newsletters, please contact Pritibha Singh

BSWG Subteams

Safety

Safety assessment is essential throughout medical product development. The goal of this subteam is to evaluate challenges associated with current methods for designing and analyzing safety trials including making the case for Bayesian meta-analyses in safety data and extending Bayesian hierarchical models for safety signal detection in clinical trials.

Noninferiority

Substantial historical data may be available on the active-control and placebo before an active controlled trial is planned in a clinical development. Bayesian approaches provide a natural framework for synthesizing the historical data that can effectively be used in designing a non-inferiority clinical trial. Despite flurry of recent research activities in this area, there are still substantial gaps in recognition and acceptance of such application in clinical trial development.

Joint Modeling

The goal is to explore Bayesian approaches to the joint modeling of longitudinal and survival-type outcomes. The aims include providing recommendations for how such models could or should be constructed, illustrating how they might be used, and elucidating the potential advantages they present and their limitations.

Missing Data

Goals: 1) Review and understand the new framework for constructing estimand from the ICH E9 (R1) addendum. 2) Use case studies to illustrate the applications of Bayesian methods under the new framework. 3) Summarize and investigate the Bayesian methods for handling missing data under the new framework in the ICH E9 (R1) addendum, and to provide recommendations and guidance to the statistical community.

Pediatrics/Small Population

Goals: 1) Explore statistical methodology that can be applicable in the design of analysis of clinical trials with particular interest in applying Bayesian methodology. 2) Illustrate and provide advice on best practices that could be used by statisticians in designing trials for pediatric and orphan therapeutics. 3) Collaborate with pharma, academia and regulatory bodies to exchange problems/issues as well as possibilities where consensus in solutions can be made 4) Disseminate information on research and best practices to broader scientific community as through conferences, workshops and seminars.

Best Practices

The increase in use and acceptance of Bayesian methodology in clinical trials has led to a need for guidance on how to report and document such methodology. ICH and various regulatory agencies recommend including language regarding the planned analyses for primary and other key analyses in the protocol and in a pre-specified analysis plan. This subteam's goal is to provide recommendations on the level of detail to include in protocols and analysis plan as well as simulation plan involving Bayesian designs and analyses.

Benefit Risk

The benefit-risk (B-R) assessment of a new medicinal product is one of the most complex tasks that sponsors, regulators, payers, physicians, and patients face. Several quantitative methods have been proposed in recent years that try to provide insight into this challenging problem. Bayesian inference, with its coherent approach for integrating different sources of information and uncertainty, along with its links to optimal decision theory, provides a natural framework to perform quantitative assessments of the B-R trade-off.

Nonclinical

In partnership with the ASA Biopharm WG, the goals are 1) Influence regulatory guidelines and standard industry practice in the context of applying Bayesian methods and philosophy in nonclinical areas 2) Foster broader awareness of the relevance, validity, and potential advantages of Bayesian methods applied in the nonclinical space among statisticians and non-statisticians 3) Develop specific use-cases within CMC space 4) Develop specific use-cases in non-CMC areas, such as in the design and analysis of animal studies

Prior/Historical Data

Methods for borrowing historical information, and the ramifications of these methods, are less well understood in terms of benefits, effects, and regulatory ramifications. The goal of this subteam is to illustrate and compare methods, understand considerations for integrating historical information into confirmatory trials, and participate in external Taskforce to influence regulatory policy change on the use of historical data.

Reporting/Tools

Although there is a wide variety of books and numerous journal articles written on Bayesian approaches in the analysis of data, not much has been written about reporting of these analyses, particularly as this pertains to clinical research. The goal of this subteam is to provide recommendations on good practices for Bayesian reporting and overview to selected software tools for Bayesian analysis.

Adaptive Design Survey

In partnership with the DIA Adaptive Design SWG, the goals are to gather information on the use of AD for clinical development programs in the device industry, in order to identify any barriers to implementing such designs and provide recommendations to overcome these challenges.

Education

The goal is to coordinate and provide Bayesian educational support which will help implement Bayesian approaches in drug development on a more regular basis as appropriate. We intend to provide education at a variety of levels, i.e., to meet the needs of statisticians and non-statisticians working in different organizations (e.g. industry and regulatory).

Medicine Adaptive Pathway to Patients

In partnership with the DIA Adaptive Design SWG, the goals: 1) Develop and publish on statistical approaches for evidence generation relevant to Expedited Approvals and other novel development approaches across product life cycles. 2) Establish and promote the role for Bayesian statistics and Adaptive Design as key drivers of Expedited Approvals 3) Engage in the subteam patient advocacy, payer, and medical reviewer perspectives 4) Facilitate visibility and networking among teams and initiatives working on different aspects of efficient and ethical drug development challenge.

Medical Outreach

In partnership with the DIA Adaptive Design SWG, the goals are to coordinate and provide adaptive and educational support, which will help our medical colleagues collaborate with statisticians in implementing adaptive and Bayesian approaches in drug development as appropriate. This includes frank and balanced discussions of both advantages and disadvantages of these methods. We intend to provide education at a variety of levels, to meet the needs of medical colleagues working in different organizations.

RWE

The inclusion of RWD/E to enhance regulatory decision making, especially for efficacy/effectiveness decision, has been advocated by FDA (and also other regulatory agencies such as EMA/MHRA/Health Canada/China NMPA) in recent years starting with the 21st Century Cures Act, PDUFA VI, and recently 2018 FDA's RWE strategic framework.

This subteam aims to leverage Bayesian methods to analyze RWD and generate RWE for regulatory decision making, which includes improving reproducibility for more credible and reliable RWE and the use of RWE in both clinical trials (e.g., hybrid control, synthetic control) and clinical planning (e.g., endpoint validation, targeting appropriate trial population).

COVID-19

This subteam has partnered with the DIA Statistical Community to find statistical opportunities to accelerate the development of COVD-19 therapeutics by way of innovative trial designs, standardized clinical outcomes, core data elements, and data sharing to enable efficient decision making and bring safe and effective therapeutics to the market.