BSWG Newsletter
Q2 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.

Sub-team Column

Bayesian efforts in the nonclinical space

Yushi Liu and Paul Faya
Eli Lilly and Company

In recent years, the Bayesian framework has developed rapidly due to the advancement of computer technology. Such development has already enabled decision making in clinical space [1]. The Bayesian framework also offers many benefits for preclinical/nonclinical space. Therefore, a nonclinical DIA-BSWG sub-team was formed in 2019 in partnership with the ASA Nonclinical Biostatistics Working Group of the Biopharm Section, focusing on promoting Bayesian methods in nonclinical area. One of its first initiative was to conduct an industry-wide survey [2] of nonclinical statisticians to understand the current state of Bayesian methods in the nonclinical space. Recently, the sub-team was divided into two work streams: discovery and CMC.

For the discovery work stream, we have statistician volunteers from Merck, AstraZeneca, Eli Lilly and Company, Biogen, JNJ, PharmaLex and BMS. The work stream has begun several initiatives to promote and bring Bayesian analysis into our daily work. One initiative was focusing on biomarker application. The team has begun to assess different Bayesian techniques such as BART, Bayesian clustering using biomarker examples. Bayesian method offered a unique and natural way to quantify the uncertainty in its prediction model, which may enhance disease/drug mechanism understanding. As a parallel effort, the team recently began to discuss in vitro/in vivo models using Bayesian meta-analytic predictive approaches to decrease the animal usage [3]. Since its formation, the team has begun to make achievements. For example, we successfully invited Dr. Jason Roy to give a short course for NCR conference this year. Right now, the team is drafting a paper to focus on introducing application of Bayesian methods in biomarker space and helping a potential invited session on Bayesian topics in ENAR 2022.

For the CMC work stream, we have members from Eli Lilly and Company, AstraZeneca, Merck, Janssen, AbbVie, Genentech, Baylor University, and statistical consulting firms. The work stream has organized two JSM sessions (2020, 2021), a session at the Nonclinical Biostatistics Conference (2021), and is currently working on two manuscripts, one of which is focused on Bayesian methods for analytical method validation. The team is also dedicating efforts to promoting the development of a regulatory guidance document for Bayesian methods in CMC, similar in spirit to the FDA Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials published in 2010.

[1] Hobbs BP, Carlin BP. "Practical Bayesian design and analysis for drug and device clinical trials", J Biopharm Stat. 2008;18(1):54-80.
[2] Faya, P., Sondag, P., Novick, S., Banton, D., Seaman, Jr, J. W., Stamey, J. D., & Boulanger, B. (2021). The current state of Bayesian methods in nonclinical pharmaceutical statistics: Survey results and recommendations from the DIA/ASA-BIOP Nonclinical Bayesian Working Group. Pharmaceutical Statistics, 20(2), 245-255.
[3] Walley R, Sherington J, Rastrick J, Detrait E, Hanon E, Watt G. Using Bayesian analysis in repeated preclinical in vivo studies for a more effective use of animals. Pharm Stat. 2016 May;15(3):277-85. doi: 10.1002/pst.1748. Epub 2016 Mar 29. PMID: 27028721.

Recent BSWG Activities

- Bayesian Key Opinion Leader (KOL) lecture series: We have held monthly Bayesian KOL series since 2018 and slides are stored in our website. The lectures for Q2/2021 are:

- 16 Apr 2021, Matt Psioda and Ethan Alt, **Incorporate External Control Data in New Clinical Trial Design and Analysis**
- 21 May 2021, Prof. Andrew Gelman (Columbia University), **Slamming the sham: A Bayesian model for adaptive adjustment with noisy control data**
- 18 Jun 2021, Saurabh Mukhopadhyay and Brian Waterhouse, **Bayesian detection of potential safety signal from blinded clinical trial data**

- The Master Protocol Working Group formed with the following sub-teams:
  - **Assess Regulatory Landscape:** Review the regulatory landscape on master protocols, both globally (i.e. ICH, CIOMS) and in each region (US, EU, Japan, China, etc.) via available literature; Contribute to evolving regulatory landscape on master protocols.
  - **Concept, methodology and framework:** General definitions/concepts on master protocols that provide multidisciplinary value:
    - Overview on statistical methods and general considerations/recommendations
    - Master protocol interdisciplinary evolving practices
    - Other aspects that relate to master protocol framework (such as case studies, road map of planning master protocol, etc.)
  - **Develop Master Protocol Implementation Standards:** Develop some standards (e.g., templates, tools) for master protocol implementations focusing on interdisciplinary areas.
  - **Patient Engagement with Patient Communities and Advocate Groups:** Incorporate evolving guidelines and standards on how to include patient input into drug development and clinical trials (including master protocols). Convey potential advantages of master protocols to patient advocacy communities.
  - **Patient Reported Outcomes and related patient experience research (e.g., QOL, preference, time-trade-off):** Incorporate evolving methodologies into statistical considerations and recommendations for master protocols.
- The Medical Outreach sub-team has completed a paper summarizing and making recommendations based on survey results regarding perceived barriers for medical researchers in using Bayesian methods.
  - To further align with our goal of educating non-statisticians in Bayesian methods, we are looking to expand this into a series of articles that would be published in the DIA TIRS journal.
  - Currently, we have groups writing perspective pieces from two FDA centers, a COVID experiences paper, and a general education paper.
  - We are looking for volunteers (both stats and non-stats folks) with expertise and experience using Bayesian methods in rare diseases or pediatric clinical trials to help in writing articles geared towards educating non-statisticians in what has previously been done. Please contact Fanni Natanegara, Jennifer Clark, or Ross Bray if you are interested.
- The Medical Device Survey Sub-team has compiled a survey on the use of Bayesian methods in trial design and analysis.
  - The survey has been completed and will be disseminated through e-mailing by the working group members leveraging network and relevant MedTech forums in July and August
  - The survey results will be summarized in Q4
  - Results will be compiled and compared to pharma survey for presentations at MedTech or DIA events and subsequent manuscript for publication.
- The COVID19 sub-team has had the following accepted and published:
  - Critical Elements in Communication of Vaccine Trials (DIA Global Forum, Mar-2021). Authors: Ivan Chan, Pritibha Singh, Jerald Schindler.
  - Vaccines After an Emergency Use Authorization (EUA): Modern Evidence Generation Approaches (Therapeutic Innovation & Regulatory Science, Mar-2021). Authors: Nevine Zariffe, Estellle Russek-Cohen.
  - Statistical Opportunities to Accelerate Development for COVID-19 Therapeutics (Statistics in Biopharmaceutical Research, Feb-2021). Authors: Fanni Natanegara , Névine Zariffa , Joan Buenconsejo , Ran Liao, Freda Cooner, Divya Lakshminarayanan, Samiran Ghosh, Jerald S. Schindler & Margaret Gamalo.

- Assessing impact of accelerated approval: Manuscript published 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.
- Xiang Zhang had a short course for JSM on Bayesian detection of potential safety signal from blinded clinical trial data, however as JSM is virtual the short course format will be implemented when F2F meetings can take place.
- Guidance documents released:
    - COVID-19: Master Protocols Evaluating Drugs and Biological Products for Treatment or Prevention

Upcoming Conferences/Webinars

2021 World Meeting of the International Society for Bayesian Analysis

June 28 – July 02, 2021
Virtual

View schedule here

DIA 2021 Annual Meeting

June 27 – July 01, 2021
Virtual

View schedule here
For more information, please contact Freda Cooner

2021 Joint Statistical Meetings (JSM)

Statistics, Data and the Stories They Tell

August 07–12, 2021
Washington State Convention Center,
Seattle, Washington

Register here
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

Register here by **August 16** for early-bird discount
For more information, please contact Freda Cooner

Accelerating Adoption of Complex Clinical Trials in Europe and beyond, October 05-October 06, 2021

For more information see this website

BASS XXVIII 28th

Annual Biopharmaceutical Applied Statistics Symposium

October 25 – 28, 2021
Charlotte, North Carolina

Master Protocols and Complex Innovative Design

November 04 – November 05, 2021
Virtual

Register here by **August 12, 2021** for early-bird rate
For more information, please contact Fanni Natanegara

Exploring the Impact of Statistics in Automated Driving Systems
Virtual

Recording of the first webinar available here

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.	***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.
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.	***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.
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.	***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.
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.	***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).
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.	***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.
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.	***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.
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.	***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).
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	***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.