BSWG Newsletter
End of 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

What's Next for Bayesian Analyses in Clinical Trials?

Scott Berry
Berry Consultants

The pandemic has seen a larger role of Bayesian analyses within clinical trials. The urgency of the pandemic and the uncertainty in the sample size and design has created an opportunity for Bayesian statistics to shine – and I believe it has. But what is next? I think the next critical role for Bayesian analyses will be in the analyses of safety and efficacy in biologically related diseases.

The science of understanding diseases is advancing at an awesome rate. We understand much more the biological and physiological aspects of diseases and as we do we are creating many biological subsets of diseases that are different but related. Some examples, include cancer, where different mutation characteristics of tumors are creating targeted therapies, but for tumors in different organs. Multiple autoimmune diseases have common biological characteristics, where different immune modulators have similarity in treatment effects. In some cases the subsets may be the same "disease," but in different severities or stage of disease. In these subsets treatments may have differential effect – heterogeneous treatment effect (including adults and pediatrics). As the science of creating different "subsets" of diseases advances the role of clinical trials has become much more challenging. Large simple trials that treat broad labeling of diseases are woefully inadequate for our new understanding of diseases. The huge challenge is that we have therapies that may have common effects (or lack of effects) across multiple disease subsets. If we analyze these trials individually by disease subsets, clinical trials will be crushingly large. If a trial/endpoint needs 400 patients for demonstrating benefit in a disease – and we now understand the "disease" as 5 related subsets we would need 2000 patients for investigating all the subsets.

So, what does the Bayesian approach have to offer? The notion of analyzing multiple related diseases is a familiar problem to Bayesians – where Bayesian hierarchical models (BHM) have great potential. BHM's are incredibly powerful tools for handling this exact construct where there are multiple, possibly related, disease subsets in which to estimate efficacy (or safety). Charles Stein, in 1956, showed (shocked) the statistical community that analyzing at least 3 potentially related groups individually is inadmissible. Also in 1956, Herbert Robbins coined the "empirical Bayes problem" – which 65 years later is exactly this same inference problem. We know analyzing the disease subsets individually is weak.

We are now, ever more often, facing exactly this problem. Basket trials have become constructs to enroll multiple subsets of diseases in a common protocol. BHM's for analyzing these multiple subsets of diseases, can provide improved estimates, manageable sample sizes, and better medical decisions. The modeling makes explicit what clinically is implicit. As with many Bayesian approaches it clashes with standard frequentist notions. Even defining type I errors can be complicated and bias is "good" in these problems, as Charles Stein showed. While the Bayesian approach was very valuable in the "surge" of COVID-19, it can similarly be beneficial in the surge in the science of understanding diseases.

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 Q3-Q4/2021 are:
    - 20 Aug 2021, Richard Payne, PhD (Eli Lilly and Company), **Bayesian Model Averaging of Longitudinal Dose-Response Models**
    - 15 Oct 2021, Melanie Quintana, PhD (Berry Consultants), **Bayesian Share Parameter Analysis of Mortality and Function within an Adaptive Platform Trials for ALS**
    - 19 Nov 2021, Mark Rothmann, PhD (FDA), **Use of Bayesian Hierarchical Models in the Presentation of Subgroup Analyses**

- DIA Master Protocol and Complex Innovative Design Workshop: Innovating for Modernized Clinical Trials
    - November 4-5, 2021 (Virtual Meeting)
    - Programming Committee consists of multiple DIA BSWG and IDSWG leaders
- Real-World Evidence (RWE) sub-team:
    - The utilization of Real-World Data (RWD) and Real-World Evidence (RWE) to enhance regulatory decision making, especially for efficacy/effectiveness claims, has been advocated by FDA in recent years starting with the 21st Century Cures Act, PDUFA VI, and 2018 FDA's RWE strategic framework, other health authorities (e.g., EMA, MHRA, NMPA, Health Canada) also had initiatives to investigate the potential use of RWD/RWE to support regulatory decisions. Most recently, FDA released a new draft RWE guidance "FDA Guidance on Real-World Data: Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision-Making for Drug and Biological Products", and more RWE guidance are expected to be released before the end of 2021.
    - This sub-team aims to leverage Bayesian methods to analyze RWD and generate more credible and reliable RWE for regulatory decision making. Currently the team members are working on 2 topics, one is the reproducibility of RWE and the other is best practice of using Bayesian methods in generating RWE for regulatory decision making.
- Medical Device Survey sub-team:
    - We have completed the survey and are currently accepting responses from those working in the medical device field. The survey, which gathers similar information to the medical outreach sub-team's survey, will be summarized and compared to the aforementioned survey results in early 2022. Results will be disclosed in a manuscript and conference presentations in mid-to-late 2022.
- Medical Outreach sub-team:
    - "Why aren't there more Bayesian Clinical Trials? Perceived Barriers and Educational Preferences among Medical Researchers involved in Drug Development", has been accepted for publication in Therapeutic Innovation & Regulatory Science.
- NCB Bayesian Preclinical Animal Biomarker and Discovery Workstream
    - This sub-team is currently identifying opportunities where Bayesian design-to-decision making strategies can introduce or improve probability-based decision making, risk assessment, laboratory resource allocations, fiscal expenditures, and the ethical treatment of animals. Implicit is increasing the stochastic intelligence, statistical literacy, and research acumen of our preclinical colleagues and their management. We expect that progress and results will be communicated through This Newsletter, white papers, and presentations and publications at both preclinical and statistical conferences, and in both preclinical and statistical journals.

Upcoming Conferences/Webinars

ASA Statistical Impact Series Webinar: ***Covid19, Vulnerable Populations and Disinformation: Research Areas from the Perspective of Migrants and Refugees***

Virtual

Recording of the first webinar available here.

ENAR 2022 Spring Meeting

March 27 – March 30, 2022

Huston TX USA

Invited Preliminary Program here.

2022 DIA Biostatistics Industy and Regulator Forum

April 06–08, 2022

Virtual

Register here for early bird rates until **February 9, 2022**.

DIA 2022 Global Annual Meeting

Innovation Through Collaboration

June 19–23, 2022

In-Person and On Demand

Chicago IL USA

Register here for early bird rates until **January 28, 2022**.

2022 World Meeting of the International Society for Bayesian Analysis

June 25 – July 01, 2022

Montreal Canada

Submissions for contributed talks and posters proposals can be submitted here until the **January 15, 2022**.

2022 Joint Statistical Meetings (JSM)

Statistics: A Foundation for Innovation

August 06–11, 2022

Washington DC USA

Submissions for topic-contributed session proposals can be submitted here until the **December 9, 2021**.

2022 ASA Biopharmaceutical Section Regulatory-Industry Workshop

Statistics Post-Pandemic: Paving the Scientific Path to Treatments, Vaccines, and Diagnostics

September 20–22, 2022

Rockville MD USA

Submissions for session proposals can be submitted here until the **December 21, 2021**.

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