Biopharmaceutical Section

American Statistical Association

Biopharmaceutical Report

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Chair: *Dionne Price*

Editors: *Paul Gallo, Ugochi Emeribe, Jerry Wang*

Note from the Editors

2014 was an exciting year for the Biopharmaceutical Section, with a number of accomplishments and initiatives that are continuing into 2015, described in this issue's transition report from Section chairs **Matilde Sanchez-Kam** (2014) and **Dionne Price** (2015).

Other articles in this issue provide more detail on specific activities mentioned in the chairs' report. This includes one of the Section's highlights for 2014, the success of the Biopharmaceutical Section FDA-Industry Statistics Workshop. A recap is provided, along with preliminary information on this year's workshop, by the two pairs of workshop co-chairs (**Cristiana Mayer**, **Shiowjen Lee**, **Richard Zink**, and **Wei Zhang**). There is also a report from **Judy Li** on the Section's Poster Competition at JSM, describing the process for this year's competition, and congratulating last year's winners.

This issue also presents updates on other exciting section initiatives, including the International Initiatives Subcommittee (from **Brian Wiens**), the Scientific Working Group Proposal Committee (from **Bruce Binkowitz** and **Ram Suresh**), and the Mentoring Program (from **Amarjot Kaur**, **Jennifer Gauvin**, and **Yue Shentue**). We also present preliminary feedback on an exciting and eagerly anticipated activity in the biopharmaceutical community, the forthcoming update of the ICH-E9 guidance, from **Tom Permutt**, a participant in that activity.

Our featured article presents some interesting results and viewpoints from **Qianying Liu** and **Xiaohai Wan** on considerations that might lead one to choose among various primary analysis approach possibilities in situations with recurrent event data.

Finally, we note the following changes in editorial responsibilities for the Biopharmaceutical Report for 2015: **Paul Gallo** slides into the Editor role, and **Ugochi Emeribe** shifts to Past Editor following her great service last year as Editor. We welcome **Jerry Wang** as the incoming Associate Editor. Lastly, we thank outgoing editor **Yongming Qu** for his great service during the past years.

Contents

Featured Article

Statistical Endpoint Selection for Recurrent Events in Clinical Trials
Qianying Liu and Xiaohai Wan 3

Biopharmaceutical Section News

Report from the Chairs The Biopharm Section: Celebrating 2014, Energized for 2015
Dionne Price and Matilde Sanchez-Kam 2

FDA-Industry Statistics Workshop: Report and Updates
Shiowjen Lee, Cristiana Mayer, Wei Zhang, Richard Zink 8

Biopharmaceutical Section Joint Statistical Meeting Poster Competition: Process for 2015 and Congratulations to 2014 Winners
Judy Li 10

International Initiatives Subcommittee: a New Project from the Biopharmaceutical Section
Brian L. Wiens 11

Update on ICH E9(R1)
Thomas Permutt 12

Biopharmaceutical Section Mentoring Program Updates
Amarjot Kaur, Jennifer Gauvin, Yue Shentu 13

Scientific Working Group Proposal Committee
Bruce Binkowitz and Ram Suresh 14

Report from the Chairs
The Biopharm Section: Celebrating 2014, Energized for 2015

Dionne Price, FDA and Matilde Sanchez-Kam, Arena Pharmaceuticals

The 175th Anniversary of the American Statistical Association (ASA) was commemorated in 2014. The theme for the year was "Celebrate our Past, Energize our Future" and indeed, the Biopharmaceutical Section positioned itself to move the theme from concept to reality. We honored our past via the creation of an informative poster that highlighted the history of the Section. Did you know the Biopharmaceutical Section was established in 1981? Such historical facts were included on the poster which was displayed at both the 2014 Joint Statistics Meetings Expo and the ASA Biopharmaceutical Section FDA/Industry Statistics Workshop. The poster outlined the early years of an informal interest group that grew into a subsection of the Biometrics Section, the road to formation of an independent Section of the ASA, the early years of the Biopharmaceutical Section, and the Section's most recent contributions.

2014 was a stellar year for the Section. The Section continued the tradition of actively participating in the Joint Statistical Meetings through sponsorship of scientific sessions, a Contributed Paper Award, a Best Student Paper Award, and a Best Poster Award. We also gathered as a group to network and report on activities during the Annual JSM Biopharmaceutical Section Business Meeting and Mixer. Throughout 2014, Section members conducted and archived a number of podcasts featuring numerous statisticians including **Bob O'Neill**, **Olga Marchenko**, **Zoran Antonijevic**, and **Karen Price**. The Section also focused on distance learning by providing several webinars on topics relevant to our membership. The Section sponsored and led the popular Biopharmaceutical Section FDA/Industry Statistics Workshop which provided a forum for scientific exchange among pharmaceutical statisticians. In 2014, the Section launched a Mentoring Program and Scientific Working Groups. Both initiatives will provide additional opportunities for our membership to have an impact on the broader statistical community. We have only highlighted a few of our many activities, accomplishments, and initiatives to exemplify the continued vitality of the Section.

We sincerely thank all who have given of their time and talent to maintain and promote the Section as an active, beneficial, and vital component for professional networking and growth. With our many activities and growing list of initiatives, we are certainly energized for the future and will continue to build upon our strong foundation. In 2015, we are poised to significantly contribute to our profession, to serve the membership of the Section, and to increase the visibility of our profession to ensure the development of future statisticians.

Dionne Price, Section Chair 2015
Matilde Sanchez-Kam, (outgoing) Section Chair 2014

Statistical Endpoint Selection for Recurrent Events in Clinical Trials

Qianying Liu, Sanofi and Xiaohai Wan, AstraZeneca

1 Introduction

Recurrent event outcomes, that is, outcomes that may occur multiple times for individual patients during a study, are important in many clinical trials for assessing efficacy or safety of investigational drugs. Examples of recurrent event outcomes include exacerbations in trials targeting respiratory diseases such as asthma, chronic obstructive pulmonary disease (COPD), or bronchiectasis [1]. Recurrent event data contain information on both the numbers of events and the times at which they occur, so that either count data methods or time-to-event approaches might be considered for primary analysis. Different approaches may have very different statistical properties, and lead to different interpretations regarding the presence and magnitude of treatment effects. For example, in a study of Azithromycin in non-cystic fibrosis bronchiectasis patients, Wong et al. [2] presented positive study results for a reduction in exacerbation rates relative to placebo; however, there was not a significant difference between treatments in the time to first symptom-based exacerbation. Therefore, in order to design, analyze and interpret clinical studies with recurrent events properly and effectively, and to choose the proper analysis approach in particular situations, it is important that differences between candidate methods be well understood.

This article discusses several statistical methods applicable to recurrent event data, to facilitate better understanding of different approaches and more appropriate selection of primary analysis methods. In particular, we will describe the use of simulations to generate recurrent event data for a negative binomial process when overdispersion is present, derive the relationship between event rate ratio and hazard ratio, and present performance evaluations of methods including time-to-event approaches such as Cox regression and Andersen-Gill models, and the count data approach of negative binomial regression.

2 Negative Binomial Process

Recurrent event data can be generated by a negative binomial (NB) process allowing overdispersion in the count data. We assume events follow a NB distribution with waiting time between adjacent events for each subject exponentially distributed, similar to a Poisson process [3]. Unlike a Poisson process, in which the rate parameter of the waiting time distribution is the same across all subjects, the NB process allows the rate parameter to vary across subjects.

First, we introduce a simulation strategy to generate recurrent event data. Assume that the duration of a two-arm clinical study is fixed as T (e.g. 6-month) and that there are no early dropouts, so that the observation duration for each subject is the same. Let y_{ij} be the number of events for subject i $(i = 1, 2, \cdots, n_j)$ in treatment group j $(j = 1, 2)$. If y_{ij} is generated from a NB process indexed by j, with mean μ_j and dispersion parameter k_j, the variance v_j follows $v_j = \mathrm{Var}(y_{ij}) = \mu_j + k_j\mu_j^2$. Such data can be modeled and simulated using the Gamma-Poisson mixture approach for a NB process as follows:

Step 1: Sample $\lambda_{ij} \sim \mathrm{Gamma}(\gamma_j, \frac{p_j}{1-p_j})$, where $\gamma_j = \frac{\mu_j^2}{v_j - \mu_j}$ is the shape parameter of the Gamma distribution, and $\frac{p_j}{1-p_j}$ is the scale parameter with $p_j = 1 - \frac{\mu_j}{v_j}$.

Step 2: Simulate independent and identically distributed (i.i.d.) time intervals between adjacent recurrent events $t_{ij,1}, t_{ij,2}, ..., t_{ij,l_{ij}} \sim \exp(\frac{\lambda_{ij}}{T})$, such that $t_{ij,1} + t_{ij,2} + ... + t_{ij,(l_{ij}-1)} \leq T$ and $t_{ij,1} + t_{ij,2} + ... + t_{ij,l_{ij}} > T$.

Step 3: Set $y_{ij} = l_{ij} - 1$ with $l_{ij} = 1, 2, \cdots$. If $l_{ij} > 1$, the time to first event $T_{ij} = t_{ij,1}$, and the failure status is denoted by $S_{ij} = 1$. Otherwise if $l_{ij} = 1$, the time to first event is censored at T, and the failure status $S_{ij} = 0$.

Note that the above approach can be easily extended in the presence of early dropouts: If the distribution of dropout times is known, one can simulate an observation time for each subject to replace T in **Steps 2** and **3**.

3 Event Rate Ratio and Hazard Ratio

For count data methods such as NB regression, the statistic of interest is commonly chosen to be the event rate ratio (ERR) between two treatment groups. The NB regression model is

$$\log(\mu_{ij}/T) = X_{ij}\beta, \tag{1}$$

where X_{ij} indicates the treatment group assignment (0 for placebo, 1 for study drug), $\beta = (\beta_1, \beta_2)$ are the regression coefficients, $\mu_{ij} = \mu_j$ is the expected number of events for subject i in treatment group j, T is the observation duration, and μ_j/T is the expected event rate. As β_2 is the estimate of the study drug effect, the exponential of β_2 is the ERR of study drug versus placebo. If the observation duration T is constant and the same for both treatment groups, we have

$$\text{ERR} = \frac{\mu_1}{\mu_2}. \tag{2}$$

In a time-to-event analysis, the hazard ratio (HR) is typically the statistic of interest. Assuming that the recurrent events are generated from a NB process, the hazard function can be derived as

$$\eta_j(t) = \frac{\mu_j}{t \cdot \mu_j k_j + T},$$

and therefore

$$\text{HR}(t) = \frac{\eta_1(t)}{\eta_2(t)} = \frac{1 + \frac{t}{T} \cdot \mu_2 k_2}{1 + \frac{t}{T} \cdot \mu_1 k_1} \cdot \text{ERR}. \tag{3}$$

It can further be shown that the time-averaged HR relates to the ERR as

$$\overline{\text{HR}} = \left(\left(\frac{1}{\mu_1 k_1} - \frac{\mu_2 k_2}{(\mu_1 k_1)^2} \right) \log(\mu_1 k_1 + 1) + \frac{\mu_2 k_2}{\mu_1 k_1} \right) \cdot \text{ERR}. \tag{4}$$

These relationships between the HR and ERR offer convenient conversions between these quantities to compare effect sizes across studies where either HR or ERR is reported. HR is usually a biased estimator of ERR, except when $\mu_1 k_1 = \mu_2 k_2$. Since the condition $\mu_1 k_1 = \mu_2 k_2$ is equivalent to an equal variance-to-mean ratio condition for the treatment groups with the NB process, we refer to it as the *equal modified coefficient of variation* (CV) condition. Note that for Poisson distributed count data without overdispersion, the modified CV condition is always satisfied with $k_1 = k_2 = 0$. If $\mu_1 k_1 \neq \mu_2 k_2$, it is important to note that the proportional hazards assumption for Cox regression would not hold. In the case where the dispersion parameters are greater than zero and equal across the treatments, i.e. $k_1 = k_2 > 0$, then unless the event rates are equal (i.e. $\frac{\mu_1}{T} = \frac{\mu_2}{T}$), the discrepancy between HR and ERR would increase as the difference between μ_1 and μ_2 increases, as the study proceeds, and as the dispersion parameter increases.

4 Study Design Example

Sample size formulas for count data and time-to-event methods have been derived in the literature [4–10]. In actual practice, interpretation of recurrent event data can be complicated by early dropouts and outliers, two issues that commonly occur in clinical trials. For a NB process, outliers refer to subjects with an unusually large number of events. We recommend using simulations to evaluate the performance of various methods and to calculate sample sizes for such complex design situations. Here, we illustrate with an example.

Consider a study with 6-month follow-up time for each patient. We would like to compare the performance of Cox regression, the Andersen-Gill model, and NB regression. To account for early dropouts, we simulate censoring by randomly assigning each subject an observation time T_{ij} sampled from a normal distribution [11] with mean 4 months and standard deviation 8 months, and then truncated to lie in the $(0, 6]$ month interval. It follows that on average 55% of subjects are observed for more than 3 months, and about 40% should complete the entire 6 months. To consider outliers, we assume that 5% of subjects in each treatment group have a higher number of events; for those subjects, a Gamma distributed event rate is set at 10 times that of the other subjects in the same treatment group. We simulate event counts from a NB process for a hypothetical randomized clinical study with two treatment groups, each with 50 subjects. We perform 10,000 independent simulations for each simulation scenario and obtain averaged type I error rate and power.

Under the null hypothesis, we consider three combinations of dispersion parameters for the two treatment groups: (1) $k_1 = k_2 = 0$; (2) $k_1 = k_2 = 0.25$; and (3) $k_1 = 0.25, k_2 = 0.5$. Also, we consider four combinations for the presence of outliers (with or without) and early dropouts (with or without). As shown in Table 1, type I error is preserved in cases without outliers, either with or without dropouts. Outliers seem to have effects on either increasing or decreasing the type I error rate for NB regression and the Andersen-Gill model, and have less effect for Cox regression, as might be expected. If we assume there are no interactions of overdispersion and modified CV condition with outliers, overdisperion and modified CV condition do not seem to have significant impact on type I error rate.

Under the alternative hypothesis, we set the means of the NB process for the two treatment groups to be 1 and 0.5. We study four combinations of dispersion parameters: (1) $k_1 = k_2 = 0$; (2) $k_1 = k_2 = 0.25$; (3) $k_1 = 0.5, k_2 = 1$; and (4) $k_1 = 0.5, k_2 = 0.25$, and again consider four combinations of the presence of outliers (with or without) and dropouts (with or without). Note that the modified CV condition is satisfied for the combination of dispersion parameters $k_1 = 0.5, k_2 = 1$ and $k_1 = k_2 = 0$, while it is not the case for $k_1 = k_2 = 0.25$ and $k_1 = 0.5, k_2 = 0.25$.

Table 1: Simulation results of type I error under the null hypothesis. The dispersion parameters for the two treatment groups are chosen as (0,0), (0.25,0.25) and (0.25, 0.5).

	No outliers			With outliers		
	(0, 0)	(0.25, 0.25)	(0.25, 0.5)	(0, 0)	(0.25, 0.25)	(0.25, 0.5)
No early drop-outs						
NB regression	4.40%	5.51%	5.33%	0.45%	2.63%	3.91%
Cox regression	4.57%	4.96%	5.74%	4.25%	4.19%	5.74%
Andersen-Gill model	5.29%	5.62%	5.51%	0.14%	1.09%	1.72%
With early drop-outs						
NB regression	4.47%	5.35%	5.58%	4.47%	6.12%	6.80%
Cox regression	4.66%	4.99%	5.19%	4.27%	4.38%	4.77%
Andersen-Gill model	5.84%	5.96%	5.88%	3.83%	4.41%	5.14%

Table 2: Simulation results of power under the alternative hypothesis. The dispersion parameters for the two treatment groups are chosen as (0, 0), (0.25, 0.25), (0.5, 1), and (0.5, 0.25).

	No outliers				With outliers			
	(0, 0)	(0.25, 0.25)	(0.5, 1)	(0.5, 0.25)	(0, 0)	(0.25, 0.25)	(0.5, 1)	(0.5, 0.25)
No early drop-outs								
NB regression	81.00%	75.61%	74.98%	67.28%	74.74%	66.47%	64.94%	59.52%
Cox regression	68.61%	59.41%	64.39%	61.52%	65.47%	56.02%	62.79%	59.75%
Andersen-Gill model	82.88%	75.96%	74.12%	66.02%	58.89%	51.32%	51.21%	47.64%
With early drop-outs								
NB regression	53.85%	50.67%	49.60%	44.60%	46.18%	43.05%	44.21%	42.29%
Cox regression	43.08%	37.40%	41.60%	38.19%	39.71%	33.89%	38.71%	37.27%
Andersen-Gill model	57.52%	52.53%	49.71%	43.84%	39.07%	36.73%	38.13%	37.41%

The simulation results in Table 2 show that the modified CV condition does help to increase power with or without the presence of outliers, and with or without the presence of dropouts. It is also clear that Cox regression lacks power when compared with the other two methods with or without outliers, and with or without dropouts. The performance of NB regression and the Andersen-Gill model is similar in settings without outliers, and NB regression seems to perform better in the presence of outliers.

5 Summary and Future Work

We have presented the relationship between hazard ratio and event rate ratio for a NB process, and demonstrated the implications of the equal modified CV condition for hypothesis testing and statistical power. Through stochastic simulations, we suggest that event rate and time to multiple events are preferred endpoints over time to first event from a statistical power perspective.

In this work, a NB process is assumed for the underlying data generation mechanisms and is expected to perform well to model recurrent event data from clinical studies. For future work, it is also of interest to study additional stochastic processes for scenarios where the NB process is not appropriate, e.g. if either the event counts do not follow the NB distribution, or the waiting time between neighboring events for individual subject does not follow exponential distribution with constant rates.

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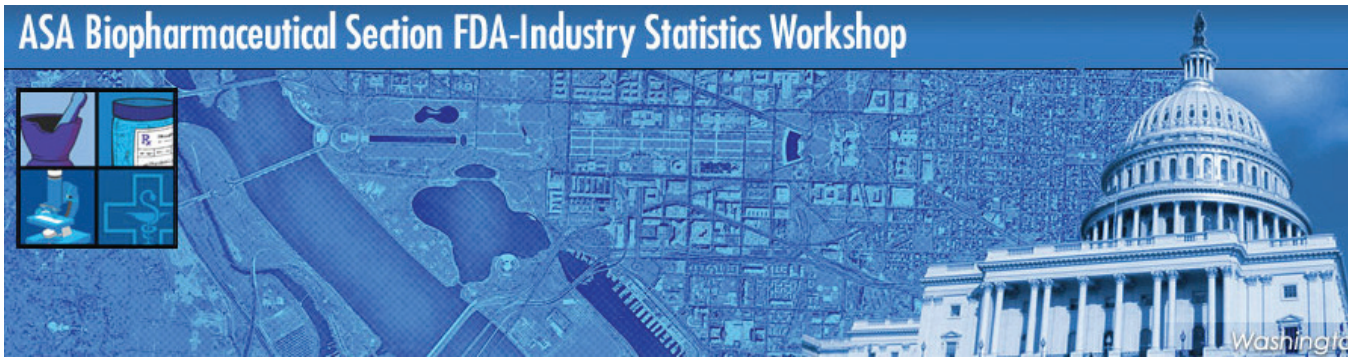

FDA-Industry Statistics Workshop: Report and Updates

Shiowjen Lee, Cristiana Mayer, Wei Zhang, Richard Zink

The 2014 ASA Biopharmaceutical Section FDA-Industry Statistics workshop was held on September 22-24 in Washington D.C. More than 810 FDA, academia and industry colleagues gathered to share insights into key trends in statistical topics relevant to pharmaceutical and device development.

Cristiana Mayer (Model-Based Drug Development, Johnson & Johnson) and **Shiowjen Lee** (FDA/CBER) co-chaired the meeting. Together they led a Steering Committee, made up of FDA and industry representatives, to develop an informative program that included 6 half-day short courses, more than 50 roundtable discussion topics, and 42 parallel sessions on a large variety of topics including but not limited to Bayesian methodologies, adaptive study designs, modeling and simulation, FDA guidances, "Big Data" analysis, biomarkers, and in-depth discussions on special disease areas such as Alzheimer's disease and oncology.

Workshop Co-Chairs Shiowjen Lee (FDA/CBER) and Cristiana Mayer (Johnson & Johnson)

The workshop opened with two plenary sessions organized by Cristiana and Shiowjen. The first focused on "Statistics in the Pharmaceutical Industry and Regulatory Sciences: We Learn From the Past, Celebrate Today, and Invigorate Our Tomorrow". The second featured a vivacious panel discussion on "Modeling and Simulations in Adaptive Designs for the Development of Drugs and Devices" that included prominent experts and senior leaders including **Bob Temple**, **Jim Hung**, and **Greg Campbell** from the FDA and **José Pinheiro** (Johnson & Johnson, MBDD), **Frank Bretz** (Novartis), **Alex Dmitrienko** (Quintiles) and **Martin Posch** (Medical U. of Vienna).

Key takeaways included:

- Enthusiasm from both industry and FDA for greater use of adaptive trial designs;
- The growing utilization of simulations and modeling not only to assess trial design operating characteristics and analysis methods, but for assessing safety signals and trial operational issues;
- The need for stronger collaboration between industry and FDA to advance the role of statisticians in clinical trial design, execution and analysis.

Throughout the workshop, session after session, the participants enjoyed informative presentations and constructive discussions addressing many critical issues in the pharmaceutical statistical science, sharing regulatory

perspectives and shaping future trends in the R&D environment for new therapies and devices. Continuing a new tradition started a year earlier, the workshop offered the opportunity for great networking at the mixer event on the second night. Overall, many records were broken: it was the most attended workshop in the last several years, with 95% of registrants attending a short course, an absolute record number of attendees of the short course program. Cristiana and Shiowjen are very grateful for the support from all who participated, including the Steering Committee members, session organizers, chairs and speakers, short course presenters and workshop participants. In addition, the co-chairs wish to single out **Christina Link**, ASA Meetings Planner, for her invaluable and extraordinary performance in managing the logistics, coordinating activities with the hotel and being the liaison with the ASA. Without the contribution of all, this successful meeting would have not been possible. Let's make it a commitment for 2015 and every year to come!

The 2015 Biopharmaceutical Section FDA-Industry Statistics Workshop takes place September 16-18 in Washington D.C. at the Marriott Wardman Park, and will feature a Personalized Medicine theme. "Given the emphasis on 'getting the right drugs to the right patients' for many of the submitted parallel and short course proposals, this theme was a natural fit," commented **Wei Zhang** (FDA/CVM) and **Richard Zink** (JMP Life Sciences, SAS Institute), co-chairs for the upcoming meeting. For the first time, eight short courses will be available, offering statisticians greater variety for training in cutting-edge methodologies including, but not limited to, missing data, propensity scores, dose finding and companion diagnostics. "We are excited at the success and growth of the short course program, which offers extremely affordable continuing education opportunities for statisticians," said Zhang and Zink. There are still opportunities to participate in the Workshop by submitting a proposal for a round table discussion (deadline March 10 at 11:59PM EST).

Biopharmaceutical Section Joint Statistical Meeting Poster Competition: Process for 2015 and Congratulations to 2014 Winners

Judy Li, CBER, FDA

If you plan to attend JSM 2015 and to present a poster, you may consider participating in the Poster Competition sponsored by the ASA Biopharmaceutical Section. You don't need to be a member of the section to participate. All authors who present posters sponsored by the Biopharmaceutical Section are qualified to compete for this award. Three awards with cash prizes of $1000, $600 and $400 will be given for 1st, 2nd, and 3rd places, respectively.

Entry criteria for the Poster Awards:

- Posters dealing with topics in statistics which are applicable to biopharmaceutical research. Suitable topics include, but are not limited to, methodological issues in preclinical or clinical trials, epidemiology studies of drug safety (device or biological), genetic studies predicting drug (or biological) response, laboratory and toxicological data analyses, methods for high-dimensional data from high-throughput screening, and non-linear pharmacokinetic modeling.

- Posters will be evaluated based on the following criteria:
  - Innovation
  - General applicability in pharmaceutical research
  - Appropriate example(s)
  - Effectiveness of presentation (well written, well organized, etc.)

- Authors who compete for the Poster Awards cannot also compete for the Student Paper Awards.

The process is as follows:

1. To have submitted an abstract through the Biopharmaceutical Section by February 2, 2015.
2. Submit your poster to Judy Li, Chair for the Poster Awards, through e-mail (*Judy.Li@fda.hhs.gov*) by May 15, 2015.

Finally, congratulations to JSM 2014 poster award winners:

- First place – **Bo Huang** and **Neal Thomas**

Optimal Designs with Interim Analyses for Randomized Studies with Long-term Time-specific Endpoints

- Second place – **Richard J. Willke**, **Ching-Ray Yu**, **Birol Emir**, **Kelly H. Zou**, **Javier Cabrera**

A Comparison and Integration of Quantile Regression and Finite Mixture Modeling

- Third Place – **Kijoeng Nam** and **Estelle Russek-Cohen**

Logistic Regression Likelihood Ratio Test Analysis and Harnessing Graphics to Explore Safety Data in the Vaccine Adverse Event Report System (VAERS)

International Initiatives Subcommittee: a New Project from the Biopharmaceutical Section

Brian L. Wiens, Portola Pharmaceuticals

Biopharmaceutical statisticians in the U.S. must be aware of activities and developments around the globe. Whether it is a colleague in the head office in London, a submission to the Japanese regulatory authority, a SAS® programmer in Bangalore, or a session at JSM organized by an academic statistician from Germany, most of us have numerous opportunities to collaborate with colleagues from outside the United States. Statisticians outside the U.S. often have different experiences and different expectations because of differences in legal requirements for approval of drugs, biological medical devices and diagnostics, or because of cultural differences, and overcoming these differences is required to work together effectively.

The Executive Committee of the Biopharmaceutical Section has chartered a small committee to find ways to further involve international statisticians in Section activities. To this end, I have recruited three colleagues to help me: **Toshimitsu Hamasaki** from National Cerebral and Cardiovascular Center, Osaka, Japan; **Sreekumar Nair** from Manipal University, Manipal, India; and **Frank Bretz** from Novartis Pharma AG, Basel, Switzerland. We have been assigned two objectives for our International Initiatives Subcommittee: find ways for the Biopharmaceutical Section to better serve statisticians who reside outside of the United States, and find ways for statisticians from outside the United States to serve members of the Biopharmaceutical Section. Importantly, we view this as a two-way interaction, with statisticians in the United States (who are the majority of current Biopharmaceutical Section members) both learning from and providing opportunities to statisticians from other countries. We will be successful if we provide value to members of the Section and recruit new members to the Section.

The International Initiatives Subcommittee has discussed various ways for the Section to meet these objectives. Some are expensive and time-consuming with benefits in the long term; others are inexpensive and easy with benefits in the short term; and of course many are somewhere between these two extremes. We have emphasized the inexpensive and easy projects for our first efforts. The first is this report to the membership of the Section, and you can expect to read more reports in upcoming issues of Biopharmaceutical Report. Another is a topic contributed session at JSM in August, 2015. Other projects will leverage current Section activities, such as podcasts that appeal to international statisticians or that explain international issues to Section members, and webinars that are scheduled at times that are convenient for statisticians in other time zones (or that are archived for their viewing, on demand).

Ideas and volunteers are welcome. Although we currently have more ideas than we now have time to implement, send your suggestions and we will consider them. We also will request volunteers for various activities from time to time, so please be on the lookout.

Biopharmaceutical Section leadership and members of the International Initiatives Subcommittee look forward to a long and fruitful collaboration, bringing new information to Section members and providing service to statisticians around the globe.

Update on ICH E9(R1)

Thomas Permutt, FDA

Until recently, I thought the International Conference on Harmonization (ICH) had happened a couple of decades ago and might happen again in the indefinite future. A few months ago I learned otherwise. Although I am in no position to speak for ICH or any of its working groups, it seems to me that many readers, like my former self, must lack even the information I now have, so that I am pleased to be able to share it.

From a statistician's viewpoint, my former understanding was not very far wrong. The only ICH document dealing mainly with statistics, Statistical Principles for Clinical Trials, known as E(fficacy)9, was promulgated as a Harmonized Tripartite Guideline in 1998 and has never been revised. "Tripartite" refers to the regulatory authorities in Europe, the United States, and Japan, though since then the process has expanded to include other regions as observers or full participants. Pharmaceutical industry associations in the three regions also took part in the deliberations.

In October the ICH steering committee approved the formation of an Expert Working Group to discuss the first-ever revision to E9, to be known as E9(R1), in the form of an addendum on two topics: Defining the Appropriate Estimand for a Clinical Trial, and Sensitivity Analyses. Shortly thereafter I found myself appointed Topic Leader for FDA, one of the least exalted titles available. **Estelle Russek-Cohen** represented FDA in the loftier position of Regulatory Chair.

I renewed my official passport and made my way to Lisbon (coach class and with the bad connections that government-contract air carriers charge extra for, Topic Leader though I was) in mid-November. There I found myself in a room with a dozen other statisticians from the three regulatory parties, their industry counterparts, and Health Canada, one of the new parties.

Thomas Paine, supporting revolution in America despite the risk of war, sardonically observed that without a war every 20 years or so, if war did come a country wouldn't have any officers who had seen one. Likewise, our working group had no one who had been an ICH expert before. Possibly the only ill effect of this deficit was our taking too seriously a generic workplan that seemed to call for us to draft a document on the spot. When we timidly intimated to steering committee members that this might be impossible, they looked puzzled and said, "Of course it is."

For four days we engaged in the most intelligent, informed, lively and cordial conversation of my working life. We did not confine ourselves to topics on which we could easily agree: we debated, we listened, we harmonized. I learned and I taught. We gave ourselves a less absurd but still optimistic workplan and assigned ourselves to go home and do it. We asked the steering committee for another face-to-face meeting in Japan in June 2015, but we realized that they might not grant it even if we managed to tell them what estimand means by then.

Biopharmaceutical Section Mentoring Program Updates

Amarjot Kaur, Jennifer Gauvin, Yue Shentu

The Biopharmaceutical Section initiated a mentoring program last year for the benefit of its members. The goal of this program is to help members further enrich and enhance their professional experiences. This program is based on the blueprint created by the ASA Committee on Applied Statisticians.

The program is well under way and is progressing well, with several mentor-mentee pairs enrolled in the program. For those currently enrolled, please keep an eye out for a survey in your mailbox sometime in the March timeframe. The purpose of the survey is to gather your feedback on this program based on your experience. We will appreciate your full participation in this survey as that will help refine the mentoring program for the future.

Some of you not enrolled in the current program have already contacted us expressing interest in the upcoming mentoring program and we have your information for future mentor-mentee matching. Additional announcements for the program for this year will be coming out in the May-June 2015 timeframe. We would look forward to hearing from you if you are interested in joining the mentoring program as a mentee or a mentor, or can nominate a statistician who may be looking for a mentorship program. This information will also be made available via the Biopharm website (*http://community.amstat.org/BioP/aboutus/mentoringprogram*).

You may also contact us at *biopharmmentoring@gmail.com* with the subject: "2015 Biopharm Section Mentoring Program" if you are interested in participating or need any additional information or clarification related to this program.

Scientific Working Group Proposal Committee

Bruce Binkowitz, Merck and Ram Suresh, GSK

The ASA Biopharmaceutical Section recognizes the value of cross-community efforts in advancing statistical and regulatory science. To enable this, the Executive Committee encourages members to submit research topics that contribute to the goals of advancing the science, enabling innovation, and leveraging the expertise of the broad membership affiliations of the section. Members are encouraged to submit proposals to the Scientific Working Group Proposal Committee for review and if appropriate, subsequent consideration by the section Executive Committee. The proposal should be formal in nature, so that, if acceptable, it can be used as the basis of a scientific working group charter, and it should include at a minimum the following items as part of a submission (additional information beyond the bulleted items presented here is welcome):

- Topic and primary goal of the scientific working group
- Who is proposing it?
- Why is this an important topic to research (e.g. potential impact)?
- Why is this an appropriate topic for ASA Biopharm Section sponsorship?
- Are there any other known scientific working groups currently addressing this topic? If yes, what unique values will this SWG bring? If yes, please discuss potential opportunity for linkage to another group if other groups already exist. If "don't know", please state how you will follow-up to make sure there is not a redundancy in the statistical community.
- Estimate of the initial # of members for the working group, and if any non-statistician consultants will be part of the effort.
- How long will do you anticipate it will take the group to reach its goals?
- Who will chair/co-chair the group? Why is/are this chair (chair/co-chair) being proposed (e.g. qualifications)?
- Is financial support needed from BIOP?
- What will be the best avenues of communication to advertise the efforts, accomplishments, papers, presentations, etc. of this SWG.

You can reach out to the Scientific Working Group Proposal Committee (SWGPC) through the Biopharmaceutical Section microsite. Once on the website, chose the "About Us" tab, and scroll down through to subcommittees, and choose the Scientific Working Group Proposal Committee. The link to email the committee is there. Or to save you those steps, the address is *asabiop.sciwg@gmail.com*

On behalf of the committee, we look forward to hearing from you.

Ram Suresh
Bruce Binkowitz
Co-chairs of the SWGPC

Calling All Volunteers!

Want to get involved in Biopharm Section activities, but not sure how? The Section is always looking for volunteers, so drop us an e-mail at *volunteer.asabiopharm@gmail.com*.

Let's Hear from You!

If you have any comments or contributions, please contact the Editors: Jerry Wang, email *jerry.wang@merckgroup.com*; Ugochi Emeribe, email *ugochi.emeribe@astrazeneca.com*; or Paul Gallo, email *paul.gallo@novartis.com*. We are looking for volunteers to write articles or suggest topics that will be of interest to our members. The topics can be technical, but non-technical articles related to biopharmaceuticals are welcome. Please send us an email.

The *Biopharmaceutical Report* is a publication of the Biopharmaceutical Section of the American Statistical Association.