Biopharmaceutical Section

American Statistical Association

Biopharmaceutical Report

Volume 20, No. 3 Summer 2013

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Editors: *Jose Alvir, Yongming Qu, Ugochi Emeribe*

Note from the Editors

Welcome to our September 2013 issue of *Biopharmaceutical Report.* As we celebrate the International Year of Statistics (IYS), we feature two articles that highlight the collaboration of statisticians in the biopharmaceutical sphere. The first article was jointly written by **Zoran Antonijevic, Jim Bolognese, Carl-Fredrik Burman, Christy Chuang-Stein, Chris Jennison, Martin Kimber, Olga Marchenko, Nitin Patel,** and **José Pinheiro**. We purposely listed all authors because this is a report on the activities of the collaborative DIA Adaptive Program Work Stream (APWS). This international effort focuses on the relation between phase II dose-finding and phase III confirmatory trials. As stated by the authors, "A key objective of the APWS is to stimulate scientists in industry, academia and regulatory agencies to consider optimization at the development program level, rather than focusing narrowly on single trials."

The second article by Olga Marchenko and colleagues describes the Center for Statistics in Drug Development at Quintiles, a group that houses thought leaders in biopharmaceutical statistics.

As the IYS marches to a close, we are fortunate to celebrate the exciting developments in our field. We the editors of the *Biopharmaceutical Report* are privileged to be able to help in disseminating information about these efforts. ■

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Letter from the Chair, Biopharmaceutical Section 2013

Dear Biopharm colleagues,
I hope you all had a great summer. It was great to see and meet many of you at the *JSM* in Montréal last month. Montreal is a fascinating multicultural city with rich history and pleasant summer weather! We met many of our old friends, co-students from our graduate school days, colleagues from the past and obviously we establish new contacts each year at JSM.

Biopharmaceutical section had a significant presence this year also. Being one of the largest sections of ASA, it is of no surprise that the section organized several invited, topic-contributed and contributed sessions across the five days. I heard that the speed poster sessions, which were new this year, went well. Based on my experience as past program-chair, I am sure our 2013 Program Chair **Estelle Russek-Cohen** must be very happy and pleased with this big event is behind her. I take the opportunity again to thank her for a wonderful job that she had done with utmost sincerity. The newly formed program committee will be greatly benefited from the wisdom, experience and valuable guidance from Estelle. **Ivan Chan** is already on this job of Program Chair for 2014; he started well before the 2013 JSM event.

I hope the section members who attended the evening mixer and the business meeting enjoyed the events. I hope you made a few new connections also during the mixer. Personally, it was a great pleasure to meet and greet so many section members during the mixer. During the JSM, the section organizes its executive committee (EC) meeting, the summary minutes of which are included in this newsletter.

ASA Biopharmaceutical Section FDA-Industry Conference (definitely a mouthful) has concluded this week with an appropriate theme on *"International Year of Statistics."* Thanks to the co-chairs **Bruce Binkowitz** and **Lilly Yue** along with the conference steering committee and ASA, the conference has continued to generate a lot of interest. We will hear more about the conference in the next biopharm report from the co-chairs. Planning for the 2014 workshop is already underway with co-chairs **Christiana Mayer** and **Shiowjen Lee**—drop them a note if you have any new suggestion.

The communication team is figuring out ways to communicate with the membership more effectively – they are also planning to include the social media presence for our section in the near future and fine-tuning the logistics. I hope you all have seen the increased traffic in our Biopharm e-group posting and more shared information this year. The effort in creating an improved, redesigned section website is in its final stage, thanks to **Ed Luo** and **Yue Shentu**.

Thanks to the effort and enthusiasm from **Rima Izem** and **Richard Zink**. You all will notice a couple of new podcasts in our website soon—please keep an eye on this space at the section website.

The *Biopharm Report* editors have so far kept the promise of publishing this newsletter every quarter in this year. Well done Y**ongming Qu, Ugochi Emeribe** and **Jose Alvir.**

The webinar series (6 done, 3 more to go in 2013) are big hits for the section members. If any of you have suggestions for a specific topic and/or an eminent speaker, please let **Shailaja Suryawanshi** and **Satrajit Roychoudhury** know – they will explore new topics and new speakers for next year.

Many of us in the executive committee are looking to collaborate with other sections and chapters, professional associations, both in the U.S. and internationally. This will help us share our knowledge with colleagues across the world and learn from others too. You will hear more about these collaborations as some of these will mature in the future.

We are always challenged with keeping up the membership in a healthy state—The number of our membership has fallen a bit this year. We are investigating the root cause, if there is one. The lower membership number could result in lesser influence and a weaker voice from our section in matters that may affect our future. I encourage all section members to actively encourage colleagues in your organization to be a member of the Biopharm section. The stronger we are, the more we can do and invest in initiatives that would serve the membership; our strong memberships help sponsor the conferences that our members would like to attend and get benefitted from. I request you all to convince at least one of your colleagues to be a new member of this section.

To sum it up all, with so many activities and initiatives ongoing during the year, I feel so privileged to work with the excellent team of section officers and other committee members over the last 9 months. I thank each one of these enthusiastic volunteers without whom the section cannot continue this journey. The section thrives on volunteers and we need more for new ideas, enthusiasm and manpower. Those interested in joining the section activities, send an email to *volunteer.asabiopharm@gmail.com*.

With best regards,
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A Progress Report from the DIA Adaptive Program Work Stream

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Overview

The first decade of the 21st century saw a great interest in the research and implementation of adaptive designs for clinical trials that went beyond the traditional group sequential design. A major driver for the increase was a strong desire to reduce the late-stage product attrition rate and to make our product development process more efficient. This common desire led statisticians working in the pharmaceutical industry to come together and form an Adaptive Designs Working Group (ADWG) in the spring of 2005, initially under the auspices of the Pharmaceutical Research and Manufacturers of America (PhRMA). The objectives were to foster and facilitate wider usage and regulatory acceptance of adaptive designs to enhance clinical development through fact-based evaluation of the benefits and challenges associated with these designs (Gallo, et al. 2006). To support these objectives, ADWG initiated various work streams to kick off a broad range of activities such as sponsoring workshops, giving short courses and publishing research and consensus papers. A work stream on regulatory interactions reached out to regulators to discuss best adaptive design practice and share experience from implementing such designs. The sponsorship for ADWG was officially transitioned from PhRMA to the Drug Information Association (DIA) in 2010. The name of the group was changed to Adaptive Design Scientific Working Group (ADSWG) after the transition. While some work streams were discontinued after completing their original charge, new work streams such as adaptive program, precision medicine and portfolio evaluation have been added since 2010.

A highly visible long-running activity of the ADSWG (and of ADWG previously) is the monthly key opinion leader lecture series. Early lectures focused on theory behind adaptive designs. More recently, lectures have focused on practice and lessons learned from implementation. The lecture series is free to the public and a lecture can sometimes attract hundreds of participants. The sharing and exchange of ideas and case studies in this pre-competitive space has encouraged many to consider adaptive design and helped others understand the importance of thorough upfront planning required for this class of new designs. We believe the effort of the ADWG in promoting a guidance on this subject in the US contributed to Food and Drug Association's decision to publish a draft guidance on adaptive designs in February 2010.

The PhRMA Adaptive Dose Ranging Studies Working Group (ADRS WG) was formed about the same time as ADWG in early 2005. Its focus was on the quantitative evaluation of adaptive designs and model-based methods for dose selection and estimation of dose response, toward making recommendations on when they should be used and how much benefit they could be expected to bring. A series of white papers was published by the ADRS WG in 2007 and 2010, two of which (Bornkamp et al. 2007; Pinheiro et al. 2010) included discussions by regulators from FDA, EMA, and PMDA. Based on their research, the ADRS WG formulated a series of recommendations and suggestions for future investigation. Chief among them was the need to place the dose selection issue in the broader context of the overall development program, and not just restrict it to the phase IIb stage in which it generally takes place. In particular, the WG recommended the evaluation of the impact of the choice of design and analysis method for dose selection on the probability of success (PoS) of the phase III and, ultimately, the expected net present value (eNPV) for the compound. The ADRS WG was absorbed into the DIA ADSWG in early 2010, with many of its members participating in the newly formed Adaptive Program work stream (APWS) and remaining active in it ever since. Several of the recommendations and suggestions from the ADRS WG were followed up and extended by the APWS.

Since its inception, the APWS has been a very active work stream of the ADSWG. This article is a progress report from the APWS.

Areas of Focus and Research

Continuing the work of the ADRS WG, the focus of the APWS has been mainly on the relation between phase II dose-finding and phase III confirmatory trials. The objective is to model the regulatory requirements for drug approval, typically using a frequentist framework. For sponsor decisions, a Bayesian decision theoretic approach can also be used. Based on previous information and expert input, we model efficacy and safety and formulate a prior (in some cases, a number of plausible scenarios). Based on this, we can assess the overall PoS for different program design alternatives. Furthermore, we may assess the eNPV, based on trial costs, time, regulatory hurdles, and a commercial model. In a practical situation, PoS and eNPV can be studied through simulations. We can evaluate different program designs and compare their performance. This approach has been applied to assess development options in three therapeutic areas, described later in this report. The approach has been found useful as it helps sponsors gain insights into the performance of different development program options and generate ideas for possible modifications to development program strategies.

On the methodological side, we are searching for the global optimum at the development program level. This is admittedly challenging, as the optimal phase III design depends on the random outcome of the phase II design, while the optimal dose-finding design depends on how the result of this phase II trial will affect the phase III design and ultimately the eNPV. A standard backward induction approach may not be computationally feasible.

In the following sections, we will report the methodological work in a generic setting. We then summarize, at a high level, findings from applying the methodological work to assess relevant development program options in three therapeutic areas. We conclude the article by describing opportunities for future collaborations.

Generic Methodology

We have tackled the general problem of design optimisation for a phase IIb dose selection trial followed by a phase III confirmatory trial or trials. Here, our model assumes the sample size of the phase IIb trial and the proportions of subjects allocated to each dose are fixed. If it is decided to continue past phase IIb, a single dose is chosen to compare against a control in phase III. For the case of two phase III trials, a positive outcome requires the null hypothesis to be rejected at the one-sided significance level of 0.025 in each trial. In the case of a single phase III trial, a significance of 0.0005 is required. We specify a four-parameter Emax dose-response model for treatment efficacy and a prior distribution for the Emax model parameters. We also specify the probability, as an increasing function of the dose selected after phase IIb, that an otherwise positive outcome is lost due to safety problems. Furthermore, we specify the net gain that arises from a positive phase III outcome with no safety problems and a cost structure that results from sampling for each patient recruited in phase IIb and phase III.

In the over-arching design problem, there is freedom to choose the total phase IIb sample size, n2, the decision rule for whether or not to proceed to phase III, the dose selection rule, and the rule for determining the phase III sample size n3. For a given value of n2, we generate a sample of phase IIb data set. For each of these data sets, we compute the posterior distribution of the Emax model parameters. From these, we derive the following:

- The Bayes optimal choice of whether or not to continue to phase III;
- If continuing, the optimal dose and phase III sample size;
- The expected net gain discounted by the cost of patients recruited.

The average of the eNPV over the sample of phase IIb data sets measures the value of the complete design. Comparing these values over choices of n2 gives the optimal phase IIb sample size.

Although the computational demands are high, we have been able to implement this methodology and obtain results for several examples. There are many directions in which to extend the problem formulation. For example, the phase IIb trial could follow an adaptive design, eliminating doses over time or modifying the proportions of observations allocated to each dose. More than one dose could be carried forward to phase III. The gain function may be generalised to depend on the true or estimated treatment effect. In the case of a single phase III trial, we have considered phase III trial designs with a group sequential stopping rule. Preliminary results suggest that a group sequential stopping rule has a considerable effect on the optimum design, reducing the optimal phase IIb sample size substantially. Our interpretation of this finding is that, while it is still important to select a good dose after phase IIb, having an accurate estimate of the treatment effect on which to base the phase III sample size may no longer be so important. A high maximum phase III sample size can be chosen and if the treatment effect is high, the group sequential design will terminate early with a smaller actual sample size.

Neuropathic Pain Case Study

A framework was presented by Patel et al (2012) to evaluate the impact that several phase II design features have on PoS and eNPV of a product for neuropathic pain. The factors considered include phase II sample size, decision rules to select a dose for phase III trials and the sample size for phase III trials.

A hybrid frequentist/Bayesian approach was used to evaluate the impact of the aforementioned design factors on phase III program success, clinical utility, and eNPV. The evaluation was done via simulation. Statistical analysis of data from each of the two phase III trials used traditional frequentist methods. Go/no-go decisions from phase II to phase III and from phase III to regulatory submission used Bayesian posterior probabilities. For example, the posterior probabilities of response at the respective doses from the simulated phase II trial were used to choose the doses for phase III.

Outcome was assessed at the development program level by the number of patients required and associated costs, PoS, and profit, which was directly linked to clinical utility. PoS was measured by the probability that both pivotal phase III trials demonstrate statistically significant drug effect and the observed mean response is at or exceeds a pre-specified magnitude. Profit was measured by eNPV. The magnitude of profit was determined by a defined relationship of efficacy and tolerability demonstrated by the phase III trials to typical profits of comparator drugs and to trial costs via a utility function developed in collaboration with experienced clinicians.

The utility function combined 4 levels of efficacy with 4 levels of safety in a 4x4 grid with entries scaled from 0 to $2B. The 4 levels were (1) substantially inferior to, (2) somewhat less, (3) similar to, and (4) better than currently marketed products. The 16 cell entries were filled in by the experienced clinicians, and then two-dimensional interpolation was used to map safety and efficacy results from simulated phase III trials into the clinical utility table on a scale where 0 represents no value, and 1 represents efficacy and tolerability similar to the best competing marketed products. Final outcomes of the simulated sequences of phase II followed by phase III trials included deductions of trial and drug product development costs. Unsuccessful phase III programs would result in negative NPVs.

Our findings from simulations of low, moderate, and high levels of each of efficacy and safety suggest that optimal sample sizes for phase II can be obtained to maximize eNPV, which in our case was directly proportional to clinical utility. These optimal sample sizes are a trade-off between increasing phase II sample size to improve phase III dose selection and therefore increase PoS, which can increase time and cost, and reducing time to market with a potential increase in revenues. This methodology offers an objective approach to quantify such a trade-off. It is not suggested to be the sole determinant of late phase drug development strategy, but rather a benchmark to inform decisions.

Our simulations included only non-adaptive, equal allocation study designs, which carry a single dose into phase III. Additional work is under way to assess the impact of adaptive dose-finding designs in phase II, and strategies for carrying more than 1 dose into the phase III trials.

Type II Diabetes Case Study

This case study, reported in Antonijevic et al. (2013), investigated a phase IIb - phase III drug development program for Type II Diabetes via simulations. The primary regulatory efficacy endpoint considered was the HbA1c change from baseline. The program consisted of a single phase IIb trial of five dose levels against placebo control, followed, if the phase II success criteria were met, by three pivotal phase III trials in parallel taking the single selected dose and comparing against placebo and two already marketed products. There were three target indications: monotherapy, add-on to metformin, and add-on to sulphonylurea. The dose selection was made based on the clinical utility function, while the program was assessed in terms of the eNPV of the selected dose based on its performance in phase III. More revenue would be anticipated if superiority were demonstrated than mere non-inferiority, with the market segments contributing separately (dependent of course on the overall PoS of the program).

The impact of the following design parameters on the PoS, and the eNPV was assessed:

- Phase IIb design (fixed or adaptive with 5 dose levels);
- Phase IIb sample size (total of 300 and 600 patients); and
- Phase III sample size (200 to 600 per arm).

The incidence of hypoglycemic events is of great medical concern, and has a significant impact on expected revenues. Consequentially the observed hypoglycemia rate is an important component of possible dose-selection criteria. In this case study this side-effect endpoint was evaluated alongside the primary HbA1c endpoint in two distinct ways:

1. With a penalty factor to reduce the revenue achieved in each segment if hypoglycemia of the selected dose exceeds background levels; and, separately,

2. As the second component of a 2D utility function U(ΔHbA1c, pHypo) as specified within version 2 of the FACTSTM simulation software package. Here ΔHbA1c denotes change in HbA1c from baseline and pHypo denotes the incidence of hypoglycemia.

The latter approach is directly tractable and was used, for the adaptive phase IIb designs, to drive adaptive allocation as well as dose selection. Placebo correction is built into the input of the utility function. The form of the 2D function is determined in advance of the investigation by biostatisticians eliciting a desirable trade-off between endpoints from the clinical team. However, the former approach, whereby estimated revenue is adjusted by penalty factors, corresponds more directly to the eNPV. It also allowed for different penalties to be applied for hypoglycemia incidence under multiple possible phase III outcomes (see Figure 2 of Antonijevic et al. (2013)). Finally, by using eNPV as effectively a form of utility function, PoS (for different types of success) is explicitly built into a multi-phase program's decision making framework.

Based on the results of simulations, Antonijevic et al. (2013) drew the following conclusions:

- Larger sample sizes in phase IIb and phase III studies provide more precise dose selection, and reduce the positive treatment effect bias and uncertainty in estimated eNPV, within the range of sample sizes studied.

- Similar improvements are seen with implementation of an adaptive design over a fixed design in phase IIb.

- Dose selection criteria have to be consistent with a sponsor's objectives. It is a very common situation that dose selection criteria are defined by R&D teams, while one of the key objectives

is to maximize the expected revenues. In order to optimize the program, the authors recommend closer collaboration between R&D clinical and commercial groups earlier in the product development.

- It is recommended that simulations be used to support optimization of any drug development program.
- This case study did not address the impact of length of development, since that would be driven primarily by a separate CV outcome study, which was out of the scope of this research. Of note is that addressing the CV requirement would have major impact on the cost and timelines.

Pancreatic Cancer Case Study

The third case study, published in Marchenko et al. (2013), deals with hypothetical oncology drug development programs that consist of a phase IIb and a single phase III study in pancreatic cancer. The work involved analyzing and comparing five oncology development scenarios in the setting where a lead and a backup compound are ready for a phase II trial which, if warranted, will be followed by a phase III trial. The compound here is considered in a general sense. This can be two different drugs for the same indication or population, two different regimens of the same drug, or two drug combinations/ adds-on therapies. Different scenarios with regard to drugs' performance were compared based on PoS and eNPV using simulation.

The 5 development program scenarios considered were:

- *Program #1*: Select one drug from 2 candidate drugs (ND1 and ND2) for treating pancreatic cancer. The selected drug, based on pre-clinical and phase 1 data, will be examined in a phase II study followed by a phase III study if warranted;
- *Program #2*: Conduct a separate phase II study for each of the 2 compounds, the phase II study identical to the phase II trial in Program #1. Select the more efficacious drug at the end of phase II for the phase III development if both are efficacious;
- *Program #3*: Is similar to Program #2 except that a single 3-arm phase II study will be conducted to investigate both compounds simultaneously and compare them with a shared control. The phase II study will be followed by a 2-arm phase III study similar to the previous programs, if warranted;
- *Program #4*: Is similar to Program #3, except that it includes a single interim analysis at which either or both ND1and ND2 can be dropped. Simulation was used to optimize when the interim analysis was scheduled and what thresholds were used for the decision to drop an arm. Simulation and evaluation of eNPV were used to select the optimum sample size for phase III. Bayesian criteria were used to determine whether to drop an arm and for the ''go''/''no go'' decision after phase II.
- *Program #5*: Is similar to Program #4, except that it includes more interim analyses and a greater degree of adaptation in phase II (e.g. adaptive reallocation of patients, possibility to drop an arm, early stop for futility or efficacy). Bayesian criteria were used to decide whether and at what sample size to conduct phase III.

The primary endpoint in both phases of development was assumed to be overall survival (OS), given the aggressive nature of pancreatic cancer and to simplify assumptions for the decision. The degree of efficacy of a new drug was expressed in terms of its hazard ratio relative to the control arm. It was assumed that the hazard ratio for each new drug ranged between 1 and 0.6 in discrete increments of 0.1. Three different settings (for each of the two new drugs) were specified: optimistic, uniform, and pessimistic with regard

to the probability of each discrete hazard ratio. The success of phase II was assessed at the applicable level of significance, as described in Marchenko et al. (2013). For programs # 2, 3, 4, and 5, if both compound tests were significant, then the compound with a smaller p-value advanced. The success in the phase III trial was defined as statistically significant comparison of the selected compound with the control at the one-sided 0.025 level.

The eNPV was calculated as a probability-weighted average of the associated costs and revenues, taking into account the probability distribution of the underlying degree of efficacy of the new drugs and the probabilities of reaching each stage of clinical development and product approval (conditional on the degree of efficacy). Detailed assumptions for cost and revenue parameters are presented in Methods section of Marchenko et al. (2013).

The following are findings concerning PoS and eNPV from the simulations, under the assumptions that, on average, both compounds are somewhat efficacious:

- Program #1 was the worst, as expected, since it includes a single compound selected based on limited clinical data, while other programs collect phase II data prior to making selection between the two compounds. Therefore, if there is no sufficient evidence to suggest that one candidate is better than the other, a sponsor is better off to develop both as done under other program strategies.

- The most striking improvement was from Program #2 to Program #3. Even though the increase in PoS was modest, the impact on eNPV was substantial. This could be a result of time/ resource savings using a shared control in a single phase II study.

- Program #3 is the second best program. Program #4 did not bring much improvement compared to Program 3. In fact it performed worse in terms of eNPV, possibly due to add-on operational costs and duration.

- Program #5 is the best choice among all. It has important adaptive features that separate it from other alternatives. Both PoS and eNPV are the highest for Program #5, justifying the use of adaptive design for phase II in the setting where there are multiple compounds to develop simultaneously. Added costs associated with complex adaptive design were well off-set by the gain in efficiency, translating into greater eNPV for this program.

- In Programs #4 and #5 the size of phase III study depends on the outcome of the phase II. A very good outcome from phase II is likely an indicator that a moderate sample size is likely to produce adequate power or PoS. On the other hand, if the phase II result is less impressive, there is a high chance a large phase III is needed to ensure enough power. This approach is essential to optimization at the program level, and it contributed to the efficiency of Program #5.

Only phase II designs were varied in this research and phase III was assumed to be a simple fixed 2-arm design trial. The assessment could be extended to varying phase III designs. The latter will introduce additional complexity and will be addressed in future research.

No clinical program strategy is optimal for all conceivable scenarios and there is no one simple metric by which decision among different strategies could be made. In practice, a sponsor should always develop a few alternatives and do detailed analysis under scenarios applicable to their particular situation.

Collaborations

A key objective of the APWS is to stimulate scientists in industry, academia and regulatory agencies to consider optimization at the development program level, rather than focusing narrowly on single trials. We welcome volunteers with diverse skills and from different organizations to join the APWS. We also welcome volunteers to collaborate on application to real drug projects and methodological work outside the formal work stream.

We are considering options to initiate methodological development work in academia. A PhD student, Vera Lisovskaja, has been working on optimizing doses in phase III. The work by the ADRS WG demonstrated that there is often considerable uncertainty regarding the best dose after phase II, even in situations where only one dose of the new drug has traditionally been tested in phase III. Because of this, Bornkamp et al. (2007) suggested that a sponsor

consider including a second active dose in phase III trials. Lisovskaja has studied how PoS depends on whether one or two active doses are included in the phase III trials, and how dose strengths could be optimized in both cases.

A new 3-year research project will be initiated in November 2013, funded by an EU research grant. The overall objective is to develop innovative methodology for clinical trials in small populations (e.g. rare diseases). The work package about Decision Analysis will be carried out in collaboration with the APWS. A PhD student will model different stakeholder perspectives (patient, payer, regulator, sponsor, etc.) and then apply and further develop Adaptive Program methodology to optimize trial programs.

APWS looks forward to the opportunity to reporting additional research findings in the future. We also look forward to learning about other ongoing work related to optimization at the development program level. To us, optimizing at the program level is the next obvious step in our search for efficient drug development strategies now that adaptations at the individual study level have reached a level of maturity. ■

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The Center for Statistics in Drug Development (CSDD) at Quintiles

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Overview

Quintiles was founded by statistician Dennis Gillings,CBE, Ph.D., and well-known statistician Gary Koch, Ph.D. was with Gillings in 1982. Drs. Gillings and Koch pioneered the use of sophisticated statistical algorithims to improve the quality of data used to determine the efficacy of various drug therapies. As Quintiles grew in the 1990s, Jonathan Smith (U.S.) and Dennis Chanter (Europe and other regions) took on fulltime consulting roles, with Smith specializing in adaptive designs, and Chanter tackling pretty much any statistical question that arose. Chanter retired in 2001 and shortly after, Jonathan Smith started what was to become the Center for Statistics in Drug Development (CSDD). Michael O'Kelly was Jonathan's first recruit in 2002. The Center grew rapidly up to five members with the focus on providing support internally to the Biostatistics Department and its clients. In 2009, King Jolly, Senior Vice President at Quintiles, was selected to lead an Innovation Unit within Quintiles and took the CSDD as one of his strategic groups. To support the changing needs of Quintiles clients, the statistical focus of the group has shifted toward the innovation of the drug development process and advanced statistical methodology. Besides clinical statisticians, Seth Berry, an experienced clinical pharmacologist, and Russell Reeve, an early development statistician with 20 years of industry experience, were added to the group. In 2011 Olga Marchenko joined Quintiles as a head of the CSDD, and enriched the group by adding talent and expertise in major areas of advanced statistics: multiplicity issues (Alex Dmitrienko), adaptive designs (Jeff Maca), data mining and biomarker discovery (Ilya Lipkovich), and Bayesian methods and techniques (Guochen Song).Today, the CSDD has eight full-time members, each with a special area of expertise, but all sharing knowledge and working together in facilitating the use of advanced statistical methods for Quintiles' customers. The team's main responsibilities include: consulting for internal Quintiles businesses and external clients, development of new methodologies and applications, providing training and support in the areas of our expertise to internal and external clients, and contributing to industry statistical thought leadership efforts.

Areas of Focus and Expertise

The main statistical areas of the CSDD expertise are adaptive designs, model based drug development, missing data methods, data mining, subgroup analysis and biomarker discovery, multiplicity issues, and Bayesian methods and techniques. While the team members are not therapeutically specialized consultants, they do have extensive experience in several therapeutic areas including oncology, Central Nervous System (CNS), diabetes, pain, and cardiovascular diseases.

Adaptive Designs

Adaptive designs are becoming increasingly popular in clinical development. An adaptive design uses predefined rules on interim data to modify some aspect of the trial design, without undermining the validity and integrity of the trial. The ability to learn from and modify ongoing studies has the possibility of

saving clinical development time and/or reducing required resources for a clinical program. However, careful consideration must be made in the design and analysis of these studies in order to ensure success.

The CSDD has been involved in the design and analysis of adaptive studies across all phases of clinical development. Each study has had unique challenges in the design of the protocol and analysis methods to be used. Trial simulation is often a key component to the development of an adaptive decision strategy, and requires custom programming for the project. Such detailed preparation is critical to ensuring the protocol will have a high likelihood of success across many scenarios. Correct statistical methods must be in place to ensure that the validity is not compromised as well as to ensure that the conclusions drawn from the study will match the desired objectives.

The CSDD has been actively involved in education and consultation/support of Quintiles' various businesses in adaptive design. The group has provided training to operation units; has assisted with complex interim analyses and modeling at interim analyses; has participated on Data Monitoring Committees (DMCs); and has played a role in the ISCs (Independent Statistical Committees).

Modeling and Simulation

Model-based drug development (MBDD), defined as the use of mathematical, pharmacological, and statistical models to improve decision making in the drug development process, has been a key area of interest of the CSDD group. MBDD uses modeling and simulation tools to identify safety and efficacy exposure-response relationships; develop population pharmacokinetic and pharmacodynamic profiles; optimize clinical trial design; form patient recruitment or retention strategies; compare risks and benefits of candidate trial analysis methodologies (including the handling of missing data); and perform competitive marketing analyses. Modeling clinical and operational processes improves decision making, optimizes resource allocation, and reduces overall development timeline.

Interest in biosimilars has grown lately, and CSDD modeling and simulation projects were successfully employed in biosimilar development to support client's needs in this area. To support trial simulation and trial design efforts, CSDD developed disease-progression models in rheumatoid arthritis and Alzheimer's. These models were then incorporated into clinical trial simulations to further explore the operating characteristics of various fixed and adaptive designs with the goal of reducing trial size and costs to our clients.

Simulations can also be used to identify the most favorable development program design, as we performed for one client recently. In evaluating the planned series of trials for an NDA filing by using trial simulation methods, the process facilitated the project team in reviewing and quantifying many assumptions on the characteristics of the drug and disease. These discussions with medical experts in the area facilitated decisions as to what assumptions were supported by prior research and which needed to be further investigated. Based on results from the simulations, we were able to explore alternative options, including different endpoints, sampling time points, and trial designs, to eventually identify an ideal drug development scenario to take forward.

Missing data

There has been a flourishing of methods for handling missing data in the nearly forty years since Rubin published "Inference and missing data" in 1976. The pharmaceutical industry has had a growing interest in how to handle missing data, even before the U.S. National Academy of Sciences (U.S. NAS) report on missing data was issued in 2010. Missing data is a fascinating area of statistics, particularly for those with an interest in statistical modeling, and two members of the CSDD, Michael O'kelly and Ilya Lipkovich, have published research on missing data. Quintiles CSDD statisticians have joined other industry experts as members of the DIA Scientific Working Group on missing data, and have contributed innovations in the form of programming code and documentation (see the DIA missing data web page at *www.missingdata.uk.org*). Because missing data affects every clinical trial, the CSDD's expertise in this area is of immediate practical use to a broad spectrum of Quintiles statisticians. Quintiles now has identified biostatisticians who are missing-data "superusers" who will attend special practical workshops

hosted by the CSDD, and who will disseminate missing data expertise to project statistical teams globally. New ways of thinking about missing data are as important as new methods, and CSDD provides training to Quintiles statisticians and clinicians, and has also been invited to provide seminars for a number of Quintiles' customers.

Both the U.S. NAS report and the new EU guidance on missing data emphasize that statistical approaches to missing data must be interpretable by clinicians. The CSDD has made this one of its guiding principles in developing new methods; the other guiding principle is quality – methods should be as simple enough to be verified by an independent statistician, and capable of straightforward review by the regulator. We have found that suitable sensitivity analyses can in fact be validated very efficiently within a study's statistical team; and the simplicity of method and transparency of approach has indeed facilitated review by the regulator.

Data Mining/ Subgroup Identification/ Biomarker Discovery

Until recently, it was only discovery statisticians who were familiar with data mining and machine learning methodologies, and used them in their daily practice whereas clinical statisticians traditionally did not focus on such data-driven ("non-prespecified") statistical analytics. Data mining was often perceived in the clinical world as data dredging. The needs of tailored therapeutics (a.k.a. personalized or precision medicine) and early safety signal detection, however, changed these perceptions and has led to a high demand for the application of more sophisticated and principled machine learning methods to clinical trial databases as well.

Within these areas, the CSDD has been focusing on exploratory subgroup analysis, which is a class of data mining methods that help identify predictive biomarkers and define subsets of subjects who are likely to experience enhanced treatment effect compared to the general population of patients. This work builds upon the SIDES method (Subgroup Identification based on Differential Effect Search) by Lipkovich *et al* (2011), which has been recently extended by Lipkovich and Dmitrienko (2013) to a more powerful SIDEScreen method. This paper will appear in the special issue of Journal of Biopharmaceutical Statistics on subgroup analysis in clinical trials later this year. The new method is capable of screening and identifying predictive biomarkers from larger sets of candidate pre-treatment covariates, which is done in the first stage of the proposed method. Further, the SIDES method is used in the second stage to identify the cut-offs associated with the biomarkers selected in the first stage.

The SIDEScreen method has been implemented in a user-friendly SIDESxl Excel add-in. The novel methodology and the software tool have been recently presented at an invited half-day course on exploratory and confirmatory subgroup analyses organized by the Office of Biostatistics at the FDA in January 2013. Ilya Lipkovich is also leading an industry working group (under the umbrella of the QSPI multiplicity working group sponsored by the Society for Clinical Trials) on evaluating current practices and methodologies of subgroup analysis in pharmaceutical industry. We also collaborate with our academia partners to develop methods and tools for identification of predictive biomarkers from large observational databases that can be confirmed in subsequent randomized clinical trials.

Multiplicity Issues

Multiplicity issues have attracted much attention across the biopharmaceutical industry, especially in the context of confirmatory Phase III clinical trials. Due to increasing emphasis on efficient drug development, Phase III clinical trials commonly employ multiple analyses to provide a comprehensive evaluation of the efficacy (and sometimes safety) of new therapies. This includes assessment of the treatment effect on several endpoints, at several dose levels, in one or more patient subpopulations, etc.

CSDD members Alex Dmitrienko and Jeff Maca have strong research and consulting records in addressing multiplicity issues arising in clinical trials. Alex Dmitrienko has been actively involved in the development of novel methods for multiplicity problems and led several collaborative research teams, (e.g., a team of over 40 multiplicity experts who contributed to a recent Chapman and Hall book edited by Dmitrienko, Tamhane and Bretz (2009)).

As part of our consulting work, we have created a standard process for building statistical solutions for multiplicity problems and custom software tools. The process we use is aimed at close collaboration with project teams to define candidate procedures for a given multiplicity problem and systematic quantitative assessment of their operating characteristics to find a solution which is aligned with the clinical objectives and maximizes statistical power.

We also specialize in the development of gatekeeping strategies for clinical trials with several sets of analyses (e.g., primary, secondary and tertiary endpoints.) Gatekeeping strategies help clinical trial sponsors enrich marketing labels by providing relevant clinical information, which is useful for prescribing physicians and patients. Gatekeeping strategies have been broadly applied to Phase III clinical trials. To give one example, Brechenmacher et al. (2011) developed powerful gatekeeping procedures that were successfully used in the lurasidone schizophrenia program (Meltzer et al., 2011). We have been working with multiple partners to help them build gatekeeping procedures to address complex clinical objectives in Phase III trials.

Additionally, CSDD statisticians have been collaborating with industry and academia experts to promote the use of novel methods to address multiplicity in clinical trials. Alex Dmitrienko has created and now chairs the QSPI multiplicity working group. This group includes representatives from more than 15 major pharmaceutical companies and offers a free online lecture series for industry statisticians (for more information, see *http://multxpert.com/wiki/QSPI_Multiplicity_Working_Group*).

Bayesian Methods and Techniques

The past twenty years witnessed rapidly growing interest in the Bayesian approaches to statistical questions, and the drug development field is no exception. One advantage of the Bayesian approach is its ability to incorporate prior information, and in drug development, data from previous studies can often provide such useful information. At CSDD, we utilize existing methodologies, as well as develop new methodologies using Bayesian methods and techniques to identify treatment effects on subpopulation, to monitor toxicity and/or control enrollment rate, to predict the probability of success for final analysis or the next phase. We cooperate with other industry thought leaders pushing forward the use of such methodologies.

Specific Therapeutic Area Designs

While the CSDD does not specialize in particular therapeutic areas, the group has an extensive experience in several therapeutic areas and has been compiling libraries of statistical designs and methods related to specific therapeutic areas.

Oncology

Oncology drug development has been a tremendous challenge. Cancer clinical programs are typically lengthy and costly, yet the failure rate is high. Heterogeneity of disease is a widely acknowledged problem in cancer, and very difficult to address in the course of a clinical trial. CSDD members have extensive experience in the oncology therapeutic area. Adaptive designs and biomarker driven designs are the most used designs by the CSDD in the oncology drug development. Last year alone, the CSDD provided support on a large oncology clinical program and consulting services on 12 studies addressing in addition to statistical design challenges the problems with delayed toxicity, lengthy outcomes, and population recruitment. The CSDD members have been collaborated with the faculty at the University of North Carolina (UNC) at Chapel Hill to create a comprehensive library on oncology designs. A review paper entitled “Advances in Statistical Approaches Oncology Drug Development” written together with the faculty at Biostatistics Department of the UNC at Chapel Hill and Oncology Biostatistics & Bioinformatics, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins will be published in the end of this year in the special issue of Therapeutic Innovation and Regulatory Science. The CSDD has been actively involved in education and consultation/support of Quintiles’ various businesses in oncology designs.

CNS

CNS trials provoke unique challenges. The CSDD's CNS Initiative aims to survey existing designs for CNS so as to identify best practices, assessing in a variety of scenarios the merit of features such as fixed versus adaptive designs; spacing and frequency of visits; and efficacy measures and endpoints. In Alzheimer's disease, for example, we have developed a disease-progression model based on publicly available data, utilizing numerous endpoints and for three different states of impairment. This Alzheimer's disease progression model has been used to assess the merits of adaptive vs. fixed designs for a Phase III trial, and allowed us to optimize the timing of the endpoint. Other CNS indications that are being explored include Parkinson's and pain. Much of this work is done in conjunction with other functional groups enabling Quintiles to be in a position to help our clients design better and more effective trials in CNS.

Diabetes

The CSDD has developed strong expertise in the design and conduct of cardiovascular outcome (CV) trials for diabetes and related products. These trials have a complex set of objectives, including a pre-marketing objective to support a regulatory submission and a post-marketing objective to assess the CV risk profile. CSDD has developed a library of traditional designs as well as adaptive designs with several interim looks that can be applied to facilitate the assessment of CV risks for new diabetes treatments. The adaptive designs support an option to terminate the trial if the post-marketing objective is achieved early and adjust the number of CV events at an interim analysis to improve the probability of success. Another important option is to use the event data at an interim analysis to adaptively switch from the standard non-inferiority analysis to a superiority analysis, which indicates that the treatment has cardioprotective properties.

Collaboration

To support our efforts to offer our clients the best statistical advice, CSDD has formed a Scientific Advisory Board (SAB) composed of key thought leaders in statistics and pharmacokinetics. The SAB was created by the CSDD in March 2012 as a forum for the industry's foremost scholars to share input and guidance on applications critical for drug development decisions. Recent topics at SAB meetings have included adaptive design practices; Bayesian methodologies to support drug development; missing data; and multiple comparison procedures for Phase III studies. SAB members include Gary Koch of UNC, Carl Peck (formerly of the U.S. Food and Drug Administration), Rod Little (University of Michigan, Ann Arbor), Anastasio Tsiatis (North Carolina State University), Nigel Stallard (Warwick University), France Mentre (Université Paris Diderot Service de Biostatistiques), and Giovanni Parvini (Harvard University).

Our research team has had the opportunity to share research with the FDA. As was mentioned above, two CSDD statisticians have been invited to contribute to an FDA lecture series by teaching a short course on subgroup analysis in clinical trials. Alex Dmitrienko has collaborated with Dr. Mohammad Huque (FDA) and Ralph B. D'Agostino (Boston University) on a paper which provides a comprehensive review of key multiplicity considerations in clinical drug development. This paper was published as a featured article in *Statistics in Medicine* (Dmitrienko et al., 2013). In addition, CSDD statisticians have been working with European regulators on key statistical issues in clinical trials. Dmitrienko and Marchenko have received invitations to contribute to expert workshops on subgroup analysis and multiplicity organized by the European Medicines Agency in 2011 and 2012.

CSDD personnel are active members of many industry working groups including the DIA Adaptive Design Scientific Working Group, the International Society for CNS Clinical Trials and Methodology Adaptive Design Working Group, working groups under the Society of Clinical Trials, and PSI Modeling and Simulation Special Interest Group. With CSDD's active participation in the working groups, internal research activities and collaborations with other experts in our industry, CSDD is at the cutting edge of novel designs and requirements across different phases of drug development.

Experience interacting with the CSDD

José Pinheiro, Senior Director, Janssen R&D

We at Janssen have had multiple opportunities of working in collaboration with members of the CSDD, and they have all been very positive. Those interactions have focused on two main areas: training and specialized consulting. Alex Dmitrienko presented a highly successful in-house short course on Key Multiplicity Issues in Clinical Trials which received high praise from the large number of people who attended it. Members of the CSDD have also been actively engaged in providing expert consultation to internal clinical teams, most noticeably in the areas of multiple comparisons (especially in complex gatekeeping problems) and adaptive designs (e.g., unblinded sample size re-estimation involving multiple hypotheses of interest) and across different disease areas, such as diabetes and pain. The expert advice provided by the CSDD always has been of high technical quality, timely and impactful. In my view, the CSDD group uniquely positions Quintiles in the CRO space, adding to its well-recognized operational capabilities, the presence of a high quality, dedicated team of renowned methodological experts, covering a wide range of essential methodological expertise and actively involved in external scientific activities. ■

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Registration desk at the Joint Statistical Meetings in Montreal

Summary of the ASA Biopharmaceutical Section Executive Committee Meeting

5 August 2013 at ENAR, Montréal, Canada

Dionne Price

Amit Bhattacharyya, Biopharmaceutical (BIOP) Section Chair, welcomed committee members and called the meeting to order. Twenty-five committee members were present, and three attended the meeting via phone.

Steve Gulyas, Past Chair, announced the newly elected officers for 2014. The officers will be:

Chair-Elect:	Dionne Price
Program Chair-Elect:	Gary Aras
Treasurer:	Heather Thomas
Council of Sections:	Alan Hartford

Steve highlighted the BIOP Section's activities commemorating the 2013 International Year of Statistics (IYS). Specifically, the BIOP Section has offered webinars at times convenient for international participants and plans to expand the employee and university lists on *www.biostatpharma.com* to include more international components. In addition, Steve Wilson and Janelle Charles are working on an IYS article, and the ASA BIOP Section FDA-Industry Statistics Workshop will have an IYS theme. The ASA will continue the momentum generated for IYS to the 2014 celebration of the 175th Anniversary of the ASA.

Matilde Sanchez, Chair-Elect, announced several appointments. The 2013 ASA BIOP Section FDA-Industry Statistics Workshop co-chairs will be Cristiana Mayer (Janssen Research and Development, Johnson & Johnson) and Shiowjen Lee (FDA). Yushen Tu will be the webmaster, and Paul Gallo has been appointed as an associate editor of the *Biopharm Report*. Since the current Secretary will assume the position of Chair-Elect in 2014, Ed Luo has been appointed to the position of Secretary for the remainder of Dionne's term.

Heather Thomas, Treasurer, notified meeting participants of the July 31, 2013 balance of $357,230.96. Revenue was generated from membership dues and webinar registration. Expenses included awards, meeting support, and contributions to other organizations. Other expenses are expected through the end of the year including the ASA BIOP Section FDA-Industry Statistics Workshop, the *www.biopstatpharma.com* site, and meeting expenses.

Olga Marchenko, Membership Committee Chair, stated that an overall goal of the committee is to retain and add to the current BIOP Section membership. She noted that many e-mail addresses of the BIOP Section members are incorrect. There will be follow-up with ASA regarding incorrect e-mail and mailing addresses. In an effort to increase membership, the Committee of Applied Statisticians (CAS) has developed a mentoring program that is being piloted this year. The BIOP Section is collaborating with CAS. The BIOP Section slide deck has been shared with various chapters.

Stephine Keeton and **Christie Clark**, Council of Sections Representatives, noted that all sections are encouraged to celebrate and energize the membership for the 175th Anniversary of the ASA in 2014. In addition, the Statistical Interest Group on Medical Devices and Diagnostics has applied to become a section of ASA. Based on the discussion and close vote among elected EC members, the Council of Sections representatives will vote narrowly in favor of a new section.

Estelle Russek-Cohen, Program Chair, reported that the BIOP Section organized 5 invited sessions, 26 topic-contributed sessions, 33 contributed sessions, and 8 roundtables at JSM 2013. The BIOP Section also participated in the pilot for the speed poster sessions.

Ivan Chan, Program Chair-Elect, reported that the BIOP Section sponsored eight roundtables covering a range of topics at JSM 2013. Planning is underway for 2014 JSM.

John Johnson, Contributed Paper Chair, announced the winners of the Best Contributed Paper Award for JSM 2012. The winners were recognized at the August 6th Business Meeting that occurred at JSM 2013. The winners were as follows:

1st place: **Scott Emerson**
Active Control Trials with Adaptive Modification of Margin to Address Nonconstancy

2nd place: **Kurt Viele/ Jason Conner**
A Case Study of a Bayesian Adaptive Cardiology Device Trial Leading to Approval

3rd place: **Steven Julious**
The ABC Assumptions of Setting a Noninferior ity Margin: When the Margin Assumptions Can Be Violated

Honorable Mention: **Ilya Lipkovich**
Strategies for Identifying Predictive Biomarkers in Clinical Trials Using Variable Importance

Honorable Mention: **Carl Dicasoli**
Interim Analysis of Constancy for Noninferiority Testing in Active Controlled Clinical Trials

Jerry Wang, Contributed Poster Chair, announced the winners of the Best Contributed Poster Award. The winners were recognized at the August 6th Business Meeting that occurred at JSM 2013. Awardees included:

1st place: Li Wang and Weihua Tang
Meta Analysis for All-cause Death for Apixaban vs. Placebo Or Control in SPAF Trials

2nd place: Jianing Di, Xin Zhao, Daniel Wang, Ming Lum and Michael Krams
Assessing the Cumulative Exposure Response in Alzheimer Disease Studies

3rd place: Kelly Zou, Ching-Ray Yu, Ye Tan, and Martin Carlsson
Comparative Effectiveness Research Using Meta-Analysis to Evaluate and Summarize Diagnostic Accuracy

Richard McNally, Student Paper Chair, announced the winners of the Student Paper Award. The winners were recognized at the August 6th Business Meeting that occurred at JSM 2013. Awardees included:

1st place: **Jing Zhou**
Information-Based Sample Size Re-estimation in Group Sequential Design for Longitudinal Trials

2nd place: **Chen Hu**
A Frailty-based Progressive Multistate Model for Progression and Death in Cancer Studies

Bruce Binkowitz and **Lilly Yue,** Workshop Co-Chairs, reiterated that the 2013 ASA Biopharmaceutical Section FDA-Industry Statistics Workshop will occur September 16 – 18 at the Marriott Wardman Park in Washington, DC. The theme of the workshop will be aligned with the International Year of Statistics. The first day of the program will boast six short courses. The second day will comprise two plenary sessions. The first session will feature Donald Rubin and Ron Wasserstein as speakers. Highlights of the workshop include a networking mixer, two town halls and two sessions associated with the *Journal of Biopharmaceutical Statistics.*

Venkat Sethuraman, Publications Officer, provided an update of all communication channels. To date, the BIOP Section has contributed six articles to *Amstat News* for this year. Two editions of the BIOP Report have been published this year, and the team is working on the third and final publication. The podcast team has been actively increasing the number of podcasts and has interviewed Stephen Senn, Amit Bhattacharyya, and Stan Altan. More podcasts are planned and will be advertised and archived on the BIOP website. Four webinars have occurred to date, and four additional webinars are planned for the remainder of the year.

Following a number of additional committee reports, **Amit** thanked the EC for the thoughtful discussion and adjourned the meeting. ■

Biopharmaceutical Section Poster Competition at 2014 Joint Statistical Meeting

If you plan to attend the 2014 JSM and plan to present a poster, you may consider participating in the Poster Competition sponsored by the ASA Biopharmaceutical Section. You do not have to be a member of Biopharmaceutical 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 place, respectively.

The entry criteria for the Poster Awards are:

- 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 Students Paper Awards.

The process is as follows:

1. Submit an abstract through the Biopharmaceutical Section by February 3, 2014.
2. Submit your poster to Jerry Wang, Chair for the Poster Awards, through email (*junyuan.wang@bms.com*) by May 9, 2014.

Finally, congratulations to 2013 JSM poster award winners:

First place

Meta Analysis for All-cause Death for Apixaban vs. Placebo Or Control in SPAF Trials
Li Wang and Weihua Tang, Bristol-Myers Squibb Company

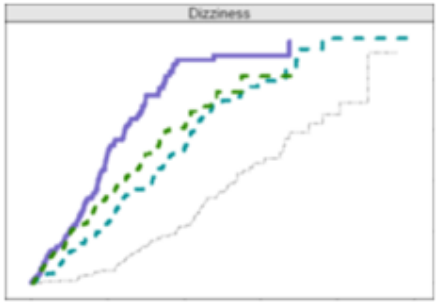
Second place

Assessing the Cumulative Exposure Response in Alzheimer Disease Studies
Jianing Di, Xin Zhao, Daniel Wang, Ming Lu, and Michael Krams, Janssen Research & Development, LLC

Third Place

Comparative Effectiveness Research Using Meta-Analysis to Evaluate and Summarize Diagnostic Accuracy
Kelly H. Zou, Ching-Ray Yu, Ye Tan, and Martin O. Carlsson, Pfizer Inc. ■

Visualize and Understand Your Safety Data: A Library of Graphical Approaches



Do you want to effectively convey your clinical development program's safety information in a visual and intuitive manner? Then visit *https://www.ctspedia.org/StatGraphHome* to learn about powerful graphical approaches for visualizing laboratory and liver toxicity, general adverse events, and ECG and vital signs. You can also learn more there about best practices for graph construction and best practices that maximize your ability to effectively convey the data's key messages.

The graphical approaches featured on the website are a byproduct of a 3 year venture of a collaborative working group. The members comprise experts from FDA regulators, the pharmaceutical industry, and academia. To represent the broad spectrum of safety information collected in a clinical trial, three key topic areas were considered.

- The ECG/Vital group focused on graphical approaches related to the assessment of ECG data and vital signs.
- The Labs/Liver group was responsible for developing graphical visualizations to assess laboratory data with a specific focus on liver function.
- The General Adverse Event group identified and developed graphical approaches to view general adverse event information, such as data coded using the MedDRA (Medical Dictionary for Regulatory Activities) dictionary.

Each of the groups identified or developed graphical approaches that addressed key clinical questions in the domain of interest. These graphical approaches were reviewed by a fourth group that was charged with applying good graphical principles and identifying best practices for graph construction. Reproducible working examples of the graphics are included. The reader is encouraged to use these vetted graphs in their own analyses, thereby creating standard graphs for identical questions across clinical programs.

The examples include a variety of graphical methods, ranging from complex (multi-panel dot plots) to simple displays (scatterplots). Users are encouraged to add their perspectives and contribute new graphical visualizations on this wiki.

Resources are also provided to aid the reader in selecting the most appropriate graph type for a given situation. The inclusion of worked examples with sample data and programming code substantially reduces the resources required to implement graphical approaches into your clinical development program.

The *https://www.ctspedia.org/StatGraphHome* site can help you effectively and efficiently convey your clinical development program's safety information in a visual and intuitive manner. Check it out! ■

Statistical Perspectives and Challenges in the Evaluation of Benefit—Risk for the Development of New Drugs

When

November 8, 2013 • 12 p.m.— 4:45 p.m.

Where

Bayer HealthCare, Whippany NJ

The New Jersey Chapter of the American Statistical Association (ASA) and Bayer HealthCare are pleased to invite you to participate in this workshop, where you will hear industry experiences, perspectives and challenges in the evaluation of benefit-risk for the development of new drugs.

There will also be an opportunity to network with industry colleagues and celebrate the International Year of Statistics.

Speakers /Panelists:

- **Christy Chuang-Stein**
  Vice President, Statistics. Pfizer, Inc.
- **Christoph Dierig**
  Head of Global Integrated Analysis and Life Cycle Management Statistics, Bayer HealthCare
- **Bennett Levitan**
  Director, Epidemiology. Janssen Research and Development (J&J)
- **Gary Koch**
  Director, Biometric Consulting Lab. Biostatistics Professor, University of North Carolina at Chapel Hill

The workshop will begin with lunch at 12 p.m. and conclude at 4:45 p.m.. If you plan to attend, please RSVP to Nancy O'Donnell (email: *nancy.odonnell@bayer.com*) by October 31. ■

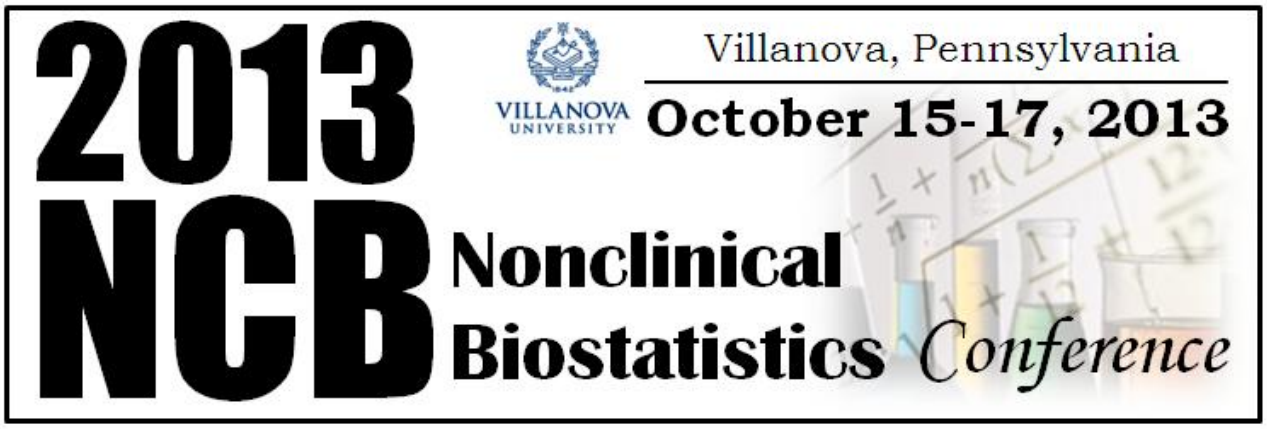
Calling All Volunteers!

Do you 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: Jose Alvir, email *Jose.Alvir@pfizer.com*; Yongming Qu, email *qu_yongming@lilly.com*; or Ugochi Emeribe, email *ugochi.emeribe@astrazeneca.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.



2013 Nonclinical Biostatistics Conference
October 15 – 17, 2013, Villanova, Pa

Nonclinical Statistics - improving pharmaceutical discovery, development and manufacturing

The third U.S. conference dedicated entirely to nonclinical biostatistics topics will take place October 15 - 17, 2013, at the Connelly Center on the campus of Villanova University. Members of the nonclinical/preclinical Statistics community are invited to submit proposals for presentations and posters discussing significant scientific and regulatory issues. Attendees will have ample opportunity to network, share experiences and discuss current scientific issues with colleagues and leaders in the field.

The conference website: **www.ncb2013.org** is open for abstract/poster submissions and registration.

PROGRAM

Keynote Speaker: ***Douglas Throckmorton MD, Deputy Director, CDER, FDA***
Featured Speaker: Marie Davidian PhD (ASA President), North Carolina State University

- Choice of half-day short course:
  - Mixture Designs (Ron Snee)
  - Bayesian Applications (Bruno Boulanger)
- 21 Invited or contributed presentations covering:
  - Discovery/Biomarkers/Diagnostics
  - Safety/Pharmacology/ pK
  - CM&C/Manufacturing
- Tuesday evening ASA Presidential Address and Reception
- Wednesday evening Wine and Cheese Mixer, Poster Presentations
- Roundtable discussions