

Biopharmaceutical Section



American Statistical Association

Biopharmaceutical Report

Volume 20, No. 2

Spring 2013

Chair: *Amit Bhattacharyya*

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

Note from the Editors

Welcome to our second issue of *Biopharmaceutical Report* in 2013. In the past few years, we published 2 or 3 issues each year. Our goal this year is to publish one for each quarter.

First, **Amit Bhattacharyya** wrote Chair's column which provides an overview of activities during the half of the year and in the next few months for Biopharmaceutical Section.

There are two feature articles on the role of statisticians in the design and analysis of observational studies and payer evidence data. The first article by **Stefan Franzén** from AstraZeneca provides an overview of real world evidence (RWE) studies, while the second article by **Claire Watkins** from AstraZeneca provides an overview of the development of payer evidence and Health Technology Assessment (HTA) framework.

The Biopharmaceutical Section Executive Meeting was held at Orlando, FL in March during the 2013 ENAR meeting. The summary of the meeting is included in this issue. This issue also highlights the key activities related to Biopharmaceutical Section at the 2013 Joint Statistical Meeting. ■

Contents

Letter from the Chair 2

Featured Articles

Real World Evidence, an Overview for Statisticians

Stefan Franzén 4

Payer Evidence and Health Technology Assessment – An Overview for Statisticians

Claire Watkins 9

Biopharmaceutical Section News

Summary of the ASA Biopharmaceutical Section Executive Committee Meeting 15

Highlights for Activities Associated with Biopharmaceutical Section at the 2013 Joint Statistical Meeting 16

Help for Potential ASA Fellows 18

Registration Open for Statistics Workshop 19

2013 Nonclinical Biostatistics Conference 20

Let's Hear from You! 21

Letter from the Chair

Dear Biopharm colleagues,

I hope you are ready for the summer. The spring was over too quickly for me. We experienced cold weather only a few weeks back. I am writing this around the half year mark, on the auspicious summer solstice day of 2013. It is a good time to share with you some of the activities of our section officers in the first 6 months in 2013.

Summer is the popular time for conference. So let me start with the two most important conferences round the corner.

I look forward to seeing many of you at the JSM in the beautiful city of Montréal in the Quebec province in Canada in just over a month's time. With the great effort from our Program Chair Estelle Russek-Cohen, Biopharm has a significant presence this year too. She had worked relentlessly over the last one year to help organize short courses, invited sessions, the topic contributed plus the contributed sessions for our section members. Estella – I am sure you are waiting for this to be over! The Program Chair-Elect, Ivan Chan has already started thinking about next years' program too. Please catch him early if you want to submit an invited or topic contributed session or the next year's JSM. We look forward to seeing you at the Biopharm section Mixer and the Business meeting on Tuesday the 6th evening. The mixer provides a great opportunity to meet with members and colleagues across the Biopharmaceutical area and learn about the activities first hand from the executive committee, and attend the award ceremony. Did I mention the food and drink ... Now you know that you have to be there ...

Biopharm section's signature annual conference, the ASA Biopharm FDA-Industry Conference is coming up in mid-September. Thanks to the co-chairs Bruce Binkowitz and Lilly Yue along with the conference steering committee and ASA. The program is being planned meticulously to make it as successful as the previous years. The short courses are scheduled on the first day, followed by two days of close to 50 applied sessions on the science and statistics associated with the development of new medical products (pharmaceuticals, biologics and devices). The workshop has been very popular since it is designed to bring statisticians from industry, academia, and the FDA for an open dialogue on issues of mutual interest. The conference added a mixer this year in response to the last year's feedback from the attendees. Please do register early because the 2012 conference registration was full before the closing date of the registration.

The new Communication team, under the leadership of the Publication Officer Venkat Sethuraman, is debating about the optimal and consistent ways to reach out to the membership to inform about our profession on a regular basis. Until we find the "best practice", I have requested the section committee chairs to use the section community egroup on the internet to share relevant information to you as needed.

By the end of the year, we are expecting to have an improved, redesigned Biopharm website. The new site will be transitioned into ASA microsites to make things more standardized across ASA and user-friendly so that we all get the required information in the website easily. Special note of thanks for this is due for Ed Luo and Yue Shentu. Thanks to the effort and enthusiasm from Rima Izem and Richard Zink, you will notice a couple of new podcasts in our website very soon. The *Biopharm Report* editors, Yongming Qu, Ugochi Emeribe and Jose Alvir are aiming to publish the Biopharm report on a quarterly basis—which definitely is more than what the section could achieve recently. The webinar co-chairs Shailaja Suryawanshi and Satrajit Roychoudhury had done an excellent job in finalizing 9 webinars for this year—4 of them had already been presented and others planned—probably a record number compared to the recent past. These webinars are very well attended and provide a great value to the Biopharm members, so please try to attend and get your colleagues to attend them with you too. I appreciate the excellent planning and execution in this effort from Shailaja and Satrajit.

Through all these activities above, our aim is to communicate and provide service of value to the members and to get them engaged through the different tools and opportunities this section can organize throughout the year. In today's world of electronic communications, we have to find ways to have the members' concerns and suggestions reach the section officers so the section officers, can address the professional needs for the membership. You will be glad to know that the membership committee, led by Olga Marchenko, has diligently laid out a long list of actions

for the section to act on. I can assure you that a few of those actions have already been completed, and a few others are being discussed and planned for future. Outside of the survey, the executive committee is always looking for feedback from the membership - please don't hesitate to send them.

The section is proud to be a part of the 2013 International Year of Statistics (IYS) celebration. We have partnered with international conferences and have also dedicated the ASA Biopharm FDA-Industry conference to this theme appropriately. ASA and many organizations in the world have signed up for celebrating this year with many activities. If you haven't checked out the IYS website for the latest details on the activities worldwide, you will be amazed to see them in <http://www.statistics2013.org>.

Another important area that the section has been strategically positioning itself is in encouragement of students' participation in the professional meetings and raise awareness about the topics relevant to the biopharmaceutical research area. This has been attempted through sponsoring student activities at relevant conferences of biopharmaceutical topics. This effort will also help the section gain visibility among the student communities in the US. I am hoping that this will also enable us to build future collaborations with other similar professional organizations and influence the programs to benefit our membership. Thank the funding committee to help the section in this regard.

As members of the section, it is our duty and privilege to vote and elect our section representatives for the various positions. I thank each member who cast their votes for the election in 2013. On behalf of the section, I take this opportunity to congratulate the following elected members who will start their new roles on January 1, 2014: **Dionne Price** (Chair-Elect), **Gary Aras** (Program Chair-Elect), **Heather Thomas** (Treasurer, 2014-2016), and **Alan Hartford** (Council of Sections Representative, 2014-2016). Also, the proposed revisions in the Biopharm section Charter has been approved by the membership in this election—you will see the revised charter updated at the ASA website under the Biopharm section.

In case you haven't noticed yet, the ASA Fellows for 2013 have also been announced within the last few days. My heartiest special congratulations to all the seven Biopharmaceutical section members who appear on that coveted list: **Keaven Anderson**, **Scott Berry**, **Ralph D'Agostino**, **Elizabeth DeLong**, **Vladimir Dragalin**, **Yili Pritchett**, and **Matilde Sanchez** (who is also the section Chair-Elect this year).

To sum it up all, I feel so privileged to work with the excellent team of section officers and other committee members who have been volunteering precious times for the section duties. I would like to thank each one of these enthusiastic volunteers without whom we could not progress so much in this year already. I look forward to continue engaging with these committees in the second half of the year, and bring some of the initiatives into completion, and probably opening a few more avenues and initiatives for the benefit of our members that will carry on to the following years. Will tell you more next time the editors asked me to share in the Fall...

Finally, I would like to call for new volunteers so that section will benefit from new ideas and enthusiasm. Those interested in volunteering into section activities, please send an email to volunteer.asabiopharm@gmail.com.

Hoping to see many of you at the JSM.

Enjoy the summer.

With best regards,

Amit Bhattacharyya

Chair, Biopharmaceutical Section (2013)

Email: Amit.Bhattacharyya@gsk.com

Real World Evidence, an Overview for Statisticians

Stefan Franzén, AstraZeneca

Introduction

The growing availability of electronic health data systems collecting clinical data from large relatively unselected patient populations has led to an increased possibility and interest to study the safety, effectiveness and cost of medical procedures and pharmaceutical treatment as they are used in clinical practice. The data is observational in nature and often contains very large numbers of patients which provides a growing and exciting field for statisticians. This article gives a brief introduction to some aspects of Real World Evidence (RWE) where statisticians can play a crucial role.

What is Real World Evidence?

By RWE we mean evidence based on observational data, taking information outside of controlled trials to create insights on diseases, products, and patient populations. For statisticians this generally means observational studies where exposure to a particular treatment is not determined through a randomization. An RWE study may be based on pre existing registry data, often created for a purpose that is different from our purpose or a custom made data base prospectively set up and collected for our specific purpose.

As RWE reflects the healthcare experience of real world patients rather than a strict clinical trial protocol it can be used to study important characteristics of patients and the healthcare system such as treatment patterns, unmet medical needs and the economic burden related to a disease. In addition RWE allows for the study of effectiveness, defined as the consequence of a treatment being applied in clinical practice in contrast to efficacy which is investigated by most Randomized Controlled Trials (RCT). A typical RCT has high internal validity due to the use of randomization and has inclusion and exclusion criteria which are designed to reduce the variability in the observed outcome and to provide an opportunity to observe a relevant clinical outcome by excluding patients that are relatively healthy and to facilitate the interpretation of safety by excluding patients with significant comorbidities. An RWE study often has broad inclusion criteria and few exclusion criteria allowing the study of a relatively unselected population of patients leading to high external validity.

In contrast to what we see in a randomized clinical trial, patients in an observational study are exposed to treatments according to a decision by the patients and the physician(s) involved. Due to the absence of randomization, the allocation of patients to treatments may be influenced by variables that also influence the outcome. In statistical terms such variables are called confounders.

Confounding results in treatment groups are not comparable and direct unadjusted comparison becomes biased and thus invalid. Confounding that is due to observed baseline covariates can be adjusted for by either including the relevant confounders and the treatment in a multiple regression model of the relevant outcome, by stratification or by ensuring that the treatment groups are balanced with respect to these covariates, by matching. There is no way to reliably adjust for confounding due to unobserved variables, nor is there any way to reliably detect their presence. However instrumental variables are often put forward as a way to provide this adjustment. As consequence the outcome of an observational study must be interpreted with caution.

The increased availability of RWE data and the growing demand for evidence on the real world's usage, effectiveness and cost of healthcare options, combined with absence of randomization and the consequential need for advanced statistical methodology, provides a challenging and growing field of work for statisticians.

Data Sources

There are a multitude of different data sources that are used to generate RWE and as a statistician it is of critical importance to understand the process that generates the data at hand as it can have a profound impact on the statistical analysis and interpretation of the study results. Some of the common data sources are:

- Insurance claims data
- Medical health records
- Research registries
- National or regional disease registries
- Randomized clinical studies and pragmatic studies

Insurance claim data are administrative data generated by a medical insurance provider, which may be a commercial insurance company as in the US or a national health insurance plan as in many European countries. Claims data often contains information related to diagnoses, medical procedures and dispensed pharmaceutical drugs including information reflecting the associated cost and are well suited to the study of health related costs from a provider perspective. Claims data generally don't include information on clinical laboratory tests or other clinically relevant information such as BMI or smoking status. When using claims data it is important to keep in mind that it reflects the way the insurance plan is constructed which for example can lead to diagnoses not covered by the insurance being under represented in the data. In some instances claims data may also provide limited possibilities of following patients for longer periods of time depending on how often people change their health insurance. Relevant endpoints are sometimes not captured directly and can only be followed using surrogate endpoints, e.g. Asthma severity where the definition commonly used in clinical trials often can't be operationalized directly using claims data. It is important to understand the mechanism that includes/excludes patients from the data set. In countries such as the US where health insurance for the working population is often provided as a part of the benefit package related to employment, additional care is needed when studying progressive diseases that potentially lead to patients leaving their employment and therefore introducing informative missing data.

In contrast to claims data medical, health records are potentially rich data sources which capture a high volume of clinical characteristics, although the cost of care is rarely captured directly. Medical records are not always available in electronic format and there is still a need for increased standardization and interoperability to allow data from several health care providers to be combined. When not in electronic format a substantial effort is needed to review the medical records and electronically capture the relevant data. Still it is important to keep in mind that the medical records data are captured to allow a treating physician to follow a particular patient and not to allow a systematic study of a selected cohort. For example progression of a cancer type is often not captured directly and needs to be derived from the data as they are observed.

Research registries are set up by research groups often for a particular purpose and can provide an excellent opportunity to follow real world patients. However, the specific nature of the registry inclusion criteria as well as the data captured, can limit the usefulness of the data for other research questions.

National or regional disease registries exist for some diseases in some parts of the world and are often created to allow the monitoring of incidence, and sometimes also prevalence and characteristics of a particular disease. They often contain limited clinical data in order to facilitate data collection for large numbers of patients. A key feature of a regional or national disease registry is that they often include all patients from a given population which allows for estimation of prevalence as well as incidence.

A critical feature of an observational data source is the ability to reliably link to other registries to allow systematic follow up of patients over long periods of time. This requires a unique patient identifier that is shared between several registries. Some registries provide approximate patient identifiers by for example combining non-unique data such as name and address. However, this can't provide the same level of quality as truly unique patient identifiers, such as the person numbers used in Scandinavian countries—these create the unique possibility of linking several registries to create a rich data source with almost 100% coverage in terms of follow-up.

RWE Designs

The most reliable and robust design is the cohort design where a well defined set of patients are identified at a certain point in time, the index, and followed forward in time with respect to an outcome. Outcomes can be described and compared by any relevant grouping, based on index or pre-index data, as long as the relevant data is collected. This may become inefficient if the outcome of interest is rare as this calls for a large number of patients

to be followed, and in cases where additional data beyond what is captured is needed, it may become unfeasible to implement.

One alternative design is the case control design where patients are identified according to their outcome. Usually all patients, “cases”, with an observed event and only a selected set of patients, “controls”, without the event are subject to further data capture. It is useful to think of a case control design as a sample from an underlying cohort. Case control designs are analyzed according to the way controls are sampled but we will not go into further details here. For further reading including other designs please see standard textbooks on epidemiology, e.g. Rothman & Greenland(year).

Comparative Effectiveness and Clinical Equipoise

In order to be able to design an observational study that investigates and compares the consequences of different treatment options as they are used in clinical practice there needs to be a genuine clinical equipoise, at the time of entry into the study, concerning the involved treatments. Clinical equipoise is defined (Freedman 1987) as existence of “genuine uncertainty within the medical expert community—not necessarily on the part of the individual investigator—about the preferred treatment” and creates the overlap in patients characteristics between the treatment groups that is needed to even have a chance to separate the causal effect of the treatment from the confounding effect of covariates correlated with the outcome. Even under the clinical equipoise any observational study is susceptible to bias from both unobserved and observed confounders where statistical methodology can only reasonably attempt to adjust for the latter.

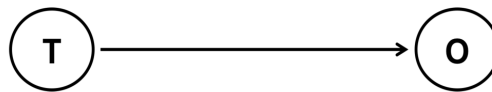


Figure 1. The causal model for a randomized clinical trial where an outcome O can be attributed to a treatment T. Here, there is on average no other systematic difference between patients receiving the different treatments, other than their treatment assignments.

In the presence of strong treatment preferences, observational studies may not be appropriate to evaluate the causal effect of the treatment.

Counterfactuals and Causal Inference

The ultimate goal of comparative effectiveness is to draw conclusions regarding the question: Does X really cause Y? In a randomized experiment comparing two treatments we know that on average there is no other difference between the two treatment groups than the treatment itself. Therefore any observed difference between the two groups can be attributed to the difference in treatment. We say that the change in treatment is the cause of a change in outcome, as illustrated in Figure 1. In an observational study patients who receive different treatments are inherently not comparable as treatment is given for reasons related to whether the individual patients might experience a benefit. We can no longer directly attribute observed differences in outcome to the difference in treatment alone as there may be a third factor influencing both exposure to treatment and the outcome as illustrated in Figure 2. The theory of causal inference and counterfactuals has been built up to facilitate an understanding of the circumstances under which causal inference is possible and how it can be achieved.

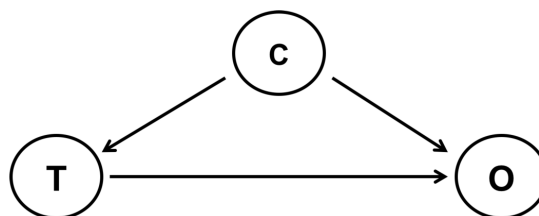


Figure 2. A simple causal model for RWE where the effect of the treatment is confounded by a third factor that is associated with both the choice of treatment and the outcome.

The framework of counterfactuals is based on each individual i having two potential outcomes, $Y_i(0)$ if the individual receives the control treatment and $Y_i(1)$ under the active treatment. Both $Y_i(0)$ and $Y_i(1)$ are random variables with some density function and can be thought of as inherent characteristics specific to each individual. The aim of causal inference is to draw conclusions by comparing the density functions of $Y_i(1)$ and $Y_i(0)$. In a particular study only one of the potential outcomes is observed for each individual and the other potential outcome becomes a counterfactual. This construction may at first seem overly complicated and abstract but allows for a precise formulation of the fundamental problem of causal inference (Holland 1986). An illustration of the concept can be found by thinking of a specific patient who is faced with a treatment option of drug A versus drug B. For the individual patient the question of interest is what will be the likely outcome under treatment with drug A compared to the likely outcome under treatment with drug B. Thus the treatment decision is made based on the probability distributions of the two potential outcomes.

Comparative, for Whom?

From observational data we can estimate the effect of being treated from two different perspectives, the Average Treatment effect for the Treated (ATT) and the Average Treatment effect for Everyone (ATE). The two approaches are aimed at answering slightly different questions where the ATT is about what would happen if the patients had received treatment A instead of giving treatment B. The ATE is comparing what would happen if everyone received treatment A versus if everyone received treatment B. In terms of the counterfactual framework the ATE is defined (Imbens 2004) as the average expected causal treatment effect across all patients given patient characteristics. Depending on the analytical technique, either ATT or ATE is estimated. Careful thought needs to go into the choice of analytical technique and how it is applied, to ensure that the treatment effect of interest is actually the one estimated.

Adjusting for Confounders

As a result of the absence of randomisation, the allocation of patients to treatments may be confounded with the outcome, with the end result that the treatment groups are not comparable, and thus direct comparison becomes invalid. Confounding that is due to observed baseline covariates can be adjusted for in a variety of ways and we will give a very brief overview of the most frequently used methods.

Regression Models

Regression models (ANCOVA) including a treatment effect as well as the effect of one or several potential confounders as independent variables can, when correctly specified and under the ignorable treatment assignment assumption, estimate the ATE in terms of a difference (in some measure) between the treatment groups, that remains unexplained by the included covariates. Under the assumption that the model is correctly specified and that there are no unobserved confounders, it can be used to produce an unbiased estimate of the treatment difference conditional on the covariates. If the deviance from the model assumptions is sufficiently large the use of ANCOVA can lead to increased rather than reduced bias (Rubin 1973). The degree of model dependence is influenced by the distribution of the baseline variables in the treatment groups and is at its minimum when the distributions overlap completely. When the distribution of the covariates differ substantially the outcome of the regression model relies increasingly on extrapolation and can be misleading (Rubin 1973, King & Zeng 2005).

Matching

The fundamental idea behind matching is to create an analysis population where the distribution of observed confounders in patients receiving treatment A and treatment B is similar by matching 1 to 1, 1 to many, or even 1 to a variable number of controls. Matching as such can in most situations be thought of as estimating the ATT (Imbens 2004). If the numbers of observed confounders included in the matching procedure is small it is feasible to match directly on those. This is often referred to as attribute matching. The number of cells to match on grows exponentially and for example four variables with 4 levels each leads to 256 cells and therefore direct or attribute matching

becomes impractical as the number of variables grows. There is no universal limit to the number of variables that can be matched on directly as this depends on the sample size as well as the distribution of the data.

To mitigate this limitation methods exist where the observations are matched on a single summary measure. The two most prominent are Mahalanobis distance and the propensity score (Rosenbaum & Rubin 1984). A relatively recent overview (Stuart 2010) is recommended for further reading on matching methods. Post match exposure groups may be compared directly or by fitting a multiple regression model including the treatment variable as well as additional explanatory variables (Thomas & Rubin 2000).

Summary

Real world evidence has an important role to play to increase our understanding of how pharmaceutical drugs and medical procedures are used in daily clinical practice and to help us understand the medical and economic consequences of different therapies and procedures. While the RCT will remain the gold standard for proof of efficacy, the increased availability of RWE data will bring new insights into the effectiveness, treatment patterns and cost of treatments outside the patient populations normally included in pivotal trials. The absence of randomization calls for advanced statistical methodology to be able to reduce the potential for bias as much as possible and provides a new and exciting challenge for statisticians.

General guidance on the design and analysis of observational studies may be found from the GRACE principles (Dreyer et al 2010) or the STROBE statement (Vandenbroucke et al 2007). ■

References

- Dreyer NA, Schneeweiss S, McNeil BJ, et al. GRACE Principles: Recognizing High-Quality Observational Studies of Comparative Effectiveness. *American Journal of Managed Care*. 2010; 16: 467-471.
- Freedman. Equipoise and the ethics of clinical research. *N Engl J Med*. 1987; 16: 141-145.
- Imbens GW. Nonparametric estimation of average treatment effects under exogeneity: A review. *The review of economics and statistics*. 2004; 86: 4-29.
- King G, Zeng, L. The dangers of extreme counterfactuals. *Political Analysis* 2005; 14: 131–159.
- Rosenbaum PR, Rubin DB Reducing bias in observational studies using sub classification on the propensity score. *Journal of the American Statistical Association*. 1984; 70: 516-524.
- Rothman, Greenland. *Modern Epidemiology*. Lippincott – Raven. 1998.
- Rubin DB. The use of matched sampling and regression adjustment to remove bias in observational studies. *Biometrics*. 1973; 29: 185-203.
- Stuart EA. Matching methods for causal inference: A review and look forward. *Statistical Science*. 2010; 25: 1-21.
- Vandenbroucke JP, von Elm E, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ, Poole C, Schlesselman JJ, Egger M. STROBE Initiative. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *Epidemiology*. 2007;18:805-35.

Payer Evidence and Health Technology Assessment – An Overview for Statisticians

Claire Watkins, AstraZeneca

Introduction

For patients to gain access to new drugs and other healthcare interventions, demonstrating efficacy and safety and thus gaining a regulatory license is no longer sufficient. Increasingly, treatments must also pass another hurdle and gain reimbursement approval from payers. Payers have additional evidence requirements that must be built in from the start of a drug development program in order to be able to present the required information in a systematic, objective and analytical way in a Health Technology Assessment (HTA) framework. Evidence of real world clinical effectiveness and value for money compared to one or several active comparators is often required.

The statistician plays a pivotal role in the design and analysis of clinical trials and other evidence sources that feed into a HTA submission. This article outlines some of the basic concepts that payers use in HTA, and highlights where the statistician can add value and improve the quality and robustness of the evidence, thus increasing the probability of reimbursement success.

Who are Payers and Why are They Important?

Payers are governmental, public or private institutions who decide on the funding of patient treatment. They may be individuals or organizations of individuals, and include highly professional people such as physicians, pharmacists, health economists and statisticians. Examples range from individual physicians or patients willing to self-pay to large national Health Technology Assessment agencies and health insurance companies.

Healthcare costs have grown relentlessly in all major pharmaceutical markets over the last decades. For example, in the US, healthcare spending neared \$2.6 trillion in 2010, over ten times the \$256 billion spent in 1980¹. The reasons for this increase are several, including more expensive, state-of-the-art medical technologies and drugs, longer life spans, an increase in chronic diseases, and increased administrative costs.

This means that payers are playing an increasingly important role as healthcare demands and expectations grow, but cost constraints increase. They are expected to deliver good quality medicine, but it must also be affordable. Payers are becoming more active now in prescribing decisions than ever before, and this trend is set to continue in the future. They may make negative or restricted recommendations about drugs or devices, even if regulatory approval has been obtained—for example, bevacizumab in metastatic breast cancer^{2,3}, non-small cell lung cancer⁴ and colorectal cancer^{5,6} in England and Wales. Hence they are having a significant impact on the pharmaceutical industry's ability to deliver medicines to patients.

Payer Needs and Expectations

Payers review drugs and devices that have been deemed safe and efficacious by regulatory agencies, and hence granted a marketing authorization. There are further hurdles that a new intervention must pass before reimbursement is granted, to reassure the payer that it should lead to improved health outcomes within their particular healthcare system:

- It should be expected to work in the real world setting for that market, and not just a clinical trials setting.
- It should be better than the relevant comparator(s) in that market, which could differ from the clinical trial comparator.
- It should be tolerable, effective, and cost beneficial.

So the needs of payers are different to the needs of regulators, where historically the pharmaceutical industry has focused most of its efforts and development program. The relative power of different groups to influence access and uptake of medicines has shifted, which means that, as an industry, we must also change the evidence that we develop to support our new products. We must start to consider the payer needs from the start of development, whilst still meeting the needs of regulators and treating physicians. We must design our programs to generate evidence on how our new product compares with existing treatments both clinically and economically—and the statistician has a critical role in this.

It is also important to recognize that different payers have different evidence requirements, as they differ both between and within countries, and in their objectives. For example, some will focus on reducing costs, others on maximizing health gain, and others on balancing costs and health gain to optimize value for money. For example, the German Gemeinsamer Bundesausschuss (G-BA)⁷ and the French Haute Autorité de Santé (HAS)⁸ assess treatments based on incremental health benefit, whilst the National Institute for Health and Care Excellence (NICE)⁹ in the UK and the Pharmaceutical Benefits Advisory Council (PBAC)¹⁰ in Australia use a cost-effectiveness approach and makes decisions based on value for money. This means that there is no “one size fits all” approach and the pharmaceutical industry must be flexible to meet the needs of each particular payer.

Health Technology Assessment

Payers usually evaluate the clinical and economic implications of a new treatment within a Health Technology Assessment, or HTA, framework. This is simply a systematic assessment of the evidence supporting the use of an intervention. The health technology may be any intervention that is used to promote health, to prevent, diagnose or treat disease, or for rehabilitation or long term care. For the pharmaceutical industry, this is usually a drug, but it may also be a device, diagnostic, procedure or organizational system. A summary of the evidence is submitted by the sponsor company to the payer in a HTA framework, so the payer can assess what the evidence tells them about the likely implications and value of using that technology in their healthcare system. This process often starts soon after regulatory approval.

The HTA framework is objective, systematic and analytical. It includes multiple evidence sources and summarizes the relative benefits, risks and costs of treatments, allowing a comparison of those measures to be made between treatments. Hence there is a clear requirement for strong statistical input to ensure that the evidence presented and analyses performed are robust, complete and appropriate.

Bridging the Evidence Gap

The gap between the type of evidence typically generated for a regulatory submission and the additional evidence required to address payer questions can be addressed by generating more information, such as:

- Patient reported outcomes – e.g. symptoms, compliance, and satisfaction. These can be important to payers for understanding the impact of a treatment on how their patient population feels and functions.
- Health economic outcomes. These enable payers to assess value for money and the impact on their budget versus currently available treatments.
- Comparative effectiveness. This is the extent to which a treatment produces benefit against one or several alternatives in a “real world” setting, as opposed to efficacy against a specified comparator in a controlled clinical trial setting. This is of key importance to payers. Two types of evidence may feed into comparative effectiveness:
 - Evidence synthesis. This is a systematic approach to identifying and synthesizing all relevant evidence, via **systematic reviews** of published literature and pooling of evidence. Relative comparisons of treatments can be done via **standard direct meta-analysis** if there are similar trials that directly compare two interventions. If the two interventions are measured in different trials with a common comparator arm, **indirect comparisons** can be used. Sometimes, both direct and indirect evidence are combined together in a **Mixed Treatment Comparison** (or Network Meta-Analysis)¹¹, which also enables more than two treatments to be compared simultaneously. All of

these analyses are based on assumptions that should be carefully assessed to ensure the analyses are appropriate and results are reliable—the role of the statistician is critical here.

- Real world evidence (RWE) is another very important source of information. This uses observational data from outside of controlled clinical trials to create insights on diseases, medicines, clinical practice and patient populations. Further detail is provided in the companion article.

Cost Effectiveness Analysis and Some Key Statistical Concepts

Different types of economic assessment are required for different payers, depending on their needs and objectives. All of these assessments involve a comparison of at least two alternative interventions.

Cost effectiveness is a term that is sometimes used to refer to all types of economic assessment. However, it does have a more specific meaning. It is a type of economic evaluation where costs are measured as monetary units and outcome is measured as natural health units, such as life years gained or clinical event avoided. Both costs and outcomes are compared between interventions.

If the outcome is measured as a health related preference, combining both the health state of the patient and a quality value or weight that is placed on that health state to generate what is called a utility, then this becomes a cost-utility analysis. The most common cost-utility analysis combines costs and **Quality-Adjusted Life Years (QALYs)**, which are described in more detail in the next section.

Other types of economic assessment include cost-benefit analysis, where costs and outcomes are both quantified in common monetary units; cost-minimisation analysis, where all factors are set to be equal apart from cost so that the intervention with the lowest cost is selected; and budget impact analysis, which estimates the planned resource use and expenditure of budget over a period of time.

There are some key statistical concepts that are also very important to payers. The most important of these is **uncertainty**. The more uncertainty there is about the results of an economic analysis, the more skeptical a payer will be about the results and a larger benefit will be required to gain a positive reimbursement decision. Sensitivity analyses and quantification of uncertainty are therefore very important in HTA.

Because economic assessments are often over a longer time horizon than the clinical trials, **extrapolation** of results beyond the trial period is often needed to **model** or **simulate** longer term consequences. This can introduce additional uncertainty.

Measuring and Presenting Costs and Benefits

In a cost-effectiveness analysis, costs and benefits of a new treatment are compared with another treatment(s) over a time horizon that captures the full impact of the interventions, and results are presented as the extra cost per additional unit of benefit. If the new treatment has worse outcomes and is more expensive, it will clearly be rejected. If it has better outcomes and is cheaper, it will clearly be adopted. However, in most situations, it has better outcomes and is more expensive and so the payer must decide if the additional health benefit is worth the additional cost. Consideration must be given to whether a greater health benefit could be gained by spending money on the new treatment, or in another way within the health system.

Some payers have a **Willingness-To-Pay (WTP)** threshold, which is the maximum amount they are willing to pay for an additional unit of health benefit. For example, NICE prefers new interventions to cost less than £20,000 per QALY gained, and requires an exceptionally strong case if the cost exceeds £30,000 per QALY gained⁹. However, other factors such as uncertainty, generalisability of results, and innovation are also taken into consideration in decisions.

The Incremental Cost Effectiveness Ratio (ICER) is a calculated quantity that payers use in assessing cost effectiveness of a new treatment A versus an existing alternative treatment B. It is simply the ratio of the difference in costs divided by the difference in outcomes, or effectiveness, between treatments:

$$\text{ICER} = \frac{(\text{Cost}_A - \text{Cost}_B)}{(\text{Outcome}_A - \text{Outcome}_B)}$$

From a statistical perspective, this ratio does not have nice properties. For example, it is not estimable if the treatments have similar outcomes, it is not always properly ordered, and it is difficult to calculate its standard error and confidence interval¹². Hence it is usual to display the results on a **cost effectiveness plane**, where the difference in costs (numerator) is plotted on one axis and the difference in outcomes (denominator) is plotted on the other. The numerator and denominator form a bivariate distribution, and joint variability can be represented on the plane as a confidence ellipse.

The costs included in the numerator can be incurred in different ways, and will depend on what the payer wishes to see. For example, they can include direct health and social care costs (e.g. drug costs, adverse events, hospital stays), non-medical direct costs (e.g. transport and prescription charges), or indirect costs (e.g. loss of productivity, reduced tax contributions, benefit payments).

The outcomes included in the denominator will again depend on the payer requirements. One commonly used measure for payers that use cost-utility analysis (e.g. NICE, PBAC) is the **QALY**. One QALY equals one year of healthy life for one person. It is calculated by multiplying the quantity of life in terms of life years by the quality of that life in terms of a utility over a long term timescale. The quality of life can change over time.

If the quantity of life is plotted versus the quality of life for two treatments, the gain in QALYs is the difference in the area under the curve for the two treatments. For example, if patients live for 5 years at full quality of life (utility of 1) on treatment A (5 QALYs) and 6 years at 90% quality of life (utility of 0.9) on treatment B (5.4 QALYs) then there are 0.4 QALYs gained on treatment B versus treatment A. Note that QALY calculations often require extrapolation of existing data from clinical trials over a longer time horizon, since usually not all patients are followed up until death. For treatments that are not expected to impact on mortality, QALY differences are driven by quality of life differences alone.

HTA Submissions

A typical HTA dossier that might be submitted to a cost-effectiveness payer would usually include three main sections:

- A description of the technology being assessed
- A clinical evidence summary, which looks at the comparative efficacy and safety of the new treatment against all relevant comparators for the payer's healthcare system.
 - This may include comparators that were not in the pivotal randomized controlled trials (RCTs).
 - The evidence can include direct randomized controlled trials, observational RWE data, and evidence syntheses such as meta-analyses, indirect comparisons and mixed treatment comparisons.
 - A comparison of the clinical trial population and design to the patient population and clinical practice in the payer's healthcare system is an important component. Justification of how and why the clinical trial results may be expected to translate to real life clinical practice is required, and results may need to be adjusted if necessary.
 - Subgroup analyses are often requested, as a treatment may not be clinically or cost effective for all subgroups of patients.
- An economic evidence summary, including the structure of the economic model, the assumptions made, the model inputs used, the model outputs (e.g. ICER, cost effectiveness plane), and sensitivity analyses. Again subgroup analyses are often requested.

A key underlying principle is to include a justification and critical appraisal of the selected evidence and methods used in the dossier.

The Role of the Statistician

Generating evidence for payers and compiling a good quality HTA submission dossier is a truly cross functional activity that requires input from a wide range of individuals. However, given the methodological, objective and systematic approach used in HTA, the input of the statistician with our strong skills in logic and analytical thinking

is vital. Additionally, with the move towards considering the needs of the payer right from the start of the development program, the statistician should be involved in discussions on generating the best payer evidence from the early stages. This helps to ensure that the study program is designed to best enable the intended eventual analysis.

Traditionally, the statistician's input to HTA has been in the area of supplying data and analyses of clinical trials data to support the clinical evidence summary, or to be used as inputs in the economic modeling. When doing this, it is very important to discuss with the health economist or other individual requesting the analysis how they plan to use the results, to ensure that the most appropriate methodology and data are used. For example, the economic model may exclude patients with a certain co-morbidity or concomitant treatment, which could make the ITT population result less relevant to the decision problem. Strive to understand the underlying question, and recognize that the analysis people initially ask for is not always the optimal way to address that question. The statistician should be flexible in considering requests for analyses that are outside the limits of the regulatory statistical analysis plan, as long as they meet genuine payer needs. But they should also act as a guardian to ensure that these additional analyses are truly required, and not entering the realms of data dredging. Although payers may consider a wider range of evidence and analysis techniques, the requirement for robustness remains.

However, as statisticians we can bring a lot more to the table, especially as the analytical techniques being used in HTA are becoming ever more sophisticated. Payers are often more comfortable than regulators with using modeling, simulation and extrapolation when full data is not available. This is often the case in HTA, considering the longer time horizon and range of potential comparators. Several methods have been developed by statistical or mathematical experts and are accepted by HTA agencies, such as Bayesian network meta-analysis and probabilistic sensitivity analysis in economic models and simulations. However, in practice they are sometimes applied formulaically by non-experts who have low awareness of the assumptions and the implications of breaking them, and a lack of ability to adapt the methods to new situations. The mathematical modeling skills of the statistician are in high demand in this area, and we can advise on the appropriate use and extensions of these approaches. The statistician's experience of dealing with probability and variability is also very valuable, as quantification of uncertainty is a key element of HTA.

Working in HTA gives us a chance to apply our statistical knowledge to new problems. It involves combining different data types from multiple sources for evidence based decision making, for example individual patient data from sponsor company RCTs, summary statistics from published RCTs in the literature, observational RWE data, patient reported outcomes, utility data, and cost data. Some of these data have interesting statistical properties and cannot be easily analyzed using standard approaches—for example, cost data is often skewed with large but important outliers, and payers cannot easily use or interpret averages on a transformed scale. Innovative statistical thinking can improve the way that problems are solved, enabling payers to make more fully informed decisions with less uncertainty.

Summary

Generating evidence for payers and building HTA submission dossiers is a fast growing area that is likely to increase in importance and complexity in the future. There are many statistical aspects to this, and it provides opportunities for statisticians to apply their skills in new ways to make a positive impact on the chance of reimbursement success. ■

References

1. Centers for Medicare and Medicaid Services, Office of the Actuary, National Health Statistics Group, *National Health Care Expenditures Data*, January 2012
2. NICE technology appraisal guidance TA263: Bevacizumab in combination with capecitabine for the first-line treatment of metastatic breast cancer. August 2012. Available from <http://guidance.nice.org.uk/TA263> (accessed 29th April 2013)

3. NICE technology appraisal guidance TA214: Bevacizumab in combination with a taxane for the first-line treatment of metastatic breast cancer. February 2011. Available from <http://guidance.nice.org.uk/TA214> (accessed 29th April 2013)
4. NICE technology appraisal guidance TA148: Bevacizumab for the treatment of non-small-cell lung cancer (terminated appraisal). June 2008. Available from <http://guidance.nice.org.uk/TA148> (accessed 29th April 2013)
5. NICE technology appraisal guidance TA212: Bevacizumab in combination with oxaliplatin and either fluorouracil plus folinic acid or capecitabine for the treatment of metastatic colorectal cancer. December 2010. Available from <http://guidance.nice.org.uk/TA212> (accessed 29th April 2013)
6. NICE technology appraisal guidance TA242: Cetuximab, bevacizumab and panitumumab for the treatment of metastatic colorectal cancer after first-line chemotherapy: Cetuximab (monotherapy or combination chemotherapy), bevacizumab (in combination with non-oxaliplatin chemotherapy) and panitumumab (monotherapy) for the treatment of metastatic colorectal cancer after first-line chemotherapy (review of technology appraisal 150 and part review of technology appraisal guidance 118). January 2012. Available from <http://guidance.nice.org.uk/TA242> (accessed 29th April 2013)
7. G-BA website. Available from <http://www.english.g-ba.de> (accessed 30th April 2013)
8. HAS General method for assessing health technologies. June 2007. Available from http://www.has-sante.fr/portail/jcms/c_541195/en/general-method-for-assessing-health-technologies?xtmc=&xtr=4 (accessed 30th April 2013)
9. NICE Guide to the methods of technology appraisal. April 2013. Available from <http://www.nice.org.uk/media/D45/1E/GuideToMethodsTechnologyAppraisal2013.pdf> (accessed 29th April 2013)
10. Australian Government Department of Health and Ageing: Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee, version 4.3. December 2008. Available from [http://www.health.gov.au/internet/main/publishing.Nsf/content/AECB791C29482920CA25724400188EDB/\\$File/PBAC4.3.2.pdf](http://www.health.gov.au/internet/main/publishing.Nsf/content/AECB791C29482920CA25724400188EDB/$File/PBAC4.3.2.pdf) (accessed 29th April 2013)
11. Hoaglin DC, Hawkins N, Jansen JP, et al. Conducting Indirect-Treatment-Comparison and Network-Meta-Analysis Studies: Report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices—Part 2. *Value in Health* 2011;14:429-37
12. Willan AR and Briggs, AH. *Statistical Analysis of Cost Effectiveness Data*. Wiley, Chichester UK, 2006

Summary of the ASA Biopharmaceutical Section Executive Committee Meeting

March 11, 2013 at ENAR, Orlando, FL

Dionne Price

Amit Bhattacharyya, Biopharmaceutical (BIOP) Section Chair, welcomed committee members and called the meeting to order. Eleven committee members were present, and thirteen attended the meeting via phone. Amit thanked the outgoing officers for their dedication and service to the BIOP Section and congratulated the newly elected officers, the Executive Committee (EC) members changing their roles, and appointed committee members.

Matilde Sanchez, Chair-Elect, announced the appointment of Cristiana Gassmann-Mayer as the industry co-chair of the 2014 ASA BIOP FDA-Industry Statistics Workshop. In addition, Matilde notified the EC that she will have a role in the continuation of the 5-year strategic plan focused on leadership of the BIOP Section.

Heather Thomas, treasurer, summarized the 2012 year-end report. Revenue was generated from membership dues, webinar registration, continuing education, and the ASA BIOP FDA-Industry Statistics Workshop. Expenses included the web clip project, awards, honorarium, and contributions to other organizations. The year-end balance of the section was \$358,686.88.

Kjell Johnson alerted the EC of a \$5000 funding request from the Nonclinical Biostatistics Conference. The conference was previously held in 2009 and 2011 with high attendance from BIOP members. Following discussion, the EC voted to provide the requested funding with a stipulation that \$2500 must be used to fund student participation. Additional stipulations may be negotiated by the Conference Funding Committee.

Olga Marchenko summarized the results of the Membership Survey and provided specific suggestions originating from the survey. Recommendations from the survey included greater transparency, increased clarity regarding deadlines for submission of session abstracts for conferences, and improved awareness of BIOP activities. The EC will actively implement strategies to address the recommendations.

Richard McNally reported that two winners of the 2013 BIOP Student Paper Competition have been selected. Awards will be given during the Biopharmaceutical Section Business Meeting to occur Tuesday, August 6th from 5:30 p.m. – 7:30 p.m. at JSM.

John Johnson announced the winners of the Best Contributed Paper Award for JSM 2012. The winners include Scott Emerson, Jason Connor, and Steven Julious. Ilya Lipkovich and Carl Dicasoli received honorable mentions. Awards will be given during the Biopharmaceutical Section Business Meeting at JSM 2013.

Bruce Binkowitz and **Lilly Yue** announced 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. Following the plenary sessions, 48 topic-themed luncheon roundtables and 18 concurrent sessions will occur. The day will end with a networking mixer. Eighteen concurrent sessions will occur on the final day of the workshop. Other highlights of the workshop include two town halls and two sessions associated with the *Journal of Biopharmaceutical Statistics*.

Estelle Russek-Cohen reported that the BIOP Section will sponsor 5 invited sessions, 21 topic-contributed sessions, and 27 contributed sessions at JSM. In addition, BIOP will co-sponsor 10 sessions. Speed sessions will be piloted at JSM 2013. Each speed session will have 20 presentations that include a 5-minute oral presentation followed by a poster presentation. Lisa LaVange will chair the oral section, and **Ivan Chan** will chair the poster session. The BIOP Section will also sponsor a short course on non-inferiority trials and a second course on clinical trials. In addition, Ivan Chan reported that the BIOP Section will sponsor eight roundtables.

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

Highlights for Activities Associated with Biopharmaceutical Section at the 2013 Joint Statistical Meeting

Estelle Russek-Cohen

Bienvenue à Montréal! The Biopharmaceutical Section welcomes everyone to JSM in Montréal.

This year we will be celebrating the International Year of Statistics at JSM and Montreal, a bilingual city, is the perfect setting for such a celebration. Our program encompasses many areas of interest to Biopharm section members, including topics ranging from preclinical to early and late phase clinical trials and postmarket surveillance. There are several sessions devoted to statistical aspects of personalized medicine and several devoted to the evaluation of product safety.

It is obvious that we have many activities on the program but we would like to highlight our **continuing education program**. We are offering two full day short courses at JSM. We are proud to be a co-sponsor of the class taught by the Excellence in CE Award Winning Instructor at JSM 2012. Brian Wiens (Alcon Labs) will teach his class on the Design and Analysis of Non-inferiority Trials on Saturday of the JSM. Brian Wiens is an author of numerous articles in the area of non-inferiority, a topic that is important to any statistician working in late phase clinical trials. On Monday of JSM, an overview of key considerations for statisticians working in clinical trials will be presented by three prominent statisticians, Devan Mehrotra (Merck), Alexei Dmitrenko and Jeff Maca (both of Quintiles). The title of the course is Analysis of Clinical Trials: Theory and Applications and I recommend it to individuals wanting a sound overview of modern clinical trial methods.

We will have **5 invited sessions at the JSM, 27 sponsored or co-sponsored topic contributed sessions, and 27 contributed sessions!** I will highlight a only a few to entice you to join us but strongly advise that you go to the ASA website (www.amstat.org) and check out the program which is now online. This year's themes are the International Year of Statistics and the role of Big Data. We have sessions on each, as we look at a session the Challenges of the Affordable Care Act and sessions devoted to multi-regional trials. The session organizer is noted in parentheses.

Sunday at JSM (August 4th)

2:00 p.m. Censoring Issues in Survival Analysis (Grace Liu, Janssen R&D)

4:00 p.m. Regulatory Considerations on Design and Analysis of Observational Studies (Lilly Yue, FDA)
Enhanced Design, Analysis of Modeling of QT Studies (Donna Kowalski, Astellas Pharma)

Monday at JSM (August 5th)

- 8:30 a.m. Analysis of Recurrent Events in the Presence of Competing Risks and Informative Censoring (Byron Jones, Novartis)
- 10:30 a.m. Issues in Building Imputation Models for Missing Data Techniques (Robert Small, Sanofi-Pasteur)
- 2:00 p.m. Impact of Bayesian Methods in Medical Product Development
Highlights the efforts of the DIA Working Group in Bayesian Statistics
Articles to appear in Pharmaceutical Statistics (Karen Price, Eli Lilly)
Pharmacogenomics: Statistical Challenges and Opportunities on the Journey to Personalized Medicine (Gary Rosner, The Johns Hopkins University)

Tuesday at JSM (August 6th)

- 8:30 a.m. Key Subgroup Analysis Issues in Clinical Trials (Alex Dmitrenko, Quintiles)
- 10:30 a.m. Critical Aspects of Dose-Finding in Drug Development (David Ohlssen, Novartis)
- 2:00 p.m. Regulatory Challenges of Non-Clinical Biostatistics (Pryia Kulkarni, Genentech)

Wednesday at JSM (August 7th)

- 8:30 a.m. Highlights of a Special Issue of SBR in Honor of Robert O'Neill's tenure as Director of Office of Biostatistics at FDA (Steven Snappin, Amgen)
Statistical Innovations Developed for Cancer Clinical Trials (Ying Wan, Janssen R&D)
- 10:30 a.m. The Affordable Healthcare Act's Statistical Challenges (Alan Sampson, University of Pittsburgh)
Consistency of Treatment Effects in Multi-Regional Trials (Gang Li, Johnson and Johnson)
- 2:00 p.m. Missing Data in Non-inferiority Trials, (Brian Wiens, Alcon)

Thursday at JSM (August 8th)

- 8:30 a.m. Challenges in Evaluation of Correlates of Protection and Immunobridging of Vaccine Trials (Ivan Chan, Merck)
Recent Advances in Methodology for CNS Clinical Trials (Pilar Lim, Janssen R & D)

We have not listed the contributed sessions but we was so impressed by the quality of so many of the submissions that we urge you not to skip these. We also have poster sessions and poster sessions are really wonderful if you like having a one on one discussion with the authors. This year we also have a novel hybrid kind of presentation, the **SPEED session** (like speed-dating...only better). In the SPEED session, you get to hear a short 5 minute talk on each presentation with 20 such talks in a session. In the following session, you get to talk with the authors and enjoy some refreshments. This is our first foray into this approach and we would like feedback from both presenters and meeting attendees.

Of course, while you tell your boss that you are coming for all the intellectual stimulation, we urge section members to attend our **reception and business meeting** on Tuesday from 5:30 p.m. to 7:30 p.m. in the Convention Center (CC-710A). Please come to this meeting and be engaged!

Keep in mind the JSM includes the programs of many ASA sections and statistical societies and it is unlike any other in terms of the exposure you get to the breadth of statistics. ■

Help for Potential ASA Fellows

Brian Wiens

Many prominent and influential statisticians are members of the Biopharmaceutical Section of the ASA. Some of these members have been recognized by the ASA with the honorary title of Fellow. The mission of the Fellows Nominations Committee of the Biopharmaceutical Section is to identify and support members of the Section who are potential ASA Fellows. In this article, I will provide some guidance on how to work with this committee to nominate yourself or a colleague.

The Fellows Nominations Committee consists of a chair (me) and at least two other members. I am fortunate to have three outstanding members this year: Alex Dmitrienko, Devan Mehrotra and John Peterson. Our tasks is to identify potential nominees, coach them on how to prepare for application, help write or review the application, write a letter of support if requested, and report to the Executive Committee on our progress.

Many potential nominees identify themselves by approaching a member of the committee to ask about the nomination process. We are happy to talk to any member, even if you think you are a few years away from an application, to help guide your career and fill in any missing pieces that may be required for a solid nomination package. We also make contact with Section members who would make good candidates to encourage them to consider a nomination. Any member of the Section can send a name to any member of the Fellows Nominations Committee, and we will follow up with a contact.

Once a potential candidate is identified, we will work with the candidate to evaluate the strengths and weaknesses of the application. The ASA Committee on Fellows, which receives the nomination packages and decides on successful candidates, looks for several characteristics in nominees. Of interest is how the nominee has influenced others—through research, teaching, advising, mentoring, managing or any other professional activity. Obviously, technical achievement such as publications in statistics journals is important, but that alone is not sufficient. Service to the organization is another requirement. Service can include appointed at elected positions, with elected positions probably being more impressive to the ASA Committee on Fellows. We can put a potential nominee in touch with the Executive Committee of the Biopharmaceutical Section to match the applicant's skills and interests to Section needs, thereby adding to the nominee's service to the organization. Employment history, whether academic, corporate or non-profit, is helpful, with a nominee showing increasing levels of responsibility during a career. Managing and mentoring provide evidence of influence on individuals and organizations. We will help potential nominees decide how well they meet the requirements, and whether they need to add some more to their accomplishments before writing a nomination package.

The nomination package includes a document summarizing the nominee's accomplishments in all areas, a curriculum vitae (or equivalent) and letters of support. The document summarizing the nominee's accomplishments follows a standard format. Up to four letters of support, most or all from current ASA Fellows, are used to judge the influence of the nominee. Quite often, a member of the Fellows Nominations Committee writes a letter summarizing the nominee's contributions to the Section. We are happy to do this with the caveat that no Fellow can write more than two letters of support in any given year. The nominations packages are due to the ASA early in the calendar year—in 2013, the deadline was March 1.

Periodically we report to the Executive Committee on our progress. Confidentiality is an important concern, so we do not announce names of nominees until they have been approved by the ASA. Notably, it is not unusual for a nominee to be rejected at first application and accepted at a later application—there is no penalty, implicit or explicit, for submitting a package and being rejected. If any Section members are unsure of whether to apply, we encourage them to start the process. At a minimum, they will receive feedback at various steps on strengths and weaknesses of the application.

Any Section member who aspires to the honorary title of Fellow is encouraged to contact a member of the Fellows Nominations Committee for additional information, advice on when and how to apply, or a letter of support. Any member can recommend another member for the honor—contact the potential nominee with encouragement, or contact one of us with a name and we will go from there.

Additional information is available on the ASA website: <http://www.amstat.org/awards/fellows.cfm>. ■



Registration Open for Statistics Workshop

ASA Biopharmaceutical Section FDA-Industry Statistics Workshop to Introduce Keynotes



The 2013 ASA Biopharmaceutical Section FDA-Industry Statistics Workshop will be held from September 16–18 at the Marriott Wardman Park, Washington, DC. The conference includes sessions co-chaired by statisticians from industry, academia, and the Food and Drug Administration (FDA). Roundtable luncheon discussions are available on the first day of sessions, and short courses on related topics are offered the day prior to the workshop.

While the format of the workshop remains the same as in the past, keynote addresses given by Donald Rubin of Harvard University and Ronald Wasserstein of the American Statistical Association will open the event.

Dr. Wasserstein, ASA executive director, will speak about the International Year of Statistics (Statistics2013, www.statistics2013.org). The 2013 ASA Biopharmaceutical Section FDA-Industry Statistics Workshop is one of about 2,000 participating organizations in Statistics2013.

Dr. Rubin is John L. Loeb Professor of Statistics at Harvard University, where he has served as chair for 13 of his more than 25 years there. He has more than 350 publications (including several books) covering an array of topics. Rubin is a Fellow of the American Statistical Association, Institute for Mathematical Statistics, International Statistical Institute, Woodrow Wilson Society, John Simon Guggenheim Society, New York Academy of Sciences, American Association for the Advancement of Sciences, American Academy of Arts and Sciences, and Alexander von Humboldt Foundation. He is also the recipient of the Samuel S. Wilks Medal, Parzen Prize for Statistical Innovation, Fisher Lectureship, and George W. Snedecor Award. According to ISI Science Watch, he has been one of the world's most highly cited writers in mathematics.

There will also be a plenary panel session, "Innovation and Best Practices for Clinical Trials," moderated by Lisa LaVange of the FDA. Panelists include Greg Campbell of the FDA, Sue-Jane Wang of the FDA, Tom Fleming of the University of Washington, Janet Wittes of Statistics Collaborative Inc., Frank Shen of Abbvie, and Kyle Wathan of J&J.

Registration closes on September 9. Make sure to register early, as the workshop filled to capacity last year.

The ASA Biopharmaceutical Section FDA-Industry Statistics Workshop is sponsored by the ASA Biopharmaceutical Section in cooperation with the FDA Statistical Association. ■

2013 NCB



Villanova, Pennsylvania

October 15-17, 2013

Nonclinical Biostatistics Conference

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

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.