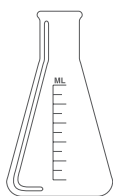


Biopharmaceutical Section



American Statistical Association

Biopharmaceutical Report

Volume 15, No. 1

Winter 2007

Chair: *Brian Wiens*

Editors: *Richard Caplan, Philip Pichotta, and Thomas Dobbins*

Note from the Editors

Publishing results from industry-sponsored clinical research has become more difficult recently, since several medical journals have imposed restrictions on analyses produced by statisticians in the pharmaceutical industry. In the feature article, Frank Rockhold and Steve Snapinn provide a balanced perspective.

The format of this winter issue of the *Biopharmaceutical Report* is designed to be more readable electronically by removing the vertical columns. Let us know what you think about it. Besides the valuable information from the Biopharmaceutical Section, we will also start including meeting announcements that will be of professional interest to some of our members.

Tom Dobbins is a welcome addition to the editorial staff. He joined in 2006.

Stacy Lindborg, our Past-Chair, had a baby girl, Emma Avis Elise Lindborg, on January 5, 2007. Mother and baby are doing well. Congratulations to Stacy and we hope that she will enjoy motherhood. ■

Letter from the Chair

Brian Wiens

It is my privilege to serve the membership of the Biopharmaceutical Section as chair in 2007. The section is healthy—financially, scientifically and professionally. My goals for 2007 are to maintain the momentum and increase the service of the section to members.

Many of the projects sponsored by the section will be continued this year. The list is long but, at the risk of leaving out an important project, here are some.

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The FDA-Industry Workshop is one of our most visible efforts, and has proven successful at uniting statisticians from the FDA and from the pharmaceutical industry for two days of talking about the science of statistics, as applied to drug development. *Biopharmaceutical Report* is another way of reaching out to membership. The section maintains formal ties to a number of other organizations, including PhRMA, the Deming Conference and the Midwest Biopharmaceutical Statistics Workshop. The section sponsors awards for the best student papers and for the best contributed papers at the Joint Statistical Meetings. The section will sponsor sessions at the ENAR spring meeting in Atlanta and JSM. These activities provide valuable service to current members and also increase membership in the section.

A few years ago, the section hit a financial tight spot. I am pleased that this has been solved. Two main initiatives have turned around our financial picture: the Corporate Sponsorship Committee, began by Len Oppenheimer and currently run by Jim Colaianne, has found new sources of income, and the chairs of the annual FDA-Industry Workshop have maintained tight budget control for several years when running the largest single annual expenditure of the section. With the financial picture looking very bright, the section is positioned not only to continue the FDA-Industry Workshop and other activities, but also to provide other initiatives which will benefit the membership.

One of the new initiatives that has generated a lot of excitement is the possibility of sponsoring web-based training on topics of interest to pharmaceutical statisticians. Such training has become popular due to flexibility and low cost: participants can learn from the comfort of their own offices, and we can provide this for a low price. Alex Dmitrienko has volunteered to lead this initiative, and is working with Rick Peterson of the ASA and others to develop this ability. The executive committee is anticipating that this will become an ongoing activity for the section. Please look for announcements of these training opportunities throughout 2007. If you have questions or suggestions for training, please contact Alex directly.

Another new initiative, led by the ASA as a whole and not just by the section, is a journal, *Statistics in Biopharmaceutical Research*, aimed at pharmaceutical industry statisticians. Joe Heyse, the founding editor, has assembled a team that is currently reviewing submitted manuscripts, with the goal of having the first issue in 2007. Although this initiative was begun by the ASA, it has the full backing of the executive committee and we look forward to this new journal.

The experienced and dedicated volunteers and supporters of the section are vital to the ability of the section to serve the members. I invite you to take a look at the list of some of the volunteers on our website (www.amstat.org/sections/sbiop/). We have a truly dedicated set of volunteers who give their time and expertise to help the section. However, there is always room for one more: anyone who has an interest in serving the section is invited to contact me. In addition, please contact any member of the executive committee with comments or suggestions. ■

Improving the Image of Pharmaceutical Industry Research: Transparency is Not Always Clear

Frank W. Rockhold, GlaxoSmithKline
Steve Snapinn, Amgen

Disclaimer: The views expressed in this article represent those of the authors as individual professionals, and do not necessarily represent the views of their respective industry employers.

1 Introduction and Preamble

It would be an understatement to say that the level of trust in many places in the world regarding the state of clinical research into new therapies, particularly with respect to research sponsored by the pharmaceutical industry has reduced considerably. The public seems to have less trust and confidence in the pharmaceutical industry, as well as in the regulators charged with overseeing the pharmaceutical industry and defending and promoting the public health. This has led to a number of legislative initiatives and proposals at the state and federal level in the US such as the **Enzi-Kennedy Bill on Drug Safety** – Title III of the "Enhancing Drug Safety and Innovation Act of 2006" (S. 3807).

It has been often stated that trust in the pharmaceutical industry while improving is just ahead of the oil and tobacco industries (Harris Interactive 2006). This is a very sad state of affairs when you consider that the pharmaceutical industry is discovering and developing products that delay, treat, or completely prevent many serious diseases. Much of the mistrust that has been engendered in the press and in the academic and journal editor community is related to a concern over lack of transparency about the research conducted by the pharmaceutical industry. “Transparency” in this context relates to the ability for the public to be aware of the existence and outcome of clinical research performed on products prescribed by their physician.

This lack of transparency has led to a perceived need for more control over the drug research and development process in general, and in particular to the part that is sponsored and overseen by the pharmaceutical industry. As is true in many situations, part of the issue is due to a general lack of understanding by the “public” about the nature of research in the pharmaceutical industry and the fact that competition fuels innovation and investment in the research that is required to generate new therapies. This perceived need is expressed in different ways by many stakeholders, including academics, journal editors, national health organizations, international health organizations, legal professionals, practicing physicians, patients, legislators, etc. The request for additional levels of “transparency” about the research process is genuine from some stakeholders and a surrogate for a desire for additional control of drug discovery and development in others.

The expectations of these stakeholder groups include complete real-time transparency in the clinical research process enabled by mandatory public knowledge of clinical studies being initiated and of study results, regardless of the outcome. There have been various levels of expectation around enforcement of these principles. Some of these concern the journal editors’ policies, national legislation or guidelines proposed by The World Health Organization (WHO). (See Section 3) All major stakeholders in the process, including the pharmaceutical industry, have publicly supported the concept of transparency in the research process; however there are differences of opinion as to the extent of disclosure and transparency. The industry has expressed a desire to disclose clinical trial design (protocol) information to the public, but wishes to do so at a time and in a way that does not compromise their competitive and/or intellectual property position, thus impeding innovation and the delivery of new treatment to patients. Opponents say that competitive pressures should never outweigh patients’ (or the public’s) right to access trial information. Striking the right balance is key: one can challenge the amount and extent of information that is truly useful to patients or physicians while a trial is ongoing.

The disclosure of clinical trial results is an equally important component to transparency; however, the stakeholders involved in that discussion have different agendas, thus making a single unified policy on transparency very difficult. It is certainly the case that the pharmaceutical industry has certain objectives or drives regarding study design and protocol disclosure, but others, such as journal editors wanting to publish meaningful manuscripts and academics wanting to get grants, publish papers and get promoted, also have other specific objectives or drivers. Thus the authors of this paper acknowledge their inherent drivers and points of view, but we have also been engaged extensively in the external debate on the issue and feel we can give a good overview and understanding of the issues.

The purpose of this review is to highlight and summarize the issues around data transparency from various perspectives. What we hope the reader takes away from this review is the importance of the issue and the complexity of the solution. It is a discussion that is important, but, as in most endeavors, in order to have the debate it is important to have the facts and the information; and that is what we hope to lay out in this review.

The purpose of this review is to highlight and summarize the issues around data transparency from various perspectives.

2 ICMJE and World Health Organization Policies on Protocol Registration

In September 2004 (and amended in June 2005) (DeAngelis et al 2004, 2005), the International Committee of Medical Journal Editors (ICMJE) issued a statement indicating that from September 2005 onwards, in order to get a paper published in any of their member journals, the trial protocol would have to have been registered in *ClinicalTrials.gov*.

This is a database set up by the National Library of Medicine (NLM) in order to implement legislation, created in 1997 and referred to as FDAMA 113, to publish the existence of clinical trials in serious and life-threatening diseases (e.g. cancer, Alzheimer's disease, AIDS) so that patients could inquire about enrolling in the trials. While the definition of serious and life-threatening is open to interpretation, it would be safe to say that compliance with the legislation has been variable. The extension of the use of *ClinicalTrials.gov* to all clinical trials as mandated by the ICMJE was not without logistical issues, but the NLM staff has dealt with them for the most part.

The primary debate around the ICMJE policy was defining the protocol design fields to be made available. This debate was conducted in many fora, including an Institute of Medicine (IOM) panel formed in late 2004 and consisting of a number of journal editors and representatives of the pharmaceutical industry, including one of the authors of this review (FR).

The premise of the ICMJE policy was to help journal editors assess the importance of an individual trial in the scope of the entire body of research. For instance, when reviewing a manuscript from a trial with a positive outcome, it was important to the editors to understand if, for example, this was one of seven trials conducted on the therapy or the sole trial. Prior to that policy, they would have had to rely on the sponsors of the trials to provide that information. It is important to note that their policy specifically excluded clinical pharmacology, phase I, and early development trials in small groups of patients. Their intent was to examine trials that would have immediate public health implications and thus were primarily focusing on large-scale trials of important clinical outcomes.

As noted above, in all of the current debates around data transparency, it is essential to understand the stakeholder's specific question and issue. A general statement of mistrust and lack of confidence are not helpful in trying to assess potential solutions. The principal discussion around the ICMJE protocol registration proposal in *ClinicalTrials.gov* was around which fields should be completed and when. The twenty basic fields proposed as a result of the IOM and WHO discussions were basic information about the study design and were largely consistent with what was being reported in FDAMA 113 in *ClinicalTrials.gov*. The discussions that took place at the WHO in April 2005 came to a compromise between all parties that all twenty fields needed to be completed at the time of trial completion, but that five of the fields (scientific title, scientific objective, sample size, primary endpoint, secondary endpoint) could be left blank at the start of the trial in an attempt to protect competitive interests. Many editorials and articles (most notably ICMJE) expressed concern that leaving these fields blank failed to properly register the trial and did not fulfill the spirit of transparency (DeAngelis et al 2005). The ICMJE would make a judgment at the time of publication whether or not any of the missing fields were critical to the interpretation by the editors, and thus leaving fields blank was at the risk of the sponsor having the paper rejected. In November 2005, the WHO formed the International Clinical Trials Registry Project (ICTRP) and formed two governing bodies around it. First was the International Advisory Board to act as a steering and policy group, but secondly and more importantly was a Scientific Advisory Group with representatives of all the stakeholders, including one of the authors (FR). The purpose of this group was for the WHO to get advice from key stakeholders to use in setting their policies in implementation of this ICTRP. The preliminary discussions revolved entirely around the registration of the twenty fields for individual studies in a number of registries around the world. Parallel discussions have involved for example selection of primary and secondary registries, data informatics and coding, but those will not be discussed in this review. The WHO in May 2006 publicly endorsed complete registration of all twenty fields at the start of all trials (including early phase clinical pharmacology and phase I). There are many who feel that the public health imperative to register normal volunteer trials is inadequate to justify the effort, but the WHO had difficulty defining all public health intervention trials, so they settled on all trials. Thus, there is some divergence between the WHO and the ICMJE policies. Numerous articles and editorials have been written on both sides of this issue, with the industry point of view being that early development trials contain the most potential for competitive information and intellectual property debates.

Major industry trade organizations such as PhRMA and the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) have issued public statements supporting the general concept of transparency, but again feeling that the complete registration of all trials was at risk for revealing competitive information (IFPMA Joint Position 2005 and PhRMA Principles 2004). The position of industry is the minimum position agreed to by all sponsor companies (to fill in 15 fields completely, but delay when necessary completing the Official Title, Intervention name, Primary and Key secondary Endpoints and sample size); however, a number of companies have

gone beyond that minimum requirement and some, in fact, intend to comply fully with WHO and ICMJE policies. Clearly there will be cases where competitive information is important and in those rare occurrences individual sponsors can debate with WHO or ICMJE or other interested parties a necessity to fill out a specific field. It must be said that if all five of those fields were left blank, significant information about the trial would be missing.

Thus, overall in the past two years, much has happened to progress the concept of transparency in the registration of clinical trial protocols in publicly accessible databases. All stakeholders should be complimented on the amount of time and energy that have gone into the debates and discussions around the definition of transparency. Clearly we have far to go to get all parties to agree on operating definitions, and perhaps over the next few years by observing what happens with both the WHO and ICMJE policies we will get an idea of what the tough issues really are and then continue to have discussions and refine the policies as necessary. If all parties have as their overarching goal to help patients and their caregivers both in better understanding ongoing research and results of research and in delivering innovation to treat and prevent disease, the spirit of compromise will be greatly facilitated.

In this discussion, it is important for all stakeholders to balance the need for detail versus the need for transparency of the existence of all trials. If driving for detail disengages any stakeholders and trials are withheld, then society loses. From the editors' and (meta analysts') perspective the detail is critical for them to assess the existence of relevant trials, and they may consider a trial with any field blank not to be registered at all (DeAngelis et al 2005). Striking this sort of balance is critical to achieving a workable system, while at the same time releasing enough information to address the need to increase the credibility of clinical research.

3 Journal of the American Medical Association Policy

Perhaps the most important event in the ongoing debate over data transparency and industry's role in clinical research was the announcement of a new editorial policy by the *Journal of the American Medical Association (JAMA)* in 2005 requiring an independent statistical analysis by an academic statistician (Fontanarosa, Flanagin and DeAngelis 2005). This policy led to a torrent of commentaries from industry and academic statisticians and professional organizations. Due to its importance, it is interesting to look at the *JAMA* policy in some detail.

The 2005 policy should not have come as a complete surprise, since it was foreshadowed by a 2001 editorial concerning conflict of interest, with specific focus on financial conflicts (DeAngelis, Fontanarosa, and Flanagin 2001). While recognizing that conflicts of interest can take many forms, their emphasis was on financial conflicts because "in addition to their potential threat to scientific objectivity, they are discretionary, relatively simple to quantify, and usually relatively easy to understand." To some in the industry, this rationale sounded a bit like taking on industry because it is an easy target.

This editorial then singled out industry-sponsored trials in two ways. First, it required that "an investigator who is not an employee of the sponsoring company ... should provide a statement that he or she 'had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analyses.'" It went on to "strongly encourage that the data analyses for industry-sponsored studies be conducted by an independent entity, such as by biostatisticians at an academic center, rather than only by statisticians employed by the company sponsoring the research."

This strong encouragement became editorial policy in 2005:

Requirements for Reporting Industry-Sponsored Studies

"... [I]ndustry-sponsored studies in which the data analysis has been conducted only by statisticians employed by the company sponsoring the research will not be accepted for publication in *JAMA*. This does not mean that the names of industry-employed statisticians, epidemiologists, or others involved with the data management or analyses should be removed from the manuscript reporting these studies; their roles as authors or nonauthor contributors should be clearly identified. However, for these studies, an additional independent analysis of the data must be conducted by statisticians at an academic institution, such as a medical school, academic medical center, or government research institute.

Conflict of interest is possible in all settings, and the review process should not be different...

“For these analyses, the entire raw data set should be given to the independent biostatistician, along with the study protocol and the prespecified plan for data analysis. The independent biostatistician should verify the appropriateness of the analytic plan and conduct an independent analysis of the raw data. The results of these analyses should be reported in the manuscript. The independent statistician should clearly describe his or her involvement in conducting the analyses, and provide written confirmation of the data analysis. Details of this independent statistical analysis, as well as the name and academic institution of the independent statistician and whether compensation or funding was received for conducting the analyses, must be reported and will be included in the published article. We recognize that this requirement for an independent statistical analysis of industry-sponsored studies entails additional effort, time, and cost, but in our view, this additional verification of the data and the analyses, as well as an additional layer of institutional oversight for these studies, are essential.”

Reaction to this new policy was swift. As might be expected, the pharmaceutical industry rose to its own defense. Writing on behalf of the industry trade organization, PhRMA, Loew (2005) wrote “PhRMA disagrees with the implication that industry-sponsored studies are at higher risk of bias and fraud than other types of studies and thus require special scrutiny. Industry-sponsored studies are carefully conducted, rigorously monitored, and subject to vigorous government oversight that ensures the integrity of data and results.” Rockhold (2006) also represented the industry viewpoint, describing industry quality control procedures and the “independence” of the industry statistician. He also proposed that industry submit

to medical journal the protocols and prespecified analysis plans along with the manuscript.

However, it wasn't just the industry that seemed to have concerns with this policy: various professional organizations and prominent academic researchers were also vocal in their criticism, sometimes using language somewhat stronger than one typically sees in these settings. Here is a sampling.

Molenberghs, Imrey and Drake, representing the International Biometric Society (2006): “We are troubled by this policy's asymmetric treatment of potential conflicts of interest, with data analysis that is submitted by industry requiring independent verification or replication, but no such requirement for studies submitted by other researchers. Conflict of interest is possible in all settings, and the review process should not be different based on the source of the manuscript.... Conflicts of interest of a commercial or other nature can arise anywhere, and an asymmetric policy can have adverse effects.”

Holt, Grieve and Bird representing the Royal Statistical Society (2005): “We believe that [JAMA's policy] will deny a level playing field, and so runs counter to the historical ethos of joint-working by statisticians, including pharmaceutical statisticians, and editors of medical journals to enhance the scientific integrity of medical research. Statisticians in the pharmaceutical industry have played a substantial role in advancing better and best practice in the design, analysis, conduct and reporting of medical research.... Further, we believe that JAMA's proposal aims at the wrong target. Rogue behaviour apart, editors of medical journals are as aware as statisticians are that routine threats to the integrity of medical research articles are selectivity in abstracting and in Discussion.”

Statement from the International Society for Pharmacoepidemiology (2005): “The International Society for Pharmacoepidemiology (ISPE) believes that the new JAMA policy will not meaningfully alter problems of bias in published research. These new instructions create an unfortunate dual standard for submission review based on the funding source of the research (commercial vs. non-commercial). The instructions also imply a hierarchy of research based on affiliation (academic vs. non-academic).

Senn (2006): “The main objection I have to the JAMA policy is not that it requires independent validation of analysis but that it seems to require it only for studies sponsored by the pharmaceutical industry.... I am not

against distrust, but I am against selective distrust. If distrust is our currency we need to make it universal and apply it to academics and journal editors as well.... After the stem cell meltdown, what justification does JAMA have for giving academics a free ride?"

Rothman and Evans (2005): "This policy is manifestly unfair. It ... denigrates the reliability and professionalism of industry-employed statisticians, whose credentials JAMA apparently considers insufficient.... [W]hat is the mark of a qualified statistician? A degree? Certification by the Royal Statistical Society? And who is academic? A retired professor who becomes an industry consultant? A retired industry statistician who joins a university? Once paid by industry, would an academic statistician remain independent? Will mail order universities be acceptable, or must the universities meet specific accreditation requirements? These questions are meant only to illuminate the absurdity introduced by these new instructions."

Despite this strong, consistent criticism, JAMA remains firmly committed to its policy. Responding to the letters from Loew and the International Biometric Society, Fontanarosa and DeAngelis (*JAMA* 2006) stated "Dr Loew and PhRMA contend that industry-sponsored studies are not at higher risk of bias and thus do not require 'special scrutiny' and that 'vigorous government oversight . . . ensures the integrity of data and results.' Despite these assurances, scientific and ethical lapses involving industry and industry-sponsored studies strongly indicate otherwise...." and "Dr Molenberghs and colleagues from the International Biometrics Society are 'troubled by [the] asymmetric treatment of potential conflicts of interest.' All authors of JAMA articles are required to report their individual financial conflicts of interest. However, there may be unique considerations for employees of study sponsors because of the vested financial interest those companies have in reporting favorable study results. Some biostatisticians employed by industry, possibly including International Biometrics Society members, might receive pressure to exclude certain data or not fully report the results of some analyses. Moreover, some statistician-employees might have individual financial incentives that could subtly influence their data analysis and reporting. Both of these possibilities are more troubling than the concerns raised by Molenberghs et al."

JAMA seemed particularly unhappy with the editorial by Rothman and Evans. In a response, Fontanarosa and DeAngelis (*BMJ* 2006) wrote, "Ironically, this blatant and unbalanced criticism of the JAMA policy was published just two days after the *New England Journal of Medicine* issued its expression of concern about the VIGOR study, which directly resulted from concerns about data integrity, analysis, and reporting in a major industry sponsored study.... We believe our policy is necessary and sound. What we find unfair and absurd is that some companies and research sponsors will resort to tactics that manipulate clinical research data and misrepresent scientific information; that some commentators, such as Rothman and Evans, apparently do not fully acknowledge the magnitude and implications of these problems...."

Rothman and Evans apparently were not fully convinced by the JAMA reply, and continued the somewhat testy exchange in a letter to the editor of the *British Medical Journal* (2006): "Citing examples of industry malfeasance, of which we agree there are many, does little to justify an inequitable policy. In which examples was the malfeasance the responsibility of the industry statistician? Which would have been prevented by having the analysis reviewed by an academic statistician? As Senn noted, 'independent' academic authors have their own biases, and they do not usually have to undergo the intense scrutiny of regulatory authorities. "

While the pharmaceutical industry in general, and pharmaceutical statisticians in particular, may consider JAMA's policy to be unfair, it is clearly true that there is some lack of confidence in the objectivity of the pharmaceutical industry in the broad medical community. For example, there are several published evaluations of the issue of conflict of interest and its impact on the reporting of clinical trial results that have all concluded that there is an industry bias (Bekelman, Li and Gross 2003; Ridker and Torres 2006; Davidoff et al 2001). In addition, there have been notable cases of misconduct in industry-sponsored trials, such as the case reported by Nathan and Weatherall (2002).

It's not the concern with financial conflict of interest *per se* that the pharmaceutical industry should find unfair, rather it's the specific solution being implemented by JAMA. Some of the issues were raised in the above references. For example, the industry finds it hard to understand why financial conflicts of interest are singled out for special treatment. It is not at all clear that financial conflicts lead to any more bias in reporting clinical trial results than the desire for fame, tenure or promotion that might exist for an academic researcher.

There are also the more practical issues with implementing this policy. Those working in the industry find more than a little naïveté associated with *JAMA*'s comment that “the entire raw data set should be given to the independent biostatistician.” Clinical trial databases can be enormous and enormously complicated; understanding them can take considerable effort, and managing them can take a staff of data management professionals. Therefore, complying with *JAMA*'s policy puts industry in a dilemma:

1. Industry can interpret “raw data set” somewhat figuratively, and give the independent statistician a patient-level dataset that's ready, or nearly ready, for analysis. The disadvantage of this approach is that considerable pre-processing is necessary, and the academic statistician would have no way of knowing whether this dataset has been manipulated to produce the desired result. Validation of an analysis using only these processed datasets would essentially be for show – it would satisfy the letter of the *JAMA* policy but would not accomplish any meaningful goal. If the industry statistician did indeed “receive pressure to exclude certain data or not fully report the results of some analyses,” it would probably not be apparent in the pre-processed datasets.
2. Industry can interpret “raw data set” literally, and give the independent statistician all the data and the resources to manage it. The disadvantage of this approach would be the difficulty of maintaining independence. The cost for a contract research organization to perform such an analysis has been estimated to be between \$50,000 and \$300,000, and there is little reason to think that an academic statistician (or the statistical analysis unit of a university) could do it for less. Could a group called upon to do many such analyses per year at that price be considered independent?

It is also interesting to note *JAMA*'s requirement that the “independent biostatistician should verify the appropriateness of the analytic plan.” One can easily imagine disagreements between the industry and academic statisticians with regard to statistical methods. The *JAMA* policy implies that the academic statistician's opinion trumps the industry statistician's, which in theory could lead to the publication abandoning the prespecified analysis plan agreed to by regulatory agencies around the world. This could lead to inconsistent results appearing in the publication and the package circular, which is an untenable situation for the sponsor.

In fact, if the academic statistician's opinion trumps the industry statistician's opinion, it's not clear what the point is of having the industry statistician involved at all. And if industry can not be trusted to choose the analysis methods or perform the analysis, then how can they be trusted to write the protocol, collect and manage the clinical database, monitor the investigator sites, interpret the results, etc? To a large extent, the *JAMA* policy seems to question industry's role in clinical research in general. It is particularly unclear why they have singled out the statistical analysis, which, due to its clear prespecification and documentation, some might consider to be one of the pieces of the process least susceptible to bias.

Although the *JAMA* policy has been in place for over a year, experience with it is still limited. It will be interesting to see how the *JAMA* policy will work over time. Will it result in a truly independent analysis that will catch errors and reduce bias? Or will it become little more than a charade designed to check a box without accomplishing anything meaningful?

4 The American Association of Medical Colleges Policy

In January 2006, the American Association of Medical Colleges (AAMC) released a document entitled “Principles for Protecting Integrity in the Conduct and Reporting of Clinical Trials.” (2006) As stated in the document, the issue being addressed is public concern regarding the timely and complete reporting of industry-sponsored clinical trials, which challenges the integrity of the academic medical community. The AAMC hopes to gain broad consensus among stakeholders, including industry, FDA and the medical community, for their set of 22 principles. The principles are meant to apply to all late-stage clinical trials (all phase 3 and 4 clinical trials, and some late phase 2 trials) conducted in academic medical institutions, regardless of the source of funding.

Regarding the publication of research results, the document emphasizes the ethical obligation to make results publicly available, even when the study is terminated early, and the sponsor's obligation to fund the cost of analysis. The document also supports clinical trial registration, including updates linking the trial to all published reports.

Their recommendations regarding authorship are reasonable, including their support for the ICMJE and the Consolidated Standards of Reporting Trials (CONSORT) principles.

While the AAMC does not formally advocate *JAMA's* requirement for an independent statistical analysis by an academic statistician, their position is similar. First, they require that every multisite trial have a publication and analysis (P&A) committee independent of the sponsor's control. The P&A committee must have access to the full data set and must have the expertise to perform additional analyses themselves. While the sponsor can conduct the prespecified analysis, the P&A committee should be able to reproduce the analysis if they deem it necessary. This policy is apparently meant to avoid situations like the one described by Nathan and Weatherall (2002), in which the pharmaceutical sponsor is perceived to have blocked publication of unfavorable results. While this proposal is reasonable for major outcomes trials, it seems to reflect a lack of understanding that these large trials are only a small proportion of the trials conducted by the industry.

Clearly, the most controversial aspect of the document is principle #5: "After publication of the results, the sponsor, the investigators, and their institutions should adopt a model for public sharing of the data underlying publications similar to that of NIH, which permits exceptions for confidential or proprietary information." That is, the sponsor is required not only to publish the results of the trials, but also to publicly release all raw patient-level data. Public release of clinical trial databases would clearly have some advantages, and in fact might be exactly the kind of step that could help restore public confidence in the pharmaceutical industry. It would help avoid any perception that industry is hiding something, and it could be a veritable gold mine to medical researchers around the world. On the other hand, it would almost certainly create substantial problems for the industry and the medical community. First, it would be extremely difficult to define standards for sharing raw data. In addition, independent publications of clinical trial results by researchers not affiliated with the sponsor could conflict with the original results for a variety of reasons, such as lack of understanding of the study or database design or use of different statistical methods that were not prespecified. In fact, we are aware of cases where study investigators with access to the clinical database have published erroneous results without input from the sponsor. Finally, commercial pressures might unleash a somewhat unseemly attempt by some companies to intentionally sow confusion and misinformation regarding a competing product.

Ultimately, the pharmaceutical industry must decide whether or not to take this bold step. If they resist, they will need to clearly articulate a rationale that does not sound self-serving.

5 How Do We Achieve Clinical Research Transparency?

In this section we will summarize some of the mechanisms to increase the transparency of clinical research. Since at its best "transparency" has a vague definition, the best that one could hope for is a consistent journey towards an end of improving public health and patient welfare. In fact, there probably is not a single goal or target that is achievable and/or will signal the end of this debate, and thus it is critical we all agree on the direction.

Much of the debate around transparency relates to conflict of interest of researchers. In addition there are logistical and practical considerations of making information available to a wide range of stakeholders. The logistics of transmitting complex information to a public with various levels of knowledge of clinical research is a daunting task. But here we will stick to the issues of policy and philosophy and leave others to sort out the logistical issues.

Everybody in industry, academia, government, and non-government organizations has some conflict of interest related to the success of their organization. Many of the cases of overt fraud in recent years have occurred in the academic environment. Fortunately the incidence is small, but the larger problem is the subtle bias that creeps into the release of information, and this has been the appropriate focus of the journal editors. But, the journal editors themselves have conflicting objectives. Their business model is to produce articles that are scientifically accurate and interesting to the readership. If people comply with the drive for transparency and put their research out on a public venue, that should be viewed as a positive if it is supplemented by appropriate peer review and editorials by learned individuals. However, if journal editors delay the release of information so they can announce the significant and interesting headlines themselves, this is also a conflict of interest. (Rockhold and Krall, 2006)

In Sections 1 and 2 above, we reviewed some of the general issues revolving around protocol registration and its importance in the transparency process. Protocol registration serves as a mechanism to create the inventory of

research and therefore plays an important role. The results are an even more important part of the process as that is what directly relates to healthcare Professionals and patients and how they should get access to a fair balance of information. Protocol registries serve as a public mechanism to “audit” the availability of research.

Results registries are even more in their infancy than protocol registries. A number of pharmaceutical companies such as GlaxoSmithKline, Lilly, AstraZeneca, and Roche have instituted results registries for their marketed compounds’ clinical trials results. (As an important note to meta analysts, these registries would not include information on research conducted by others on those products) This is done to various standards, but the minimum standard has been dictated by PhRMA (PhRMA Principles 2004) and IFPMA (IFPMA Joint Position 2005) in documents that highlight that “confirmatory” trials for marketed products are made public once the product is on the market. In fact, PhRMA has a registry that they manage, ClinicalStudyResults.org, that is intended to contain all the results (or links to peer-reviewed publications) for products marketed by pharmaceutical companies doing business in the United States. The compliance with posting these results is not known. There are no results registries that are comprehensive although it is under discussion as part of the WHO, ICTRP initiative discussed earlier.

As was the case with protocol registration, understanding the target audience for results is critical. The level of detail for a person doing meta analyses is vastly different than the level of detail that would make sense for a patient or a practicing physician. As noted above, we think the argument of breath over depth is the way to drive transparency of research; i.e., providing more trials with some information disclosed is better for the public health than providing tremendous levels of detail within any one given trial. Having complete detail on every single trial will result in a huge effort, will slow down the implementation, and will go largely unused by the vast majority of the stakeholders.

It is unclear who is going to manage the overall process of protocol registration or results registration. Who is going to judge the overall accuracy or quality of these databases? We contend that starting registration in the spirit of transparency is an important first step but we all must recognize that it is nearly impossible to provide a worldwide enforcement network. At some level, as indicated in the discussion of the *JAMA* policy above, we must accept the integrity of the clinical researcher, the data management staff, the person analyzing the data, etc. We will never have a way to monitor the literally hundreds of thousands of individuals performing clinical research. Without some level of trust in the system, with necessary checks and balances, the concept of transparency loses its appeal, as it is no longer a principle of transparency in research, it is a policed activity.

Researchers in the pharmaceutical industry ask about how academic and government sponsors will be monitored. Government sponsorship probably has some hope of achieving a reasonable level of monitoring because funds are made available on a public basis and there is some control over the flow of information. But there are many thousands of academic institutions around the world performing clinical research, and it is impractical to think there is any central body that can actually monitor the quality and complete transparency of all those institutions.

So, who owns the truth? Can we trust no one? Do we do away with peer review because it is getting in the way of transparency or do we expand it to have every clinical trial have a peer review system and get published in a journal? Should we just have online journals with complete access to raw data by all? Who oversees the journals? Don’t they live off of advertising dollars? What if that stopped? Is the system really that broken? Some have suggested that all clinical research should be conducted by government or academia. Surely they also have conflicts of interest and in fact, given the level of risk in development of new treatments (particularly small molecules and vaccines), it is only a for profit enterprise that is going to accept that risk versus a potential payoff. Society would not thrive with the loss of innovation. Without someone willing to accept that risk, the medicines being used today by you and me would be the same medicines that were used by our parents.

Making relevant information available to the public (at all levels) would go a long way to restoring trust. In order to understand that people are getting fair balance and information in results disclosure, the protocol registration process is an important step. While it would be very idealistic to believe that there could be a central worldwide organization to manage the overall clinical research enterprise, we must believe that whatever malfeasance and poor intent that exists in the system is rare enough that by improving the level of transparency we will force those who are performing poor clinical research to be exposed, while at the same time allowing those doing perfectly good research to demonstrate and prove that to the general public.

In doing this however, all of the various entities have to work together, create solutions that are workable and have the patience to see them implemented before moving on to improving them or adding to the level of information. If we do not approach this with a positive spirit and are continually ratcheting up the demands, people will resist strongly and say enough is enough. In trying to help make things more transparent we can't accommodate every single wish of every single stakeholder.

We support the concept of transparency of clinical research in the pharmaceutical industry, in academia, and in government. We all share the desire to improve public health and to make sure that physicians and patients have the information they need to have diseases appropriately treated. However, we cannot put information into the public that contradicts what is approved by the regulatory agencies or we could run the risk of doing more harm than good. We must also accept that the incentives that drive clinical research, whether it be pharmaceutical, academic, or government are real and have for decades driven innovations in the treatment of many diseases. If we improperly tilt the balance, the very people we are trying to protect and support, i.e. the patients, will suffer in the long run. And thus we must strike an appropriate balance between absolute and complete transparency for everything versus the drive for innovation. We believe the cases where innovation is harmed by transparency are relatively rare but they do exist and need to be accounted for.

We recommend that the pharmaceutical industry adopt not only the agreement set forth by PhRMA and IFPMA but seriously consider those principles being put forward by the WHO. We believe if all researchers adopt the principles of transparency being recommended by the WHO in the vast majority of research that the public health and the patients themselves will benefit.

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Biopharmaceutical Section Executive Committee Minutes

August, 2006

Seattle, Washington

Attendees (in person or by phone): Stacy Lindborg, Margaret Minkwitz, Kay Larholt, Mani Lakshminarayanan, Len Oppenheimer, Amit Bhattacharyya, Brian Wiens, Andy Mugglin, David Manner, Christie Clark, Steve Gulyas, Anna Nevius, Keith Soper, Gregg Campbell, Shuguang Huang, Neal Thomas, Jim Colaienne, Jim Whitmore, Steve Snappin, Frank Shen, Joe Heyse, Naitee Ting, Aparna Raychaudhuri, Daniel Christen, Philip Pichotta, Mike Hesney

Election results were announced. Elected officers for 2007 will be Kannan Natarajan (chair-elect); Kalyan Ghosh (program chair-elect) Neal Thomas (publications officer) and Margaret Minkwitz (council of sections representative). Len Oppenheimer will chair the nominations committee for the 2007 ballot. Offices to be filled by election.

The section currently has a healthy budget. The executive committee will evaluate additional services to the membership that can be provided with the stable budget. Members were asked to bring ideas to the transition meeting in November.

Program chair for 2006 Christie Clark reported that the section-supported 40 sessions (7 invited, 13 topic contributed and 20 regular contributed). The section also sponsored about 35 round table luncheons. The section did not participate in the breakfast round table coffees this year.

Program chair for 2007 Amit Bhattacharyya reported that he received 25 proposals for invited sessions at JSM 2007. Of these, 4 to 7 will be accepted. In addition he expects about 5 proposals for continuing education courses.

Student paper chair Aparna Raychaudhuri reported that the number of student paper submissions continues to decline. Committee members discussed various ways of increasing the visibility of these awards to increase participation of students.

Best contributed paper award chair Shuguang Huang reported on the winners from 2005 JSM and plans for 2006 and futures years.

Co-editors Rick Caplan and Phil Pichotta reported on the issues of *Biopharmaceutical Report*. Past issues of the newsletter are available on the web, and future issues will continue to be distributed electronically.

FDA/Industry Workshop co-chairs Lee Kaiser and Richard Kotz reported that 370 people have already registered for the meeting. Two of the 4 short courses have sold out and the others are nearing capacity.

Corporate sponsorship chair Jim Colaianne reported that the number of corporate sponsors has declined slightly this year. The committee continues to work on contacting companies to arrange sponsorship. The full list of sponsors is on the web page.

Council of Sections representatives Steve Gulyas, Naitee Ting and Anna Nevius reported on issues that the council has been discussing. The various student paper awards that are sponsored by the various sections are being compiled so that students have a place to go for a comprehensive list. Sections that sponsored coffee roundtable discussions reported positive feedback and these will probably be continued. Posters have been well received but suggestions were taken to increase the visibility.

Keith Soper volunteered for another year at the helm of the Fellows Committee.

Founding editor Joe Heyse reported on the progress of *Statistics in Biopharmaceutical Research*, the new journal sponsored by the FDA. Submissions are currently being received and evaluated. Joe plans the first issue in 2007. ■

2006 Treasurer's Report

Mani Lakshminarayanan

We just completed yet another year with a budget surplus out of a total income amounting to \$40,500. We continue to support the Annual FDA/Industry Workshop and the Executive Committee has already started exploring ways of offering additional services to the sections members using this surplus, which include sponsoring web-based training and possibly reduce the cost of membership fee. At the time of writing this report, the Executive Committee has already submitted a proposal for web-based training to the ASA Board of Directors for their approval.

The 2007 budget has been finalized and submitted to ASA and is summarized below:

	Income	Expenses
General	\$37,000	\$4,755
Proceedings	\$2,700	
Conference	\$18,000	
Total	\$57,700	\$4,755

As in previous years, Kathleen Wert of the ASA will be handling the paper version of the budget for the FDA/Industry Workshop this year also except for the fact that we have been asked to add a line item under the "conference" column for the "net share" as \$18,000 as shown above. As stated above, the Executive Committee is considering several options (including offering web-based training to its members) for improving services of the section to its members. The Biopharmaceutical Section is still the largest and one of the most active groups within ASA, has an annual budget approximately twice that of any other sections, and, still continues to lead in terms of service to its membership. The Executive Committee is looking for any suggestions from the members for any additional services that they would like to see in 2007 and beyond. ■

Corporate Sponsorship Program

Jim Colaianne

Again this year, we are deeply indebted to our corporate sponsors for their generous support of our section's ongoing programs and activities. This year we have 29 corporate sponsors as listed below.

The Biopharmaceutical Section with over 2000 members is one of the largest and most active sections within ASA. Thanks in a large part to the help and support of our corporate sponsors we have been able to provide unique and substantial contributions to our members and the greater biopharmaceutical community at large. We are able to sponsor or co-sponsor several professional meetings throughout the year, including the FDA/Industry Workshop, the Midwest Biopharmaceutical Statistics Workshop and the Deming Conference. We are also able to provide cash awards for the Student Paper Awards program and Best Contributed Paper program at the annual Joint Statistical Meetings.

Invitations to become corporate sponsors are mailed out in January of each year. Any company interested in becoming a corporate sponsor can contact the chair of the Biopharmaceutical Section, Brian Wiens (Brian.Wiens@gilead.com) or the chair of the Corporate Sponsorship Committee, Jim Colaianne (jcolaian@prdus.jnj.com).

The other members of the Corporate Sponsorship Committee are Russ Helms of RHO, Inc., Kay Larholt of Abt Associates, and Alaknanda Preston, of GlaxoSmithKline. Without their able assistance this committee would not be viable. ■

2006 Biopharmaceutical Section Corporate Sponsorship List

Abt Associates	Insightful Corp.
Allergan	Johnson & Johnson, PRD.
Amgen, Inc.	Merck & Co., Inc.
Averion, Inc.	Novartis Pharmaceuticals
Biogen – IDEC	Pfizer, Inc.
Boehringer Ingelheim Pharmaceuticals	Proctor and Gamble Pharmaceuticals
Boston Scientific	Quintiles Innovex
Bristol-Myers Squibb	RHO Inc.
Centocor, Inc.	Sanofi – Aventis
Cytel Software, Corp.	SAS Institute
Eli Lilly & Co.	Schering-Plough Res. Inst.
GlaxoSmith Kline	Takeda Global Research
Genentech, Inc.	Waban Software
Hoffman-LaRoche, Inc.	Wyeth Consumer Healthcare
ICON Clinical Research	

New Distance Training Program

Alex Dmitrienko

The Biopharmaceutical Section is preparing to launch a web-based distance training program. Web-based training is becoming increasingly popular across a variety of industries as a low-cost alternative to live training courses, and the Section is excited about offering the program as a service to our membership.

The first webinar in the series, "Multiple Comparisons in Clinical Trials" taught by Alex Dmitrienko (Eli Lilly and Company), will take place on March 21 (noon-2:00pm EST). The two-hour webinar will give an overview of key topics in multiple comparisons with emphasis on multiplicity issues arising in clinical trials. It will cover traditional methods as well as novel approaches, present practical advice from experts and discuss regulatory considerations in this area. This webinar is based on an award-winning full-day course that was offered at JSM 2005 and 2006 (ASA Excellence in Continuing Education Award, 2005).

The Section has subsidized this training program to provide our members with the lowest possible rate. The registration fee for this two-hour webinar is only \$34 for section members. ASA members have an option to join the section for \$8 and receive the section member rate. In addition, departments are encouraged to have multiple participants share a single session (for example, by projecting the webinar in a conference room).

For more information about the web-based training series and to register for the March 21 webinar, please visit the Section's web site at <http://www.amstat.org/sections/sbiop/webinarseries.html>.

We encourage you to share this information with your colleagues. ■

Biopharmaceutical Section Student Paper Award 2007 Submission Guidelines

Aparna Raychaudhuri

Student paper awards (cash award, honorable mention) are presented annually at the JSM meeting for student research papers with statistical content applicable to the Biopharmaceutical arena. The following guidelines will help in making the judging process fair and unbiased:

- Submissions should be labeled as a "student paper submission" and sent to Amit Bhattacharyya, chair for the Biopharmaceutical Section, Amit.Bhattacharyya@gsk.com.
- Submissions of papers for consideration must be received electronically in WORD format.
- In order to facilitate blinding, the student's name should appear only on the first page, names for references should not be included in the text (numbers for references used in text, names on reference page only). References which would un-blind a reviewer to the student's name or the student's advisor/collaborator will be removed for the review.
- The length of the paper should not exceed 15 pages of double-spaced type of text with no more than 5 additional pages of appendices (20 pages maximum). Please consider a manuscript style for the paper to facilitate publication in the proceedings for JSM or to another appropriate journal.
- Deadline for submission is March 31st, 2007.

Please visit www.amstat.org/sections/sbiop/award.htm to see the list of past winners and honorable mentions and also learn about the Biopharmaceutical Section of ASA. ■

The 30th Annual Midwest Biopharmaceutical Statistics Workshop

May 21 – 23, 2007 • Ball State University, Muncie, Indiana

Preliminary Program

Monday, May 21

8:30 am – 4:30 pm

Workshop Registration

FEE: \$150 until May 1 (\$50 for students), \$180 after May 1

9:00 am – 1:00 pm

Short Course (Separate Registration Fee: \$55)

Presenters: PETER THALL, U. of Texas, M.D. Anderson Cancer Center

Topic: Bayesian Dose Finding

2:15 pm – 2:30 pm

Introduction And Welcome

Mani Lakshminarayanan, Pfizer

DR. MICHAEL MAGGIOTTO, Dean of College of Sciences and Humanities, Ball State University

2:30 pm – 3:30 pm

Plenary Session

Speaker: NORMAN BRESLOW, University of Washington

Topic: Design and Analyses of Two-Phase Stratified Case-Cohort Studies

3:30 pm – 4:30 pm

Plenary Session

Speaker: JASON HSU, Ohio State University

Topic: All Things are Connected From Bioequivalence to Pharmacogenomics

5:00 pm – 7:00 pm Monday Night Mixer

Tuesday Morning, May 22

Concurrent Sessions

8:30 am – 11:30 am

A. Statistical Considerations in Drug Development in the East and West

Organizer/Chair: Rob Muirhead, Pfizer

1. "Topic to be announced", Michael Mann, Pfizer
2. "Topic to be announced", Shein-Chung Chow, Duke University
3. "Topic to be announced", Thomas Cook, Merck
4. "Topic to be announced", James Hung, FDA

B. Modeling the Relationship Between Clinical Outcome and Animal Models

Organizer/Chair: Kim Crimin, Wyeth

1. "Improving the Quality of Clinical Candidates: A Multi-Criteria Optimization Strategy", Phil Burton, ADMETRx
2. "Preclinical Pharmacokinetic/Pharmacodynamic Modeling in Drug Discovery and Development", Jing Liu, Pfizer
3. "Topic to be announced", Speaker to be announced
4. "Discussant", Tom Vidmar, Pfizer

C. **Data Mining Tools and Resources**

Organizer/Chair: Jonathan Schildcrout, Vanderbilt University

1. "Using Open Source Software for Data Mining: Issues and Solutions", Gregory Warnes, University of Rochester
2. "Topic to be announced", Srinivasan Parthasarathy, Ohio State
3. "Information Mining Tools for Heterogeneous Clinical Trials Data", Fatih Altiparmak, Ohio State
4. "Making the Best of the Data You Have, Instead of the Data You Want", Andy Liaw, Merck
5. "Topic to be announced", FDA Speaker to be announced

11:30 am – 1:00 pm Lunch Buffet

Tuesday Afternoon, May 22

Poster Session

12:00 pm – 1:30 pm

Chair: Kim Perry, Innovative Analytics

Posters will be accepted on any biopharmaceutical statistical topic.

Abstracts must be received by April 27, 2007. Students may qualify for the Charlie Sampson poster award if abstract, poster panels, and a paper briefly describing the poster are received by April 27.

For more information contact Kim Perry at (269)-488-3204.

Concurrent Sessions

1:30 pm – 4:30 pm

A. Modeling and Simulation

Organizer/Chair: Alan Hartford, Merck

1. "Sample Size and Power Calculations for a Longitudinal Endpoint in Clinical Trials: A Case Study of Using Modeling and Simulation", Jose Pinheiro, Novartis
2. "Examining Clinical Utility: A New Formulation for an Old Drug", Kevin Dykstra, Pharsight
3. "Topic to be announced, Jim Bosley, Rosa Pharmaceuticals
4. "Discussant", Discussant to be announced

B. Specification Setting

Organizer/Chair: Kim Vukovinsky, Pfizer

1. "Setting Specifications for Bioassays", Tim Schofield, Merck
2. "Considerations in Stability Data Analysis for Specification Setting", Suntara Cahya, Jeff Hofer, Lilly
3. "Setting CU Acceptance Criteria for Moderate Sample Sizes", Greg Larner, Kim Vukovinsky, Pfizer, Soren Anderson, Novo Nordisk, Myron Diener, Sanofi-Aventis, Jim Pazdan, Novartis, Lori Pfahler, Merck, Dennis Sandell, Siegfried, Helen Strickland, GSK
4. "Specification Setting for Combination Products", Greg Steeno, Wenqing Li, Lenny Margulis, Pfizer
5. "Specification Setting in Parenterals", Brent Harrington, Wyeth

C. Data Mining Methods in Genomics and Proteomics

Organizer/Chair: Scott Chasalow, BMS

1. "Linking Metabolic Profiles to Biological Outcome", Stanley Young, NISS

2. "Multiplicity and Meta-Analysis in Genetic Association Studies", Katy L. Simonsen, BMS.
3. "Developing Predictive Classifiers and Their Use in the Design of Pivotal Trials", Richard Simon, NIH
4. "Discussant", Scott Chasalow, BMS

Tuesday Evening Banquet

Dr. Terry King, Provost and Vice President for Academic Affairs, Ball State University

Announcement of Student Winner of Charlie Sampson Poster Award

Speaker: **Mary Ellen Bock**, Purdue University and President, ASA

Topic: Directions in Statistics

Wednesday Morning, May 23

Concurrent Sessions

8:30 am – 11:30 am

A. Non-parametric/Rank-Based Methods

Organizer/Chair: Donna Kowalski, Astellas

1. "Rank-Based Analysis of Crossover Trials for Classic and Novel Designs", Mary Putt, University of Pennsylvania
2. "Efficient Rank-Based Inference for Stratified Trials", Devan Mehrotra, Merck
3. "Adjusting for Ordinal Covariates by Inducing a Partial Ordering", Vance Berger, National Cancer Institute
4. "Discussant", John Spurrier, University of South Carolina

B. Bayesian Approaches in Stability, QbD, Random Effects Modeling, and Dose Finding

Organizer/Chair: David LeBlond, Abbott

1. "Bayesian Hierarchical Modeling of Drug Stability Data", Jie Chen, Merck
2. "Posterior Predictive Approach to Pharmaceutical Process Optimization for Quality by Design", Gregory Stockdale, GSK
3. "Bayesian Approach to Constructing Tolerance Intervals for the 1-Way Random Effects Model", Stan Altan, Johnson & Johnson
4. "Bayesian Continuous Reassessment Method in Phase I Dose Finding Studies", Yi-Lin Chiu, David LeBlond, Abbott
5. "Bayesian Specification Setting", Shea Watrin, Amgen

C. Data Mining Methods in Drug Safety and Post-Marketing

Organizer/Chair: Alan Menius, GSK

1. "Large-Scale Logistic Regression for Pharmacovigilance", David Madigan, Rutgers University
2. "Statistical Modeling of Pre- and Post-Marketing Safety Data", Michael O'Connell, Insightful
3. "Safety Case-Studies Using Propensity Adjustments for Bias", Bob Obenchain, Lilly
4. "Leveraging Observational Data for Pharmacovigilance", Patrick Ryan, GSK

11:30 am – 1:00 pm Lunch Buffet

Closing Remarks

Mani Lakshminarayanan, Pfizer

For more information on the workshop, please contact **Mir Ali**, Ball State University, (765) 285-8670, Email: mali@bsu.edu or **Melvin Munsaka**, Takeda Global Research & Development, (224) 554-5912, Email: mmunsaka@tgrd.com. The preliminary program will be updated periodically at the web site <http://www.mbswonline.com/>. Registration will be available on the website in February. ■

Workshop in Bayesian Biostatistics

Amy Herring

The Department of Biostatistics at The University of North Carolina at Chapel Hill will hold a workshop in Bayesian Biostatistics, co-sponsored by SAS Institute, that will showcase new options for Bayesian analysis available in SAS® software. The workshop will be held May 17-18, 2007, on the historic UNC campus. Led by Joseph G. Ibrahim, Alumni Distinguished Professor of Biostatistics, the workshop will provide an introduction to Bayesian methods as well as practical examples using upcoming new software in SAS. The target audience for the workshop includes practicing biostatisticians and other public health researchers at the MS or PhD level in the pharmaceutical industry, in consulting, and in government or academics. No prior knowledge of Bayesian methods will be assumed; some familiarity with SAS will be useful. Additional details, including online conference registration, are available at <http://www.sph.unc.edu/bios>. ■

Let's Hear from You!

If you have any comments or contributions, contact the Editor: Richard Caplan, phone: 302-885-5915, email: richard.caplan@astrazeneca.com; or Associate Editors: Philip Pichotta, phone: 203-882-9321, email: pichottapm@optonline.net and Thomas Dobbins, phone: 215-328-2092, email: thomas_dobbins@merck.com.

We are looking for volunteers to write articles that will be of interest to our members. Some authorless topics that have been suggested include validating endpoints and working with SEALD, enhanced trial designs, recent changes in oncology research, animal studies and veterinary medicine, bioequivalence in biologics and personalized medicine. Non-technical articles related to our work are welcome. If you have been working in an area and would like to suggest a topic or volunteer to write, please send us an email.

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