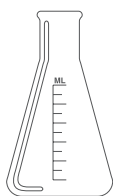


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Note from the Editors

Comparative effectiveness research (CER) is increasingly a field in which statisticians in the pharmaceutical industry will have to involve themselves. Health care reform legislation builds on \$1.1 billion designated for this research in the American Recovery and Reinvestment Act (ARRA) of 2009, commonly known as the Stimulus Act. The health care legislation creates an institute specializing in comparative studies, named the Patient Centered Outcomes Research Institute (PCORI), with at least \$500 million in annual funding starting in 2013. The feature article in this issue, written by David Vanness, discusses the use of mixed treatment comparison metaanalysis, another hot topic in the field, in the design of comparative effectiveness trials and demonstrates how their use could result in more efficient and less risky trials. ■

Contents

Featured Article

Using Bayesian Mixed Treatment Comparison
Meta Analysis to Improve the Design of
Comparative Effectiveness Trials
David J. Vanness, Ph.D. 2

Biopharmaceutical Section News

Note from the Editors 1

Letter from the Chair 10

Biopharmaceutical Section Calendar 11

Summary of 23 October 2009
Biopharmaceutical Section Executive
Committee Meeting. 12

Report on the 2009 Non-Clinical
Biostatistics (NCB2009) Conference 14

66th Annual Deming Conference on
Applied Statistics. 16

The Second International Symposium
on Biopharmaceutical Statistics 17

Let's Hear from You! 17

Using Bayesian Mixed Treatment Comparison Meta Analysis to Improve the Design of Comparative Effectiveness Trials

David J. Vanness, Ph.D.*

Introduction

According to the Institute of Medicine, comparative effectiveness research (CER) “is the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat and monitor a clinical condition, or to improve the delivery of care” (1). The American College of Physicians recently stated that a lack of CER prevents physicians and patients from making effective, informed treatment choices that meet the unique needs of patients (2). The recent allocation of \$1.1 billion to CER in the American Recovery and Reinvestment Act (ARRA) was an initial step toward closing this evidence gap. With the further creation under the recently enacted Patient Protection and Affordable Care Act of a Patient Centered Outcomes Research Institute (PCORI), to be funded by a separate trust taking in up to \$500 million per year, it is likely that the banner of comparative effectiveness (CE) will advance with some urgency.

The CER agenda promises to use a variety of data sources and methods, including observational research, simulation and evidence synthesis. But, in order to provide the robust information necessary to influence clinical practice, randomized controlled trials (RCTs) will still need to play a central role (3; 4). The evidence necessary to inform real-world treatment decisions must assess a broad range of outcomes, comparing clinically relevant alternatives in typical patient care settings serving diverse populations (1). Unfortunately, while “pragmatic” RCTs meeting these requirements are more relevant to decision-makers, they also can be dramatically more costly in terms of time and resources compared to “explanatory” trials used to gain marketing approval (3). Notably, the pragmatic Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) (5) cost over \$130 million and took over eight years from first enrollment to first results. By the time ALLHAT was complete, new interventions had already come to market, leading AHRQ Director Carolyn Clancy to note, “You might be answering a question that by the time you are done, no longer feels quite as relevant” (6). Unless there are major changes in how RCTs are designed, conducted and analyzed, the nation risks spending its limited research resources inefficiently — either answering the wrong questions or the right questions too late (4).

While synthesizing existing evidence and conducting new RCTs may seem to be substitutes for one another in the CER enterprise, it ultimately may be more useful to think of them as complements. If the results of a hypothetical new CE trial ultimately are to be synthesized with the existing evidence base to inform decision-making, then it may be in the best interests of trial sponsors to design the new CE trial with this in mind (7). This article suggests that Bayesian Mixed Treatment Comparison meta-analysis methods could be useful in the design of new CE trials — perhaps making them more efficient and less risky.

Sample Size for Comparative Effectiveness Trials

In theory, determining the sample size for a classical explanatory RCT is a straightforward (though context-specific) process built on the discernment of truth — how many observations are required to be confident one is rejecting the null hypothesis when it is false (by a pre-defined margin of clinical significance) given a pre-specified tolerance

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for rejecting the null hypothesis when it is true (8)? In practice, however, power depends on *ex ante* estimates of the unknown mean and variance of outcomes in the control group and specification of a clinically meaningful difference in outcomes. Systematic approaches to obtaining these estimates from prior data are not widely practiced (9). Powering a trial is a complex process in which sometimes supporting data on the mean or variance of treatment response — or even the concept of what constitutes a clinically significant difference — is sought to justify a pre-determined sample size. Such maneuvers have been called doing the “sample size samba (10).”

CE trials are, by their nature, pragmatic rather than explanatory (3). They are designed not to test a posited biological mechanism of action as the explanation of a treatment response in a controlled environment, but rather to help decision-makers choose the treatment with the highest expected benefit as would be obtained in the messy real world of clinical practice (11). This means a wide variety of practice settings, potentially heterogeneous treatment effects in an array of subpopulations and use of patient-reported outcomes, each of which would be expected to increase the variance of observed treatment responses. Because comparisons are made among active treatments, the expected differences between any two treatments can be expected to be smaller than the difference between active and minimal or placebo treatment. Large variances and small relative effect differences translate into larger sample sizes required to differentiate treatments.

Furthermore, because CE trials are conducted after treatments have come to market, they pose considerable risk to manufacturers; hence, the majority of CE trials have been government-funded (12). However, with the new influx of resources being devoted to CER and the increasing demand (both in the private market and among government payors) for manufacturers to establish the relative value of their interventions (13), manufacturers may no longer be able to avoid sponsoring CE trials. For any sponsor of a CE trial, it would seem to be logical that the trial be designed with the end-use of the data kept in mind.

A fully Bayesian approach to trial design would weigh the utility/loss (in money and/or health) associated with correct/incorrect decisions made as a result of the trial versus the costs associated with larger sample sizes (14). The expected net benefit of a trial would be calculated with respect to prior distributions summarizing *ex ante* knowledge about the outcomes under each treatment. A hybrid Bayesian-classical approach described by O’Hagan, Stevens and Campbell (2005) seeks to optimize the “assurance” of a trial — the probability of obtaining a “positive outcome” (i.e., a significant difference according to a classical test), which is a function of the true (unknown) parameter with respect to the same prior distributions (15).

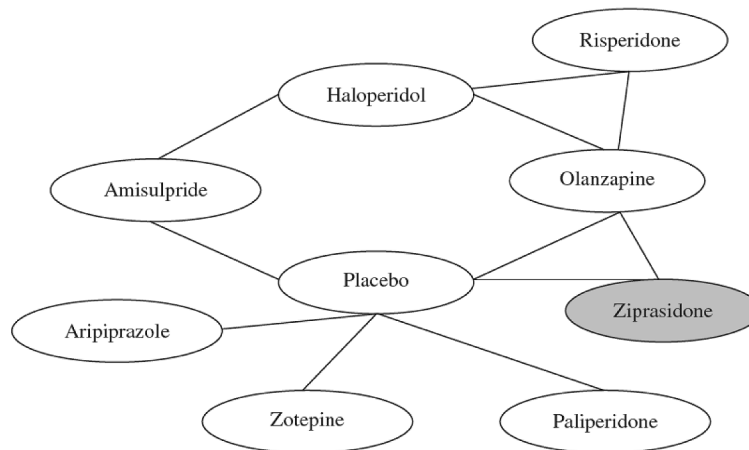
Recently, Sutton and colleagues (2007) proposed an important extension to the concept of assurance (16). Specifically, they suggest using systematic review and meta-analysis to construct the prior distributions necessary to predict the outcomes of a future trial, but importantly, whether the outcome of the trial is judged to be positive does not depend solely on the trial results themselves, but rather on the results of an updated meta-analysis. The remainder of this article will demonstrate how similar use of indirect and mixed treatment comparison network meta-analysis could yield more efficient trials with lower risk to trial sponsors for head-to-head CE trials, particularly as use of network meta-analysis for CER grows.

Use of Indirect and Mixed Treatment Comparisons

Mixed treatment comparison (MTC) is a generalization of pair-wise hierarchical Bayesian meta-analysis (17) that allows synthesized comparisons among treatments (say, B and C) when both direct (B versus C) and indirect, with common comparator (B versus A and C versus A) data is available. Note, if there is no head-to-head trial data, essentially identical methods can be used to synthesize what is more properly called an indirect comparison (IC). A key paper from whose methods much of the technology assessment related MTC literature derives is Lu and Ades (2004) (18). A central assumption of IC/MTC analysis is that the direct estimate of a treatment effect between C and B, d_{BC} , is equivalent to the difference in treatment effects between B, C and A, their common comparator: $d_{BC} = d_{AC} - d_{AB}$ (19). In assessing d_{BC} , strength is borrowed from studies in which d_{AC} or d_{AB} are assessed. When multiple interventions are linked by a connected network of evidence, IC/MTC allows for treatments to be rank-ordered in terms of their effectiveness on an absolute (e.g., probability) scale for all connected interventions. Such estimates can be directly incorporated as parameters in decision-analytic or economic modeling, with variability in the estimates representing uncertainty over parameter values given the evidence synthesis.

IC/MTC meta-analysis has begun to play an increasingly important role in health technology assessment both in the U.S. and abroad (19; 20). According to the UK National Institute of Health & Clinical Excellence (NICE) Guide to the methods of technology appraisals (5.3.13), “If data from head-to-head RCTs are not available, indirect treatment comparison methods should be used (an ‘indirect comparison’ is a synthesis of data from a network of trials)” (21). Such an approach was taken in NICE’s recently updated clinical guidance for the treatment of schizophrenia (22). Systematic reviews identified a number of placebo-controlled and head-to-head trials involving eight active treatments, but no single trial compared all eight (see Figure 1).

Evidence network derived from data on relapse, treatment discontinuation because of intolerable side effects and treatment discontinuation for other reasons



Note: Ziprasidone (in grey-shaded oval) was considered in the mixed treatment comparison analysis because it allowed indirect comparison between olanzapine and placebo, thus strengthening inference. However, it was not included in the economic analysis because it is not licensed in the UK.

Figure 1. Source: National Institute of Health & Clinical Excellence. The NICE Guideline on Core Interventions in the Treatment and Management of Schizophrenia in Adults in Primary and Secondary Care. Updated Edition. National Clinical Guideline Number 82 (p. 182)

Markov chain Monte Carlo (MCMC) was then used to estimate Bayesian hierarchical MTC models, and iterations from the resulting posterior distributions of effectiveness parameters were used as inputs for an economic model assessing the relative cost-effectiveness of all interventions. The probabilistic cost-effectiveness analysis rank-ordered the seven UK-licensed treatments in terms of cost-effectiveness as follows: 1) zotepine; 2) olanzapine; 3) haloperidol; 4) paliperidone; 5) risperidone; 6) amisulpride; 7) aripiprazole (22). It is noteworthy that NICE relied extensively on the combination of MTC meta-analysis and economic modeling despite the existence of two pragmatic CE trials: Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1) in the U.K. (23) and Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) in the United States (24). The existence of head-to-head RCTs did not lead the assessment group to discard all information from previous trials. Rather, the head-to-head data was synthesized with the existing evidence base to produce coherent guidance in light of the whole body of knowledge.

MTC Methods

Consider the case of a binomial outcome (response or non-response). Let (r_{sa}, n_{sa}) be the number of responses and observations in arm a of study s . The likelihood for the data can be modeled as:

$$1) r_{sa} \sim \text{bin}(p_{sa}, n_{sa})$$

where p_{sa} , the probability of treatment response in arm a of study s , is modeled on the log-odds scale as the sum of a baseline treatment response rate μ_s and a relative treatment effect Δ_{sa}

$$2) \log\left(\frac{p_{sa}}{1-p_{sa}}\right) = \mu_s + \Delta_{sa}$$

Each study's baseline log-odds of response, μ_s can be treated as a nuisance parameter and assigned a minimally informative prior:

$$3) \mu_s \sim N(0, 1E + 06), s = 1 \dots S$$

Let $t = 1 \dots T$ index the T treatments being compared in the evidence network, where $t[sa]$ indicates the treatment assigned in arm a of study s . We assume that treatments are ordered such that $t = 1$ is assigned to the lowest comparator (e.g., placebo) and that the "baseline" comparator in study s (which may or may not be $t = 1$) is listed as the first arm such that $t[s1] \leq t[sa]$. The relative treatment effect on the log-odds scale, Δ_{sa} , can either be modeled as a fixed effect:

$$4a) \Delta_{sa} = d[t[sa]] - d[t[s1]]$$

or as a random effect:

$$4b) \Delta_{sa} = 1(t[sa] \neq t[s1]) \cdot \delta_{sa}$$

$$4b') \delta_{sa} \sim N(d[t[sa]] - d[t[s1]], \sigma_\delta^2)$$

In the absence of prior information about $d[t]$, each is assigned a minimally informative prior:

$$5) d[t] \sim N(0, 1E + 06), t = 1 \dots T$$

The fundamental parameters of interest, $d[t]$, are the effects of each treatment t relative to treatment 1 (note: $d[1] = 0$ by definition). The difference between the fixed and random effects specifications is the treatment of heterogeneity of these relative treatment effects observed between studies. In the fixed effect model (4a), observed relative treatment effects differ between trials only due to sampling variability. In the less restrictive random effect model (4b and 4b'), relative treatment effects estimated in one trial may differ from the same effect estimated in a different trial not simply due to sampling variability but also due to differences in the trial design, context and population. However, the sources of variability are assumed to be well-behaved, causing study estimates of relative treatment effects to vary normally around a true mean relative treatment effect, with a common variance σ_δ^2 . Heterogeneity that violates this assumption of "exchangeability" can pose problems for validity and should be assessed (25).

Monte Carlo Simulation

A simple Monte Carlo simulation was constructed to illustrate the potential value of using MTC to determine sample size of a CE trial, assuming trial results will be incorporated in an updated MTC. In the simulation, it was assumed that there are three treatments: A , B and C with dichotomous outcomes (response or non-response). In this example, A can be assumed to be placebo, while B and C are active treatments. Because this is a simulation, we know the true response rates under each treatment are: $\theta_A = 50\%$, $\theta_B = 60\%$ and $\theta_C = 70\%$. Suppose we already have evidence from four studies: Trial 1 of A vs. B with 100 patients in each arm; Trial 2 of B vs. A with 100 patients in each arm; Trial 3 of C versus A with 100 patients in each arm and Trial 4 of C vs. B vs. A , with 100 patients in each arm. It was assumed that a new trial would cost \$1 million plus \$2,000 per patient enrolled. The sponsor was assumed to receive a reward of \$10 million if the trial is successful (showing C is more effective than B) or incur a penalty of \$10 million if the trial fails.

Treatment response probabilities for each study and treatment were randomly generated according to the formula:

$$6) \log\left(\frac{\theta_{st}}{1-\theta_{st}}\right) = \log\left(\frac{\theta_t}{1-\theta_t}\right) + \mu_s + \epsilon_{st}$$

$$7) \mu_s \sim N(0,0.01), s = 1 \dots 4$$

$$8) \epsilon_{st} \sim N(0,0.01), s = 1 \dots 4, t = A, B, C$$

Observed responses for each treatment in each study were drawn randomly given the above response probabilities as $r_{st} \sim \text{bin}(\theta_{st}, n_{st})$. Note responses were simulated for treatments that may not have been present in each study (i.e., treatment C in Trials 1 and 2 and treatment B in Trial 3) and have indexed by treatment rather than study arm. This simulation assumes substantial heterogeneity both between studies and even between study arms within the same study. The standard deviation of the combined sources of heterogeneity (0.2) is twice the size of the relative treatment effect between A and B (10%) and B and C (10%).

Given a set S of four simulated previous studies, sample size was first determined through a simple classical power analysis by calculating pooled success rates $\hat{\theta}_B, \hat{\theta}_C$ for treatments B and C and finding the number of patients necessary to have 80% power to detect a difference of $|\hat{\theta}_C - \hat{\theta}_B|$, assuming a type I error rate of 5%. The trial was assumed to go forward if the expected benefit of the trial exceeded the expected cost, given the sample size and 80% probability of success.

The MTC-prior approach used a random-effects MTC model to estimate distributions of $P(\theta_B | S)$ and $P(\theta_C | S)$. Given these distributions, trials (and their associated costs) were simulated at various sample sizes; each simulated trial was deemed successful if, based on an updated MTC, $P(\theta_C - \theta_B | S') \geq 95\%$, where S' denotes the previous four trials augmented with the new trial. The number of patients in each arm was chosen to maximize the expected net benefit of the new trial. The trial was assumed to go forward if the expected net benefit of a trial at the optimal size was positive.

A third hybrid (flat prior) approach was also conducted where a random-effects MTC model was used to estimate distributions of $P(\theta_B | S)$ and $P(\theta_C | S)$, which were used to simulate trials of varying size as before. This time, however, it was assumed that the new trial results would be judged successful by whether $P(\theta_C - \theta_B | S) \geq 95\%$ (as opposed to S' , i.e., the trial results will be judged alone and not combined with previous studies in an updated MTC). Although this is a Bayesian hypothesis test, *ex ante* it is similar to a classical t-test with type I error rate of 5%. The trial was assumed to go forward if the expected net benefit of a trial at the optimal size was positive.

Results

A set of 1,000 simulated trials were conducted using R (v. 2.9.0), WinBUGS (v. 1.4.3) and the R2WinBUGS package (v. 2.1). The results in Figure 2 show that trials designed using prior information in a Bayesian MTC analysis, assuming that the MTC would be updated with the new trial results to make a decision based on comparative effectiveness, tended to be the smallest, most likely to be “successful” and have highest expected net benefit. However, such trials were the least likely to be undertaken.

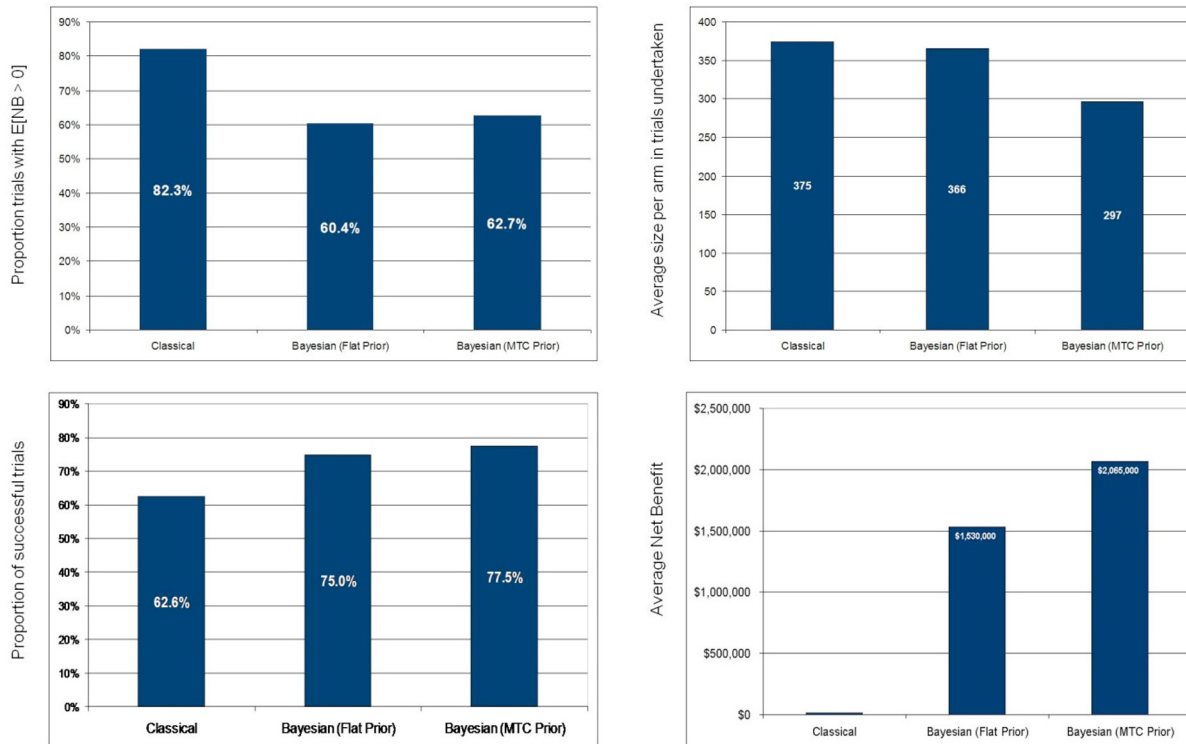


Figure 2

Discussion

This simple Monte Carlo simulation is meant to illustrate a point, not prove it. The specification of benefits and costs, the underlying models generating the data and the trial designs are highly stylized and do not reflect many of the complexities involved in real world conduct of trials. However, there are a few take away lessons.

While the classical approach to sample size taken in the simulations (using pooled estimates of treatment success to design the trial) is admittedly simple, it did systematically use available data and formally consider expected benefits and costs in light of that data. Therefore, it could be said to be more coherent than the sample size sambas being danced today. Given that treatment *C* really is more effective than treatment *B*, why did the classical approach perform so poorly (having a success rate of 62.6% despite power or assurance of 80%)? Most likely because the pooled estimates ignored the potential for heterogeneity between trials, while the MTC approaches both at least partially accounted for it. The average sizes of the classical trials and the hybrid (flat prior) trials were similar, perhaps because both involved judging the success of each trial based on the trial data alone and not on the basis of updated MTC meta-analysis. However, the hybrid trials were also more “conservative” in the sense that fewer were undertaken (but with a higher resulting success rate), most likely because the MTC approach correctly assessed that there was additional risk to the sponsor due to heterogeneity between trials.

In this example, the “informative prior” MTC approach, which assumes new trial results will be used to update the MTC meta-analysis, offered smaller sample sizes and higher net benefit when compared to the MTC approach that analyzes new trial results in a vacuum. Using the prior information to make a decision seems to get to the truth (that treatment *C* is more effective than treatment *B*) more efficiently. However, fewer trials were predicted to be actually undertaken. This raises an interesting point. To the extent that additional knowledge about the effectiveness of *B* and *C* has social value (beyond the net benefit to the trial sponsor), it may be in the best interest of society to subsidize sponsors to undertake such trials or perhaps provide some sort of insurance policy against trial failure.

Notably, this paper has not discussed other approaches to improve RCT efficiency, such as Bayesian adaptive trial design (26). Adaptive design is fully consistent with the methods sketched above. The prior distributions necessary for Bayesian adaptation could be constructed using MTC methods, and loss functions used to guide the adaptation process could be based on the predicted results of updated MTC meta-analysis. Bayesian trial adaptation methods, combined with informative priors constructed based on empirical evidence, could bring great efficiency gains to pragmatic CE trials (4).

Conclusion

CER is likely here to stay in the U.S. and around the world. While its methods are varied, pragmatic randomized clinical trials and MTC meta-analysis will very likely play central roles in the CER enterprise. Combining the two methods in a coherent approach to synthesizing and supplementing our evidence base could improve treatment decision-making, making efficient use of both our health care and health research dollars.

Acknowledgments/Disclosures

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Letter from the Chair

Katherine Monti (Rho, Inc.)

The Biopharmaceutical Section is thriving! The credit goes to a small army of volunteers who enthusiastically support our “regular” section activities, those who develop and implement initiatives, and those who engage in one way or another with meetings (eg, presenting papers, chairing sessions, collecting “Best Contributed Paper” ballots, presenting short courses).

So who does support the “regular” activities? There is not room to list everyone who contributes to the health of the chapter, but kudos are due to many, including: Dionne Price (FDA) and Jeff Maca (Novartis) who are the program chair and chair-elect, respectively; Ivan Chan (Merck) and Qian Graves (FDA), who are FDA/Industry Workshop co-chairs; officers Anna Nevius (FDA, past-chair), Steve Wilson (FDA, chair-elect), Richard Caplan (AstraZeneca, Secretary), Steve Gulyas (Lilly, treasurer), and Devan Mehrotra (Merck, publications officer); and of course the Biopharmaceutical Report editors David Henry (Bristol-Myers Squibb), Jose Alvir (Pfizer), Debbie Panebianco (Merck), and Amit Bhattacharyya (Glaxo-Smith Kline). Patricia Stephenson (Rho, Inc.) and Anna Legedza (Vertex) are new appointees to the Executive Committee, joining Ram Suresh (Merck), Venkat Sethuraman (Novartis), Tom Keefe (Colorado State University), and Veronica Taylor (FDA). The section representatives to the Council of Sections are Mani Lakshminarayanan (Merck), Alex Dmitrienko (Lilly), and David Breiter (eV3); and committee chairs include Russ Helms (Rho, Inc., Corporate Sponsorship), Neal Thomas (Pfizer, Inc., Fellowship), Christie Clark (RPS, Student Paper Competition), Heather Thomas (Watson Labs, Contributed Paper Award), Yongming Qu (Lilly, Contributed Poster Award). Mani and Venkat (see above) also co-chair the Distance Learning program. And there are others: liaisons, non-chair committee members, ad hoc committee members...the list goes on.

Although the list is long, we are always looking for interested parties. Good contacts are Steve Wilson (who is in charge of appointments for next year), the chair of any committee on which you would like to serve and, of course, me (Katherine Monti)—the current chair.

One highlight of the year is the up and coming website. Look in *Amstat News* for the launch date and please take a look at the website when it is launched. Jeremy Jokinen and Steve Gulyas have worked with the Creative Street Media Group to get an excellent start on this website, designed to entice high school and undergraduates to join our profession. And the thrilling news is that it has already worked! An AP teacher showed an early version of the site to her students, one of whom decided to apply only to colleges that have biostat programs, based on the video clips of statisticians that were filmed last year at JSM. Our first documented success! We plan to launch the website this year, but we expect it to grow and expand once it is up and going. Suggestions for additions and improvements will be welcome at any time (JJokine1@its.jnj.com). We may not be in ASQ, but we are looking for continuous quality improvement.

Other successes are sure to be both JSM and the FDA/Industry workshop. JSM is coming soon, and I hope to see you there. We have another strong program, with a short course offering (Analysis of Clinical Trials: Theory and Applications presented by Devan V. Mehrotra, Merck Research Laboratories, Alex Dmitrienko, Eli Lilly and Company, Keaven M. Anderson, Merck Research Laboratories) and numerous roundtable luncheons in addition to the rich program of invited sessions, topic contributed sessions, contributed sessions and—not to be missed—the mixer/business meeting (scheduled for Tuesday 5:30 – 7:00 pm, CC-209 West). Check the program online at www.amstat.org for program details. The FDA/Industry workshop will be in the fall—September 20-22. Some details of that program are also available on-line (click on Meetings/Other ASA Meetings). Rumor has it from an exceedingly well-placed, independent source (no, not one of the co-chairs) that the program is going to be exceptional this year, so make your plans to attend.

Other upcoming activities include a summary of results from the Membership Survey that has been recently conducted. Alas, section members had a high non-response rate, and we all know what a high non-response rate

does to the reliability of the results. Well, there will be results nonetheless. Thanks to Ram Suresh and Ed Luo for leading that charge.

The last item to mention is the updating of the Operations Manual. Having gathered dust for over a decade, the manual was in serious need of an overhaul. Kannan Natarajan (2008 Chair) got started on the project, and then Anna Nevius and I took the next steps. The Executive Committee added the next round of changes and it is vastly improved even if we are not yet quite done. Anna is leading the charge of updating the out-of-date section charter. The old manual is still the “on line” version, but the updated version should be available soon after some final issues have been resolved at JSM.

As you can tell, we have an active section! It is vibrant and fiscally healthy. Thanks go to all the members who support the section. I hope to see you at a meeting soon. ■

Biopharmaceutical Section Calendar

June 23, 2010

Webinar: A Predictive Approach to Process Optimization with Applications to Pharmaceutical Development and Manufacturing

John Peterson (GlaxoSmithKline)

Noon–2pm (Eastern Time)

<http://www.amstat.org/sections/sbiop/webinarseries.html>

July 31–Aug 5, 2009

Joint Statistical Meetings

Vancouver, British Columbia, Canada

<http://www.amstat.org/meetings/jsm/2010/index.cfm>

Biopharmaceutical Section Mixer and Business Meeting:

Tuesday, August 3, 5:30–7:00, CC-209 West

Sept. 20–22, 2010

FDA Industry Workshop

Grand Hyatt Washington

Washington, DC

<http://www.amstat.org/meetings/fdaworkshop>

December 5–10, 2010

66th Annual Deming Conference on Applied Statistics

Atlantic City, NJ

<http://www.demingconference.com> ■

Summary of 23 October 2009 Biopharmaceutical Section Executive Committee Meeting

Submitted by Rick Caplan (Secretary)

The following are elected new officers of the Executive Committee for 2010:

- Chair – Steve Wilson
- Program Chair – Jeff Maca
- Council of Sections Representative – David Breiter
- Publications Officer – Devan Mehrotra

Katherine Monti made the following appointments for 2010:

- Executive Committee: Patricia Stephenson and Anna Legedza
- Web Master: Daniel Christen
- ASQ Liaison: Walter Young
- FDA/Industry Chair: Qian Graves and Ivan Chan
- Corporate Sponsors Chair: Russ Helms
- Distance Education: Mani Lakshminarayanan and Venkat Seturaman
- Contributed Paper: Heather Thomas and Allan Izu
- Contributed Poster: Yongming Qu and Jingli Song
- Student Paper: Christie Clark
- Fellows Committee: Neal Thomas, Greg Campbell, Stacy Lindborg, Demissie Alemayehu

Budget (*Steve Gulyas*)

- The Biopharmaceutical Section balance as of 15 October 2009 was \$336,695.54, reflecting a revenue of \$71,630.33 and expenses of \$84,921.44.
- Items from the 2009 FDA/Industry Workshop budget were discussed and resolved.
- Steve presented the proposed 2010 budget, which will include \$10,000 to Creative Street to start Phase II of the Web Clip Project.

Fellows Committee (*Neal Thomas*)

- The Committee has met and identified candidates.

2009 Program Chair Report (*Matilde Sanchez/Dionne Price*)

- There were 18 roundtables, all sold out.

2010 Program Chair Report (*Dionne Price/Jeff Maca*)

- There were 30 proposals for invited sessions. BIOP will sponsor 5 invited sessions.

Biopharmaceutical Report (*David Henry/Jose Alvir/Deborah Panebianco*)

- The next issue will be published in November. The lead article will be on propensity scores.

2009 FDA/Industry Workshop (*Tammy Massie/Carmen Mak*)

- The meeting was held in September. It was a great success, with about 750 attendees.
- There were 8 short courses on day 1.
- The roundtable format was different, with smaller roundtables. There were over 100 roundtable leaders.

2010 FDA/Industry Workshop (*Ivan Chan/Qian Graves*)

- The meeting will be September 20-22 at the Grand Hyatt.
- The format will be similar to 2009.
- ASA is helping set up an online proposal submission system.
- All email should be sent to fda_industry_WKSP2010@yahoo.com

Council of Sections Report (*Margaret Minkwitz/Mani Lakshminarayanan/Alex Dmitrienko*)

- The COS voted to change the notification of a new Section to 90 days to ASA before the meeting and to 60 days to other Sections.

Contributed Paper (*Heather Thomas*)

- 71% of the sessions had at least 10 ballots, which was required to be eligible.
- Data entry and tallying of the ballots should be completed by the end of the year.

Web Clip Statistical Outreach Program (*Jeremy Jokinen/Steve Gulyas*)

- The video was viewed during the meeting; reactions were positive.
- Since JSM, most of the effort has been put into editing the video.
- Work to be completed for phase I, within the allocated funds, includes completing 2 more career profiles, creating a send-to-a-friend application and make the site appear more dynamic.
- Suggestions for Phase II were discussed.

Use of webinars to aid in ASA Education Program (*Rick Peterson*)

- Webinars will be made available online from the ASA web site on a pay-per-view basis.
- ASA has recordings of the last [approx] 8 webinars. All future webinars will be recorded.
- Rick works with statisticians in other countries in very different time zones. They are enthusiastic about the webinar recordings being made available online.
- If the webinars become part of a continuing education program for accreditation in the future, there would need to be individual testing and a processing fee.

Manual of Operations (*Kannan Natarajan/Katherine Monti/Anna Nevius*)

- Katherine Monti reviewed proposed changes, and the manual is being updated.

AOB (*Anna Nevius/Katherine Monti*)

- The Section received a proposal from the Biometrics Section to help support their outreach program. We agreed that we would not offer money. We would inform them of our Outreach program and discuss whether it could be a vehicle for some of their projects. In particular, Jeremy Jokinen will contact Jeremy Taylor to see if the web clip effort would be a useful vehicle for them.
- The Section received a proposal from the Statistical Learning and Data Mining Section to help sponsor a joint conference in 2011. We agreed to ask for more information. ■

Report on the 2009 Non-Clinical Biostatistics (NCB2009) Conference

The 2009 Non-Clinical Biostatistics Conference was held October 21-23, 2009 at the Joseph P. Martin Conference Center, Harvard School of Public Health, in Boston, Massachusetts. This was the first conference dedicated entirely to non-clinical and preclinical pharmaceutical topics held in the U.S.

Planning for the conference began the previous October by an organizing committee of academic, pharmaceutical industry and FDA statisticians. A core committee consisting of 5 members handled overall management of the conference and 3 sub-committees each targeted a major non-clinical subject area:

1. **Discovery/Early Development/-omics** Chair: Fred Immermann (Wyeth)
D. Amaratunga (Johnson & Johnson), D. Bennett¹ (Biogen Idec), B. Gunter (Genentech), J. Manro (Lilly), L. Sirota (FDA), M. Thoma² (Harvard)
2. **Pharmacology/Safety/Toxicology/pK** Chair: Keith Soper (Merck)
J. Chen (FDA), J.Colaianne³ (Johnson & Johnson), W. Hoffman (Lilly), K.Lin (FDA), T. Lin (Abbott), B. Pikounis³ (Johnson & Johnson), L. Zhou (Amgen)
3. **Chemistry, Manufacturing & Control** Chair: C. Tan (Merck) & J. Zhong (FDA)
S. Altan³ (Johnson & Johnson), S. Cahya (Lilly), D.J. Downing (GlaxoSmithKline), J. Liao (Merck), T. Schofield (BCG), J. Schwenke (Boehringer), Y.Tsong (FDA)

The conference theme was “Statistical Methodologies: Key to Discovery and Development”, and opened with a half-day short course by Professor G. Fitzmaurice on ‘Analysis of Longitudinal Data’, followed by 2 full days of invited and contributed presentations. Keynote speaker Dr. ShaAvhree Buckman (FDA) offered a fascinating insight speaking on “FDA’s Critical Path Initiative: Opportunities and Challenges”. Invited speakers were Ralph Kodell, on Tumorigenicity assessment; John Peterson on ICH Q8 Design Space development; Emery Brown on neural signal analysis; Keith Baggerly on high throughput biology and forensic statistics; Dennis Sandell on specifications; and Dan Holder on biomarker qualification. There were 22 contributed presentations and 47 posters. The invited dinner speaker was Steve Ruberg, on the topic of ‘Megatrends for the Statistics Profession’. Victor DeGruttola delivered the formal welcoming address on behalf of the Department of Biostatistics, Harvard School of Public Health.

The 149 participants, including 13 from outside the U.S, represented a broad spectrum of organizations from industry, academia and health care institutions, with 77% coming from the pharmaceutical industry. The percentages by institutional categories are shown in Figure 1.

¹ Conference co-chair and core committee member representing the Non-Clinical Biostatistics Leaders’ Forum

² Conference co-chair and core committee member representing the Biostatistics Department, Harvard University

³ Core committee member

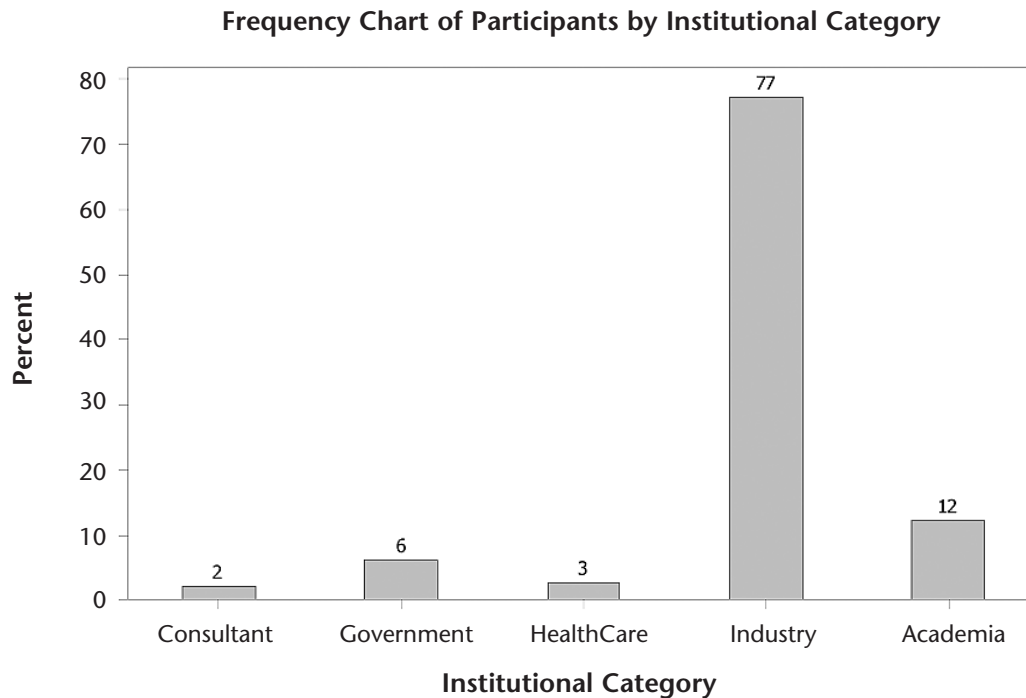


Figure 1 – Frequency Chart of Participants


In addition to the Biopharmaceutical Section of the ASA, financial support for the conference was provided by the Adolphe Quetelet Society (Belgian region of the International Biometric Society), The National Institute for Statistical Sciences, SAS Institute, SAS/JMP, PointCross, Abbott Laboratories, Biogen-Idec, Genentech, GlaxoSmith-Kline and Johnson & Johnson.










The conference provided opportunities for career development, professional networking, and discussions on current scientific and regulatory issues important to the non-clinical/preclinical pharmaceutical statistics community. Attention was drawn to the importance of non-clinical statistics to the drug development and commercialization process, and in that sense created greater visibility and recognition for the field of Statistics generally. A survey conducted of conference participants showed high marks for the conference contents and format, as well as support for establishing a biennial non-clinical conference.

On behalf of the organizing committee as well as all the participants we would like to thank the Biopharmaceutical Section for its generous support of this unprecedented non-clinical biostatistics conference.

Additional information and photographs are available at www.NCB2009.org. The NCB2009 conference will be followed by a counterpart non-clinical statistics European conference in Lyon, France, September 27-29, 2010 (<http://www.ncsc2010.org>). Early planning for the 2011 conference is in progress. ■

66th Annual Deming Conference on Applied Statistics
ASA Biopharmaceutical Section ASQ NY/NJ Metropolitan Section
Event Dates: Sunday, December 05 – Friday, December 10, 2010
City: Atlantic City State: New Jersey Country: USA

The purpose of the three-day Deming Conference on Applied Statistics and the following two parallel two-day short courses is to provide a learning experience on recent developments in statistical methodologies. The conference is composed of twelve three-hour tutorials on current statistical topics of interest. Recognized experts in the field of applied statistics are invited to give the lectures and short courses. Those with the  symbol are based on their recently published books that are available at about a 40% discount. Attendees receive bound proceedings of all conference presentations. The full program with conference and hotel registration is available on the conference website. The conference will be held in the state-of-the-art Havana Tower of the Tropicana Casino Resort whose shops and dining experiences mimic the atmosphere of Old Havana. Walter Young, chair of this conference for 41 consecutive years, should be contacted for any additional information.

Monday	8:30-11:30	Jason Hsu (Ohio State) Principles and Techniques of Multiple Testing and Multiple Comparisons 	Yi Tsong (FDA) and V. Venkatasubramanian (Purdue University) Continuous Manufacturing & Large Sample Dose Content Uniformity Sample Acceptance Plan
	1-4	Alex Dmitrienko (Eli Lilly) Gatekeeping Procedures in Clinical Trials 	Wan Tang (University of Rochester) Applied Categorical and Count Data Analysis 
	4-5	Three student scholars give 20-minute presentations of their award winning papers	
Tuesday	8:30-11	Diane Fairclough (UCHSC) Design & Analysis of Quality of Life Studies in Clinical Trials 	Brian Wiens (Alcon Laboratories) Design and Analysis of Non-inferiority Trials 
	1-4	David Banks (Duke University) Statisticians & Metabolomics: Collaborative Possibilities for the Next *omics Revolution?	Jim Hung (FDA) Emerging Challenges of Clinical Trial Methodologies
Wednesday	8:30-11:30	Scott Evans (Harvard School of Public Health) Benefit:Risk Assessment, Subgroup Analyses, and Prediction for Interim Data Monitoring	Mark Chang (Amag Pharmaceuticals) Monte Carlo Simulation for the Pharmaceutical Industry: Concepts, Algorithms, & Case Studies 
	1-4	Karl E. Peace (Georgia Southern University) Clinical Trial Methodology: Case Studies 	Scott Berry (Berry Consultants) What Drug Development and The Medical Community Could Learn From Sports
Thur-Friday	Short Course	Brad Carlin (University of Minnesota) and Scott Berry (Berry Consultants) Bayesian Adaptive Methods and Software for Clinical Trials 	Ramon Littell (University of Florida) and Walter W. Stroup (University of Nebraska) SAS for Mixed Models: Applications for Repeated Measures, Generalized Linear Mixed Models, and Sample Size Computation 

www.demingconference.com

Submitter: Walter R. Young

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The International Society for Biopharmaceutical Statistics (ISBS) proudly announces:

The Second International Symposium on Biopharmaceutical Statistics

Jointly organized by European Medicines Agency (EMA)
International Society for Biopharmaceutical Statistics (ISBS)
International Biometric Society – Deutsche Region (IBS-DR)

February 28 – March 3, 2011

The Palace Hotel (<http://www.palace.de/englisch/index.php>)

Berlin, Germany

The purposes of this symposium are (1) to bring together worldwide statisticians and related professionals who are involved in quantitative biopharmaceutical research, development and regulations to share and exchange information, experience and research findings, and (2) to improve and promote the harmonization of statistical practice in the industry at the international front. The theme of the second symposium is “Statistics in Bridging Drug and Vaccine Development from Research to Marketing.” Prominent statisticians from regulatory agencies, academics and the industry will deliver keynote speeches on various perspectives. Invited and contributed presentations will cover a wide range of topics from non-clinical statistics, preclinical discovery, clinical development, post-licensure surveillance, to regulatory science and statistics. A series of pre-conference half-day short courses will be given by experts in their respective professional fields.

For more information, please check this web site www.isBioStat.org, or contact: Richardus Vonk, Bayer Schering Pharma AG (richardus.vonk@bayerhealthcare.com), or Amit Bhattacharyya, GlaxoSmithKline USA (amit.bhattacharyya@gsk.com). ■

Let's Hear from You!

If you have any comments or contributions, please contact the Editors: Jose Alvir, email Jose.Alvir@pfizer.com; Deborah Panebianco, email deborah_panebianco@merck.com; Amit Bhattacharyya, email Amit.Bhattacharyya@gsk.com; or David Henry, email David.Henry@bms.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 bioequivalence in biologics and personalized medicine. If you have been working in an area and would like to suggest a topic or volunteer to write, please send us an email. Non-technical articles related to our work are welcome. One example might be an article about outsourcing statistical programming to Asia. Perhaps someone could write an article about how to effectively work when the statistical programming is outsourced. How is it different from using a regular CRO? How will our function change?

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