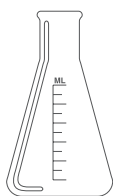


Biopharmaceutical Section



American Statistical Association

Biopharmaceutical Report

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Spring 2011

Chair: *Steve Wilson*

Editors: *Jose Alvir, Deborah Panebianco, Amit Bhattacharyya*

Note from the Editors

The editors have tried to introduce the readers to topics that are outside the comfort zone of the statistician in the biopharmaceutical setting. It is hoped that the knowledge gained will help to make the statistician a more proactive partner in the drug development and evaluation process. In this issue, we feature two articles that go beyond the usual concerns of the clinical trial statistician. Zoran Antonijevic (Quintiles, Innovation) and Natasa Rajcic (Pfizer, Inc.) argue that the drug development process should be based on quantifiable and measurable actions and introduce methods to achieve these. This is especially important given the reductions in research and development budgets and the perceived need among developers

Demissie Alemayehu (Pfizer, Inc.) contributes a review of activities in Comparative Effectiveness Research (CER), as well as methodological issues and challenges associated with CER. He then reviews traditional and emerging methods that attempt to deal with these challenges.

We would also like to acknowledge David Henry for his outstanding service as an editor of the *Biopharmaceutical Report*. David completed his term with the Fall 2010 issue. During his tenure, David was instrumental in resuscitating the Report from a two year period during which the Report was not published. ■

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Some Words from the Section Chair

For those of us who like to think about how we got here, “The History of the Biopharmaceutical Section of the American Statistical Association (ASA), 1966-1988” by **Robert Davis**, et al. published in the winter 2005 edition of the *Biopharmaceutical Report* (Volume 13, No. 1) is a “great read”—graphically describing the motivations and actions leading to the creation of our Section.

On February 1, 1980, in Washington DC, the Biometrics Section and the BPSS [Biopharmaceutical Sub Section] squared off with dueling presentations for and against full-section status for the BPSS ... The Boardroom was packed... After much passionate discussion with some rather discouraging remarks being made by a few Board members, Joe Fleiss, the ASA Board member representing the Biometrics Section, rose to speak. Fleiss said that the BPSS had shown much initiative, an activity level greater than the other current sections, and therefore it would be shame to deny this petition. That speech won the day... The vote was taken, and the Biopharmaceutical Subsection had passed their greatest hurdle in becoming a SECTION.

Thus, the new Biopharm Section became only the eighth in existence at ASA... The accomplishment of that day was a fitting end to the long road the BPSS had to take in seeking full-section status. There were a number of political land mines which, in the end, the BPSS successfully navigated.

The time was ripe for leaders, our “forefathers,” to step-up. Agitating/politicking effectively for change, they were deeply motivated by a commonly felt need for statisticians, working in the pharmaceutical industry, regulatory agencies and academic institutions, to develop and test applied methodologies, to innovate, to document, to talk to/learn from each other about their profession and their “business.” In the years since, numerous dedicated volunteers have built our Section into an organization that (I hope you would agree) effectively contributes to our professional lives -- that gives us many of the spaces and opportunities that we need to think, to collaborate and to improve.

I feel that the position of Section Chair may be one of those jobs where you only really figure out what you were supposed to do when you are finished with your term. Fortunately, I am surrounded by talented, caring individuals and a history of good work. This was really “brought home to me” in preparing for the ASA Biopharm Section Executive Meeting that traditionally attaches itself to the ENAR Meeting (one of those things learned by doing). Fortunately, **Kathy Monti** (the former Chair) and **Steve Gulyas** (the current Chair-elect and former Treasurer) were there to help, guiding me in the right direction to make the arrangements (room reservation requirements, catering, IT/phone services, ASA support for a web connection, etc.) and pointing me to the agenda for the previous year as a model for the 2011 “order of service.”

The final agenda for the meeting included 20 business/activity items and 18 presenters (7 present at the meeting and 11 calling in their contributions). Each report was allotted 10 minutes. They were all there, reflecting the work that it takes for our many, dedicated volunteers to conduct the business of the Section ... to provide the members with opportunities to enhance/enrich our professional experience: Appointments, Minutes, Finances, Council of Sections, Publications, *Biopharmaceutical Report*, Webmaster, Web Project, Fellows, Manual of Operations Update, 2011 JSM Program (including Invited Sessions, Topic Contributed Sessions, Regular Contributed Sessions, Round Table Luncheons, Short courses), Best Contributed Paper, Student Paper, Poster, FDA-Industry Workshop, Web-based Training, Meeting Sponsorship/Liaison, and Corporate Sponsorship. Miraculously, even with the requisite IT glitches, we managed to successfully stay on schedule. I had started the agenda drafting process thinking/hoping that we would have sufficient time after

the “routine stuff” to reflect on the work that had been accomplished in rewriting the Manual of Operations, complex policy issues (like requested financial support for meetings and other activities) and all of those new initiatives that I had been cooking up in my head. In the end, we were left with only ten wanting-to-get-out-of-here-and-whose-going-to-take-the-leftover-fruit minutes for discussion/reflection on our “new business.”

Len Oppenheimer, as an incoming Chair in the winter 2005 edition of the *Biopharm Report* judged that “everything is going well” and then asked himself “So what would I like to work on during my one-year tenure?” I now find myself with 1) a similar assessment (i.e., as evidenced by the ENAR Biopharm Executive Committee Meeting described above, we have an incredibly well-motivated, active, financially well-off section, that is meeting the needs of its members and a broader ASA / Industry / Government / Academic constituency—a veritable well-oiled machine) and 2) Len’s eternal question —how I can contribute?

As many of you may know, I am one of those annoying people who feel that even when things are really going great, we can still make everything even better ... a true “continuous improvement” junky. So, very briefly, here’s how I hope to help us this year:

- 1) Maintain/improve/expand the Section’s current activities and services;
- 2) Make the appointments and enlist the highly motivated volunteers needed to do the real work (in this regard, **Jose Pinheiro** from J&J and **Joan Buenconsejo** from FDA/CDER, two outstanding biopharm professionals/statistical leaders, have graciously accepted invitations to join the Executive Committee, each for a three-year term); and
- 3) Create and support an ad hoc committee to examine issues associated with statistical leadership (please get in touch with me if this is a topic of interest to you).

Congratulations and many, many thanks to our newly-elected slate of officers for 2012:

Chair-Elect

Amit Bhattacharyya, GlaxoSmithKline R&D, USA

Council of Sections Representative

B. Christine Clark, ReSearch Pharmaceutical Services, Inc.

Program Chair-Elect

Estelle Russek-Cohen, US Food and Drug Administration

Secretary

Dionne L Price, Food and Drug Administration

This is great!

As 2011 flies by, I continue to look forward to working with you and for you. It’s very certain to me that I am already growing/learning a great deal—thank you for this opportunity.

Steve Wilson, 2011 Chair
stephen.wilson@fda.hhs.gov

Value-Driven Drug Development (VDDD)

Zoran Antonijevic (Quintiles, Innovation) and Natasa Rajcic (Pfizer, Inc.)

The challenges that the pharmaceutical industry has been facing for some time, along with increasing costs and diminishing returns, have been well known even to an occasional follower of the industry. It appears that the existing business model is no longer sustainable, particularly the process of decision making, which has for a long time been *siloed* within individual departments, and based on executives' "gut feeling" rather than on quantitative methods. A successful planning and management of a single clinical trial, a series of trials, a drug development program, and finally a portfolio of drug products could and should be based on quantifiable and measurable actions (Mayer Brown International, 2009). The ultimate goal for drug developers has to be to maximize the expected value of drug development programs and portfolios of programs/trials (DDP hereafter).

Scope

We outline a *value-driven* approach as a basis for drug development. In this approach, design parameters and various decision criteria are defined such that the expected value of a DDP is maximized. This is only possible with a thorough knowledge of both internal (data, study designs) and external (market) factors impacting the value. Therefore, this concept requires an integrated approach and close collaboration between pharmaceutical R&D and commercial groups. In this article, our primary aim is to familiarize our biostatistical colleagues with the aforementioned concepts, with a hope that we can energize statistical minds to take a more active and broader role in an effort to move our industry forward.

Assessing the value of a DDP

There are three key components for assessing the value of a pharmaceutical product:

- Cost
- Expected Revenues
- Risk, or inversely, the Probability of Success (PoS) of a DDP.

Specific to the pharmaceutical industry, each of these three main concepts can be further categorized:

- Factors that affect the overall cost include subject recruitment, investigator and clinician costs, pharmaceutical product, monitoring costs, data analysis and reporting, interaction with regulatory authorities, administrative costs, and many others;
- Factors impacting the expected revenues include indication/affected population size, class/asset share, remaining patent time, external market dynamics, and compliance, among others;
- The drug development path is a series of stages that take place from an early discovery, through clinical development phases, to regulatory approval, product launch, and commercialization. The PoS represents a series of probabilities of progressing from one stage to another along this path.

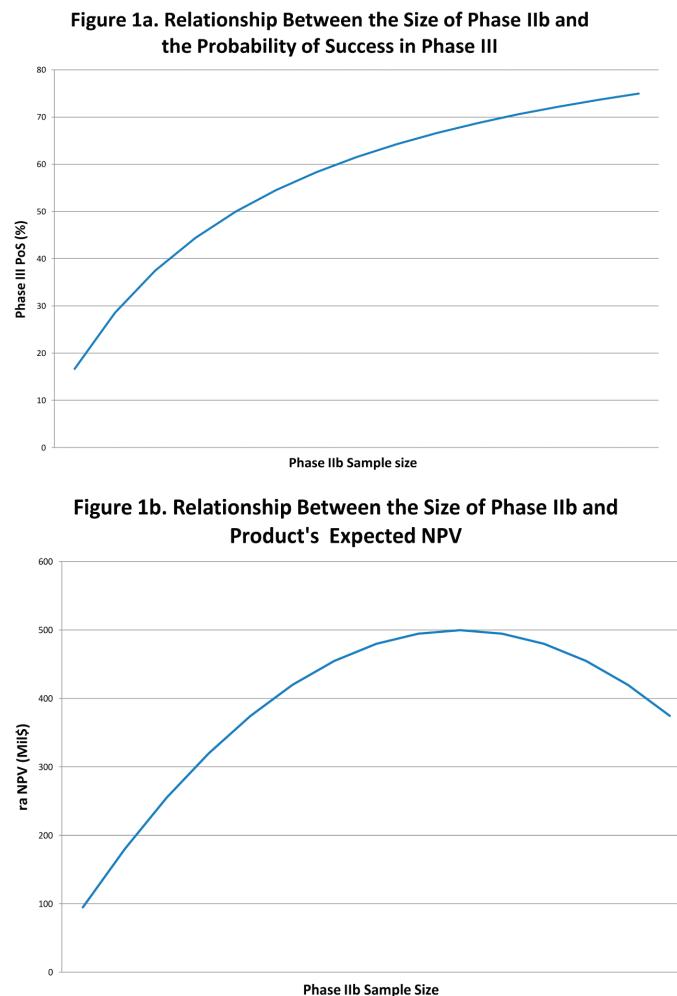
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Risk-adjusted Net Present Value as a metric for valuation

In a typical DDP, considerable amounts of resources are invested early-on with the expectation of recovering the costs and accruing revenues during the latter, commercialization phase, given that a marketing authorization is granted. At the core of that process is a series of clinical trials whose successes ultimately define the successes of a drug development program. Furthermore, the realization of returns is dependent on successfully progressing along a drug development path. Net present value (NPV) is a measurement tool that can be used to evaluate future returns. NPV is the difference between the present value of the future returns from an investment and the amount of investment. Simply put, NPV compares the value of a dollar today to the value of that same dollar in the future. However, as the realization of returns depends on successful development process, NPV needs to be adjusted for various forms of risk (e.g., a product not being approved). A more appropriate measure to consider is thus a risk-adjusted NPV (raNPV). For further introduction to NPV, relevant to the drug development lifecycle, see Antonijevic (2009). The raNPV is an attractive outcome to be used in the evaluation and planning of DDPs, as it incorporates all three parameters listed in the previous section.

There are other advantages of using the raNPV as the outcome of interest for value-based drug development. One is that the raNPV naturally accommodates optimization. As illustrated in Figure 1a, the function of PoS vs. sample size is a monotonically increasing one. The function of raNPV vs. sample size (Figure 1b) would have an inflection point where the value is maximized. We can then think of the corresponding sample size as being an optimal one. See Antonijevic (2009) for further discussion.

Figure 1— PoS and Expected NPV Relationship to Sample Size



Source: Reproduced with permission from Antonijevic (2009).

There is, however, one note of caution when looking at the raNPV function. For most indications the cost of drug development is a small fraction of what would be the realized revenues. Therefore the PoS and factors impacting the revenues, time of development in particular, would have much larger impact than costs. Cost is, however, a very important factor to consider, given that in the real world budgets are limited. Consider Figure 1b again; it is very possible that improvements in the PoS could drive the inflection point to the far right, where desired sample size would correspond to investments that exceed available resources, or is in the region where the investment would be so large that it would make the sponsor uncomfortable to invest. Methods to address this issue are beyond the scope of this article.

Value-driven optimization of raNPV

The use of raNPV in the evaluation of DDPs has long been recognized as a financial tool in portfolio management and valuation of investments, both by a company's inside and outside stakeholders. But merely maximizing the raNPV without taking into account the uncertainties of inputs does not adequately characterize the level of risk (Patel, 2007).

We now describe an approach to relate raNPV to the various parameters that comprise its inputs. The argument follows the simple basics of updating the current information using Bayesian reasoning. Consider the following expression where (θ) stands for parameters and inputs which could potentially impact the raNPV and which are summarized above in the three major groups (Cost, Revenues, Risk), and y represents currently available information regarding some or all of those parameters:

$$E(\text{raNPV}) = u(\text{raNPV}|\theta)\Pr(\theta|y).$$

Here, $u(\text{raNPV}|\theta)$ represents the relationship between parameters (θ) and raNPV . Furthermore, to account for the uncertainty in parameters (θ) ,

$$\Pr(\theta|y) = \Pr(y|\theta)\Pr(\theta).$$

Optimization of raNPV thus provides a way of incorporating various uncertainties of the development process while updating the incremental knowledge as one progress down the drug development life-cycles. In these settings, Bayesian statistical approaches are a natural tool for combining various sources of prior information while incorporating uncertainties. If very little prior information is available, then one can consider a Bayesian approach where industry averages and/or clinical opinion are used as priors. The updates can then be made by using the observed data from ongoing trials.

In order to account for various sources of risk, it is essential to account for uncertainty in observed parameters when calculating various transitional probabilities along the development path. One approach to addressing uncertainty in development programs is to adopt a concept of assurance, or unconditional probability of a positive outcome (O'Hagan et al., 2005). Here "unconditional" differentiates from the traditional approach of calculating power, which is "conditional" on pre-specified assumptions. The idea of computing the expected (or 'average') power with respect to the prior distribution of the parameter of interest is not a new concept; however, it has rarely been implemented by statisticians when planning new studies. While most of our non-statistical colleagues do understand that $\text{power} \neq \text{Prob}(\text{Success})$, they are less likely to appreciate the extent of reliance on the unknown. For detailed discussion of Bayesian/frequentist approach to study design see Spiegelhalter et al. (1986, 2004).

Example

Patel and Ankolekar (2007) presented a hybrid Bayesian/frequentist approach to selecting optimal sample sizes for Phase III clinical trials that considers economic factors relevant to drug development. Their model of the utility, U , (measured as profit) considers factors such as the exclusivity period of the drug, time delay between the trial results and realization of sales, fixed costs per patient during the setup

and running of the trial, costs associated with the positive outcome of the Phase III trial (e.g., production, marketing, sales and distribution processes), per patient costs, and patient accrual rate. Specifically, considering ‘Go’ and ‘No Go’ decisions to proceed following a regulatory outcome, expected utility is expressed as:

$$E(U) = \Pr(\text{Go})E(U|\text{Go}) + \Pr(\text{No Go})E(U|\text{No Go}).$$

Here, $E(U|\text{Go})$ and $E(U|\text{No Go})$ are calculated as linear functions of the above listed economic parameters:

$E(U|\text{Go}) = E(\text{cash revenue from sales})(\text{exclusivity period} - \text{setup time} - \text{accrual duration}) - \text{fixed and per-subject costs},$

$E(U|\text{No Go}) = -(\text{per-subject and trial costs}).$

Furthermore, note that the probability of “Go” and the corresponding “No Go” decisions is computed for a given sample size using the above described concept of ‘assurance’ over whether the null (H_0) or alternative hypothesis (H_1) is correct:

$$\Pr(\text{Go}) = \Pr(\text{Go}|H_0)\Pr(H_0) + \Pr(\text{Go}|H_1)\Pr(H_1).$$

The authors then further account for the risk of the investment by considering the variance of U and thus formulating the distribution of U for a given sample size. See Patel and Ankolekar (2007) for additional comments on the measurements of risk as well as the extension of the approach to optimization of a portfolio of clinical trials using nonlinear integer mathematical programming formulation.

Modeling and Simulations (M&S)

M&S can be used for assessment of a DDP value at any stage of the development. As with predictive probabilities, the more prior information there is, the more reliable the simulation output would be. M&S allow:

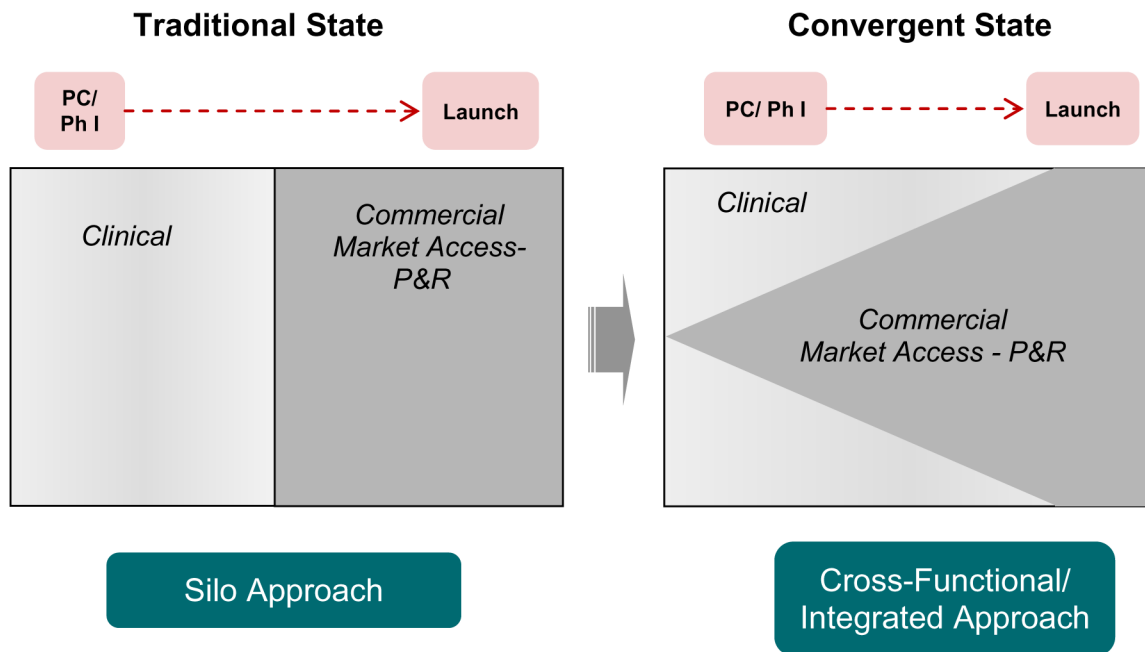
1. Integration of information from multiple areas, from pre-clinical development through the submission stage. Outputs from earlier stages can be used to define assumptions for simulation parameters. Finally, M&S allow for incorporation of commercial outcomes (e.g., through the incorporation of utility functions and the optimization of the raNPV), and as such accommodate the integrated development approach.
2. Assessing multiple scenarios such as differing study designs and endpoints, or even more diverse inputs such as cost of study start-up, accrual rates, and per-subject costs.
3. DDP optimization, as a result of features described in the first two bullet points. M&S offer an approach to deal with the computational complexity of maximizing raNPV subject to various constraints.
4. Accounting for uncertainty, especially when coupled with Bayesian approaches.
5. Distributional output.

As such, M&S are very well suited for planning and optimization of DDP. Burman et al. (2005), Nixon et al. (2009), and Antonijevic et al. (2010) provide further discussion and/or examples.

Value-Driven, Integrated R&D/Commercial approach

In this section we will briefly describe why the integrated approach, as illustrated in Figure 2 below, is necessary in order to maximize the value of DDPs. We will first address this from the commercial point of view, then from that of R&D.

Figure 2: Integrated R&D/Commercial Approach to DDP



Source: Reproduced (modified), with permission, from 'Integrated Approach' plot: Fred Sorensen, Life Sciences Forum, Basel 2010.

Commercial View

There is an increasing demand for demonstration of healthcare value and expanding of stakeholder influence. There is a growing recognition that the traditional, *siloed* organizational focus on product development separate from launch and beyond will no longer meet post-launch product needs. This is also illustrated by an increasing call for value-based therapies with a clear and differentiated value proposition (Sarnes, 2009). As a result, an integrated approach is needed that considers value proposition earlier in the clinical development process by incorporating marketing, commercial, and medical affairs perspectives.

R&D View

Commercial decisions are based on the top level understanding of drug development. It is the R&D team that has deep understanding of the data collected, regulatory and clinical strategies, different development options and their impact on the approval process.

Statisticians specifically are uniquely equipped with skills and knowledge to assess how different development and design options would impact the likelihood of a product approval. They can help quantify decisions, and assess uncertainties in key parameters that are studied.

Multiple development options (e.g., doses, designs, endpoints, budget constraints) should then be compared based on the expected utility, as the expected value of a product clearly depends not only on the quality of the product itself but also on the quality of the development program.

Examples where an integrated approach is necessary

Dose Selection. A well selected dose with an optimal safety/efficacy/health outcomes profile would impact many parameters that we discussed before. It would improve the probability of regulatory success, and would also potentially increase the market share. In order to improve the chance of selecting such a dose, however, one needs to invest into a more robust Phase II that would increase the cost, and lengthen the time of development. Finding an optimal solution for this problem can be done only with joint input from R&D and commercial. Please refer to Antonijevic (2010) for further discussion.

Program-level optimization. Another example, and a much broader one, is the optimization in general, and particularly when done at the portfolio level. Calculating sample sizes has been one of the main tasks for statisticians, ever since they have become involved with drug development. Financial outcomes and optimization, however, have rarely been considered when sample size assumptions are selected. During Phase III planning, power is usually arbitrarily pre-specified, without assessing the extent by which the raNPV would be affected by changes in sample sizes, or what would be the “optimal” power. Likewise, proof-of-concept (PoC) decisions and interim decision rules are rarely set such that the expected revenues can be optimized.

Portfolio-level optimization. The optimization of various decision parameters can be done at the program level, but is better assessed in the context of a portfolio. Consider a portfolio with several clinical trials addressing different indications for which the expected costs and revenues largely differ. Why would the power for Phase III trials be equal for these programs? Shouldn't the decision criteria following interim analyses be based on expected financial losses and gains, and ultimately be specified such that the expected value of the portfolio be maximized? Please see Chen (2009) and Patel (2007) for an excellent discussion.

Summary

Numerous economic factors are important in the planning, design, and management of PPDs. In value-driven drug development (VDDD) decisions regarding various development options are defined such that the expected value of a product is maximized. This is to be done through the process of quantitative optimization of development decisions. While this optimization could focus on individual development programs, it is preferable that these decisions are made at the portfolio level, as individual programs are interdependent. Integration of various sources of information and input is essential in order to successfully deliver VDDD. This organizational shift represents a new challenge, as well as an opportunity for statisticians to add value to the overall development process.

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Summary of the ASA Biopharmaceutical Section Executive Committee meeting 21-March-2011 at ENAR in Miami

Submitted by Rick Caplan

Steve Wilson, Chair, announced his 2011 appointments:

- **John Johnson** for contributed paper competition
- **Veronica Taylor** to assist with contributed paper competition
- **Jose Pinheiro** as an appointed member of the Executive Committee
- **Joan Buenconsejo** as an appointed member of the Executive Committee

Steve Gulyas, Chair-elect, announced his 2012 appointment:

- **Alan Hartford** for FDA/Industry Workshop

Matilde Sanchez gave the Treasurer's Report. In 2010, the Section added \$8276.18 to the budget. Less money was spent on webinars than was budgeted. The FDA/Industry Workshop made \$24,075.10, half of which goes to ASA.

Web Outreach Project: www.biostatpharma.com

Steve Gulyas reported on progress with the Web Outreach Project, which is a website created by the Biopharm Section to give information to students considering a career in biopharmaceutical statistics. There is a need for more content. And it needs a webmaster. Interested people can contact Steve. The link to the site is www.biostatpharma.com.

Neal Thomas reported that the Fellows Committee supported one candidate this year for ASA Fellow. In the past 6 years, the Biopharm section has successfully supported 10 candidates.

Kathy Monti, past Biopharm EC Chair, completed an update of the Manual of Operations. It describes the responsibilities of roles in the Biopharm Section. The manual is available on the Section's website.

Jeff Maca and **Carmen Mak** reported on plans for 2011 JSM. There will be 6 invited sessions, 17 topic-contributed sessions, 28 regular contributed sessions, 18 roundtables and 2 short courses. The Biopharm Section will have more sessions at JSM than any other Section. For the Contributed Paper Competition, **John Johnson** and **Veronica Taylor** will seek volunteers from local students and possibly retirees at JSM to help with the competition.

Christie Clark reported that last month, academic departments were contacted with instructions for submitting papers to the student paper competition.

Joan Buenconsejo and **Brenda Crowe** reported that the 2011 FDA/Industry Workshop, which is a Biopharm Section activity, will be held September 19-21 at the Washington Marriott Wardman Park. There will be 34 sessions and 6 short courses.

Mani Lakshminarayanan and **Venkat Sethuraman** reported on web-based training offered by the Section. Some speakers dropped out at the end of last year. There will be a more complete program this year.

Steve Wilson is establishing an ad hoc committee on continuous improvement to further develop the Biopharm Section and develop leadership of its members.

Biopharmaceutical Section Best Contributed Paper from the 2010 JSM meeting

Congratulations to the winners of the Biopharmaceutical Section Best Contributed Paper from the 2010 JSM meeting in Vancouver, B.C. Winners were chosen based on presentation scores from audience attendees. The winners, presentation title, and the contributed session are presented below. Congratulations to all winners for their outstanding presentations!

1st Place: Eugene Demidenko (Dartmouth Medical School)—Statistical Modeling of Tumor Regrowth and the Assessment of Drugs Synergy in Animal Experiments (Session 57 – Statistical Methods for Assessing Anti-Tumor Activity).

2nd Place: Walt Stroup (University of Nebraska-Lincoln) and Michelle Quinlan (University of Nebraska-Lincoln)—Alternative Shelf Life Estimation Methodologies (Session 17 – Pharmaceutical Stability Shelf Life: Philosophy, Intent, and Estimation).

3rd Place: Sharon C. Murray (GlaxoSmithKline), John F. Toso (GlaxoSmithKline), John W. Bauman (GlaxoSmithKline)—A Bayesian Design for a Proof-of-Concept Study Comparing Rituxan in Combination with a New Drug to Rituxan Alone (Session 503 – Applications of Bayesian Methodology to Clinical Trials in Oncology).

Honorable Mention: Donald Arthur Berry (MD Anderson Cancer Center), Kyle Wathen (MD Anderson Cancer Center), Nebiyou Bekele (MD Anderson Cancer Center), Laura Esserman (University of California, San Francisco)—I-SPY2: Identifying Biomarker Signatures for Therapeutic Agents in Neoadjuvant Breast Cancer (Session 332 – Adaptive Design for Drug/Diagnostic Combination Trials).

Honorable Mention: Byron Jones (Pfizer, Inc.), Michael G. Kenward (London School of Hygiene and Tropical Medicine), James Henry Roger (GlaxoSmithKline)—The Use of Baseline Covariates in Cross-Over Studies (Session 329 – The Design and Analysis of Crossover Trials: Some Recent Developments).

Meeting Announcements

Joint Statistical Meeting

July 30–August 4
Miami Beach Convention Center,
Miami Beach, Florida



The Biopharm section has succeeded in organizing and is the primary sponsor for many interesting short courses and sessions for the JSM conference on applications of statistics in many aspects of biopharmaceutical research areas.

The section has organized 2 short courses:

Analysis of Clinical Trials: Theory and Applications (Instructors: Alex Dmitrienko, Eli Lilly and Company; Devan V Mehrotra, Merck Research Laboratories; Keaven Anderson, Merck & Co., Inc); and

Multiple Comparisons Using R and SAS (Instructors: Peter Westfall, Texas Tech University, Frank Bretz, Novartis Pharma AG).

Members are encouraged to sign up for these popular courses as the JSM registrations are already open: <http://www.amstat.org/meetings/jsm/2011/index.cfm?fuseaction=registration>.

The section has been the primary sponsor for 5 invited sessions on topics such as missing data, multiplicity and adaptive designs. There were 17 topic-contributed sessions and over 28 regular contributed sessions sponsored by the section. There will at least 2

biopharmaceutical section sponsored sessions occurring at every time slot during the conference. In total, Biopharm has the maximum number of sessions of all of the ASA sections.

The section is also sponsoring 18 luncheon roundtables on a variety of topics such as missing data, adaptive designs and outcome studies for discussion at JSM 11. The luncheon roundtables are always a big hit at the JSM and seats go fast for many of these tables – so members are also encouraged to register for them sooner.

We would like to thank our members for organizing and contributing to these significant numbers of section-sponsored sessions. We hope to see you all in August.

*Jeff Maca (Program Chair) &
Carmen Mak (Program Chair-Elect)*

The 2011 FDA/Industry Statistics Workshop

September 19–21, 2011

Washington Marriott

Wardman Park, Washington D.C.

Registration will be open beginning June 1, 2011 for the 2011 FDA/Industry Statistics Workshop!

This year's workshop will be held September 19-21, 2011 at the Marriott Wardman Park, Washington D.C. The three-day workshop is one of a series of annual meetings that have been sponsored by the ASA Biopharmaceutical Section in cooperation with the FDA Statistical Association since 1996. Short Courses are scheduled on the first day, followed by two days of sessions on the science and statistics associated with the development of new medical products (pharmaceuticals, biologics and devices). The FDA/Industry Statistics Workshop is designed specifically and provides a unique opportunity to bring together statisticians from industry, academia, and the FDA for an open dialogue on issues of mutual interest.

Please visit <http://www.amstat.org/meetings/fdaworkshop/index.cfm?fuseaction=main> for more information and to reserve your spot today.

Brenda Crowe & Joan Buenconsejo (Co-chairs)

The 9th International Conference on Health Policy Statistics

October 5–7, 2011

The Ritz-Carlton Cleveland,
Cleveland, Ohio



Photo of the Cleveland Skyline

The International Conference on Health Policy Statistics (ICHPS), organized by the Health Policy Statistics Section of the American Statistical Association plays a vital role in the dissemination process of health policy (and health services) statistics. ICHPS provides a unique forum for discussing research needs and solutions to the methodological challenges in the design of studies and analysis of data for health policy research. ICHPS's aim is to create interfaces between methodologists and sophisticated health service researchers, health economists, and policy analysts so they can exchange and build on ideas that they will disseminate to the broader health policy community.

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These upcoming conferences are either of recurring general interest to our membership or have been brought to our attention.

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August 29–September 1, 2011
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The 7th International Conference on Multiple Comparison Procedures will be held on August 29 - September 01, 2011 at the Hilton Rockville Hotel, MD. The main goal of the conference is to promote research and applications of multiple comparison procedures. The application areas of multiple comparison procedures are a rich and important source of cross-disciplinary statistical research. This conference will provide a forum for technical interactions among industry practitioners, research scientists from different subject matter areas and statisticians.

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Trends in Comparative Effectiveness Research

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Abstract

Comparative effectiveness research (CER) has received enhanced attention in the United States, thanks in part to the funding earmarked for CER through the American Recovery and Reinvestment Act of 2009. Over the last few years considerable progress has been made in establishing the infrastructural and conceptual requirements to advance CER. In this paper, we review progress in CER activities, outline some of the methodological issues, highlight the challenges associated with CER, and indicate emerging areas of research that require increased focus to ensure a more effective strategy for the use and implementation of CER results.

Keywords: Systematic review; indirect comparison; nonrandomized studies; evidence based medicine; health technology assessment

1. Introduction

Comparative Effectiveness Research (CER) has been defined as “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. The purpose of CER is to assist consumers, clinicians, purchasers, and policy makers to make informed decisions that will improve health care at both the individual and population levels.¹ While aspects of CER have long been widely recognized in some parts of the developed world, including Australia, Canada and several European countries, the topic had not been given significant attention in the United States until fairly recently. The activities in the US have been limited to efforts of certain healthcare providers and academic centers, with minimal government or private funding. Thanks in part to the funding earmarked for CER through the American Recovery and Reinvestment Act of 2009, the topic has now garnered considerable interest, and over the last couple of years, important progress has been made in establishing the infrastructural and conceptual requirements to advance CER.

Efforts to promote CER are now coordinated among both government and non-government institutions, including the Agency for Healthcare Research and Quality (AHRQ),² the Center for Medical

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Technology Policy,³ and several private entities, universities and medical centers.^{4,5} The activities of the institutions range from development of guidelines to the investigation of complex methodological approaches. A few institutions are directly involved in systematic reviews of clinical data, while others are focused on conducting basic research in CER. An important recent development in this regard is the establishment of the so-called Patient Centered Outcomes Research Institute (PCORI) through the Affordable Care Act (P.L. 111-148 and P.L. 111-152). As a non-profit, non-government organization, PCORI is charged with identification of CER research priorities, establishing a research project agenda, and conducting research either in-house or through public and private entities. A branch of PCORI, called the Methodology Committee, is particularly commissioned to develop methodological standards to improve CER science and methods in the initial phase.

In this paper, we outline some of the methodological issues, highlight the challenges associated with CER, and propose steps that must be taken to ensure a more effective strategy for the use and implementation of CER results. In Section 2, we provide a review of the commonly used approaches and their limitations. In Section 3, active areas of research are discussed and in Section 4 we provide concluding remarks.

2. Methodological Considerations

In view of the broad scope of CER, the associated methodological challenges range from basic statistical techniques to handle specific inferential problems to the development of guidelines pertaining to therapeutic indices in major disease areas. In the following we shall restrict the discussion to the methodological approaches that are relevant in systematic reviews in CER, the gaps in the current state of knowledge, and the implications for further work in these areas.

CER vs. Meta-analysis

In contrast to classical meta-analysis that deals with the synthesis of information from different sources about the relative effectiveness of two treatment options, a typical goal of CER is more ambitious and involves a range of available treatment options. In some sense the latter mirrors the dilemma that patients, physicians, policymakers and other healthcare providers routinely face in making decisions about optimal treatment strategy for a given condition. Nonetheless, CER also shares some of the known limitations and pitfalls of classical meta-analysis.

Reporting bias is a major problem that requires careful attention in any systematic review, including complex CER activities. Thanks to the aggressive initiatives by journal editors and other public and private institutions, there have been major efforts to minimize the tendency not to publish negative or neutral results from randomized clinical trials (RCTs). Nonetheless, the practice is not totally eliminated, and there is no adequate mechanism to control for or assess the impact of publication bias. Traditional techniques, such as the funnel plot, are not wholly satisfactory to handle even the relatively less complex cases in ordinary systematic reviews. In CER the issue is further complicated by the scope of the problem under consideration, as the assessment now includes a range of available treatment options.

For standard meta-analysis, the two commonly used analytical approaches are the fixed effects model and random effects formulation, whether one prefers a frequentist or a Bayesian paradigm.⁶ Despite their use in routine systematic reviews, there is no general consensus on a commonly accepted procedure. Fixed effects models are typically appealing because of their simplicity and ease of interpretation. However, their validity is heavily dependent on a tenuous assumption of lack of heterogeneity of effect across studies – an assumption that is often difficult to verify conclusively.^{7,8} On the other hand, the mathematical elegance of random effects models makes them appealing to modelers, but these techniques run into problems of interpretation in the face of known heterogeneity of effects. Since CER exercises typically depend on results of such standard meta-analyses as input, especially when dealing with more complex syntheses, they indirectly suffer from the limitations of these procedures.

Indirect and Mixed Treatment Comparisons

In addition to the familiar problems of classical meta-analyses, CER is also constrained by the absence of data from head-to-head comparisons. This is important because unlike routine meta-analysis, the scope of CER involves synthesizing information on a variety of competing interventions. The indirect treatment comparison technique proposed recently by Bucher et al.⁹ was a first step in addressing this gap. The method aims at preserving, at least partially, the benefits of the initial randomization in the original RCTs through the use of the relative treatment effect, rather than individual treatment effects. More specifically, suppose we are interested in estimating the relative efficacy of treatments A and C, denoted d_{AC} , that has not been investigated in a head-to-head RCT, but each has been compared to a common treatment B in separate RCTs, with corresponding estimated treatment effects d_{AB} , and d_{CB} , respectively. The approach estimates d_{AC} as a simple function of d_{AB} and d_{CB} . Compared to the naïve or direct approach, which does not take into account any aspect of the original randomization, the indirect approach partially preserves it. Moreover, if the original estimators of treatment effects possess standard large-sample properties, so does the indirect estimate.

While the indirect comparison approach is appealing due to its simplicity and partial preservation of the randomization, its validity relies on very important assumptions. In addition to the typical problems associated with analyses that involve pooling data across studies, the technique is based on a supposition of exchangeability, i.e., the requirement that the same relative treatment effects would be realized if the two comparisons were performed under the experimental conditions of the other trial. This is, of course, a hypothetical construct, and cannot be verified using data in a rigorous mathematical setting. The proper interpretation and use of results from such analyses, therefore, presupposes a careful evaluation of the tenability of this important condition.

The simple indirect comparison approach of Bucher et al is also limited in handling more complex settings that require incorporation of evidence from direct and indirect comparisons from several trials. Network meta-analysis and other mixed treatment comparison techniques have been proposed to handle such complex scenarios. Lumley's network meta-analysis in particular has been suggested for comparisons that involve closed loops.¹⁰ More specifically, suppose we are interested in comparing A vs. C, using data from three RCTs that compared A vs. B, B vs. D, and D vs. C, respectively. The approach uses a mixed effects model that includes terms for the pairwise effects, residual effect of each treatment, and a quantity for evaluating "incoherence of network". This approach is limited by its requirement of a closed loop, in addition to the other issues discussed earlier. Further, it cannot handle multi-arm situations, where the assumption of independence cannot be supported. One appealing feature of the method is its incorporation of a term for assessing coherence. This, however, requires a substantial number of studies, a condition that is rarely satisfied in such analyses.

Other techniques have been proposed for more complex cases, including direct and indirect evidence. These mixed treatment comparison approaches are commonly implemented using standard meta-analytic framework, and are often conducted in Bayesian settings.^{11,12} Like the simpler approaches, mixed treatment comparison techniques also have to rely on strict assumptions, including exchangeability. In addition, one needs to verify consistency of results from direct and indirect comparisons. For further discussions on indirect and mixed treatment comparisons, see, e.g., references 13-21.

3. Emerging Areas of Research

While substantial progress has been made in recent years in advancing CER in the United States, much work remains to be done in developing new techniques and approaches to address issues that are peculiar to CER. This often requires exploring approaches that hitherto have been neglected both for logistical and/or technical reasons, and revisiting other methods that have only been tailored to address problems that arise in traditional clinical trial settings.

Assessing Exchangeability

As pointed out above, the exchangeability issue is of primary concern in indirect comparison techniques, and calls for further research. Although it is theoretically impossible to conclusively establish the validity of the assumption, indirect approaches must be explored to assess the robustness of the findings to known departures from this assumption. The approaches may involve a multi-pronged strategy, including evaluation of qualitative data about study design and patient characteristics, quantitative tools to assess degree of heterogeneity of treatment effects, and simulation techniques to fill in for data gaps.

Heterogeneity and Confounding in CER

The assessment and management of heterogeneity play a central role in CER. From a statistical standpoint, the issues associated with heterogeneity analysis in CER are generally similar to those known when one deals with subgroup analysis in clinical trials. However in the context of CER, the problems are compounded by the fact that the number of treatment options involved is typically large, the scope of the analyses wide, and the associated issues with interpretation of the results relatively more complex.

In addition, every time a data analyst is confronted with aggregate data, there is no obvious way of adjusting for or explaining the impact of relevant covariates. In traditional meta-analysis, one preferred option has been meta-regression. However even in those simple cases, use of study level data covariates in tandem with aggregate patient-level data is fraught with problems.^{14, 22}

Role of Nonrandomized Studies in CER

It's well recognized that RCTs provide the most robust estimates of comparative treatment effects. However, RCTs have limited external validity, since by design they seldom mimic real-world conditions. Further, not all available treatment options are necessarily studied in RCT settings, even when there is interest to synthesize available data. Therefore, there is ongoing review of the role of nonrandomized or observational studies to address critical issues in CER.^{23, 24}

The use of data from nonrandomized studies to make reliable healthcare decisions, however, requires a thorough appreciation of their inherent limitations. Most importantly, the absence of randomization introduces an element of bias due to the obvious lack of balance in relevant covariates, which may be known or hidden. The value of such data is therefore a function of the reliability of the methods employed to adjust for overt confounders and to evaluate the uncertainty emanating from hidden or latent covariates. Overt biases are customarily managed through suitable statistical adjustment techniques, including matching, stratification or analysis of covariance. Propensity score analysis is particularly used in routine applications, due to its ease of implementation [see, e.g., 25, 26]. For latent covariates, an effective strategy often involves measures that need to be taken both at the design and analysis stages. However, despite intensive research in the analytical front, including the use of instrumental variables, there is no universally accepted approach to mitigate the associated confounding problem. See, e.g., Basu et al²⁷ and Tannen et al²⁸ for recent developments in the study of hidden covariates.

In addition to the methodological issues with the control of bias, nonrandomized studies also pose considerable challenges relating to data quality and standards. In contrast to the situation with randomized clinical trials, the infrastructure for nonrandomized studies is not well developed. While there has been encouraging progress in the formulation of guidelines for the design, analysis and reporting of data from nonrandomized studies, coordinated efforts are needed among key stakeholders to address issues ranging from coding conventions to managing missing values. Examples of recent activities on good practices for design, analysis and reporting of data from secondary sources may be found in references 29–33, among others.

Simulated Clinical Trials

When there is no head-to-head comparative data from RCTs, the use of Monte Carlo (MC) techniques to simulate clinical trials is a promising approach in CER. In a recent study, Caro and Ishak³⁴ proposed a method based on discrete event simulation algorithms to simulate missing arms into an existing trial. Their approach involves simulating an index trial, building predictive models, and calibrating the model using separate data. The validity of this and other MC approaches is, of course, dependent on the tenability of the underlying assumptions, including exchangeability. Further, most of the proposed methods require patient level data. Much work is still needed to investigate simulation of individual patient level outcome when the available information is aggregate data at the study level.

Laying the Foundation for CER

Lastly, there is a growing realization of the need to lay effective infrastructural foundation for CER. This involves standards for databases, quality control and analytical tools. In a recent communication, the U.S. Food and Drug Administration highlighted an elaborate plan to tackle the infrastructural requirement that includes development of a clinical trial data repository, conversion of legacy data into a common structure, and implementation of modern analytical tools.³⁵ For the wider CER initiative, such an approach would require the coordination of efforts among various stakeholders, including non-profit organizations, medical centers and private entities in the healthcare industry.

4. Summary and Conclusion

With the establishment of the Patient Centered Outcomes Research Institute (PCORI) and the release of funds that were made available through the American Recovery and Reinvestment Act of 2009, CER has gained considerable prominence in the United States. Over the past few years, significant progress has been made in laying the underpinning for methodological research, and work has gathered momentum on extending approaches for traditional systematic reviews to more complex CER situations.

By virtue of the scope of the problems addressed in CER, the area has also opened up a fresh window of research opportunities. In the absence of head-to-head comparative data from RCTs, there is renewed interest in indirect comparison or mixed treatment comparison methods. Novel methods to assess basic assumptions in indirect comparisons are under study, as are approaches to assess effects of confounders when using aggregate data. There is budding interest in the role of simulations to fill the data gaps created by limitations of traditional RCTs data analysis. At the same time there is a growing recognition of the potential value of revisiting issues associated with non-randomized or observational studies, in light of the paucity of data from RCTs to address major CER objectives. In addition, a key focus of research in the coming years will be on the assessment of heterogeneity of treatment effects, with emphasis on the generalizability of results from traditional RCTs that target a given population to individual patients or subgroups of patients.

Without sound methodological foundation, there is always the potential for major decisions to be made with data analyzed using less-than optimal procedures, thereby adversely impacting public health. Therefore, given the broad implications of CER, all concerned stakeholders should be actively engaged to understand the underlying issues, to lay the groundwork for a robust CER infrastructure, and to participate in or promote the efforts to develop appropriate analytical methodologies and strategies to effectively communicate the research findings.

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