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Issues and Algorithms in Cost-Effectiveness Inference

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Contents

Introduction

Recent efforts to control health care expenditures in many countries around the world have tended to focus attention on the cost-effectiveness of alternative treatment methods, including pharmacotherapy. There appears to be an emerging consensus that, in addition to traditional randomized clinical trials, new forms of study design and analysis methodology are needed to address the wide array of questions now being asked by regulators, payers, health care providers, and patients. Drummond (1992) concluded "Maintenance of good methodological standards is, in the long run, the best policy both for pharmaceutical industry sponsors and economic analysts."

A number of organizations are in the process of developing guidelines for pharmacoeconomic practice [PhRMA (1994, 1995), A*P*O*R (1996), PCEHM (1996); see also the review by Genduso and Kotsanos (1996)]. As statisticians, our interests in these sorts of guidelines tend to focus on methods of **accounting for uncertainty** in cost-effectiveness inference. A wide variety of methodological advances have already appeared in published literature; see Drummond, Heyse, and Cook (1996) as well as the list of references at the end of this article. In reality, little is currently known about the relative advantages and disadvantages of these alternative approaches to statistical inference.

A primary purpose of this article is to encourage interested biopharmaceutical statisticians and econometricians from industry, academia, and government to actively participate in a new, standing **Cost-Effectiveness Inference** committee, cosponsored by ASA, PhRMA, and A*P*O*R. This working group is expected to have a technical focus, with initial emphasis limited to reviewing inference methods for the special case where just two alternative therapies are being compared using an incremental cost-effectiveness ratio (*ICER*) statistic. Thus, the remainder of this article introduces a few of the many unresolved **issues** surrounding *ICER* analyses in pharmacoeconomics.

As well as performing research on the advantages and disadvantages of alternative methods, our committee will also collect and distribute computational **algorithms** for cost-effectiveness inference. Current pharmacoeconomic guidelines stress "full disclosure" of methods and data, and distribution of algorithms (source code) would greatly expedite this disclosure process.

Committee members will cross-validate computer algorithms primarily by verifying that software (appropriately compiled or interpreted) produces correct output for a suite of benchmark numerical examples. Source code, test data, and executable modules for the algorithms we have reviewed will be posted to StatLib (**http://lib.stat.cmu.edu/DOS/general**) on the Internet so that they may be downloaded by any interested party. Researches will then have the options either to use the algorithms we have evaluated or else to cross-validate their own algorithms against our standards.

Incremental Cost-Effectiveness Ratios (ICERs)

In a two-sample cost-effectiveness analysis, the data consist of a (continuous) cost variable, C_{Ti} , and a treatment effectiveness indicator, E_{Ti} (which may be binary, with 0→no, 1→yes or continuous), for each of the $i = 1, \ldots, NT$ patients who received the new treatment, *T*. Similarly, a pair of (C_{Sj}, E_{Sj}) values would be collected for each of the $j = 1, \ldots, NS$ patients who received the standard treatment, *S*.

The "incremental" cost-effectiveness ratio, *ICER*, Black (1990), is the ratio defined as the difference in average per patient costs divided by the corresponding difference in effectiveness average.

$$ICER = \frac{\overline{C}_T - \overline{C}_S}{(\overline{E}_T - \overline{E}_S)},$$

where a T subscript denotes an average over patients on the new treatment while subscript S denotes the corresponding average for patients on the standard treatment.

Transformations of *ICER* statistics in the form of simple "scale changes" are sometimes needed. For example, this occurs in converting a numerator cost difference from one currency into another or in discounting charges relative to a different base year. Similarly, when one's effectiveness measure is binary (0 → ineffective, 1 → effective), one might re-express the denominator in **percentage points** as follows:

$$ICER = \frac{\overline{C}_T - \overline{C}_S}{100 \times (\overline{E}_T - \overline{E}_S)}.$$

Unfortunately, some inference methods are sensitive to these sorts of simple scale changes.

Two very different types of methodology for placing statistical confidence limits around Incremental Cost-Effectiveness Ratios (*ICERs*) appear to be currently in active use. These two approaches are (i) parametric methods for analysis of ratio estimates, including Fieller's theorem; and (ii) nonparametric, bootstrap methods.

Fieller's Theorem

Like older methods based upon a Taylor series approximation, the Fieller's theorem approach recognizes that the *ICER* is a "ratio estimator" in the sense of Cochran (1977) and, thus, is asymptotically normally distributed. The characteristic property of the Fieller approach is that it treats the numerator and denominator between cohort differences as if they were a pair of correlated normal variables. This allows the Fieller approach to recognize (small sample) situations where the stochastic distribution of the *ICER* is actually highly skewed.

Technical Note: Descriptions of the Fieller and Taylor series approaches are given in Willan and O'Brien (1994, 1996), O'Brien *et al.* (1994), Sacristan *et al.* (1995), and Chaudhary and Stearns (1996).

ISSUE: Confidence intervals based upon Taylor series approximations are too narrow (anti-conservative) relative to the corresponding intervals from Fieller's theorem.

ISSUE: Fieller's theorem confidence intervals correspond to "bow tie" shaped confidence regions on the cost-effectiveness plane; see Figure 3. It follows that Fieller's theorem confidence intervals are themselves "too narrow" when the estimated mean of the joint distribution of between cohort average differences, $(\overline{E}_T - \overline{E}_S, \overline{C}_T - \overline{C}_S)$, is not highly significantly different from (0,0).

ISSUE: The Fieller method of forming *ICER* confidence intervals is not "rescaling commutative." In other words, rescaling an *ICER* statistic by a multiplicative factor changes its upper and lower Fieller confidence limits by a different factor.

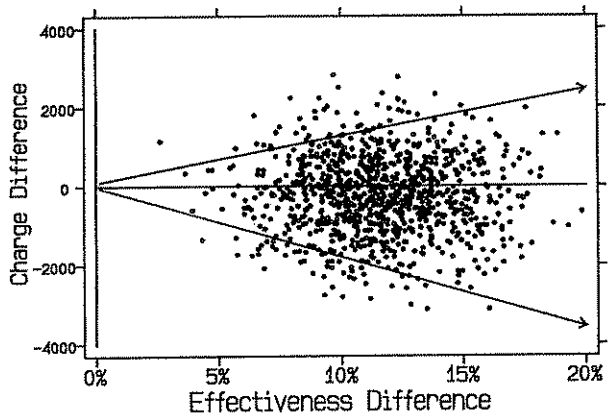
Bootstrap Analyses

Bootstrapping approaches resample (with replacement) from all of the observed data, as described in Drummond, Heyse and Cook (1996), Chaudhary and Stearns (1996), and Obenchain *et al.* (1997).

ISSUE: The observed data pairs, (C_{Ti}, E_{Ti}) or (C_{Sj}, E_{Sj}), for all patients in both treatment groups are needed to construct bootstrap confidence intervals. In other words, bootstrap intervals cannot be computed from the sorts of simple *summary statistics* (sample means, variances, and correlations) commonly reported in health economics studies and journal articles. On the other hand, bootstrap approaches to *ICER* confidence intervals do not need to make possibly unrealistic assumptions about parametric forms for stochastic distributions and, thus, offer great potential for increased realism, accuracy and robustness.

ISSUE: The bootstrap approach yields a rather dramatic graphical display of the variability in two-sample cost and effectiveness differences that result when an entire study is literally "redone" hundreds of times; see Figure 1, reproduced from Obenchain *et al.* (1997). Bootstrap analyses are thus actually much easier to explain and to appreciate than are the rather elaborate calculations and approximations used in parametric, "ratio estimator" approaches.

Figure 1. A bootstrap analysis of ICER slopes.



ISSUE: Like all methods based upon simulation or re-sampling, numerical values for bootstrap confidence limits can be sensitive to "parameters" such as the *total number of replications performed* and the *initial seed value* for the random number generator. Thus, to satisfy pharmacoeconomic "full disclosure" guidelines, these sorts of technical details usually need to be reported. Furthermore, "sensitivity" analyses should be performed to assure that bootstrap limits are not reported with inappropriate precision (too many decimal places).

ISSUE: No implementation of *ICER* bootstrap analysis is currently available (mid 1997) in commercial statistical analysis software. On the other hand, algorithms needed to perform bootstrap analyses are all either straightforward or else published in statistical literature; see Efron and Gong (1983), Efron and Tibshirani (1986), L'Ecuyer (1988), O'Brien *et al.* (1994), and Westfall and Young (1992) for basic concepts. Obenchain (1997) provides examples of highly portable algorithms for *ICER* confidence limits using bootstrapping or Fieller's theorem.

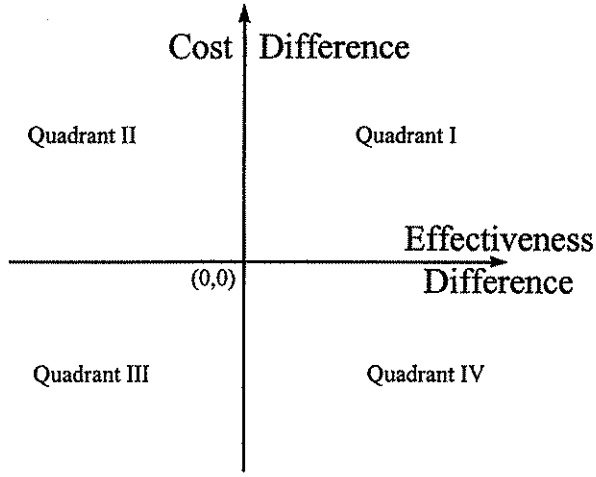
Technical Note: In addition to *ICER* rescaling commutivity, Chaudhary and Stearns (1996) discuss the closely related property of "transformation-respecting" methods. Bootstrap procedures yield confidence interval endpoints that change correctly and automatically under general monotone transformations as well as under simple rescalings.

ICER Interpretation

A health economics study comparing a new treatment, T, with a standard treatment, S, can be viewed as producing a single "point" on the **cost-effectiveness** plane of Black (1990), shown in Figure 2. The horizontal coordinate of this point is a between-cohort effectiveness difference, $\overline{E}_T - \overline{E}_S$, while the vertical coordinate is a measure of the corresponding cost difference, $\overline{C}_T - \overline{C}_S$. Here, we number the quadrants of the cost-

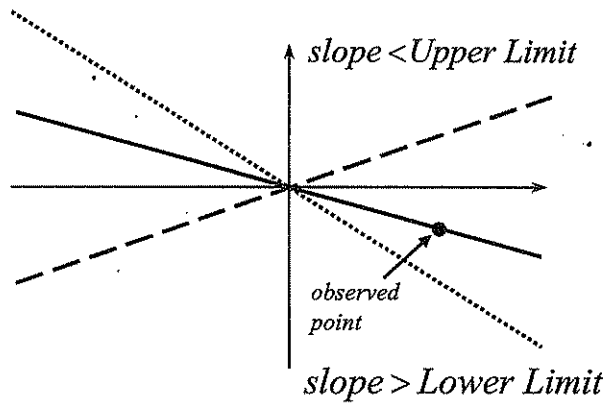
effectiveness plane (I, II, III and IV) in the "standard" way, also shown in Figure 2.

Figure 2. The cost-effectiveness plane.



On this graphical display, the *ICER* is nothing more than the **slope of the line** connecting that health economics study point, $(\Delta E, \Delta C) = (\overline{E}_T - \overline{E}_S, \overline{C}_T - \overline{C}_S)$, with the origin, (0,0). And the corresponding Fieller confidence limits on this *ICER* slope form a "bow tie" shaped region. These concepts are illustrated in Figure 3.

Figure 3. An ICER slope and its Fieller limits.



We do not always find ourselves in the **simple situation** (depicted in Figure 1) where all of the results generated in an *ICER* bootstrap analysis fall within Quadrants I and IV of the cost-effectiveness plane. In other words, some bootstrap effectiveness differences, $\Delta E = \overline{E}_T - \overline{E}_S$, may turn out to be **negative**, rather than all positive. But we still want a cost-effectiveness confidence region that is "wedge" shaped, as in Figure 4, rather than "bow tie" shaped.

While the vast majority of bootstrap replicates in Figure 4 fall into Quadrant IV (900 of 1000) or Quadrant I (77 of 1000), a few outcomes fall into Quadrant III (20 of 1000) and even into Quadrant II (3 of 1000). In particular, notice also that negative values for the *ICER* slope arise from outcomes in either Quadrant IV or Quadrant II. But these two types of outcomes have *diametrically opposite interpretations!*

Specifically, consider the two health economic studies depicted in Figure 5, where the numerical value of the ***ICER* slope** is minus one, say, in both cases.

Figure 4. A bootstrap analysis with points in all 4 quadrants.

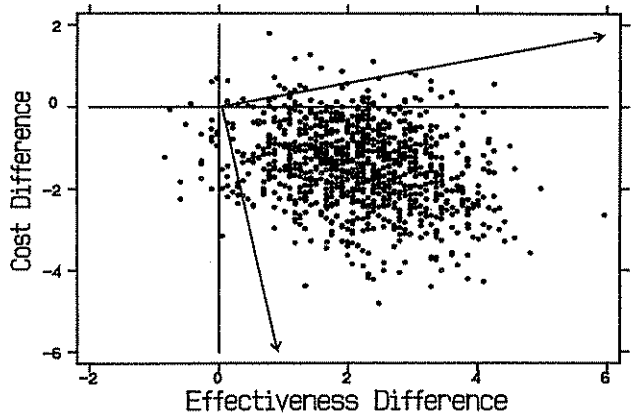
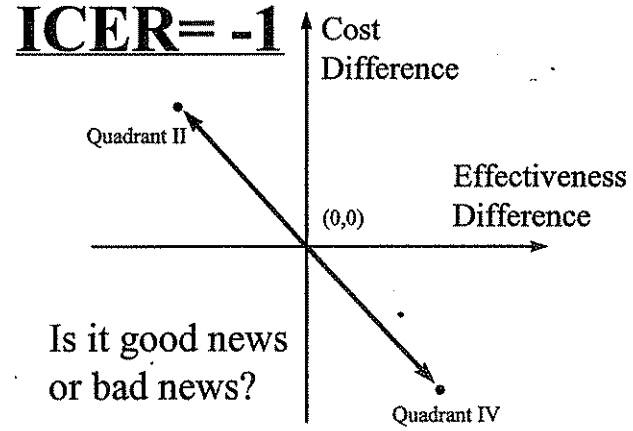


Figure 5. The ICER slope tells only half of the story!



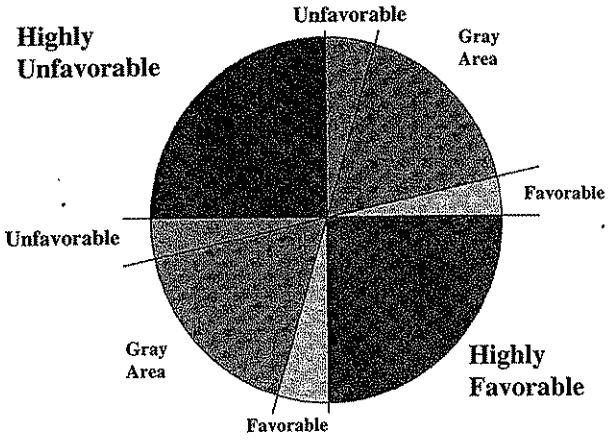
Note that a health economics study that produces a point in Quadrant IV suggests that the new treatment, *T*, completely dominates the standard treatment, *S*. After all, $\overline{E}_T - \overline{E}_S > 0$ and $\overline{C}_T - \overline{C}_S < 0$ together mean that *T* is both more effective and less costly than *S*. In sharp contrast, S completely dominates *T* when a health economics study produces a point in Quadrant II. This time $\overline{E}_T - \overline{E}_S < 0$ and $\overline{C}_T - \overline{C}_S > 0$, meaning that *T* is now less effective and more costly than *S*. And yet both of the hypothetical studies depicted in Figure 5 yielded the same numerical value (-1) for the *ICER* slope!

ISSUE: In some situations, the ***ICER* slope** is not, by itself, a sufficient statistic for making cost-effectiveness inferences.

Figure 6 divides the cost-effectiveness plane into *Five Sections* that span the full range of possible outcomes of health economic studies comparing a new treatment, *T*, with a standard treatment, *S*. For example, Quadrant IV is labeled "Highly Favorable," while Quadrant II is labeled "Highly Unfavorable." Again, these are the two quadrants of the cost-effectiveness plane where the *ICER* is negative.

The *ICER* slope is positive in Quadrants I and III, and these quadrants are divided into 3 parts each. A small, positive *ICER* slope is "Favorable" if the health economics study point falls in Quadrant I but "Unfavorable" when that point falls in Quadrant III. Similarly, a large, positive *ICER* slope is "Favorable" if the health economics study point falls in Quadrant III but "Unfavorable" when that point falls in Quadrant I. The fifth section is a "Gray Area" within Quadrants I and III where the *ICER* slope is positive but neither very big nor very small.

Figure 6. Dividing up the cost-effectiveness plane.



ISSUE: An unambiguous way to quantify cost-effectiveness, using *ICER* **angles**, is our next topic.

ICER Angles

The **scales** used along the horizontal (effectiveness-difference) and vertical (cost-difference) axes of the cost-effectiveness plane need to be **standardized** in order to define meaningful cost-effectiveness **angles**, Heyse and Cook (1992). One reasonable standardization is achieved by dividing each difference in treatment averages by the estimated standard deviation of a treatment difference between individual patients. In other words, we define standardized effectiveness = **x** and cost = **y** coordinates as follows:

$$x = \frac{(\bar{E}_T - \bar{E}_S)}{\sqrt{V_{ar}(\bar{E}_T) + V_{ar}(\bar{E}_S)}} \quad \text{and} \quad y = \frac{(\bar{C}_T - \bar{C}_S)}{\sqrt{V_{ar}(\bar{C}_T) + V_{ar}(\bar{C}_S)}}.$$

Note, specifically, that the standardized **x** coordinate above is **unchanged** no matter what scaling (percentages, fractions, etc.) is used to measure effectiveness. Similarly, the standardized **y** coordinate above is **unchanged** no matter what monetary unit (dollars, yen, etc.) or base year is used to measure costs or charges. This type of scaling was used in Figure 4, above.

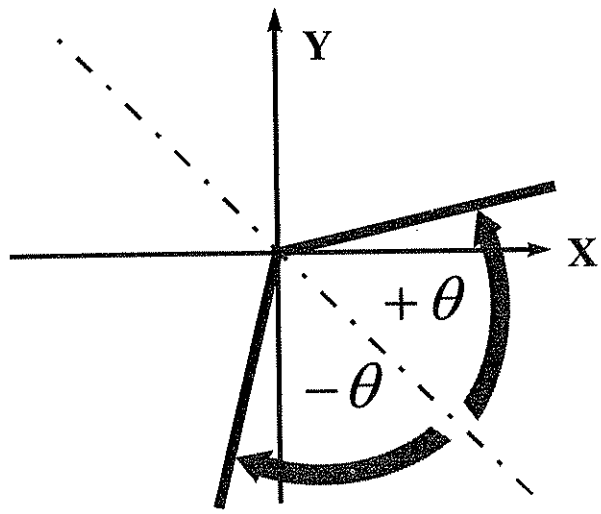
Technical Note: Standardized effectiveness = **x** and cost = **y** coordinates could also be defined using the estimated standard deviations of differences in treatment averages, *std. dev.*$(\bar{E}_T - \bar{E}_S)$ and *std. dev.*$(\bar{C}_T - \bar{C}_S)$, as their denominators. This alternative is easier to define and explain to laymen and would lead to identical *ICER* angles, at least when treatment cohort sample sizes are equal, $NT = NS$. Unfortunately, this alternative scaling also means that the resulting **x** and **y** coordinates would be expected to "grow" in size at a rate proportional to the *square root of the sample size* if additional patients were added to a study.

Returning to Figure 6, note the *symmetry* of each of the different types of cost-effectiveness region about the standardized $^{-}45°$ line, $x + y = 0$. Thus, one can define **Contours of Constant Cost-Effectiveness** (of the new treatment *T* relative to the standard treatment *S*) as in Figure 7. Note that each such contour consists of a pair of line segments, joined at $(x,y) = (0,0)$, and making equal angles, $\pm\theta$ with the standardized $^{-}45°$ line, $x + y = 0$. The angles associated with the two segments of this contour are $^{+}\theta$ and $^{-}\theta$, respectively.

Relative to this same $x + y = 0$ line, the ***ICER* angle** for a standardized **(x,y)** point would be defined on $0° \le |\theta| \le 180°$ by...

$$|\theta| = \arctan(|x + y| / (x - y)) \text{ when } x \neq y$$
$$= 90° \text{ when } x = y.$$

Figure 7. A contour of constant cost-effectiveness.



Technical Note: In the above notation, the *ICER* slope can be written as

$$s = y/x = \tan(\theta - 45°).$$

Thus the *ICER* slope, *s*, is easily expressed as a function of the *ICER* angle, θ, but θ is not a one-to-one function of *s* alone because *s* is not a sufficient statistic. Notice also that $\tan(^{-}\theta - 45°) = 1/\tan(\theta - 45°)$, so that the *ICER* slopes associated with *ICER* angles of θ and $^{-}\theta$ are reciprocals of each other.

Table 1 lists proposed terminology for various ranges of values for *ICER* angles, *ICER* slopes, and the corresponding quadrants of the cost-effectiveness plane.

Table 1. Does a health economic study favor T over S?

Description	*ICER* Angle	*ICER* Slope	Cost-Effectiveness Quadrant
Highly Favorable	$0° \le \lvert\theta\rvert < 45°$	Negative	IV
Favorable	$45° \le \lvert\theta\rvert < 60°$	Positive (extreme)	I or III
Mixed ("Gray Area")	$60° \le \lvert\theta\rvert < 120°$	Positive (neither very large nor very small)	I or III
Unfavorable	$120° \le \lvert\theta\rvert < 135°$	Positive (extreme)	I or III
Highly Unfavorable	$135° \le \lvert\theta\rvert < 180°$	Negative	II

ISSUE: The 60° and 120° values proposed in Table 1 as boundaries between the "Favorable," "Mixed," and "Unfavorable" sections are really somewhat arbitrary. Values of the form $45° + A°$ and $135° - A°$ could just as easily have been used with, say, $A° = 5°$, 10° or 20° instead of $A° = 15°$. In fact, the numerical value considered most appropriate for A° might vary between therapeutic areas.

On the other hand, taking $A° = 15°$ does allow the mixed ("Gray Area") regions to occupy exactly 1/3 of the total cost-effectiveness plane, leaving 1/3 either favorable (1/12) or highly favorable (1/4) as well as 1/3 either unfavorable (1/12) or highly unfavorable (1/4).

ICER Angle Bootstrap Confidence Regions

Definition One: The bootstrap $100(1-\alpha)\%$ confidence region for cost-effectiveness is the wedge-shaped region subtending the smallest total angle at the origin and yet containing $100(1-\alpha)\%$ of the simulated cost-effectiveness pairs.

Note, however, that this minimum subtended angle may be quite large (greater than 180° or even 270°) when a cost-effectiveness study provides only very "weak" information.

Technical Note: It is essential to measure the angle subtended between pairs of *ICER* angle order statistics in a consistent way [say, always clockwise]. For example, with 1000 bootstrap replicates (numbered 0 to 999) and a 95% confidence level, the subtended angle between order statistic 999 ($^{+}173°$) and order statistic 49 ($^{-}6°$) would be $173° - (^{-}6°) = 179°$. Similarly, the subtended angle between order statistic 500 ($^{+}10°$) and order statistic 550 ($^{+}20°$) would be $^{+}350°$ rather than $10° - 20° = {}^{-}10°$.

Technical Note: Figure 4 displays a 95% confidence, bootstrap *ICER* interval of this minimum-subtended-angle form. The *ICER* angle point estimate from this study was 10.69°, while 1000 bootstrap replications produced *ICER* angles ranging from $^{-}144.83°$ to $^{+}145.60°$, with mean = 12.05° and median = 11.92°. The minimum subtended angle was 96.49° and occurred between order statistic 981 ($^{+}60.68°$) and order statistic 31 ($^{+}35.80°$) out of 1000. This 95% confidence region thus lies almost entirely within the "highly favorable" and "favorable" sectors of the cost-effectiveness plane; only the last 0.68° laps over into the Quadrant I "Gray Area."

Definition Two: The bootstrap "central" $100(1-\alpha)\%$ confidence region for cost-effectiveness is the wedge-shaped region formed by excluding both the top $100(\alpha/2)\%$ of simulated cost-effectiveness pairs with largest (most positive) *ICER* angles as well as the bottom $100(\alpha/2)\%$ of simulated cost-effectiveness pairs with smallest (most negative) *ICER* angles.

ISSUE: If any bootstrap replicates fall into Quadrant II (Highly Unfavorable), this second definition rather artificially divides them into two groups: $^{-}180° < \theta < {}^{-}135°$ and $^{+}135° < \theta \leq {}^{+}180°$, say. Note that an *ICER* angle of exactly $\pm 180°$ could actually be placed into either group! This second definition becomes unambiguous when all bootstrap effectiveness differences turn out to be positive (Quadrants I and IV), as in Figure 1. Again, these are the special cases where *ICER* angles are restricted to the $^{-}45° < \theta < {}^{+}135°$ range, and *ICER* slopes turn out to be sufficient statistics for cost-effectiveness.

Technical Note: Figure 1 displayed a 90% confidence bootstrap interval of the "central" form. Without actually rescaling and redrawing the figure, we can gain cost-effectiveness insights by simply expressing those bootstrap results in terms of *ICER* angles. The *ICER* angle point estimate for this study was 42.41°, while 1000 bootstrap replications produced *ICER* angles ranging from $^{+}4.24°$ to $^{+}94.84°$ with mean = 41.83° and median = 41.74°. The "central" interval between order statistic 950 ($^{+}63.92°$) and 50 ($^{+}18.89°$) out of 1000 subtends an angle of 45.03°. By way of contrast, the region with minimum angle subtended at the origin (44.88°) occurs between order statistic 953 ($^{+}64.19°$) and order statistic 53 ($^{+}19.30°$) out of 1000. These 90% confidence regions also lie almost entirely within the "highly favorable" and "favorable" sectors of the cost-effectiveness plane.

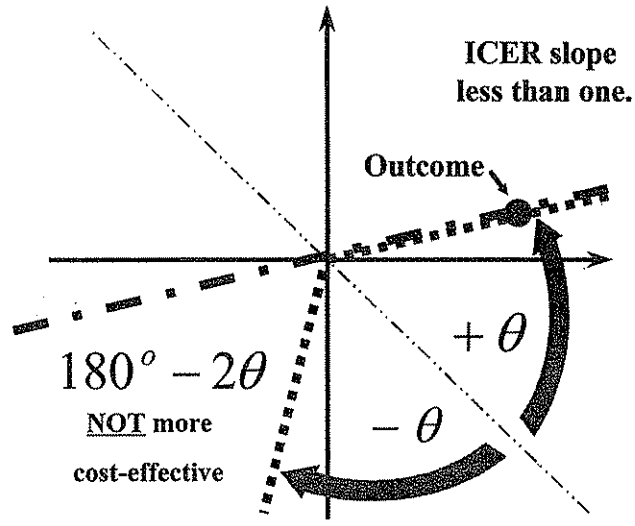
ISSUE: Chaudhary and Stearns (1996), Briggs, Wonderling, and Mooney (1996) and Stinnet (1996) point out that the central intervals of definition two are biased, i.e. the mean and median of the bootstrap distribution of the *ICER* slope can tend to deviate from the *ICER* slope point estimate. When is this bias large enough to cause concern, and how should one correct for it? Similarly, is a corresponding correction for minimum *ICER* angle confidence intervals needed?

ICER Angle Acceptability Curves

Van Hout, *et al.* (1994) introduced the concept of the **Acceptability Curve** associated with positive *ICER* slopes. This curve is a plot of the function $AC(s)$ = "integrated (estimated) probability density over the cost-effectiveness plane under the $ICER = s$ line" versus s over the range $0 \leq s < {}^{+}\infty$. Furthermore, Van Hout *et al.* point out that $AC(0)$ measures the "probability that the new therapy will save costs" [Quadrants III or IV] while $AC(^{+}\infty)$ measures the "probability that the new therapy is effective" [Quadrants I or IV] . . . both relative to the standard therapy.

ISSUE: Because the *ICER* slope is not a sufficient statistic for cost-effectiveness, $AC(s)$ probabilities for $s > 0$ and $s < {}^{+}\infty$ apparently do not have simple interpretations. Specifically, the Van Hout *et al.* definition of outcomes "more" cost-effective than a given value, s, for the *ICER* slope is curious, at least to me. For example, Figure 8 depicts a study outcome in Quadrant I with an *ICER* slope in the $0 < s < 1$ range, which corresponds to an *ICER* angle in the $45° < \theta < 90°$ range. Note that the Van Hout *et al.* region "below and/or to the right of a line of slope s" includes a wedge-shaped section of Quadrant III (subtending an angle of $180° - 2\theta$) containing outcomes that do not strike me as actually being more cost-effective than the observed outcome.

Figure 8. Which outcomes are "more" cost-effective than a given ICER slope?



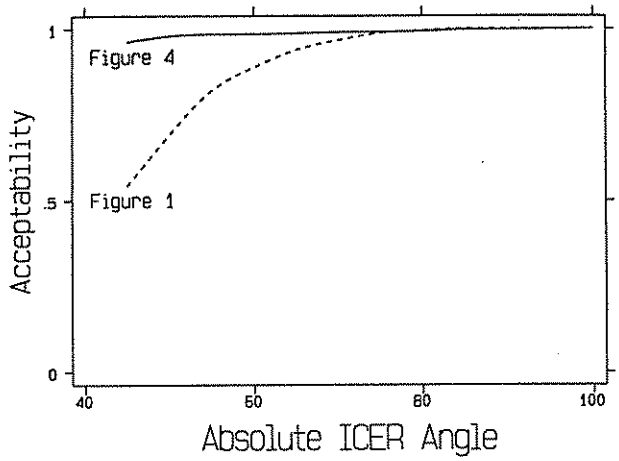
On the other hand, if the observed outcome in Figure 8 had fallen in Quadrant III (an *ICER* angle in the $^{-}135° < \theta < {}^{-}90°$ range), then the Van Hout *et al.* region would exclude a wedge-shaped section of Quadrant I (subtending an angle of $2|\theta| - 180°$) containing outcomes that strike me as being more cost-effective than the observed outcome!

The *ICER Angle Acceptability Curve* is a plot of the function $AC(t)$ = "integrated (estimated) probability density over the cost-effectiveness plane within the wedge-shaped segment $^{-}t° \leq \theta \leq {}^{+}t°$" versus t over the range $45° \leq t \leq 135°$. According to this reformulation using *ICER* angles, $AC(45°)$ measures the

"probability that the new therapy saves costs **and** is more effective relative to the standard" [Quadrant IV]. Similarly, *AC*(135°) measures the "probability that the new therapy saves costs **or** is more effective relative to the standard" [Quadrants I, III or IV].

Figure 9 displays *ICER* Angle Acceptability Curves for the bootstrap examples of Figures 1 and 4. Note that bootstrap resampling provides **direct estimates** of the probabilities (integrated probability densities) of interest. Specifically, the estimated probability of any region of the cost-effectiveness plane is simply the number of bootstrap replicates that fall within that region divided by the total number of replicates generated. Note also that the figure displays only the *ICER* angle range from 45° to 100°, rather than all the way out to 135°; acceptability probabilities already exceed 0.990 at θ=100° in these two studies, both of which highly favor the "new treatment" over the "standard."

Figure 9. Estimated ICER angle acceptability curves for figures 1 and 4.



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Summary

Here, I have attempted to outline key issues in *ICER* cost-effectiveness inferences. Some issues question the philosophical basis for using *ICER* slopes while others simply question how statistics should be reported and interpreted in actual practice. These are open questions; my comments here should not be construed as any sort of consensus answers. For example, the practical advantages and disadvantages of *ICER* slopes relative to *ICER* angles is a subject worthy of much continued debate. In reality, these two types of measures actually complement each other. To satisfy the information needs of all participants in cost-effectiveness debates, it is probably most appropriate to report outcomes in terms of both *ICER* slopes and *ICER* angles.

Why not join us working on the **Cost-Effectiveness Inference** committee? Our charter is to help pave the way for development of consensus views by researching statistical issues in cost-effectiveness inference and setting standards for computer algorithms and validation of software.

To express interest or get additional information about our committee, please direct E-mail to ochain@lilly.com, call (317) 276-3150, or write to me at Health Services and Policy Research, Eli Lilly Corporate Center, Indianapolis, IN 46285-1850, USA.

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Section News

Treasurer's Report for 1996

Jeff B. Meeker
Secretary/Treasurer

As many are aware, the Biopharmaceutical Section had developed a large cash-on-hand position, almost four times its annual operating budget of approximately $20,000. That position, $83,000 by December 31, 1995, resulted from aggressive dues and a golden touch; anything we tried produced income. To stem the increase, we reduced corporate member dues from $500 to $300, only to realize additional income as more corporations joined. We reduced individual member dues from $11.00 to $9.00 and again to $5.00 (ASA keeps $1.00 of dues for processing costs). That at least stemmed the increase. During 1996, we took several steps to aggressively reduce our cash-on-hand, with a proposed budget designed to lose $29,900. These steps included both one-time expenses and reductions in the cost of our services designed to reduce the costs of those services to members who were taking advantage of what the Section had to offer. Specifically, in addition to the reduced dues:

- We reduced the cost of Proceedings so that the Section would forego its profit, without affecting ASA's (we share the profits). Unfortunately, this did not get implemented in 1996, but will occur in 1997 and 1998.
- We conducted the Adverse Events Workshop which, by design, lost $2,500, thereby reducing the registration cost for attendees. A similar project is planned for 1997.
- We instituted a mixer just prior to the Section Business Meeting at the Joint Statistical Meetings (JSM). The mixer is designed to provide a time when Section members can meet each other in a casual atmosphere. The mixer is free.
- We conducted a survey of the Section's membership to provide feedback to the Executive Committee and provide the Executive Committee with information that will allow them to better plan for the desires of our members. Several hundred of you are now owners of T-shirts with the Section's logo. The cost of the survey was $12,500.

The bottom line for 1996 is that we showed income of approximately $20,000, not quite half of which came from member dues. We spent $47,000. producing a drop in cash-on-hand by December 31, 1996 of $27,100 to our current position of $56,000, within $2,000 of our budget. We budgeted an additional loss of $10,000 for 1997, which will put us at our target. However, we must watch carefully, that we don't overshoot our target. We will closely watch 1997 income and expenses. Our annual expenses have increased (for example, we intend to continue the mixer), so it is possible we may have to increase dues in 1998, not to the original $11.00, but maybe to $6.00. We are also considering continuing the workshops past 1997, but budgeted to break even.

For those of you who want the actual numbers, I plan to make them available at the Section meeting at the JSM.

Biopharmaceutical Section Executive Committee Meeting Minutes

March 25, 1997, Memphis, Tennessee

Attendees

Tom Capizzi, Christy Chuang-Stein, Chuck Davis, Bob Davis, Richard Entsuah, Sally Greenberg, Sandy Heft, Ken Koury, Jeff Meeker, Anne Meibohm, Phil Pichotta, Bruce Rodda, Bob Small, Lianng Yuh, Curtis Wiltse.

Members introduced themselves. Bob Davis announced that the Section has requested to have the Executive Committee meeting 7:30-Noon, Monday, August 11; and the reception 6:00-6:30 and the Business meeting 6:30-7:30 on Tuesday, August 12, at the Joint Statistical Meetings in Anaheim, California. Janet Begun resigned as Publications Officer, and Bob Davis is assuming that role until a new one is elected. Spencer Hudson resigned, and no replacement appointment is planned. Bob distributed the list of Executive Committee members. He distributed a diskette with a Word 6.0 version of the Section stationery. He reviewed the list of volunteers provided at the transition meeting to see where the Section has taken advantage of those individuals' interest. Finally, he announced that ASA has made its annual call for nominations for ASA Committees.

Assignment: Gary Neidert has expressed an interest in the ASA Committee on Membership. Bob Davis and Jeff Meeker will both write letters recommending him.

Transition Meeting Minutes

The minutes of the October 30, 1996, transition meeting held in Bethesda, Maryland, were approved.

Treasurer's Report

Jeff Meeker indicated he has not received the December 31, 1996, expense report from ASA and has, in fact, received a second report for September 30, 1996, which conflicts substantially with one received earlier. He requested that Stephen Porzio, the new Director of Finance and Administration for ASA, resolve the discrepancy. He distributed a copy of the budget that was submitted to ASA for 1997. It is still approximately $6,000 short of our targeted reduction in cash on hand.

Manual of Operations Update

Jeff Meeker presented the proposed update in the Manual of Operations for the Biopharmaceutical Section associated with the addition of the third Executive Committee (transition) meeting, addition of the Fellows Nominations Committee, deletion of the Committee to Recommend Statisticians to FDA Advisory Committees, and the new structure of the editorship of the Biopharmaceutical Report to include an Associate Editor, Editor, and Past Editor. Those changes were approved with minor changes.

Assignment: Jeff Meeker will distribute the Manual of Operations after the changes have been made.

Executive Committee and Business Meeting

The Executive Committee discussed ways to increase attendance at the Section Business meeting. Suggestions included a sign outside the meeting room door, more advertising such as a flier and announcements in the Biopharmaceutical Report, and more promotion of the meeting and mixer.

Invited and Contributed Paper Sessions, 1997 Joint Statistical Meetings

Lianng Yuh reviewed the program for the 1997 Joint Statistics Meeting in Anaheim, August 10-14.

Sunday, August 10

2:00 Analysis of Categorical Data. Mani Lakshminarayanan.

4:00 Special Contributed Paper Session I. Impact of Trial Conduct Change in Clinical Trials. James Hung.

Monday, August 11

8:30 Design and Analysis of Clinical Trials I. Robert Chew.

Special Contributed Paper Session II. Health-Related Quality of Life Assessment in Cancer Clinical Trials. Wayne Weng

10:30 Methods of Interim Analysis/Sequential Analysis. Ron Kershner.

Design and Analysis of Bioavailability/ Bioequivalence Studies. Guangrui Ray Zhu.

2:00 Invited Session I. Decision Analysis in the Pharmaceutical Industry. Jay Anderson.

Pharmacokinetics/Pharmacodynamics/Assay Validation. Jeffrey Dawson.

Tuesday, August 12

8:30 Special Contributed Paper III. FDA Session on Special Statistical Issues. Satya Dubey.

10:30 Invited Session II. The Impact of ICH-9 Biostatistics Guidelines. Frank Rockhold.

Bioassay, Analysis of Toxicology and Laboratory Data. Dave Stock.

2:00 Issues in Multiple Testing Procedures. Mike Mosier.

Analysis of Longitudinal Data I. Naitee Ting.

Wednesday, August 13

8:30 Time to Event Analysis I. Shu-Ping Lan.

10:30 Analysis of Longitudinal Data II. Sandy Heft.

Design and Analysis of Phase I/II Trials. Gordan Lan.

2:00 Special Contributed Paper IV. Robust Inferences/Analysis of Clinical Trials. Norman Bohidar.

Therapeutical Equivalence, Bioequivalence and Dissolution Similarity Testing with Multiple Variables. Yi Tsong.

Thursday, August 14

8:30 Invited Session III. Applications of Bayesian Methods in Clinical Trials. Don Berry.

Design and Analysis of Clinical Trials II. Rohini Chitra.

10:30 Time to Event Analysis II. George Carides.

Short Courses, 1997 Joint Statistical Meetings

Lianng Yuh announced that two short courses are scheduled for the 1997 Joint Statistical Meetings in Anaheim:

An Overview of the Role of the Biopharmaceutical Statistician: For Students and Statisticians Considering a Career in the Pharmaceutical Industry. Bruce Rodda and Bob Starbuck.

An Introduction to the Quantitative Basis of Laboratory Medicine. Craig Trost.

Luncheon Round Tables, 1997 Joint Statistical Meetings

Richard Entsuah announced the following Luncheon Round Tables for the 1997 Joint Statistical Meetings in Anaheim:

Active Control Equivalence Trials. James B. Whitmore.

Analysis of Incomplete Multicenter Cross-Over Design with Covariates. Kao-Tai Tsai.

Considerations in Designing Dose Response Studies. Naitee Ting.

Design and Analysis for Assessment of Onset of Treatment Effect in Clinical Studies. Kon Fung.

Interim Analysis and Early Termination in Clinical Trials. Sung Choi.

Modeling the In vitro-in vivo Relationship of a Drug Product. David Mauger.

Primary and Secondary Endpoints in Clinical Trials. George Chi.

Regulatory Uses of Meta-Analysis: Case Studies. I. Elaine Allen.

1997 Best Paper Presentations

Sandy Heft was assigned responsibility for the 1997 best paper presentations. There are 14 regular contributed paper sessions and 4 special contributed paper sessions. The question was raised as to whether there might be a bias toward special contributed papers since they are longer. It was moved, seconded, and passed that both types of papers would be included this year, but the issue would be revisited at the Spring, 1998 Executive Committee meeting. It was recommended that the chairs announce in each session that the papers are to be rated. It was also recommended that feedback be provided to the individual presenters.

1997 Best Student Papers

Denise Roe is handling the 1997 Best Student papers. The deadline for papers is June 1.

1996 Best Paper Awards

Shein Chow will be in Anaheim to present the awards.

Council of Sections

Sally Greenberg reported on the February, 1997, meeting of the Council of Sections Governing Board.

Sections can get help developing a Web page from Dan Jacobs (301-405-6379) or by mail at University of Maryland, Maryland Sea Grant College, 0102 Skinner Hall, College Park, Maryland, 20742. He has prepared a tutorial for developing Web pages.

Only sections with a large surplus of funds need to prepare a fiscal plan. Scott Gilbert (Council of Sections treasurer) can address questions or give assistance.

The Biopharmaceutical Section raised a concern about the increase in ASA dues to corporate members. The Governing Board responded that this is the first increase in 7 years, but Richard Gunst, Council of Sections representative to the ASA Board of Directors, felt that a graduated increase over time would be better than this large increase. ASA has had 3-4 communications about this issue. By the April Board meeting, Marie Argana will have some data on the impact of the increase on renewals, and it may be appropriate to raise the issue again.

Assignment: Jeff Meeker will communicate concerns with Richard Gunst.

As to concerns on room allocation, each Section program chair is asked to provide an estimate of the number of attendees expected. Perhaps the experience from this year can be used to develop better estimates in the future.

The Biometrics Section would like to provide discounted fees on continuing education courses to students and in other special cases. This question will be discussed further at the August Council of Sections meeting. The Executive Committee proposed that a differential also be considered based on Section membership.

There is strong ASA interest in developing short courses/workshops that will appeal to "applied" statisticians. We've been asked to canvas the Section and begin to develop successful short courses from past continuing education lists that might be brought to ASA's attention. If appropriate, these might be developed further for distribution, not just at the Joint Statistical Meetings, but also on the road to ASA chapters and even made into some form of telecourse. The need is for basic material presented by good instructors. ASA would like to know if sections have any short courses they could do for applied statisticians, similar to those done by the Council of Chapters.

There is an agreement among the participating societies in the Joint Statistics Meeting that the total number of invited sessions cannot be increased at the present time, even if new sections are formed. We have been asked to discuss the following:

What are our feelings about the policy of permitting each member to contribute a paper? Should this continue or should some constraints be put into place? What about the practice of presenting both an invited and a contributed paper?

Is the total number of invited paper sessions at the annual meetings satisfactory? Should ASA try to renegotiate the total number of invited sessions with the other sponsoring societies? If sections want to increase the total number of invited sessions, how can they compensate without having an impact on the number of contributed sessions?

This input will be coordinated by the Council of Sections Governing Board and brought to the ASA Board of Directors for consideration.

Assignment: Lianng Yuh, Tom Capizzi, Ken Koury, and Steve Snapinn will draft a response for submission by the August meeting of the Council of Sections.

What other E-mail services do sections want? The Council of Sections Governing Board suggested looking at the paper "What Electronic Services Should the ASA Provide?" accessible through ASA's Web site.

The following section officers are asked to attend planning and/or orientation meetings appropriate for their positions at the Joint Statistical Meetings: chair responsibility reviews for chair-elects and chair-elect-elects; fiscal planning for treasurers and chairs; program orientations for program chairs, and publications reviews for publication officers. Times and dates for these meetings will be sent to the various individuals prior to the Joint Statistical Meetings.

The ASA is now in the process of revising its constitution. The Biopharmaceutical Section's comments from the transition meeting were sent to the Constitution Committee. We've been asked to address the following additional questions prior to August, 1997:

Should the president-elect position be changed to two president-elect positions (*i.e.*, should an additional year be added to the term of an elected ASA president for additional acclimation, so that s/he serves 4 years)?

Should the Executive Director be a non-voting member of the Board of Directors? (Currently, the Executive Director is Secretary to the Board and does vote at all Board functions.)

Should Canadians be eligible for nomination as International Representatives?

Publications and Proceedings

Bob Davis indicated the 1997 Proceedings of the Biopharmaceutical Section would be $25 for members and $38 for nonmembers. There will be 600 copies.

Fellows Nominations Committee

Bruce Rodda reported that the Fellows Nominations Committee consists of himself as chair, Charles Goldsmith, and Larry Gould. Four nominations have been made for Fellow. Larry Gould will be the chair for next year.

Midwest Biopharmaceutical Workshop

Jeff Meeker distributed the program for the Midwest Biopharmaceutical Workshop in Muncie, Indiana, on May 19-21, 1997. Jeff had discussions with both of the 1997 co-chairs, Jim Bergum and Tony Segreti. They indicated they were interested in improving the relationship with the Biopharmaceutical Section and also wanted to have more papers in the Section's Proceedings. Jeff was able to get ASA to provide them with mailing labels for the Biopharmaceutical Section. He also reported the organizers had trouble getting ASA to publish the program in *Amstat News*.

Assignment: Bob Davis will write a letter to ASA reminding them which meetings we cosponsor (Midwest Biopharmaceutical Workshop and Atlantic City Conference).

Assignment: Bob Davis will invite Jim Bergum and/or Tony Segreti to our meeting in August for a report and further discussions.

Atlantic City Applied Statistics Meeting

Neeti and Norman Bohidar are stepping down as liaison to the Atlantic City Applied Statistics Meeting. Walter Young has indicated he will handle Neeti's duties, but has asked us to provide someone to replace Norman. The responsibilities include arranging two tutorials and one short course. Norm found Kalyan Ghosh and Ivan Chan to cover this assignment. The section might get asked to provide a second liaison next year, in which case Bob Davis suggests we ask Kalyan and Ivan to each serve as liaison.

Adverse Events Working Group

Curtis Wiltse agreed to head the Adverse Events Working Group and will establish the group based on the list of people who expressed an interest at the workshop. There was a discussion as to whether we should include the FDA and it was the decision of the Executive Committee that we should. It was also recommended we support the working groups, at least providing breakfast at their meetings at the Joint Statistical Meetings.

Proposed Section Communications Policy

Bob Small proposed an overall policy for the Section's communication with its members. He proposed a Communications Committee consisting of the editor of the *Biopharmaceutical Report*, the Webmaster, the Mail List Moderator, and the Publications Officer. The Publications Officer would handle communications in *Amstat News*, now the responsibility of the Secretary/Treasurer, and would chair the Committee, in addition to his/her present responsibilities as editor of the Proceedings. The proposal was approved by the Executive Committee.

Assignment: Jeff Meeker will coordinate the necessary changes in the Manual of Operations.

Biopharmaceutical Report

Three issues are planned for 1997. The lead article in the summer issue will be "Issues and Algorithms in Cost Effectiveness Inferences" by Bob Obenchain. Sally Greenberg felt the Biopharmaceutical Report could be published on the Web site. She did ask, however, that she be sent the issue article by article, rather than as one document. The last two 1996 issues have been received and converted to HTML code. Both issues should be available on-line by mid-April. Receiving the documents as Word files makes the process much easier.

Web Site

Lothar Tremmel was identified as a co-moderator. Major updates are expected to be completed by mid-April.

Electronic Mail List

Sally Greenberg reported the electronic mail list has been running since November, 1996. David Carlin was identified as a co-moderator. As of March 24, there were 80 subscribers, or 4.5% of the section membership. We could use more discussion, and Sally requested ideas for generating more discussion. There have been no abuses of the list so far. Since list traffic is low, Sally recommended removing the digest option for now. It can be reinstated if traffic increases.

Workshop on FDA/Industry Interaction

Christy Chuang-Stein presented a proposal for a workshop FDA and Industry—Working Together to Expedite the Development of New Pharmaceutical Products. The workshop would be held in October or November in the Washington, D.C., area. Several FDA speakers have been identified. All industry speakers would be set by the end of April. The format would be similar to the one held last year on Adverse Events.

Assignment: Christy and Jeff Meeker will work out financial details.

Section Survey

Phil Pichotta reported that of the 1770 surveys sent, 1139 were returned. Eight hundred seventy T-shirts were sent at a cost of $12,800. Postage was the largest expense. The three open ended questions provided a good mechanism to elicit comments and suggestions. An article was published in the March, 1997, issue of Amstat News and an abstract was submitted for a presentation at the August Joint Statistics Meeting. Work has started on a full report for the *Biopharmaceutical Report*.

There was a discussion of the best ideas from the survey. One was to have a workshop annually. A second was to publish the results or proceedings of the Adverse Events workshop. A third idea was to get names of new Section members from ASA for follow-up.

Membership Committee

Phil Pichotta contacted the ASA membership office to get a quarterly list of new members to the Section. Welcome materials need to be prepared. The Section brochure needs to be updated and copies printed for the Joint Statistical Meetings.

Assignment: Phil Pichotta will look into updating the Membership Brochure.

Statistics Courses for Other Societies

Sandy Heft indicated they set a goal to determine two organizations to which we would propose providing courses.

We discussed the organizations and connections we already had. We also wanted to develop an inventory of other organizations with whom we want to have a liaison.

ENAR Program

Tom Capizzi reported a lack of process with ENAR. The ENAR meeting is currently cosponsored by six ASA sections. This year we have three sessions we organized plus one additional session. However, everything is up to the program chair. This item was on the agenda for the Regional Advisory Board meeting on March 24. Currently, all sections of ASA have input, but there is no guarantee for allocations.

Assignment: Bob Davis will check with ASA on their arrangements with ENAR.

The current ENAR program chair is interested in practicing statisticians and students, and therefore is most interested in case studies. Ideas for sessions are requested by June 1.

Program for 1998 Joint Statistical Meetings

Since there is a new section in ASA, one of the sections will have one session cut. Which section that will be is unknown, but only a few have multiple sessions. One proposal is that all sections will have one session, with the remaining sessions open to competition. The proposals so far include Use of Computational Chemistry Techniques, Design of Dose Response Studies, and Statisticians' Contribution to AIDS Trials. A request was made for further suggestions of topics and organizers.

1998 Best Student Paper Awards

Tom Capizzi will form a committee.

1998 Best Presentations

This was postponed until the August Executive Committee meeting.

1998 Short Courses

The short courses should be determined in the fall. One proposal is a short course for mixed models by Tony Orlando.

Committee on Nominations

The Biopharmaceutical Section Committee on Nominations for the 1998 election, to nominate individuals to take office in 1999 are Gary Neidert (chair), Bob Small, and Phil Pichotta. The officers up for election are chair-elect, program chair-elect, secretary/treasurer, and Council of Sections representative. E-mail any recommendations to Gary Neidert.

Workshop on the FDA/Industry Partnership

Christy Chuang-Stein
Continuing Education Chair

The Biopharmaceutical Section of The American Statistical Association is sponsoring a workshop on "FDA/Industry: Working Together to Expedite the Development of New Pharmaceutical Products" on October 27-28 in the Hyatt Bethesda Hotel, Washington D.C. Presenters at the workshop include representatives from the FDA, the pharmaceutical industry, clinical research organizations, and the NIH. The workshop covers a wide variety of subjects such as: from discovery to early clinical trials, planning the confirmatory activities, the assembly of NDAs, QA and QC, preparation for Advisory Committee Meetings, as well as challenges in the development of biologics and devices, etc. In addition to the subject matter, this workshop offers a unique opportunity for individuals in the industry to meet with their government colleagues in a cordial environment conducive to the exchange of ideas. Business casual dress will be appropriate. A detailed program and the registration form for this workshop can be obtained in the July issue of *Amstat News*. A copy of the preliminary program can be found at the Web site of the Biopharmaceutical Section. For further information, please contact Christy Chuang-Stein at (616) 833-0209; fax (616) 833-0226, E-mail: jcchuang@am.pnu.com.

Let's Hear from You!

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