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Editor's Note

Curtis Wiltse

The lead articles by Bob Northington and Lothar Tremmel kick off a series of articles on the general topic of adverse events. The other articles will appear in an issue of the Biopharmaceutical Report which will be issued before the Workshop on Adverse Events, which takes place on October 28 and 29, 1996 (see announcement in this issue). These articles are intended to "stir the pot" on the issue of adverse events, as a warm-up to the presentations and discussion at the workshop.

A Review of Issues in the Collection and Reporting of Adverse Events

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1. Introduction

The collection of comprehensive data on adverse events has for many years been accepted as a critical part of any well-designed clinical trial. However, there are still numerous unresolved issues surrounding the collection and reporting of such data. In the absence of any standard approach being used to collect and report these data, the interpretation of the adverse rates from a given study and any attempt to compare rates between studies are complicated by the fact that the rates may to some extent be a function of the methods used.

A set of guidelines that would lead to a more uniform approach to adverse event collection and reporting could allow for a better understanding of what the data represent. A long-term goal might be the establishment of a set of industry-wide guidelines. A more immediate goal might be for each company to review their own policies regarding adverse events and, if they do not already exist, develop a set of internal guidelines that can be applied across projects. This would avoid the possibility of each therapeutic group developing their own slightly different, or perhaps even greatly different, approach. While it is recognized that allowance must be made for some degree of flexibility in the adverse event process, a set of agreed-upon basic standards should prove beneficial.

Much of what follows in this article is based on experiences as part of team that was put together at Wyeth-Ayerst to develop guidelines for adverse event collection and reporting. This team consisted of representatives from a variety of disciplines including Data Management, Forms Design, Regional Clinical Associates, Clinical Programming, Biostatistics, Clinical Research, and Clinical Writing. Representatives from each group spoke to their colleagues in different therapeutic areas to obtain feedback on how they were dealing with adverse event issues.

The intention of this article is to point out some of the areas that were identified as sources of confusion or inconsistencies and to suggest possible approaches to addressing these problems. The three main points of discussion will be (1) What is an adverse event?, (2) What is a treatment-emergent adverse event?, and (3) How long

see ADVERSE, *page 2*

Contents

Lothar Tremmel continues the series on adverse events in his article, "Describing Risk in Long-Term Clinical Trials"— *page 5*

ADVERSE, *continued from page 1*

should a patient be followed for adverse experience information after the last dose of study drug?

2. What Is an Adverse Event?

At its most basic, an adverse event may be defined as:

> Any negative event that a patient/subject experiences during the course of a clinical trial.

The term "negative event" is rather broad and leaves room for interpretation of exactly what is intended. The following alternate definition, thought much longer, is also much more precise in identifying what should be considered a "negative event."

> Any unfavorable change in the structure (signs), function (symptoms), or chemistry (laboratory data) of the body temporally associated with participation in the clinical trial, irrespective of the believed relationship to the study drug. This definition would include intercurrent illnesses or injuries, clinically significant results from laboratory tests or other medical procedures, and clinically significant findings uncovered during a physical examination.

An important distinction between the first and second definitions is that the latter makes it clear that what should be reported goes beyond what is volunteered by the patient or is apparent from observation of the patient. In particular, the latter definition would encompass events that might have no immediate negative impact on the patient (e.g., increased blood pressure, decreased hemoglobin values), but would nevertheless be of concern when trying to evaluate the true safety profile.

Neither of the preceding definitions specifically addresses one of the most difficult issues related to defining what constitutes an adverse event. That is, how should medical conditions that have been a long-standing part of the patient's medical history be handled? For example, suppose a patient has a history of asthma attacks and experiences an asthma attack during the course of the study. This would certainly qualify as a negative event; therefore, by the first definition it would be reported as an adverse event. The second definition is expressed in terms of unfavorable changes in the patient's condition and implies that pre-existing conditions would be reported only if they were exacerbated during the course of the study. Therefore, an asthma attack would not be reported unless the investigator feels there is an increase in the severity or frequency of the attack(s).

With respect to stable medical conditions, strict adherence to the first definition would increase the number of events reported, but it also would increase the likelihood that all potentially important events would be captured. Proponents of the second viewpoint feel that reporting events related to stable medical conditions that are part of the patient's history creates additional work while serving only to add superfluous information that clouds the true safety picture of the study drug. There are costs associated with the collection and processing of these data that need to be considered. Furthermore, conditions that have nothing to do with the study drug may be unfairly associated with it.

The perspective taken on this issue may be influenced by the patient population in question. In a population that is generally healthy except for the condition being treated, anything observed might be of interest. However, if the study is being done in an elderly or sick population with a lot of background conditions, reporting all events can lead to a great deal of extra work collecting data that might be viewed as unnecessary.

Having heard much debate on this issue, it seems unlikely that unanimous agreement will ever be reached. However, regardless of which side one takes on the issue of how all-encompassing the definition of adverse events should be, most would probably agree that there should be a mechanism for identifying those events which are most critical to a true understanding of the safety of the study drug. This is where the treatment-emergent concept comes into play.

Depending on how the treatment-emergent concept is interpreted and applied, the final tabulation of a study's treatment-emergent adverse events could turn out to be identical regardless of whether all pre-existing conditions that show up during the study are reported as adverse events or only those that worsen during the study. This leads directly to the next topic.

3. What Is a Treatment-Emergent Adverse Event?

The treatment-emergent concept began to gain wide attention when reference to it was made in the 1988 FDA Guideline for the Format and Content of the Clinical and Statistical Section of an NDA (1). In the guideline, the FDA stated that an adverse event tabulation of particular interest that should be produced for all studies would include "all new adverse events (i.e., those not seen at baseline or that worsened during treatment)." This definition is open to a number of different interpretations, which can lead to inconsistencies in the way the treatment-emergent adverse event (TEAE) concept is applied in practice. The most troublesome phrase is "seen at baseline."

Three common possible interpretations for "seen at baseline" are:

(1) Present at the time study drug begins (baseline viewed as a point in time corresponding to the first administration of the study drug).

(2) Present at any time during some specified period that precedes the start of study drug (baseline is viewed as a period of fixed duration, such as a washout period, that is defined in the protocol).

(3) Present as part of the patient's medical history (baseline is of no defined length).

Nobody is likely to disagree with the first definition in the sense that an event which satisfies this definition would certainly be considered as seen at baseline. The question arises as to whether it is overly conservative to restrict the interpretation to only those events which satisfy this definition.

The second interpretation attempts to expand the time frame but can introduce problems. For example, suppose a new compound being studied has properties similar to that of an existing, marketed drug. Further suppose that the study being designed to evaluate the new test compound will include a two-week washout period from previous therapy prior to starting the investigational drug. If this washout period were considered a baseline period, and all events reported during this period were considered present at baseline, this could result in an underestimation of the true adverse event rate for the study drug.

As an example, assume an event related to a prior drug is present at the start of the washout period and then disappears as the effects of the prior drug are washed out. It may be inappropriate to exclude this event from consideration for "emerging" on the study drug. This would be especially true if the patient is being washed out from a prior drug that, as is often the case, has properties similar to the experimental drug and may be expected to have a similar safety profile. This approach could result in adverse events that are particularly likely to occur with the study drug being excluded for consideration for treatment emergence. The idea of an

extended baseline period would have to be carefully thought out to avoid misleading results.

Of the two approaches discussed thus far, the single point in time baseline versus the baseline period, the former is preferable because it is simple to apply, requiring only determination of whether the adverse was present at the time of the first dose of study drug, and its conservative nature makes it the least likely to be challenged by regulatory authorities.

Further consideration of the "seen at baseline" question leads to the previously discussed issue of how to handle pre-existing conditions. The conservative position is to report all conditions that occurred during therapy regardless of whether they were pre-existing. The alternative is to not report these conditions as adverse events unless they worsened during the study.

The TEAE concept can allow for a compromise between these two positions if seen at baseline is defined as a combination of (1) and (3). Events associated with a chronic medical condition would be considered seen at baseline in the sense that they are present as part of the patient's medical history. If this approach is adopted, pre-existing conditions that remain stable could be reported but would not be considered TEAEs unless they worsened during treatment. Therefore, tabulations of all reported adverse events might differ considerably depending on whether or not pre-existing conditions are reported; however, tabulations of TEAEs would be identical.

Though not as problematic as the "seen at baseline" phrase, others terms in the FDA definition could also be open to different interpretations. For example, what is meant by a "new event?" Suppose a particular event is present at baseline and continues to be present during the first two weeks of therapy. The event then disappears and is absent for the next several months of a six-month study. During the last month of the study, the event reappears and is present for the remainder of the study. Should this be considered a new event or a new report of an old event?

The interpretation that seems most in keeping with the FDA definition is to not consider this a new event. The event was seen at baseline and whether or not it was continuously present during the study should not impact on the TEAE decision. Therefore, it would not be considered new and would not be treatment-emergent unless the new report indicates a worsening relative to baseline.

This leads to consideration of exactly what constitutes worsening. An increase in the severity of the event during the course of the trial would certainly qualify. In addition, the frequency of the event should also be taken into account when making this decision. A patient may have a history of migraine headaches that over the years have occurred once or twice a month. During the study, migraine headaches, though no more severe, are reported weekly. This is important information that should be considered when making the TEAE determination.

Another issue which needs to be reconciled before an explicit definition of TEAE can be established concerns how to handle studies which have a placebo washout period prior to the start of therapy. One of the purposes of the washout period might be to identify events that patients are prone to report as soon as they are given the opportunity to do so as participants in a clinical trial, and which may bear no relationship to the study drug. Events that occur during the washout and which are present at the time patients receive their first dose of study drug would not be eligible to be TEAEs unless the event worsened during active treatment. Thus, the washout can help to screen out superfluous events.

The preceding assumes that the placebo is not considered a study drug and events reported while patients are receiving placebo alone should not be attributed to the study drug. However, it can be argued that events associated with the placebo, especially if it is identical to the study drug in all ways except for the inclusion of the active component(s), should be attributed to the study drug since they could be caused by components that make up the study compound even if they are not viewed as the active components. Since there can be different points of view on how to handle situations such as the placebo washout, it is important to clearly define the time-frame in which an adverse event must occur to be considered a candidate for being a TEAE. Adverse events that occur during a placebo washout period would always be considered study-emergent, but they may or may not be considered treatment-emergent.

With the preceding in mind, a more explicit definition of TEAE than the FDA definition might be as follows:

> An adverse event that occurs during the active phase of the study will be considered a TEAE if (1) it was not present at the time the active phase of the study began and it is not a chronic condition that is part of the patient's medical history, or (2) it was present at the start of the active phase of the study or as part of the patient's medical history but the severity or frequency increased during therapy.

The term "active phase of the study" is used instead of "during treatment" or "on-therapy" because of the added flexibility it allows. Though it may frequently be the case that the start of the active phase of the study is identical to the start of the during treatment/on-therapy portion of the study, the latter terminology could be confusing when there is a placebo washout or lead-in-period. The definition of active phase will depend primarily on whether there is a lead-in or washout period at the start of the study. If there is no such period, then it is recommended that the definition be:

> The active phase of the study begins at the time of the first dose of study drug.

For studies with a placebo lead-in period, the wording should be modified to more clearly define the active phase since placebo could be considered a study drug but it would not typically be considered active. In a study with a single-blind placebo lead-in period followed by double-blind therapy, the following definition would be preferred:

> The active phase of the study begins at the time of the first dose of double-blind therapy.

4. Treatment Emergence and the CRF

Having established a definition of TEAE, the next step is to determine how to collect adverse event data in a manner that will allow for accurate and efficient application of this definition to determine treatment-emergent status. One approach would be to collect complete information on start dates, stop dates, and the severity of all adverse events and then programmatically determine TEAE status through comparison of adverse event dates to medical history records and to start and stop dates for study drug, and also through checks for increases in severity or frequency during the course of the study. This programmatic approach can prove cumbersome to apply. It can also be complicated by such factors as terms used on the medical history record not corresponding directly to terms used to describe adverse events even though they were intended to describe the same event or condition. Also, many standard adverse event forms do not include questions about frequency and it would not be possible to check for increase in frequency unless this information were collected.

An alternative approach would be to ask specific questions about each adverse event that would be directed toward answering the TEAE question. These questions would rely on the investigator's history with the patient and overall clinical

judgment and would serve as the basis for the TEAE decision. These questions might be phrased as follows:

Condition existed prior to start of active phase of study? ❑ Yes ❑ No
If yes, has severity or frequency increased? ❑ Yes ❑ No

Accompanying instructions for completion of the form would be provided to clarify how the questions should be answered. For example, instructions for answering the first question might read as follows:

> Indicate Yes if the study event is an acute condition present at the start of the active phase of the study, regardless of whether the event has been continuously present during the course of therapy. Also answer Yes if there is a history of this chronic condition. Indicate No if neither of the above apply. Significant history of any sign or symptom should be recorded as medical history.

TEAE status could be programmatically determined based on the responses to these questions as follows:

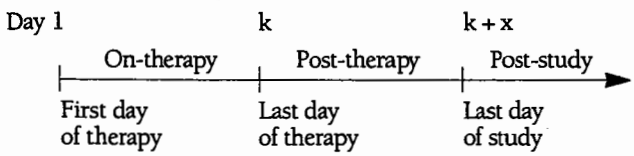
Condition existed prior to start of active phase of study?	If yes, has severity or frequency increased?	TEAE Status
Yes	Yes	Yes
Yes	No	No
No	—	Yes

As an aid to the investigator in answering the first question, the completion of an adverse events record at baseline should be considered. In studies with a placebo washout period, the record completed at the end of the washout can typically serve this role. If there is no washout, then a baseline record may prove helpful. Otherwise, the first study event record would not be completed until the first scheduled on-therapy visit, which might be two or more weeks after the start of therapy. At that time, there may be some uncertainty as to the start date of the event, and if so, it would not be possible to reliably determine whether it started before or after the first dose of study drug.

5. Post-Therapy Adverse Events

Adverse events which occur while patients are taking study drug are typically given the most attention. The treatment-emergent concept is generally applied only to events that occur while the patient is on therapy. However, in most studies there are usually some adverse events that are reported after the last day of study drug. This may happen unintentionally if a patient stopped taking drug as scheduled and reported an event that began in the period between the last dose taken and the final visit. Other times these events may be collected at a planned post-therapy visit. In any case, there should be some policy in place for collecting and reporting post-therapy events.

The discussion which follows presumes agreement that there is an ethical and legal obligation to follow patients beyond their last day of study medication. Much of the discussion focuses on how long this follow-up should be. To facilitate discussion, the following diagram shows how the periods of a study might be broken down.



This diagram introduces a post-study period as well as a post-therapy period. Both will be addressed in the discussion which follows.

The value of k, which represents the last day of therapy, should be defined on an individual patient basis. For each patient, it will correspond to his or her last day of therapy. Its value will vary from patient to patient depending on how long they remain in the study and take study drug.

The definition of x is a more complex issue. Most would agree that the follow-up should not go on indefinitely. However, exactly how long this follow-up should be is not clear-cut. A fixed period of follow-up that can be applied to all studies is not practical because of the differing natures of the compounds under investigation. Instead, it would be more appropriate for the duration of follow-up to be project and protocol-dependent, based on available information on the half-life and PK/PD characteristics of the study drug. Sufficient information may not always be available to make an informed decision on this basis, especially in the early phases of the drug development process. In the absence of this information, it is recommended that minimally an effort be made to capture all events that occur within 14 days of the last day of study medication. This figure is somewhat arbitrary, but a two-week follow-up period seems a reasonable minimum in the absence of any information to suggest that longer follow-up is necessary.

It might be argued that anything after the last day of therapy is post-therapy and there is no need to define a value for k + x to mark the end of the study. Though it might be reasonable to have a value for k + x to mark the timing of a follow-up visit, adverse events reported thereafter, for whatever reason, should not be considered any different from those reported before day k + x.

As previously stated, however, the position being taken in this paper is that the post-therapy period should not extend indefinitely. At some point in time, the information collected thereafter becomes superfluous and unlikely to have any relationship to the study drug. Presumably the value of x has been carefully defined in the protocol to mark that point in time. The value of x should have been defined to cover the period that would be most likely to include events that could be related to the continued presence of study drug or its withdrawal.

Adverse events which have a start date beyond the planned last day of study, defined by k + x, would be considered post-study events which were not intended to be collected as part of the study. Some of the more common circumstances under which such events could be reported would be (1) the patient is late for the scheduled post-therapy visit, (2) the patient is being followed for a persistent event that was present at the planned end of the study and new events are reported during the course of this follow-up, or (3) there is an unscheduled visit or contact with the patient which takes place after the defined last day of the study. Since most, if not all, of these events can be expected to bear no relationship to the study drug, it seems appropriate to tabulate and report them separately from on-therapy events and post-therapy events.

Regarding the value of x, it is recommended that its value be identical for all patients. It should be equal to the number of days between the last day of therapy and the last scheduled post-therapy visit as defined in the protocol. It is recognized that not all patients will be followed for exactly x days. Some will be lost to follow-up and have no information, while others may be late for visits or for some other reason provide information for more than x days beyond the last day of therapy. Nevertheless, there are at least two advantages to this approach of having the value of x be a fixed value.

One advantage is that the post-therapy period is of equivalent duration for all patients. A tabulation of post-therapy events would be easily interpretable since it would include for all patients only those events which occurred within x days of the last day of study drug.

Secondly, this approach prevents the situation in which an adverse event that occurs y days after therapy (y>x) is considered post-therapy for one patient and post-study for another. For example, suppose the post-therapy visit is scheduled 28 days after the last day of therapy. Patient A is late for this visit and it takes place 42 days after the last day of therapy. At that time, an adverse event with a start date 40 days after the last day of therapy is reported. If x is defined according to when the last scheduled visit took place, then x would be 42 for this patient and the event would be considered post-therapy. On the other hand, suppose Patient B had a post-therapy visit as scheduled on day 28 and then another unscheduled visit on day 42. No events were reported at the day 28 visit but an event with a start date on day 40 was reported at the day 42 visit. This event would be post-study for this patient since it first occurred 12 days after the last scheduled visit. Thus, an event reported 40 days after the last day of therapy is post-therapy for Patient A and post-study for Patient B.

6. Discussion

The intention of this article is to point out some of the complexities associated with the adverse event data that are collected as part of a clinical trial. It has been assumed that many of the issues raised herein have been faced or will be faced by anyone who works with adverse event data. By presenting some of the more common problems encountered and proposing some solutions, it is hoped that others will be encouraged to share their own thoughts on these issues. Consideration might then be given to the development of a set of guidelines that would standardize to the extent possible such basic concepts as what constitutes an adverse event, what constitutes a treatment-emergent adverse event, and what is an appropriate duration for patient follow-up after therapy has been stopped. Though a certain amount of flexibility will be necessary, any steps toward a standard approach could simplify the adverse event reporting process, make it more consistent, and allow for more clearly interpretable results.

As for the role of statisticians in this process, they are not expected to be the source of final decisions as to exactly how the adverse event collection and reporting process should be carried out. However, since statisticians plays a key role in taking the data from its raw state to a summary form, they are especially aware of the problems that can arise in trying to produce a clear and accurate final summary. The statistician, therefore, is an a position to make an important contribution, in conjunction with representatives from other disciplines, to the development of adverse event guidelines.

References

1. *Guideline for the Format and Content of the Clinical and Statistical Section of an Application*, Center for Drug Evaluation and Research, Food and Drug Administration, July 1988, p. 36.

Describing Risk in Long-Term Clinical Trials

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Abstract

Existing methods of describing long-term risk in clinical trials will be evaluated, based on their validity, potential biases and artifacts, and their usefulness for patients and prescribing physicians. Methods considered are simple measures of risk (crude rate, cumulative rate), exposure-adjusted risk estimation (risk per unit time, hazard function), and various approaches to describe recurrent risk. The applicability of the methods for clinical data will be discussed, and final recommendations will be derived.

Keywords: Hazard; risk set; Crude rate, cumulative rate, exposure adjusted risk, prevalence rate, intensity function, multiple failure time models.

1. Introduction

We want to measure *risk as a function of exposure*. Exposure varies in terms of time and dose, and the aspects of risk we consider here are occurrence, frequency, and duration of a certain event of interest.

Desirable properties of measures of risk. When is a method to assess and describe risk a good method? We propose the following criteria:

(1) **Validity:** Given that risk is a function of exposure, merely describing outcome without considering the input side is invalid. Exposure must be adequately taken into account in any measure of risk.

(2) **Unbiasedness:** The true risk should not be systematically over- or underestimated.

(3) **Relevance:** The ultimate destination of descriptions of adverse events is the package insert. We need measures "to convey the concept of risk to nonstatisticians whose use or choice of a drug may depend on this information" (O'Neill, 1988).

Different adverse events will raise different sorts of concerns in the patient. Notably, the questions are different for irreversible or "absorbing" events which can occur only once, and for events that can occur repeatedly. Also, for many events not only the occurrence, but also the duration, is of importance for the patient's quality of life. Table 1 lists these three event types along with typical concerns.

Table 1
Patient's concerns, by type of adverse events

Event type	Example	Question
"Absorbing" (irreversible)	Death Blindness	"Will I get it?" "When will I get it?"
Repeating, short duration	Seizures	"How often will I get it?" "Will I develop tolerance?"
Long duration	Depressive episodes Neutropenia	"How much of my time will I suffer from it?"

2. Measures of Risk for Absorbing Events

2.1. Crude Incidence Rate

The crude incidence rate is defined as the number of subjects with the event, divided by the number of patients "at risk." In most cases, "at risk" is interpreted as "enrolled and treated."

Validity: The basic assumption is that every patient has the same chance of getting the event. A necessary condition for that would be that every patient is exposed for the same amount of time, in the sense of *one unit exposure* for each patient, which is probably justified only in single-dose studies.

But even if the basic assumption stated above is met, a more important problem persists: The crude rate is confounded with observation time. The longer one observes, the more events one will see! Therefore, this measure is not interpretable without simultaneously considering exposure. Also, crude rates cannot be compared between studies of different exposure times.

Bias: The crude rate takes the full initial patient sample as the denominator, even for events that occur late in the trial

when only a few patients are left. The true risk of acquiring the event within the observation period may be higher than indicated by the crude rate (see Abt et al. 1989; O'Neill 1988, p. 549 for some striking examples).

Relevance: Due to their simplicity and intuitive appeal, the crude rate is the measure of risk most commonly found in package inserts, even when the conditions discussed above do not hold. Whenever exposure is long and varies among subjects, the crude rate is not meaningful.

2.2. Survival Rate (Cumulative Rate)

The survival rate S(t) indicates the rate of subjects not yet affected by the event at time t. Several researchers (e.g. Abt et al. 1989; O'Neill 1988) have proposed to use S(t) instead of the crude rate because S(t) is based on risk estimates using the correct denominators at each event time. This eliminates the bias of the crude rate discussed above.

As for the crude rate, S(t) is not adjusted for length of exposure; both crude rate and cumulative rate are monotonically increasing functions of time and cannot be interpreted without also considering observation time.

2.3. Events per unit time

A common measure in epidemiology (e.g. Rothman 1986) is the estimated number of 'absorbing' events (such as deaths) per time unit of exposure. A common time unit is year, yielding "Deaths per patient year" (DPPY). As Rothman emphasizes, DPPY is *not* a probability, but an expected frequency than can be greater than one. The underlying probability estimate can be constructed as:

h = # of positive person-time units / # of all person-time units,

with 'patient-time unit' referring to the minimal time 'quantum' of the observations. Normally, this is a day, so that

DPPY = h * 365,

which reveals DPPY's essence as the cumulative hazard at time 365, H(365), and to the intensity function discussed later.

Validity: With increasing exposure time, both numerator and denominator of DPPY will increase, and hence DPPY will not necessarily increase. It will remain constant if the constant hazard assumption holds.

Bias: The basic assumption is that each person-time unit is an observation from a binomial distribution with the probability h to display the event. Or, as Rothman (1986, p. 25) puts it in simple terms: "One unit of person-time is assumed to be equivalent to and independent of another unit of person-time." If the implied assumption of a constant hazard holds, then h is basically identical with the life-table estimate of this constant hazard for the whole one-year period.

In the case of nonconstant hazards, there is a bias. DPPY will then depend on the distribution of observation periods in time. Consider—similar to O'Neill 1988—the following two scenarios: a) 10 patients observed for five weeks; b) 50 patients observed for one week. Although the total exposure is 50 patient-weeks in both cases, the expected number of events will be higher in scenario a) if the hazard is decreasing over time, and lower if it is increasing.

Relevance: To some, DPPY looks deceptively like a probability; '0.5 per patient year' is not a probability! It is an expected frequency which can be greater than 1. For instance, if seven events were observed based on a total exposure of 700 days, the expected NPPY is 7/700 * 365 = 3.65 events per patient year.

More importantly, DPPY refers to populations, whereas "risk" is an individualistic concept. DPPY may be a handy measure for the epidemiologist, but for the individual patient, an expected number of events is meaningless for absorbing events, such as death, which can occur only once.

2.4. The Hazard as a Function of Time

If h is not constant over time, h(t) needs to be estimated separately for time intervals of a given width, such as a day, week, or month:

h(t) = # of events at time interval t / # of all patient-time units within time interval t.

This is basically the life-table estimate of the hazard. If it reveals increasing or decreasing trends, parametric models such as the Weibull model can be fitted, and more formal tests can be conducted to answer the important question if the hazard increases, decreases, or is constant in time (Shapiro, 1994).

Relevance: To the researcher, the shape of h(t) may yield hints about a causal link between drug and event. Hazard functions that peak initially, followed by a steep decay, may indicate a causal drug effect (Abt et al. 1989). For the patient, the shape may contain answers to questions such as "will I develop resistance, or will I get it as long as I take the drug?" Salsburg (1993) demonstrates in various examples the usefulness of hazard functions for prescribing physicians.

Furthermore, hazard functions can be translated into survival functions and estimates of median event-free times, an intuitive and meaningful measure of risk for the patient.

3. Measures of Risk for Recurrent Events of Short Duration

Most adverse events observed in clinical trials are "nonabsorbing;" the patient remains under observation after the onset of the event, and (s)he can get the same adverse event repeatedly. Examples of such events are reinfections, seizures, and sensitivity reactions.

Statistically, analyses of non-absorbing and potentially repeating events must allow a subject to return to his risk set after undergoing the event for a period of time. This introduces 'subject' and 'number of preceding events' as potential independent variables for the hazard function. Subjects can be characterized by fixed effects risk scores, such as $r_i = \exp(\underline{\beta}' \underline{x}_i)$, and/or by a random subject factor; the 'number of preceding events' can be treated as a time-dependent covariate. This allows us to classify the different models being discussed in the literature:

Table 2
Models for the hazard functions for recurring events

Independent variables	Hazard function	Model
None	h=constant	Events per unit time
Time	h=f(t)	Hazard functions
Time, fixed effects for subjects	$h=f(t, r_i)$	Anderson-Gill
Time, fixed effects for subjects, preceding events	$h=f(t, r_i, n_{it})$	"Modified" Anderson-Gill
Subject	$h=f(t,..., subject_i)$	Frailty models

3.1. Number of Events per Unit Time

The DPPY statistic introduced above generalizes effortlessly to a 'Number of events per patient year' statistic:

NPPY = Expected number of events / One patient-year of exposure.

Bias: This measure is based on the same constant-hazard assumption as in the case of "absorbing events." In addition, it assumes *homogeneity between subjects*; all subjects are thought to have the same constant hazard function, and hence the same expected event frequencies per time. Under this assumption, it is reasonable to give larger weights to subjects with more data

(longer exposures), and this is what NPPY does, in contrast to the average $NPPY_{avg}$ of $NPPY_i$, the *individual* numbers of events per patient year, which would give equal weight to each subject.

If all subjects have the same hazard, $NPPY_{avg}$ would tend to be the same as NPPY. Otherwise, the statistics will tend to differ. For instance, susceptible subjects could drop out earlier than "robust" subjects. This will lead to an underestimation of the "typical" or average hazard in NPPY but not in $NPPY_{avg}$. Approaches to diagnose and handle subject heterogeneity will be discussed below.

Relevance: In spite of its problems, the measure NPPY attempts to answer the right question for recurrent events, "How many events do I need to expect within a certain time frame?"

3.2. Expected Number of Events as Function of the Hazard

The hazard h(t) for recurring events is the instantaneous risk at time t of getting the event for the first time *or again*. It can be estimated by the number of events in an interval, divided by the patient-exposure in the interval.

Counting process models allow us to predict the number of events in the presence of more complicated hazard models than assuming the same constant hazard for all times and subjects. The models are based on the fact that *the predicted count is just the cumulative hazard function, integrated over the risk interval(s)*:

$$\begin{aligned}\text{Expected AE count} &= \sum_i \int_0^t y_i(s)\, h(s)\, ds \\ &= \int_0^t \sum_i y_i(s)\, h(s)\, ds \\ &= \int_0^t r(s)\, h(s)\, ds \\ &= \int_0^t i(s)\, ds = I(t).\end{aligned}$$

$y_i(s) = 1$ if subject i is at risk at time s; =0 otherwise.

The function i(s) is the so-called *intensity function*; it is the integrated hazard, multiplied with the risk sets at each (infinitesimally small) time interval. Its integral I(t) is the expected number of events at time t (Andersen et al. 1993, page 51). This holds true in general, independently from the specific hazard function. The only assumption needed is random censoring.

The predicted 'number of events in the *first* year,' NPFY, can be estimated based on an uninterrupted risk interval for a single patient (y(s) = 1 for all s):

$$NPFY = \int_s = {}_{[1\ldots365]}1 * h(s)^* \, ds.$$

In practice, the Nelson-Aalen estimator, generalized for repeating events, is used to estimate the cumulative hazard $\int^t h(s)\, ds$. Confidence intervals can be constructed for this estimate (e.g. Andersen et al. 1993, p. 207), which should allow us to put confidence boundaries around our predicted event counts.

Comparison with NPPY: For a constant hazard, this is h * 365, equal to the crude NPPY statistic discussed before. In all cases of nonconstant hazards, NPFY is a more precise estimate because it is based on local estimates of the hazard, using the correct local risk set sizes. NPPY depends on number of events and exposure only; NPFY depends also on the distribution of the event incidences in time. If they tend to occur late, when patients have dropped out and risk sets are smaller, the local hazards h_s will be higher than when they occur early, and hence the cumulative intensity function and the expected counts will be higher.

3.3. Hazard=f(t): Simple Anderson-Gill model

The Cox proportional hazards model allows for different, but proportionally related, hazard functions for subjects with different predictor values. Anderson and Gill's (1982) influential extension is based on the same idea; the hazard *depends only on risk score and time*. Their extension of the Cox likelihood consists of the same factors as the Cox model. The only difference is that now the product is both over subjects and time rather than over event times because now one subject can have multiple events.

The cumulative baseline hazard can be estimated based on the Nelson-Aalen estimator and the estimated ß weights from the Cox regression (see Fleming & Harrington 1991, p. 151/152). For a particular patient, this function needs to be multiplied by his or her risk score $\exp(\underline{ß}' \underline{x_i})$. This estimated cumulative hazard can then be used to predict numbers of events, as shown above.

3.4. Modeling the Effect of Preceding Events

If one assumes proportionality between the functions $h_j(t)$ for the hazards after j preceding events, the number of preceding events can be introduced into the basic Anderson-Gills model as a time dependent covariate. Whereas estimation of the baseline hazard $h_0(t)$ is relatively straightforward, a prediction of an integrated hazard and expected counts for a particular subject requires additional assumptions because these depend on "the stochastic structure of the future development of the covariates" (Andersen et al. 1993, p. 531).

3.5. Heterogeneity Among Subjects

Subject effects impose a dependency structure on time-to-event data in cases like paired survival data or multiple observations (events) for each subject. Oakes (1992) introduced models to handle this by random effects for the subjects' "frailties", i.e., subject-specific random proportionality factors w_i applied to the hazard function. With this, the expected count for subject i is $\int_t w_i\, h(s)\, ds = w_i \int_t h(s)\, ds = w_i\, H(t)$, and for a constant baseline hazard, this yields

$$\text{Expected AE count} = w_i * h * t,$$

where t is the exposure time. This enables us to estimate w_i by w'_i:

$$h^* w'_i = \text{Observed AE count / Exposure time},$$

which is the patient-wise 'number of events per patient years' statistics $NPPY_i$ discussed before.

A simple graphical device can help detect heterogeneity, by plotting each $NPPY_i$ against another variable thought to be influential or indicative of a subject's frailty. "Exposure time" is a good candidate because high frailty may lead to short stays in a study (thus violating the random censoring assumption). Plots of frailty versus exposure can reveal violations of the random-censoring assumption and subject heterogeneity.

4. Measures of Risk for Events with a Longer Duration

For events of a longer duration, methods based on incidences may be grossly inappropriate. For instance, a patient suffering from a depressive episode for a whole contiguous week would be considered less severely affected than a patient who is depressive on two noncontiguous days.

In the preceding sections, the patient was taken out of both nominator and denominator for the time periods he or she suffered from the event. For events with nonnegligible durations, this is not satisfactory, because not only the incidence, but also the duration has an impact on the patient's quality of life and needs to be considered in any measure of risk.

4.1. Prevalence Rates

The simplest fix is just to leave the patient in both the numerator and the denominator for the times when (s)he is affected. The measure obtained is well known to epidemiologists; it is the *(point) prevalence*, defined as the "proportion of a population that is affected by disease at a given point in time" (Rothman 1986).

Assuming constant prevalences, the prevalence can be described for all data in a time window, by calculating the numbers of patient-time units affected divided by the numbers of patient-time units observed, just as we did before for the hazard rate h. A statistically more satisfactory estimation of the prevalence will be discussed in the next section.

Relevance: While the hazard function yields the key to a statistically satisfying estimation of expected event frequencies, the concept of prevalence enables us to estimate the percentage of time one will be affected by the event. For events with longer durations, estimates of the probability of *having* rather than *acquiring* the event is indeed what we need.

4.2. Markov Models

Assuming a Markov model, the prevalence can be estimated based on the transition probabilities to enter and to exit the affected state (Rothman 1986, p. 32, 33). Andersen et al. (1993, p. 304) demonstrate with Andersen's and Gill's original dataset how Markov models can be used to estimate prevalences and their confidence bands.

The basic assumption of Markov models is that each transition probability depends on the current state and time only. In other words, previous history does not count. In clinical datasets, this is not very plausible. The number of previous events may, and in Andersen and Gill's dataset, do have an impact.

5. Practical Considerations

Whereas the recording of the first start date of adverse events is sufficiently accurate in clinical trials, there are multiple problems with recording the stop dates of the episodes and the dates of recurrences. Have investigators been clearly instructed to record recurrent events? When is an event recurrent, when is it 'continuing?'

The use of 'continuing' and 'ongoing' fields necessitates 'collapsing' of adverse events recorded into different records. Perhaps a summary page at the end of the study to capture all adverse events instead of a visit-wise capturing would help to record accurately both start and stop dates of all episodes of an event.

6. Summary

In most cases, traditional measures of risk for adverse events may be biased or irrelevant. In particular, some measures ignore crucial independent variables (such as exposure time), others ignore essential dependent variables, such as number of recurrences, or length of events.

How should risk be measured? Based on our discussions, this depends on the type of event and the type of data collected. Final recommendations are summarized in Table 3.

Table 3
Meaningful Measures of Risk by AE type and Data Available

Type of clinical trial	Type of AE	Meaningful measure of risk
Short term	All	Crude rate Cumulative rate
Long term	Absorbing	Hazard function Median survival time
	Recurring, short duration	Hazard function Expected count
	Long duration	Prevalence function Expected proportion of time affected

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Section News

Workshop on Adverse Events

Christy Chuang-Stein

Pharmacia & Upjohn, Inc.

The Continuing Education Committee of the Biopharmaceutical Section of the ASA is sponsoring a Workshop on Adverse Events, October 28 and 29, 1996, in Bethesda, Maryland. The purpose of this workshop is to consider problems in the definition, collection, and reporting of adverse events during Phases I-III of the drug development process. The workshop is designed to address issues such as the collection of symptoms vs. syndromes, the time window of event collection after discontinuation of study treatment, collection of adverse events at baseline, analysis of adverse event data, presentation of adverse events in drug labeling, events in long-term trials and in short-term closely-monitored trials, intermittent events, analysis of laboratory data, alternatives to current approaches, etc. U.S. and European regulatory perspectives will be discussed. After the workshop, a working group will develop a Section "position paper" on the topic.

The cost is $125 for Section members and attendees from academia and the government; $150 otherwise. The registration fee covers breakfasts, breaks, a reception on the 28th, and all workshop materials. The program and registration information will be in the August/September issue of *Amstat News*, with a registration deadline of October 1. Although the workshop is sponsored by a Section of the ASA, attendance by non-statisticians (e.g., clinicians, regulatory scientists) is encouraged; please share the program and registration information with colleagues at your institution. For more information, contact the Chair of the Continuing Education Committee, Christy Chuang-Stein (E-mail: JCCHUANG@PWINET.UPJ.COM; phone: 616-833-0209; fax: 616-833-0226). Other members of the organizing committee are Bob Northington (Wyeth-Ayerst), Thomas Lin (Sandoz), and Curtis Wiltse (Eli Lilly).

Letter from the Chairman

Gary Neidert

You should be reading this article just before the beginning of the 1996 Joint Statistical Meetings in Chicago from August 4-8. I will use this opportunity to describe the upcoming Biopharmaceutical Section-sponsored events and activities that will occur at the Meetings.

The Section is sponsoring four invited sessions at which 16 papers will be presented:

- **Sunday, 4:00 p.m.**: *The Hidden Issues Concerning Lab Data Evaluation*
- **Monday, 2:00 p.m.**: *Greater Efficiency in Clinical Trials While Preserving Statistical Validity*
- **Wednesday, 10:30 a.m.**: *Methods for Analyzing Recurrent Events*
- **Thursday, 8:30 a.m.**: *Statistical Analysis of Combination Drugs.*

The Section will also be sponsoring 10 Luncheon Round Tables on Wednesday.

As can be seen in the Meetings' registration packet, a wide variety of relevant topics will be discussed. I hope those members attending found a topic of interest and plan on participating.

A one-day short course, sponsored by the Section, entitled Designing and Implementing Economic Evaluations in Health Care, will be taught by Joe Heyse, Michael Drummond, and John Cook.

A working demonstration of the ASA home pages will be available for review during the Meetings. If you have not visited the Biopharmaceutical Section's home page yet, you may want to take this opportunity to do so.

The Section's Executive Committee Meeting will be held on Tuesday from 7:30-12:00 in the Ogden Room at the Hyatt Regency. Although this meeting is closed to the public, any committee member will gladly review the proposed agenda with those who are interested. The minutes from the meeting will appear in the edition of The Biopharmaceutical Report immediately following the meetings.

The Section's Reception and Business Meeting will be held on Tuesday, August 6, from 6:00-7:30 p.m., in the Toronto Room of the Hyatt Regency. If you are attending the meetings, please mark that date on your calendar and attend. The business meeting is the major forum for discussing the Section's business activities. Members' input on planned activities and financial decisions are needed. We will also be presenting awards to Best Presenters of Biopharmaceutical contributed papers from previous meetings and to the winners of the 1995 Student Paper Competition. A reception for Section members is scheduled to begin at 6:00 p.m., with the business meeting scheduled for 6:30 p.m. We have plenty of food and beverages on order, so please join us.

I hope you find this summary helpful as you plan your Meetings' week. I am even ore hopeful that you will be able to participate in a Section-sponsored activity. See you in Chicago!

Biopharmaceutical Section Census

Phil Pichotta

Abbott Laboratories

How many people belong to the Biopharmaceutical Section? What state has the most members? What state has the second most members? What 8 states don't have any members? How many members live outside the U.S.? What country other than the U.S. has the most members? These are interesting trivia questions which will be answered at the end of this article. Unfortunately, we don't know anything about our membership beyond their location, which we determined from the mailing list.

The Biopharmaceutical Section will be conducting a complete census of its members this year. When you receive the Census questionnaire, please complete it and mail it back quickly. Once a completed form is returned, a T-shirt with the Biopharmaceutical Section logo will be sent to the member. We hope that this will encourage a high response rate and will also provide our members with something that identifies them as members of the Biopharmaceutical Section.

We hope that the results of the census will help us know our membership better so that we will be able to provide services to our members. How many members work for a pharmaceutical company or a contract research organization or are in academia or government? What is their interest: clinical, pre-clinical, or other? These are a couple of questions that we hope to answer. We would also like to know how members update their statistical skills.

We hope to provide much more information about the Biopharmaceutical Section in future issues of this journal or *Amstat News*.

If you have ideas about increasing membership in the Biopharmaceutical Section, please contact me or any Section officer. Phil Pichotta; E-mail: philip.pichotta@abbott.com; Phone: (847) 938-3708.

Answers: As of November 1995, the Biopharmaceutical Section had 1637 members. New Jersey, not surprisingly, has the most members (214). California was second with 175 members (that surprised me). Other states with a large number of members are: Pennsylvania (155), Massachusetts (84), and New York (73). One hundred fifty-five (155) members live outside the U.S. Canada has the most with 43 members, followed by Germany with 24 and Switzerland and Japan, each with 11 members.

Minutes of ASA Biopharmaceutical Section Executive Committee Meeting

March 19, 1996, Richmond, Virginia

Attendees:

Christy Chuang-Stein	Jeff Meeker	Steve Snapinn
Bob Davis	Gary Neidert	Lianng Yuh
Sally Greenberg	Phil Pichotta	Curtis Wiltse
Spencer Hudson	Denise Roe	

Gary Neidert welcomed the members of the Executive Committee. Each person introduced themselves. Gary reviewed the agenda.

Minutes

The minutes were approved. There was a discussion concerning the timing of any review vs. the publication of the minutes in the Biopharmaceutical Report. It was also decided that draft minutes should be sent to all attendees for review.

Treasury Report

The report from the Biopharmaceutical Section Restricted Treasury as of March 13, 1996, was distributed. It was noted that ASA staff has only posted membership dues as of

November, 1995. They hope to be caught up within six weeks. It was also noted that Corporate Member dues notices were late in being mailed, so no receipts for Industrial Members are reported for 1995. A question was raised as to what the line item for Net Share, Inc. is. Also, it was noted that a proposed payment for a mailing for an Epidemiology Section meeting for 1995 has not appeared.

Assignment: Jeff Meeker will contact Penny Young concerning the two questions raised.

Post-meeting note: The line item for Net Share, Inc., is our share from continuing education courses.

Forms for reimbursement for the meeting were distributed. It was decided that those eligible for reimbursement included the Executive Committee, elected officers, and those invited to the meeting for business purposes. Reimbursed expenses would include those specifically for attending the Executive Committee meeting and not expenses associated with a concurrent meeting. Expenses would include one night hotel, transportation, ground transportation, and reasonable meals.

1996 Section Financial Plan

Bob Davis distributed the financial plan for 1996 that was submitted to ASA. A conflict in the plan was noted in that it specifies annual donations to the electronic communications project, but the Committee is to be disbanded at the end of 1996. It was too late to change the pricing structure for the 1995 Proceedings (which will be issued in 1996). However, the 1996 Proceedings will be reduced to $18 prepublication, $20 for ASA members, and $30 for others.

Assignment: Jeff Meeker will check with Penny Young on a planned donation for 1995 of $1500 to the ASA committee responsible for transferring film to an electronic medium, and donations for 1996 of $500 to the electronic communication project and $500 to the undergraduate data analysis competition.

Council of Sections Report.

The Council of Sections Governing Board met on February 9-10, 1996.

There is a proposed revision to the cost sharing algorithm for continuing education courses. The current algorithm for a full day course is a step function:

- **<15 registrants**—the course is canceled or run if the Section agrees to assume losses.
- **15-34 registrants**—the course runs, but the Section receives no profit
- **35-49 registrants**—the Section gets $2000.
- **50-74 registrants**—the Section gets $3000.
- **75 or more registrants**—the Section gets $4000.

The Section's share for a half day course is one half the amount above. The proposal is to change the algorithm so that the Section will receive a proportion of the difference between the course income and expenses. If the course is co-sponsored by more than one Section, the Section revenues are shared equally among the sponsors for both algorithms. The Executive Committee voted to approve the change.

We were reminded that we should discuss our financial plan before the August meetings, so it can be approved during the August executive and business meetings. The Executive Committee felt that, since they also meet in the fall, there was no reason to discuss it prior to August, but plan on approving it at the fall meeting.

Nancy Hiett, the new Section Relations Coordinator, will serve as the focal point for contact between the Sections and the ASA office.

Lorraine Denby presented an update from the February 13, 1996, Council of Sections Electronic Communications Initiative meeting to the Council of Sections Board of Directors.

- Six Sections currently have home pages. The Biopharmaceutical Section is the seventh.
- The October, 1995, *Amstat News* contained three articles with information about the web site. The hardware and software are in place in the ASA office and functioning.
- The ASA Board approved a plan to create a new position of ASA Online Editor. This will be similar to a journal editorship and will be filled by a volunteer member who will have continuing responsibility for the home page structure and content, and who will interface with the ASA office. A search committee has been formed with the goal of having an appropriate individual in place by July 1.
- Searching will be over ASA home pages first. If possible, searching will go to Section and Chapter pages, also.
- Two demonstrations will be running at the 1996 Joint Statistical Meetings: one in the registration/membership area and another in the exhibit area. A flyer will be available. We will plan a session on what is available on the web in the virtual statistical world, to include a number of short talks.
- At the Council of Sections Board of Directors meeting, the term of the Electronics Communication Committee was extended from July 1 to September 1.
- At the Council of Sections Board of Directors meeting, minimum requirements for a Section home page was proposed to be:
  - —A one paragraph mission statement
  - —A listing of officers
  - —A statement regarding member services.

  The Section Executive Committee was asked to concur with this requirement, which it did.

Policy issues about the web site included:

- **Advertising:** A plan for paid advertisements will be sent to the ASA Board of Directors for its April meeting. The proposal is for job ads first. Care will be taken not to adversely affect *Amstat News* advertising. The Committee will be soliciting feedback from top advertisers. The plan is to offer ads free for a couple of months and then start charging. When the plan is in place, a letter will be sent to all institutional/corporate members and all who advertised in the last year letting them know about the offer.
- **Institutional and Corporate Members:** The question was raised as to whether it is okay to link to their home pages. If yes, the Electronic Communication Committee would like a letter to go to them telling them of this opportunity and asking for their link.
- ENAR wants ASA to host their site. Space considerations are trivial, but access to ASA files and traffic considerations are not trivial. If their only worry is about an address changing location as their officers change, ASA could offer an address that points outside of the ASA server.

Accomplishments and future target dates for the Committee were also provided. After the COS Board of Directors meeting, Penny Young provided a detailed accounting of funds for the project. To date, $28,000 has been spent.

Jeff Meeker indicated a potential problem arose in the Individual Membership Subcommittee concerning the proposed directory. Apparently, some employers are objecting to having an E-mail address in a directory on the Internet. The concern is the potential for junk E-mail and for sabotage attempts to bring down the corporate servers.

Program Report

We have four invited paper sessions for the 1996 Joint Statistical Meetings which include 16 papers:

- **Sunday 4:00**—*The Hidden Issues Concerning Lab Data Evaluation*
- **Monday 2:00**—*Greater Efficiency in Clinical Trials While Preserving Statistical Validity*
- **Wednesday 10:30**—*Methods for Analyzing Recurrent Events*
- **Thursday 8:30**—*Statistical Analysis of Combination Drugs*

There are 15 contributed paper sessions, including two Special sessions, for the 85 papers that were contributed for the Section. Steve Snapinn worked with the program chairs of ENAR and the Biometrics Section to make the sessions more coherent. There are six posters. The FDA submitted nine papers for the FDA special contributed paper session. Five of the papers are in the session; the other four have been distributed to general contributed paper sessions. Five student papers were received.

No invited sessions were arranged for 1995 ENAR. The deadline for proposed sessions for 1996 is June 1. Any proposals for sessions should be given to Lianng Yuh. Also, we will put a request in the Biopharmaceutical Report for topics for the 1996 Joint Statistical Meetings.

Assignment: Steve Snapinn will draft a letter to ENAR documenting the problems we had in working with them on the 1995 meetings.

Joint Statistical Meetings Luncheon Round Tables

There are 10 round table luncheons scheduled for the Joint Statistical Meetings:

Janet Wittes—*Reporting Adverse Events—What can we Statisticians Contribute?*

C. Thomas Lin—*Use of Statistics in Pharmaceutical Product Development*

Carl Metzler—*PK/PD Modeling in Drug Development*

Lisa Kammerman—*Challenges in AIDS Clinical Trials: Study Design Issues*

Lora Schwab—*CRO Statisticians: Significant Differences, Significant Opportunities*

Steven Piantadosi—*Advising the FDA on Product Approval*

Donald Berry—*Bayesian Methods and Ideas in Medical Research*

Roy Tamura—*Adaptive Techniques in Clinical Trials*

Laura Meyerson—*Are Double Blind, Placebo Controlled Studies Really Blinded?*

Perry Haaland—*New Optimization Strategies for Complex Chemical, Biochemical and Physical Processes.*

Biopharmaceutical Report

The latest issue is supposed to have been mailed, but there has been a delay in ASA.

Several papers are in preparation for the Biopharmaceutical Report in line with the proposed workshop on Adverse Event Reporting. These include:

Lothar Tremmel—Long term toxicity

Bob Northington—Treatment emergent events, Post therapy events

Janet Wittes—Events in long-term trials, Censoring, Severity, Proximity to drug administration, Taxonomy, Laboratory data, Intensity of surveillance, Multiple events per patient, Who to include (treated vs. intent to treat)

Balakrishna Hosmane—Analytical Issues

Curt Wiltse & Joel Scherer—Short term CV trials

Ona Szarfman from FDA will be a discussant. Articles are due by the end of May to give time for Ona to include in her discussion. In addition, Steve Snapinn and Joe Heyse are preparing an article on Multiple Endpoints. Tom Bradstreet has taken responsibility for book reviews. The books include those to recommend to clients. He has 11 reviewers and has distributed a list of potential books for review.

Three issues of Biopharmaceutical Report are planned per year, one more in the summer and one prior to the workshop.

Midwest Biopharmaceutical Statistics Workshop

The program for this meeting has been mailed. The plenary session this year is in two parts, a talk on Bayesian Biostatistics by Don Berry and a session of three papers on AIDS Clinical Trials Design and Analysis.

Continuing Education Committee Report—Adverse Event Reporting Workshop

A proposal was made to have the Adverse Event Reporting workshop on October 24 and/or 25 at the Crystal City Holiday Inn. A discussion was held on who the audience was and the consensus was that it was a mixture of people who are involved and people who want to learn. It was also decided the purpose was not to reach a consensus at this meeting, but that a core cadre consisting of presenters and others present would be asked to form a working group to develop a consensus paper by the Joint Statistical Meetings in August, 1997. Based on this scenario, it was decided the meeting should be two days, but a better hotel might be the Bethesda Hyatt or something similar in the Washington, D.C. area.

The Section voted an additional $5000 to the conference (in addition to the previously allocated $5000) as a contingency.

ASA and Biopharmaceutical Section Web Site

The Section concurred with the proposed minimum requirements of mission statement, list of officers, and list of member services for a Section home page. They also indicated meeting minutes, activities and upcoming events should also be included. Whether to include E-mail addresses of Section members was discussed and the decision was to delete them if the member so desired.

Student Awards

Five papers have been submitted for student awards for the Joint Statistical Meetings. Denise Roe will handle the student awards. A committee consisting of Denise, Chuck Davis, Christy Chuang-Stein and Steve Snapinn will review the papers.

Joint Statistical Meetings Section Meetings

It was decided 7:30 a.m. Tuesday would be requested for the Section Executive Committee meeting. A continental breakfast would be requested. It was also decided the first choice for the Section business meeting and reception would be 6:00-7:30 p.m. Tuesday, with the second choice of 7:00-8:30 p.m.

Joint Statistical Meetings Short Courses

A proposal has been submitted for the Section to sponsor the one-day short course Designing and Implementing Economic Evaluations in Health Care by Joe Heyse, Michael Drummond, and John Cook. The Section voted to sponsor the course.

Bob Starbuck contacted Gary Neidert to see if we were interested in again sponsoring the half day short course by Bob and Bruce Rodda for New Pharmaceutical Statisticians.

Assignment: Gary Neidert will contact ASA to see whether or not it is passed the deadline. If not, we will try to sponsor the course.

Fellows Nomination

Since Lilliam Kingsbury was not present, there was no discussion. It is already passed the dead line for 1996 nominations.

Assignment: Gary Neidert will contact Lilliam to determine what action needs to be taken for 1997.

New Section Initiatives

The proposed video of a day in the life of a statistician was discussed. It was pointed out that the minutes of the November 3 meeting indicated this project was referred to the Continuing Education and Membership Committee, to be considered for 1997. Planning for the video should occur during 1996.

Assignment: Christy Chuang-Stein will contact Steve Ruberg to get input on a project of this type.

Listing available jobs on the web site was also mentioned. Sally Greenberg is the focal point for activities concerning the Sections web page.

Lianng Yuh will serve as a focal point for disseminating information of ICH guidelines.

Gary Neidert has not followed up on the discussion at the November 3 meeting on the Committee to Recommend Statisticians to FDA Advisory Committees.

Assignment: Gary Neidert will contact FDA Biometrics (Bob O'Neill) to see if there is continued interest on their part in nominations from this committee.

Note on Exclusions

See previous and following articles for information on the Section Census and the Best Paper Awards.

Best Paper Awards for 1995 JSM

C. S. Wayne Weng
Schering Laboratories

The winners of the Best Presenters Award for presentations at the Biopharmaceutical Contributed Paper Session at the 1995 Joint Statistical Meetings are:

- **First place**—Keith Soper, *Estimation of Median Lethal Dose (LD50) for Sequential Designs with Small Samples*;
- **Second place**—Lisa J. Suchower and Steven M. Snapinn, *The Use of Adjusted Means in Presenting Clinical Trial Data*;
- **Third place**—Thomas E. Bradstreet and Milton Parnes, *Distributions of Order K in Passive Avoidance Testing.*

Awards of $500 will be made to the first-place presenter and $250 to the second-and third-place presenters during the Session Business Meeting at the 1996 JSM.

The Best Presenters Award was established to enhance the quality of presentations in the Biopharmaceutical Contributed Paper Session at the annual JSM. The evaluation consists of 6 categories: Contribution, Organization, Verbal Delivery, Visuals, Handouts, and Overall. We encourage all presenters at the Biopharmaceutical Contributed Paper Session to pursue this award.

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