

## How To Use Clinical-Trial Data In Court

*Law360, New York (July 03, 2012, 12:14 PM ET)* -- Biostatistical data are most commonly associated with health outcomes research that is conducted by biopharmaceutical and medical device companies. Increasingly, however, these data are being brought into the courtroom as inputs for assessing allegations raised in health care-related litigation or potential damages associated with these matters.

Clinical trial results and other biological data have been at the center of patent infringement disputes involving the intellectual property embedded in blockbuster drugs or devices. They have also been central in 10b-5 securities matters involving the nature and “timely” disclosure of information about a drug or product, both of which could affect the manufacturer’s stock price.

Multiple stakeholders in the U.S. health care system are also paying closer attention than ever to the safety and efficacy of treatments and monitoring how pharmaceutical companies report the results of their clinical trials. A consequence of this scrutiny is the number of mass tort and product liability cases in which pharmaceutical companies’ analyses, interpretations and reporting of biological data have been examined and challenged.

Biostatistics is the application of advanced statistical methods to clinical trials and other biologic data. Accurate analysis of biostatistics data can help triers of fact make sense of signals — the patterns, outcomes and events that may have been associated with the use of a drug, device or other method of treatment. Such signals may be impossible to observe in real-time but can become clearer once experts have applied appropriate methodologies to biological data.

In intellectual property disputes, for instance, biostatistics experts may be able to determine whether the results of the clinical trials cited in a patent application are accurate and whether the findings of those trials are new relative to prior art.

In mass tort cases, biostatistics experts may be able to demonstrate that a safety concern related to a drug or device could have been detected earlier than reported, or, conversely, that despite the adverse events reported, no statistically meaningful patterns of harm to patients exist.

There is, of course, a major obstacle to using biostatistics data in the courtroom: The implementation of the methodologies associated with these data is often complex and somewhat inaccessible to triers of fact, given the wide variety of study designs, sample sizes, patients’ dropout patterns, risk profiles and comorbidities, as well as other potential sources of bias.

More fundamentally, the inherently mathematical nature of biostatistics can make it forbidding for lawyers, judges and juries alike.

The appropriate use of biostatistics experts, however, can help litigators distinguish between observations that are the result of chance and those that are statistically meaningful. In this article, we discuss the role of biostatistics in various litigation contexts and propose some best practices for evaluating biostatistics experts and results. But first, we review a few fundamentals.

## **What is Biostatistics?**

Put simply, biostatistics is the branch of statistics that is applied to biological data, and it is most relevant in the analysis and review of clinical trials. Researchers apply biostatistics to clinical trial data to answer a fundamental question: Are the results observed in the sample of patients enrolled in the clinical trial indicative of the “truth” or the results that would be expected in the underlying population?

Clinical trials are carefully designed and conducted to explore the efficacy or safety of a particular intervention — for instance, a drug or a medical device — relative to an alternative treatment or no treatment (placebo). The trials may compare several interventions simultaneously by including multiple groups of patients (or study arms). They usually adhere to strict, predefined protocols that delineate multiple dimensions of the trial, such as the target population and sample size, the time frame for investigation, the clinical outcomes of interest, the drug or drugs to be administered, and the relevant statistical tests to be used.

Patients may be randomly assigned to alternative treatments in what is known as randomized controlled trials, or they may all receive the same treatment. Clinical trials are often blinded, meaning that neither the patient nor the physician knows what drug is being administered to any given patient.

Unless biostatistics tools are applied to the data, the findings from a clinical trial provide information only on the patients enrolled in that trial. This level of analysis is of little use in most health care-related lawsuits, where the concern often is not about the limited number of patients enrolled in a clinical trial but about the larger, underlying population that received the drug or device in the real world.

By applying biostatistics methodologies to the data, however, the researcher can determine whether the clinical trial results are specific to the sample enrolled — that is, not statistically significant and likely the result of chance — or whether the results reflect a true phenomenon that can be expected to occur within the underlying population — that is, statistically significant and highly unlikely to be the result of chance.

## **Biostatistics in the Context of Litigation**

There are many possible applications of biostatistics in the context of litigation, including the ones outlined below.

### *Patent Infringement Claims*

Every drug or device that comes to market comprises a portfolio of intellectual property that is protected by patents. These patents are sometimes based on clinical trial data that demonstrate the incremental value of, say, a new compound or drug delivery method over existing ones.

Consider a recent infringement case involving a blockbuster drug: A published study that had postdated the patent application associated with the drug-at-issue seemed to invalidate the patent. However, a review of the biostatistics used by the study authors demonstrated that the authors had overstated their conclusions. Their data and findings were, in fact, perfectly consistent with the statistical results that had been used as the basis for the patent application.

## *Mass Torts*

If a drug or device is alleged to be associated with adverse events — for example, weight gain, cardiovascular symptoms or even death — a careful comparison of existing clinical trials with data from other sources, such as insurance claims or medical records, may help determine whether the adverse events are disproportionately associated with the drug, or whether the rate of adverse incidents observed is similar to what would be expected without the treatment.

Biostatistics techniques such as meta-analyses can be helpful in assessing an alleged causal connection between a particular drug and an adverse event. These analyses can be complex, particularly when data are incomplete because patients drop out of clinical trials prematurely; this so-called “dropout effect” may introduce biases that require specific biostatistical correction methods.

## *Securities Fraud/10b-5 Issues*

In instances in which unexpected drug efficacy or safety outcomes are revealed — for example, an increased risk of death, or the lack of clinically meaningful improvements in patients — biostatistical analyses can help triers of fact determine whether clinical trials known to the company demonstrated these outcomes and should have been released earlier, whether the published clinical trials results were presented accurately given all the statistical evidence and whether declines in the stock price of a drug- or device-at-issue would have occurred had additional clinical evidence of safety issues been disclosed earlier or differently.

Consider a recent case involving plaintiffs’ claims that false and misleading statements had been made about the safety of a drug, which had artificially inflated the stock price. Biostatistical tools were applied, and a review of all the clinical evidence demonstrated that while a few studies suggested elevated risk associated with the drug-at-issue, the larger body of literature indicated none; those few studies did not constitute meaningful signals of risk associated with the drug. Therefore, no disclosure should have been expected from the company.

## **Some Best Practices**

As these examples suggest, there is no singular approach to applying biostatistical analyses in the context of litigation. However, there are certain best practices that attorneys and triers of fact may want to use when reviewing biostatistics data and results and bringing them into the courtroom.

Do not take all published work as gospel. The results of clinical trials based on biostatistical analyses are often published in peer-reviewed journals thereby guaranteeing some measure of quality control.

However, publication is not an absolute assurance of quality, particularly when the statistical applications are complex. When we are provided with data from published articles, we sometimes find that the results are sensitive to the researchers’ methodological choices, and, on occasion, we have found computational or methodological errors that went undetected by referees.

Thus, a careful review of the biostatistical methods and results from published works can shed new light on claims of efficacy or safety. Published articles may provide support for legal action and can demonstrate previously uncovered safety or efficacy concerns. However, a review of the methods and data in published articles can also prove valuable in alleviating these very safety or efficacy concerns.

Be wary of the Monday morning quarterback. Suppose that in a given year, clinical trials are conducted for 100 different drugs, and that the associated publications report on potential safety concerns. By chance alone, five of the articles are likely to report statistically significant ( $p < .05$ ) safety concerns about the particular drug examined even if all the drugs are perfectly safe.

After the fact, plaintiffs may review these 100 results, focus on the five that suggest safety issues, and inquire further about the safety of these five drugs. Such inquiry will undoubtedly reveal further adverse events as it would for any drug, whether safe or not.

Therefore, the findings may be because the drugs are associated with true safety signals or because adverse events occur routinely to patients because of their medical condition, whether the drugs they take are safe or not. In at least some circumstances, then, the perceived elevation of risk after the fact may prompt plaintiffs to file suit even if there is no unusual safety risk.

In all instances, a careful review of all the evidence will help confirm whether findings of elevated risk are real or just statistical artifacts with no implication for the underlying population of patients being treated.

Watch out for the needle in the haystack. Many 10b-5 securities matters involving pharmaceutical companies start with the following core question: "Why wasn't this problem disclosed by management earlier?" Pharmacovigilance departments at pharmaceutical companies manage "portfolios" of drugs and receive reports about their drugs' safety from a number of channels, including the U.S. Food and Drug Administration's MedWatch adverse events system, directly from medical professionals and through their sales forces or clinical-affairs department.

Drug companies then must review all these potential safety signals and attempt to distinguish routine patterns from unusual ones — an exercise akin to identifying the proverbial needle in the haystack. In hindsight, tell-tale signs of unusual patterns (the needle) can become obvious; in real time, however, the early warning signs are often invisible when considered as part of the flood of information received.

Biostatistics can be used to analyze the data as it was available to the company at the relevant point in time and determine whether a potential safety signal could have been identified and disclosed earlier.

## **Conclusion**

Statistics in general, and biostatistics in particular, are rarely the subject of dinner conversation. That is because the field of biostatistics is complicated, the language used obscure and the mathematics forbidding.

However, biostatistics is only the application of mathematics to concepts that should be quite intuitive. For example, all else being equal, larger patient samples allow for more inferences than smaller ones, large differences in patient outcomes are easier to detect than small ones and events that are repeatedly observed are more likely to be true than those that are rarely observed or reported.

To successfully use biostatistical data in the courtroom, litigators and experts must use clear, simple, jargon-free language to help jurors and judges make the connections between mathematical analyses, statistical findings, and the intuition and common sense of the triers of fact.

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