Statistical Practices of Safety Monitoring: An Industry Survey

Michael W. Colopy, PhD¹ , Robert Gordon, MS²,
Faiz Ahmad, MPhil, MS³, William W. Wang, PhD⁴,
Susan P. Duke, MS⁵, and Greg Ball, PhD⁴

Abstract

The Biopharmaceutical Section of the American Statistical Association (ASA) formed a Safety Monitoring Working Group to strengthen collaborations between biostatisticians and safety scientists. The task began by surveying current needs and practices regarding available statistical safety tools and methods, regulatory guidance, and processes needed to support their implementation. The goal is for biostatisticians to become fully engaged safety team members by having the necessary safety skill set including appropriate methodology, regulatory guidance and access to appropriate tools. In this publication, we will discuss our survey results that reveal current practices at 22 pharmaceutical companies and demonstrate how the survey instrument can be used to map an action plan for meeting the demand for improved quantitative safety monitoring.

Keywords

safety monitoring, regulatory guidance, interviews, survey, biostatistician

Motivation

For the safety for our patients, as well as for regulatory compliance, improved safety monitoring is becoming increasingly important. The 2010 FDA Investigational New Drug (IND) Safety Reporting Final Rule,¹ the 2012 final guidance,² and the 2015 draft guidance³ state that sponsors should notify the agency and participating investigators of only those adverse events where “there is a reasonable possibility that the drug caused the adverse event.” Within the 2012 guidance the agency offers numerous examples, suggesting a causal relationship and references 21 CFR 312.32 (c)(1)(i) for more details. This effort is intended to minimize uninformative reports and “noise” in the data, which has the possibility of masking safety signals. Compliance with this guidance would require a collaborative approach between safety scientists and biostatisticians to establish a quantitative framework to measure the true safety signals. Biostatisticians need to help their drug safety department move from submitting all safety reports to only those where there is a reasonable possibility that the drug caused the event. Working as a team to conduct earlier aggregated analyses and minimize the submission of uninformative and uninterpretable reports would be a valuable contribution by biostatisticians.

For late-stage biostatisticians, this may require a paradigm shift in thinking from formally testing drug efficacy to exploring drug safety. An evolving set of analyses are needed to fully characterize the safety profile of the product (ongoing aggregate safety evaluation) and help prepare for safety assessments presented in safety-related documents (scientific

evaluation of safety data). Decision making based on accumulating evidence and clinical judgment is different for unplanned safety events than decision rules for primary efficacy endpoints. In response, the Biopharmaceutical Section of the American Statistical Association (ASA) formed a working group to identify opportunities for biostatisticians to work with their fellow safety scientists.

Background

To gauge current use of the safety monitoring toolset in clinical trials, the working group conducted a survey in 2016 (see Supplemental Appendix). The group first drafted a 40-question survey and administered it to 14 companies represented by the group. After reviewing the results, the open-ended questions

¹ Statistical Sciences & Innovation, UCB BioSciences Inc, Research Triangle Park, NC, USA

² Statistics and Decision Sciences, Janssen Research & Development LLC, Spring House, PA, USA

³ US Biostatistics, Galderma R&D, Fort Worth, TX, USA

⁴ Biostatistics and Research Decision Sciences, Merck Research Laboratories, North Wales, PA, USA

⁵ Department of Statistics, AbbVie, North Chicago, IL, USA

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Corresponding Author:

Michael W. Colopy, PhD, Statistical Sciences & Innovation, UCB BioSciences, PO Box 110167, Research Triangle Park, NC 27709, USA.

Email: michael.colopy@ucb.com

Table 1. Company Description.

	Percentage
No. of employees	
Very small (<1k)	4
Small (<10k)	17
Medium (<50k)	33
Large (<100k)	21
Very large ($\geq 100k$)	25
No. of clinical trial biostatisticians	
1-9	4
10-19	4
20-49	17
50-99	31
≥ 100	44
No. of safety biostatisticians	
0	50
1	13
2	0
3-5	8
6-9	13
≥ 10	16

Table 2. How Do Biostatisticians Support the Safety Management Team?

Level of Support	Percentage of Responses
1. No support	5
2. Document reviewer	64
3. Internal statistical consultant	64
4. Collaborator	68
5. Core team member	50

were changed to multiple-choice questions, and the survey was reduced to 17 well-focused questions that were easier to summarize and interpret. Biostatisticians paired with clinical safety scientists representing 30 biopharmaceutical companies were invited to participate, of which 22 (73%) responded. To protect the anonymity, the company name and responder(s) name were not collected.

The participating companies ranged in size from less than 1000 to over 100,000 employees and covered all therapeutic areas surveyed. The number of biostatisticians ranged from less than 10 to over 100 per company. Although only 2 of the larger companies had a separate safety statistics group, half of all companies had 1 or more biostatisticians dedicated to safety statistics (Table 1).

While biostatisticians serve as document reviewers, consultants, and collaborators to their safety management team, only half of the companies responded that biostatisticians serve as core safety team members (Table 2).

To recommend how statistical groups can play a more meaningful and collaborative role in monitoring drug safety, we focused on 3 key areas of our survey: scientific engagement, visual and analytic tools, and effective processes.

Cross-Disciplinary Scientific Engagement

Safety physicians often conduct qualitative reviews of case reports, looking at individual or small clusters of events. This has required little or no statistical input. With the increasing emphasis on aggregate reviews of safety data, biostatisticians need to help cross-disciplinary safety management teams to think more quantitatively. The type of statistical support will depend on the type of analyses required and who is currently conducting the analyses.

As shown in Table 3, clinical trial biostatisticians heavily contribute in most aspects of safety analysis except analysis of unblinded data from ongoing trials and spontaneous events. As expected, independent biostatisticians analyze unblinded data from ongoing trials for their data-monitoring committees, while trial biostatisticians analyze unblinded data at the end of trials.

Recent advances in safety signal detection methodologies and new guidance requirements provide an opportunity for biostatisticians to aid safety scientists' clinical judgement with quantitative evidence for both ongoing trials and spontaneous reports. Screening blinded data provides an opportunity for biostatisticians to collaborate with their safety scientists in selecting safety topics of interest, background rates and critical values, as well as confidence intervals in a Frequentist framework or probability thresholds in a Bayesian framework. These procedures for detecting safety signals are not decision rules but rather provide an objective trigger for safety scientists to fully assess a safety endpoint.¹⁵

Another opportunity for biostatisticians is to support benefit-risk assessment, which places safety events in context with the drug's benefits, using qualitative, semi-quantitative and quantitative methods.¹⁰ Given that a safe drug is not one without risks, but rather one where the benefits outweigh the risks, biostatisticians need to collaborate with a multidisciplinary team to weigh the trade-offs.

Given the different safety analysis as presented in Table 3, a Bayesian decision approach may prove valuable at key decision points. Goodman used the example of the multidisciplinary FDA advisory panel's discussion of the cardiovascular drug carvedilol. The medical discussion turned from supporting evidence to the interpretation of p-values. Goodman states "the most important contribution of Bayesian methods is the way in which they affect both who participates in a scientific dialogue, and what is discussed. With the emphasis moved from "error rates" to evidence, content experts have an opportunity for their input to be meaningfully incorporated, making it easier for regulatory decisions to be made correctly."²²

Another opportunity is for biostatisticians to collaborate on Program Safety Analysis Plans (PSAPs) proposed by Crowe et al, as well as periodic meta-analyses using the CIOMS's Working Group X guidance.^{8,14} Safety evaluation is a continuum of monitoring, analyzing, and reporting accumulating data, so a plan is essential.²³ Meta-analyses of accumulating

Table 3. Who Performs the Various Safety Analyses?

Type of Analysis	Trial Biostatistician, %	Independent Biostatistician, %	Safety Statistics Group, %	Drug Safety Scientist, %	Epidemiologist, %	References
Unblinded data at end of studies	100	32	11	32	0	4
Integrated safety summary	95	21	11	26	0	5-7
Investigator brochure	95	16	11	37	11	1
Meta-analysis of completed studies	83	17	17	22	0	8, 9
IND submission	79	5	5	47	5	2, 3
Benefit-risk assessment	78	11	22	61	39	2, 6, 7, 9-13
Program Safety Analysis Plan (PSAP)	71	6	18	35	6	14
Blinded treatment data of ongoing trials	67	39	22	44	0	15, 16
Unblinded data of ongoing trials	21	74	5	26	0	3, 17, 18
Analysis of spontaneous reports	6	6	11	100	11	19-21

Abbreviation: IND, Investigational New Drug.

Table 4. Who Characterizes Background Rates and What Data Sources Are Used?

Data Source	Biostatistician, %	Epidemiologist, %	Safety Scientist, %	Clinical Scientist, %	No One, %	References
Pooled analysis of clinical data	89	17	39	39	0	3, 4
Meta-analysis of aggregated data	88	24	29	47	6	8, 9
Prior elicitation methodology	53	13	7	20	47	25, 26
Vital statistics	31	50	13	25	13	
Literature review	29	59	76	71	0	
Public health databases	24	71	29	24	6	27

data can be used at any time before and after drug approval, for example, in the Integrated Summary of Safety in an NDA or in the Post Marketing Benefit-Risk Evaluation Reports. Given the methodology is quickly evolving, a meta-analysis group of safety scientists, biostatisticians, epidemiologists, and clinicians may be required.

Our survey results indicate that the area least covered by industry biostatisticians is analysis of spontaneous reports. As the statistical separation between pre- and post-approval monitoring diminishes, we will view spontaneous reports not as inferior to trial reports but as having greater uncertainties we must address.¹⁹

In preparation for working with safety scientists, it is important to use the same safety terminology, which can have subtle differences regarding degree of drug association. CIOMS VI provides a list of terms that define “signal” and distinguish between causality gradients “probably,” “possibly,” and “likely.”²⁴

Another opportunity for cross-disciplinary scientific engagement is selecting a treatment comparator or event background rate to put the safety signal into context. Most safety scientists surveyed use background rates found in the literature and provided by key opinion leaders, while biostatisticians use pooled data sources and meta-analysis to estimate rates (Table 4). Biostatisticians also use prior elicitation techniques to estimate background rates, whereby they aggregate multiple opinions into a prior distribution and conduct a Bayesian decision analysis.²⁵ This technique is an application of combining

medical judgment and quantitative analysis, particularly useful in early-phase studies where data are scarce.

Visual and Analytic Tools

The attention given to developing and implementing methods for safety analysis is slowly catching up to that given to efficacy analysis.²³ Yet, many companies have not instituted Program Safety Analysis Plans (PSAPs) and may be unaware of current safety methodologies available in the literature. Now our industry faces the pressure of establishing causality between interventions and adverse events, reducing the volume of less meaningful serious adverse events (SAEs) reporting, and identifying subgroups for risk mitigation and precision medicine. Our survey questions help ascertain what methods are useful in setting and identifying resource priorities.

Survey responses indicate a strong interest to advance in benefit-risk assessment and visualization (Table 5). Benefit-risk methods combine quantitative assessment and clinical judgment to play a role in transparent decision making, and certain methods can be used to determine maximum acceptable risk (as opposed to maximum tolerable risk).⁴⁹ Recent regulatory guidance has provided a decision framework but leaves it to biostatisticians, safety scientists, and regulatory professionals to figure out best implementation practices.^{11,50}

Visualization tools have advanced dramatically since the 2008 article “Graphical Approaches to the Analysis of Safety Data From Clinical Trials.”²⁹ Where static graphs have

Table 5. Importance to Advance in the Following Areas During the Clinical Development Phases.

Topic	No Importance, %	Low, %	Medium, %	High, %	References
Benefit-risk assessment	5	5	11	79	10
Graphical displays / data visualization	5	21	21	53	28-32
Ways of communicating risk	5	16	32	47	33
Handling rare events	5	5	42	47	34, 35
Criteria for handling early or rare safety signals	5	5	42	47	35-37
Predictive modeling	12	18	29	41	38
Exploring electronic health care databases	17	11	39	33	39, 40
Treatment discontinuation	5	11	50	33	36, 41
Standards for safety biomarker validation	11	33	28	28	
Bayesian approaches, including prior probabilities	16	21	42	21	42-46
Text mining of unstructured data	28	44	22	6	47, 48

Table 6. Use Static and Interactive Graphical Tools for Safety Monitoring.

Application	Static Displays (Reporting), %	Interactive Graphics (Data Exploration), %	Both, %	Neither, %
Patient-level graphs (patient profiles, rare events, outliers)	26	0	68	5
Group and subgroup level (placebo background rates, high-risk patients)	17	0	67	17
Program level (data exploration, meta-analysis)	26	0	58	16
Study Level (quality control, lab values, ECG, AEs, vital signs)	37	0	58	5
Mega-study level (high density plots)	21	0	47	32
Benefit-risk (value trees, forest plots, utilities)	37	0	26	37
Regulatory review	58	0	26	16
Data monitoring committees	63	0	26	11

Abbreviations: AEs, adverse events; ECG, electrocardiogram.

Table 7. What Companies Gear Their Statistical Methods for Safety Data Toward.

	Former, %	Latter, %	Both, %
Blinded vs unblinded data	5	21	74
Study-level vs product-level analysis	21	5	74
Patient profiles vs summary statistics	0	32	68
Individual vs aggregated studies	11	21	68
Tabular vs graphical displays	42	5	53
Predictive vs statistical modeling	11	39	50
Descriptive vs inferential statistics	63	0	37
Qualitative vs quantitative benefit-risk assessment	58	11	32
Frequentists vs Bayesian approaches	79	0	21

traditionally been used for reporting and publications, interactive visualization is now being used for exploring and monitoring safety data in near real time.⁵¹ Our survey indicated a wide incorporation of interactive visualization across numerous applications (Table 6). While new point-and-click software has made visualization easier, biostatisticians are still needed to aid in the design of appropriate visualizations and make results unbiased and generalizable. At the very least, biostatisticians, who comprehend probability and uncertainty, can help to effectively communicate risk.⁵² One surprising but not unexpected result concerning the importance of advancement

Table 8. Current Formal Operational Process for Safety Monitoring.

Topic	Yes, %	No, But Planned, %	No, %	References
Data monitoring committees	94	6	0	54, 55
Blinded analysis of ongoing trials	88	6	6	15
Unblinded analyses of ongoing trials	78	0	22	17
Causality determination	74	13	13	36, 56
Benefit-risk assessment	70	24	6	11
Program Safety Analysis Plan (PSAP)	64	12	24	14, 36
Interactive graphics	52	24	24	51
Meta-analyses of completed studies	44	12	44	8

was the weak interest in Bayesian approaches. This may reflect the past focus on generating safety summary tables at the end of a study. Looking toward the future with aggregating accumulating data, Bayesian approaches can be used to incorporate multiple sources of data and clinical judgment into an analysis. Bayesian posterior probabilities of rare events based on prior beliefs are more informative than Frequentist *P* values and confidence intervals.

Per Table 7, most companies rely on traditional methods for descriptive statistics, and frequentist approaches. Descriptive

Table 9. Regulations, Guidance, and Reports That Influence the Quantitative Group's Operations and Deliverables.

Document	Year	Percentage of Responders	References
FDA IND Safety Reporting Requirements for Human Drug and Biological Products and Safety Reporting Requirements for Bioavailability and Bioequivalence Studies in Humans—Final Rule	2010	89	2, 56
FDA Safety Reporting Requirements for INDs and BA/BE Studies	2012	89	1
FDA Establishment and Operation of Clinical Trial Data Monitoring Committees	2006	84	54
FDA Safety Assessment for Investigational New Drug Application Safety Reporting	2015	84	3
CIOMS VII: Development Safety Update Report (DSUR) Harmonizing the Format and Management of Safety Information from Clinical Trials	2005	84	7
ICH Development of Safety Update Report	2010	79	7, 57
ICH E2B Maintenance of the ICH Guideline on Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports	2001	74	58
ICH E2E Pharmacovigilance Planning	2004	74	59
ICH E2A Clinical Safety Data Management: Definitions and Standards for Expedited Reporting	1994	68	60
ICH E2C (R2) Periodic Benefit-Risk Evaluation Report (PBRER)	2012	68	13
EMA Guideline on Good Pharmacovigilance Practices Module IX—Signal Management	2012	68	61
CIOMS VI: Management of Safety Information from Clinical Trials	2005	68	24
EMA Guideline on the Use of Statistical Signal Detection Methods in the EudraVigilance Data Analysis System	2008	63	62
FDA Determining the Extent of Safety Data Collection Needed in Late-Stage Premarket and Post Approval Clinical Investigations	2016	58	63
PhARMA Safety Planning, Data Collection, Evaluation and Reporting (SPERT) Recommendations	2009	58	37
EMA Concept paper on the need to revise the “Guideline on the Evaluation of Anticancer Medicinal Products in Man” in order to provide guidance on the reporting of safety data from clinical trials	2015	53	64
EMA Concept paper on extrapolation of efficacy and safety in medicine development	2013	53	65
Other (FDA DILI Guidance, ICH-E14, Local country guidance, etc.)	2009, 2005	16	36, 66

Abbreviations: CIOMS, Council for International Organizations of Medical Sciences; ICH, International Conference on Harmonization; IND, Investigational New Drug.

statistics might have their place with adverse events that are too infrequent for meaningful hypothesis tests or too numerous for controlling Type I error rates.²³ Use of Bayesian approaches is clearly lagging behind Frequentist approaches. Two areas where Bayesian methods may be advantageous are Bayesian decision making and dynamic monitoring⁴⁶ and safety signal detection.⁵³ Biostatisticians can enhance safety monitoring by estimating priors, updating their model parameters as data accrues, and setting signal thresholds for their posterior probabilities.

Effective and Efficient Operational Process

Biostatisticians typically have processes in place for Data Monitoring Committees and analyses of ongoing trials (blinded or unblinded), but there are opportunities for meta-analysis of completed studies, interactive graphics and Program Safety Analysis Plans (see Table 8). A process for meta-analysis appears to be particularly overlooked but can be guided by the CIOMS X guidance released in December 2016. As expected, processes around newer topics such as interactive graphics and PSAPs are slower to evolve.

A company's operations and deliverables are influenced greatly by the regulatory documents listed in Table 9. A challenge to biostatisticians is implementing the FDA safety reporting requirements known as the Final Rule. To clarify the Final

Rule, the 2012 final guidance requires sponsors to systematically evaluate accumulating aggregated safety data. Rather than submit every serious adverse event occurring during an active clinical trial, the sponsor needs to determine reasonable possibility of an association with study drug. In December 2015, more detail was provided requiring that sponsors periodically review accumulating safety data integrated across multiple studies both completed and ongoing and provide a quantitative framework for measuring the evidence of an association between events and study drug. Ball provided a framework for early warning and early stopping of ongoing blinded clinical trials, though it requires biostatisticians and safety scientists to collaborate on designing safety screens with good operating characteristics.¹⁵ The FDA also recommended broad and frequent unblinding of serious adverse events by a Safety Assessment Committee with analyses prespecified and documented in a Safety Surveillance Plan. The challenge to biostatisticians is how to implement the FDA safety reporting requirements as seamlessly as possible into existing operational activities considering traditional issues such as maintaining blinding and sequestering data.

A biostatistician pursuing safety statistics needs to be familiar with the various regulatory reporting requirements, such as the individual IND safety reports and aggregated PSUR/PBRER/DSUR.^{7,13,57} The DSUR (E2F Development Safety Update Report) covers premarketed drugs, while the PSUR

(E2C Periodic Safety Update Reports) covers marketed drugs. In 2016 the FDA replaced the PSUR with the PBRER (E2C (R2) Periodic Benefit-Risk Evaluation Report. The PBRER includes benefit as well as safety. For a complete picture of IND reporting, the second and fourth guidance below are good places for biostatisticians to start reading. The fourth guidance recommends having a systematic approach to safety surveillance, including a safety surveillance plan and a safety assessment committee.

Two other informative CIOMS reports not listed in the table above are (a) CIOMS IV: Benefit-Risk Balance for Marketed Drugs: Evaluating Safety Signals¹² and (b) CIOMS X: “Considerations for applying good meta-analysis practices to clinical safety data within the biopharmaceutical regulatory process.”⁸

Discussion

It is for each company to determine its level of engagement between biostatisticians and safety scientists. Given recent regulations, biostatisticians can significantly contribute to the increased focus on safety during drug development through their inherent skills and expertise understanding and analyzing data. Using the survey above, each company can see how it compares to other companies, and know other companies are advancing in Bayesian approaches, benefit-risk, visualization, etc. The survey can also be used to set priorities for developing expertise, tools, and processes. Recommendations have been given for getting started on the topics most needing to be addressed. By reading the referenced materials, biostatisticians new to the world of drug safety will learn the terminology and issues through the eyes of safety scientists and experts. The next step will be applying existing methods appropriately and developing new methods to use on new types of data. Unlike confirmatory phase 3 efficacy trials, the safety biostatistician will be exploring the data with analytic and visualization tools and using signal detection, meta-analysis, and Bayesian decision analysis on events with uncertain associations, that is, what biostatisticians do best!

Summary

The Safety Monitoring Working Group representing the Biopharmaceutical Section of the American Statistical Association is providing a development opportunity for its biostatisticians to help safety scientists use quantitative methods to aid their medical judgment and play an important role in ensuring the safety of our patients. We acknowledge that our expertise in well-planned, well-powered efficacy analysis and descriptive safety tables might not always be applicable to safety analysis. However, we believe we have the expertise and skill sets not fully utilized in current safety assessment processes. The working group hopes statisticians will begin with our recommendations based on survey results, so they can better take advantage of more detailed, actionable materials in 2018-2019.

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ORCID iD

Michael W. Colopy, PhD <https://orcid.org/0000-0002-1806-8818>

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