ASA Biopharm's Safety Monitoring Working Group:
Survey of statisticians, thought leaders and regulatory guidance

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Abstract

The ASA Biopharm Safety Monitoring Working Group reviewed safety monitoring regulation, interviewed industry leaders and surveyed statisticians on current safety monitoring practices. In this report, we will give a high level overview of the safety regulatory landscape, summarize the thought leader interview into 4-pillars of safety statistics and provide a preliminary preview on the recent industry survey.

Key Words: safety monitoring, regulatory guidance, interviews, survey.

1. Introduction

An industry wide safety monitoring working group was established in 2015 by the Biopharmaceutical section of the American Statistical Association (ASA). It is a sub-group under the larger ASA safety working group. Some factors driving the development of this working group were the numerous regulations for ongoing safety monitoring across the globe and the conventional lack of attention on statistical methodology for safety monitoring. The ASA Safety Monitoring Working Group is addressing the issue of whether current safety monitoring practices are keeping pace with regulatory guidance and statistical methodology. Our mission and goal are to help develop a stronger biostatistics community for improved safety monitoring, risk management and communication empowering the community to play a more proactive role and better enable high quality quantification in safety monitoring.

To achieve this goal, the Working Group has the following key objectives:

- Evaluate quantitative tools, methods and processes for safety monitoring during clinical development
- Review and understand existing literature, methodology, regulatory guidance and current practices
- Engage the broader clinical, statistical, safety and regulatory communities to understand current approaches, practices and concerns
- Develop general recommendations and best practices
- Educate the broader statistical community

The ASA Safety Monitoring Working Group consists of two workstreams (WS1 and WS2) with the following initial goals: WS1, review safety regulations, interview thought

leaders and survey industry; WS2, review statistical methodologies used across the spectrum of safety monitoring and reporting.

In addition to these proceedings, during 2016 we have presented at the annual DIA meeting, JSM Biopharmaceutical Section, DIA China Science Forum and will be presenting at the Deming conference in December. Our current work is tailored to collating the data and developing a concise final deliverable of our findings and recommendations to our community in early 2017.

2. Overview of the Safety Monitoring Working Group

The Working Group asked itself,
- What are the roles & opportunities for statisticians supporting safety monitoring?
- How do we collaborate effectively with safety physicians & scientists?
- Are we facing a gap between our current practices and new methods, tools and regulatory guidance?

Our goals, key activities and deliverables for 2015-16 are elucidated in Figure 1. Our working group members, advisors and thought leaders are listed in Figures 2-3.

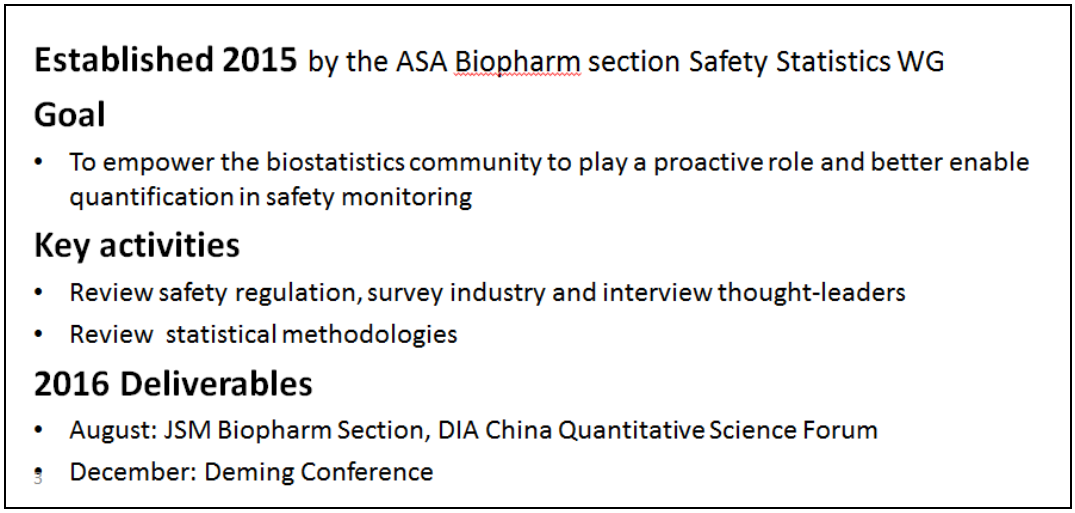

Figure 1: Safety Monitoring WG goals, key activities and deliverables for 2015-16.

Figure 2: Safety Monitoring WG and advisors

Figure 3: Safety Monitoring WG thought leaders

The intent of WS1 is to communicate to our statistical colleagues the goals, regulatory motivation, insights from thought leaders, and insights from a survey initiated before JSM and completed in the weeks afterward. We'll expand on each of the sources of information, beginning with a review of safety regulations.

3. Regulatory Motivation

3.1 CIOMS Working Group on Safety

CIOMS (Council for International Organization of Medical Sciences) is an international, non-governmental, non-profit organization established by WHO (World Health Organization), headquartered in Geneva Switzerland[1]. It is not a regulatory agency but its recommendations have been adopted by ICH (International Conference on Harmonization), FDA (Food and Drug Administration), and EMA (European Medicines

Association). Over the last 20 plus years, it has had 10 working groups, each producing reports available on its website (Figure 4).

CIOMS WG	Descriptions	Resulting Regulatory Guidance
I	International Reporting of Adverse Drug Reactions (1990)	ICH E2A
II	International Reporting of Periodic Drug-Safety Update Summaries (1992)	ICH E2C
III	Guidelines for Preparing Core Clinical-Safety Information on Drugs (1999)	
IV	Benefit-Risk Balance for Marketed Drugs: Evaluating Safety Signals (1998)	ICH E2C R2 (PBRER)
V	Current Challenges in Pharmacovigilance: Pragmatic Approaches (2001)	
VI	Management of Safety Information from Clinical Trials (2005)	IND Reporting Rule
VII	Development Safety Update Report (DSUR) (2006)	ICH E2F
VIII	CIOMS Working Group on Signal Detection (2006)	GVP Module IX
IX	Practical Approaches to Risk Minimisation for Medicinal Products (2010)	
X	Considerations for applying good meta-analysis practices to clinical safety data within the biopharmaceutical regulatory process (In press)	

Figure 4: The ten CIOMS Working Groups on Safety.

CIOMS was very early on the scene for standardizing terminology, coding and reporting. It has one of the first documents for balancing benefits and risks, which influenced the PBRER (Periodic Benefit-Risk Evaluation Report). CIOMS VI is of primary interest because it is the earliest description of ongoing safety monitoring process in clinical trials. Pharmacovigilance has traditionally focused on post-marketing signal detection and evaluation; however, CIOMS VI recognized the need to move aggregate reviews of safety data earlier in the drug development process.

3.2 CIOMS VI: Close Linkage with Clinical Trial Safety

CIOMS VI received expert input from thought leaders as well as from its own survey results from 24 companies. This CIOMS report covers everything from collection, analysis, and reporting, which is no surprise, its 306 pages! It introduces proposals for enhancing the collection, analysis, evaluation, reporting and overall management of safety information from all safety data sources. It is a shift from the management of post-marketing safety information (spontaneous reports), to the management of clinical trial information.

Of paramount importance is having a systematic approach to managing risk during the entire development phase.

"Although the term "pharmacovigilance" has traditionally been associated with post-marketing activities, the CIOMS VI Working Group recommends that the term be applied to the pre-marketing process for collecting, managing and assessing safety information during development. Likewise, the concepts of risk assessment and risk minimization, components of risk management, are terms that are as applicable to the pre-marketing environment as they are to the post-marketing environment."

3.3 Unique Regional Safety Regulations

The working group is reviewing guidance by CIOMS, ICH, FDA, EMA, Japan and China (Figure 5) with respect to similarities and differences in the statisticians' roles, analysis and reporting. CIOMS and ICH have been remarkably helpful for aligning regulatory guidance across regions for many aspects of safety monitoring; however, important differences remain. The EMA in Europe has the EudraVigilance database for determining whether risks have changed that alter the benefit-risk balance. The PMDA (Pharmaceutical and Medical Devices Agency) in Japan has a unique three pillar system, consisting of safety (post-marketing safety measures for risk mitigation), review (review services for risk reduction) and relief (relief services for adverse health effects). The China Food Drug Administration (CFDA) has minimum sample size requirements for Chinese patients in clinical trials and provisions for nationalized monitoring of adverse drug reactions, including a 2013 draft guidance on intensive post-marketing safety monitoring. In Sep 2010, the US FDA established a final rule for IND safety reporting. In a recent draft guidance (Dec 2015) to guide implementation of the final rule, it further recommended that the IND aggregate safety reports be based on unblinded data, it also recommended that sponsors develop a Safety Assessment Committee and a Safety Surveillance Plan as key elements of a systematic approach to safety surveillance. More details will be available at the December 2016 Deming conference tutorial.

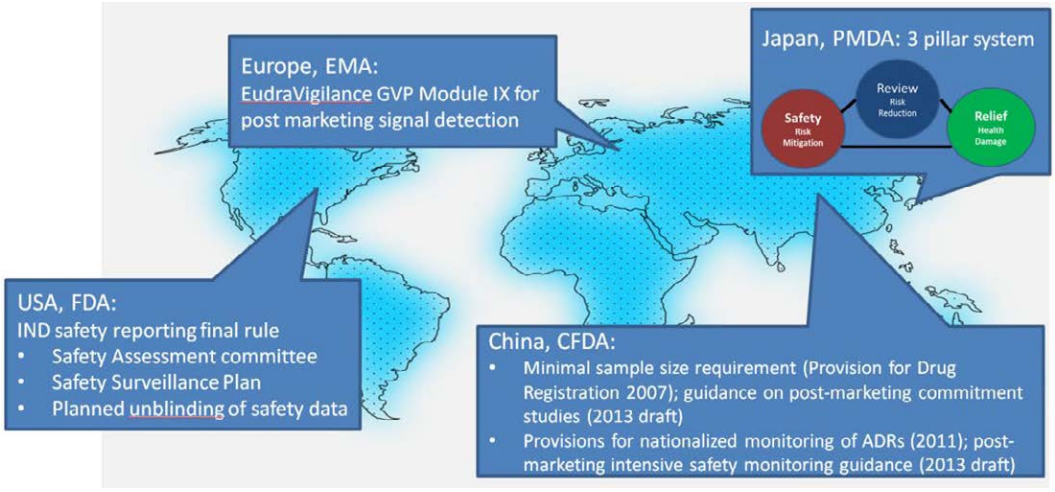

Figure 5: Unique Regional Safety Regulations

4. The Four Pillars of Safety Statistics

We interviewed 18 thought leaders in March - April 2016 (Figure 3). In statistics, we interviewed heads of departments and leaders in safety statistics. In drug safety, we interviewed leaders in several sponsor companies known for their clarity on this important topic and their understanding of the analytics of safety data. From FDA, several from Clinical and Statistics met with us together in a focus group. Each interview was an hour. We would have preferred to interview more thought leaders, but even 18 was a big job! Our conjecture is that their feedback takes us somewhere near the asymptote of the overall landscape.

The majority of their feedback fit into these four categories: scientific engagement, effective operational process, visual and analytic tools, and intelligent data architecture (Figure 6). One of the thought leaders said it well: There is a lack of understanding of information as a science. We rely too much on information from so many sources, which are diverse in their quality and depth. Physicians are trained in clinical science; statisticians are trained in probability, structured thinking, and how to organize information. The adjunct of the statisticians' strengths to those of safety physicians creates an even stronger platform for assessing drug safety.

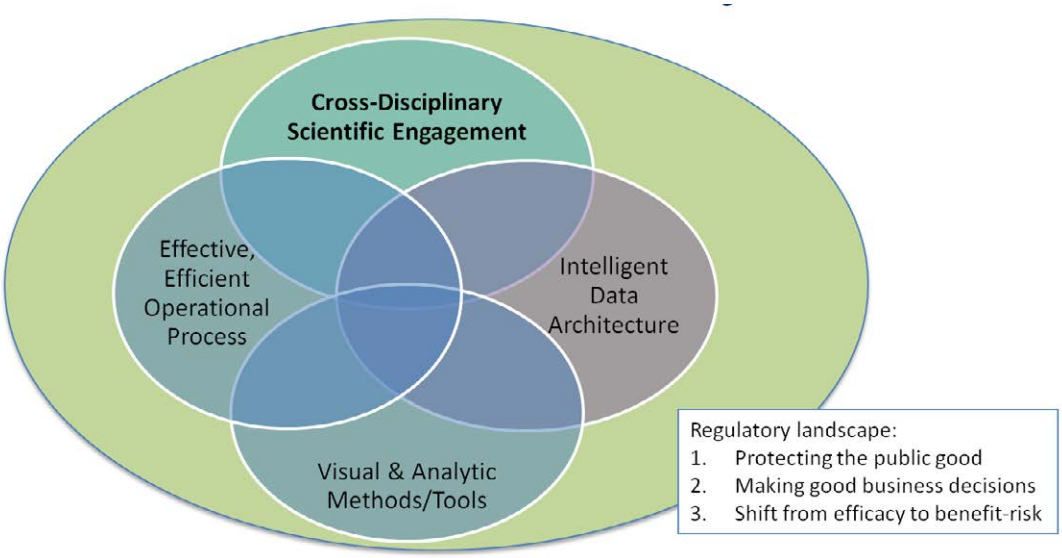

Figure 6: The four pillars of safety statistics, motivated by the underlying regulatory landscape

4.1 Cross-Disciplinary Scientific Engagement

In 2010 the US instituted the Investigational New Drug (IND) Safety Reporting Final Rule[3], compelling drug manufacturers to submit to the FDA only those adverse events they deemed to be drug related. This law and two associated guidance documents have encouraged the evolution of pharmaceutical companies' drug safety departments from process-oriented (sending all safety reports to regulators) toward ever more quantification, with the sponsor expected to assess drug relatedness. From the FDA website,[3]

"This final rule is expected to improve the quality of safety reports submitted to FDA, thereby enhancing the safety of patients in clinical trials. The final rule lays out clear definitions and standards so that critical safety information about investigational new drugs will be accurately and rapidly reported to the agency, minimizing uninformative reports and enhancing reporting of meaningful, interpretable information."

The first guidance, finalized in December 2012, clarified what was meant by "reasonable possibility" for submitting expedited reports and the requirement that sponsors should have in place a systematic approach for evaluating the accumulating safety data. The FDA has been flooded with so many reports creating increased noise in the data that they have difficulty identifying true signals. By attempting to shift more of the burden to the sponsors for making judgments about serious adverse events, the first guidance aimed to reduce the number of individual reports. Although there has been slow uptake by some, those who have implemented have seen reductions in reporting as great as 90%. In addition to reducing the burden on FDA, companies who have implemented may also be gaining a more in-depth knowledge of the safety of their medicines too.

The success of the first guidance highlighted a gap that had been obscured before, events that require an aggregate analysis to determine reasonable possibility of an association with study drug. For example, in a large cardiovascular outcomes trial with thousands of patients and an anticipated event with a background rate of 5%, there could be hundreds of cases. This would be overwhelming to analyze on a case by case basis. The FDA published a second guidance (still draft) in December 2015. This draft is more prescriptive on what is needed, 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. They are also recommending broad and frequent unblinding of serious adverse events by a Safety Assessment Committee with analyses pre-specified and documented in a Safety Surveillance Plan. The emphasis is on a quantitative framework, not a statistical test, which helps a multi-disciplinary safety management team make a judgment about the need for an IND safety report. This is certainly a challenge, but also an opportunity. The FDA is ahead of other regions in regards to having a systematic approach for safety monitoring during clinical development and they are providing an opportunity for sponsors to partner with them to focus on important safety issues.

Safety is the new efficacy (see Figure 7). This is a direct quote from one of our thought leaders; however, each of them made similar assertions. This has two key meanings. First of all, safety is important; it's a public health issue. But also, safety is no longer just pharmacovigilance and spontaneous reports. It requires experienced statisticians to interact with other disciplines and do this with a safety mindset. Statistics in the past was focused on efficacy, which is different than safety. Efficacy is more about testing and confirming. Safety is more exploratory. Safety statisticians need to have a safety mindset for learning and decision making.

Safety physicians have relied a lot on qualitative analyses of case reports, looking at individual or small clusters of events. There has been an increased emphasis on aggregate reviews of safety data. This requires statisticians to increase their engagement and help cross-disciplinary safety management teams to think more quantitatively. Siloed discussions of the past are not in the patients' best interest. We statisticians need to be a more active part of the conversation and understand the "why" before jumping in

to answer the "how". A safety mindset can help us develop a set of analyses that allows the whole multi-disciplinary team to understand the aggregate safety profile and, along with medical judgment, to make good decisions.

The scientific engagement between physicians and quantitative scientists – epidemiologists and statisticians – benefits patients because both clinical and quantitative disciplines have different strengths. It is the discussion between physician and statistician as they bring to bear their respective knowledge – this is where deeper insights into the science of the medicine and disease applied to the safety concern at hand begin. As both disciplines understand the low hanging fruit that arises from their respective engagement, we are poised to learn even more about the safety of our medicines.

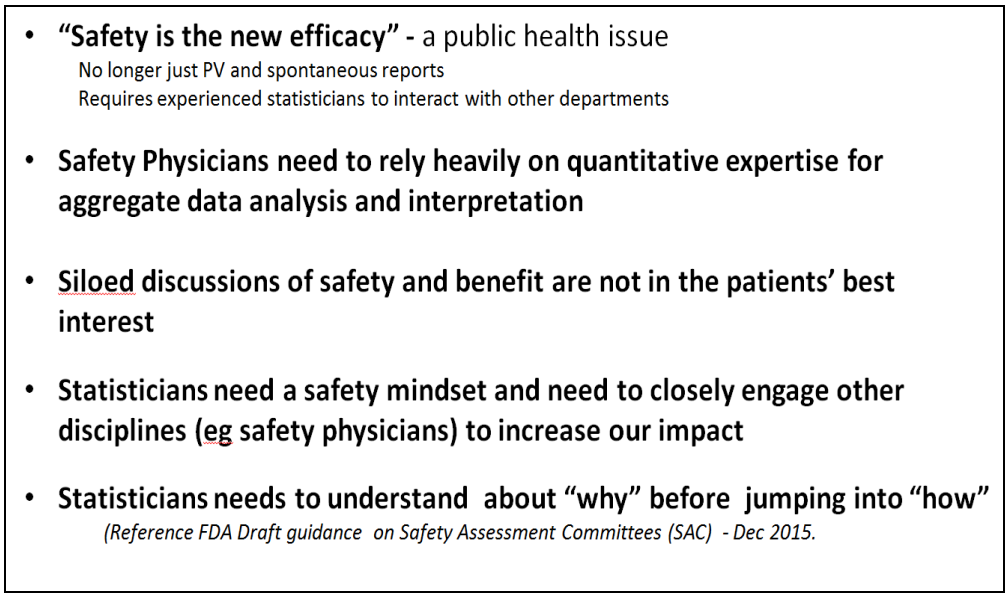

Figure 7: The first pillar: Cross-Disciplinary Scientific Engagement

4.2 Effective, Efficient Operational Process

There has been much discussion by safety physicians and statisticians since the draft guidance, Safety Assessment for IND Safety Reporting Guidance for Industry, was released in December 2015. If anything became clear, based on the amount of discussion and feedback to FDA on this draft, it is that the structured thinking inherent in the discipline of statistics can aid in clarifying the 'ecology' of the flow of clinical data (Figure 8).

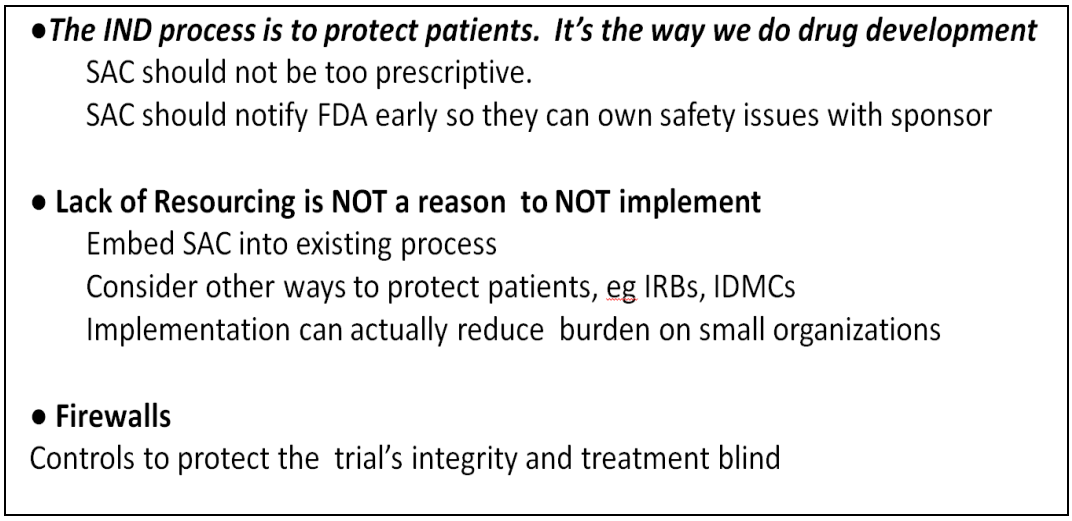

Figure 8: The second pillar: Effective, efficient operational process

Several thought leaders commented on the need for quality training of DMC participants, and by extension training for SAC members too. Some sponsor companies have elected to create safety statistics departments. Such groups (and the ASA Biopharm Safety Statistics WG too) encourage broader and deeper solutions to issues of quantitative safety monitoring.

4.3 Visual and Analytic Methods and Tools

Due to the nature of safety data, where new questions surface throughout the premarketing and post-marketing phases, graphical methods are especially useful for assessment of safety and the benefit-risk balance. This includes both static graphs for dossiers and publications and, more to the point of safety monitoring, interactive visualization tools for the monitoring process itself (Figure 9). Protection of patient safety is the primary goal. Well-designed graphics that clearly and transparently address the safety and/or benefit-risk questions of importance to decision makers are an excellent way to allow the data to speak for themselves.

Our current regulatory landscape demands better methods and tools for safety questions we face: to establish causality between interventions and AEs, to reduce the volume of less meaningful SAE reporting, and to use subgroup analysis for risk mitigation and precision medicine. These were some of the points made by the thought leaders.

In addition to graphics, Bayesian approaches were viewed by most thought leaders as the safety tools of the future. Aggregation of data is the approach that is needed, but the methodology must always incorporate clinical judgment in decision making processes. Thresholds are valuable for developing a quantitative framework, as long as clinical judgment has been used in defining them and interpreting the results.

Trial integrity is important. Blinded reviews during the safety monitoring process deserve more attention. Whether the question is trial integrity or how to analyze ongoing safety monitoring, the thought leaders cautioned we should always keep in mind why we are doing this and what value this brings to public health.

We also learned from thought leaders that safety monitoring and benefit-risk go hand-in-hand. When is a decision of safety monitoring a safety-only decision? It is always in the context of benefits, other available treatment options (and their benefit-risk profiles) and the like.

Bringing together safety information at key stages in a dashboard approach, both pre- and post-marketing is a vision for the future. Data-driven safety monitoring with the addition of key efficacy endpoints enables quantitative benefit-risk analysis across the drug development lifecycle.

On the topic of benefit-risk balance, several thought leaders reminded us to bring patient perspectives into safety and benefit-risk evaluation.

Figure 9: The third pillar: Visual and analytic methods and tools

4.4 Intelligent Data Architecture

Intelligent data architecture is the backbone of safety data 'ecology' and is intertwined with an effective safety process (Figure 10). From toxicology, animal studies and modeling, to clinical trials, to spontaneous and other observational studies in post-marketing, amalgamating data sources is a challenge in assessment of safety that is not found in the more controlled hypothesis testing environment of clinical trials.

Data architecture that integrates disparate sources of data together accommodating controlled access and blinding is now a possibility in the age of CDISC. So much of safety, from adverse events coding to lab measurements, by its nature, is amenable to standardization. Data standardization in a smart architectural data design means dashboards can become reality where, with a lack of data standards, they could not.

Some thought leaders commented on the potential for data quality to improve with use of standards as well, leading to more effective analysis, which leads to benefits in timely safety assessment and subsequent communication.

It's important to do more on the methodology of data quality monitoring. Not all data sources have the same level of quality and reliability. Just as clinical judgment is important, statisticians' judgment of data quality/variability is needed to make quality decisions to protect the public good. One case in point is that regulators around the world assess identical information in different ways. Surely one way must be more ideal than others. Statistical rigor in tandem with clinical judgment will serve the public good better than either discipline alone.

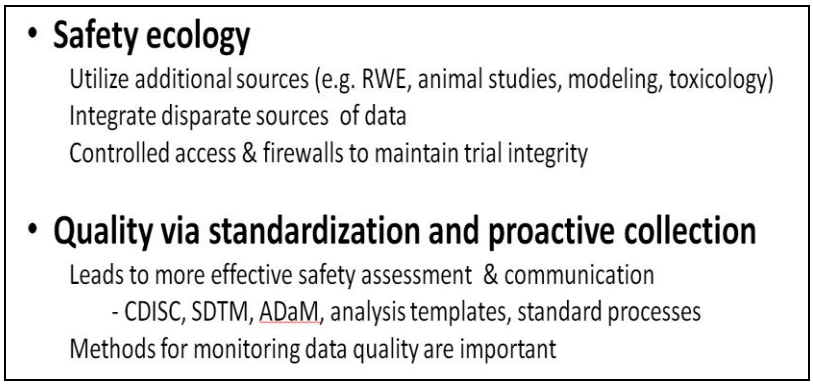

Figure 10: The fourth pillar: Intelligent data architecture

5. Industry Survey of Statisticians and Safety Professionals

After interviewing experts as to what they see as our future, we conducted an online survey of 24 companies as to their current practices. We wanted to see how statisticians are engaged with their drug safety scientists. We asked what formal processes they have in place, and what tools and methods they commonly use. And perhaps most importantly, where do they want to progress? What training will be required?

We surveyed all size companies, from under 1,000 to over 100,000 employees. The survey just recently closed and analyses will be stratified by size of company and size of statistical group (Table 1-2).

No. Employees	No. Companies	% Companies
Very small (<1k)	1	4.17
Small (<10k)	4	16.67
Medium (<50k)	8	33.33
Large (<100k)	5	20.83
Very large (100k+)	6	25.00
	24	100.00

Table 1: Size of Companies by Number of Employees

No. Biostatisticians	No. of Companies	% Companies
1-9	1	4.35
10-19	1	4.35
20-49	4	17.39
50-99	7	30.43
100+	10	43.48
	23	100.00

Table 2: Size of Statistics Departments by Number of Biostatisticians

6. Summary

Our Working Group is endeavoring to empower statisticians to play a more meaningful and collaborative role in monitoring drug safety. Through our in depth interviews, surveys and regulatory guidance reviews, we are identifying areas where current practice may not be keeping pace with the additional quantitative rigor of FDA's IND Reporting Rule. The companion efforts of WS2 have identified methods and tools to address these needs. To close this gap, we recommend four supporting pillars for safety science: scientific engagement, effective processes, intelligent data architecture, and visual and analytic tools.

The group's full report (including survey results) will be released in early 2017.

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References

1. Council for International Organizations in Medical Sciences (CIOMS) publications. http://www.cioms.ch/index.php/publications/available-publications/540/showCategory/62/drug-development-and-use. Accessed on Sep 29, 2016

2. US FDA Final Rule: Investigational New Drug Safety Reporting Requirements for Human Drug and Biological Products and Safety Reporting Requirements for Bioavailability and Bioequivalence Studies in Humans http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm226358.htm Accessed on Sep 29, 2016

3. US FDA Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE Studies (Final) 2012; http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM227351.pdf accessed on Sep 29, 2016

4. US FDA Draft Guidance: Safety Assessment for IND Safety Reporting Guidance for Industry: 2015 http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM477584.pdf , Accessed on Sep 29 2019

5. Ministry of Health and China Food Drug Administration. Adverse Drug Reaction Reporting and Monitoring Provision. May 2011. http://www.sfda.gov.cn/WS01/CL0053/62621.html . Accessed on Sep 29, 2016.

6. China Food Drug Administration, Center for Drug Re-evaluation, Guidance on Key Safety Monitoring Activities. March 2013. http://www.sda.gov.cn/WS01/CL0778/79321.html. Accessed on Sep 29, 2016.