

Practical applications of regulatory requirements for signal detection and communications in pharmacovigilance

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Abstract: Pharmacovigilance is a field where communication is crucial, and exchange of information is expected to be done in a timely manner. Information from individual case reports is transmitted from pharmaceutical industry and health professionals to the regulatory authorities. The safety profile of a drug is established by analyzing individual cases and aggregate reports. The cumulative information, obtained from these reports, can be used to assist pharmacovigilance professionals in the detection of potential safety signals by monitoring evolving trends. If there is a message identifying concern as potential safety signal, the transmission of individual case reports, as well as cumulative and aggregate reports will occur from pharmaceutical industry to the regulators; and based on their assessments of causality in relationship to the drug, the regulatory decisions will be made. Once regulators confirming a signal as a possible safety alert have made the decision, the decisions and the reasons must be communicated to health professionals, the pharmaceutical industry, and other parties involved (e.g. clinical trials participants, investigators, consumers and medical professionals at post-marketing stage, etc.).

Keywords: benefit–risk assessment, communications in pharmacovigilance, signal detection, signal management benefit–risk

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Introduction

Pharmacovigilance is a field in which communication is very crucial, and the exchange of information is expected to be done in a timely manner and in accordance with applicable regulatory requirements.¹ Information from individual case reports is transmitted from pharmaceutical industry and health professionals to the regulatory authorities.

The safety profile of a drug is established by analyzing individual cases and aggregate reports. The cumulative information, obtained from these reports, can be used to assist pharmacovigilance professionals in the detection of potential safety signals by monitoring evolving trends.^{1–3} If there is a message identifying concern for a potential safety signal, the transmission of individual case reports, as well as aggregate reports, will occur

from the pharmaceutical industry to regulators; based on their assessments of causality in relationship to the drug, the regulatory decisions will be made.^{1–3} Once regulators confirming a signal as a possible safety alert have made the conclusion, the decisions and their reasons must be communicated to health professionals, the pharmaceutical industry, and any other parties involved (e.g. clinical trials participants, investigators, consumers, and medical professionals at the postmarketing stage, etc.).

Safety signal detection and management

Pharmacovigilance is a field of science that involves the collection of data on adverse events (AEs), which then must be analyzed and trends evaluated to establish a safety profile of the drug or biologic. Signal detection in this field involves

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looking at the patterns in AEs data that suggest a new, potentially causal association between a drug and an event or a series of related events. Newly detected signals should serve as a trigger for further in-depth investigations.¹ This could be an event that previously has never been suspected as associated with the drug/biologic or a known event, which is now occurring within a patient group for whom it has not been documented before. In addition, it can be a signal occurring with greater frequency or severity than anticipated.¹ The signal may be generated from qualitative analysis of spontaneous reports or quantitative analysis through data mining and statistical assessment.¹

The term ‘signal’ is mostly associated with biomedical products during the postmarketing phase, although it can be used during premarketing phase in clinical trials. The definition of a signal as provided by the Council for International Organizations of Medical Sciences (CIOMS) Working Group VIII is:

‘. . . information that arises from one or multiple sources (including observations and experiments), which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verifactory action’.¹

Signal management is activities performed to determine whether there are newly detected risks associated with a drug, or if known risks have changed and some action is required to reassess the drug safety profile.^{2,3} The signal management process includes the following steps: signal detection, validation, confirmation, analysis, prioritization, evaluation, and recommended actions, tracking of follow-up activities, communication, and risk minimization (Figure 1). All actions taken and recommendations made must be accurately tracked and documented at every stage. There are resulting legal obligations that must be fulfilled by the investigational new drug (IND) sponsor/drug manufacturer in an accurate and timely manner. The main goal is to confirm or collect evidence to disprove whether there is some new issue with the safety of a drug, so that action might then be taken to mitigate the risk.^{2,3}

Signals can be detected from multiple different sources, which include the following: postmarketing

data (e.g. spontaneous reporting, individual case safety reports (ICSRs), aggregate data from active surveillance programs, or active interventional studies (clinical trials), noninterventional studies (e.g. pharmacoepidemiology studies), nonclinical data (e.g. acute and chronic animal toxicology studies), systematic review of the published literature, meta-analyses (e.g. mathematical pooling of all the clinical trial data), or events associated with other products in the same therapeutic class and other relevant sources.¹⁻⁴

Healthcare providers are encouraged to report adverse reactions *via* national spontaneous reporting systems. Consumers and patients may also report adverse reactions *via* voluntarily reporting systems as well as *via* a wide variety of media, including the internet.^{5,6} Relevant information can also be made available from other sources, such as poison control centers.^{5,6} Signals arising from spontaneous reports also could be detected *via* following sources^{4,5}:

1. monitoring large adverse drug reaction databases such as EudraVigilance and the Food and Drug Administration (FDA) AE reporting system;
2. published articles;
3. postmarketing periodic safety update reports (PSURs);
4. ongoing benefit–risk monitoring.^{4,5}

The primary objective of signal detection is to protect patient safety. It is important to emphasize that the goal of signal management is more than just identifying signals; an investigation must be done to determine whether the signal is a safety issue and what should be done about it. Signals can be qualitative or based on spontaneously reported data and case series, or quantitative, which are based on data mining, epidemiologic data, or obtained from ongoing clinical trial data. Signaling detection and management presents many challenges. A high level of alertness and prompt actions are needed once a new signal, possibly related to the drug, is detected.^{3,5-7}

Special considerations in signal detection include: polypharmacy, medication errors, and drug–drug and other interactions, such as cytochrome P450 (CYP) activation or inhibition by drug substances, which is a major source of adverse drug interactions since changes in CYP enzyme activity may affect the metabolism and clearance of

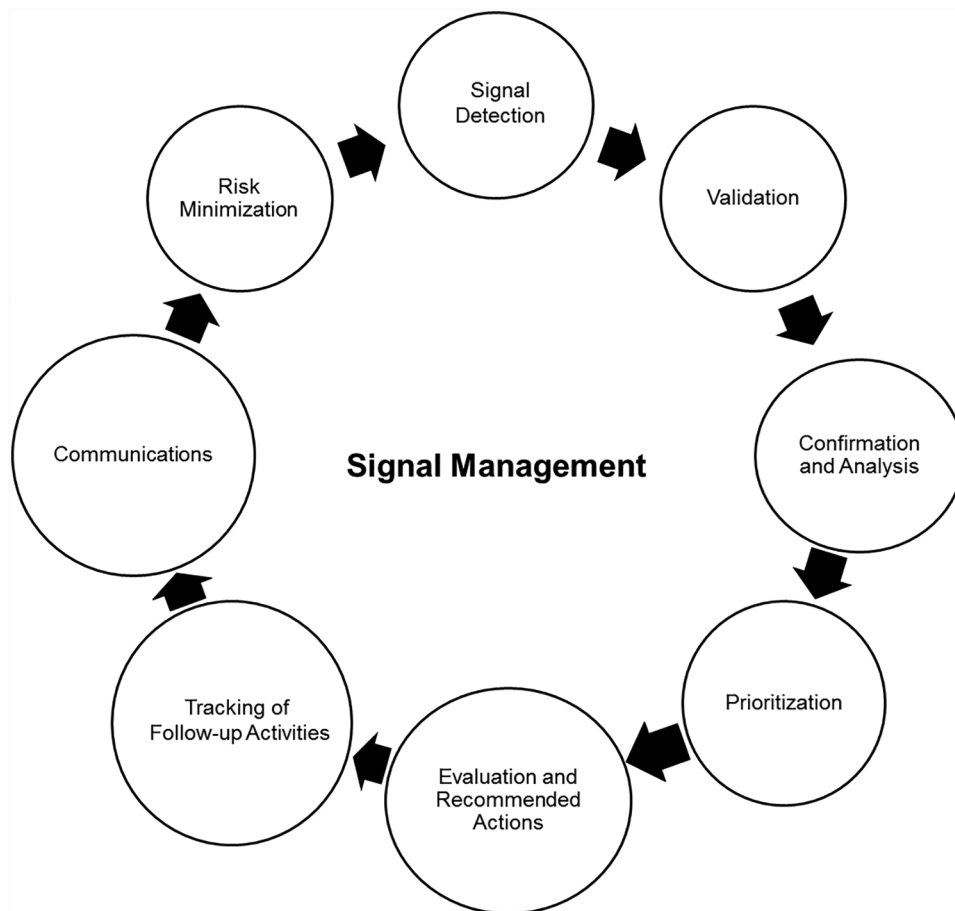


Figure 1. Signal management is a set of activities performed to determine whether there are newly detected risks with a drug or whether known risks have changed, and some action is required to re-evaluate drug safety profile.

various drugs.^{2,3,5} Pharmacovigilance professionals must be actively looking for signals and be prepared to handle them when they find them. One size does not fit all with signal detection and management. There are many factors that can influence the approach to be taken.

Signaling regulations and guidelines

Regulations and guidelines on signal identification and management are specified in the following documents.

1. CIOMS VIII: Practical Aspects of Signal Detection in Pharmacovigilance.¹
2. FDA Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment.²
3. European Medicines Agency (EMA) Guideline on Good Pharmacovigilance Practice (GVP) Module IX: Signal Management.³

The FDA's Good Pharmacovigilance Practices guidance provides information on identifying and describing safety signals using case reports, case series, cohort, case control, or nested case control studies, registries, and surveys.² In addition, it provides guidance on interpreting signals. Requirements for signaling are implied but not specified in the FDA Amendment Act, though they are well described in the guidance.²

A well-documented process for signal detection and escalation is essential in order to meet European regulatory requirements. EMA's GVP Module IX, Signal Management, specifies what should be done in the steps of the signal management process: signal detection, signal validation, signal analysis, and prioritization, signal assessment, recommendation for action, and exchange of information with stakeholders. It also spells out the marketing authorization holders (MAHs) responsibilities for pharmacovigilance.³

In addition, the CIOMS Working Group VIII report, *Practical Aspects of Signal Detection in Pharmacovigilance*, provides key definitions and describes approaches to signal detection, management, and interpretation of results.¹

Premarketing clinical trial safety

Patient safety monitoring is a critical component of the clinical trial process. The objective of collecting safety data from clinical trials is the early detection of important safety signals to achieve the following:

1. protect current research subjects and provide information about new risks;
2. assess the potential risk to future patients and develop safety profile/product label of the drug contributing to its benefit–risk assessment;
3. gather information to guide drug development for a selection of populations and a selection of doses/regimens;
4. explore for new indications.

Safety data, obtained from ongoing clinical trials, have a direct effect on the safety and clinical care of research subjects enrolled in these trials. The ultimate goal of safety signal detection in clinical trials is to translate clinically significant safety information to the product label under development and protect research subjects from experiencing adverse drug reactions.⁸ Guidelines issued by regulatory authorities specifically for the documentation and reporting of serious events have evolved significantly to help ensure the safety of clinical trial subjects.^{8–11}

During the last decade, the regulatory landscape for safety monitoring of biomedical products has changed considerably. In September of 2010, the FDA published a final rule¹² amending the safety reporting requirements under 21 code of federal regulations (CFR) part 312 (IND studies)⁹ and 21 CFR part 320 (Bioavailability and Bioequivalence studies).^{8,13} The US regulations (effective March 2011)¹² and the European Commission's detailed guidance (CT 3, June 2011)¹⁰ on the collection, verification, and presentation of AE/reaction reports detected in clinical trials put a strong emphasis on early reporting of serious events with a reasonable possibility of being associated with the drug so that safety analysis is not confounded by unnecessary noise

and product safety can be assessed more meaningfully.^{10,12} Under the previous regulations, the IND sponsors were often reporting to the regulatory agencies and clinical investigators, in an expedited manner, a substantial number of serious AEs whether or not they have had any relationship to the study drug.^{13,14} This caused the safety systems to be overloaded with a lot of potentially distracting information, which can possibly lead to masking of adverse drug reactions. Under the current regulations the IND sponsors must report to the regulatory agencies and the investigators, on an expedited basis, only those events that are serious, unexpected (not listed previously in the Investigator's Brochure), and are suspected to be caused by the drug (i.e. there is a reasonable possibility or scientific evidence to suggest that the drug caused it).^{9,10,12}

In order to ensure research subjects' safety on an active clinical study, clinical investigators must report to the sponsors all serious AEs on an expedited basis, regardless of whether they are considered drug-related or not,¹¹ thus relieving them of the burden of making a judgment on the causal association with the drug, which they can still indicate on the reports to the sponsors as treating physician investigators who are still closest to the subject and familiar with the details of their health history and clinical care.¹¹ However, individual investigators will not have access to entire drug safety databases in order to properly evaluate new AEs and assess causality in the broader context of the whole study population. Current regulations recognize that the sponsor has the broadest view of the drug's history and characteristics and is therefore in the best position to attribute causality. In addition, current guidance for industry calls for oversight of clinical investigations by sponsors based on the utilization of risk-based approach for monitoring.^{12,15,16}

Events, which cannot be analyzed as single cases, need to be assessed on an aggregate basis and reported if there is a difference in the reporting rates between the drug and the control groups.¹⁷ Currently, the emphasis on putting expedited, individual reports in the context of aggregate reviews is more pronounced in the US as compared with the EU, where companies still make the assessments and perform expedited reporting for one event at a time for the EMA, as they are not fully aligned with the FDA on this point.

In addition, the regulations make a distinction between the AEs and mortality and morbidity endpoints, which need to be analyzed as per the study protocol.^{10,12} As an additional measure to protect patient safety, the FDA also recommends that summaries/reports of the Data Safety Monitoring Boards (DSMB) meetings will be sent to the institutional review board (IRB) for review.^{12,17}

Utilization of DSMBs is increasing for both industry-sponsored and investigator-initiated, National Institutes of Health funded projects due to the growing number of industry-sponsored trials with mortality and major morbidity endpoints, increasing collaboration between industry and government in sponsoring major clinical trials heightening awareness within the scientific community of problems in clinical trial conduct.¹⁸

The DSMB/Data Monitoring Committee is an independent group of individuals with relevant expertise that review on a regular basis data collected from ongoing clinical trials, which advises the sponsor regarding the safety of current and future participants and on the validity and scientific merit of the trial. Among the duties of DSMB are the following:¹⁸

1. Review the research protocol and plans for data safety and monitoring.
2. Evaluate the progress of the trial with periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk *versus* benefit, and reports from related studies.¹⁸
3. Make recommendations to the IRB and investigators concerning continuation or conclusion of the trial.¹⁸

Typically, DSMB is required if any of listed below conditions apply:¹⁸

1. The trial is intended to provide definitive information about the effectiveness and/or safety of a medical intervention.
2. Prior data suggest that the intervention being studied has a potential to induce potentially unacceptable toxicity.
3. The trial is evaluating mortality or another major endpoint, such that inferiority of

one treatment arm has safety as well as effectiveness implications.

4. There is a question of ethical importance for the trial to stop early if the primary question addressed has been definitively answered, even if secondary questions or complete safety information were not fully addressed.¹⁸ For further details, on how to determine if DSMB is needed, refer to Figure 2.

Under the current European regulations (CT3, 2011/C, 172/01, June 2011) the investigator must report all serious AEs immediately to the sponsor, with exception for those that the protocol or Investigator's Brochure define as not requiring immediate reporting.¹⁰ The sponsor needs to report on an expedited basis only the serious, unexpected, suspected, and adverse reactions (SUSARs), preferably unblinded, within 7 days for fatal or life threatening events and 15 days for the other SUSARs (refer to Figure 3 for the time-frame for AEs reporting).¹⁰ The sponsor reports the SUSAR directly as an ICSR to the national competent authority (CA) of the relevant member state, and also indirectly through the electronic gateway to the EudraVigilance Clinical Trial Module.¹⁰ The latter requires registration with the EudraVigilance. The sponsors who may not have the resources and experience for electronic reporting may delegate indirect reporting to a partner.¹⁰ Communication channels of safety information between different stakeholders involved in drug development process are illustrated on Figure 4.

Annual safety reports must be generated throughout the life cycle of the clinical trial and sent to the national CA and the ethics committees/IRBs. These reports must contain a listing of all suspected serious adverse reactions, which have occurred over this period, and a report of the subjects' safety. Investigators at all participating sites should receive an update with a summary of newly evolving safety issues (Figure 3).¹⁰ There are separate guidelines on periodic safety update reports during the developmental phase, in the form of developmental safety update reports in the EU, and annual safety reports in the US.^{9,12,19} Although the regulations are focused on serious AEs, the sponsor is expected to monitor all AEs throughout the life cycle of the drug development process, including nonserious events.^{9,19}

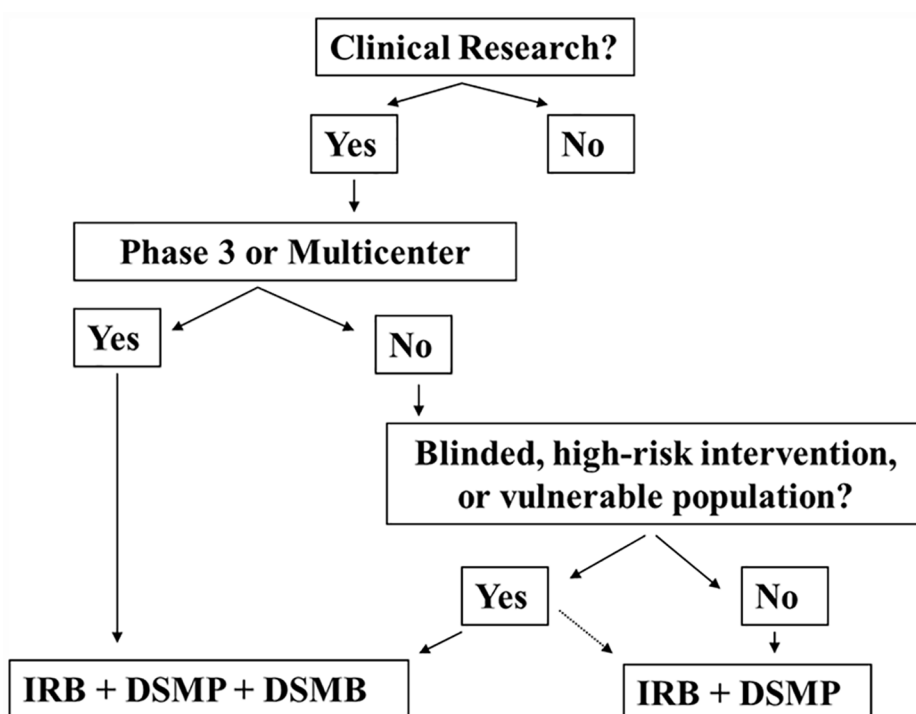


Figure 2. Determination chart for Data Safety Monitoring Board (DSMB) requirement. Clinical research conducted as a multicenter, phase III study which is intended to provide definitive information about the effectiveness or safety of a medical intervention will require institutional review board (IRB) approval, Data Safety Monitoring Plan (DSMP) and DSMB. Also, DSMB will be required for phase I and II studies (if these are blinded), utilizing high risk interventions (i.e. intervention being studied has a potential to induce unacceptable toxicity or there is an uncertainty about toxicity in humans at early phases of drug development), involving vulnerable populations or trial evaluating mortality as a major endpoint. All other clinical research projects will need an IRB approval and possibly DSMP.

The Investigator Brochure needs to be updated by the IND sponsor promptly, according to changing safety profile as AEs evolved on the clinical trial.

European CAs (e.g. the EMA) specifically require their approval of IB updates.^{6,7} Whereas, FDA's regulations do not specifically require that the Investigator's Brochure be updated or submitted to FDA as the trial advances from phase to phase. However, the regulations require that investigators be informed of new observations discovered by or reported to the sponsor on the drug under Title 21 CFR 312.55(b).⁹ This information may be distributed to investigators by means of periodically revised Investigator's Brochures. A copy of the revised IB is to be submitted to the FDA in the annual report for the IND along with a description of the revisions according to Title 21 CFR 812.33(d).⁹

In addition, the FDA recognized guidance, the International Conference on Harmonization (ICH) guidance E6: Good Clinical Practice,¹⁶ provides additional recommendations relating to the IB (as indicated in section 7). This guidance recommends that the investigator's brochure be reviewed at least annually and revised as necessary, and that more frequent revisions may be appropriate depending on the stage of development and the generation of relevant new information (as indicated in section 7.1).¹⁶

All participating institutions, investigators, and IRBs will need to be informed and an updated IB provided with tracked changes. Safety information from the IB needs to be translated into changes in risk/benefits ratio in the informed consent form, with an updated list of AEs provided in order to fully appraise research subjects on changing the safety profile of the study drug. Study

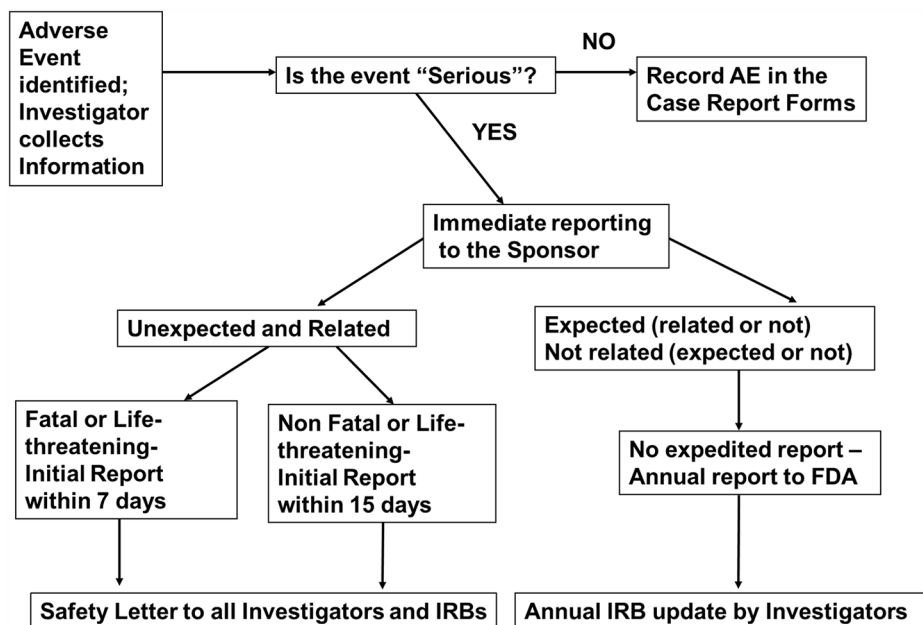


Figure 3. Adverse event (AE) reporting algorithm. Timeframe for adverse event reporting to national competent authority (i.e. Food and Drug Administration (FDA) in the United States and European Medicines Agency in European Economic Area) can vary, depending upon the seriousness, expectedness, and causality determined by the investigational new drug sponsor. Adverse events related or possibly related to the drug need to be reported in an expedited manner to regulatory authorities. Safety updates will need to be send out by the sponsor to all participating investigators at individual clinical research sites and institutional review boards (IRBs).

participants then can make a decision whether or not to accept these new risks and continue with the study or withdraw from it. It has to be an informed decision based on the most up-to-date information provided on study procedures, if there are any changes, and an updated safety profile.

The physician investigator at the clinical site level is responsible for the review of all internal and external AEs and to ensure research subjects' well-being and protection.¹¹ IRB can put a clinical trial on hold for enrollment at participating institutions if they deem that there is a serious AE (internal or external) related or possibly related to the study drug; pending further clarification and additional information from the sponsor of the trial, the hold can be lifted if safety the concern is resolved. Often, institutional policies for local IRBs vary and require even more extensive AE reporting than the sponsor is looking for on a specific clinical trial. Based on the half-life of the drug, the IND sponsor may require AEs to be collected for shorter periods of time (only for treatment phase) than the local IRB, which may

require subjects to be followed as long as they remain on the study, including the follow-up period after the active treatment phase is completed, and for all unanticipated events to be reported (related or not to the study drug). The difference in interpretation and requirements needs to be discussed upfront between the IND sponsors and participating institutions before the trial commences at each participating clinical site in order to avoid any communication issues and standardize the safety reporting process.

The FDA can put a clinical trial on hold if an annual report is not provided or safety information is incomplete, inaccurate, or safety claims are not supported by the data provided.

Based on the drug safety profile established during the clinical trials and information provided in premarket new drug application (NDA), the FDA can request formal postmarketing phase IV clinical trials to further monitor and evaluate the drug safety profile. In clinical trials, data are collected on a limited number of patients in a strictly controlled environment (e.g. subjects must meet

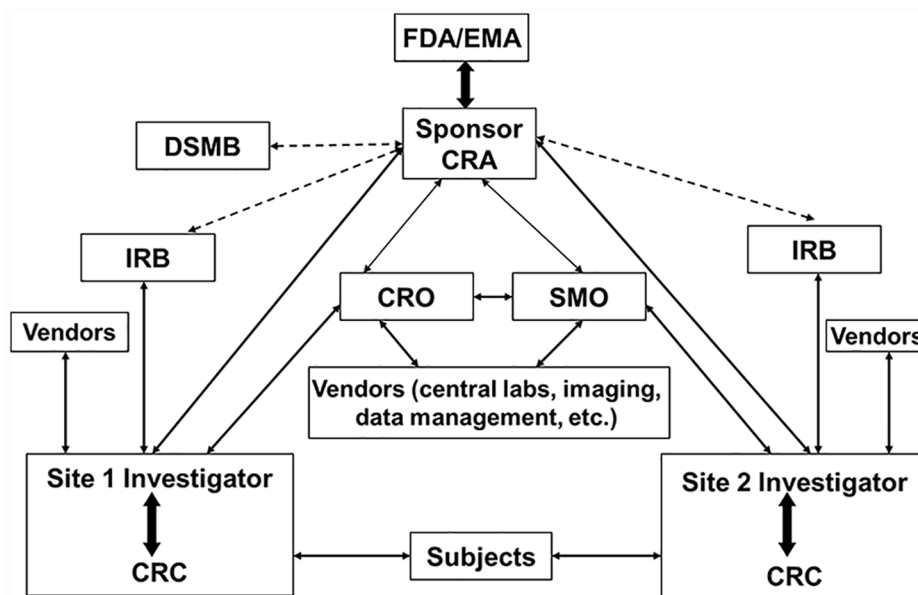


Figure 4. Communications in pharmacovigilance scheme. A Data and Safety Monitoring Board (DSMB) is an independent group of experts that advises the investigational new drug sponsor and the study investigators. The members of the DSMB serve in an individual capacity and provide their expertise and recommendations. The DSMB advises the sponsor regarding the continuing safety of trial subjects and those yet to be recruited to the trial, as well as the continuing validity and scientific merit of the trial. Institutional review boards (IRBs) can be local to the participating sites or centralized, chosen by the sponsor. IRBs provide oversight for ethical conduct of the study to ensure well-being and safety of clinical research subjects. The sponsor must update the Investigator's Brochure and inform investigators at participating sites about adverse events, so investigators can appraise research subjects and local IRBs on any safety profile changes. The sponsor can outsource part of their duties, including safety monitoring, to the contract research organizations (CROs), Site management organizations (SMO) or third-party vendors. If critical value is detected by the vendors (i.e. central laboratories, imaging facilities, data management vendors, etc.), it has to be promptly communicated to the site investigators for assessment of clinical significance and relationship to the investigational product. It is important to establish upfront clear channels of communications, define roles and responsibilities, and escalation processes for all parties involved in signal detection and drug safety management. CRA- clinical research associate; CRC, clinical research coordinator.

eligibility criteria and adhere to study protocol and procedures, in which drug regimens are constantly monitored), and only for certain periods of time. In the real world, patients do not always adhere to prescribed drug regimens and larger number of subjects gets exposed for longer periods of time, especially if a drug is taken for chronic indications.

Over the last few decades, the clinical trials landscape has changed significantly, including the expansion of research conducted on a global scale; divergence in regulatory requirements for safety reporting based on geographic location; diverse populations, often with significant underlying comorbidities, are being evaluated; and development of new technologies. The pharmaceutical industry has to modernize according to advances in technology, complexity of clinical trials, and globalization. In an attempt to address

divergence in regulations for safety reporting in ongoing clinical trials and reharmonize pharmacovigilance regulations globally, TransCelerate championed a collaborative effort of 19 pharmaceutical companies, including most of the largest ones, which identified a concerning trend of diverging regulations with regard to the handling of pharmacovigilance findings from ongoing clinical trials.²⁰

Singh and colleagues pointed out that examples include the processes for determining whether AEs reported by investigators are related to investigational drugs and are expected (i.e. consistent with the known safety profile of the product or events anticipated in the population).²⁰ Unexpected and related serious AEs may be subject to expedited reporting to inform investigators and regulators of potential risks. Recent European guidelines require comprehensive expedited reporting of serious

events,¹⁰ while FDA guidance restricts reporting to key (sponsor adjudicated) related events.^{11,12} While taking into consideration separately, the rationale for each of the above guidelines is commendable. However, the divergence of these requirements is complicating the consistent communication of safety profile updates to stakeholders. Communication of safety data by sponsors on ongoing clinical trials to other stakeholders has become especially important. If regulatory requirements will be harmonized on a global scale for pharmacovigilance, investigators and regulators across all geographic regions will have comparable insights into the evolving safety profile of new products. To meet these goals, TransCelerate took an initiative to implore representatives for regulatory authorities to work with industry sponsors, in collaboration with the ICH, to identify potential ways to reharmonize global pharmacovigilance processes and requirements.²⁰

Postmarketing safety management and communications process

Spontaneous reporting

Because premarketing clinical trial safety information about a drug is limited, ongoing monitoring of the drug is critical after it is introduced to the market in order to obtain an accurate safety profile for the drug and ensure the safety of consumers.

In the postmarketing environment, spontaneous reporting is an unsolicited, voluntary reporting of AEs by health care professionals, patients, and other individuals. Spontaneous reporting is the primary way that sponsors monitor drugs for safety in the postmarketing phase.

Different regulatory authorities require different forms for reporting spontaneous reports. Many maintain an online reporting site that patients and health care professionals can use, such as the FDA's MedWatch Online Voluntary Reporting Form and the The Medicines and Healthcare products Regulatory Agency's (MHRA) Yellow Card Scheme.^{21,22}

If the company receives information about an AE, if the event is valid, serious, and unexpected, the company must submit a 15-day alert report, or an expedited report, to the appropriate regulatory authority within 15 calendar days of receipt of the

information. In the EU, all valid, serious reports, regardless of 'expectedness', must be submitted to the EMA within 15 calendar days.^{19,22}

According to EMA and FDA guidelines, 'Unexpected adverse drug reaction is an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator's Brochure for an unapproved investigational medicinal product or package insert for marketed product)'.^{19,21,22}

Postmarketing expedited reporting requirements are similar to those for premarketing, except that 7-day reporting does not exist in postmarketing, and there is no assessment of causality since it is assumed.^{19,21,22}

Spontaneous reporting presents challenges to obtaining an accurate safety profile for a drug, including the Weber effect,²³ the secular effect,²⁴ and under-reporting of AEs.

In many recent publications, the Weber effect is implied to operate in various global AE databases.²³ It is often too simply summarized as 'after regulatory approval of a drug, AE reporting increases over the first 2 years, peaks near the end of year 2, and then reliably, and rapidly, diminishes with further time on the market'.²³ The secular effect refers to the changes over a long period of time, generally years or decades in a drug safety profile.²⁴

Other challenges with the spontaneous reporting system include the sheer number of AEs, complexities in determining true safety issues from many signals and reports, long time periods to identify new issues (during which morbidity and mortality occur), conflicting data, AEs from manufacturing problems, misuse, counterfeiting, and other reasons, and the fact that there is no single repository for AEs around the world. There are also organizational issues due to individual process variabilities, internal communication issues within the company, as well as health agency issues with spontaneous reporting.

Solicited reports

Solicited reports are reports derived from organized data collection systems, which include the following sources: clinical trials, postapproval named

patient use programs, other patient support and disease management programs, surveys of patients or healthcare providers, or information gathering on efficacy or patients' adherence to prescribed dose regimen and compliance with instructions for use. AE reports obtained from any of these sources should not be considered spontaneous. For the purposes of safety reporting, solicited reports should be handled as if they were study reports and, therefore, should have an appropriate causality assessment.

In the postmarketing environment there are some challenges around solicited reports, as these turned out to be the main source of lower-quality safety reports (e.g. issues with classification, causality assessment, completeness, and validity of reports, etc.) that is now subject to revision by the ICH.

Aggregate reporting

The ICH first harmonized aggregate reporting to regulatory authorities in a common format in 1996, with the ICH Guideline E2C, Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs (the PSUR). The primary objective of the PSUR was to provide a comprehensive picture of the safety of approved drugs.¹⁴

In 2012 the ICH issued the revised ICH E2C (R2), Periodic Benefit–risk Evaluation Report (PBRER). The PBRER includes a formal evaluation of benefit–risk. The European Economic Area requires the PBRER, which is still referred to as the PSUR or the 'new PSUR'.²⁵

In the US, the current periodic report is the Periodic Adverse Drug Event Report (PADER). Companies may choose to use the PBRER/new PSUR and FDA offers waivers for companies that wish to do this.²⁵ On a global scale, countries outside of the EU and US typically use the PSUR.

Significant advancements in global harmonization efforts in pharmacovigilance have been made in the recent ICH's largest biannual meeting.²⁶ It is emphasized in the press release from this meeting that the assembly reviewed the excellent progress made by ICH working groups both at and prior to the meeting, approved new areas for harmonization, discussed ICH revision of the postapproval safety reporting requirements E2D,² and took

decisions in support of the recognized importance of training in ensuring a globally consistent approach to ICH guideline implementation.²⁶

Safety information communication to patients through the patient package inserts

The healthcare providers play a critical role in drug safety in a postmarketing phase by adhering to the instructions for use listed on drug labels, also referred to as a package insert in the US, which is a technical document oriented towards medical professionals as prescribers of FDA approved medications.²⁷ Package inserts for prescription drugs often include a separate document called a 'patient package insert' with information written in plain language and intended for the end-user such as the person who will take the drug or give the drug to a minor.²⁷

Inserts for over-the-counter medications are also written in plain language.^{27,28} These instructions promote the correct, and hence safe, use of medicines. In the US, the FDA determines the requirements for patient package inserts, and it will occasionally issue revisions to previously approved package inserts.²⁷

In the EU, the EMA has jurisdiction and the relevant technical documents are called the 'summary of product characteristics' (SPC or SmPC) and the document for end-users is called the 'patient information leaflet' or 'package leaflet'.²⁹ The SPC is not intended to give general advice about treatment of a condition but does state how the product is to be used for a specific treatment. It forms the basis of information for health professionals to know how to use the specific product safely and effectively. The package leaflet supplied with the product is aimed at end users.²⁹

Patients play an important role in drug safety. They are the people who experience the adverse effects, and without their input, we cannot develop systems that would enable us to identify side effects that have not emerged from clinical trials. Individual patients, by monitoring the beneficial as well as adverse effects of their treatment, can take timely treatment decisions if required. New technologies are becoming available that will allow patients to monitor their conditions in the comfort of their own homes, thus further enhancing the opportunities for more actively empowered health-care consumers. Yet, in order to

ensure that a qualified person is at the controls in drug therapy, adequate, timely, and unequivocal information should reach the patient.

The growing number of different sources of information to which a patient is exposed causes some concerns among those involved in drug safety, not least when there is a drug scare. In the modern world, the landscape of information is very diverse. Not only are there patient package inserts and the medical professionals available as sources of information, but also the specialized health magazines, health or self-care sections in popular magazines, and numerous health advertisements on radio and television programs, not to mention the flood of health information on the internet. However, patient package inserts are the most direct source with verifiable content, which is issued *via* regulated channel and delivers information from the scientifically evaluated drug safety database directly to the patient. The latter feature is a significant asset because each human link in a communication chain can change a message due to inaccuracies in receiving, interpreting, evaluating, or recoding before the message is passed on to the next recipient.

Significant distortions, however, may be less likely to occur when a medically trained professional serves as the single communication link. This is why the doctor should remain the main living information channel on prescription drugs and why pharmacists and nurses should keep their very important complementary supportive roles in the therapeutic process.³⁰

Amery³⁰ in his review emphasized that the different messages a patient receives should be mutually consistent otherwise the patient may be bewildered and fail to comply with the instructions for use. In addition, since the public is not homogeneous in any respect, patients may differ in their receptivity to different communication modes, although they are all entitled to receive the same message.³⁰ It is important to improve the patients' knowledge of their medicines, and a well written patient package insert should help patients to deal with a risk situation such as a side effects or dose omission. However, the availability of information doesn't ensure compliance with treatment regimens.

Patients can develop a strategy on how to manage AEs if they receive the information they need in

order to construct it; hence the necessity of information on likelihood, characteristics, and expected time of occurrence of side effects, as well as on measures that will prevent, relieve, or eliminate them. Such information enhances a patients' confidence that they can cope when confronted with an adverse effect and, as a consequence, increases the likelihood that they will continue the treatment as prescribed.³⁰

Amery³⁰ pointed out that individuals exposed to most medicines are spread out geographically. The benefit–risk balance of a medicine is thus primarily a personal issue, however it has public-health ramifications. Moreover, in the area of health care, benefit–risk analyses and the associated trade-offs are predefined as personal matters as people's values and beliefs play a crucial role.³⁰

The communicator of safety information must be aware of specific patient's needs in order to address their specific concerns and have detailed knowledge of efficacy and safety information listed in a specific patient package insert.

The treating physician's skill in translating general benefit–risk information into common terms/language that is meaningful to their patient remains a very important one. The doctor should tell the patient if they are choosing from a number of treatment options, if there are common side effects and what the patient might expect, how to act to avoid problems, and what to do if a problem occurs. In addition, doctors and pharmacists need to be educated and trained on how to deal effectively with safety information when they speak with patients and how to pay proper attention to the emotional component of the patients' struggle with their illness.³⁰ Patient package inserts are a channel for conveying benefit–risk information to patients, and they supplement the physician's, nurse's, and pharmacist's more direct roles. These medical professionals play a crucial role in patient education about prescription medications. In addition, the patient package insert may be particularly helpful in dealing with the overwhelming emotional state that patients may experience at home after their visit to the doctor while trying to deal with their health condition or changing health status and digest all information they have received. It will help them to make more informed decisions about their treatment options, and understand the risks and benefits associated with the proposed drug therapy.

Benefit–risk assessment

Recent changes to drug safety and pharmacovigilance regulations around the world emphasize benefit–risk evaluation rather than only an evaluation of the safety of a product.^{10,12,25} Benefit–risk assessments are complex and difficult to make since different people have different risk tolerance levels. Efforts are underway internationally to develop a standardized methodology for quantitative or qualitative benefit–risk assessment.

A rudimentary quantitative benefit/risk ratio can be calculated by dividing the number needed to benefit by the number needed to harm.³¹ The FDA has developed a qualitative grid to identify key issues for benefit–risk evaluation for biomedical products. The Medical Device Innovation Consortium works closely with Center for Devices and Radiological Health (CDRH) on the Patient Centered Benefit–Risk Project.³¹ The project was created to support the benefit–risk assessment component of CDRH approvals of medical devices,³¹ the ProACT-URL framework, which lists eight steps in determining the benefit–risk balance of a product.³²

The Centre for Innovation in Regulatory Science (CIRS) has two initiatives underway. The unified methodologies for benefit–risk assessment was developed to provide a platform for the coordinated development of benefit–risk methodologies that can be used internationally.³³ The goals are to increase transparency, predictability, and consistency.

The CIRS-BRAT tool allows users to generate tabular and graphical displays to assist in the interpretation of benefit and risk findings.³³ The purpose of the tool is to enable users to generate value trees, key benefit–risk summary tables, and forest plots.³³

The ICH guideline M4E entitled “Common technical document for the registration of pharmaceuticals for human use – Efficacy” was revised in order to standardize the content and presentation of benefit–risk information in regulatory submissions. The Revised ICH M4E(R2) guideline specifies a structure for the Common Technical Document (CTD) in Section 2.5.6, Benefits and Risk Conclusions. This section of the CTD should represent the thought process behind the

applicant’s weighing of benefits and risks and communicate a critical and succinct presentation of the benefit–risk assessment.³⁴

Effective, clear, and timely risk information is key to protecting public health. The FDA has established the Risk Communication Advisory Committee and maintains an informational webpage on potential signals of serious risks and new safety information.

The EU covers safety communications in GVP Module XV, Safety Communication.⁶

Risk management plans

In the European Economic Area, an EU risk management plan (RMP) is a required part of the marketing application for all new products.⁷ This requirement is in addition to the product labeling (SPC). If additional measures are needed, a risk minimization plan will be required. In addition, 2012 legislation requires an electronic benefit/risk management plan.⁷

Not all products require an EU RMP. An EU RMP may need to be submitted at any time of a product’s life cycle. Certain situations require an RMP, such as a new marketing authorization application, an application for a pediatric use, or an application involving a significant change in marketing authorization.⁷

The EU risk management system is specified in GVP Module V, Risk Management System.⁷ Details on risk minimization and measurement of its effectiveness are included in Module XVI.³⁵

The RMP must include sections for product overview, safety specification, pharmacovigilance plan, plan for postauthorization efficacy studies, risk minimization measures, summary of the RMP, and annexes.³⁵

Risk minimization activities may require restricted access, education programs, control of a prescription, named patient registries, or continuing follow-up.

MAHs must conduct direct, periodic measurements of the effectiveness of risk minimization activities, and submit periodic updates to the EMA or national CAs, and include a summary in the PSUR. The MAH and the applicant should evaluate the

need for additional risk minimization activities beyond the standard (including information in the label), based on the safety specification.^{35,36}

Risk evaluation and mitigation strategies in the US

In the US, risk minimization and management plans are called risk evaluation and mitigation strategies (REMS). A REMS is an operational manual, which includes strategies on how to handle risks associated with a product. It allows patients to use the product but under certain conditions and surveillance.^{37,38}

The FDA gained the authority to require a REMS under the Food and Drug Administration Amendments Act legislation enacted in 2007.

A REMS may include a medication guide, a communication to HCPs, or elements to assure safe use (ETASU) such as special training for HCPs who prescribe, dispense only in certain settings, or monitor and register patients.^{37,38} A REMS must always include a timetable and metrics for assessment of its effectiveness, at a minimum at 1.5 years, 3 years, and in 7 years.^{37,38} There is a formal submission and approval process by the FDA. The vast majority of products do not require a REMS. The FDA can require a REMS at the time of an initial NDA submission, at the time of submission for a line extension, or when new safety information is received for an approved product. ‘Class’ REMS are evolving, such as those that have been developed for extended-release and long-acting opioid medications.³⁷

A REMS must follow a specified format that includes goals, a medication guide or patient package insert, a communication plan, ETASUs, an implementation system, a timetable for submission of assessments, and an appendix.^{37–39}

The majority of initial REMS were medication guide-only REMS, which put too much burden on the healthcare system. A new guidance released in 2011 reversed the policy, not requiring a medication guide to be a part of a REMS.³⁸ In total about 200 REMS have been approved since 2008.³⁹

Conclusion

In conclusion, regulations are aimed to ensure that the assessment of safety during clinical

development is meaningful and sponsors need to have a systematic approach for the safety assessment of their investigational products. Managing clinical trial safety data is a collaborative process. Investigators, sponsors/CROs, ethics committees, data safety monitoring boards, and regulators all share the responsibility for protecting clinical trial subjects by scrutinizing and evaluating safety data proactively and on an ongoing basis. According to current regulatory guidelines, in the post marketing environment new safety signals also should be evaluated promptly by the marketing authorization holders and communicated to regulatory authorities, healthcare professionals and consumers in a timely fashion to ensure safety of drug products.

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