White paper

FSP solutions

PPD Functional Service Partnership (FSP) Pharmacovigilance solutions – Safety reporting in clinical trials: Six core considerations for success

In the realm of clinical trials, the paramount concern is patient safety. This commitment to safety is built on the cornerstones of meticulous monitoring and reporting of adverse events. As investigational products progress through the phases of clinical research, the landscape of pharmacovigilance becomes an intricate global network, demanding continuous adaptation, meticulous planning, and expert execution.

This white paper delves into the complex and evolving world of safety reporting in clinical trials. It uncovers the challenges faced by sponsors as they traverse the web of multi-national, national, and local entities, including Regulatory Authorities (RAs), Ethics Committees (EC), investigator sites, and business partners.

With a focus on six core considerations, this paper navigates the terrain of pharmacovigilance to facilitate a deeper understanding of the pivotal role played by safety reporting in clinical research.

- From safety reporting to investigators in diverse global locales to managing multiple clinical vendors, each consideration brings to light unique complexities and nuances. The paper offers insights into achieving safety reporting compliance, discerning country-specific idiosyncrasies, adapting to the electronic reporting era, and embracing pharmacovigilance regulatory intelligence as a guiding principle amidst regulatory changes.
- By exploring these considerations, stakeholders in clinical research, from pharmaceutical companies to clinical investigators, gain a comprehensive perspective on the intricacies of safety reporting. This knowledge equips them to navigate the multifaceted challenges, uphold rigorous standards of patient safety, and ensure unwavering adherence to regulatory requirements throughout the clinical trial journey.

Six core considerations for safety reporting

Consideration 1: Safety reporting to investigators

Sponsors put in hard work successfully completing early clinical trial phases. Progressing into Phase III, they look at a wider net of sites, more patients and perhaps an expanded list of countries. From a pharmacovigilance standpoint, safety reporting — which up until this point may have been relatively straightforward — is now becoming more complex and requires thoughtful consideration to ensure regulatory reporting requirements and timelines are being adhered to.

With Phase II studies and later in Phase III studies, the number of sites increases exponentially. As seen in Figure 1, with the increase in sites and the variation in geographic locations of sites, there comes an additional level of complexity for completing safety reporting and maintaining compliance. To ensure success, sponsors must be informed of regulatory requirements for investigator reporting on a country level and ensure a robust process is in place to ensure submissions of safety reports are distributed appropriately to investigators. As Phase III planning is underway, understanding the individual country requirements is a critical preparation step.

Figure 1

"The sponsor must notify FDA and all participating investigators (i.e., all investigators to whom the sponsor is providing drug under its investigational new drug (IND) applications or under any investigator's IND) in an IND safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting."

Country-Specific Guidance

When reporting to sites in the United States (U.S.), for example, sponsors must consider the Federal Drug Administration's (FDA) requirements in Code of Federal Regulations (CFR) 21 312.32, which states, further evaluation needs to occur for safety reporting to U.S. investigators when considering the FDA's guidance on reporting serious adverse experiences. The FDA clarifies that the onus for determining the likelihood of an adverse event being caused by an investigational product sits with the sponsor, which has the aggregate data needed to make the determination of causality. Therefore, for U.S. investigator safety reporting, the sponsor's assessment of causality may differ from the investigator's assessment; this guidance in the U.S. can result in an extra layer of complexity for global reporting as U.S. sites may subsequently receive fewer safety reports than non-U.S. sites.

When considering countries outside of the U.S., the requirement to report individual IND safety reports in a 15-calendar day timeframe can also differ. For example, the Australia Therapeutic Goods Administration (TGA) states in "Safety monitoring and reporting in clinical trials involving therapeutic goods" section C.1.

"Sponsors may be required to follow global company policies that mandate the reporting of individual case Suspected Unexpected Serious Adverse Reactions (SUSARs) and six monthly line listings to investigators; however, this practice is not required by this guidance. Sponsors can discharge this responsibility by placing these reports on a portal or by sending them via e-mail. When the sponsor confirms that the report has no bearing on participant safety or trial conduct, confirmation of receipt of the communication may be requested, but there should be no requirement for investigators to print, review and file these reports."

Furthermore, in the European Union (EU), sponsors' pharmacovigilance groups must consider whether a protocol is approved under the Clinical Trial Regulation (CTR) versus Clinical Trial Directive (CTD) 2001/20/EC. For those studies approved under EU CTD, the directive indicates (Article 17(1)(a), (b) and (d) of 2001/20/EC).

Did you know?

Auxiliary Medicinal Products (AxMPs)

An AxMP is defined in EU CTR as a medicinal product used for the needs of a clinical trial, as described in the protocol, but not as an investigational medicinal product (previously called a non-IMP).

"The sponsor shall ensure that all relevant information about suspected serious unexpected adverse reactions that are fatal or life-threatening is recorded and reported as soon as possible to the competent authorities in all the Member States (MS) concerned, and to the Ethics Committee (EC), and in any case no later than seven days after knowledge by the sponsor of such a case, and that relevant follow-up information is subsequently communicated within an additional eight days. All other suspected serious unexpected adverse reactions shall be reported to the competent authorities concerned and to the EC concerned as soon as possible but within a maximum of 15 days of first knowledge by the sponsor. The sponsor shall also inform all investigators."

This wording is in line with the U.S. FDA's regulation for safety reports to be submitted to all investigators. In contrast, EU CTR specifies that of most importance is for the sponsor to inform investigators of safety profile changes, not individual SUSAR reports. The safety information for investigators should be concise and practical. When possible, the information on SUSARs should be, at least, a list of SUSARs that occurred at their MS, together with a summary analysis of safety profile and updated benefit risk for the ongoing clinical trials. From here, EU CTR aligns with the guidance from the Australia TGA to focus on trends in safety profile changes versus single safety occurrences in Individual Case Safety Reports (ICSRs). The differences between the EU CTD and EU CTR can be seen further in Figure 2.

Figure 2: Differences in EU CT directive and regulation

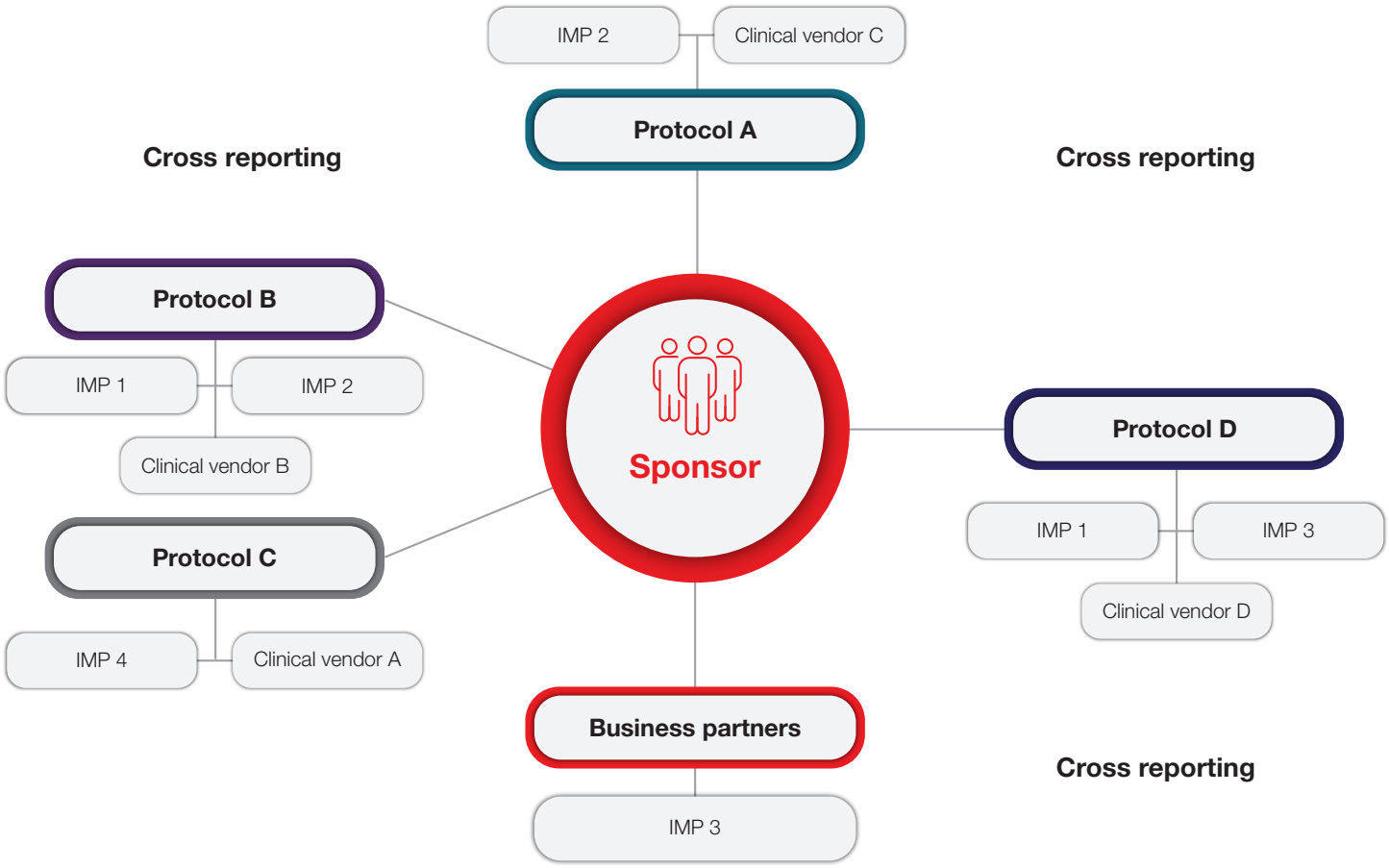
EU CT directive 2001/20/EC (EU CTD)	EU CT regulation EU No 536/2014 (EU CTR)
SUSAR reporting for RAs submitted to both the European Medicines Agency (EMA) as well as to country-level RAs for EU Member States and European Economic Area (EEA) countries	Simplified SUSAR Reporting for RA submissions to only the EMA for EU Member States and EEA countries
EC reporting is required based on local country regulations	EC reporting is no longer required in the EU/EEA
Development Safety Update Reports (DSUR) submitted to individual RAs based on local country regulations	DSURs submitted via the Clinical Trials Information System (CTIS) only
Individual safety reports submitted to investigators	Safety information for investigators should be concise and practical

Consideration 2: Managing multiple clinical vendors

Expansion into Phase III studies often involves multiple clinical vendors managing each individual study or individual regions within a single study. Working with different vendors offers its own set of challenges, including:

- Different processes and systems for tracking data that are key to safety reporting
  - In initiating safety reporting on time and in compliance with regulatory requirements, it is pivotal for sponsors to know when an RA or EC application has been submitted and received approval. When multiple clinical vendors are involved, each is likely to have its own clinical trial management system and its own nomenclatures for tracking application submission activities, making tracking of this critical information a higher burden.
- Numerous project teams and points of contact
  - If a situation arises involving a pending submission, there must be a clear communication pathway for each clinical vendor to get the situation resolved quickly and without impacting safety reporting compliance.
  - Clinical vendors may be in the position of Clinical Trial Application (CTA) holder in some countries, leading to challenges on a country level where local regulation requires the CTA holder to perform safety reporting.
  - When relying on multiple parties to perform safety reporting, the management and tracking of submission dates and compliance becomes more complex with sponsor oversight becoming more difficult. In the event of regulatory inspections, the sponsor is faced with gathering safety information from multiple sources, increasing the risk of untimely inspection responses as well as perceived gaps in sponsor oversight.
  - If not utilizing a single pharmacovigilance vendor to provide safety reporting services, it also becomes necessary for sponsors to map reporting responsibilities across countries and investigational products, to reduce the risk of over- or under-reporting to RAs.

Figure 3

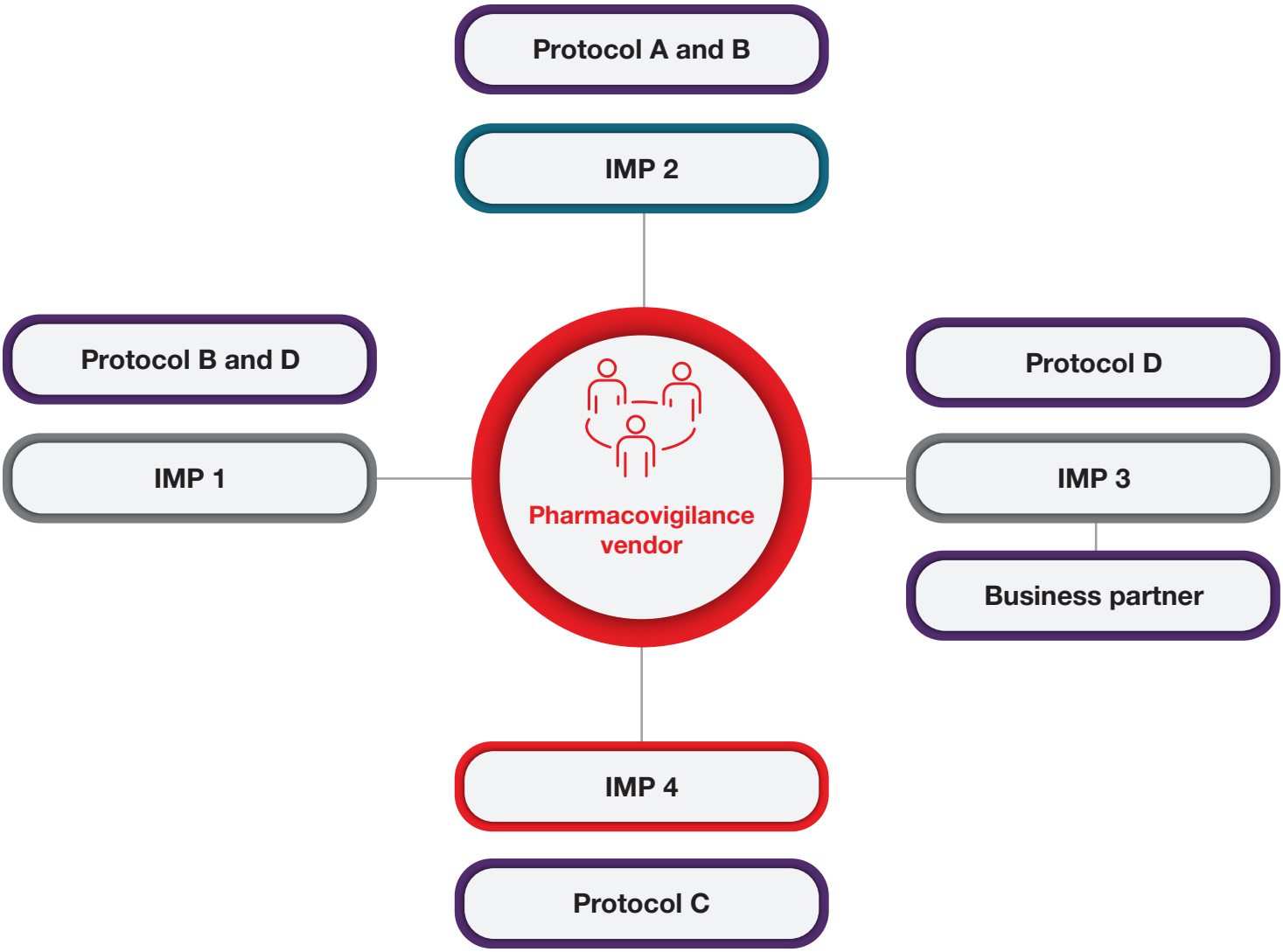


A solution to the challenges faced when managing multiple clinical vendors is to utilize a single-source pharmacovigilance vendor for safety reporting, which downsizes the complexity of working with multiple vendors and allows for a centralized approach to compliance oversight.

As seen in Figure 3, there are a lot of moving parts for sponsors to understand and track the authorities to which safety reports must be submitted. When a single pharmacovigilance vendor takes on ownership of this complex safety reporting network, it becomes the central source of information for all safety reporting dates and submission evidence — greatly easing the burden for the sponsor. The pharmacovigilance vendor also takes on the responsibility of communicating with each clinical vendor to create processes around the sharing of key safety reporting data in a consistent and concise format.

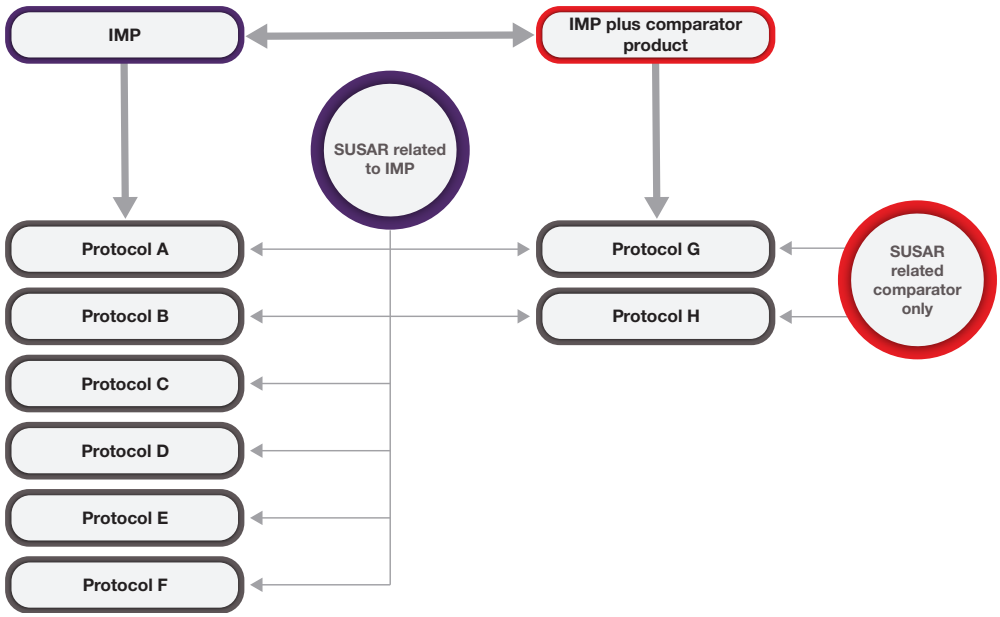
Centralization to a single pharmacovigilance vendor shifts safety reporting from a per-protocol model to a per-Investigational Medicinal Product (IMP) model, as seen in Figure 4. This shift introduces simplified reporting and promotes efficiencies by reducing the volume of safety reporting distribution. In parallel, centralization of safety reporting improves regulatory compliance by eliminating the risk of over reporting and reduces the overall pharmacovigilance costs. By using a single pharmacovigilance vendor, sponsors establish a sustainable long-term model for safety reporting success.

Figure 4



Once the IMPs are confirmed, it's recommended that each product is clearly listed within a Safety Management Plan along with detailed guidance on cross-reporting responsibilities to ensure compliance is met.

Figure 5



As protocols become more complex, in particular for oncology studies, other medicinal products are often introduced in addition to the primary IMP, whether in combination or as a comparator. Any product that is categorized as an IMP within the CTA requires safety reporting across any protocol using that IMP, as demonstrated in Figure 5. When working with different clinical CTA holders and potential partners, it's imperative that sponsors identify which products are in use and how they are classified during start-up of the study.

Consideration 3: Safety reporting compliance

Within the field of pharmacovigilance, the top reason to have a fully developed, experienced network of safety reporting experts is to ensure patient safety by meeting the regulatory requirements set forth by each country-level governing body.

As we've seen so far, the approach to safety reporting for investigators varies and is often country specific. Such complexity becomes even more apparent when looking at RAs and ECs. Approaches can vary in terms of safety report format, as to when to submit a safety report and in the method of reporting. However, regardless of the distinctions between countries, the sponsor is still expected to provide oversight of all safety reporting activities, making compliance tracking a key consideration.

To achieve this level of oversight, sponsors should address the following points:

- **Key performance indicators (KPIs)**
  - The pinnacle for safety reporting is always to meet a 100% reporting compliance; however, it's necessary to set KPIs to monitor the threshold for when investigation and possible intervention are needed. For example, setting a KPI of >98.5% allows for a degree of expected variability in reporting compliance. Anything below this threshold requires defined corrective and preventative actions to ensure compliance is maintained post-investigation.
  - Once KPIs are established, sponsors should consider the frequency in which metrics are to be shared by the pharmacovigilance vendor. Typically, the frequency of KPI review as a standard should be monthly to offer opportunities to identify potential risks or trends. However, this can be dependent on the volume of safety reports, as lower-volume studies may be better aligned with quarterly reviews.
- **Interpretation of reporting requirements**
  - When working with multiple clinical vendors and CTA holders, the likelihood of each organization having different interpretations of regulatory requirements increases. This can result in variances with compliance when, for example, one Japan In-Country Clinical Caretaker (ICCC) determines an event is reportable and another Japan ICCC assesses the event as non-reportable. A single pharmacovigilance vendor to encompass regulatory intelligence helps address possible differences in interpretation and the need for alignment across all involved parties. Additionally, the regulatory intelligence provider facilitates queries back to RAs when needed to resolve unclear legislation.
- **Location of submission date tracking**
  - To have accurate metrics to monitor KPIs, it's important to have clear processes around where and when submission dates will be tracked. When increasing the number of clinical trials in your pipeline, or when expanding into countries that may have the capability to receive safety reports via an E2B gateway, the standard approach is to utilize the safety database as the primary repository for RA submission dates. Additionally, common practice is to utilize the configured safety reporting rules within the safety database to document which regulatory recipients require a safety report. Where possible, establishing E2B gateways allows for automation of the reporting process to those authorities, including the benefit of an automated record of the submission date and associated acknowledgement.
  - Outside of RA submission dates, the safety database does not maintain ECs and investigator submission dates. Configured reporting rules for ECs can become overly complex due to the potentially significant number of ECs involved in a study as well as the variations in reporting requirements across ECs. Likewise, with investigators, the volume of individual investigator recipients makes tracking submission dates through a distribution tool a necessary requirement.
  - To ensure accuracy of metrics and reduce the risk of human error when tracking submission dates, it's crucial for sponsors to use automation when completing submissions to non-E2B RAs, ECs, and investigators, especially when dealing with multiple ongoing protocols.
- **Centralized safety reporting metrics**
  - Automating the tracking of safety report submission dates is essential when dealing with larger safety reporting volumes or multiple recipient destinations; however, it's also equally important that a sponsor produces those submission dates and overall safety reporting metrics in a centralized and consolidated format. Pulling the different sources of metrics together (safety database, EC tracking tool, investigator distribution tool) can be time-consuming and, in the case of a regulatory inspection, detrimental to providing timely responses to an inspector. Integration of these various sources is an optimal solution and provides the sponsor better oversight of safety reporting compliance without having to assemble data.

In-Country Clinical Caretaker (ICCC)

When a sponsor that is not domiciled in Japan is conducting a clinical trial in Japan, to prevent the occurrence or spread of health hazards associated with a sponsor's investigational product, an individual or organization domiciled within Japan shall be selected as the ICCC. This individual/organization will perform the procedures necessary for sponsoring the trial.

Consideration 4: Country-specific nuances

When further delving into the nuances of global safety reporting, there are several countries that require more in-depth planning and consideration. Many of these countries require support on the ground, in country, due to local regulatory requirements or logistics (e.g., hand delivery of safety reports). In addition to potentially needing a global network of support for safety reporting, it's also important for sponsors to know which countries have restrictions as to which party can complete safety reporting after the submission of the CTA/Clinical Trial Notification (CTN), such as Japan.

Country spotlights

Japan

- The obligation for commencing safety reporting to the Pharmaceuticals and Medical Device Agency (PMDA) commences from the date of CTN submission to PMDA, not the date of approval.
- When an investigational product has been approved for commercial use in other countries, but not yet in Japan, the sponsor/ICCC needs to cross-report overseas post-marketing cases to the PMDA until the point of marketing approval in Japan or development discontinuation.
- Any follow-up safety reports assessed as fatal/life-threatening must continue to be reported following a 7-day timeline after the initial submission. Therefore, follow-up reports do not follow a 15-day timeline for fatal/life threatening safety reports.
- Following case finalization in English, Japan-specific case information must be entered into the safety database including Japan-specific E2B fields and a Japanese narrative as applicable. Additionally, coding must be completed based on MedDRAj and the Japanese Drug Dictionary (JDD).
- Safety reporting to investigators/heads of institution (HoI) commences from the point of site contract execution. There are no defined timelines for investigators/HoI reporting, but within 30 days is standard. Safety information must be provided in Japanese.
- The HoIs are responsible for onward reporting to the Institutional Review Board (IRB).
- All U.S. IND safety reports should be provided to Japan investigators within 15 calendar days.
- Additional safety reporting considerations include the requirement to submit measures taken overseas for medicinal products with the same active pharmaceutical ingredient reports and research reports, both local and overseas.
- International Council for Harmonization DSUR format is acceptable with Japan-specific attachments, including an executive summary/status update in Japanese and a domestic, serious adverse drug reaction (ADR) listing.

Like Japan, there are other countries that have translation requirements when performing safety reporting. In China, safety and aggregate reports are required to be submitted in Chinese; however, it's important to note that the team performing safety reporting does not have to be in China.

Some countries require a delegation of authority/power of attorney letter to be submitted in advance of a party, not the CTA/IND holder submitting safety reports. The power of attorney letter may require translation, apostille and notarization prior to being submitted to the regulatory authority.

China

- The obligation for commencing IMP safety reporting is from the domestic clinical trial approval/license date until the date of marketing authorization in China or until the research and development of the drug is terminated in China.
- For a fatal/life-threatening SUSAR, the safety report should be submitted as soon as possible and no more than 7 days after first becoming aware of it. A follow-up report should be submitted with maximum information within 8 days of the initial report. When new information is submitted through the follow-up report, the reporting timeline is 15 days after the new information is obtained.
- Safety reports in E2B (R3) eXtensible Markup Language (XML) format with China local elements is mandatory for the China CDE (Center of Drug Evaluation) and National Medical Products Administration (NMPA), per local E2B (R3) implementation guidance effective from 01-Jul-2022.
- Method of submission can vary depending on volumes of safety reports. Gateway and web portal E2B R3 report upload via the CDE application window are both acceptable methods of transmission.
- All safety reports, including the DSUR, should be submitted in Chinese.

China and other countries have been recently impacted by regulation and guidance updates that are important to understand prior to the CTA being submitted.

India

- Any local serious adverse events (SAEs) occurring during a clinical trial, shall, after due analysis, be forwarded to the Central Licensing Authority, the chairperson of the Ethics Committee and the institute where the trial has been conducted within 14 days of its occurrence.
- All local SAEs should be submitted via the SUGAM portal, an online e-governance portal (per Notice F. No. CT/SAE-Misc-10/2020, effective 25-Feb-2021). Only local SAEs are required to be reported to Drugs Controller General of India, as foreign safety reports are no longer required as of 14-Mar-2021.
- The CTA holder in India is required to submit safety reports via SUGAM. This task cannot be delegated to another party.
- Foreign SUSARs should be reported to Investigators and the Chairman of Ethics Committees and Heads of Institution (HoI). Timelines for reporting of foreign SUSARs are not specified in regulation, but the standard approach is to follow a 7/15-day timeline.

In some countries, like Singapore, Taiwan and Turkey, in order to submit safety reports via the in-country web portals, a citizen identification number is required.

Taiwan

In Taiwan, regulation updates within the past couple of years have changed the way safety reports are submitted. The Taiwan Food and Drug Administration's (TFDA) more technical requirements change was at the forefront of the global E2B (R3) XML movement, as detailed below.

- Local SUSARs can only be submitted via the ADR system individually and manually – E2B (R3) format is not acceptable. Inclusion of a TFDA-specific ADR form in Mandarin is required. Foreign SUSARs can be submitted via the ADR system in E2B (R3) format and can be in English or Mandarin.
- Local SUSARs with a fatal outcome require a TFDA Local Death SUSAR follow-up form in Mandarin.
- From 05-Jun-2019, TFDA announced that, from a safety reporting standpoint, a drug used under a clinical trial protocol should follow Article 106 of Regulations for Good Clinical Practice. This means that only SUSAR reporting is required for a drug under the clinical trial protocol even if the drug is marketed in Taiwan. Therefore, the reporting of serious ADR for an approved drug is not required when it is used under the clinical trial protocol.
- From 01-Jan-2023, DSURs are submitted to the TFDA via web portal, with a cover letter in Mandarin.

Region spotlight

The Mexican pharmacovigilance authority is preparing to soon enable the e-Reporting portal for submission using E2B (R3) in XML format. This format adheres to the ICH E2B structure and includes local requirements for specific sections of the data elements that comprise the E2B file. The file specifications can be found in the Mexican pharmacovigilance authority technical guidance document.

Latin America

After several years of relying on paper submissions and locally owned pharmacovigilance portals for safety reporting, the pharmacovigilance regulatory authorities of Mexico, Colombia and Brazil are transitioning to e-Reporting, an electronic, internationally harmonized submissions portal with direct interaction with the World Health Organization (WHO) pharmacovigilance system and its safety database.

- These platforms enable ICH E2B (R2) submissions; therefore, sponsors conducting studies in any of these countries should be prepared to generate XML files in compliance with the structure of the standard E2B (R2) format.
- Of note, there are timeline variations in the region; for example, authorities in Mexico and Colombia require domestic SAEs (not only SUSARs) with submission timelines that differ from the standard 7/15 calendar days.
- In addition, some Latin American countries require aggregate reports utilizing country-specific formats. For example, Colombia requires two monthly line-listings and an annual report, while Mexico requires an annual safety report in addition to a final safety report at study closure.

The Food and Drug Administration (FDA) acknowledges in **guidance for Clinical Investigators, Sponsors, and IRBs** that sponsors might require additional support in identifying which adverse events should be considered unanticipated problems that warrant reporting to an IRB.

Sponsors determine if a safety event is unexpected and potentially a SUSAR. However, an unanticipated problem (UAP or UP) is different and requires further evaluation. Apart from being serious and unexpected, a UAP/UP would have implications for the conduct of the study (e.g., requiring a significant and usually safety-related change in the protocol such as revising inclusion/exclusion criteria, or a new monitoring requirement, informed consent or investigator's brochure amendment).

Consideration 5: Adapting to electronic reporting requirements

In addition to changing regulations and regulatory nuances detailed in Consideration 4, there has been a shift in the delivery method of safety reporting across the globe for RAs and ECs. The increased use of web portals has been prevalent in the past several years and is important to understand from a pharmacovigilance perspective, as the portals are often a shared area between pharmacovigilance and other functional groups within the clinical trial space.

Clinical Trial Information System (CTIS)

With the rollout of EU CTR came the use of CTIS for the support of information flow between clinical trial sponsors, EU/EEA countries and the European Commission. From a safety reporting perspective, CTIS is primarily used for the submission of DSURs; however, prior to the submission of a DSUR, 'ASR submitter' access to CTIS must first be granted. Access for this role is controlled by the CTA holder, making open communication channels between pharmacovigilance and the CTA holder key during start-up of projects within the EU.

FDA Electronic Submissions Gateway (ESG) web trader

As sponsors await the transition to the FDA Adverse Event Reporting System (FAERS) for all clinical trial and post-marketing safety reporting to the FDA, to prepare for marketing approval in the U.S., sponsors must ensure web trader submissions can occur.

The account set up process requires a Letter of Authorization and a Letter of Non-Repudiation, which must be shared and acknowledged by the FDA help desk to receive access to FAERS. A series of test cases may be required to validate the start of submissions.

Medicines and Healthcare Products Regulatory Authority (MHRA)

Web portals for safety reporting to the MHRA include the ICSR submission portal or via E2B gateway.

If a sponsor does not have the capability to transmit via gateway, the MHRA ICSR submission portal should be set up.

- Within the ICSR submission portal, only the organization leads can add users to the portal, but if the user has access to other organization(s) that the organization lead does not have access to, a request can be sent via email to the MHRA.
- The set up of the submission portal and the approval of access when requested via email to the MHRA can be lengthy, so it is advised to start well in advance of expected clinical trial approval in the U.K.

Eudra Vigilance (EV)

EV registration should occur in advance of the first anticipated CTA approval in the EU. There are several considerations prior to initiating the process of EV registration.

- The sponsor organization must be registered in the Substances, Products, Organizations and Referential (SPOR) Organization Management System (OMS).
- If from outside the EEA, the sponsor must have an assigned EU legal representative.
- The responsible person for EV does not have to be an EEA resident. If the sponsor is a marketing authorization holder, the Qualified Person responsible for Pharmacovigilance (QPPV) must be an EEA resident.
- The EV profile set up is requested to the EMA by submitting a service desk ticket with the required documents (such as a cover letter and user declaration).

The US FDA is planning to implement gateway transmissions in E2B format for clinical trial IND safety reports by the end of 2023. A gateway transmission involves electronic submission via database-to-database that requires configuration and testing prior to the go-live date. If the gateway submission is not feasible, the FDA will make available the FAERS database for manual entry and upload of clinical trial safety report submissions.

Consideration 6: Pharmacovigilance regulatory intelligence

The ever-changing requirements for pharmacovigilance require sponsors to be vigilant and proactive in preparing for changes to limit any impact to compliance. In previous considerations, we have addressed some of the more recent and upcoming regulatory changes that have had direct impacts on safety reporting, including EU CTR, the upcoming changes to E2B (R3) requirements in Latin America, and the anticipated transition to FAERS in the U.S.

A common thread throughout each consideration and within the pharmacovigilance industry is the need to understand regulatory intelligence as it relates to safety reporting and agility when dealing with quickly changing regulatory requirements. Though there are several commercial systems available to aid in the monitoring of regulatory changes, each change does require an element of interpretation and the ability to operationalize the change within organizations. A prime example of the importance of being agile and proactive are the upcoming changes to medical device regulations.

Medical devices are regulated differently across the globe and medical device regulations have evolved rapidly in recent years. Each country or region has mandated the requirements around what medical devices and in vitro diagnosis medical devices are, their classification rules, the obligations that need to be met to place medical devices on the market, and the post-market requirements once commercialization has taken place. Manufacturers need to understand and keep track of continuous changes to comply with vigilance reporting requirements from all the jurisdictions under which they operate. Sponsors need to have a robust, well-documented vigilance reporting process in place to ensure regulatory compliance, considering variations in events to be reported, reporting forms, reporting timelines and reporting methods, including portals.

Safety reporting in clinical investigations of medical devices under the Regulation (EU) 2017/745 was explained in guidance document MDCG 2020-10/1 released by Medical Device Coordination Group (MDCG). Since the electronic system, European Databank on Medical Devices (EUDAMED), referred to in Article 73 is not available and fully functional at the date of application of the MDR, the MDCG guidance outlines the procedures for safety reporting in clinical investigations in the absence of EUDAMED. MDCG 2020-10/1 covers below investigations and guides at a high level on how to remain compliant with requirements of safety reporting to all national competent authorities where clinical investigation is being performed until EUDAMED is fully functional. However, sponsors must still consider national requirements while implementing safety reporting of:

- Pre-market clinical investigations
- Post-Market Clinical Follow Up (PMCF) investigations
- Other post-market clinical investigations

Conclusion

In the complex landscape of global clinical trials, effective safety reporting is paramount to ensuring patient safety and regulatory compliance. As clinical research advances and expands into new regions, sponsors must navigate a web of evolving and nuanced requirements for pharmacovigilance. This white paper has explored six core considerations for safety reporting, highlighting key challenges and strategies to address them.

1. **Safety reporting to investigators:** As clinical trials progress into Phase 3 and beyond, the increased number of sites and geographic diversity add complexity to safety reporting. Understanding country-specific requirements and ensuring robust reporting processes are in place are essential for success.
2. **Managing multiple clinical vendors:** Collaboration with multiple clinical vendors can introduce challenges related to data tracking, communication and compliance. Using a single pharmacovigilance vendor streamlines reporting processes and centralizes compliance oversight.
3. **Safety reporting compliance:** Meeting regulatory reporting requirements across diverse regions requires careful monitoring and oversight. Establishing key performance indicators (KPIs), interpreting reporting requirements consistently and automating submission date tracking are crucial components of compliance.
4. **Country-specific nuances:** Different countries have unique safety reporting requirements and translation needs. Understanding these nuances is essential for preparing and executing safety reporting effectively, especially in countries like Japan, China, India and Taiwan.
5. **Adapting to electronic reporting requirements:** The shift toward electronic reporting through platforms like CTIS, FDA ESG Web Trader, MHRA portals and EudraVigilance necessitates proactive preparation. Sponsors must adapt to evolving electronic reporting systems to ensure timely and accurate submissions.
6. **Pharmacovigilance regulatory intelligence:** Keeping abreast of regulatory changes and being agile in response is crucial. Commercial systems can aid in monitoring regulatory updates, but interpretation and operationalization within organizations remain essential.

In a rapidly evolving global regulatory environment, pharmaceutical companies must be proactive, flexible and well-informed to navigate the intricacies of safety reporting. Compliance with safety reporting requirements not only ensures regulatory adherence but also upholds the highest standards of patient safety throughout the clinical trial process. By addressing these core considerations, sponsors can lay a strong foundation for success in their clinical trials while maintaining country-specific compliance to advance their clinical research priorities.

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Lear more about how PPD FSP Pharmacovigilance solutions can help you navigate safety reporting requirements.

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