EXECUTIVE SUMMARY

Optimizing Global Safety Reporting in Clinical Trials

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KEY TAKEAWAYS

- Automation addresses safety reporting challenges and reduces the associated costs for the pharmaceutical industry.
- Roche recognized that safety document distribution made it difficult for investigators and ethics committees to manage clinical trials and patient safety.
- Roche's first step was a process improvement initiative for safety document distribution.
- Roche's new safety document distribution process includes changes that distinguish it from other sponsors and research partners.
- Roche has dramatically decreased safety alerts and associated costs for sites and monitors.
- Looking ahead, Roche will evolve its safety document distribution process using process management practices.

Optimizing Global Safety Reporting in Clinical Trials

OVERVIEW

In 2011, the FDA issued guidance on the reporting of adverse reactions in clinical trials, which called on trial sponsors to issue fewer, more informative reports. However, a recent survey conducted by the Clinical Trials Transformation Initiative (CTTI) and published in Clinical Trials shows that sponsors are finding it hard to put this guidance into practice.

One way to stop over-distribution of safety documents is to implement a technology-enabled solution. Roche recently partnered with ePharmaSolutions to streamline and automate the safety reporting process, while increasing patient safety and reducing costs.

CONTEXT

Kendra Hayden and Steven Beales reviewed how Roche worked with ePharmaSolutions and WCG to upgrade its Clinical Trials Portal. They discussed how this project has eliminated over-distribution of safety documents, reduced site burden, and increased patient safety.

KEY TAKEAWAYS

Automation addresses safety reporting challenges and reduces the associated costs for the pharmaceutical industry.

Safety reporting is one of the largest hidden costs in the pharmaceutical industry. It is also an area with the greatest potential for efficiency gains. In many ways, safety reporting is still a manual process.

In June 2017, the Clinical Trial Transformation Initiative (CTTI) published a paper about sponsors' and sites' perceptions of the current investigational new drug safety reporting (INDSR) process. One of the key findings was that 20% of sites have refused to process a safety report that was over-distributed to them.

Pharmaceutical companies often burden sites by sending too much information.

On the sponsor side, the experts cited three major challenges:

1. Lack of global harmonization in reporting rules
2. Determining causality
3. Fear of regulatory repercussions

Fortunately, automation solutions exist that can address these issues. In March 2017, for example, ePharmaSolutions - a WCG Company - had already completed an upgrade to the Roche Clinical Trials Portal that solved the three challenges in the CTTI research. This initiative automated country-alerting rules and distribution in 107 countries. It also automated safety report distribution based on investigator or sponsor causality and introduced end-to-end quality oversight and metrics to monitor the process.

Roche recognized that safety document distribution made it difficult for investigators and ethics committees to manage clinical trials and patient safety.

At Roche, over-distribution of safety reports was a common theme in feedback from trial sites in the U.S. and around the world. In response, the company began evolving its approach to safety document distribution six years ago. Four factors pushed the company in this direction:

1. **Lack of global harmonization.** Different countries have different safety reporting requirements. It is often unclear who is accountable for defining rules and interpreting what local laws mean. Once the company identifies the rules, it must apply them consistently worldwide so everyone understands what they must do. All parties must be trained and informed.

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2. **Fragmented safety document distribution processes.** To address the lack of global harmonization, many additional processes were injected into safety document distribution.
3. **Resource consumption.** Over-distribution of safety reports is a resource drain for sites, study teams, and monitors. Sites and investigators spend valuable time filtering through reports that aren't needed to manage patient safety. Study teams also consume precious resources distributing safety information to sites worldwide. Many trials have hundreds of sites. Monitors strive to address information gaps, so they spend considerable time tracking and reconciling what is provided to sites.
4. **Quality oversight.** As a study sponsor, Roche must retain its global quality oversight. This is difficult when processes are fragmented.

All of these issues made it difficult for investigators and ethics committees to manage clinical trials and patient safety. To address the problem, Roche created a business case outlining the rationale for changing safety report distribution.

Roche's first step was a process improvement initiative for safety document distribution.

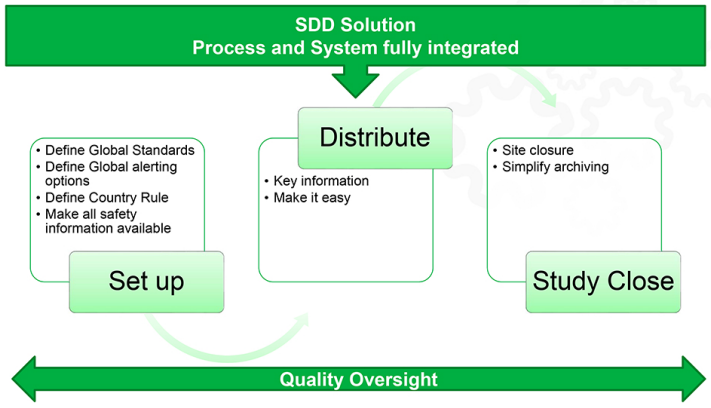
To better understand the safety document distribution process, the Roche team applied Six Sigma process management methodology.

The first stage was defining and measuring the problem. This included:

- **Reviewing years of feedback from sites, IRBs, and regulators to identify process pain points and their root causes.** The goal was to simplify life for sites and IRBs. All relevant details were moved up front in the original notifications and training was simplified. Safety document distribution stopped when the sites closed, not when studies closed. Archiving was also simplified, so sites had evidence of what they received during the study.
- **Examining how the safety document distribution process fit with the broader process landscape, including interdependencies with other key processes.** The team engaged with other organizational stakeholders to define the global standards that would be used for safety document distribution. The group also identified the decision-making process for determining what safety documents to distribute to sites and IRBs.
- **Determining whether the right roles were performing the right tasks.** The team identified two new roles in the safety document distribution process. One role was accountable for defining the country rules that all participating sites in a study would comply with. The other role defined the rules associated with the quality oversight aspects of the end-to-end process.

The team defined the end-to-end process, which included distributing safety documents, closing out sites and studies, and implementing quality oversight throughout.

Understanding the Safety Document Distribution Solution



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Roche's new safety document distribution process includes changes that distinguish it from other sponsors and research partners.

Four important changes Roche included in its safety document distribution process are:

1. **A global process.** The team defined a single, end-to-end process that all sites and study partners participating in trials must follow. This addressed the process fragmentation issues.
2. **Compound-level distribution.** Many sites and investigators participate in three to four studies at a time, often with the same compounds. The profiles of Roche's compounds are managed on a compound level, rather than a study level. As a result, one safety document is now generated per recipient for all studies.
3. **Aligned global vs. local law.** Roche implemented a process to capture compliance with local laws. The company defined global standards as an organization. It also identified safety document characteristics. For example, some countries only want domestic reports and some IRBs only want aggregate reports. Roche established country rules that define how safety documents are distributed. Each country has a key contact accountable for defining those rules.
4. **Direct distributions to the principal investigator.** Roche includes the relevant information for principal investigators in an executive summary at the front of safety documents. This eliminates the dependency of going to the Portal to see the sponsor's evaluation of the event. Country rules alert investigators to the type of documents they need, but everything is available if they need more information. Roche also no longer requires investigators to complete training prior to receiving safety information.

> When we looked at defining our process, we defined our purpose. Our purpose was about providing the framework to deliver timely, relevant safety information to our investigators and IRBs to meet their requirements, satisfy regulatory requirements, and ensure patient safety.
>
> *Kendra Hayden, Roche*

Roche has dramatically decreased safety alerts and associated costs for sites and monitors.

To measure the success of the new safety document distribution system, Roche developed metrics in two areas:

1. **Implementation and sustainment of the end-to-end process.** Part of Roche's process management methodology is measuring process performance. The team's target was to have 100% of sites trained on the process; Roche is close to achieving that. An exemption process was also defined. Email and alert transmissions to sites are monitored. The failure rate is less than 1%.
2. **Monitoring and analyzing the process and system usage.** Over the last seven years, Roche has seen a 65% reduction in all safety alerts transmitted compared to the previous process. This is attributable to the single, end-to-end process and to managing activity at the compound level. After incorporating causality distribution changes into the system, the company has also seen a 47% reduction in U.S. safety alerts since March. By automating country alerting rules, Roche issues one million fewer safety alerts per month.

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> Roche's results are better than what we projected after automating the country alerting rules. The cost savings for the sites and monitors is mind-boggling. Each site used to spend two hours reading and filing a safety report. Monitors also spent time following up.
>
> *Steven Beales, ePharmaSolutions*

Looking ahead, Roche will evolve its safety document distribution process using process management practices.

Three future focus areas for Roche are:

1. **Continue to listen and learn.** Important learnings come from key stakeholders, affiliates, and regulators.
2. **Evolve and mature the process.** Roche wants to ensure the process continues to meet the needs of sites, regulators, and the internal business. This means monitoring the regulatory landscape, as well as the process and use analytics. The company will also evaluate technology changes and align processes and systems to maintain a sustainable solution.
3. **Implement enhancements.** Potential enhancements include oversight of distributions to IRB/IEC, automation of the site archiving process, and support for precision medicine studies.

BIOGRAPHIES

Kendra Hayden

Global Process Owner, Safety Document Distribution, Roche

Kendra Hayden has been part of the Roche team for over 20 years. Kendra's current focus is on process management of safety document distribution within clinical operations. Within this focus, she serves as the Global Process Owner and Business Sponsor of all Safety Portal projects. Her involvement began in 2006 and in 2011 and was involved in the launch of Roche's Clinical Trial Safety Portal with ePharmaSolutions. Collaboration continued after the launch and in March of this year, ePharmaSolutions rolled out the next major version of the Safety Portal to Roche. This latest version is currently supporting over 3,000 studies and 300 compounds.

Steven Beales

Senior Vice President, IT, Market Owner, Safety Solutions,WCG

Steven Beales is the Senior Vice President of IT and the Market Owner of Safety Solutions at ePharmaSolutions, a WIRB-Copernicus Group (WCG) Company. An expert in the field of safety reporting technology, Mr. Beales has 25 years of experience in IT, and has spent over 16 years in the pharmaceutical industry.

He joined ePS in in 2009 and led implementation of the Company's Clinical Trial Portal at Genentech across 100+ countries. In 2015, he led implementation of Clinical Trial Safety Portal at a top 5 pharma organization, which included a data-driven rules engine configured with safety regulations from those countries, which saved this organization hundreds of millions of dollars. Over 50 million safety alerts have been distributed by these two portals via the cloud.

Prior to joining ePS, Mr. Beales was the Chief Software Architect at mdlogix, where he led the implementation of the CTMS systems for Johns Hopkins University, Washington University at St. Louis, the University of Pittsburgh, and the Interactive Autism Network for Autism Speaks.