

How to Build Risk Management into Clinical Trials

To Err is Human, to De-Risk Divine

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We live in an age in which we wish to “de-risk” our investments. In the highly competitive pharmaceutical sector, if you don’t spot potential risks before they become a danger to the patient, and a regulator can prove you had the information to mitigate them, you are liable to face one or more of the following: closure of your business unit, a prosecution case that could lead to a jail sentence, and personal responsibility for the serious illness or death of a patient. The need to de-risk is obvious.

Never before has it been so important for clinical trials teams to be alert for signals that point them toward possible risks. Clinical teams should avoid the trap of being locked into rules, regulations, and habits that mean they are failing to pay attention to all available evidence about the potential risks of a trial or product. The old-fashioned approach of ignoring negative findings—where contract research organizations (CROs) who don’t want to provide their sponsor with “bad” news ignore or gloss over concerns expressed by patients or doctors because they do not “fit” the protocol or the regulations—must be discarded. Sponsors need to actively encourage CROs to share all observations and findings. The temptation just to focus on “the positives,” perceived as regulatory requirements for approval, should be resisted. Processes must be in place to capture all pieces of information, both expected and unexpected, so that data can be extracted where required, and so that decisions can be made about how this information contributes to the accrual of knowledge about risk/benefit ratios. Sponsors need to actively encourage CROs to share all observations and findings. The temptation just to focus on “the positives,” perceived as regulatory requirements for approval, should be resisted.

Out with Old Habits, In with Imagination

Traditionally, the clinical trials environment is structured to deliver certain information according to good clinical practice (GCP). However, if GCP is not applied in a “risk-based” way, with staff trained to spot, record, and mitigate risks early on, compliance becomes too bureaucratic and obscures what matters. The pharmaceutical sector must promote and accelerate a change in behavior and processes across clinical teams to ensure that staff and CROs embrace information that is “spontaneously” (as opposed to predictably) generated from informed consent, feasibility studies, and clinical trial protocols. A balance needs to be found to redefine risk-based approach to GCP compliance. We should work together to reduce the bureaucratic and box-ticking mentality

that adds nothing to our quest for true safety improvements. With increased GCP inspections in the European Union, working with regulators to define and develop risk-based compliance is required if we want to avoid situations in which everything becomes important *after* an inspection. Clinical teams should become more open to picking up the vital clues often found early in trials.

Where might clinical trials teams find this evidence and how might it be used? We must examine how investigators obtain patients' information. Could there be a better way, a way that paints a broader picture, with wider feedback and perspective on the product? Perhaps relatives have noticed a change in patient behaviour that the patient has not noticed or cannot articulate, and which can tell us something interesting about the trial design or use of the drug? Perhaps doctors are not recommending the drug to their clients. Is there something about its ease of use or after-effects that, if reported now, can be refined to mitigate potential risk down the line?

Clinical teams need to develop best practices for collecting as much knowledge as possible in their trials. More cohesive thinking is needed across the team, and the clinical research associate (CRA) and project manager responsible will need to be alert to all types of information. They should be coached in spotting, reporting, and sharing risk. Ultimately, it is key stakeholder's attitudes that will make the difference and influence the success of the new approach. The CRA, in particular, has a fundamental safety responsibility to be a gatekeeper—to link what is happening in the field to what is taking place internally, and to spot trends and pickup and share best practices across global sites.

More Protection, Less Risk

It is clear that our era requires a change in behavior from CROs and a change in mindset for many clinical teams, but what about a framework that supports

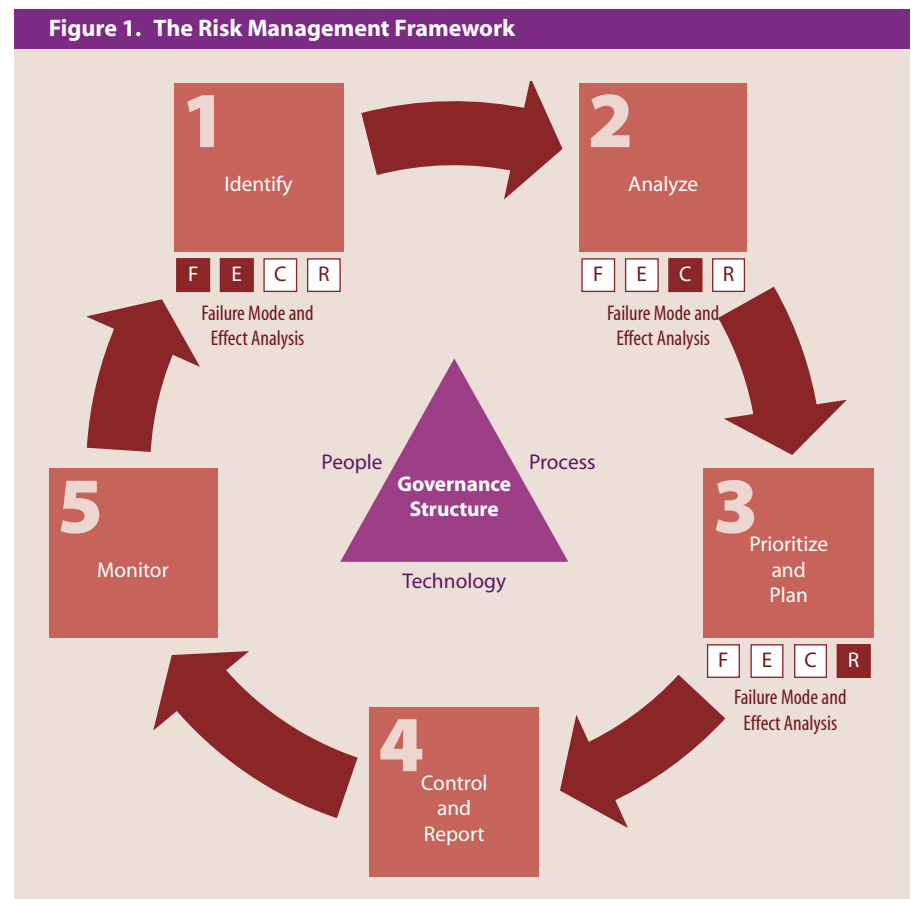
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this new approach and offers best practices and a structured way to build risk management into all key processes?

Risk management is the process of first identifying and then measuring, or

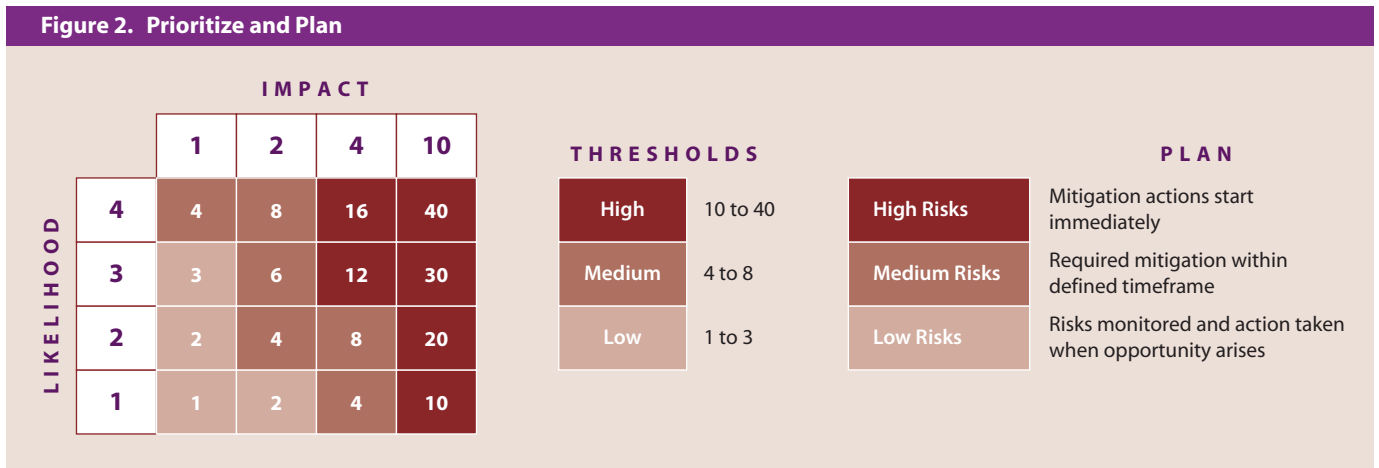
assessing, risk and developing strategies to manage it. Strategies include transferring the risk to another party, avoiding the risk, reducing the negative effect of the risk, and accepting some or all of the consequences of a particular risk. In ideal risk management, a prioritization process is followed whereby the risks with the greatest impact and the greatest probability of occurring are handled first, and risks with lower probability of occurrence and lower impact are handled in descending order. In practice, the process can be very difficult, and balancing between risks with a high probability of occurrence but lower impact versus a risk with high impact but lower probability of occurrence can often be mishandled.

Intangible risk management identifies a new type of risk—a risk that has a 100% probability of occurring but is



Legend: F = Failure; E = Effect; C = Cause; R = Risk Index. Highlighting of the letter indicates the area(s) addressed in that particular step.

Figure 2. Prioritize and Plan



ignored by the organization due to a lack of identification ability. For example, when deficient knowledge is applied to a situation, a knowledge risk materializes. Relationship risk appears when ineffective collaboration occurs. Process-engagement risk may be an issue when ineffective operational procedures are applied. These risks directly reduce workers' productivity and decrease cost effectiveness, profitability, service, quality, reputation, brand value, and earnings quality. Intangible risk management allows risk management to create immediate value from the identification and reduction of risks that reduce productivity.

A Tried and Tested Risk Management Framework

There is now a tried and tested risk management framework that will enable you to spot, record, and mitigate drug safety risks before their impact occurs, in a structured way. The new approach merges proven methodologies such as Failure Mode Effect Analysis (FMEA) with best-practice risk management.

FMEA is a method that examines potential failures in products or processes. It may be used to evaluate risk management priorities for mitigating known threat-vulnerabilities. FMEA helps select remedial actions that reduce cumulative impacts of life-cycle consequences (risks) from a systems failure

(fault). The FMEA methodology first formally emerged in the late 1940s, when it was developed and used in the aerospace sector to help avoid costly errors when building small samples of rocket technology. Word of its usefulness in helping to manage errors spread to other complex and heavily regulated industries, and in the 1970s the Ford Motor Company introduced FMEA to help ensure safety, regulatory compliance, and production and design improvement. Process and safety experts working in the manufacturing industries saw how it could be useful to life sciences, and have worked with pharma experts to tailor techniques for their specific clinical and safety needs.

The basic process is to take a description of the parts of a system and list the

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consequences if each part fails. In most formal systems, the consequences are then evaluated by three criteria and associated risk indexes: severity (S), likelihood of occurrence (O), and detectability (D). Each index ranges from lowest risk to highest risk. The overall risk of each failure is called *Risk Priority Number (RPN)* and the product of (S), (O), and (D) rankings: $RPN = S \times O \times D$. The RPN is used to prioritize all potential failures to decide upon actions leading to reduce the risk, usually by reducing likelihood of occurrence and improving controls for detecting the failure. The process is a unique amalgamation of the classic risk management steps and FMEA that breaks down into five key steps (see Figure 1).

The first step is to **identify** the risk—tracking information gleaned from sources such as questionnaires, audit reports, meetings, and conference calls. Step two is **analysis**—what system, process, or component is affected by the risk? Step three is to **prioritize and plan**, which requires that the risk's impact be measured. How big would the risk be if it happened? Could it harm the patient, the business, or both? Each risk is assessed and scored as to its scale of impact. Calculate the likelihood of it happening by the scale of impact and you have your priorities, and a clear indication of where to focus your resources (see Figure 2). This prioritization allows you to plan mitigation actions to stop the high prior-

ity risks turning into anything more serious. Step four is **control and report**, which enables you to finally **monitor** your actions in step five. Monitor the risks continuously as work takes place—is there a chance the risk could return? Take it through a risk cycle until you are sure it is completely mitigated.

A good governance structure is also crucial. Not only will it provide overall accountability for the risk management framework, it will define who is ultimately accountable for operations and processes, ensure appropriate escalation of high risks to the accountable parties, and make the risks visible to key stakeholders. Key stakeholders will also have risk management objectives in place for them; the responsibility for executing risk mitigation will reside at the root cause of the risk. The overall benefits of putting a structured de-risk approach in place include enabling a better understanding of current safety-related risks (operational and process), a reduction of

clinical-related risks, and the assurance of a systematic and consistent approach that enables teams to identify risks early and mitigate them. Sue Gammons, director of pharmacovigilance risk assessment at GlaxoSmithKline, explains how she feels the framework has helped her organization:

Adopting this approach in GSK . . . has enabled us to have a better understanding of risks within our pharmacovigilance activities worldwide, including identifying new risks and measuring the worldwide existence of risks that had already been identified in isolated instances through internal audits. As a result, we have been able to develop action plans to address the risks in a time frame determined by the priority of that risk. We believe that by utilizing this risk management framework, we can ensure consistent high standards in our pharmacovigilance operations in both our global safety department and the local affiliates.

Further Reading

- CGMPs for the 21st Century—A Risk-Based Approach, September 2004.
- History of FMEA available at www.quality-one.com/services/fmeahistory.cfm.
- Six Sigma. Can Any Body Help Me for FMEA? Forum discussion; available at <http://main.ixsigma.com/forum/showmessage.asp?messageID=30127>.
- University of Cambridge, Institute of Manufacturing. FMEA (Failure Modes and Effects Analysis), forum discussion; available at <http://www.ifm.eng.cam.ac.uk/ctm/idm/tools/process/fmea.html>.
- U.S. Department of Health and Human Services, U.S. Food and Drug Administration. Pharmaceutical. **ACRP**

Chris Holmes is a principal consultant with WCI and leads the European Drug Safety and Compliance Practice. He manages consulting teams that improve performance and compliance for the pharmaceutical and biotechnology industry, with a particular focus on drug safety, pharmacovigilance, and risk management. He can be contacted at chris.holmes@wcigroup.com.

Oliver Steck is a managing consultant with WCI. Since joining the organization three years ago, he has helped global pharmaceutical clients optimize their processes in content management, compliance-related issues, and risk management. He can be contact at oliver.steck@wcigroup.com.