

# Quality Risk Management in Clinical Trials – A Chance for More Effective Product Development

Sponsors of clinical investigations are required to provide oversight to ensure adequate protection of the rights, welfare and safety of human subjects, and the quality and integrity of the resulting data submitted to the FDA<sup>1</sup>. In the past two decades, the number and complexity of clinical trials have grown dramatically<sup>2</sup>. In light of these developments, the FDA and EMA wish to encourage more effective monitoring of clinic investigations, to ensure adequate protection of human subjects and the quality and integrity of clinical trial data<sup>2,3</sup>. Sponsors are expected to cope with this challenge and to move towards a more systematic and risk-based approach<sup>3</sup>.

Quality risk management is a systematic process for assessing, controlling, communicating and monitoring risks that might affect the quality of pharmaceuticals<sup>3</sup>. Since publication of ICH Q9, "Quality Risk Management", the subject of risk management is seen as a company-wide challenge. Lectures on quality risk management are held at numerous congresses on the subject of clinical trials. The traditional GMP areas of qualification and validation certainly feature the most, yet the definition of quality risk management shows that all product areas from research to discontinuation of the product should be accompanied by risk management<sup>3,4,5</sup>.

With the publication of reflection papers of the EMA and FDA guidance on QRM it can be assumed that GXP inspectors will expect implementation of a risk-based quality management system in companies, and will themselves work or inspect on this basis in the public agencies. The reflection paper on quality risk management in the clinical division of the EMEA suggests that the implementation of such systems will not remain just a recommendation for long, but will become a legal requirement<sup>7</sup>.

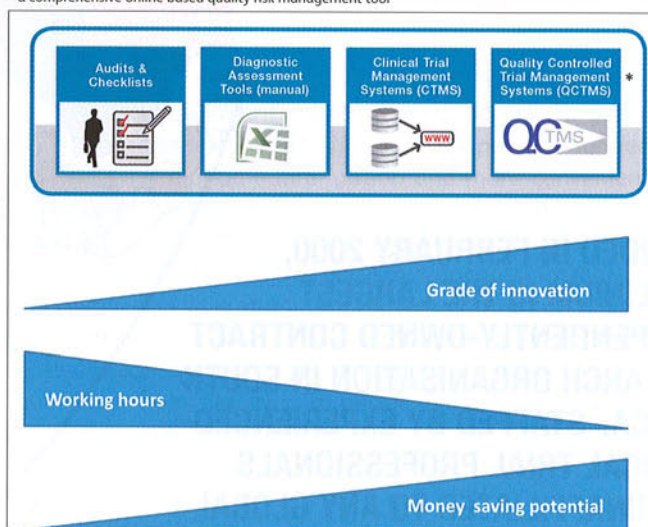
Many companies react to the growing enlargement of clinical trials by extending outsourcing, as their own resources are insufficient to cope responsibly with the flood of information. However, the CRO market has become large and non-transparent. At some CROs the idea of supplying quality and know-how externally has given way to profit-maximisation. Therefore, outsourcing per se poses a new and, in some cases, bigger risk potential. Mostly it is representatives of large companies who present their future-orientated activities in this field<sup>6,7,8,9</sup>. Hoffmann-La Roche is virtually demanding that other sponsors jointly pursue the avenue of quality risk management, as the number of external service providers, study centres, projects, patients, information, etc. can no longer be managed using traditional QA methods<sup>7</sup>. However, these systems frequently seem to be too expensive, time-consuming and unfeasible for small and mid-sized companies. This is regrettable, as, particularly for these companies, an effective risk-based quality management system could be very practical for achieving optimum product quality with limited resources.

## Current Situation

Most companies currently use traditional auditing methods, involving checklists and the maintenance and manual checking of Excel sheets, to process quality-related information within a clinical trial. The use of online-based clinical trial management systems (CTMS) has certainly made the maintenance of information easier compared to maintaining Excel sheets (Fig. 1).

Figure 1: Quality assurance tools.

\*Quality Controlled Trial Management System (QCTMS): a comprehensive online based quality risk management tool



However, these systems have been developed as management systems in order to support the project management with their administrative tasks like cost tracking, invoice preparation etc. They are often overloaded with information and features which do not comply with the idea of QRM, of focusing on the most essential information of a project. The opposite might be the case; these complex clinical trial management systems which require an extremely intensive training for the users rather increase the risks of poor data quality or patient harm, instead of minimising them.

Audits are certainly the norm as a means of carrying out quality assurance in companies. The number of audits is often calculated according to the old rule of thumb formula,  $m = n - 1$  ( $m$  = number of audits,  $n$  = number of study centres)<sup>8</sup> or simply a set number of 5-10% of study centres is defined. In the case of clinical studies with 100 study centres, both methods would mean that approximately 5-10 of 100 study centres would be audited. The number of audited study centres in relation to the total number is construed to be a maximum of 5-10 study centres in the case of small trials as a representative random sample. For larger international multi-site studies, the amount that can be checked during an audit is comparable to the visible part of an iceberg above the ocean. The majority, which is underwater, remains unknown.

ICH GCP demands the protection of rights, safety and the wellbeing of study subjects, and the integrity of study data.

Figure 2: Traditional random quality check through audits



Efficient quality assurance involves the systematic concentration on risks that endanger the safety of study patients and data quality, and that is what ICH Q9 describes.

**Quality Risk Management**

The initiatives that have been introduced in the pharmaceutical industry with ICH Q9 have long been implemented in other industrial sectors, such as in the computer or motor industry. The medical products industry is shaped very much by risk management, which is already reflected in the single classification of medical products into risk classes<sup>11</sup>.

To pursue quality risk management, a basic framework must be created. All the people in charge, including the management, must be aware that carrying out clinical studies entails risks. If no risks are to be taken, no clinical trials should be conducted. This realisation is the first step towards implementing a quality risk management system. If one refuses to accept this and sticks to old ineffective traditions it leads to problems in many cases, which are frequently a lot more time-consuming and expensive to remedy than if one had dealt with the risks beforehand. One of the things that stops people coming to this realisation is that the word "risk" is often equated with the word "problem". However, this is not the correct approach.

People constantly expose themselves to risks in daily life, such as cigarette consumption, obesity, use of solariums and many more. The majority of people are also aware that this lifestyle entails risks. Whether the risk becomes a problem depends on whether the risk is accepted or minimised. Acceptance of the above-mentioned risks can lead to disorders such as lung cancer, metabolic diseases, cardiovascular diseases, accelerated skin aging and skin cancer. By minimising the risks, the problems could be ruled out, or at least reduced. It can be assumed that similar forms of risk management also take place in many companies. Decisions are taken based on gut feelings without analysing risks. However, the application of professional risk management in industry must be carried out in a much more

systematic and standardised fashion to meet the requirements of ICH Q9.

ICH Q9 describes in very simple terms what process steps quality risk management should contain (Figure 3). The first thing is to define the risks. If we take clinical trials and the requirements of ICH GCP, the main risks arising in the context of any clinical study are the danger to study patients and/or data quality. These risks are more or less fixed parameters in any clinical trial, whereby the extent of the risks depends on the complexity of the study design and the effect of the test preparation. However, in some cases there are other fundamental risks that could derail a project, such as non-adherence to a budget, non-compliance with deadlines, and rejection of studies by the authorities. The next step is to identify the risks. Risks are identified indirectly by recording specific key risk factors, such as the number of protocol deviations, number of queries, enrolled patients and monitoring visits per patient, the deadlines for reporting SAEs, and also the experience of the study centre or CRAs. These indicators must first be quantified to make them measurable. Afterwards, the source of information needs to be identified e.g. monitoring reports, eCRF, central lab, and medical devices. With the identified sources, information about risks can be collected in the course of the studies (risk identification) and reported as a risk via specific individually created algorithms (risk reporting). Thus, for example, the occurrence of protocol deviations per patient could be highlighted as an indication of lacking protocol compliance and therefore be identified and reported as a risk. However, the identification of risks can be carried out in a substantially more subtle form using modern technical systems. Thus, the occurrence of three protocol deviations per patient in the case of an experienced well-known monitor could be rated as a risk, whereas in the case of an inexperienced monitor one protocol deviation per patient would already lead to a risk being reported, as there could be a risk of protocol deviations being "underreported". Once a risk has been identified, it must be reported proactively to the responsible persons, like the project management team. Within the context of evaluating the reported risk, this team has to initiate corrective and/or preventive steps to reduce the risk, otherwise the risk would continue to exist and remain marked in the system.

The well-known traffic-light system has proved worthwhile for reporting risks. Here risks are subdivided into different classes. A green light means that there is no risk, a yellow light means that there is a low risk, and a red light indicates a high risk. Besides the signal function, which would include the manual control of risks, parallel to this risk reporting can be underscored by an email, so that acknowledgement by the person in charge is guaranteed. As not every person in charge has to be confronted with each risk, different thresholds of risk-reporting should be introduced. As an initial threshold, a low risk could, for example, just be reported to the project manager and/or the lead CRA, whereas a large risk could also be reported to the higher management and/or the QA management. If we take as an example the adherence to deadlines for SAE reporting by a study centre, the delayed reporting of an SAE could be rated as a high risk (Fig. 4).

Reporting an SAE with an incorrect code (e.g. hospitalisation instead of the medical indication) within the statutory reporting period would be classed as a low risk, of which only the project management would be informed (Fig.4). It can then initiate the renewed training of study personnel.

Figure 3: Risk management according to ICH Q9

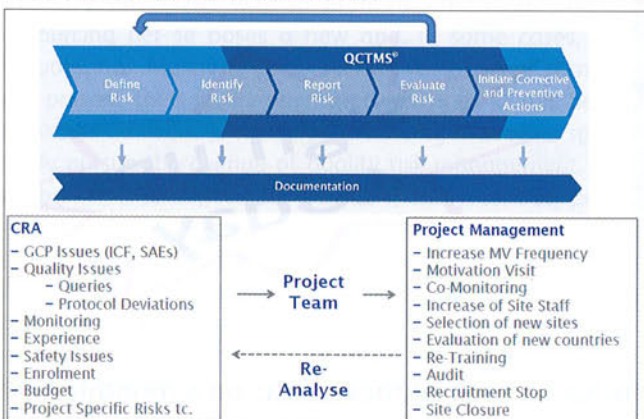
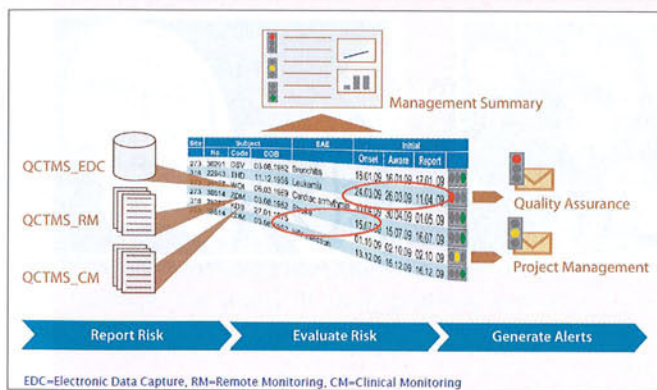


Figure 4: Automatic risk reporting in clinical studies



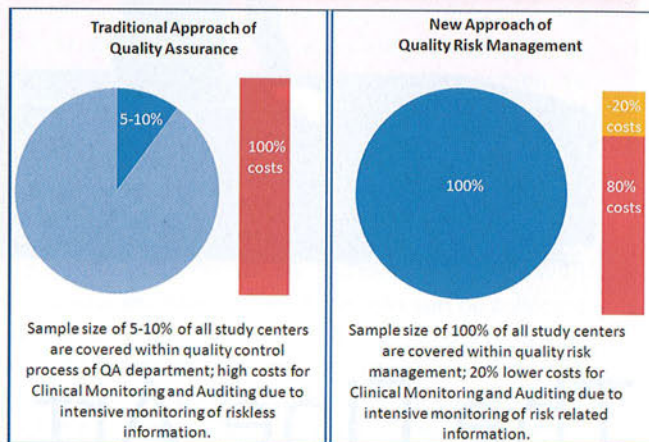
The use of online systems is certainly not essential to implement ICH Q9 in the clinical trial<sup>5</sup>. Excel sheets can also be programmed in such a way that the information which indicates a risk is marked in colour. However, the maintenance and mandatory validation of Excel sheets with an algorithmic application in the case of large projects are very costly and inconvenient. The bigger and more diverse the projects, the more advisable it is to use automatic online-based software applications for risk-reporting<sup>2</sup>. It must be stressed that systems which are flexible should be chosen. As the risks between companies, projects, products, trial phase, etc. differ, the risks must, as a necessity, be redefined prior to implementation of a project. The project management should work closely with the people in charge of the system to define and determine new project risks and adapt the risk management system accordingly. Adaptation of the system in the course of the project must be

possible so that the learning process can be implemented in the system during a project. New risks must be incorporated in the system and information which has turned out to not be risky in the course of a study must be adapted in the system.

**Summary**

The implementation of a quality risk management system is advisable for companies of any size, and it is only a question of time until the implementation of such systems is prescribed by law. Companies and authorities are faced with a huge quantity

Figure 5: Traditional QA/QC process versus control of the entire project through quality risk management



of information in clinical research. As it is no longer possible and therefore no longer feasible to process all the information, the focus should be on risks. Key points to watch out for with regard



to risk management are as follows:

- The system must be supported by upper management.
- The system must be understood and implemented by the company as a whole.
- The execution of a clinical trial per se entails risks.
- Risks should be dealt with systematically and require that people learn how to quantify, identify, evaluate and minimise risks.
- Understanding that an existing risk in a study is not a sign of bad quality.
- The use of automated risk management systems should not mean additional costs, but should lower the costs when conducting clinical studies.
- Quality risk management is not a system organised by the quality assurance department, but rather by the project manager.

If risks are detected in a project, they should not be regarded as a failure by the people in charge, but rather as an opportunity to tackle problems before they arise. The philosophy of quality risk management is logical and easy to understand. It should concentrate on the essentials, but also reflect on the situation of the project in its entirety (all the study centres).

Consequently, the assumption that introducing systems which concentrate on risks causes additional costs is not right. By focusing on risks and the automated reporting of risk-related information, project managers can use their time more productively and thereby work more cost-effectively. Quality risk management does not increase costs, but rather holds saving potential through the more efficient use of resources. The manual control of countless Excel sheets and online-based trial management systems overloaded with information is no longer necessary. The identification of risks takes place before the study commences. The reporting of risks is carried out automatically. A project budget can be adapted to the risks accordingly. For example, study centres with a higher number of reported risks can be monitored more frequently than study centres with fewer reported risks (adaptive clinical monitoring)<sup>1,2</sup>.

Likewise the audit planning by the QA managers should be based on the number of reported risks and not on the number of recruited patients. As there is a positive correlation between the number of risks and the audit findings, they would have a different significance than if the study centres had been chosen randomly. In this case too finances can be used more sensibly and costs can be cut.

The clinical research industry is extremely innovative. Such high innovation intensity leads to higher project complexity, larger clinical studies and higher costs, which makes rethinking necessary. New innovative products require also new innovative systems and processes to also ensure data integrity and patient welfare for larger project sizes, which is the basic idea of ICH GCP. Old tried and trusted processes will no longer be feasible. Whether the potential of such systems will be recognised remains to be seen.

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