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Audits in GCP and Beyond

Methods and Experiences

3rd revised and enlarged edition

EDITIO CANTOR VERLAG

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Methods and Experiences

3rd, revised and enlarged edition

Edited by the
German Society for Good Research Practice (DGGF)

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Contents

Preface to the 3rd edition

The second edition of this book was published in 2007. Since then, there have been significant changes in the area of quality management. The field of activity of Auditors in regard to the development of medicinal products and medical devices has expanded significantly. As audits now go beyond GCP, we want to address these changes with the 3rd edition of this book.
New chapters have been added:

- Auditing in Clinical Research: Aligning Auditing and Risk Management. Challenges and Opportunities
- Auditing in Clinical Research: Auditing in a Risk-management Environment. Challenges and Opportunities
- Preparation, Hosting, and Follow-up of GCP Inspections
- Clinical Investigator Audit as Part of the System Audit
- Quality Management and Audits in Non-interventional Trials
- Auditing Medical-device Trials in the EU
- Auditing Trials in Vulnerable Subject Populations
- Audits at the Interface Between GCP and GMP
- Auditing Contract Archives
- Auditing in Low and Mid-income Countries
- Investigating Suspected Scientific Fraud or Misconduct

We would like to point out that all individual contributions represent the opinion of the respective authors and do not necessarily reflect that of the other authors.
I would like to thank the authors for their work, their enthusiasm, and the meticulous revision of their contributions.
Special thanks goes to John Norton for his review of the English texts and translations and to Kerstin König for her support in reviewing and editing the manuscripts as well as her valuable contribution.
Finally, ECV • Editio Cantor Verlag and its editorial office deserve our gratitude for their care and expertise in the preparation of this book.
We hope that the third edition of this work will once more become successful as a reference book for Quality Assurance experts.

Mannheim (Germany), September 2015

Steffen König
President of the DGGF

1 Quality Management Systems in Clinical Drug Development

What Audits May Contribute

Regina Freunscht

Quality is usually defined as the level of compliance to a set of predefined conditions or specifications.
A **Quality Management System** (QMS) consists of various elements, business processes, and tools in an organisational structure focused on achieving quality objectives, the implementation of quality management, sustainability, and the effective interaction of all QMS components.
These are the most prominent elements of a modern QMS in clinical drug development:

- **Organisational Charts**—provide an overview of the entire organisation, outlining all major functions and divisions and how they interact with each other. All individuals in an organisation are able to identify whom they have to report to, who their peers are and to which part of the organisation they belong. The position of the quality-assurance (QA) unit is generally recognised as being critical to ensure independence of audits and auditors, as per section 5.19 of ICH E6. Today's industry standards keep QA units separated from the operational functions in order to avoid conflicts that might arise if QA had the same reporting lines as those departments they have to audit and whose quality they are intended to assure.
- **Definition of Roles and Responsibilities**—ensure that responsibilities and authorities are defined and communicated within the organisation. Usually job or role descriptions are used to make sure that people know what they have to do and who is entitled to do what. While it may sound obvious, in many organisations it remains unclear who has the authority for making certain decisions and who can sign what type of documents. Furthermore, it is of special importance to identify the need for quality-control measures during the day-to-day activities in individual job descriptions.
- **Standard Operating Procedures (SOPs)**—are used as a set of written instructions to achieve uniformity in the performance of a specific function. Harmonisation of work and consistency between individuals are seen as a key element to ensure quality. SOPs usually provide a structure aimed at simplifying processes and preventing excessive overlap. The SOP system should define which people, actions, and documents are going to be employed in order to carry out the work in a consistent manner, while documenting what has happened. This may include manuals, handbooks, procedures, policies, records, and templates. The terminology used is less important than the purpose and use of the documents. The fundamentals of a SOP system are the same regardless of what kind of work is involved.
- **Qualification and Training**—as specified by ICH E6—requires each individual who contributes to the clinical drug development to be qualified by

education, experience, and training to perform his or her respective tasks. Written evidence is usually provided in Curricula vitae (CVs) and training records. The regulatory environment in the pharmaceutical industry is very short lived and industries' best practice is improving quickly. Therefore, continuous learning and keeping abreast of developments is essential and the personal responsibility of each individual who specialises in auditing.

- **Quality Control (QC)**—is assured by a quality-management system, which should consist of clearly defined and appropriate quality-control (QC) systems. The output of quality-control activities should be reviewed to indicate the degree of adequacy of performance and also to monitor trends if there is any improvement or even deterioration. Quality Control is a pivotal part of the quality-management system because the quality of the process directly depends on QC. Therefore, QC usually has to be included in every step of the operational work and conducted by those performing, managing or supervising the process to ensure that the required standards are met. QC comprises routine procedures generally undertaken by the same personnel that carry out the process in order to check and ensure that this process meets defined requirements. These checking, inspection and surveillance activities form a part of the quality-management system. Simple QC activities target the correctness, completeness, and accuracy of content as well as compliance to certain standards. Common self-managed QC activities involve tools such as checklists, forms, and templates while supervision, co-monitoring and compliance monitoring involve independent observation. Quality Control may also involve external quality-control systems and inter-laboratory testing to demonstrate that processes are providing results that may be compared between different organisations (Fig. 1).

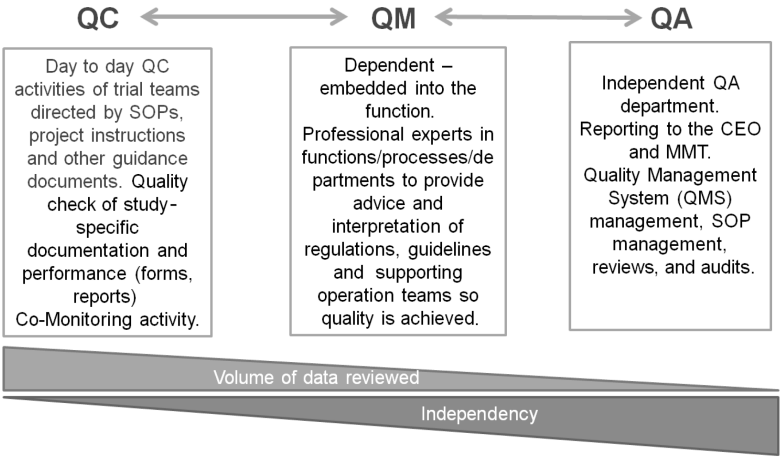

Fig. 1. Interdependencies between Quality Control, Quality Management and Quality Assurance.

- **Change Control** and **Deviation Management**—the best way to manage any change is to plan for it beforehand rather than to simply document it af-

terwards. Furthermore, it is important to consider the potential impact the change will have on those involved (as well as the process, the system or equipment) prior to its implementation. Consultation with those involved will help identify potential risks early on and can help to mitigate them prior to the execution of the change. While changes are usually pre-planned, deviations are defined as any unplanned departure from approved instructions or established structures (e.g., protocols, SOPs, plans, agreements, tools, etc.). Identified failures to comply are usually used as lessons learnt from things that went wrong and are, therefore, retrospective activities. It is important to assess the root cause of any deviation carefully and to learn from the corrective and preventive activities to avoid recurrence of the same or similar deviation in future.

- **CAPA Management** and **Continuous Improvement**—specifically apply to measures, i.e., Corrective and Preventive Actions (CAPA) taken to eliminate causes of non-conformities or other undesirable situations and, thereby, improve processes of an organisation. It focuses on the systematic investigation of the root causes of identified problems or identified risks in an attempt to prevent recurrence (for corrective actions) or to prevent occurrence (for preventive actions). A common misconception is that the purpose of preventive action is to avert the occurrence of a similar potential problem. However, such a process is part of corrective action, because it is a process of determining similarities that might take place in the event of a discrepancy. Corrective and Preventive Actions both include investigation, action, review, and further action if so required. It can be seen that both fit into the PDCA philosophy (plan-do-check-act). To ensure that Corrective and Preventive Actions are effective, the systematic investigation of the root causes of failure is pivotal.
- A continuous improvement process is the ongoing effort to improve products, services, or processes. It can be seen as a meta-process for QMS following input e.g., from KPIs, metrics, CAPAs, changes and deviations and it is used as part of the QMS, whereby feedback from the process and functions are continuously evaluated against the anticipated standards and organisational or functional goals. The fact that it can be called a management process does not mean that it needs to be executed by the "management"; but rather that continuous improvement is an elementary part of the decision-making process within an organisation (Fig. 2).

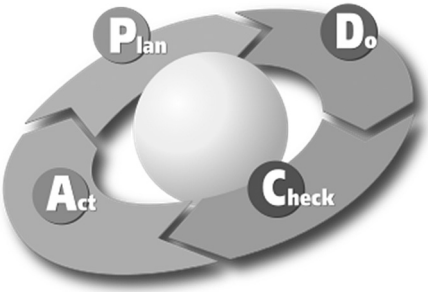

Fig. 2. The PDCA cycle.

- **Quality Assurance (QA)**—is a way of preventing mistakes or defects and avoiding problems when applying procedures or delivery services. QA seeks to ensure that certain specifications and regulatory requirements are met. QA is also applied to verify that features and functionality meet business objectives. Quality Assurance is an administrative and procedural activity, implemented in a Quality-management system so that requirements and goals for a service, activity or product will be fulfilled. The work of a quality-assurance department is usually seen as the systematic measurement, comparison with standards, monitoring of processes, and an associated feedback loop that facilitates error prevention. This can be contrasted with Quality Control, which is focused on process output.

Today three principles are included in QA work:

1. "Fit for purpose": Quality and services should be suitable for the intended purpose
2. "Quality by Design/Right the first time": Quality should be planned and thus mistakes should be avoided
3. "Quality Risk Management": Early potential areas of risk should be identified, risks mitigated, and focus put on areas that really matter.

In general, quality-assurance activities include consultation and advice (proactive quality approach) as well as audits and inspections (retrospective quality validation).

- **Escalation and Management Review**—support an organisation's senior management who carries the formal and overarching responsibility for the effectiveness of the quality-management system.
  This is often done by periodic review of:
  – Quality objectives and achievement
  – Overall level of compliance
  – Periodic review of assessment of performance indicators (to monitor the effectiveness of processes)
  – Suggestions for changes, necessary to achieve quality objectives.

  Depending on the organisation's policies, senior management may want to review or at least have access to the QA and QC reports and quality-related performance data. The classic example comprises a look at the number of observations made during a QA audit, the categorisation of these observations (e.g., critical, major or minor), as well as the numbers of observations in different categories and using them for the analysis of trends and priority areas for immediate improvement. These measurements are often known as quality metrics. Identified problems and potential risks that have a certain criticality or represent an immediate business risk will be brought to the attention of senior management immediately. This is done in a professional way either in writing or by phone call. It is important always to notify the appropriate level in the hierarchy where individuals are able to come to the right decision or to intervene. A concise summary of the issue or risk together with background information needs to be provided as well as a clear statement of what is expected or needed within which time frame. If possible, an impact analysis or potential consequences must be outlined in case the expected action is not taken in time.
- **Audits and Inspections**—are generally defined as planned and documented activities performed by qualified personnel to determine—by investigation, examination or evaluation of objective evidence or applicable docu-

ments—the adequacy and compliance with established procedures as well as the effectiveness of implementation.

While auditing, auditors perceive and recognise the underlying situation requiring examination, collect evidence, evaluate it; and on this basis formulate an assessment that is communicated through the audit report. The results of an audit provide an opinion on the adequacy of quality and compliance within a specific environment. Auditors must have an adequate understanding of the environment in which they audit and a high level of expertise, experience and seniority to conduct their work in an unbiased, objective, balanced and fair manner. An audit is a sampling process seeking independent confirmation that standards have been met (and to which level). As such, it provides a snap shot of the scene with only limited scope but not a prognosis of the broader level of compliance in an organisation. Audits are usually conducted by the quality-assurance unit and may use similar techniques to QC activities but the fundamental difference is that Quality Assurance is independent of the activities that are being audited. In contrast to audits, who are usually conducted and sponsored by the company, the inspection is conducted by regulatory agencies or supervisory monitoring bodies. Authority inspection results can uncover serious infringements, lead to termination of certain activities (e.g., debarring of an investigator), the revocation or non-prolongation of certifications (e.g., in the GLP arena) or partial or permanent cessation of a clinical trial or program (e.g., in case of safety or quality issues of an Investigational Medicinal Product). In each case, by their nature and scope audits and inspections are limited to reviewing and inspecting what has already happened. Due to the sample technique applied and their retrospective approach, audits and inspections are limited in their ability to predict the future. Their outcome can and should contribute to an effective CAPA management and finally result in continuous improvement activities. Therefore, they should be seen as a validation tool to assess the effectiveness of the entire quality management system, including all previously described components rather than a stand-alone tool for quality management. Especially in days where risk-based monitoring and quality-risk-management approaches are receiving more and more attention from industry and regulatory agencies, the value of audits is experiencing a renaissance. The value of audits should not be underestimated as a source of information and tool for designing appropriate protocols. They can help to verify the effectiveness of clinical trial risk-management plans and help in the verification and adaptation of clinical trial management and monitoring activities.

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2 Auditing in Clinical Research: Aligning Auditing and Risk Management

Peter Schiemann, Beat Widler, and Steffen König

1. Introduction

The approach to quality management in an environment of Good Clinical Practice (GCP) and Good Pharmacovigilance Practice (GPvP) has traditionally focused on on-site monitoring, QC verifications, and audits to enforce quality and compliance.

However, the latest publications by FDA (US Food and Drug Administration) and EMA (European Medicines Agency) on risk-based monitoring (RbM) [1] and risk-based quality management in clinical trials [2], respectively, put forward a more proactive approach to managing quality in clinical trials and ensuring data integrity and patient safety.

The proposed risk-based approach is superior to the traditional approach because it allows to identify potential problems more rapidly and to achieve long-term solutions. In essence, the described risk-based approach combines "quality by design" planning techniques when designing a protocol or a process, setting up a trial (structures, countries involved, outsourcing, IMP, etc.), qualifying and selecting sites with the support of data-mining processes as well as established risk-management methodologies, e.g., FMEA (Failure Mode and Effect Analysis). Through innovative and structured processes, this approach improves risk awareness from the onset and accelerates detection of potential issues by analysing and comparing existing data from a quality perspective. Such a risk-based approach to quality management ensures that resources are deployed in a timely and expeditious manner to areas that need them most.

This chapter provides an overview of the components supporting a risk-based approach to managing quality in clinical trials and thus ensuring oversight by the sponsor and ultimately quality and compliance.

It is important to mention that a risk-based approach cannot eliminate risk in clinical research and pharmacovigilance. However, it can help to identify and improve the management of high-risk situations and settings in order to address such situations before they turn into problems. In other words: it helps you focusing on your priorities with an objective eye.

2. Importance of a Solid Risk-based Approach to Managing Quality in Clinical Trials

The overall objective of quality management in clinical research is to ensure *patients' safety, rights* and *integrity* as well as *data integrity,* which finally ensures compliance with GCP and pharmacovigilance guidelines.
The EMA lists several reasons such as costs of clinical development and limitation of resources, development deadlines, pressure from investors, fragmentation of roles carried out by many niche players with their own priorities and unclear distribution of roles, globalisation of trials with complex regulatory, business and scientific environments, little appreciation of risks or what risks actually are (quite often confused with "problems"), stifling of innovation by restrictive business practices and many more [2].
The proactive risk-management approach will ensure business continuity by avoiding significant 'showstoppers', creating transparency of potential issues in their infancy and allowing subsequent mitigation before they manifest as real problems. In addition, a standardised risk-management methodology allows to better transfer experience gained from errors or process deficiencies observed in a given trial or activity to the totality of trials or other parts of the process within a sponsor organisation.
Now more than ever there is a need for more effective and efficient processes to meet quality management (QM) objectives. In companies with rich drug-development pipelines, the number of ongoing clinical trials and the size of patient pools are increasing substantially. This increase is compounded by the growing number of trials that are performed with partners (e.g., site-management organisations, collaborative groups, and other parties conducting safety and efficacy studies). Increasing scrutiny by Competent Authorities and heightened public awareness of quality issues also create challenges for QM objectives. Reforms led by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA), among others, further highlight the limited potential of quality oversight by auditing alone. EMA's Volume 9A, for example, encourages new governance and control standards, shifting the focus of regulators from ad-hoc to much broader oversight of operations. This is matched by a corresponding shift in accountability from operational units of pharmaceutical companies such as the drug safety department to their executive management.
In addition, the above-mentioned recently published papers demand even more from a sponsor of clinical trials:

- Planning the program and studies from the very beginning with the end in mind
- Using a risk-based approach that is based on data
- Decisions and final reports are also guided by data instead of being personal opinions.

Such reforms challenge us to keep up compliance by establishing an effective risk-based planning and oversight environment. This allows coping with future changes and to achieve even more than by the traditional approach.

3. What Is Needed for a Solid Risk-based Approach to Managing Quality in Clinical Trials?

According to FDA, EMA, MHRA (British Health Authority – Medicines and Healthcare Products Regulatory Agency), BfArM (German Health Authority – Bundesinstitut für Arzneimittel und Medizinprodukte), and others, the approach to planning, setting up, running, and reporting on clinical trials has to change significantly.

In a nutshell, regulators demand that the current situation, as described above, requires a clear prioritisation of compliance activities in order to address the topics and areas that are essential to clinical trials to ensure patient safety and data integrity. Correctly, the regulators also highlight that if there is a discrepancy between protocol complexity and allocated budget or if a sponsor has unrealistic timeline expectations, inadequate quality is "built" into a clinical trial and they are concerned that poor understanding of the basic requirements for a risk-based approach results in non-compliance or even critical GCP findings. Therefore, in the view of the agencies, a risk-based approach is the only solution to the described situation. This seems simple enough, since everyone has heard of "risk" before and has an opinion on what risk is and how it should be assessed.

However, that also seems to be the problem. Usually if ten people are asked to give a definition of what "risk" is, usually ten different answers are given. Therefore, it is important to ask: "What do the employees at a sponsor company or service provider know about risk management?"

The most common methodology to assess risk is the *Failure Mode and Effect Analysis* (FMEA, see Fig. 1). Its application is quite simple; however, regulators are demanding that risk assessments as well as the actions following risk assessments must be consistent. How can consistency be ensured when people are discussing the FMEA elements of the cycle in Fig. 1 and giving their personal opinions? What happens if the team that made the first assessment changes in the course of time? Or, what happens when another group replaces the entire group? Will the outcome be consistent with what the first group had come up with?

Decisions need to be based on data that are verifiable and traceable. This is a clear statement in the EMA reflection paper. However, this does not only imply collecting data and then have individuals review them and take a decision. That is not what this is all about. Decision algorithms need to be defined well in advance so that decisions are consistent and not influenced by human error [3]. This is especially important in our current work environment when many decisions need to be taken under pressure, by different stakeholders or even changing stakeholder communities. An example coming to mind in this context is the practice of in- and out-licensing of development projects.

The most important areas that need to embrace the risk-based approach are:

- Protocol design—designing protocols with the value proposition of the clinical program in mind (i.e., the study rationale with one question to be answered), assessing the risks of the design while the protocol is being written.
- Study start-up—setting up a clinical trial and assessing the infrastructural risks of the operational model, i.e., risks represented by contractors, countries and sites involved as well as those represented by the characteristics of the IMP, i.e., route of administration, documentation, regulatory require-

ments (local and global), specific safety items of the IMP and sampling, to mention but a few.

- Site qualification and enrolment optimisation—risk assessment to select the "right" sites that on the one hand fulfil the compliance requirements and on the other will enrol the agreed number of patients into the trial.
- Metrics—key risk indicators and performance indicators need to be defined to continuously assess risk at sites as well as other entities and their processes.
- Risk-based or—better—data-driven monitoring—based on the four above-mentioned criteria and assessments, a framework of decision making needs to be established to guide monitoring into the different activity channels for oversight.

All of the above areas need a thorough set up with subject-matter experts from all functions involved, including Quality Assurance.

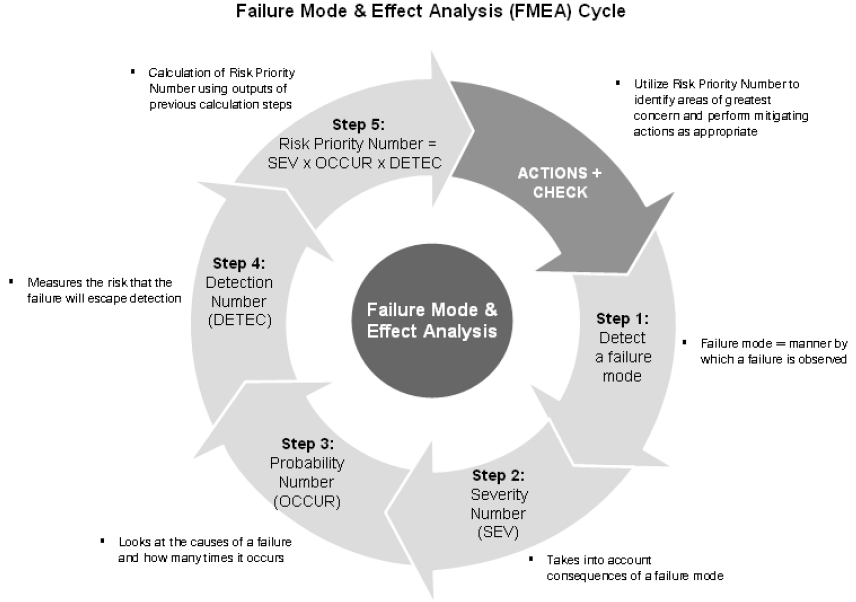

Fig. 1. Diagram of the "Failure Mode & Effect Analysis (FMEA) Cycle".

4. Will a Risk-based Approach Allow the Discontinuation of Source-document Verification (SDV) and Reduce the Burden of On-site Monitoring?

Traditionally, SDV was used to help improve data quality in clinical trials, but research has shown that SDV has no significant impact on the quality of data [4].

However, SDV reduction without any other action is one of the major risk-based monitoring (RbM) pitfalls, since SDV fulfils more than the one purpose of checking the source vs. the transcribed data for data quality.
Source-document verification in a risk-based environment is a tool in the study team's toolbox to supplement information that cannot be obtained through central review and to confirm conclusions drawn based on the central review. Through the systematic use of a centralised review of the study data, a reduction in the burden of on-site monitoring, improvements in clinical data quality as well as an increase in the clinical monitors' effectiveness can be expected. All sources of data should be mined and analysed such as the data from the CRF, its metadata (e.g., audit-trail data), the CTMS, the TMF, safety database, etc. When such an approach to study management is applied, SDV will serve as a root-cause analysis tool when needed rather than a data-comparison tool. We should always keep in mind that the goal of any monitoring activity—regardless of the tools used—is to protect patients' safety, integrity and rights as well as to ensure data integrity. A proactive approach to study oversight increases efficiency by reducing the need for corrective actions.

5. What Are KRIs and KPIs, and How Can They Support a Risk-based Approach?

A key risk indicator (KRI) is an objective measurement of a study-related parameter against a pre-set threshold (therefore digital, i.e., "on" or "off"), providing a signal about the risk of a study process or any of its deliverables. It is important to realise that KRIs and KPIs (Key Performance Indicators) are not the same. A KPI measures the achievement of an operational or performance target such as completing enrolment of patients within the planned timelines. Moreover, KRIs can be distinguished as 'leading' or 'lagging'. A leading KRI measures parameters that indicate a problem is building up before it materialises so there is still time for correction. Lagging KRIs indicate deviations that have already happened, but as a singular event would not have a great impact, however, when piling up, impose a risk on the process/deliverables looked at. Generally, leading KRIs are more effective but are also more difficult to measure than lagging ones. A proper suite of KRIs combining leading and lagging KRIs allows a study management team to plan and execute a risk-based strategy, and KRIs can be benchmarked via empirical data analyses.
When defining KRIs, study teams must practice caution to measure what really has an impact on compliance and process effectiveness and not what can be measured easily. For instance, measuring compliance against timelines may induce team members to take short cuts, which can be the root cause of new deficiencies.

6. What Role Does Auditing Play in a Risk-based Approach to Managing Quality in Clinical Trials?

A change in focus of audits is to be expected. Most of the GCP audits in clinical trials were and still are focusing on the clinical site. However, with a risk-

based approach and increased utilisation of electronic technology in clinical trials, investigator-site audits will become less important. Even today the question may be asked: what conclusion can actually be drawn on the whole of a clinical trial if the resources only allow auditing about 5–10% of the sites or less? As is well known, no conclusion can be drawn, since the pool of clinical trial centers auditors select their samples from—even if selected with utmost care—is not homogenous and, therefore, the application of any conclusion derived from the sample of sites audited to all of the sites in that particular trial is not robust.

This does not mean that audits are becoming obsolete—on the contrary! As we embark on the newly proposed journey of a risk-based approach to managing quality in clinical trials, audits will be essential in order to ensure that the whole approach to risk-based quality management works and delivers on its promise. In other words, when the wealth of data is analysed and conclusions are drawn with the help of all the algorithms that have been created and put in place on the quality level of a trial, we need to make sure that our assessments are reflecting reality. And what better method can there be than comparing the assessments with what is going on in the trial verified by an audit? In that regard, clinical-trial-centre audits will become an integral part of a system audit.

7. Outlook

In conclusion, this new approach to quality management in GCP and drug safety clearly distinguishes itself from traditional quality management by combining a strategic with a systemic approach to risk management.

While the full impact of a risk-based approach on the drug-development process may take many years to demonstrate value, benefits within an organisation can still be expected shortly after implementation. Involving all business partners as part of the risk-based processes can be expected to create immediate benefits both in quality and compliance through a clearer understanding of relevant risks by all parties. Moreover, by establishing the processes of risk assessment and mitigation of risks in a consistent way will have a lasting impact on operational processes.

In companies in which risk management is already used, key decision makers give very positive feedback on this new quality-management concept, especially if it relates to the planning of a clinical study. Quality risk management has been shown to proactively reveal issues that may not have been recognised from the outset, but which are likely to cause problems during study conduct. It is fair to say that this assessment helps all parties involved in clinical trials to be aware of the risks and to avoid mistakes from the very beginning.

In summary, a risk-based approach to managing quality in clinical trials is a new quality-management principle that will overcome the traditional approach of using on-site monitoring visits, QC verification or audits alone to maintain quality oversight.

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3 Auditing in Clinical Research: Auditing in a Risk-management Environment

Beat Widler, Steffen König, and Peter Schiemann

1. Introduction

As described in the previous chapter, a more proactive approach to managing quality in pharmacovigilance and clinical trials ensures a more systematic and proactive protection of patients' safety, integrity and rights as well as integrity of data.
This chapter provides an overview of an "audit-compliance" strategy if a risk-based approach to managing quality in clinical trials including risk-based monitoring is adopted. It discusses how audits should be used in order to provide assurance that the risk-based approach is working as planned and produces consistent results and actions.

2. Will Audits Become Obsolete—or Will the Role of Quality Assurance and Auditing Need to Change to Accommodate a Risk-based Approach to Clinical Study Management?

Audits will not become obsolete. For one, they are mandated by GCP and regulatory guidance such as the "EU Guideline on Good Pharmacovigilance Practices (GPvP)" and are also called for by Regulatory Authority inspectors, who verify that a sponsor or Marketing Authorisation Holder (MAH) has implemented an audit strategy and plan.
However, the way a sponsor/MAH plans the audits and auditors conduct them has to change. The role of the auditor in a classical sense was mostly focused on auditing clinical trial centres to ensure that the data collected were reliable. It then evolved into having to audit a variety of internal and third-party systems. But as explained in the previous chapter, the sampling approach—even though risk-based and, therefore, prioritised—has always been retrospective, not chosen from a homogenous pool of entities, therefore not representative and could only address very few (typically about 1–15%) of all centres involved. With regard to systems results, the selection or frequency of audits occurs in a rather haphazard manner.
This approach will need to change significantly in the new environment of a risk-based approach in managing quality in clinical trials and risk-based monitoring.
In the "new world of a quality risk-management" approach audits will continue to play a key role in quality oversight. Audits will support the quality risk

management in the following ways:

- By verifying and confirming that data used to drive risk assessments are true, credible, and accurate. This can be done through routine audits; very much in the way audits have been performed in the past. This is a good opportunity for newly trained auditors to develop auditing skills.
- By using audits to collect information that is otherwise not easily accessible, e.g., on the robustness of company and third-party processes, their validation status, verifying that "what is declared, is also being done and documented", etc.
- By using audits to assess that Corrective and Preventive Actions (CAPA) have been completed, are adequate, and do address the root causes of findings.
- By challenging quality risk-management assessments, i.e., testing whether a "no-risk" or "acceptable-risk" assessment made can be corroborated through an audit performed by skilled auditors who know what the potential weak links in the process or system are. If such a weakness is detected, it challenges the risk assessment but is not "bad news" as it triggers its revision. In other words, a significant finding challenging the risk assessment contributes to an improvement of the risk-assessment methodology while absence of such findings corroborates its validity.

3. How Can Quality Assurance and Audits Become More Effective?

A risk-based approach to clinical study management is largely an "intelligence game", i.e., it builds on the systematic collection of data about quality and performance indicators and its timely analysis for trends, outliers, deviations, etc.; the more actionable quality-related data is available, the more reliable the risk assessment is. As audits are a very valuable source of information about compliance and robustness of a process, the sharing of audit outcomes would significantly enrich the risk information available to a given sponsor. This holds particularly true for third-party audits such as audits of vendors, CROs, laboratories, etc.

Such an approach is not a dream: In the area of auditing of contract manufacturing organisations (CMOs), suppliers of API or inactive ingredients audit outcomes are shared between companies participating in the Pharmaceutical Supply Chain Initiative (PSCI: see http://www.pharmaceuticalsupplychain.org/).

For other GxP audits, Alliance for Clinical Research Excellence and Safety (ACRES: www.acresglobal.net) is in the process of setting up a similar approach in other GxP areas.

The sharing of audit findings between concerned stakeholders does not only share "bad news", i.e., "critical" and "major" findings and even misconduct, but as importantly—if not more—also positive audit outcomes, i.e., absence of significant audit findings. Generally, bad news such as reports of misconduct/fraud travel quickly through the grapevine, while positive experience is kept "under the lid". Such sharing of audit experience would not only enrich information needed to perform or confirm a risk assessment but also result in significant financial savings both for the auditing company as well as the

auditees by avoiding repetitive audits of the same scope.

4. How Will Health Authorities React if They Discover a "Major" or "Critical" Finding That Was Not Detected or Not Addressed Through the Risk-management Approach?

A critical finding is—either detected through internal audits or Health Authority inspections—any process or data deficiency that confirms or fails to demonstrate absence of a breach of patients' safety, integrity and rights, or data integrity. Even though audits are only a snapshot of the current situation, if a critical finding is detected, the impact on the credibility and integrity of the clinical study must be assessed carefully and a sensitivity analysis should be performed. A risk-based monitoring approach does not eliminate the possibility that audits or inspections detect unknown critical deficiencies and GCP violations. However, through focusing on areas where it matters, most deficiencies that would lead to a critical finding can be addressed in time, especially with leading key risk indicators (KRIs) in place.

This aspect has been discussed multiple times with Health Authority inspectors and their feedback was clear and consistent with regulators' messages about risk-based management: "Errors in clinical trials are acceptable to regulators as long as it holds true that if perfect data would have been available, the same decision would have been made and the same conclusion would have been drawn". In other words, inspectors will continue to detect and report non-compliances. However, if inspectors and reviewers come to the conclusion that through such non-compliance the safety integrity and rights of patients as well as data integrity has not been compromised, a trial/system/process will still be considered compliant in the sense that the goal of GCP (patients' safety, rights, integrity, and data integrity) has been reached. Obviously, even if such findings have not been considered as critical, the sponsor must, however, implement adequate CAPAs.

Additionally, the risk-management approach has the advantage of knowledge formalisation and incorporation of the critical findings into the future risk-monitoring process, which leads to continuous improvement.

5. Outlook

In summary, a risk-based approach to managing quality in clinical trials requires the audit strategy and approach to be reinvented in a way that audits will contribute to a holistic risk assessment by ensuring that risk-management procedures are set up and run correctly.

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