Risk Management in Clinical Trials

The New ICH E6 Focus

FDANEWS

By Dr. Susan Leister

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Table of Contents

Introduction

As clinical trials have continued to become more complex, sponsors have turned to technology to increase efficiency. But with increased reliance on electronic systems comes more opportunity for risk if the technology is not managed appropriately. The 2016 update to the International Council on Harmonisation's good clinical practices guideline, ICH E6, is intended to address the shift from paper to electronic records, while building in more flexibility for clinical trials. The revised guideline focuses on electronic data, its maintenance and integrity, as well as on quality risk management targeting human subject protection and data integrity.

The most revised segment of the guideline, Section 5 – Sponsors, emphasizes the importance of risk-based thinking in all stages of a clinical trial. Under ICH E6(R2), the quality management system should take a risk-based approach to the following processes:

- Centralized monitoring;
- Clinical monitoring; and
- Software validation.

This report examines the key changes in Section 5, explains why they were made and reviews steps sponsors and other organizations must take to adjust to the requirements.

About the Authors

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Addressing Risk in Clinical Trial Quality Management

There has been a shift in clinical trials from many different perspectives – they have become larger, more complex and more expensive. In response to this shift, the International Council on Harmonisation (ICH) updated its good clinical practices guideline, ICH E6, to accommodate "more efficient approaches to clinical trial design, conduct, oversight, recording and reporting, while continuing to ensure human subject protection and reliability of trial results" (see Appendix A).

ICH begins its revisions by introducing three new quality management concepts in E6's glossary:

- ***1.63 Certified Copy***

  A copy (irrespective of the type of media used) of the original record that has been verified (i.e., by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original.

- ***1.64 Monitoring Plan***

  A document that describes the strategy, methods, responsibilities, and requirements for monitoring the trial.

- ***1.65 Validation of Computerized Systems***

  A process of establishing and documenting that the specified requirements of a computerized system can be consistently fulfilled from design until decommissioning of the system or transition to a new system. The approach to validation should be based on a risk assessment that takes into consideration the intended use of the system and the potential of the system to affect human subject protection and reliability of trial results.

The key word for trial sponsors in ICH E6(R2) is "risk." ICH has emphasized risk-based thinking in other guidelines, such as Q9 – Statistical Principles for Clinical Trials (see Appendix B), for years before applying the concept to its major GCP guideline.

Section 5 of E6(R2) lays out the requirements for trial sponsors to create risk-based quality management systems:

> *"Sponsors should focus on trial activities essential to ensuring human subject protection and the reliability of trial results. Quality management includes the design of efficient clinical trial protocols and tools and procedures for data collection and processing, as well as the collection of information that is essential to decision making.*
>
> *The methods used to assure and control the quality of the trial should be proportionate to the risks inherent in the trial and the importance of the information collected. The sponsor should ensure that all aspects of the trial are operationally feasible and should avoid unnecessary complexity, procedures, and data collection. Protocols, case report forms, and other operational documents should be clear, concise, and consistent."*

The quality management system is meant to be an integration of process management and continual improvement practices providing increased effectiveness and efficiency throughout the organization. It is imperative that the quality system be aligned with corporate strategies and promoted in a positive atmosphere with executive-level support to ensure its long-term success.

Creating a Risk-Based Quality System

Benefits of risk-based thinking include:

- Ensuring resources are focused on the critical areas of human subject protection and clinical trial data;
- Improving trial efficiency;
- Making trials more cost effective; and
- Identifying areas of weakness and targeting items of highest risk.

A risk-oriented approach also concentrates on reallocating existing resources efficiently rather than locating new or additional resources after problems are identified.

Risk-based thinking helps trial sponsors make the shift from a reactive approach – waiting for a problem to occur – to a proactive one in which potential problems are identified and addressed before a trial starts. Proactive management helps avoid major issues or at least greatly reduce the impact of the event to a manageable level. This proactive, systematic approach to mitigating high-risk events assures and controls the trial's quality.

Taking a systematic approach to risk management also helps guide risk review. The results of the risk review will provide important data to the organization and can provide guidance in decisionmaking at the system level. And the process of identifying critical elements of a trial promotes fact-based decisionmaking to improve the reliability of trial results and patient safety.

ICH E6(R2) emphasizes the importance of creating a risk review process that includes representation from all the key stakeholders in the quality system:

> *"Decision makers should … take responsibility for coordinating quality risk management across various functions and departments of their organization."*

Decisionsmakers must select personnel who are familiar with both the therapeutic area of the trial and its protocol. Subject matter experts representing each area of the protocol help identify and assess specific risks in those areas.

Top management support is critical to the overall success of the risk review team. Managers with a broad corporate view can make sure appropriate resources are available when needed. Keep in mind that resources can go beyond just staff allocation, time and expenses. Decisions made at the corporate level can include purchase of software, assignment of meeting space, employee training and other necessary tools to complete the risk management process.

Aspects of Risk-Based Thinking

The most prominent change to Section 5 of ICH E6 is the addition of Subsection 5.0 – Quality Management, in which ICH explains the principles of risk-based thinking in quality trial management:

> *"The methods used to assure and control the quality of the trial should be proportionate to the risks inherent in the trial and the importance of the information collected."*

Subsection 5.0 breaks the concept of risk-based management into seven key aspects:

- Critical process and data identification;
- Risk identification;
- Risk evaluation;
- Risk control;
- Risk communication;
- Risk review; and
- Risk reporting.

Critical Process and Data Identification

> *"During protocol development, the sponsor should identify those processes and data that are critical to ensure human subject protection and the reliability of trial results."*

Critical processes and data are those items and functions that are essential to the dependability of the overall clinical trial results. What data must be collected to satisfy the clinical endpoints? Are there any lab analyses, clinical procedures or other processes that must be done correctly to guarantee human subject protection and the trial data integrity? If not, what is the impact? Are there some processes and/or data that are more significant than others? If so, consider focusing on these as critical processes and data for the clinical trial and the risk review.

Risk Identification

> *"The sponsor should identify risks to critical trial processes and data. Risks should be considered at both the system level (e.g., standard operating procedures, computerized systems, personnel) and clinical trial level (e.g., trial design, data collection, informed consent process)."*

A successful risk identification effort includes all the key people associated with the system or clinical trial. This is where one asks the question, "What might go wrong?" Look for risks associated with the critical data elements.

The European Medicines Agency weighed in on the subject in a 2013 paper on risk-based quality management in clinical trials (see Appendix C):

> "*Those system related risk factors may have impact across projects and or clinical trials. It is essential that systematic use of information on the quality management system of the sponsor organisation as well as of involved collaborators is obtained and evaluated to identify risks. This would include: organisation structures and responsibilities (e.g. organograms, communication plans, contractual partners); quality systems and processes (e.g. standardised procedures); facilities and computerised systems (e.g. Information technology infrastructure, document management system, data management system, IVRS, eCRF system); human resources including training and qualifications of personnel (e.g. job descriptions, training plans, performance management); compliance metrics, performance measurements, quality audit and/or inspection outcomes; regulatory and ethical framework (e.g. knowledge of national and local approvals and notification required and their timelines).*"

The EMA recommends three different clinical trial risk categories:

- Investigational medical products (IMP);
- Trial design issues; and
- Operational risks.

While these categories are just suggestions they can help guide the risk identification process.

> "*IMP related risk area: any available information about the physico-chemical properties of the active ingredient(s), the manufacturing process of the active ingredient(s) as well as of the investigational medicinal product(s), and the pharmacokinetic, pharmacological and toxicological properties of the investigational medicinal product(s), derived (on-going) from preclinical and clinical trials, including the concerned trial, the requirements for the labelling and packaging of the IMP.*
>
> *Trial design related risk area: complexity of trial design, trial population (e.g. vulnerability, morbidity), therapeutic area (e.g. difficult recruitment associated with rare disease), sample size calculation, practicability and adequateness of the eligibility criteria, non-medicinal protocol related activities (e.g. risk associated with biopsies).*
>
> *Operational risk area: study budget (e.g. inadequate planning for resourcing monitoring or other trial activities), development deadlines, staff resource level and study specific training (e.g. lack of GCP experience at a trial site), study management team and responsibilities (e.g. lack of revision of documents), clinical trial site selection and management, contract research organisation involvement, clinical trial supply processes and management, clinical site set up and infrastructure, laboratory setup, setup of trial databases (e.g. trial specific IVRS, eCRF with controlled access of the study eCRF and specific site training), site monitoring and central monitoring, management of clinical data including adapted safety monitoring (e.g. lack of SUSARS reporting), reporting and/or communication lines.*"

Risk Evaluation

Each new risk must be evaluated for likelihood, detectability, and impact.

> *"The sponsor should evaluate the identified risks, against existing risk controls by considering:*
>
> *(a) The likelihood of errors occurring.*
>
> *(b) The extent to which such errors would be detectable.*
>
> *(c) The impact of such errors on human subject protection and reliability of trial results."*

Risk evaluation can be conducted using either a quantitative or qualitative method. ICH Q9 explains:

> *"The output of a risk assessment is either a quantitative estimate of risk or a qualitative description of a range of risk."*

Qualitative definitions and/or quantitative scales should be defined in an SOP and used throughout an organization consistently. Qualitative risk scales (or a risk matrix) use words with a definition tied to them. Qualitative scales tend to be high, medium and low, or very high, high, medium, low and very low. For example, "very low" would be a very minimal to no impact on human subject protection and/or data integrity.

A quantitative scale is numerical; a lower number is associated with a lower risk and a higher number is associated with a higher risk event. Quantitative clinical risk evaluation scales typically use a one-to-five or one-to-ten scale.

Regardless of the approach being quantitative or qualitative, strive to define the scale and stick to it. Using the overall risk priority ranking the team will decide which risk events need further attention.

There are many risk evaluation tools available, including several outlined in ICH Q9:

- FMEA (Failure Mode Effect Analysis): FMEA identifies potential failure modes, their causes and their effects on the system and presents them in an easily readable format. "*FMEA relies on product and process understanding. FMEA methodically breaks down the analysis of complex processes into manageable steps. It is a powerful tool for summarizing the important modes of failure, factors causing these failures and the likely effects of these failures."*
- Fault Tree Analysis (FTA): The fault tree analysis "*assumes failure of the functionality of a product or process. This tool evaluates system (or sub-system) failures one at a time but can combine multiple causes of failure by identifying causal chains. The results are represented pictorially in the form of a tree of fault modes."*
- Hazard Analysis and Critical Control Points (HACCP): HACCP uses a *"structured approach that applies technical and scientific principles to analyze, evaluate, prevent, and control the risk or adverse consequence(s) of hazard(s) due to the design, development, production, and use of products.*

- Hazard Operability Analysis (HAZOP): HAZOP "*is based on a theory that assumes that risk events are caused by deviations from the design or operating intentions. It is a systematic brainstorming technique for identifying hazards using so-called "guide-words."*

Other risk evaluation aids include:

- The Strengths, Weakness, Opportunities and Threats method (SWOT): SWOT identifies risk categories for brainstorming, but is not a risk evaluation tool by itself.
- Bowtie Analysis: The qualitative bowtie analysis method examines one major risk in a graphical manner to identify possible causes and consequences.
- Risk register/log: The risk register or log is a document used to capture risk evaluations in a quantitative or qualitative manner. It is used to track all risk events, document risk treatment plans, and communication to stakeholders. It can show the status of all risks associated with the project.
- Cause and Effect Diagram: The cause and effect diagram is used to identify the root cause of a specific problem or risk event. The cause can be positive or negative. The issues/risks are examined in detail to identify appropriate corrective and preventive action plans.

Risk Control

> "*The sponsor should decide which risks to reduce and/or which risks to accept. The approach used to reduce risk to an acceptable level should be proportionate to the significance of the risk."*

Risk control is a decision to manage a risk. Based on the risk evaluation, the sponsor should determine which risks need to be reduced and which ones can be accepted. The decision to accept a risk should be documented on the risk evaluation tool or other appropriate documentation. Risk control also involves setting quality tolerance limits for key processes. Establishing the quality tolerance limits early in the trial allows for rapid identification of issues and proper oversight.

Some questions one might use for risk control include the following:

- Is the risk above the acceptable risk level?
- What can be done to mitigate the risk?
- Are any new risks introduced after mitigating or accepting the risk?
- Is the appropriate balance of resources adequate for the risks?

To establish quality tolerance limits, review your critical success factors. Keep in mind that not every metric requires a quality tolerance limit. Sponsors should focus on factors they can control.

The EMA also encourages setting tolerance limits:

> *"One of the benefits of setting tolerance limits early at the time of risk identification or prior to the start of the trial is to allow detection of the deviations from the tolerance range. This would be conducive to rectify or modify the processes to improve the conduct of the study. The other benefit of introducing quality tolerance limits is that it directs the*

oversight and the monitoring on the parameters that matter to the study objectives and help to design more risk based oversight, management and monitoring strategies.

Some key areas to consider for quality tolerance limits include:

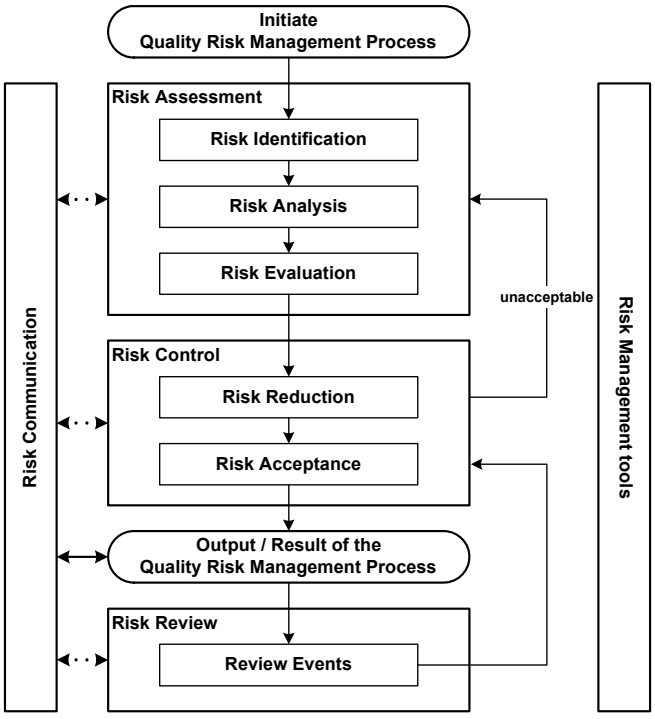
- Safety event reporting;
- Protocol deviations;
- Screen failures;
- Staff turnover; and
- Other high-risk areas.

Risk Communication

"The sponsor should document quality management activities. The sponsor should communicate quality management activities to those who are involved in or affected by such activities, to facilitate risk review and continual improvement during clinical trial execution."

Continuous communication is necessary throughout the risk management process and other quality management processes for overall clinical trial success. ICH Q9 provides a flowchart for the quality risk management process that presents risk communication on the left side, feeding into and out of all risk management activities (see Figure 1). Risk communication should be a two-way process and can take many different forms, such as email, telephone, in-person discussion, and/or written. There is no limit to the frequency of the communication process. Establish a risk communication process that provides all appropriate parties with the necessary information in a timely manner.

Figure 1: Overview of a Typical Quality Risk management Process



Source: ICH Q9 – Statistical Principles for Clinical Trials

Risk Review

> *"The sponsor should periodically review risk control measures to ascertain whether the implemented quality management activities remain effective and relevant, taking into account emerging knowledge and experience."*

Risk review should include new information and experiences associated with the risks that may impact them. Guidance for scheduled frequency of risk reviews should be stated in a risk management SOP. For example, a risk review should be conducted in a timely manner when one of the following events occurs:

- Major protocol amendment;
- Major changes in regulations;
- Major organizational changes; or
- When several significant quality tolerance limits have been exceeded.

During a periodic risk review, a major decision is whether or not to "retire" the risk. Some questions to ask to determine if a risk can be retired include:

- Does the risk event continue to exist? If yes, then the risk should not be retired.
- How likely is the risk event to recur? If unlikely, the sponsor may choose to retire the risk.
- If the risk event were to recur, would the impact be very minimal? If so, the risk can safely be retired.

Once a risk is retired, resources that were focused on that risk event are now available for other tasks. Keep in mind, retiring a risk does not mean deleting the risk data. This information should be available to refer to at a later date. Periodic review can also help reduce the overall cost by not continuing to allocate resources to risks that have been fully mitigated.

Risk Reporting

> "*The sponsor should describe the quality management approach implemented in the trial and summarize important deviations from the predefined quality tolerance limits and remedial actions taken in the clinical study report."*

ICH E6(R2) requires several specific items be included in the clinical study report:

- A description of the quality management approach implemented in the trial;
- A summary of the important deviations from the predefined quality tolerance limits; and
- A summary of remedial actions taken.

At a high-level, discuss the overall quality management program that was utilized during the clinical trial. Having the quality management program in place will make it much easier to briefly describe the overall system. Establishing predefined quality tolerance limits and tracking them throughout the clinical trial will help meet this requirement, along with documenting

any major deviations. Having a quality management program in place will also link these processes together and capture any necessary remedial actions to the quality tolerance limits.

Long-Term Benefits

Keep in mind that there is some level of risk inherent in all activities. Risks will vary in their significance. What might be a high risk in one clinical trial may not be a high risk in another. The same is true for system level risks versus clinical trial level risks. A sponsor should identify and attempt to eliminate known risks, but it is not possible to conduct a clinical trial without any risk.

Developing a formalized process for risk management with appropriate tools for analysis can help a sponsor be more proactive, efficient, and focused on human subject protection and data integrity issues. Having the appropriate teams involved in the risk analysis and staff properly trained on the risk management process will also benefit the sponsor and the trial. Top management must support the overall process, including providing the necessary resources for the program to be successful.

Completing a risk assessment before a clinical trial starts takes time and resources, but if done properly will pay off in the long run. Understanding a trial's risks early allows for proper mitigation to avoid potential costly shortcomings down the road.

Questions and Answers About Risk Management

Question: *What is the recommended retention period for risk management documentation?*

Answer: Consider defining the retention period within your risk management procedures, but also refer to the regulations to determine what risk-related documents will be considered essential documents in a regulatory inspection.

Q: *Can other terms besides "likelihood" and "impact" be used, such as "probability" and "severity?"*

A: Yes. When identifying risks, the organization should clearly define in an SOP what terms they will use to evaluate an identified risk and enforce the consistent use of such terms.

Q: *Can a risk be transferred?*

A: A risk can be transferred through a transfer of regulatory obligation. However, the sponsor should be very careful in what activities are chosen to be transferred. A full transfer of risk is rare.

Quality System Role in Risk Management

The revised E6 advises clinical trial sponsors to take the following steps in creating a quality management plan.

First, implement a system to manage quality throughout all stages of the clinical trial process. Again, the emphasis on early creation of a system is important to successfully meeting regulators' expectations.

Second, focus the system on trial activities essential to ensuring human subject protection and the reliability of trial results. For example, have a plan for rapidly responding to calls from patients and/or their families reporting unexpected health problems. These can be signals of a possible adverse event, so trial personnel must know how to evaluate them.

Third, use methods that are proportionate to the risks. Don't throw all your resources into managing a simple, low-risk trial.

Fourth, avoid unnecessary complexity, such as procedures and data collection that cannot reasonably be managed by the staff members who will interact with patients. A protocol is only as good as those who are carrying it out in their daily work. Ask staff members whether the instructions are clear. They should not be distracted by a series of elaborate steps designed for large urban teaching hospitals, for example.

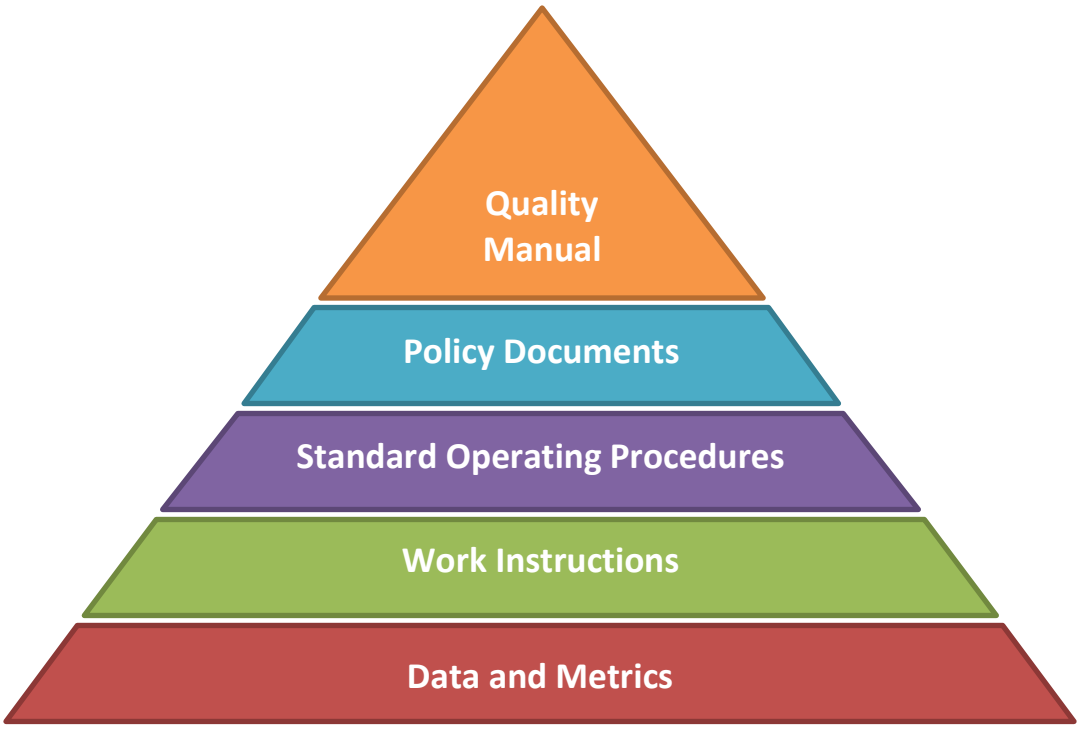
Risk management processes should be used in all the key components of a trial sponsor's quality management system, including:

- Document control and format;
- Internal audit program;
- Vendor audit/qualification program;
- Deviation reporting;
- Corrective and preventive action (CAPA);
- Change control;
- Complaint management; and
- Management review.

Document Control and Format

Document control focuses on the maintenance and security of SOPs, work instructions, templates, forms, policies and other quality documentation, including version control with an archival process. The document control system should be based on a hierarchy of data, starting with quality metrics at the base and culminating in a quality manual that expresses the organization's quality goals, objectives and procedures (see Figure 2).

Figure 2. Quality Documents and Data Hierarchy for the QMS



Other things to consider within the document control process are a periodic review requirement, maintaining a table of contents of all documents, and how and where the organization will securely maintain all documents.

Furthermore, a standardized format for all procedures is easier for end users to follow and aids in compliance. Document formatting typically includes naming conventions, numbering instructions, font size requirements and other style elements.

Internal Audit Program

Internal audits are intended to help verify the effectiveness of procedures and whether processes are in compliance with the regulations. They should also aide in keeping the organization prepared for any regulatory inspections. In addition, internal audits are performed to ensure the organization:

- Protects its subjects;
- Maintains data integrity; and
- Includes continuous improvement activities.

The areas or scope of internal audits should be well-defined, and audits should be scheduled and conducted using a risk-based approach. The audit SOP should describe auditor qualifications, the audit schedule or how it is determined, and what is included in an audit plan and report. Documented timelines for report issuance and report response help keep the audit process moving forward.

Vendor Audit/Qualification

The vendor audit SOP should include the risk-based approach to vendor qualification. Define timeframes for deliverables, such as an audit plan and report. Describe when a vendor is qualified from the audit perspective, as well as other possible categories based on the audit outcome. The vendor's risk level should dictate the audit frequency.

Deviation Reporting

An SOP on deviation reporting should be created and implemented. When a deviation from an SOP and/or the regulations occurs, it should be documented. Consider defining different deviation levels, such as minor, major and critical. The higher risk deviations may need to be moved into the CAPA system. Make sure appropriate root cause analysis is performed to identify the real reason for the deviation. Sometimes it is obvious, other times it requires analysis.

Corrective and Preventive Action

Implementing preventive actions is highly desirable, as it reduces costs compared to spending time and money to correct a problem that has already impacted a clinical trial. Therefore, organizations should focus resources on reviewing potential risks, categorizing them by level, such as minor, major and critical, and implementing measures to mitigate them. The risk-based approach helps filter and prioritize CAPAs. All CAPAs are not created equal. Prioritizing them helps focus resources on the most urgent needs.

CAPA activities should follow the Plan-Do-Check-Act (PDCA) model:

- Plan: Define the problem to be addressed, collect relevant data and ascertain the problem's root cause;
- Do: Develop and implement a solution, test the change on a small scale, do the work, identify measurement guidelines to show effectiveness once the solution is implemented;
- Check: Confirm or check the results through verification (review) to attest that the implementation was successful; and
- Act: Document the results of the prior steps, communicate with others about process changes, and make any other recommendations to be considered in the next PDCA cycle.

The PDCA model establishes a system of continuous improvement.

Change Control

A change control SOP is used to document changes to a process or equipment in real time. Remember a change should take into account an addition, removal or modification to a system process, equipment, material or product. The change should be assessed for risk and impact, then documented. For example, a change to an organization's security system may impact the organization's access control procedures. Having a change control process in place will help ensure a thorough evaluation by applicable stakeholders prior to the change being implemented.

The evaluation should include an assessment to understand the impact of the change in advance so that all documents affected by the change are updated and the risk review is documented.

Complaint Management

A customer complaints process is a valuable continuous improvement loop. Reviewing, investigating and trending complaints can help spot and deal with potential risks.

Investigator Responsibilities

The revised E6 adds several clauses regarding the role and responsibilities of principal investigators in a clinical study. Key among them are new descriptions of how investigators should supervise trial personnel (sections 4.2.5 and 4.2.6):

> *4.2.5 "The investigator is responsible for supervising any individual or party to whom the investigator delegates trial-related duties and functions conducted at the trial site."*
>
> *4.2.6 "If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated."*

To avoid an unclear chain of command in complex trials or ones that use outside vendors, create an organizational chart or delegation log to track roles and responsibilities of study staff.

Recordkeeping and documentation are also a primary responsibility for investigators. E6(R2) states in Section 4.9.0 that:

> *"The investigator/institution should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial subjects. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g., via an audit trail)."*

Questions and Answers About the Quality Management System

Question: *How do you find preventive actions?*
Answer: It typically takes time to get in a proactive mindset, but once you shift to this approach, risk-based thinking on potential issues will become more apparent. Some of the best sources for preventive actions can be audit recommendations, customer feedback and staff process improvement.

Q: *What happens if the effectiveness check for a CAPA fails?*
A: You should specify in your SOP whether the CAPA will be reopened or a new one initiated CAPA. Regardless, the failure means that the issue was not resolved, so the initial steps

of root cause analysis and resolution plans did not work. Going back to the beginning of the CAPA investigation and reviewing all the information with a new perspective tends to be most helpful in a successful resolution. Make sure to document all the steps in the resolution.

Q: *Can you give an example of how to apply quality management during the conduct of the study?*

A: Your internal auditing is your quality management practice throughout the trial. So if you're auditing, whether you're doing process audits, departmental audits, or whatever the case might be, you would be adding in that layer of quality, ensuring that your processes, procedures and trial management are all in compliance with E6(R2).

Q: *Is auditing the only quality management activity, or are there other ways to apply this?*

A: Your basic quality management functions are typically ongoing throughout all of your trials and include:

- Document control;
- Corrective and preventive action program;
- Investigation and evaluation of deviations/nonconformances;
- Risk management and analysis;
- Internal auditing program, including vendor auditing;
- Training program; and
- Complaint management.

Q: *Internal audits consume internal resources; how do they benefit an organization?*

A: It is true that internal audits require a lot of resources, but the benefits typically outweigh the time and effort of the audit. Internal audits allow staff the opportunity to practice audit interview techniques prior to an actual regulatory agency inspection. In addition, internal audits verify compliance to procedures, regulations, and other requirements. Auditing is part of the process improvement loop that helps make the quality system stronger over the years.

Software and System Validation

A risk assessment that focuses on the intended use of the system and the impact on human subject protection and the reliability of trial results is needed.

> *"When using electronic trial data handling and/or remote electronic trial data systems, the sponsor should:*
>
> *(a) Ensure and document that the electronic data processing system(s) conforms to the sponsor's established requirements for completeness, accuracy, reliability, and consistent intended performance (i.e., validation).*
> *The sponsor should base their approach to validation of such systems on a risk assessment that takes into consideration the intended use of the system and the potential of the system to affect human subject protection and reliability of trial results.*
>
> *(b) Maintain SOPs for using these systems.*
> *The SOPs should cover system setup, installation, and use. The SOPs should describe system validation and functionality testing, data collection and handling, system maintenance, system security measures, change control, data backup, recovery, contingency planning, and decommissioning. The responsibilities of the sponsor, investigator, and other parties with respect to the use of these computerized systems should be clear, and the users should be provided with training in their use."*

The approach should start prior to the data system being placed in use and the validation maintained until the decommissioning of the system. Keep in mind that software validation can be time consuming, so having a formalized risk-based system linked to a documented risk assessment will guide the methodology and resources required.

ICH E6(R2) defines validation of computerized systems as:

> "*A process of establishing and documenting that the specified requirements of a computerized system can be consistently fulfilled from design until decommissioning of the system or transition to a new system. The approach to validation should be based on a risk assessment that takes into consideration the intended use of the system and the potential of the system to affect human subject protection and reliability of trial results."*

The risk assessment should be performed based on an understanding of business processes and business risks, user and regulatory requirements, and known functional areas. Key areas to consider for system validation risk include the impact of the system and the integrity of the data, system complexity, system novelty, and the ability to leverage vendor validation tools/services. Training on the use of a computerized system should be provided prior to use and documented.

SOPs should be maintained for computerized systems and their use, including the following:

- System setup, installation and use;
- System validation;
- Data collection and handling system;

- System maintenance;
    - System security measures;
    - Change control;
    - Data backup and recovery;
    - Contingency planning; and
    - System decommissioning.

The SOP on system setup, installation and use should discuss the requirements of the system as well as its intended use. The software validation SOP needs to describe the risk-based approach to validation and how it is done. For example, if different approaches will be used for different types of software – such as custom, configurable, Software as a Service, etc. – make sure to describe this in sufficient detail so that validations are performed consistently. A functionality testing procedure needs to cover the minimum requirements the organization will use for validation testing. The SOP also should describe the environments for testing.

The procedure on data collection and handling must cover the key requirements for data handling, usage and other security information. The SOP on system maintenance should describe the requirements for upgrades and repairs. The procedure on system security measures needs to cover access control, password requirements and other important security measures associated with the computerized system.

The change control SOP should describe the requirements for documenting a change and evaluating the change prior to implementation. Some essential times to use change control are when a new function is introduced, when system upgrades are planned and when major changes to the overall system are planned.

The backup and recovery SOP needs to cover the data backup process and its restoration options for the data within the system. It should include timeframes for how long data will be kept in a safe and secure location. The contingency plan needs to provide various options for short- and long-term business continuity, such as options available if the system is not functioning or if there is a loss of power.

The decommissioning SOP provides details on the controlled deactivation of a computerized system along with the appropriate documentation. Consider using templates to help capture required information in a consistent manner for some of these key items.

The guideline also requires trials to:

> "*Ensure the integrity of the data including any data that describe the context, content, and structure. This is particularly important when making changes to the computerized systems, such as software upgrades or migration of data.*"

This provision is consistent with the FDA's Part 11 regulation on electronic systems and signatures (see Appendix D), which states, "Validation of systems to ensure accuracy, reliability, consistent intended performance, and ability to discern invalid or altered records." The main

questions to ask when evaluating a change include "Did we build the right thing?" and "Does it meet the specifications/requirements?" The objective is to demonstrate with a high degree of assurance that the computerized system meets its intended use, including content, context and structure, when in its intended environment.

All software validation changes should be documented and maintained for later reference.

Certified Copies

What does the term "certified copy" mean? A copy needs to have the same attributes, context, content and structure as the original record. The copies must have been generated by a validated process that ensures all participants are consistent in verifying that clinical study information when it is copied.

The copy must be verified by date and signature. And the rules apply to paper-to-paper copies as well as paper-to-electronic records.

Electronic records present a special challenge, Leister adds. "If it's electronic, you have to start looking at attributes of the actual electronic file," she says. "And it can get complicated if you want to start drilling down to the real details of it." One person could take a very limited view of attributes, she says, while another could go really deep. "If you set the standard in a policy, then everybody's doing the same thing."

Questions and Answers About Software Validation

Question: *What are some potential regulatory agency inspection risks associated with software validation?*

Answer: Besides not completing the actual validation, problem areas tend to be not maintaining user accounts, change controls, lack of training on the system, insufficient audit trails, lack of data transfer testing and lack of SOPs around the software validation process.

Q: *Why is there a need to use a risk-based approach for software validation?*

A: It is not reasonable to test every possible combination of functions or features in a data processing system. Therefore, suitable testing approaches are determined based on the potential risk introduced by the function or feature. For example, calculations or transference of data from equipment require more testing than a data field entry for a subject's temperature reading.

Clinical Monitoring

The 2016 revision of ICH E6 clarified requirements for risk-based monitoring and clearly defined the expectations for centralized monitoring. The approach described in the updated E6 is consistent with the FDA guidance for risk-based monitoring issued in 2013 (see Appendix E):

> *"Monitoring activities should focus on preventing or mitigating important and likely sources of error in the conduct, collection, and reporting of critical data and processes necessary for human subject protection and trial integrity. Sponsors should prospectively identify critical data and processes, then perform a risk assessment to identify and understand the risks that could affect the collection of critical data or the performance of critical processes, and then develop a monitoring plan that focuses on the important and likely risks to critical data and processes."*

The FDA encourages sponsors to conduct a risk assessment and act early to identify critical data that could impact the clinical trial. This data should be used to develop the monitoring strategy from a risk-based approach and captured in the monitoring plan.

Flexibility in Monitoring

ICH E6(R2) does not prescribe a specific approach to monitoring; rather it allows sponsors to shape their monitoring program to meet their own needs, as long as the risk-based strategy is documented in the monitoring plan.

> *"The sponsor should develop a systematic, prioritized, risk-based approach to monitoring clinical trials. The flexibility in the extent and nature of monitoring described in this section is intended to permit varied approaches that improve the effectiveness and efficiency of monitoring. The sponsor may choose on-site monitoring, a combination of on-site and centralized monitoring, or, where justified, centralized monitoring. The sponsor should document the rationale for the chosen monitoring strategy (e.g., in the monitoring plan).*
>
> *On-site monitoring is performed at the sites at which the clinical trial is being conducted. Centralized monitoring is a remote evaluation of accumulating data, performed in a timely manner, supported by appropriately qualified and trained persons (e.g., data managers, biostatisticians)."*

Examples of critical data elements for monitoring to consider may include, but are not limited to:

- Protocol deviations;
- Primary study endpoints;
- Inclusion/exclusion criteria;
- Informed consent processing and management;
- Investigational product accountability and administration;

- Study blind; and
- Specimen management/shipping.

Develop a monitoring plan for each clinical trial and describe the overall monitoring strategy based on risk, frequency of monitoring visits and modality (i.e., on-site, remote or a combination of the two?).

Centralized Monitoring

The revised ICH E6 promotes the use of centralized monitoring to increase efficiency and produce additional data that can be used for continuing improvement.

> *"Centralized monitoring processes provide additional monitoring capabilities that can complement and reduce the extent and/or frequency of on-site monitoring and help distinguish between reliable data and potentially unreliable data. Review, that may include statistical analyses, of accumulating data from centralized monitoring can be used to:*
>
> *(a) identify missing data, inconsistent data, data outliers, unexpected lack of variability and protocol deviations.*
>
> *(b) examine data trends such as the range, consistency, and variability of data within and across sites.*
>
> *(c) evaluate for systematic or significant errors in data collection and reporting at a site or across sites; or potential data manipulation or data integrity problems.*
>
> *(d) analyze site characteristics and performance metrics.*
>
> *(e) select sites and/or processes for targeted on-site monitoring."*

Centralized monitoring that includes data analytics and metrics review provides another view of the clinical trial data in a remote manner. Using centralized monitoring data can help reduce on-site monitoring and provide more targeted on-site monitoring requests based on the data analysis. Make sure data review is conducted by staff qualified to perform statistical analysis.

Reporting timeframes should be established and documented in data analysis SOPs.

> "*Reports of on-site and/or centralized monitoring should be provided to the sponsor (including appropriate management and staff responsible for trial and site oversight) in a timely manner for review and follow up. Results of monitoring activities should be documented in sufficient detail to allow verification of compliance with the monitoring plan. Reporting of centralized monitoring activities should be regular and may be independent from site visits."*

Make sure to establish a process for review of the data and follow up. For example, if data is associated with a quality tolerance limit that has been exceeded, how will this be communicated and managed? Determine the communication pathways for potential items of concern in advance to make sure problems are not overlooked or forgotten about.

Monitoring plans must focus on both human subject protection and data integrity.

> *"The sponsor should develop a monitoring plan that is tailored to the specific human subject protection and data integrity risks of the trial. The plan should describe the monitoring strategy, the monitoring responsibilities of all the parties involved, the various monitoring methods to be used and the rationale for their use. The plan should also emphasize the monitoring of critical data and processes."*

Develop the monitoring plan prior to the start of the clinical trial to ensure all the critical items are incorporated. Make sure to reference all applicable procedures in the plan. Consider using a template that covers all the required elements to help maintain consistency.

Questions and Answers About Clinical Monitoring

Question: *How should an organization start a centralized monitoring program?*

Answer: Consider starting small, such as with a pilot program. Starting with a pilot program will allow the company to make adjustments and fine-tune the process before rolling out the large program to the entire organization. In addition, this can help in the training provided to a large group.

Q: *What are the key topics to consider including in a clinical monitoring plan beyond the four items listed in ICH E6(R2) (monitoring strategy, monitoring responsibilities, monitoring methods to be used and the rationale for their use)?*

A: The four components provided in ICH E6(R2) are very important to incorporate in a monitoring plan. In addition, consider including training requirements, management of non-compliance, reference SOPs and other resources, communication plan and procedures for updating the plan.

Consequences of Noncompliance

Requirements for dealing with noncompliance were covered in the first revision of ICH E6, but revision 2 expands the topic to emphasize its impact on human subject protection and the integrity of clinical trial data.

> "*If noncompliance that significantly affects or has the potential to significantly affect human subject protection or reliability of trial results is discovered, the sponsor should perform a root cause analysis and implement appropriate corrective and preventive actions.*"

Root cause analysis should look past the obvious symptoms to the basic reason the problem occurred. Investigators should ask what happened, why it happened and what to do to reduce the likelihood the problem will recur.

Once you get to the bottom of the problem, you need to take corrective and preventive action. First, fix the problem, then put measures in place so it doesn't happen again.

Not all CAPAs are equally important, so you need to establish methods to categorize and rank them according to risk.

An additional item to address is deciding when and how to escalate a major noncompliance to the regulatory agencies.

Questions & Answers About Noncompliance

Question: *Could study data failings cause the sponsor's application for product approval to be rejected?*

Answer: Yes, failure to have completed and validated your data may result in the FDA or another regulator rejecting the application and requiring further study at a different facility with different investigators. This increases the time delay in achieving the approval, requires a new set of data to be generated at extra cost, and is very likely to affect the stock price of the sponsor corporation if it is a publicly traded company.

Q: *Could this failure have a long term effect?*

A: Perhaps. The FDA's Application Integrity Policy (AIP) keeps a list of institutions or companies whose "integrity" is in some question. The consequence of being on the AIP list is that a future application, such as an Investigational New Drug or Investigational Device Exemption, would not be processed because the FDA presumes that the source or the testing institution lacks sufficient compliance or can't be trusted.

In the case of a company whose pipeline includes other drugs or devices, the AIP listing shuts the pipeline, and the company's ability to remain in a growth and development mode is foreclosed. The FDA does not take this listing lightly, so a routine data error will not trigger this status. But if the inspection at the clinical site finds that the data cannot be validated or the investigator team has manipulated or faked the data, then the sponsor's future drug pipeline may be in grave jeopardy.

Q: *Will one nation's rejection of this study for failure to achieve E6 norms affect the market entry of the same product in other nations?*

A: Probably so. It will result in a common response by each of the ICH member entities that this sponsor's failure of data quality, failure of patient protection, etc., will be treated with the same negative consequences in each of the ICH participating nations.

Q: *What can happen to investigators who fail to control their studies?*

A: After an inspection, a warning, and a hearing, the FDA may disqualify these doctors or their institutions from conducting any more clinical studies. When the Government Accountability Office studied FDA's inability to make a timely inspection of clinical study sites, it recommended more resources and more use of debarments. This could become the "career death penalty" for a physician whose disqualification must be reported to the National Practitioner Data Bank.

Q: *What other consequences could follow?*

A: Two types of litigation consequences may follow from a serious breach of the E6 norms. The injured patient (or the family, if death occurs) could sue the sponsor, the investigator and the clinic/hospital where the actual study medication was given. Injury resulted from failure to follow E6 norms for protection of the human subject. Such claims are rare and in most instances the insurance companies settle these quickly to avoid the long slog through the courts. Of course, another consequence could be that the institution's insurance rates go up, and its managers could dismiss that physician investigator for what appears to be misconduct or improper manipulation of data in the clinical trial supervision.

A second type of litigation targets the financial status of the sponsor company. A shareholder group sues for the sponsor's management's failure to adequately protect the share price of the company stock asserting that the failure should have been made public to save shareholders harm from bad publicity resulting in losses on the holdings by the entity that is suing.

Q: *Can a clinical investigator or manager of a sponsor's clinical trials be criminally prosecuted?*

A: Yes. Section 355(i) of the Food Drug & Cosmetic Act provides the FDA with unambiguous authority to promulgate regulations requiring clinical investigators to adhere to specific record-keeping and reporting requirements. So an investigator is required to comply.

A failure to establish or maintain any record or make any report as required under § 355(i) is a prohibited act. The statute does not indicate that it only serves to prohibit a failure to establish or maintain records and reports submitted directly to the FDA. By reviewing FDA rules in conjunction with the law, the U.S. Court of Appeals for the Fifth Circuit ruled that the scope of the statute allows clinical investigators to be subjected to criminal liability.

The Future of GCP Renovation

This revision likely will not be the last E6 sees in this decade. ICH already is planning a more comprehensive overhaul of the guideline. In a January 2017 paper titled *ICH Reflection on "GCP Renovation:" Modernization of ICH E8 and Subsequent Renovation of ICH E6*, the council lays out its ideas for revamping its suite of clinical trial guidelines (see Appendix F).

Work on updating E8 *General Considerations for Clinical Trials* is scheduled to begin in 2018 (see Appendix G). When the first stage of that revision is complete, ICH would begin a four-part effort to expand E6.

The council plans to first rewrite E6 to cover overarching principles of good clinical practice, including patient protection, data integrity and risk-based monitoring. The revision would address concerns about the guideline's flexibility expressed by research organizations and researchers in a February 2016 letter to ICH. The aim would be to "anticipate and address a broader range of study types and data sources, while retaining the current E6 focus on good clinical investigative site practices."

Modernization of ICH E8

ICH plans to overhaul its guideline, E8 *General Considerations for Clinical Trials*, to incorporate current quality by design principles for clinical trial design and planning. The guideline, which has not been updated since its creation in 1997, would be revised to incorporate the role of critical-to-quality factors in generating reliable data, a concept not addressed in the original E8.

The intent of the council is to "incorporate the most current concepts achieving fit-for-purpose data quality as one of the essential considerations for all clinical trials."

E8 is a broad guideline that serves as a roadmap to all of ICH's other clinical trial-related guidelines.

The next stage would be creation of an annex to E6 focusing on traditional interventional trials of approved or unapproved drugs. The annex would reflect current risk-based approaches and likely would include the elements of E6(R2), according to the paper.

A second annex would deal with nontraditional interventional trials and/or data sources, reflecting the new interest in using more "real world" evidence in drug approval submissions.

Finally, a third annex would address nontraditional trial designs, including observational studies, patient registry studies and others that rely on alternative data sources such as electronic health records and claims data.

Throughout the revision process, ICH plans to invite comments and hold meetings to get input from stakeholders. The working groups undertaking the E6 and E8 revisions could be comprised of experts from a variety of disciplines, such as statistical, data science and outcome assessment, ICH says.

Appendices

A. ICH E6 R2 – *Guideline for Good Clinical Practice*

B. ICH Q9 – *Quality Risk Management*

C. EMA Reflection Paper on Risk-Based Quality Management in Clinical Trials

D. FDA Guidance – *Part 11, Electronic Records; Electronic Signatures – Scope and Application*

E. FDA Guidance – *Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring*

F. ICH Reflection on "GCP Renovation": Modernization of ICH E8 and Subsequent Renovation of ICH E6

G. ICH E8 – *General Considerations for Clinical Trials*

Appendix A: ICH E6 R2 – *Guideline for Good Clinical Practice*

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE (ICH)

ICH HARMONISED GUIDELINE

INTEGRATED ADDENDUM TO ICH E6(R1): GUIDELINE FOR GOOD CLINICAL PRACTICE

E6(R2)

Current *Step 4* version

dated 9 November 2016

E6(R1)
Document History

First Codification	History	Date	New Codification **November 2005**
E6	Approval by the Steering Committee under *Step 2* and release for public consultation.	27 April 1995	E6
E6	Approval by the Steering Committee under *Step 4* and recommended for adoption to the three ICH regulatory bodies.	1 May 1996	E6

E6(R1) *Step 4* version

E6	Approval by the Steering Committee of *Post-Step 4* editorial corrections.	10 June 1996	E6(R1)

Current E6(R2) Addendum *Step 4* version

Code	History	Date
E6(R2)	Adoption by the Regulatory Members of the ICH Assembly under *Step 4*. Integrated Addendum to ICH E6(R1) document. Changes are integrated directly into the following sections of the parental Guideline: Introduction, 1.63, 1.64, 1.65, 2.10, 2.13, 4.2.5, 4.2.6, 4.9.0, 5.0, 5.0.1, 5.0.2, 5.0.3, 5.0.4, 5.0.5, 5.0.6, 5.0.7, 5.2.2, 5.5.3 (a), 5.5.3 (b), 5.5.3 (h), 5.18.3, 5.18.6 (e), 5.18.7, 5.20.1, 8.1	9 November 2016

ICH HARMONISED GUIDELINE

INTEGRATED ADDENDUM TO ICH E6(R1): GUIDELINE FOR GOOD CLINICAL PRACTICE ICH E6(R2)

ICH Consensus Guideline

TABLE OF CONTENTS

INTEGRATED ADDENDUM TO ICH E6(R1): GUIDELINE FOR GOOD CLINICAL PRACTICE ICH

E6(R2)

INTRODUCTION

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

The objective of this ICH GCP Guideline is to provide a unified standard for the European Union (EU), Japan and the United States to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions.

The guideline was developed with consideration of the current good clinical practices of the European Union, Japan, and the United States, as well as those of Australia, Canada, the Nordic countries and the World Health Organization (WHO).

This guideline should be followed when generating clinical trial data that are intended to be submitted to regulatory authorities.

The principles established in this guideline may also be applied to other clinical investigations that may have an impact on the safety and well-being of human subjects.

ADDENDUM

Since the development of the ICH GCP Guideline, the scale, complexity, and cost of clinical trials have increased. Evolutions in technology and risk management processes offer new opportunities to increase efficiency and focus on relevant activities. When the original ICH E6(R1) text was prepared, clinical trials were performed in a largely paper-based process. Advances in use of electronic data recording and reporting facilitate implementation of other approaches. For example, centralized monitoring can now offer a greater advantage, to a broader range of trials than is suggested in the original text. Therefore, this guideline has been amended to encourage implementation of improved and more efficient approaches to clinical trial design, conduct, oversight, recording and reporting while continuing to ensure human subject protection and reliability of trial results. Standards regarding electronic records and essential documents intended to increase clinical trial quality and efficiency have also been updated.

This guideline should be read in conjunction with other ICH guidelines relevant to the conduct of clinical trials (e.g., E2A (clinical safety data management), E3 (clinical study reporting), E7 (geriatric populations), E8 (general considerations for clinical trials), E9 (statistical principles), and E11 (pediatric populations)).

This ICH GCP Guideline Integrated Addendum provides a unified standard for the European Union, Japan, the United States, Canada, and Switzerland to facilitate the mutual acceptance of data from clinical trials by the regulatory authorities in these jurisdictions. In the event of any conflict between the E6(R1) text and the E6(R2) addendum text, the E6(R2) addendum text should take priority.

1. GLOSSARY

1.1 Adverse Drug Reaction (ADR)

In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established: all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase responses to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

Regarding marketed medicinal products: a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

1.2 Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

1.3 Amendment (to the protocol)

See Protocol Amendment.

1.4 Applicable Regulatory Requirement(s)

Any law(s) and regulation(s) addressing the conduct of clinical trials of investigational products.

1.5 Approval (in relation to Institutional Review Boards)

The affirmative decision of the IRB that the clinical trial has been reviewed and may be conducted at the institution site within the constraints set forth by the IRB, the institution, Good Clinical Practice (GCP), and the applicable regulatory requirements.

1.6 Audit

A systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analyzed and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

1.7 Audit Certificate

A declaration of confirmation by the auditor that an audit has taken place.

1.8 Audit Report

A written evaluation by the sponsor's auditor of the results of the audit.

1.9 Audit Trail

Documentation that allows reconstruction of the course of events.

1.10 Blinding/Masking

A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Single-blinding usually refers to the subject(s) being unaware, and double-blinding usually refers to the subject(s), investigator(s), monitor, and, in some cases, data analyst(s) being unaware of the treatment assignment(s).

1.11 Case Report Form (CRF)

A printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject.

1.12 Clinical Trial/Study

Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous.

1.13 Clinical Trial/Study Report

A written description of a trial/study of any therapeutic, prophylactic, or diagnostic agent conducted in human subjects, in which the clinical and statistical description, presentations, and analyses are fully integrated into a single report (see the ICH Guideline for Structure and Content of Clinical Study Reports).

1.14 Comparator (Product)

An investigational or marketed product (i.e., active control), or placebo, used as a reference in a clinical trial.

1.15 Compliance (in relation to trials)

Adherence to all the trial-related requirements, Good Clinical Practice (GCP) requirements, and the applicable regulatory requirements.

1.16 Confidentiality

Prevention of disclosure, to other than authorized individuals, of a sponsor's proprietary information or of a subject's identity.

1.17 Contract

A written, dated, and signed agreement between two or more involved parties that sets out any arrangements on delegation and distribution of tasks and obligations and, if appropriate, on financial matters. The protocol may serve as the basis of a contract.

1.18 Coordinating Committee

A committee that a sponsor may organize to coordinate the conduct of a multicentre trial.

1.19 Coordinating Investigator

An investigator assigned the responsibility for the coordination of investigators at different centres participating in a multicentre trial.

1.20 Contract Research Organization (CRO)

A person or an organization (commercial, academic, or other) contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions.

1.21 Direct Access

Permission to examine, analyze, verify, and reproduce any records and reports that are important to evaluation of a clinical trial. Any party (e.g., domestic and foreign regulatory authorities, sponsor's monitors and auditors) with direct access should take all reasonable precautions within the constraints of the applicable regulatory requirement(s) to maintain the confidentiality of subjects' identities and sponsor's proprietary information.

1.22 Documentation

All records, in any form (including, but not limited to, written, electronic, magnetic, and optical records, and scans, x-rays, and electrocardiograms) that describe or record the methods, conduct, and/or results of a trial, the factors affecting a trial, and the actions taken.

1.23 Essential Documents

Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced (see 8. Essential Documents for the Conduct of a Clinical Trial).

1.24 Good Clinical Practice (GCP)

A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

1.25 Independent Data-Monitoring Committee (IDMC) (Data and Safety Monitoring Board, Monitoring Committee, Data Monitoring Committee)

An independent data-monitoring committee that may be established by the sponsor to assess at intervals the progress of a clinical trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop a trial.

1.26 Impartial Witness

A person, who is independent of the trial, who cannot be unfairly influenced by people involved with the trial, who attends the informed consent process if the subject or the subject's legally acceptable representative cannot read, and who reads the informed consent form and any other written information supplied to the subject.

1.27 Independent Ethics Committee (IEC)

An independent body (a review board or a committee, institutional, regional, national, or supranational), constituted of medical professionals and non-medical members, whose responsibility it is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, reviewing and approving/providing favourable opinion on, the trial protocol, the suitability of the investigator(s), facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

The legal status, composition, function, operations and regulatory requirements pertaining to Independent Ethics Committees may differ among countries, but should allow the Independent Ethics Committee to act in agreement with GCP as described in this guideline.

1.28 Informed Consent

A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.

1.29 Inspection

The act by a regulatory authority(ies) of conducting an official review of documents, facilities, records, and any other resources that are deemed by the authority(ies) to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or contract research organization's (CRO's) facilities, or at other establishments deemed appropriate by the regulatory authority(ies).

1.30 Institution (medical)

Any public or private entity or agency or medical or dental facility where clinical trials are conducted.

1.31 Institutional Review Board (IRB)

An independent body constituted of medical, scientific, and non-scientific members, whose responsibility is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review of trial protocol and amendments and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

1.32 Interim Clinical Trial/Study Report

A report of intermediate results and their evaluation based on analyses performed during the course of a trial.

1.33 Investigational Product

A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.

1.34 Investigator

A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator. See also Subinvestigator.

1.35 Investigator/Institution

An expression meaning "the investigator and/or institution, where required by the applicable regulatory requirements".

1.36 Investigator's Brochure

A compilation of the clinical and nonclinical data on the investigational product(s) which is relevant to the study of the investigational product(s) in human subjects (see 7. Investigator's Brochure).

1.37 Legally Acceptable Representative

An individual or juridical or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial.

1.38 Monitoring

The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

1.39 Monitoring Report

A written report from the monitor to the sponsor after each site visit and/or other trial-related communication according to the sponsor's SOPs.

1.40 Multicentre Trial

A clinical trial conducted according to a single protocol but at more than one site, and therefore, carried out by more than one investigator.

1.41 Nonclinical Study

Biomedical studies not performed on human subjects.

1.42 Opinion (in relation to Independent Ethics Committee)

The judgement and/or the advice provided by an Independent Ethics Committee (IEC).

1.43 Original Medical Record

See Source Documents.

1.44 Protocol

A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents. Throughout the ICH GCP Guideline the term protocol refers to protocol and protocol amendments.

1.45 Protocol Amendment

A written description of a change(s) to or formal clarification of a protocol.

1.46 Quality Assurance (QA)

All those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded), and reported in compliance with Good Clinical Practice (GCP) and the applicable regulatory requirement(s).

1.47 Quality Control (QC)

The operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial-related activities have been fulfilled.

1.48 Randomization

The process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.

1.49 Regulatory Authorities

Bodies having the power to regulate. In the ICH GCP Guideline the expression Regulatory Authorities includes the authorities that review submitted clinical data and those that conduct inspections (see 1.29). These bodies are sometimes referred to as competent authorities.

1.50 Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (Serious ADR)

Any untoward medical occurrence that at any dose:

- results in death,

- is life-threatening,

- requires inpatient hospitalization or prolongation of existing hospitalization,

- results in persistent or significant disability/incapacity,

or

- is a congenital anomaly/birth defect

(see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

1.51 Source Data

All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

1.52 Source Documents

Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).

1.53 Sponsor

An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial.

1.54 Sponsor-Investigator

An individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a subject. The term does not include any person other than an individual (e.g., it does not include a corporation or an agency). The obligations of a sponsor-investigator include both those of a sponsor and those of an investigator.

1.55 Standard Operating Procedures (SOPs)

Detailed, written instructions to achieve uniformity of the performance of a specific function.

1.56 Subinvestigator

Any individual member of the clinical trial team designated and supervised by the investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions (e.g., associates, residents, research fellows). See also Investigator.

1.57 Subject/Trial Subject

An individual who participates in a clinical trial, either as a recipient of the investigational product(s) or as a control.

1.58 Subject Identification Code

A unique identifier assigned by the investigator to each trial subject to protect the subject's identity and used in lieu of the subject's name when the investigator reports adverse events and/or other trial related data.

1.59 Trial Site

The location(s) where trial-related activities are actually conducted.

1.60 Unexpected Adverse Drug Reaction

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product) (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

1.61 Vulnerable Subjects

Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate. Examples are members of a group with a hierarchical structure, such as medical, pharmacy, dental, and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, members of the armed forces, and persons kept in detention. Other vulnerable subjects include patients with incurable diseases, persons in nursing homes, unemployed or impoverished persons, patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors, and those incapable of giving consent.

1.62 Well-being (of the trial subjects)

The physical and mental integrity of the subjects participating in a clinical trial.

ADDENDUM

1.63 Certified Copy

A copy (irrespective of the type of media used) of the original record that has been verified (i.e., by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original.

1.64 Monitoring Plan

A document that describes the strategy, methods, responsibilities, and requirements for monitoring the trial.

1.65 Validation of Computerized Systems

A process of establishing and documenting that the specified requirements of a computerized system can be consistently fulfilled from design until decommissioning of the system or transition to a new system. The approach to validation should be based on a risk assessment that takes into consideration the intended use of the system and the potential of the system to affect human subject protection and reliability of trial results.

2. THE PRINCIPLES OF ICH GCP

2.1 Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).

2.2 Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.

2.3 The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.

2.4 The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.

2.5 Clinical trials should be scientifically sound, and described in a clear, detailed protocol.

2.6 A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favourable opinion.

2.7 The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.

2.8 Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).

2.9 Freely given informed consent should be obtained from every subject prior to clinical trial participation.

2.10 All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.

ADDENDUM

This principle applies to all records referenced in this guideline, irrespective of the type of media used.

2.11 The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

2.12 Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.

2.13 Systems with procedures that assure the quality of every aspect of the trial should be implemented.

ADDENDUM

Aspects of the trial that are essential to ensure human subject protection and reliability of trial results should be the focus of such systems.

3. INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

3.1 Responsibilities

3.1.1 An IRB/IEC should safeguard the rights, safety, and well-being of all trial subjects. Special attention should be paid to trials that may include vulnerable subjects.

3.1.2 The IRB/IEC should obtain the following documents:

trial protocol(s)/amendment(s), written informed consent form(s) and consent form updates that the investigator proposes for use in the trial, subject recruitment procedures (e.g., advertisements), written information to be provided to subjects, Investigator's Brochure (IB), available safety information, information about payments and compensation available to subjects, the investigator's current curriculum vitae and/or other documentation evidencing qualifications, and any other documents that the IRB/IEC may need to fulfil its responsibilities.

The IRB/IEC should review a proposed clinical trial within a reasonable time and document its views in writing, clearly identifying the trial, the documents reviewed and the dates for the following:

- approval/favourable opinion;

- modifications required prior to its approval/favourable opinion;

- disapproval / negative opinion; and

- termination/suspension of any prior approval/favourable opinion.

3.1.3 The IRB/IEC should consider the qualifications of the investigator for the proposed trial, as documented by a current curriculum vitae and/or by any other relevant documentation the IRB/IEC requests.

3.1.4 The IRB/IEC should conduct continuing review of each ongoing trial at intervals appropriate to the degree of risk to human subjects, but at least once per year.

3.1.5 The IRB/IEC may request more information than is outlined in paragraph 4.8.10 be given to subjects when, in the judgement of the IRB/IEC, the additional information would add meaningfully to the protection of the rights, safety and/or well-being of the subjects.

3.1.6 When a non-therapeutic trial is to be carried out with the consent of the subject's legally acceptable representative (see 4.8.12, 4.8.14), the IRB/IEC should determine that the proposed protocol and/or other document(s) adequately addresses relevant ethical concerns and meets applicable regulatory requirements for such trials.

3.1.7 Where the protocol indicates that prior consent of the trial subject or the subject's legally acceptable representative is not possible (see 4.8.15), the IRB/IEC should determine that the proposed protocol and/or other document(s) adequately addresses relevant ethical concerns and meets applicable regulatory requirements for such trials (i.e., in emergency situations).

3.1.8 The IRB/IEC should review both the amount and method of payment to subjects to assure that neither presents problems of coercion or undue influence on the trial subjects. Payments to a subject should be prorated and not wholly contingent on completion of the trial by the subject.

3.1.9 The IRB/IEC should ensure that information regarding payment to subjects, including the methods, amounts, and schedule of payment to trial subjects, is set forth in the written informed consent form and any other written information to be provided to subjects. The way payment will be prorated should be specified.

3.2 Composition, Functions and Operations

3.2.1 The IRB/IEC should consist of a reasonable number of members, who collectively have the qualifications and experience to review and evaluate the science, medical aspects, and ethics of the proposed trial. It is recommended that the IRB/IEC should include:

(a) At least five members.

(b) At least one member whose primary area of interest is in a nonscientific area.

(c) At least one member who is independent of the institution/trial site.

Only those IRB/IEC members who are independent of the investigator and the sponsor of the trial should vote/provide opinion on a trial-related matter.

A list of IRB/IEC members and their qualifications should be maintained.

3.2.2 The IRB/IEC should perform its functions according to written operating procedures, should maintain written records of its activities and minutes of its meetings, and should comply with GCP and with the applicable regulatory requirement(s).

3.2.3 An IRB/IEC should make its decisions at announced meetings at which at least a quorum, as stipulated in its written operating procedures, is present.

3.2.4 Only members who participate in the IRB/IEC review and discussion should vote/provide their opinion and/or advise.

3.2.5 The investigator may provide information on any aspect of the trial, but should not participate in the deliberations of the IRB/IEC or in the vote/opinion of the IRB/IEC.

3.2.6 An IRB/IEC may invite nonmembers with expertise in special areas for assistance.

3.3 Procedures

The IRB/IEC should establish, document in writing, and follow its procedures, which should include:

3.3.1 Determining its composition (names and qualifications of the members) and the authority under which it is established.

3.3.2 Scheduling, notifying its members of, and conducting its meetings.

3.3.3 Conducting initial and continuing review of trials.

3.3.4 Determining the frequency of continuing review, as appropriate.

3.3.5 Providing, according to the applicable regulatory requirements, expedited review and approval/favourable opinion of minor change(s) in ongoing trials that have the approval/favourable opinion of the IRB/IEC.

3.3.6 Specifying that no subject should be admitted to a trial before the IRB/IEC issues its written approval/favourable opinion of the trial.

3.3.7 Specifying that no deviations from, or changes of, the protocol should be initiated without prior written IRB/IEC approval/favourable opinion of an appropriate amendment, except when necessary to eliminate immediate hazards to the subjects or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change of monitor(s), telephone number(s)) (see 4.5.2).

3.3.8 Specifying that the investigator should promptly report to the IRB/IEC:

(a) Deviations from, or changes of, the protocol to eliminate immediate hazards to the trial subjects (see 3.3.7, 4.5.2, 4.5.4).

(b) Changes increasing the risk to subjects and/or affecting significantly the conduct of the trial (see 4.10.2).

(c) All adverse drug reactions (ADRs) that are both serious and unexpected.

(d) New information that may affect adversely the safety of the subjects or the conduct of the trial.

3.3.9 Ensuring that the IRB/IEC promptly notify in writing the investigator/institution concerning:

(a) Its trial-related decisions/opinions.

(b) The reasons for its decisions/opinions.

(c) Procedures for appeal of its decisions/opinions.

3.4 Records

The IRB/IEC should retain all relevant records (e.g., written procedures, membership lists, lists of occupations/affiliations of members, submitted documents, minutes of meetings, and correspondence) for a period of at least 3-years after completion of the trial and make them available upon request from the regulatory authority(ies).

The IRB/IEC may be asked by investigators, sponsors or regulatory authorities to provide its written procedures and membership lists.

4. INVESTIGATOR

4.1 Investigator's Qualifications and Agreements

4.1.1 The investigator(s) should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial, should meet all the qualifications specified by the applicable regulatory requirement(s), and should provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation requested by the sponsor, the IRB/IEC, and/or the regulatory authority(ies).

4.1.2 The investigator should be thoroughly familiar with the appropriate use of the investigational product(s), as described in the protocol, in the current Investigator's Brochure, in the product information and in other information sources provided by the sponsor.

4.1.3 The investigator should be aware of, and should comply with, GCP and the applicable regulatory requirements.

4.1.4 The investigator/institution should permit monitoring and auditing by the sponsor, and inspection by the appropriate regulatory authority(ies).

4.1.5 The investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties.

4.2 Adequate Resources

4.2.1 The investigator should be able to demonstrate (e.g., based on retrospective data) a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

4.2.2 The investigator should have sufficient time to properly conduct and complete the trial within the agreed trial period.

4.2.3 The investigator should have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.

4.2.4 The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.

ADDENDUM

4.2.5 The investigator is responsible for supervising any individual or party to whom the investigator delegates trial-related duties and functions conducted at the trial site.

4.2.6 If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.

4.3 Medical Care of Trial Subjects

4.3.1 A qualified physician (or dentist, when appropriate), who is an investigator or a sub-investigator for the trial, should be responsible for all trial-related medical (or dental) decisions.

4.3.2 During and following a subject's participation in a trial, the investigator/institution should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the trial. The investigator/institution should inform a subject when medical care is needed for intercurrent illness(es) of which the investigator becomes aware.

4.3.3 It is recommended that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

4.3.4 Although a subject is not obliged to give his/her reason(s) for withdrawing prematurely from a trial, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights.

4.4 Communication with IRB/IEC

4.4.1 Before initiating a trial, the investigator/institution should have written and dated approval/favourable opinion from the IRB/IEC for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements), and any other written information to be provided to subjects.

4.4.2 As part of the investigator's/institution’s written application to the IRB/IEC, the investigator/institution should provide the IRB/IEC with a current copy of the Investigator's Brochure. If the Investigator's Brochure is updated during the trial, the investigator/institution should supply a copy of the updated Investigator’s Brochure to the IRB/IEC.

4.4.3 During the trial the investigator/institution should provide to the IRB/IEC all documents subject to review.

4.5 Compliance with Protocol

4.5.1 The investigator/institution should conduct the trial in compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority(ies) and which was given approval/favourable opinion by the IRB/IEC. The investigator/institution and the sponsor should sign the protocol, or an alternative contract, to confirm agreement.

4.5.2 The investigator should not implement any deviation from, or changes of the protocol without agreement by the sponsor and prior review and documented approval/favourable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change in monitor(s), change of telephone number(s)).

4.5.3 The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.

4.5.4 The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB/IEC approval/favourable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted:

(a) to the IRB/IEC for review and approval/favourable opinion,

(b) to the sponsor for agreement and, if required,

(c) to the regulatory authority(ies).

4.6 Investigational Product(s)

4.6.1 Responsibility for investigational product(s) accountability at the trial site(s) rests with the investigator/institution.

4.6.2 Where allowed/required, the investigator/institution may/should assign some or all of the investigator's/institution's duties for investigational product(s) accountability at the trial site(s) to an appropriate pharmacist or another appropriate individual who is under the supervision of the investigator/institution..

4.6.3 The investigator/institution and/or a pharmacist or other appropriate individual, who is designated by the investigator/institution, should maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative disposition of unused product(s). These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational product(s) and trial subjects. Investigators should maintain records that document adequately that the subjects were provided the doses specified by the protocol and reconcile all investigational product(s) received from the sponsor.

4.6.4 The investigational product(s) should be stored as specified by the sponsor (see 5.13.2 and 5.14.3) and in accordance with applicable regulatory requirement(s).

4.6.5 The investigator should ensure that the investigational product(s) are used only in accordance with the approved protocol.

4.6.6 The investigator, or a person designated by the investigator/institution, should explain the correct use of the investigational product(s) to each subject and should check, at intervals appropriate for the trial, that each subject is following the instructions properly.

4.7 Randomization Procedures and Unblinding

The investigator should follow the trial's randomization procedures, if any, and should ensure that the code is broken only in accordance with the protocol. If the trial is blinded, the investigator should promptly document and explain to the sponsor any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event) of the investigational product(s).

4.8 Informed Consent of Trial Subjects

4.8.1 In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Prior to the beginning of the trial, the investigator should have the IRB/IEC's written approval/favourable opinion of the written informed consent form and any other written information to be provided to subjects.

4.8.2 The written informed consent form and any other written information to be provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revised written informed consent form, and written information should receive the IRB/IEC's approval/favourable opinion in advance of use. The subject or the subject's legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information should be documented.

4.8.3 Neither the investigator, nor the trial staff, should coerce or unduly influence a subject to participate or to continue to participate in a trial.

4.8.4 None of the oral and written information concerning the trial, including the written informed consent form, should contain any language that causes the subject or the subject's legally acceptable representative to waive or to appear to waive any legal rights, or that releases or appears to release the investigator, the institution, the sponsor, or their agents from liability for negligence.

4.8.5 The investigator, or a person designated by the investigator, should fully inform the subject or, if the subject is unable to provide informed consent, the subject's legally acceptable representative, of all pertinent aspects of the trial including the written information and the approval/ favourable opinion by the IRB/IEC.

4.8.6 The language used in the oral and written information about the trial, including the written informed consent form, should be as non-technical as practical and should be understandable to the subject or the subject's legally acceptable representative and the impartial witness, where applicable.

4.8.7 Before informed consent may be obtained, the investigator, or a person designated by the investigator, should provide the subject or the subject's legally acceptable representative ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial should be answered to the satisfaction of the subject or the subject's legally acceptable representative.

4.8.8 Prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion.

4.8.9 If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written informed consent form and any other written information to be provided to subjects, is read and explained to the subject or the subject's legally acceptable

representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's participation in the trial and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject or the subject's legally acceptable representative, and that informed consent was freely given by the subject or the subject's legally acceptable representative.

4.8.10 Both the informed consent discussion and the written informed consent form and any other written information to be provided to subjects should include explanations of the following:

(a) That the trial involves research.

(b) The purpose of the trial.

(c) The trial treatment(s) and the probability for random assignment to each treatment.

(d) The trial procedures to be followed, including all invasive procedures.

(e) The subject's responsibilities.

(f) Those aspects of the trial that are experimental.

(g) The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant.

(h) The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this.

(i) The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks.

(j) The compensation and/or treatment available to the subject in the event of trial-related injury.

(k) The anticipated prorated payment, if any, to the subject for participating in the trial.

(l) The anticipated expenses, if any, to the subject for participating in the trial.

(m) That the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.

(n) That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.

(o) That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subject's identity will remain confidential.

(p) That the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial.

(q) The person(s) to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of trial-related injury.

(r) The foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated.

(s) The expected duration of the subject's participation in the trial.

(t) The approximate number of subjects involved in the trial.

4.8.11 Prior to participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects. During a subject's participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated consent form updates and a copy of any amendments to the written information provided to subjects.

4.8.12 When a clinical trial (therapeutic or non-therapeutic) includes subjects who can only be enrolled in the trial with the consent of the subject's legally acceptable representative (e.g., minors, or patients with severe dementia), the subject should be informed about the trial to the extent compatible with the subject's understanding and, if capable, the subject should sign and personally date the written informed consent.

4.8.13 Except as described in 4.8.14, a non-therapeutic trial (i.e., a trial in which there is no anticipated direct clinical benefit to the subject), should be conducted in subjects who personally give consent and who sign and date the written informed consent form.

4.8.14 Non-therapeutic trials may be conducted in subjects with consent of a legally acceptable representative provided the following conditions are fulfilled:

(a) The objectives of the trial can not be met by means of a trial in subjects who can give informed consent personally.

(b) The foreseeable risks to the subjects are low.

(c) The negative impact on the subject's well-being is minimized and low.

(d) The trial is not prohibited by law.

(e) The approval/favourable opinion of the IRB/IEC is expressly sought on the inclusion of such subjects, and the written approval/ favourable opinion covers this aspect.

Such trials, unless an exception is justified, should be conducted in patients having a disease or condition for which the investigational product is intended. Subjects in these trials should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed.

4.8.15 In emergency situations, when prior consent of the subject is not possible, the consent of the subject's legally acceptable representative, if present, should be requested. When prior consent of the subject is not possible, and the subject's legally acceptable representative is not available, enrolment of the subject should require measures described in the protocol and/or elsewhere, with documented approval/favourable opinion by the IRB/IEC, to protect the rights, safety and well-being of the subject and to ensure compliance with applicable regulatory requirements. The subject or the subject's legally acceptable representative should be informed about the trial as soon as possible

and consent to continue and other consent as appropriate (see 4.8.10) should be requested.

4.9 Records and Reports

ADDENDUM

4.9.0 The investigator/institution should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial subjects. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g., *via* an audit trail).

4.9.1 The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.

4.9.2 Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained.

4.9.3 Any change or correction to a CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry (i.e., an audit trail should be maintained); this applies to both written and electronic changes or corrections (see 5.18.4 (n)). Sponsors should provide guidance to investigators and/or the investigators' designated representatives on making such corrections. Sponsors should have written procedures to assure that changes or corrections in CRFs made by sponsor's designated representatives are documented, are necessary, and are endorsed by the investigator. The investigator should retain records of the changes and corrections.

4.9.4 The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (see 8.) and as required by the applicable regulatory requirement(s). The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

4.9.5 Essential documents should be retained until at least 2-years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2-years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained (see 5.5.12).

4.9.6 The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution.

4.9.7 Upon request of the monitor, auditor, IRB/IEC, or regulatory authority, the investigator/institution should make available for direct access all requested trial-related records.

4.10 Progress Reports

4.10.1 The investigator should submit written summaries of the trial status to the IRB/IEC annually, or more frequently, if requested by the IRB/IEC.

4.10.2 The investigator should promptly provide written reports to the sponsor, the IRB/IEC (see 3.3.8) and, where applicable, the institution on any changes significantly affecting the conduct of the trial, and/or increasing the risk to subjects.

4.11 Safety Reporting

4.11.1 All serious adverse events (SAEs) should be reported immediately to the sponsor except for those SAEs that the protocol or other document (e.g., Investigator's Brochure) identifies as not needing immediate reporting. The immediate reports should be followed promptly by detailed, written reports. The immediate and follow-up reports should identify subjects by unique code numbers assigned to the trial subjects rather than by the subjects' names, personal identification numbers, and/or addresses. The investigator should also comply with the applicable regulatory requirement(s) related to the reporting of unexpected serious adverse drug reactions to the regulatory authority(ies) and the IRB/IEC.

4.11.2 Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations should be reported to the sponsor according to the reporting requirements and within the time periods specified by the sponsor in the protocol.

4.11.3 For reported deaths, the investigator should supply the sponsor and the IRB/IEC with any additional requested information (e.g., autopsy reports and terminal medical reports).

4.12 Premature Termination or Suspension of a Trial

If the trial is prematurely terminated or suspended for any reason, the investigator/institution should promptly inform the trial subjects, should assure appropriate therapy and follow-up for the subjects, and, where required by the applicable regulatory requirement(s), should inform the regulatory authority(ies). In addition:

4.12.1 If the investigator terminates or suspends a trial without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB/IEC, and should provide the sponsor and the IRB/IEC a detailed written explanation of the termination or suspension.

4.12.2 If the sponsor terminates or suspends a trial (see 5.21), the investigator should promptly inform the institution where applicable and the investigator/institution should promptly inform the IRB/IEC and provide the IRB/IEC a detailed written explanation of the termination or suspension.

4.12.3 If the IRB/IEC terminates or suspends its approval/favourable opinion of a trial (see 3.1.2 and 3.3.9), the investigator should inform the institution where applicable and the investigator/institution should promptly notify the sponsor and provide the sponsor with a detailed written explanation of the termination or suspension.

4.13 Final Report(s) by Investigator

Upon completion of the trial, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB/IEC with a summary of the trial's outcome, and the regulatory authority(ies) with any reports required.

5. SPONSOR

ADDENDUM

5.0 Quality Management

The sponsor should implement a system to manage quality throughout all stages of the trial process.

Sponsors should focus on trial activities essential to ensuring human subject protection and the reliability of trial results. Quality management includes the design of efficient clinical trial protocols and tools and procedures for data collection and processing, as well as the collection of information that is essential to decision making.

The methods used to assure and control the quality of the trial should be proportionate to the risks inherent in the trial and the importance of the information collected. The sponsor should ensure that all aspects of the trial are operationally feasible and should avoid unnecessary complexity, procedures, and data collection. Protocols, case report forms, and other operational documents should be clear, concise, and consistent.

The quality management system should use a risk-based approach as described below.

5.0.1 Critical Process and Data Identification

During protocol development, the sponsor should identify those processes and data that are critical to ensure human subject protection and the reliability of trial results.

5.0.2 Risk Identification

The sponsor should identify risks to critical trial processes and data. Risks should be considered at both the system level (e.g., standard operating procedures, computerized systems, personnel) and clinical trial level (e.g., trial design, data collection, informed consent process).

5.0.3 Risk Evaluation

The sponsor should evaluate the identified risks, against existing risk controls by considering:

(a) The likelihood of errors occurring.
(b) The extent to which such errors would be detectable.
(c) The impact of such errors on human subject protection and reliability of trial results.

5.0.4 Risk Control

The sponsor should decide which risks to reduce and/or which risks to accept. The approach used to reduce risk to an acceptable level should be proportionate to the significance of the risk. Risk reduction activities may be incorporated in protocol design and implementation, monitoring plans, agreements between parties defining roles and responsibilities, systematic safeguards to ensure adherence to standard operating procedures, and training in processes and procedures.

Predefined quality tolerance limits should be established, taking into consideration the medical and statistical characteristics of the variables as well as the statistical design of the trial, to identify systematic issues that can impact subject safety or reliability of trial

results. Detection of deviations from the predefined quality tolerance limits should trigger an evaluation to determine if action is needed.

5.0.5 Risk Communication

The sponsor should document quality management activities. The sponsor should communicate quality management activities to those who are involved in or affected by such activities, to facilitate risk review and continual improvement during clinical trial execution.

5.0.6 Risk Review

The sponsor should periodically review risk control measures to ascertain whether the implemented quality management activities remain effective and relevant, taking into account emerging knowledge and experience.

5.0.7 Risk Reporting

The sponsor should describe the quality management approach implemented in the trial and summarize important deviations from the predefined quality tolerance limits and remedial actions taken in the clinical study report (ICH E3, Section 9.6 Data Quality Assurance).

5.1 Quality Assurance and Quality Control

5.1.1 The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s).

5.1.2 The sponsor is responsible for securing agreement from all involved parties to ensure direct access (see 1.21) to all trial related sites, source data/documents , and reports for the purpose of monitoring and auditing by the sponsor, and inspection by domestic and foreign regulatory authorities.

5.1.3 Quality control should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

5.1.4 Agreements, made by the sponsor with the investigator/institution and any other parties involved with the clinical trial, should be in writing, as part of the protocol or in a separate agreement.

5.2 Contract Research Organization (CRO)

5.2.1 A sponsor may transfer any or all of the sponsor's trial-related duties and functions to a CRO, but the ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor. The CRO should implement quality assurance and quality control.

5.2.2 Any trial-related duty and function that is transferred to and assumed by a CRO should be specified in writing.

ADDENDUM

The sponsor should ensure oversight of any trial-related duties and functions carried out on its behalf, including trial-related duties and functions that are subcontracted to another party by the sponsor's contracted CRO(s).

5.2.3 Any trial-related duties and functions not specifically transferred to and assumed by a CRO are retained by the sponsor.

5.2.4 All references to a sponsor in this guideline also apply to a CRO to the extent that a CRO has assumed the trial related duties and functions of a sponsor.

5.3 Medical Expertise

The sponsor should designate appropriately qualified medical personnel who will be readily available to advise on trial related medical questions or problems. If necessary, outside consultant(s) may be appointed for this purpose.

5.4 Trial Design

5.4.1 The sponsor should utilize qualified individuals (e.g., biostatisticians, clinical pharmacologists, and physicians) as appropriate, throughout all stages of the trial process, from designing the protocol and CRFs and planning the analyses to analyzing and preparing interim and final clinical trial reports.

5.4.2 For further guidance: Clinical Trial Protocol and Protocol Amendment(s) (see 6.), the ICH Guideline for Structure and Content of Clinical Study Reports, and other appropriate ICH guidance on trial design, protocol and conduct.

5.5 Trial Management, Data Handling, and Record Keeping

5.5.1 The sponsor should utilize appropriately qualified individuals to supervise the overall conduct of the trial, to handle the data, to verify the data, to conduct the statistical analyses, and to prepare the trial reports.

5.5.2 The sponsor may consider establishing an independent data-monitoring committee (IDMC) to assess the progress of a clinical trial, including the safety data and the critical efficacy endpoints at intervals, and to recommend to the sponsor whether to continue, modify, or stop a trial. The IDMC should have written operating procedures and maintain written records of all its meetings.

5.5.3 When using electronic trial data handling and/or remote electronic trial data systems, the sponsor should:

(a) Ensure and document that the electronic data processing system(s) conforms to the sponsor's established requirements for completeness, accuracy, reliability, and consistent intended performance (i.e., validation).

ADDENDUM

The sponsor should base their approach to validation of such systems on a risk assessment that takes into consideration the intended use of the system and the potential of the system to affect human subject protection and reliability of trial results.

(b) Maintains SOPs for using these systems.

ADDENDUM

The SOPs should cover system setup, installation, and use. The SOPs should describe system validation and functionality testing, data collection and handling, system maintenance, system security measures, change control, data backup, recovery, contingency planning, and decommissioning. The responsibilities of the sponsor, investigator, and other parties with respect to the use of these computerized systems should be clear, and the users should be provided with training in their use.

(c) Ensure that the systems are designed to permit data changes in such a way that the data changes are documented and that there is no deletion of entered data (i.e., maintain an audit trail, data trail, edit trail).

(d) Maintain a security system that prevents unauthorized access to the data.

(e) Maintain a list of the individuals who are authorized to make data changes (see 4.1.5 and 4.9.3).

(f) Maintain adequate backup of the data.

(g) Safeguard the blinding, if any (e.g., maintain the blinding during data entry and processing).

ADDENDUM

(h) Ensure the integrity of the data including any data that describe the context, content, and structure. This is particularly important when making changes to the computerized systems, such as software upgrades or migration of data.

5.5.4 If data are transformed during processing, it should always be possible to compare the original data and observations with the processed data.

5.5.5 The sponsor should use an unambiguous subject identification code (see 1.58) that allows identification of all the data reported for each subject.

5.5.6 The sponsor, or other owners of the data, should retain all of the sponsor-specific essential documents pertaining to the trial (see 8. Essential Documents for the Conduct of a Clinical Trial).

5.5.7 The sponsor should retain all sponsor-specific essential documents in conformance with the applicable regulatory requirement(s) of the country(ies) where the product is approved, and/or where the sponsor intends to apply for approval(s).

5.5.8 If the sponsor discontinues the clinical development of an investigational product (i.e., for any or all indications, routes of administration, or dosage forms), the sponsor should maintain all sponsor-specific essential documents for at least 2-years after formal discontinuation or in conformance with the applicable regulatory requirement(s).

5.5.9 If the sponsor discontinues the clinical development of an investigational product, the sponsor should notify all the trial investigators/institutions and all the regulatory authorities.

5.5.10 Any transfer of ownership of the data should be reported to the appropriate authority(ies), as required by the applicable regulatory requirement(s).

5.5.11 The sponsor specific essential documents should be retained until at least 2-years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2-years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirement(s) or if needed by the sponsor.

5.5.12 The sponsor should inform the investigator(s)/institution(s) in writing of the need for record retention and should notify the investigator(s)/institution(s) in writing when the trial related records are no longer needed.

5.6 Investigator Selection

5.6.1 The sponsor is responsible for selecting the investigator(s)/institution(s). Each investigator should be qualified by training and experience and should have adequate resources (see 4.1, 4.2) to properly conduct the trial for which the investigator is selected. If organization of a coordinating committee and/or selection of coordinating investigator(s) are to be utilized in multicentre trials, their organization and/or selection are the sponsor's responsibility.

5.6.2 Before entering an agreement with an investigator/institution to conduct a trial, the sponsor should provide the investigator(s)/institution(s) with the protocol and an up-to-date Investigator's Brochure, and should provide sufficient time for the investigator/institution to review the protocol and the information provided.

5.6.3 The sponsor should obtain the investigator's/institution's agreement:

(a) to conduct the trial in compliance with GCP, with the applicable regulatory requirement(s) (see 4.1.3), and with the protocol agreed to by the sponsor and given approval/favourable opinion by the IRB/IEC (see 4.5.1);

(b) to comply with procedures for data recording/reporting;

(c) to permit monitoring, auditing and inspection (see 4.1.4) and

(d) to retain the trial related essential documents until the sponsor informs the investigator/institution these documents are no longer needed (see 4.9.4 and 5.5.12).

The sponsor and the investigator/institution should sign the protocol, or an alternative document, to confirm this agreement.

5.7 Allocation of Responsibilities

Prior to initiating a trial, the sponsor should define, establish, and allocate all trial-related duties and functions.

5.8 Compensation to Subjects and Investigators

5.8.1 If required by the applicable regulatory requirement(s), the sponsor should provide insurance or should indemnify (legal and financial coverage) the investigator/the institution against claims arising from the trial, except for claims that arise from malpractice and/or negligence.

5.8.2 The sponsor's policies and procedures should address the costs of treatment of trial subjects in the event of trial-related injuries in accordance with the applicable regulatory requirement(s).

5.8.3 When trial subjects receive compensation, the method and manner of compensation should comply with applicable regulatory requirement(s).

5.9 Financing

The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution.

5.10 Notification/Submission to Regulatory Authority(ies)

Before initiating the clinical trial(s), the sponsor (or the sponsor and the investigator, if required by the applicable regulatory requirement(s)) should submit any required application(s) to the appropriate authority(ies) for review, acceptance, and/or permission (as required by the applicable regulatory requirement(s)) to begin the trial(s). Any notification/submission should be dated and contain sufficient information to identify the protocol.

5.11 Confirmation of Review by IRB/IEC

5.11.1 The sponsor should obtain from the investigator/institution:

(a) The name and address of the investigator's/institution's IRB/IEC.

(b) A statement obtained from the IRB/IEC that it is organized and operates according to GCP and the applicable laws and regulations.

(c) Documented IRB/IEC approval/favourable opinion and, if requested by the sponsor, a current copy of protocol, written informed consent form(s) and any other written information to be provided to subjects, subject recruiting procedures, and documents related to payments and compensation available to the subjects, and any other documents that the IRB/IEC may have requested.

5.11.2 If the IRB/IEC conditions its approval/favourable opinion upon change(s) in any aspect of the trial, such as modification(s) of the protocol, written informed consent form and any other written information to be provided to subjects, and/or other procedures, the sponsor should obtain from the investigator/institution a copy of the modification(s) made and the date approval/favourable opinion was given by the IRB/IEC.

5.11.3 The sponsor should obtain from the investigator/institution documentation and dates of any IRB/IEC reapprovals/re-evaluations with favourable opinion, and of any withdrawals or suspensions of approval/favourable opinion.

5.12 Information on Investigational Product(s)

5.12.1 When planning trials, the sponsor should ensure that sufficient safety and efficacy data from nonclinical studies and/or clinical trials are available to support human exposure by the route, at the dosages, for the duration, and in the trial population to be studied.

5.12.2 The sponsor should update the Investigator's Brochure as significant new information becomes available (see 7. Investigator's Brochure).

5.13 Manufacturing, Packaging, Labelling, and Coding Investigational Product(s)

5.13.1 The sponsor should ensure that the investigational product(s) (including active comparator(s) and placebo, if applicable) is characterized as appropriate to the stage of development of the product(s), is manufactured in accordance with any applicable GMP, and is coded and labelled in a manner that protects the blinding, if applicable. In addition, the labelling should comply with applicable regulatory requirement(s).

5.13.2 The sponsor should determine, for the investigational product(s), acceptable storage temperatures, storage conditions (e.g., protection from light), storage times, reconstitution fluids and procedures, and devices for product infusion, if any. The sponsor should inform all involved parties (e.g., monitors, investigators, pharmacists, storage managers) of these determinations.

5.13.3 The investigational product(s) should be packaged to prevent contamination and unacceptable deterioration during transport and storage.

5.13.4 In blinded trials, the coding system for the investigational product(s) should include a mechanism that permits rapid identification of the product(s) in case of a medical emergency, but does not permit undetectable breaks of the blinding.

5.13.5 If significant formulation changes are made in the investigational or comparator product(s) during the course of clinical development, the results of any additional studies of the formulated product(s) (e.g., stability, dissolution rate, bioavailability) needed to assess whether these changes would significantly alter the pharmacokinetic profile of the product should be available prior to the use of the new formulation in clinical trials.

5.14 Supplying and Handling Investigational Product(s)

5.14.1 The sponsor is responsible for supplying the investigator(s)/institution(s) with the investigational product(s).

5.14.2 The sponsor should not supply an investigator/institution with the investigational product(s) until the sponsor obtains all required documentation (e.g., approval/favourable opinion from IRB/IEC and regulatory authority(ies)).

5.14.3 The sponsor should ensure that written procedures include instructions that the investigator/institution should follow for the handling and storage of investigational product(s) for the trial and documentation thereof. The procedures should address adequate and safe receipt, handling, storage, dispensing, retrieval of unused product from subjects, and return of unused investigational product(s) to the sponsor (or alternative disposition if authorized by the sponsor and in compliance with the applicable regulatory requirement(s)).

5.14.4 The sponsor should:

(a) Ensure timely delivery of investigational product(s) to the investigator(s).

(b) Maintain records that document shipment, receipt, disposition, return, and destruction of the investigational product(s) (see 8. Essential Documents for the Conduct of a Clinical Trial).

(c) Maintain a system for retrieving investigational products and documenting this retrieval (e.g., for deficient product recall, reclaim after trial completion, expired product reclaim).

(d) Maintain a system for the disposition of unused investigational product(s) and for the documentation of this disposition.

5.14.5 The sponsor should:

(a) Take steps to ensure that the investigational product(s) are stable over the period of use.

(b) Maintain sufficient quantities of the investigational product(s) used in the trials to reconfirm specifications, should this become necessary, and maintain records of batch sample analyses and characteristics. To the extent stability permits, samples should be retained either until the analyses of the trial data are complete or as required by the applicable regulatory requirement(s), whichever represents the longer retention period.

5.15 Record Access

5.15.1 The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) provide direct access to source data/documents for trial-related monitoring, audits, IRB/IEC review, and regulatory inspection.

5.15.2 The sponsor should verify that each subject has consented, in writing, to direct access to his/her original medical records for trial-related monitoring, audit, IRB/IEC review, and regulatory inspection.

5.16 Safety Information

5.16.1 The sponsor is responsible for the ongoing safety evaluation of the investigational product(s).

5.16.2 The sponsor should promptly notify all concerned investigator(s)/institution(s) and the regulatory authority(ies) of findings that could affect adversely the safety of subjects, impact the conduct of the trial, or alter the IRB/IEC's approval/favourable opinion to continue the trial.

5.17 Adverse Drug Reaction Reporting

5.17.1 The sponsor should expedite the reporting to all concerned investigator(s)/institutions(s), to the IRB(s)/IEC(s), where required, and to the regulatory authority(ies) of all adverse drug reactions (ADRs) that are both serious and unexpected.

5.17.2 Such expedited reports should comply with the applicable regulatory requirement(s) and with the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.

5.17.3 The sponsor should submit to the regulatory authority(ies) all safety updates and periodic reports, as required by applicable regulatory requirement(s).

5.18 Monitoring

5.18.1 Purpose

The purposes of trial monitoring are to verify that:

(a) The rights and well-being of human subjects are protected.

(b) The reported trial data are accurate, complete, and verifiable from source documents.

(c) The conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirement(s).

5.18.2 Selection and Qualifications of Monitors

(a) Monitors should be appointed by the sponsor.

(b) Monitors should be appropriately trained, and should have the scientific and/or clinical knowledge needed to monitor the trial adequately. A monitor's qualifications should be documented.

(c) Monitors should be thoroughly familiar with the investigational product(s), the protocol, written informed consent form and any other written information to be provided to subjects, the sponsor's SOPs, GCP, and the applicable regulatory requirement(s).

5.18.3 Extent and Nature of Monitoring

The sponsor should ensure that the trials are adequately monitored. The sponsor should determine the appropriate extent and nature of monitoring. The determination of the extent and nature of monitoring should be based on considerations such as the objective, purpose, design, complexity, blinding, size, and endpoints of the trial. In general there is a need for on-site monitoring, before, during, and after the trial; however in exceptional circumstances the sponsor may determine that central monitoring in conjunction with procedures such as investigators' training and meetings, and extensive written guidance can assure appropriate conduct of the trial in accordance with GCP. Statistically controlled sampling may be an acceptable method for selecting the data to be verified.

ADDENDUM

The sponsor should develop a systematic, prioritized, risk-based approach to monitoring clinical trials. The flexibility in the extent and nature of monitoring described in this section is intended to permit varied approaches that improve the effectiveness and efficiency of monitoring. The sponsor may choose on-site monitoring, a combination of on-site and centralized monitoring, or, where justified, centralized monitoring. The sponsor should document the rationale for the chosen monitoring strategy (e.g., in the monitoring plan).

On-site monitoring is performed at the sites at which the clinical trial is being conducted. Centralized monitoring is a remote evaluation of accumulating data, performed in a timely manner, supported by appropriately qualified and trained persons (e.g., data managers, biostatisticians).

Centralized monitoring processes provide additional monitoring capabilities that can complement and reduce the extent and/or frequency of on-site monitoring and help distinguish between reliable data and potentially unreliable data.

Review, that may include statistical analyses, of accumulating data from centralized monitoring can be used to:

(a) identify missing data, inconsistent data, data outliers, unexpected lack of variability and protocol deviations.

(b) examine data trends such as the range, consistency, and variability of data within and across sites.

(c) evaluate for systematic or significant errors in data collection and reporting at a site or across sites; or potential data manipulation or data integrity problems.

(d) analyze site characteristics and performance metrics.

(e) select sites and/or processes for targeted on-site monitoring.

5.18.4 Monitor's Responsibilities

The monitor(s) in accordance with the sponsor's requirements should ensure that the trial is conducted and documented properly by carrying out the following activities when relevant and necessary to the trial and the trial site:

(a) Acting as the main line of communication between the sponsor and the investigator.

(b) Verifying that the investigator has adequate qualifications and resources (see 4.1, 4.2, 5.6) and remain adequate throughout the trial period, that facilities, including laboratories, equipment, and staff, are adequate to safely and properly conduct the trial and remain adequate throughout the trial period.

(c) Verifying, for the investigational product(s):

  (i) That storage times and conditions are acceptable, and that supplies are sufficient throughout the trial.

  (ii) That the investigational product(s) are supplied only to subjects who are eligible to receive it and at the protocol specified dose(s).

  (iii) That subjects are provided with necessary instruction on properly using, handling, storing, and returning the investigational product(s).

  (iv) That the receipt, use, and return of the investigational product(s) at the trial sites are controlled and documented adequately.

  (v) That the disposition of unused investigational product(s) at the trial sites complies with applicable regulatory requirement(s) and is in accordance with the sponsor.

(d) Verifying that the investigator follows the approved protocol and all approved amendment(s), if any.

(e) Verifying that written informed consent was obtained before each subject's participation in the trial.

(f) Ensuring that the investigator receives the current Investigator's Brochure, all documents, and all trial supplies needed to conduct the trial properly and to comply with the applicable regulatory requirement(s).

(g) Ensuring that the investigator and the investigator's trial staff are adequately informed about the trial.

(h) Verifying that the investigator and the investigator's trial staff are performing the specified trial functions, in accordance with the protocol and any other written agreement between the sponsor and the investigator/institution, and have not delegated these functions to unauthorized individuals.

(i) Verifying that the investigator is enroling only eligible subjects.

(j) Reporting the subject recruitment rate.

(k) Verifying that source documents and other trial records are accurate, complete, kept up-to-date and maintained.

(l) Verifying that the investigator provides all the required reports, notifications, applications, and submissions, and that these documents are accurate, complete, timely, legible, dated, and identify the trial.

(m) Checking the accuracy and completeness of the CRF entries, source documents and other trial-related records against each other. The monitor specifically should verify that:

  (i) The data required by the protocol are reported accurately on the CRFs and are consistent with the source documents.

  (ii) Any dose and/or therapy modifications are well documented for each of the trial subjects.

  (iii) Adverse events, concomitant medications and intercurrent illnesses are reported in accordance with the protocol on the CRFs.

  (iv) Visits that the subjects fail to make, tests that are not conducted, and examinations that are not performed are clearly reported as such on the CRFs.

  (v) All withdrawals and dropouts of enrolled subjects from the trial are reported and explained on the CRFs.

(n) Informing the investigator of any CRF entry error, omission, or illegibility. The monitor should ensure that appropriate corrections, additions, or deletions are made, dated, explained (if necessary), and initialled by the investigator or by a member of the investigator's trial staff who is authorized to initial CRF changes for the investigator. This authorization should be documented.

(o) Determining whether all adverse events (AEs) are appropriately reported within the time periods required by GCP, the protocol, the IRB/IEC, the sponsor, and the applicable regulatory requirement(s).

(p) Determining whether the investigator is maintaining the essential documents (see 8. Essential Documents for the Conduct of a Clinical Trial).

(q) Communicating deviations from the protocol, SOPs, GCP, and the applicable regulatory requirements to the investigator and taking appropriate action designed to prevent recurrence of the detected deviations.

5.18.5 Monitoring Procedures

The monitor(s) should follow the sponsor’s established written SOPs as well as those procedures that are specified by the sponsor for monitoring a specific trial.

5.18.6 Monitoring Report

(a) The monitor should submit a written report to the sponsor after each trial-site visit or trial-related communication.

(b) Reports should include the date, site, name of the monitor, and name of the investigator or other individual(s) contacted.

(c) Reports should include a summary of what the monitor reviewed and the monitor's statements concerning the significant findings/facts, deviations and deficiencies, conclusions, actions taken or to be taken and/or actions recommended to secure compliance.

(d) The review and follow-up of the monitoring report with the sponsor should be documented by the sponsor's designated representative.

ADDENDUM

(e) Reports of on-site and/or centralized monitoring should be provided to the sponsor (including appropriate management and staff responsible for trial and site oversight) in a timely manner for review and follow up. Results of monitoring activities should be documented in sufficient detail to allow verification of compliance with the monitoring plan. Reporting of centralized monitoring activities should be regular and may be independent from site visits.

ADDENDUM

5.18.7 Monitoring Plan

The sponsor should develop a monitoring plan that is tailored to the specific human subject protection and data integrity risks of the trial. The plan should describe the monitoring strategy, the monitoring responsibilities of all the parties involved, the various monitoring methods to be used, and the rationale for their use. The plan should also emphasize the monitoring of critical data and processes. Particular attention should be given to those aspects that are not routine clinical practice and that require additional training. The monitoring plan should reference the applicable policies and procedures.

5.19 Audit

If or when sponsors perform audits, as part of implementing quality assurance, they should consider:

5.19.1 Purpose

The purpose of a sponsor's audit, which is independent of and separate from routine monitoring or quality control functions, should be to evaluate trial conduct and compliance with the protocol, SOPs, GCP, and the applicable regulatory requirements.

5.19.2 Selection and Qualification of Auditors

(a) The sponsor should appoint individuals, who are independent of the clinical trials/systems, to conduct audits.

(b) The sponsor should ensure that the auditors are qualified by training and experience to conduct audits properly. An auditor's qualifications should be documented.

5.19.3 Auditing Procedures

(a) The sponsor should ensure that the auditing of clinical trials/systems is conducted in accordance with the sponsor's written procedures on what to audit, how to audit, the frequency of audits, and the form and content of audit reports.

(b) The sponsor's audit plan and procedures for a trial audit should be guided by the importance of the trial to submissions to regulatory authorities, the number of subjects in the trial, the type and complexity of the trial, the level of risks to the trial subjects, and any identified problem(s).

(c) The observations and findings of the auditor(s) should be documented.

(d) To preserve the independence and value of the audit function, the regulatory authority(ies) should not routinely request the audit reports. Regulatory authority(ies) may seek access to an audit report on a case by case basis when evidence of serious GCP non-compliance exists, or in the course of legal proceedings.

(e) When required by applicable law or regulation, the sponsor should provide an audit certificate.

5.20 Noncompliance

5.20.1 Noncompliance with the protocol, SOPs, GCP, and/or applicable regulatory requirement(s) by an investigator/institution, or by member(s) of the sponsor's staff should lead to prompt action by the sponsor to secure compliance.

ADDENDUM

If noncompliance that significantly affects or has the potential to significantly affect human subject protection or reliability of trial results is discovered, the sponsor should perform a root cause analysis and implement appropriate corrective and preventive actions.

5.20.2 If the monitoring and/or auditing identifies serious and/or persistent noncompliance on the part of an investigator/institution, the sponsor should terminate the investigator's/institution's participation in the trial. When an investigator's/institution's participation is terminated because of noncompliance, the sponsor should notify promptly the regulatory authority(ies).

5.21 Premature Termination or Suspension of a Trial

If a trial is prematurely terminated or suspended, the sponsor should promptly inform the investigators/institutions, and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC should also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

5.22 Clinical Trial/Study Reports

Whether the trial is completed or prematurely terminated, the sponsor should ensure that the clinical trial reports are prepared and provided to the regulatory agency(ies) as required by the applicable regulatory requirement(s). The sponsor should also ensure that the clinical trial reports in marketing applications meet the standards of the ICH Guideline for Structure and Content of

Clinical Study Reports. (NOTE: The ICH Guideline for Structure and Content of Clinical Study Reports specifies that abbreviated study reports may be acceptable in certain cases.)

5.23 Multicentre Trials

For multicentre trials, the sponsor should ensure that:

5.23.1 All investigators conduct the trial in strict compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority(ies), and given approval/favourable opinion by the IRB/IEC.

5.23.2 The CRFs are designed to capture the required data at all multicentre trial sites. For those investigators who are collecting additional data, supplemental CRFs should also be provided that are designed to capture the additional data.

5.23.3 The responsibilities of coordinating investigator(s) and the other participating investigators are documented prior to the start of the trial.

5.23.4 All investigators are given instructions on following the protocol, on complying with a uniform set of standards for the assessment of clinical and laboratory findings, and on completing the CRFs.

5.23.5 Communication between investigators is facilitated.

6. CLINICAL TRIAL PROTOCOL AND PROTOCOL AMENDMENT(S)

The contents of a trial protocol should generally include the following topics. However, site specific information may be provided on separate protocol page(s), or addressed in a separate agreement, and some of the information listed below may be contained in other protocol referenced documents, such as an Investigator's Brochure.

6.1 General Information

6.1.1 Protocol title, protocol identifying number, and date. Any amendment(s) should also bear the amendment number(s) and date(s).

6.1.2 Name and address of the sponsor and monitor (if other than the sponsor).

6.1.3 Name and title of the person(s) authorized to sign the protocol and the protocol amendment(s) for the sponsor.

6.1.4 Name, title, address, and telephone number(s) of the sponsor's medical expert (or dentist when appropriate) for the trial.

6.1.5 Name and title of the investigator(s) who is (are) responsible for conducting the trial, and the address and telephone number(s) of the trial site(s).

6.1.6 Name, title, address, and telephone number(s) of the qualified physician (or dentist, if applicable), who is responsible for all trial-site related medical (or dental) decisions (if other than investigator).

6.1.7 Name(s) and address(es) of the clinical laboratory(ies) and other medical and/or technical department(s) and/or institutions involved in the trial.

6.2 Background Information

6.2.1 Name and description of the investigational product(s).

6.2.2 A summary of findings from nonclinical studies that potentially have clinical significance and from clinical trials that are relevant to the trial.

6.2.3 Summary of the known and potential risks and benefits, if any, to human subjects.

6.2.4 Description of and justification for the route of administration, dosage, dosage regimen, and treatment period(s).

6.2.5 A statement that the trial will be conducted in compliance with the protocol, GCP and the applicable regulatory requirement(s).

6.2.6 Description of the population to be studied.

6.2.7 References to literature and data that are relevant to the trial, and that provide background for the trial.

6.3 Trial Objectives and Purpose

A detailed description of the objectives and the purpose of the trial.

6.4 Trial Design

The scientific integrity of the trial and the credibility of the data from the trial depend substantially on the trial design. A description of the trial design, should include:

6.4.1 A specific statement of the primary endpoints and the secondary endpoints, if any, to be measured during the trial.

6.4.2 A description of the type/design of trial to be conducted (e.g., double-blind, placebo-controlled, parallel design) and a schematic diagram of trial design, procedures and stages.

6.4.3 A description of the measures taken to minimize/avoid bias, including:

(a) Randomization.

(b) Blinding.

6.4.4 A description of the trial treatment(s) and the dosage and dosage regimen of the investigational product(s). Also include a description of the dosage form, packaging, and labelling of the investigational product(s).

6.4.5 The expected duration of subject participation, and a description of the sequence and duration of all trial periods, including follow-up, if any.

6.4.6 A description of the "stopping rules" or "discontinuation criteria" for individual subjects, parts of trial and entire trial.

6.4.7 Accountability procedures for the investigational product(s), including the placebo(s) and comparator(s), if any.

6.4.8 Maintenance of trial treatment randomization codes and procedures for breaking codes.

6.4.9 The identification of any data to be recorded directly on the CRFs (i.e., no prior written or electronic record of data), and to be considered to be source data.

6.5 Selection and Withdrawal of Subjects

6.5.1 Subject inclusion criteria.

6.5.2 Subject exclusion criteria.

6.5.3 Subject withdrawal criteria (i.e., terminating investigational product treatment/trial treatment) and procedures specifying:

(a) When and how to withdraw subjects from the trial/ investigational product treatment.

(b) The type and timing of the data to be collected for withdrawn subjects.

(c) Whether and how subjects are to be replaced.

(d) The follow-up for subjects withdrawn from investigational product treatment/trial treatment.

6.6 Treatment of Subjects

6.6.1 The treatment(s) to be administered, including the name(s) of all the product(s), the dose(s), the dosing schedule(s), the route/mode(s) of administration, and the treatment period(s), including the follow-up period(s) for subjects for each investigational product treatment/trial treatment group/arm of the trial.

6.6.2 Medication(s)/treatment(s) permitted (including rescue medication) and not permitted before and/or during the trial.

6.6.3 Procedures for monitoring subject compliance.

6.7 Assessment of Efficacy

6.7.1 Specification of the efficacy parameters.

6.7.2 Methods and timing for assessing, recording, and analysing of efficacy parameters.

6.8 Assessment of Safety

6.8.1 Specification of safety parameters.

6.8.2 The methods and timing for assessing, recording, and analysing safety parameters.

6.8.3 Procedures for eliciting reports of and for recording and reporting adverse event and intercurrent illnesses.

6.8.4 The type and duration of the follow-up of subjects after adverse events.

6.9 Statistics

6.9.1 A description of the statistical methods to be employed, including timing of any planned interim analysis(ses).

6.9.2 The number of subjects planned to be enrolled. In multicentre trials, the numbers of enrolled subjects projected for each trial site should be specified. Reason for choice of sample size, including reflections on (or calculations of) the power of the trial and clinical justification.

6.9.3 The level of significance to be used.

6.9.4 Criteria for the termination of the trial.

6.9.5 Procedure for accounting for missing, unused, and spurious data.

6.9.6 Procedures for reporting any deviation(s) from the original statistical plan (any deviation(s) from the original statistical plan should be described and justified in protocol and/or in the final report, as appropriate).

6.9.7 The selection of subjects to be included in the analyses (e.g., all randomized subjects, all dosed subjects, all eligible subjects, evaluable subjects).

6.10 Direct Access to Source Data/Documents

The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s), providing direct access to source data/documents.

6.11 Quality Control and Quality Assurance

6.12 Ethics

Description of ethical considerations relating to the trial.

6.13 Data Handling and Record Keeping

6.14 Financing and Insurance

Financing and insurance if not addressed in a separate agreement.

6.15 Publication Policy

Publication policy, if not addressed in a separate agreement.

6.16 Supplements

(NOTE: Since the protocol and the clinical trial/study report are closely related, further relevant information can be found in the ICH Guideline for Structure and Content of Clinical Study Reports.)

7. INVESTIGATOR'S BROCHURE

7.1 Introduction

The Investigator's Brochure (IB) is a compilation of the clinical and nonclinical data on the investigational product(s) that are relevant to the study of the product(s) in human subjects. Its purpose is to provide the investigators and others involved in the trial with the information to facilitate their understanding of the rationale for, and their compliance with, many key features of the protocol, such as the dose, dose frequency/interval, methods of administration: and safety monitoring procedures. The IB also provides insight to support the clinical management of the study subjects during the course of the clinical trial. The information should be presented in a concise, simple, objective, balanced, and non-promotional form that enables a clinician, or potential investigator, to understand it and make his/her own unbiased risk-benefit assessment of the appropriateness of the proposed trial. For this reason, a medically qualified person should generally participate in the editing of an IB, but the contents of the IB should be approved by the disciplines that generated the described data.

This guideline delineates the minimum information that should be included in an IB and provides suggestions for its layout. It is expected that the type and extent of information available will vary with the stage of development of the investigational product. If the investigational product is marketed and its pharmacology is widely understood by medical practitioners, an extensive IB may not be necessary. Where permitted by regulatory authorities, a basic product information brochure, package leaflet, or labelling may be an appropriate alternative, provided that it includes current, comprehensive, and detailed information on all aspects of the investigational product that might be of importance to the investigator. If a marketed product is being studied for a new use (i.e., a new indication), an IB specific to that new use should be prepared. The IB should be reviewed at least annually and revised as necessary in compliance with a sponsor's written procedures. More frequent revision may be appropriate depending on the stage of development and the generation of relevant new information. However, in accordance with Good Clinical Practice, relevant new information may be so important that it should be communicated to the investigators, and possibly to the Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) and/or regulatory authorities before it is included in a revised IB.

Generally, the sponsor is responsible for ensuring that an up-to-date IB is made available to the investigator(s) and the investigators are responsible for providing the up-to-date IB to the responsible IRBs/IECs. In the case of an investigator sponsored trial, the sponsor-investigator should determine whether a brochure is available from the commercial manufacturer. If the investigational product is provided by the sponsor-investigator, then he or she should provide the necessary information to the trial personnel. In cases where preparation of a formal IB is impractical, the sponsor-investigator should provide, as a substitute, an expanded background information section in the trial protocol that contains the minimum current information described in this guideline.

7.2 General Considerations

The IB should include:

7.2.1 Title Page

This should provide the sponsor's name, the identity of each investigational product (i.e., research number, chemical or approved generic name, and trade name(s) where legally permissible and desired by the sponsor), and the release date. It is also suggested that an

edition number, and a reference to the number and date of the edition it supersedes, be provided. An example is given in Appendix 1.

7.2.2 Confidentiality Statement

The sponsor may wish to include a statement instructing the investigator/recipients to treat the IB as a confidential document for the sole information and use of the investigator's team and the IRB/IEC.

7.3 Contents of the Investigator's Brochure

The IB should contain the following sections, each with literature references where appropriate:

7.3.1 Table of Contents

An example of the Table of Contents is given in Appendix 2

7.3.2 Summary

A brief summary (preferably not exceeding two pages) should be given, highlighting the significant physical, chemical, pharmaceutical, pharmacological, toxicological, pharmacokinetic, metabolic, and clinical information available that is relevant to the stage of clinical development of the investigational product.

7.3.3 Introduction

A brief introductory statement should be provided that contains the chemical name (and generic and trade name(s) when approved) of the investigational product(s), all active ingredients, the investigational product (s) pharmacological class and its expected position within this class (e.g., advantages), the rationale for performing research with the investigational product(s), and the anticipated prophylactic, therapeutic, or diagnostic indication(s). Finally, the introductory statement should provide the general approach to be followed in evaluating the investigational product.

7.3.4 Physical, Chemical, and Pharmaceutical Properties and Formulation

A description should be provided of the investigational product substance(s) (including the chemical and/or structural formula(e)), and a brief summary should be given of the relevant physical, chemical, and pharmaceutical properties.

To permit appropriate safety measures to be taken in the course of the trial, a description of the formulation(s) to be used, including excipients, should be provided and justified if clinically relevant. Instructions for the storage and handling of the dosage form(s) should also be given.

Any structural similarities to other known compounds should be mentioned.

7.3.5 Nonclinical Studies

Introduction:

The results of all relevant nonclinical pharmacology, toxicology, pharmacokinetic, and investigational product metabolism studies should be provided in summary form. This summary should address the methodology used, the results, and a discussion of the

relevance of the findings to the investigated therapeutic and the possible unfavourable and unintended effects in humans.

The information provided may include the following, as appropriate, if known/available:

- Species tested
- Number and sex of animals in each group
- Unit dose (e.g., milligram/kilogram (mg/kg))
- Dose interval
- Route of administration
- Duration of dosing
- Information on systemic distribution
- Duration of post-exposure follow-up
- Results, including the following aspects:
  - Nature and frequency of pharmacological or toxic effects
  - Severity or intensity of pharmacological or toxic effects
  - Time to onset of effects
  - Reversibility of effects
  - Duration of effects
  - Dose response

Tabular format/listings should be used whenever possible to enhance the clarity of the presentation.

The following sections should discuss the most important findings from the studies, including the dose response of observed effects, the relevance to humans, and any aspects to be studied in humans. If applicable, the effective and nontoxic dose findings in the same animal species should be compared (i.e., the therapeutic index should be discussed). The relevance of this information to the proposed human dosing should be addressed. Whenever possible, comparisons should be made in terms of blood/tissue levels rather than on a mg/kg basis.

(a) Nonclinical Pharmacology

A summary of the pharmacological aspects of the investigational product and, where appropriate, its significant metabolites studied in animals, should be included. Such a summary should incorporate studies that assess potential therapeutic activity (e.g., efficacy models, receptor binding, and specificity) as well as those that assess safety (e.g., special studies to assess pharmacological actions other than the intended therapeutic effect(s)).

(b) Pharmacokinetics and Product Metabolism in Animals

A summary of the pharmacokinetics and biological transformation and disposition of the investigational product in all species studied should be given. The discussion of the findings should address the absorption and the local and systemic bioavailability of the investigational product and its metabolites, and their relationship to the pharmacological and toxicological findings in animal species.

(c) Toxicology

A summary of the toxicological effects found in relevant studies conducted in different animal species should be described under the following headings where appropriate:

- Single dose
- Repeated dose
- Carcinogenicity
- Special studies (e.g., irritancy and sensitisation)
- Reproductive toxicity
- Genotoxicity (mutagenicity)

7.3.6 Effects in Humans

Introduction:

A thorough discussion of the known effects of the investigational product(s) in humans should be provided, including information on pharmacokinetics, metabolism, pharmacodynamics, dose response, safety, efficacy, and other pharmacological activities. Where possible, a summary of each completed clinical trial should be provided. Information should also be provided regarding results of any use of the investigational product(s) other than from in clinical trials, such as from experience during marketing.

(a) Pharmacokinetics and Product Metabolism in Humans

- A summary of information on the pharmacokinetics of the investigational product(s) should be presented, including the following, if available:
- Pharmacokinetics (including metabolism, as appropriate, and absorption, plasma protein binding, distribution, and elimination).
- Bioavailability of the investigational product (absolute, where possible, and/or relative) using a reference dosage form.
- Population subgroups (e.g., gender, age, and impaired organ function).
- Interactions (e.g., product-product interactions and effects of food).
- Other pharmacokinetic data (e.g., results of population studies performed within clinical trial(s).

(b) Safety and Efficacy

A summary of information should be provided about the investigational product's/products' (including metabolites, where appropriate) safety, pharmacodynamics, efficacy, and dose response that were obtained from preceding trials in humans (healthy volunteers and/or patients). The implications of this information should be discussed. In cases where a number of clinical trials have been completed, the use of summaries of safety and efficacy across multiple trials by indications in subgroups may provide a clear presentation of the data. Tabular summaries of adverse drug reactions for all the clinical trials (including those for all the studied indications) would be useful. Important differences in adverse drug reaction patterns/incidences across indications or subgroups should be discussed.

The IB should provide a description of the possible risks and adverse drug reactions to be anticipated on the basis of prior experiences with the product under investigation and with related products. A description should also be provided of the precautions or special monitoring to be done as part of the investigational use of the product(s).

(c) Marketing Experience

The IB should identify countries where the investigational product has been marketed or approved. Any significant information arising from the marketed use should be summarised (e.g., formulations, dosages, routes of administration, and adverse product reactions). The IB should also identify all the countries where the investigational product

did not receive approval/registration for marketing or was withdrawn from marketing/registration.

7.3.7 Summary of Data and Guidance for the Investigator

This section should provide an overall discussion of the nonclinical and clinical data, and should summarise the information from various sources on different aspects of the investigational product(s), wherever possible. In this way, the investigator can be provided with the most informative interpretation of the available data and with an assessment of the implications of the information for future clinical trials.

Where appropriate, the published reports on related products should be discussed. This could help the investigator to anticipate adverse drug reactions or other problems in clinical trials.

The overall aim of this section is to provide the investigator with a clear understanding of the possible risks and adverse reactions, and of the specific tests, observations, and precautions that may be needed for a clinical trial. This understanding should be based on the available physical, chemical, pharmaceutical, pharmacological, toxicological, and clinical information on the investigational product(s). Guidance should also be provided to the clinical investigator on the recognition and treatment of possible overdose and adverse drug reactions that is based on previous human experience and on the pharmacology of the investigational product.

7.4 APPENDIX 1:

TITLE PAGE *(Example)*

SPONSOR'S NAME

Product:

Research Number:

Name(s): Chemical, Generic (if approved)

Trade Name(s) (if legally permissible and desired by the sponsor)

INVESTIGATOR'S BROCHURE

Edition Number:

Release Date:

Replaces Previous Edition Number:

Date:

7.5 APPENDIX 2:

TABLE OF CONTENTS OF INVESTIGATOR'S BROCHURE *(Example)*

NB: References on 1. Publications
2. Reports

These references should be found at the end of each chapter

Appendices (if any)

8. ESSENTIAL DOCUMENTS FOR THE CONDUCT OF A CLINICAL TRIAL

8.1 Introduction

Essential Documents are those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents serve to demonstrate the compliance of the investigator, sponsor and monitor with the standards of Good Clinical Practice and with all applicable regulatory requirements.

Essential Documents also serve a number of other important purposes. Filing essential documents at the investigator/institution and sponsor sites in a timely manner can greatly assist in the successful management of a trial by the investigator, sponsor and monitor. These documents are also the ones which are usually audited by the sponsor's independent audit function and inspected by the regulatory authority(ies) as part of the process to confirm the validity of the trial conduct and the integrity of data collected.

The minimum list of essential documents which has been developed follows. The various documents are grouped in three sections according to the stage of the trial during which they will normally be generated: 1) before the clinical phase of the trial commences, 2) during the clinical conduct of the trial, and 3) after completion or termination of the trial. A description is given of the purpose of each document, and whether it should be filed in either the investigator/institution or sponsor files, or both. It is acceptable to combine some of the documents, provided the individual elements are readily identifiable.

Trial master files should be established at the beginning of the trial, both at the investigator/institution’s site and at the sponsor's office. A final close-out of a trial can only be done when the monitor has reviewed both investigator/institution and sponsor files and confirmed that all necessary documents are in the appropriate files.

Any or all of the documents addressed in this guideline may be subject to, and should be available for, audit by the sponsor’s auditor and inspection by the regulatory authority(ies).

ADDENDUM

The sponsor and investigator/institution should maintain a record of the location(s) of their respective essential documents including source documents. The storage system used during the trial and for archiving (irrespective of the type of media used) should provide for document identification, version history, search, and retrieval.

Essential documents for the trial should be supplemented or may be reduced where justified (in advance of trial initiation) based on the importance and relevance of the specific documents to the trial.

The sponsor should ensure that the investigator has control of and continuous access to the CRF data reported to the sponsor. The sponsor should not have exclusive control of those data.

When a copy is used to replace an original document (e.g., source documents, CRF), the copy should fulfill the requirements for certified copies.

The investigator/institution should have control of all essential documents and records generated by the investigator/institution before, during, and after the trial.

8.2 Before the Clinical Phase of the Trial Commences

During this planning stage the following documents should be generated and should be on file before the trial formally starts

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	**Sponsor**
8.2.1	**INVESTIGATOR'S BROCHURE**	To document that relevant and current scientific information about the investigational product has been provided to the investigator	X	X
8.2.2	**SIGNED PROTOCOL AND AMENDMENTS, IF ANY, AND SAMPLE CASE REPORT FORM (CRF)**	To document investigator and sponsor agreement to the protocol/amendment(s) and CRF	X	X
8.2.3	**INFORMATION GIVEN TO TRIAL SUBJECT**		X	X
	- INFORMED CONSENT FORM (including all applicable translations)	To document the informed consent		
	- ANY OTHER WRITTEN INFORMATION	To document that subjects will be given appropriate written information (content and wording) to support their ability to give fully informed consent	X	X

	- ADVERTISEMENT FOR SUBJECT RECRUITMENT (if used)	To document that recruitment measures are appropriate and not coercive	X	
8.2.4	**FINANCIAL ASPECTS OF THE TRIAL**	To document the financial agreement between the investigator/institution and the sponsor for the trial	X	X

	Title of Document	**Purpose**	**Located in Files of**	
			Investigator/ Institution	**Sponsor**
8.2.5	**INSURANCE STATEMENT** (where required)	To document that compensation to subject(s) for trial-related injury will be available	X	X
8.2.6	**SIGNED AGREEMENT BETWEEN INVOLVED PARTIES,** e.g.:	To document agreements		
	- investigator/institution and sponsor		X	X
	- investigator/institution and CRO		X	X (where required)
	- sponsor and CRO			X
	- investigator/institution and authority(ies) (where required)		X	X

8.2.7	**DATED, DOCUMENTED APPROVAL/FAVOURABLE OPINION OF INSTITUTIONAL REVIEW BOARD (IRB) /INDEPENDENT ETHICS COMMITTEE (IEC) OF THE FOLLOWING:** - protocol and any amendments - CRF (if applicable) - informed consent form(s) - any other written information to be provided to the subject(s) - advertisement for subject recruitment (if used) - subject compensation (if any) - any other documents given approval/ favourable opinion	To document that the trial has been subject to IRB/IEC review and given approval/favourable opinion. To identify the version number and date of the document(s)	X	X

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	**Sponsor**
8.2.8	**INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE COMPOSITION**	To document that the IRB/IEC is constituted in agreement with GCP	X	X (where required)
8.2.9	**REGULATORY AUTHORITY(IES) AUTHORISATION/APPROVAL/ NOTIFICATION OF PROTOCOL** (where required)	To document appropriate authorisation/approval/notification by the regulatory authority(ies) has been obtained prior to initiation of the trial in compliance with the applicable regulatory requirement(s)	X (where required)	X (where required)
8.2.10	**CURRICULUM VITAE AND/OR OTHER RELEVANT DOCUMENTS EVIDENCING QUALIFICATIONS OF INVESTIGATOR(S) AND SUB-INVESTIGATOR(S)**	To document qualifications and eligibility to conduct trial and/or provide medical supervision of subjects	X	X
8.2.11	**NORMAL VALUE(S)/RANGE(S) FOR MEDICAL/ LABORATORY/TECHNICAL PROCEDURE(S) AND/OR TEST(S) INCLUDED IN THE PROTOCOL**	To document normal values and/or ranges of the tests	X	X

8.2.12	**MEDICAL/LABORATORY/TECHNICAL PROCEDURES /TESTS** - certification or - accreditation or - established quality control and/or external quality assessment or - other validation (where required)	To document competence of facility to perform required test(s), and support reliability of results	X (where required)	X

	Title of Document	**Purpose**	**Located in Files of**	
			Investigator/ Institution	**Sponsor**
8.2.13	**SAMPLE OF LABEL(S) ATTACHED TO INVESTIGATIONAL PRODUCT CONTAINER(S)**	To document compliance with applicable labelling regulations and appropriateness of instructions provided to the subjects		X
8.2.14	**INSTRUCTIONS FOR HANDLING OF INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED MATERIALS** (if not included in protocol or Investigator's Brochure)	To document instructions needed to ensure proper storage, packaging, dispensing and disposition of investigational products and trial-related materials	X	X
8.2.15	**SHIPPING RECORDS FOR INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED MATERIALS**	To document shipment dates, batch numbers and method of shipment of investigational product(s) and trial-related materials. Allows tracking of product batch, review of shipping conditions, and accountability	X	X

8.2.16	**CERTIFICATE(S) OF ANALYSIS OF INVESTIGATIONAL PRODUCT(S) SHIPPED**	To document identity, purity, and strength of investigational product(s) to be used in the trial		X
8.2.17	**DECODING PROCEDURES FOR BLINDED TRIALS**	To document how, in case of an emergency, identity of blinded investigational product can be revealed without breaking the blind for the remaining subjects' treatment	X	X (third party if applicable)

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	**Sponsor**
8.2.18	**MASTER RANDOMISATION LIST**	To document method for randomisation of trial population		X (third party if applicable)
8.2.19	**PRE-TRIAL MONITORING REPORT**	To document that the site is suitable for the trial (may be combined with 8.2.20)		X
8.2.20	**TRIAL INITIATION MONITORING REPORT**	To document that trial procedures were reviewed with the investigator and the investigator's trial staff (may be combined with 8.2.19)	X	X

8.3 During the Clinical Conduct of the Trial

In addition to having on file the above documents, the following should be added to the files during the trial as evidence that all new relevant information is documented as it becomes available

8.3.1	**INVESTIGATOR'S BROCHURE UPDATES**	To document that investigator is informed in a timely manner of relevant information as it becomes available	X	X

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	**Sponsor**
8.3.2	**ANY REVISION TO:** - protocol/amendment(s) and CRF - informed consent form - any other written information provided to subjects - advertisement for subject recruitment (if used)	To document revisions of these trial related documents that take effect during trial	X	X

8.3.3	**DATED, DOCUMENTED APPROVAL/FAVOURABLE OPINION OF INSTITUTIONAL REVIEW BOARD (IRB) /INDEPENDENT ETHICS COMMITTEE (IEC) OF THE FOLLOWING:**
	- protocol amendment(s)
	- revision(s) of:
	  - informed consent form
	  - any other written information to be provided to the subject
	  - advertisement for subject recruitment (if used)
	- any other documents given approval/favourable opinion
	- continuing review of trial (where required)
		To document that the amendment(s) and/or revision(s) have been subject to IRB/IEC review and were given approval/favourable opinion. To identify the version number and date of the document(s).	X	X

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	**Sponsor**
8.3.4	**REGULATORY AUTHORITY(IES) AUTHORISATIONS/APPROVALS/NOTIFICATIONS WHERE REQUIRED FOR:** - protocol amendment(s) and other documents	To document compliance with applicable regulatory requirements	X (where required)	X
8.3.5	**CURRICULUM VITAE FOR NEW INVESTIGATOR(S) AND/OR SUB-INVESTIGATOR(S)**	(see 8.2.10)	X	X
8.3.6	**UPDATES TO NORMAL VALUE(S)/RANGE(S) FOR MEDICAL/ LABORATORY/ TECHNICAL PROCEDURE(S)/TEST(S) INCLUDED IN THE PROTOCOL**	To document normal values and ranges that are revised during the trial (see 8.2.11)	X	X
8.3.7	**UPDATES OF MEDICAL/LABORATORY/ TECHNICAL PROCEDURES/TESTS** - certification or - accreditation or - established quality control and/or external quality assessment or - other validation (where required)	To document that tests remain adequate throughout the trial period (see 8.2.12)	X (where required)	X
8.3.8	**DOCUMENTATION OF INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED MATERIALS SHIPMENT**	(see 8.2.15.)	X	X

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	**Sponsor**
8.3.9	**CERTIFICATE(S) OF ANALYSIS FOR NEW BATCHES OF INVESTIGATIONAL PRODUCTS**	(see 8.2.16)		X
8.3.10	**MONITORING VISIT REPORTS**	To document site visits by, and findings of, the monitor		X
8.3.11	**RELEVANT COMMUNICATIONS OTHER THAN SITE VISITS** - letters - meeting notes - notes of telephone calls	To document any agreements or significant discussions regarding trial administration, protocol violations, trial conduct, adverse event (AE) reporting	X	X
8.3.12	**SIGNED INFORMED CONSENT FORMS**	To document that consent is obtained in accordance with GCP and protocol and dated prior to participation of each subject in trial. Also to document direct access permission (see 8.2.3)	X	
8.3.13	**SOURCE DOCUMENTS**	To document the existence of the subject and substantiate integrity of trial data collected. To include original documents related to the trial, to medical treatment, and history of subject	X	

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	**Sponsor**
8.3.14	**SIGNED, DATED AND COMPLETED CASE REPORT FORMS (CRF)**	To document that the investigator or authorised member of the investigator's staff confirms the observations recorded	X (copy)	X (original)
8.3.15	**DOCUMENTATION OF CRF CORRECTIONS**	To document all changes/additions or corrections made to CRF after initial data were recorded	X (copy)	X (original)
8.3.16	**NOTIFICATION BY ORIGINATING INVESTIGATOR TO SPONSOR OF SERIOUS ADVERSE EVENTS AND RELATED REPORTS**	Notification by originating investigator to sponsor of serious adverse events and related reports in accordance with 4.11	X	X
8.3.17	**NOTIFICATION BY SPONSOR AND/OR INVESTIGATOR, WHERE APPLICABLE, TO REGULATORY AUTHORITY(IES) AND IRB(S)/IEC(S) OF UNEXPECTED SERIOUS ADVERSE DRUG REACTIONS AND OF OTHER SAFETY INFORMATION**	Notification by sponsor and/or investigator, where applicable, to regulatory authorities and IRB(s)/IEC(s) of unexpected serious adverse drug reactions in accordance with 5.17 and 4.11.1 and of other safety information in accordance with 5.16.2 and 4.11.2	X (where required)	X
8.3.18	**NOTIFICATION BY SPONSOR TO INVESTIGATORS OF SAFETY INFORMATION**	Notification by sponsor to investigators of safety information in accordance with 5.16.2	X	X
8.3.19	**INTERIM OR ANNUAL REPORTS TO IRB/IEC AND AUTHORITY(IES)**	Interim or annual reports provided to IRB/IEC in accordance with 4.10 and to authority(ies) in accordance with 5.17.3	X	X (where required)

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	**Sponsor**
8.3.20	**SUBJECT SCREENING LOG**	To document identification of subjects who entered pre-trial screening	X	X (where required)
8.3.21	**SUBJECT IDENTIFICATION CODE LIST**	To document that investigator/institution keeps a confidential list of names of all subjects allocated to trial numbers on enrolling in the trial. Allows investigator/institution to reveal identity of any subject	X	
8.3.22	**SUBJECT ENROLMENT LOG**	To document chronological enrolment of subjects by trial number	X	
8.3.23	**INVESTIGATIONAL PRODUCTS ACCOUNTABILITY AT THE SITE**	To document that investigational product(s) have been used according to the protocol	X	X
8.3.24	**SIGNATURE SHEET**	To document signatures and initials of all persons authorised to make entries and/or corrections on CRFs	X	X
8.3.25	**RECORD OF RETAINED BODY FLUIDS/ TISSUE SAMPLES (IF ANY)**	To document location and identification of retained samples if assays need to be repeated	X	X

8.4 After Completion or Termination of the Trial

After completion or termination of the trial, all of the documents identified in Sections 8.2 and 8.3 should be in the file together with the following

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	**Sponsor**
8.4.1	**INVESTIGATIONAL PRODUCT(S) ACCOUNTABILITY AT SITE**	To document that the investigational product(s) have been used according to the protocol. To documents the final accounting of investigational product(s) received at the site, dispensed to subjects, returned by the subjects, and returned to sponsor	X	X
8.4.2	**DOCUMENTATION OF INVESTIGATIONAL PRODUCT DESTRUCTION**	To document destruction of unused investigational products by sponsor or at site	X (if destroyed at site)	X
8.4.3	**COMPLETED SUBJECT IDENTIFICATION CODE LIST**	To permit identification of all subjects enrolled in the trial in case follow-up is required. List should be kept in a confidential manner and for agreed upon time	X	
8.4.4	**AUDIT CERTIFICATE** (if available)	To document that audit was performed		X
8.4.5	**FINAL TRIAL CLOSE-OUT MONITORING REPORT**	To document that all activities required for trial close-out are completed, and copies of essential documents are held in the appropriate files		X

8.4.6	**TREATMENT ALLOCATION AND DECODING DOCUMENTATION**	Returned to sponsor to document any decoding that may have occurred		X
	Title of Document	**Purpose**	**Located in Files of**	
			Investigator/ Institution	**Sponsor**
8.4.7	**FINAL REPORT BY INVESTIGATOR TO IRB/IEC WHERE REQUIRED, AND WHERE APPLICABLE, TO THE REGULATORY AUTHORITY(IES)**	To document completion of the trial	X	
8.4.8	**CLINICAL STUDY REPORT**	To document results and interpretation of trial	X (if applicable)	X

Appendix B: ICH Q9 – *Quality Risk Management*

Guidance for Industry

Q9 Quality Risk Management

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

June 2006
ICH

Guidance for Industry

Q9 Quality Risk Management

Additional copies are available from:

Office of Training and Communication
Division of Drug Information, HFD-240
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
(Tel) 301-827-4573
http://www.fda.gov/cder/guidance/index.htm

Office of Communication, Training and
Manufacturers Assistance, HFM-40
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Rockville, MD 20852-1448
http://www.fda.gov/cber/guidelines.htm.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

June 2006
ICH

TABLE OF CONTENTS

Contains Nonbinding Recommendations

Guidance for Industry[1]

Q9 Quality Risk Management

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION (1)[2]

Risk management principles are effectively utilized in many areas of business and government including finance, insurance, occupational safety, public health, pharmacovigilance, and by agencies regulating these industries. Although there are some examples of the use of *quality risk management* in the pharmaceutical industry today, they are limited and do not represent the full contributions that risk management has to offer. In addition, the importance of *quality systems* has been recognized in the pharmaceutical industry, and it is becoming evident that quality risk management is a valuable component of an effective quality system.

It is commonly understood that *risk* is defined as the combination of the probability of occurrence of *harm* and the *severity* of that harm. However, achieving a shared understanding of the application of risk management among diverse *stakeholders* is difficult because each stakeholder might perceive different potential harms, place a different probability on each harm occurring and attribute different severities to each harm. In relation to pharmaceuticals, although there are a variety of stakeholders, including patients and medical practitioners as well as government and industry, the protection of the patient by managing the risk to quality should be considered of prime importance.

[1] This guidance was developed within the Expert Working Group (Quality) of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and has been subject to consultation by the regulatory parties, in accordance with the ICH process. This document has been endorsed by the ICH Steering Committee at *Step 4* of the ICH process, November 2005. At *Step 4* of the process, the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan, and the United States.

[2] Arabic numbers reflect the organizational breakdown in the document endorsed by the ICH Steering Committee at Step 4 of the ICH process, November 2005.

The manufacturing and use of a drug product, including its components, necessarily entail some degree of risk. The risk to its quality is just one component of the overall risk. It is important to understand that product *quality* should be maintained throughout the *product lifecycle* such that the attributes that are important to the quality of the drug product remain consistent with those used in the clinical studies. An effective quality risk management approach can further ensure the high quality of the drug product to the patient by providing a proactive means to identify and control potential quality issues during development and manufacturing. In addition, use of quality risk management can improve the decision making if a quality problem arises. Effective quality risk management can facilitate better and more informed decisions, can provide regulators with greater assurance of a company's ability to deal with potential risks, and can beneficially affect the extent and level of direct regulatory oversight.

The purpose of this document is to offer a systematic approach to quality risk management. It serves as a foundation or resource document that is independent of, yet supports, other ICH Quality documents and complements existing quality practices, requirements, standards, and guidelines within the pharmaceutical industry and regulatory environment. It specifically provides guidance on the principles and some of the tools of quality risk management that can enable more effective and consistent risk-based decisions, by both regulators and industry, regarding the quality of drug substances and drug products across the product lifecycle. It is not intended to create any new expectations beyond the current regulatory requirements.

It is neither always appropriate nor always necessary to use a formal risk management process (using recognized tools and/or internal procedures, e.g., standard operating procedures). The use of informal risk management processes (using empirical tools and/or internal procedures) can also be considered acceptable. Appropriate use of quality risk management can facilitate but does not obviate industry's obligation to comply with regulatory requirements and does not replace appropriate communications between industry and regulators.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. SCOPE (2)

This guidance provides principles and examples of tools for quality risk management that can be applied to different aspects of pharmaceutical quality. These aspects include development, manufacturing, distribution, inspection, and submission/review processes throughout the lifecycle of drug substances, drug products, biological and biotechnological products (including the use of raw materials, solvents, excipients, packaging and labeling materials in drug products, biological and biotechnological products).

III. PRINCIPLES OF QUALITY RISK MANAGEMENT (3)

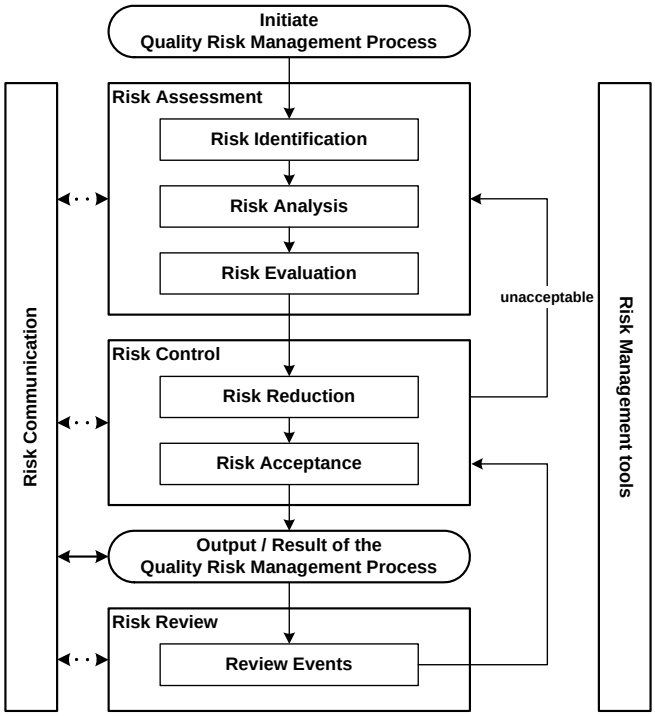
Two primary principles of quality risk management are:

- The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient; and
- The level of effort, formality, and documentation of the quality risk management process should be commensurate with the level of risk.

IV. GENERAL QUALITY RISK MANAGEMENT PROCESS (4)

Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of the drug product across the product lifecycle. A model for quality risk management is outlined in the diagram (Figure 1). Other models could be used. The emphasis on each component of the framework might differ from case to case but a robust process will incorporate consideration of all the elements at a level of detail that is commensurate with the specific risk.

Figure 1: Overview of a typical quality risk management process



Decision nodes are not shown in the diagram above because decisions can occur at any point in the process. These decisions might be to return to the previous step and seek further information, to adjust the risk models or even to terminate the risk management process based upon information that supports such a decision. Note: “unacceptable” in the flowchart does not only

refer to statutory, legislative, or regulatory requirements, but also to indicate that the risk assessment process should be revisited.

A. Responsibilities (4.1)

Quality risk management activities are usually, but not always, undertaken by interdisciplinary teams. When teams are formed, they should include experts from the appropriate areas (e.g., quality unit, business development, engineering, regulatory affairs, production operations, sales and marketing, legal, statistics, and clinical) in addition to individuals who are knowledgeable about the quality risk management process.

Decision makers should

- take responsibility for coordinating quality risk management across various functions and departments of their organization and
- ensure that a quality risk management process is defined, deployed, and reviewed and that adequate resources are available.

B. Initiating a Quality Risk Management Process (4.2)

Quality risk management should include systematic processes designed to coordinate, facilitate and improve science-based decision making with respect to risk. Possible steps used to initiate and plan a quality risk management process might include the following:

- Define the problem and/or risk question, including pertinent assumptions identifying the potential for risk
- Assemble background information and/or data on the potential hazard, harm or human health impact relevant to the risk assessment
- Identify a leader and critical resources
- Specify a timeline, deliverables, and appropriate level of decision making for the risk management process

C. Risk Assessment (4.3)

Risk assessment consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards (as defined below). Quality risk assessments begin with a well-defined problem description or risk question. When the risk in question is well defined, an appropriate risk management tool (see examples in section 5) and the types of information that will address the risk question will be more readily identifiable. As an aid to clearly defining the risk(s) for risk assessment purposes, three fundamental questions are often helpful:

1. What might go wrong?
2. What is the likelihood (probability) it will go wrong?
3. What are the consequences (severity)?

Risk identification is a systematic use of information to identify hazards referring to the risk question or problem description. Information can include historical data, theoretical analysis, informed opinions, and the concerns of stakeholders. Risk identification addresses the "What might go wrong?" question, including identifying the possible consequences. This provides the basis for further steps in the quality risk management process.

Risk analysis is the estimation of the risk associated with the identified hazards. It is the qualitative or quantitative process of linking the likelihood of occurrence and severity of harms. In some risk management tools, the ability to detect the harm (detectability) also factors in the estimation of risk.

Risk evaluation compares the identified and analyzed risk against given risk criteria. Risk evaluations consider the strength of evidence for all three of the fundamental questions.

In doing an effective risk assessment, the robustness of the data set is important because it determines the quality of the output. Revealing assumptions and reasonable sources of uncertainty will enhance confidence in this output and/or help identify its limitations. Uncertainty is due to combination of incomplete knowledge about a process and its expected or unexpected variability. Typical sources of uncertainty include gaps in knowledge, gaps in pharmaceutical science and process understanding, sources of harm (e.g., failure modes of a process, sources of variability), and probability of detection of problems.

The output of a risk assessment is either a quantitative estimate of risk or a qualitative description of a range of risk. When risk is expressed quantitatively, a numerical probability is used. Alternatively, risk can be expressed using qualitative descriptors, such as "high," "medium," or "low," which should be defined in as much detail as possible. Sometimes a *risk score* is used to further define descriptors in risk ranking. In quantitative risk assessments, a risk estimate provides the likelihood of a specific consequence, given a set of risk-generating circumstances. Thus, quantitative risk estimation is useful for one particular consequence at a time. Alternatively, some risk management tools use a relative risk measure to combine multiple levels of severity and probability into an overall estimate of relative risk. The intermediate steps within a scoring process can sometimes employ quantitative risk estimation.

D. Risk Control (4.4)

Risk control includes decision making to reduce and/or accept risks. The purpose of risk control is to reduce the risk to an acceptable level. The amount of effort used for risk control should be proportional to the significance of the risk. Decision makers might use different processes, including benefit-cost analysis, for understanding the optimal level of risk control.

Risk control might focus on the following questions:

- Is the risk above an acceptable level?
- What can be done to reduce or eliminate risks?
- What is the appropriate balance among benefits, risks and resources?
- Are new risks introduced as a result of the identified risks being controlled?

Risk reduction focuses on processes for mitigation or avoidance of quality risk when it exceeds a specified (acceptable) level (see Fig. 1). Risk reduction might include actions taken to mitigate the severity and probability of harm. Processes that improve the detectability of hazards and quality risks might also be used as part of a risk control strategy. The implementation of risk reduction measures can introduce new risks into the system or increase the significance of other existing risks. Hence, it might be appropriate to revisit the risk assessment to identify and evaluate any possible change in risk after implementing a risk reduction process.

Risk acceptance is a decision to accept risk. Risk acceptance can be a formal decision to accept the residual risk or it can be a passive decision in which residual risks are not specified. For some types of harms, even the best quality risk management practices might not entirely eliminate risk. In these circumstances, it might be agreed that an appropriate quality risk management strategy has been applied and that quality risk is reduced to a specified (acceptable) level. This (specified) acceptable level will depend on many parameters and should be decided on a case-by-case basis.

E. Risk Communication (4.5)

Risk communication is the sharing of information about risk and risk management between the decision makers and others. Parties can communicate at any stage of the risk management process (see Fig. 1: dashed arrows). The output/result of the quality risk management process should be appropriately communicated and documented (see Fig. 1: solid arrows). Communications might include those among interested parties (e.g., regulators and industry; industry and the patient; within a company, industry, or regulatory authority). The included information might relate to the existence, nature, form, probability, severity, acceptability, control, treatment, detectability, or other aspects of risks to quality. Communication need not be carried out for each and every risk acceptance. Between the industry and regulatory authorities, communication concerning quality risk management decisions might be effected through existing channels as specified in regulations and guidances.

F. Risk Review (4.6)

Risk management should be an ongoing part of the quality management process. A mechanism to review or monitor events should be implemented.

The output/results of the risk management process should be reviewed to take into account new knowledge and experience. Once a quality risk management process has been initiated, that process should continue to be utilized for events that might impact the original quality risk management decision, whether these events are planned (e.g., results of product review, inspections, audits, change control) or unplanned (e.g., root cause from failure investigations, recall). The frequency of any review should be based upon the level of risk. Risk review might include reconsideration of risk acceptance decisions (section IV.D.4).

V. RISK MANAGEMENT METHODOLOGY (5)

Quality risk management supports a scientific and practical approach to decision making. It provides documented, transparent, and reproducible methods to accomplish steps of the quality risk management process based on current knowledge about assessing the probability, severity, and, sometimes, detectability of the risk.

Traditionally, risks to quality have been assessed and managed in a variety of informal ways (empirical and/or internal procedures) based on, for example, compilation of observations, trends, and other information. Such approaches continue to provide useful information that might support topics such as handling of complaints, quality defects, deviations, and allocation of resources.

In addition, the pharmaceutical industry and regulators can assess and manage risk using recognized risk management tools and/or internal procedures (e.g., standard operating procedures). Below is a nonexhaustive list of some of these tools (further details in Annex 1 and section VIII):

- Basic risk management facilitation methods (flowcharts, check sheets, etc.)
- Failure Mode Effects Analysis (FMEA)
- Failure Mode, Effects, and Criticality Analysis (FMECA)
- Fault Tree Analysis (FTA)
- Hazard Analysis and Critical Control Points (HACCP)
- Hazard Operability Analysis (HAZOP)
- Preliminary Hazard Analysis (PHA)
- Risk ranking and filtering
- Supporting statistical tools

It might be appropriate to adapt these tools for use in specific areas pertaining to drug substance and drug product quality. Quality risk management methods and the supporting statistical tools can be used in combination (e.g., Probabilistic Risk Assessment). Combined use provides flexibility that can facilitate the application of quality risk management principles.

The degree of rigor and formality of quality risk management should reflect available knowledge and be commensurate with the complexity and/or criticality of the issue to be addressed.

VI. INTEGRATION OF QUALITY RISK MANAGEMENT INTO INDUSTRY AND REGULATORY OPERATIONS (6)

Quality risk management is a process that supports science-based and practical decisions when integrated into quality systems (see Annex II). As outlined in the introduction, appropriate use of quality risk management does not obviate industry’s obligation to comply with regulatory requirements. However, effective quality risk management can facilitate better and more informed decisions, can provide regulators with greater assurance of a company’s ability to deal

with potential risks, and might affect the extent and level of direct regulatory oversight. In addition, quality risk management can facilitate better use of resources by all parties.

Training of both industry and regulatory personnel in quality risk management processes provides for greater understanding of decision-making processes and builds confidence in quality risk management outcomes.

Quality risk management should be integrated into existing operations and documented appropriately. Annex II provides examples of situations in which the use of the quality risk management process might provide information that could then be used in a variety of pharmaceutical operations. These examples are provided for illustrative purposes only and should not be considered a definitive or exhaustive list. These examples are not intended to create any new expectations beyond the requirements laid out in the current regulations.

Examples for industry and regulatory operations (see Annex II):

- Quality management

Examples for industry operations and activities (see Annex II):

- Development
- Facility, equipment, and utilities
- Materials management
- Production
- Laboratory control and stability testing
- Packaging and labeling

Examples for regulatory operations (see Annex II):

- Inspection and assessment activities

While regulatory decisions will continue to be taken on a regional basis, a common understanding and application of quality risk management principles could facilitate mutual confidence and promote more consistent decisions among regulators on the basis of the same information. This collaboration could be important in the development of policies and guidelines that integrate and support quality risk management practices.

VII. DEFINITIONS (7)

Decision maker(s): Person(s) with the competence and authority to make appropriate and timely quality risk management decisions.

Detectability: The ability to discover or determine the existence, presence, or fact of a hazard.

Harm: Damage to health, including the damage that can occur from loss of product quality or availability.

Hazard: The potential source of harm (ISO/IEC Guide 51).

Product lifecycle: All phases in the life of the product from the initial development through marketing until the product's discontinuation.

Quality: The degree to which a set of inherent properties of a product, system, or process fulfills requirements (see ICH Q6A definition specifically for *quality* of drug substance and drug products).

Quality risk management: A systematic process for the assessment, control, communication, and review of risks to the quality of the drug product across the product lifecycle.

Quality system: The sum of all aspects of a system that implements quality policy and ensures that quality objectives are met.

Requirements: The explicit or implicit needs or expectations of the patients or their surrogates (e.g., health care professionals, regulators, and legislators). In this document, *requirements* refers not only to statutory, legislative, or regulatory requirements, but also to such needs and expectations.

Risk: The combination of the probability of occurrence of harm and the severity of that harm (ISO/IEC Guide 51).

Risk acceptance: The decision to accept risk (ISO Guide 73).

Risk analysis: The estimation of the risk associated with the identified hazards.

Risk assessment: A systematic process of organizing information to support a risk decision to be made within a risk management process. It consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards.

Risk communication: The sharing of information about risk and risk management between the decision maker and other stakeholders.

Risk control: Actions implementing risk management decisions (ISO Guide 73).

Risk evaluation: The comparison of the estimated risk to given risk criteria using a quantitative or qualitative scale to determine the significance of the risk.

Risk identification: The systematic use of information to identify potential sources of harm (hazards) referring to the risk question or problem description.

Risk management: The systematic application of quality management policies, procedures, and practices to the tasks of assessing, controlling, communicating, and reviewing risk.

Risk reduction: Actions taken to lessen the probability of occurrence of harm and the severity of that harm.

Risk review: Review or monitoring of output/results of the risk management process considering (if appropriate) new knowledge and experience about the risk.

Severity: A measure of the possible consequences of a hazard.

Stakeholder: Any individual, group, or organization that can affect, be affected by, or perceive itself to be affected by a risk. Decision makers might also be stakeholders. For the purposes of this guidance, the primary stakeholders are the patient, healthcare professional, regulatory authority, and industry.

Trend: A statistical term referring to the direction or rate of change of a variable(s).

VIII. REFERENCES (8)

ICH *Q8 Pharmaceutical Development*.

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ISO/IEC Guide 51:1999 - Safety aspects - Guideline for their inclusion in standards.

Process Mapping, American Productivity & Quality Center, 2002, ISBN 1928593739.

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Failure Mode and Effect Analysis: FMEA from Theory to Execution, 2nd Edition 2003, D. H. Stamatis, ISBN 0873895983.

Guidelines for Failure Modes and Effects Analysis (FMEA) for Medical Devices, 2003, Dyadem Press, ISBN 0849319102.

The Basics of FMEA, Robin McDermott, Raymond J. Mikulak, Michael R. Beauregard, 1996, ISBN 0527763209.

WHO Technical Report Series No. 908, 2003, Annex 7 Application of Hazard Analysis and Critical Control Point (HACCP) methodology to pharmaceuticals.

IEC 61882 - Hazard Operability Analysis (HAZOP).

ISO 14971:2000 - Application of Risk Management to Medical Devices.

ISO 7870:1993 - Control Charts.

ISO 7871:1997 - Cumulative Sum Charts.

ISO 7966:1993 - Acceptance Control Charts.

ISO 8258:1991 - Shewhart Control Charts.

What is Total Quality Control?: The Japanese Way, Kaoru Ishikawa (Translated by David J. Liu, 1985, ISBN 0139524339.

ANNEX I: RISK MANAGEMENT METHODS AND TOOLS

The purpose of this annex is to provide a general overview of and references for some of the primary tools that might be used in quality risk management by industry and regulators. The references are included as an aid to gain more knowledge and detail about the particular tool. This is not an exhaustive list. It is important to note that no one tool or set of tools is applicable to every situation in which a quality risk management procedure is used.

I.1 Basic Risk Management Facilitation Methods

Some of the simple techniques that are commonly used to structure risk management by organizing data and facilitating decision making are:

- Flowcharts
- Check Sheets
- Process Mapping
- Cause and Effect Diagrams (also called an Ishikawa diagram or fish bone diagram)

I.2 Failure Mode Effects Analysis (FMEA)

FMEA (see IEC 60812) provides for an evaluation of potential failure modes for processes and their likely effect on outcomes and/or product performance. Once failure modes are established, risk reduction can be used to eliminate, contain, reduce, or control the potential failures. FMEA relies on product and process understanding. FMEA methodically breaks down the analysis of complex processes into manageable steps. It is a powerful tool for summarizing the important modes of failure, factors causing these failures, and the likely effects of these failures.

Potential Areas of Use(s)
FMEA can be used to prioritize risks and monitor the effectiveness of risk control activities.

FMEA can be applied to equipment and facilities and might be used to analyze a manufacturing operation and its effect on product or process. It identifies elements/operations within the system that render it vulnerable. The output/results of FMEA can be used as a basis for design or further analysis or to guide resource deployment.

I.3 Failure Mode, Effects, and Criticality Analysis (FMECA)

FMEA might be extended to incorporate an investigation of the degree of severity of the consequences, their respective probabilities of occurrence, and their detectability, thereby becoming a Failure Mode, Effects, and Criticality Analysis (FMECA; see IEC 60812). In order for such an analysis to be performed, the product or process specifications should be established. FMECA can identify places where additional preventive actions might be appropriate to minimize risks.

Potential Areas of Use(s)
FMECA application in the pharmaceutical industry should mostly be utilized for failures and risks associated with manufacturing processes; however, it is not limited to this application. The output of an FMECA is a relative risk "score" for each failure mode, which is used to rank the modes on a relative risk basis.

I.4 Fault Tree Analysis (FTA)

The FTA tool (see IEC 61025) is an approach that assumes failure of the functionality of a product or process. This tool evaluates system (or subsystem) failures one at a time but can combine multiple causes of failure by identifying causal chains. The results are represented pictorially in the form of a tree of fault modes. At each level in the tree, combinations of fault modes are described with logical operators (AND, OR, etc.). FTA relies on the experts' process understanding to identify causal factors.

Potential Areas of Use(s)
FTA can be used to establish the pathway to the root cause of the failure. FTA can be used to investigate complaints or deviations in order to fully understand their root cause and to ensure that intended improvements will fully resolve the issue and not lead to other issues (i.e. solve one problem yet cause a different problem). Fault Tree Analysis is an effective tool for evaluating how multiple factors affect a given issue. The output of an FTA includes a visual representation of failure modes. It is useful both for risk assessment and in developing monitoring programs.

I.5 Hazard Analysis and Critical Control Points (HACCP)

HACCP is a systematic, proactive, and preventive tool for assuring product quality, reliability, and safety (see WHO Technical Report Series No. 908, 2003, Annex 7). It is a structured approach that applies technical and scientific principles to analyze, evaluate, prevent, and control the risk or adverse consequence(s) of hazard(s) due to the design, development, production, and use of products.

HACCP consists of the following seven steps:

(1) conduct a hazard analysis and identify preventive measures for each step of the process
(2) determine the critical control points
(3) establish critical limits
(4) establish a system to monitor the critical control points
(5) establish the corrective action to be taken when monitoring indicates that the critical control points are not in a state of control
(6) establish system to verify that the HACCP system is working effectively
(7) establish a record-keeping system

Potential Areas of Use(s)
HACCP might be used to identify and manage risks associated with physical, chemical, and biological hazards (including microbiological contamination). HACCP is most useful when product and process understanding is sufficiently comprehensive to support identification of

critical control points. The output of a HACCP analysis is risk management information that facilitates monitoring of critical points not only in the manufacturing process but also in other lifecycle phases.

I.6 Hazard Operability Analysis (HAZOP)

HAZOP (see IEC 61882) is based on a theory that assumes that risk events are caused by deviations from the design or operating intentions. It is a systematic brainstorming technique for identifying hazards using so-called *guide words*. Guide words (e.g., No, More, Other Than, Part of) are applied to relevant parameters (e.g., contamination, temperature) to help identify potential deviations from normal use or design intentions. HAZOP often uses a team of people with expertise covering the design of the process or product and its application.

Potential Areas of Use(s)
HAZOP can be applied to manufacturing processes, including outsourced production and formulation as well as the upstream suppliers, equipment and facilities for drug substances and drug products. It has also been used primarily in the pharmaceutical industry for evaluating process safety hazards. As is the case with HACCP, the output of a HAZOP analysis is a list of critical operations for risk management. This facilitates regular monitoring of critical points in the manufacturing process.

I.7 Preliminary Hazard Analysis (PHA)

PHA is a tool of analysis based on applying prior experience or knowledge of a hazard or failure to identify future hazards, hazardous situations and events that might cause harm, as well as to estimate their probability of occurrence for a given activity, facility, product, or system. The tool consists of: (1) the identification of the possibilities that the risk event happens, (2) the qualitative evaluation of the extent of possible injury or damage to health that could result, (3) a relative ranking of the hazard using a combination of severity and likelihood of occurrence, and (4) the identification of possible remedial measures

Potential Areas of Use(s)
PHA might be useful when analyzing existing systems or prioritizing hazards where circumstances prevent a more extensive technique from being used. It can be used for product, process and facility design as well as to evaluate the types of hazards for the general product type, then the product class, and finally the specific product. PHA is most commonly used early in the development of a project when there is little information on design details or operating procedures; thus, it will often be a precursor to further studies. Typically, hazards identified in the PHA are further assessed with other risk management tools such as those in this section.

I.8 Risk Ranking and Filtering

Risk ranking and filtering is a tool for comparing and ranking risks. Risk ranking of complex systems typically involves evaluation of multiple diverse quantitative and qualitative factors for each risk. The tool involves breaking down a basic risk question into as many components as needed to capture factors involved in the risk. These factors are combined into a single relative

risk score that can then be used for ranking risks. “Filters,” in the form of weighting factors or cut-offs for risk scores, can be used to scale or fit the risk ranking to management or policy objectives.

Potential Areas of Use(s)
Risk ranking and filtering can be used to prioritize manufacturing sites for inspection/audit by regulators or industry. Risk ranking methods are particularly helpful in situations in which the portfolio of risks and the underlying consequences to be managed are diverse and difficult to compare using a single tool. Risk ranking is useful for management to evaluate both quantitatively-assessed and qualitatively-assessed risks within the same organizational framework.

I.9 Supporting Statistical Tools

Statistical tools can support and facilitate quality risk management. They can enable effective data assessment, aid in determining the significance of the data set(s), and facilitate more reliable decision making. A listing of some of the principal statistical tools commonly used in the pharmaceutical industry is provided:

- Control charts, for example:
  - — Acceptance control charts (see ISO 7966)
  - — Control charts with arithmetic average and warning limits (see ISO 7873)
  - — Cumulative sum charts (see ISO 7871)
  - — Shewhart control charts (see ISO 8258)
  - — Weighted moving average
- Design of experiments (DOE)
- Histograms
- Pareto charts
- Process capability analysis

ANNEX II: POTENTIAL APPLICATIONS FOR QUALITY RISK MANAGEMENT

This Annex is intended to identify potential uses of quality risk management principles and tools by industry and regulators. However, the selection of particular risk management tools is completely dependent upon specific facts and circumstances.

These examples are provided for illustrative purposes and only suggest potential uses of quality risk management. This Annex is not intended to create any new expectations beyond the current regulatory requirements.

II.1 Quality Risk Management as Part of Integrated Quality Management

Documentation
To review current interpretations and application of regulatory expectations

To determine the desirability of and/or develop the content for SOPs, guidances, etc.

Training and education
To determine the appropriateness of initial and/or ongoing training sessions based on education, experience, and working habits of staff, as well as on a periodic assessment of previous training (e.g., its effectiveness)

To identify the training, experience, qualifications, and physical abilities that allow personnel to perform an operation reliably and with no adverse impact on the quality of the product

Quality defects
To provide the basis for identifying, evaluating, and communicating the potential quality impact of a suspected quality defect, complaint, trend, deviation, investigation, out of specification result, etc.

To facilitate risk communications and determine appropriate action to address significant product defects, in conjunction with regulatory authorities (e.g., recall)

Auditing/Inspection
To define the frequency and scope of audits, both internal and external, taking into account factors such as:

- Existing legal requirements
- Overall compliance status and history of the company or facility
- Robustness of a company's quality risk management activities
- Complexity of the site
- Complexity of the manufacturing process
- Complexity of the product and its therapeutic significance
- Number and significance of quality defects (e.g., recall)
- Results of previous audits/inspections
- Major changes of building, equipment, processes, key personnel

- Experience with manufacturing of a product (e.g., frequency, volume, number of batches)
- Test results of official control laboratories

Periodic review
To select, evaluate, and interpret trend results of data within the product quality review

To interpret monitoring data (e.g., to support an assessment of the appropriateness of revalidation or changes in sampling)

Change management/change control
To manage changes based on knowledge and information accumulated in pharmaceutical development and during manufacturing

To evaluate the impact of the changes on the availability of the final product

To evaluate the impact on product quality of changes to the facility, equipment, material, manufacturing process, or technical transfers

To determine appropriate actions preceding the implementation of a change, e.g., additional testing, (re)qualification, (re)validation, or communication with regulators

Continual improvement
To facilitate continual improvement in processes throughout the product lifecycle

II.2 Quality Risk Management as Part of Regulatory Operations

Inspection and assessment activities
To assist with resource allocation including, for example, inspection planning and frequency, and inspection and assessment intensity (see Auditing section in Annex II.1)

To evaluate the significance of, for example, quality defects, potential recalls, and inspectional findings

To determine the appropriateness and type of postinspection regulatory follow-up

To evaluate information submitted by industry, including pharmaceutical development information

To evaluate impact of proposed variations or changes

To identify risks that should be communicated between inspectors and assessors to facilitate better understanding of how risks can be or are controlled (e.g., parametric release, Process Analytical Technology (PAT)).

II.3 Quality Risk Management as Part of Development

To design a quality product and its manufacturing process to consistently deliver the intended performance of the product (see ICH Q8)

To enhance knowledge of product performance over a wide range of material attributes (e.g., particle size distribution, moisture content, flow properties), processing options, and process parameters

To assess the critical attributes of raw materials, solvents, active pharmaceutical ingredient (API) starting materials, APIs, excipients, or packaging materials

To establish appropriate specifications, identify critical process parameters, and establish manufacturing controls (e.g., using information from pharmaceutical development studies regarding the clinical significance of quality attributes and the ability to control them during processing)

To decrease variability of quality attributes:

- reduce product and material defects
- reduce manufacturing defects

To assess the need for additional studies (e.g., bioequivalence, stability) relating to scale up and technology transfer

To make use of the *design space* concept (see ICH Q8)

II.4 Quality Risk Management for Facilities, Equipment and Utilities

Design of facility/equipment

To determine appropriate zones when designing buildings and facilities, e.g.,

- flow of material and personnel
- minimize contamination
- pest control measures
- prevention of mix-ups
- open versus closed equipment
- clean rooms versus isolator technologies
- dedicated or segregated facilities/equipment

To determine appropriate product contact materials for equipment and containers (e.g., selection of stainless steel grade, gaskets, lubricants)

To determine appropriate utilities (e.g., steam; gases; power source; compressed air, heating, ventilation, and air conditioning (HVAC); water)

To determine appropriate preventive maintenance for associated equipment (e.g., inventory of necessary spare parts)

Hygiene aspects in facilities
To protect the product from environmental hazards, including chemical, microbiological, and physical hazards (e.g., determining appropriate clothing and gowning, hygiene concerns)

To protect the environment (e.g., personnel, potential for cross-contamination) from hazards related to the product being manufactured

Qualification of facility/equipment/utilities
To determine the scope and extent of qualification of facilities, buildings, and production equipment and/or laboratory instruments (including proper calibration methods)

Cleaning of equipment and environmental control
To differentiate efforts and decisions based on the intended use (e.g., multi- versus single-purpose, batch versus continuous production)

To determine acceptable (specified) cleaning validation limits

Calibration/preventive maintenance
To set appropriate calibration and maintenance schedules

Computer systems and computer-controlled equipment
To select the design of computer hardware and software (e.g., modular, structured, fault tolerance)

To determine the extent of validation, e.g.,

- identification of critical performance parameters
- selection of the requirements and design
- code review
- the extent of testing and test methods
- reliability of electronic records and signatures

II.5 Quality Risk Management as Part of Materials Management

Assessment and evaluation of suppliers and contract manufacturers
To provide a comprehensive evaluation of suppliers and contract manufacturers (e.g., auditing, supplier quality agreements)

Starting material
To assess differences and possible quality risks associated with variability in starting materials (e.g., age, route of synthesis).

Use of materials
To determine whether it is appropriate to use material under quarantine (e.g., for further internal processing)

To determine appropriateness of reprocessing, reworking, use of returned goods

Storage, logistics and distribution conditions
To assess the adequacy of arrangements to ensure maintenance of appropriate storage and transport conditions (e.g., temperature, humidity, container design)

To determine the effect on product quality of discrepancies in storage or transport conditions (e.g., cold chain management) in conjunction with other ICH guidances

To maintain infrastructure (e.g., capacity to ensure proper shipping conditions, interim storage, handling of hazardous materials and controlled substances, customs clearance)

To provide information for ensuring the availability of pharmaceuticals (e.g., ranking risks to the supply chain).

II.6 Quality Risk Management as Part of Production

Validation
To identify the scope and extent of verification, qualification, and validation activities (e.g., analytical methods, processes, equipment, and cleaning methods

To determine the extent for follow-up activities (e.g., sampling, monitoring, and re-validation)

To distinguish between critical and noncritical process steps to facilitate design of a validation study

In-process sampling & testing
To evaluate the frequency and extent of in-process control testing (e.g., to justify reduced testing under conditions of proven control)

To evaluate and justify the use of process analytical technologies (PAT) in conjunction with parametric and real time release

Production planning
To determine appropriate production planning (e.g., dedicated, campaign, and concurrent production process sequences)

II.7 Quality Risk Management as Part of Laboratory Control and Stability Studies

Out of specification results
To identify potential root causes and corrective actions during the investigation of out of specification results

Retest period/expiration date
To evaluate adequacy of storage and testing of intermediates, excipients, and starting materials

II.8 Quality Risk Management as Part of Packaging and Labeling

Design of packages
To design the secondary package for the protection of primary packaged product (e.g., to ensure product authenticity, label legibility)

Selection of container closure system
To determine the critical parameters of the container closure system

Label controls
To design label control procedures based on the potential for mix-ups involving different product labels, including different versions of the same label

Appendix C: EMA Reflection Paper on Risk-Based Quality Management in Clinical Trials

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 November 2013
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Compliance and Inspection

Reflection paper on risk based quality management in clinical trials

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Reflection paper on risk based quality management in clinical trials

Table of contents

Glossary

1. Central technical facility

Laboratory or other technical facility in which the measurements or assessments of the laboratory, ECG or other tests are centralised.

2. Central monitoring

Document review, data review and analysis performed remotely from the investigator site by the sponsor to examine the data collected in order to check compliance, identify unusual data patterns, deviations from protocol or missing or invalid data. Examples of central monitoring techniques include checks of submitted documents (e.g. checklists for TMF content completed by investigators, training evidence etc.), clinical data checks (e.g. range checks, calendar checks etc., rate of reporting adverse events), compliance data/metrics checks (e.g. number of reported deviations from the protocol, rate of reporting adverse events... etc.).

3. Data safety monitoring board (DSMB)

Also referred as Independent Data-Monitoring Committee (IDMC)

An independent data-monitoring committee that may be established by the sponsor to assess at intervals the progress of a clinical trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop a trial.

4. Electronic data capture (EDC)

A system that allows collecting clinical trial data in electronic form and importing them without the use of paper. Electronic data capture systems are varied and can include eCRF: electronic Case Report Form, IVRS/IWRS (Interactive Voice/Web Response System), transfer of laboratory data from one system to another.

5. Failure mode and effects analysis (FMEA)

A FMEA is mainly a qualitative analysis to help to identify potential failure modes.

6. Good clinical practice (GCP)

As defined by the principles of ICH E6 guidelines [1] (ICH GCP), is a set of internationally recognised ethical and scientific standards for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical trials.

7. Project

A project may be a single clinical trial or a clinical programme which includes several trials.

8. Quality assurance

All those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded), and reported in compliance with Good Clinical Practice (GCP) and the applicable regulatory requirement(s).

9. Quality risk management

Quality risk management is a systematic process for the assessment, control, communication and review of risks associated with the planning and conduct of clinical trials and clinical development programmes.

10. Quality management system

A management system used to direct and control an organisation with regard to quality. It is the system that an organisation uses to manage the quality of their services or products. It usually consists of formal controlled procedural documents, such as policies, standard operating procedures, work instructions, forms & templates. As part of the quality system there are usually quality control and quality assurance processes.

11. Sponsor

An individual, company, institution, or organisation, which takes responsibility for the initiation, management, and/or financing of a clinical trial.

12. Sponsor-investigator

An individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a subject. The term does not include any person other than an individual (e.g., it does not include a corporation or an agency). The obligations of a sponsor-investigator include both those of a sponsor and those of an investigator.

13. Suspected Unexpected Serious Adverse Reaction (SUSAR)

An adverse reaction that is both unexpected (not consistent with the applicable product information) and also meets the definition of a Serious Adverse Event/Reaction.

14. System

The system in a company or an organisational structure that provides the framework under which the work of the company can be managed efficiently and effectively. It relates to people (individuals, groups or organisations), facilities, technology and data (information for decision making).

1. Introduction

Good clinical practice (GCP)[1], is a set of internationally recognised ethical and scientific standards for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical trials.

ICH GCP requires in Section 5.1, that the sponsor implements and maintains systems for quality assurance and quality control; similarly the Article 2 of the GCP Directive 2005/28/EC requires the implementation of procedures necessary to secure the quality of every aspect of the trial. The aim of these quality management procedures is to provide assurance that the rights, safety and well-being of trial subjects are protected, and that the results of the clinical trials are credible. The same requirements apply to Contract Research Organisations (CROs), vendors or other service providers to whom the sponsor has delegated any trial related duties and functions of the sponsor.

The key elements of the quality system include:

- documented procedures and validated methods being developed, implemented and kept up-to-date;
- documentation system that preserves and allows for the retrieval of any information/documentation (quality records/essential documents) to show actions taken, decisions made and results;
- appropriate training of sponsor personnel as well as of the personnel in affiliates, at the Contract Research Organisations (CROs), vendors or other service providers and at trial sites;

- validation of computerised systems;
- quality control, for example monitoring of trial sites and central technical facilities on-site and/or by using centralised monitoring techniques;
- quality assurance including internal and external audits performed by independent auditors.

The current manner in which some elements of a quality system are implemented by sponsors and their agents (CROs etc.) is generally acknowledged to be time-consuming and constitutes a major proportion of the cost of development of medicines. In addition, the ICH GCP guideline was finalised in 1996 when clinical research was largely paper based, but the available technology and the approach to the conduct of clinical trials has evolved considerably in the meantime.

Whilst often successful in achieving a good quality clinical trial, the current practice can however be expensive and there are too many trials in which avoidable quality problems arise. This is illustrated by the nature and extent of findings, identified by European GCP inspectors, during inspections. The combination of these findings and the high cost of the oversight of clinical trials strongly suggests that current approach to clinical quality management is in need of review and reorientation.

The general problem can be summarised by stating that current practices in clinical research are not proportionate to risk nor well adapted to achieving the desired goals. The origins of the problem are multifactorial and include:

- cost of clinical development and limitations on the resource that can be made available;
- development deadlines, pressure from investors and other factors determining project deadlines;
- fragmentation of roles into many niche players, often without clear distribution of tasks or coordinated organisation, and each with its own priorities, risks and business environment. This is also reflected in piecemeal implementation of technology, with fragmented, unconnected and poorly standardised solutions;
- globalisation of clinical trials, complicating the regulatory, business and scientific/medical environment and patient population within which they operate;
- risk aversion – society and its institutions (public and private) is increasingly risk averse, often with little appreciation of the actual or relative risk of different activities, leading to imbalanced or disproportionate risk mitigation;
- stifling of innovation by restrictive practices, preconceived ideas, incorrect perceptions, leading to a failure to evolve processes and resistance to the implementation and acceptance of new approaches or technologies e.g. application and adoption of a single model of monitoring to the management of all trials, which is neither appropriate nor effective;
- the regulatory environment may be over-interpreted, or misunderstood, resulting in a failure to achieve its actual intent;
- poor design of studies and study processes, often being much more complicated than necessary to achieve what is required, thus diminishing focus and resource available to achieve the quality necessary for the more important objectives;
- failure to identify priorities. Both study and process design is often cluttered by data collection requirements or quality control activities (e.g. monitoring etc.) of limited importance that distract greatly from the most important issues;
- poor risk identification and poor risk mitigation – a lack of use or understanding of risk-management tools and techniques, is often associated with a reactive, fire-fighting approach to

problem management. This results in processes largely based on corrective rather than preventive action;

- lack of proportionality (one size fits all) in the implementation of quality control activities (e.g. monitoring etc.) often related to a lack of understanding of the impact of variability in trial conduct and measurement or data collection on the study results and their reliability;
- lack of knowledge or more particularly real understanding of the goals of the legal framework and guidelines, and the flexibility that they currently present;
- lack of capabilities of at least one of the parties to operationally fulfil the requirements of the study.

These issues are often deeply embedded in the culture and thinking of the organisations and people involved and are consequently very difficult to change. This paper intends to open up the discussion on approaches to clinical trials to new thinking, in order to facilitate the development of proportionate clinical trial processes.

Areas that are most often raised as causing particular concern are the design and complexity of the study protocols and data to be collected, the extent and nature of the monitoring that is implemented, as well as the related data management and the extent and nature of documentation required to be completed and retained for a given study.

A proportionate approach is required and should be adapted to the risk of the research conducted by any sponsors (academic researchers, small medium sized enterprises (SMEs) and large multi- national pharmaceutical companies). Sponsors are expected to cope with this challenge and to move towards a more systematic and risk based approach. There is a need to find better ways to make sure that limited resources are best targeted to address the most important issues and priorities, especially those associated with predictable or identifiable risks to the wellbeing of trial subjects and the quality of trial data and results.

As part of the EU implementation of the ICH Q9[2] and Q10[3] principles and concepts, amendments to Chapter 1 of the GMP Guide (Pharmaceutical Quality systems) were published. Quality Risk Management has become an accepted standard. This concept can be adapted and described for clinical research with medicinal products.

2. Purpose and content

The purpose of this reflection paper is to encourage and facilitate the development of a more systematic, prioritised, risk-based approach to quality management of clinical trials, to support the principles of Good Clinical Practice and to complement existing quality practices, requirements and standards.

Quality in this context is commonly defined as fitness for purpose. Clinical research is about generating information to support decision making while protecting the safety and rights of participating subjects. The quality of information generated should therefore be sufficient to support good decision making.

Each step of the clinical trial process is setting the stage for decision making by one or more of the parties involved. Quite a number of these decisions are formalised by legislation and by GCP. From protocol design, submission to the ethics committee and competent authority, initiation of a trial, informed consent, protection of the subjects and on-going oversight of the risk benefit of the trial to trial reporting, decisions are made at various levels and documented. The process continues, in the case of the development of new products, through finalisation of the first study report[4], initiation of new trials, and finally if the continued development of the product has been permitted and the sponsor

decides to progress, the process reaches the marketing authorisation stage. Clinical trial results are also published in peer review journals where they influence other research and may lead to changes in medical practice and treatment strategies.

Every decision is made on the basis of knowledge founded on the data and information accumulated to date. Each of those decisions will only be as good as the processes used to collect, analyse, interpret and report the information to the decision maker, in a format that they can use. Many of these formats in themselves are standardised, such as the protocol, informed consent document, safety reports, clinical study report, marketing authorisation application dossier or journal publications.

Since perfection in every aspect of an activity is rarely achievable or can only be achieved by disproportionate allocation of resource, it is necessary to establish a risk based quality management system for which the ultimate principles are reliability of the trial results and the well being and safety of trial subjects. This system is based on identification of trial priorities and mitigation of the significant and serious risks and establishing tolerance limits within which different processes can operate.

This paper has been developed taking into account the activities of other groups in this field (e.g. ADAMON[5], ECRIN[6], OPTIMON[7] MRC/DH/MHRA joint project: Risk adapted approaches to the management of clinical trials[8], the Organisation for Economic Co-operation and Development (OECD)[9]), the CTTI (Clinical Trial Transformation Initiative)[10], FDA "Guidance for Industry Oversight of Clinical Investigations — A risk-based approach to monitoring[11], the principles of ICH Q8 Pharmaceutical Development[12], ICH Q9[2] Quality Risk Management and ICH Q10[3] Pharmaceutical Quality System).

The examples given within the text fulfil the purpose of illustration of the topics addressed.

3. Risk based quality management

The basic idea of risk based quality management is the identification of the risks on a continuous basis for risk-bearing activities throughout the design, conduct, evaluation and reporting of clinical trials. The process should start at the time of protocol design so mitigation can be built into the protocol and other trial related documents (e.g. monitoring plan).

In addition to the mitigation of identified risks, opportunities to introduce beneficial and proportionate adaptation of conventional practices regarding the management, monitoring and conduct of the trial should also be identified. Risk based quality management is a systematic process put in place to identify, assess, control, communicate and review the risks associated with the clinical trial during its lifecycle. The principles of risk management and the overview of the process as outlined in ICH Q9[2] apply as much to clinical trials as to other areas and a simple illustration of the process as applied to clinical trials can be seen in Figure 1. ICH Q9[2] provides references to various tools that can be used to assist in the risk management process, in particular for risk assessment. Application of risk based quality management approaches to clinical trials can facilitate better and more informed decision making better utilisation of the available resources. Risk management should be appropriately documented and integrated within existing quality systems. It is the responsibility of all involved parties to contribute to the delivery of an effective risk-based quality management system.

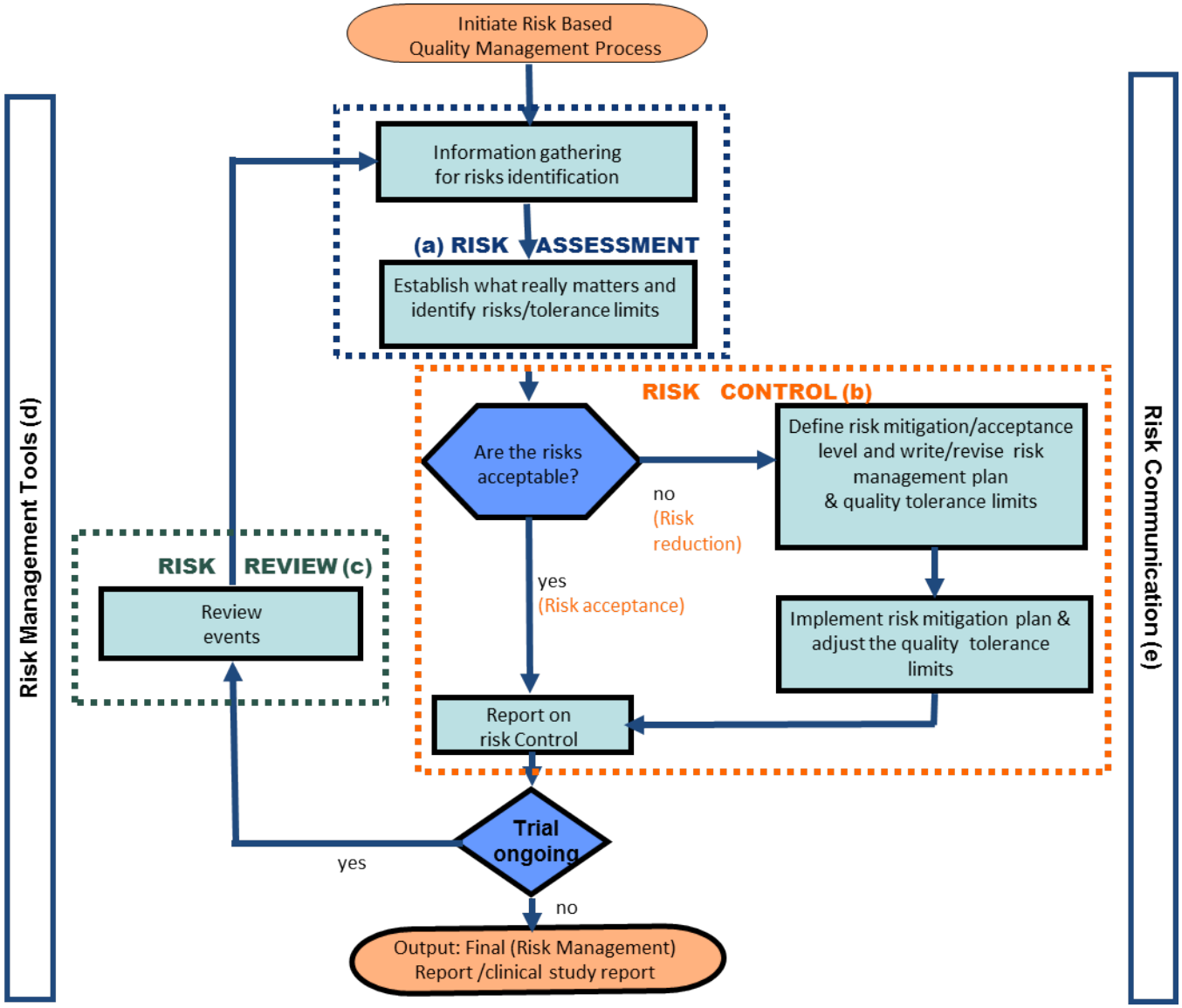

Figure 1: Illustration of a risk based quality management system for clinical trials

(a) Risk assessment requiring knowledge and understanding of what really matters for the establishment of priorities and the identification of risks: what may go wrong? What is the probability (chance/likelihood) of the occurrence of a negative outcome? What, in particular, would be the impact on trial subjects' rights/well-being/safety and/or on the reliability of the trial results? With the priorities in perspective, the assessment of risks consists of the identification of the negative outcomes, their impact and their chance/probability of occurrence.

(b) Risk control: decision making to accept risks or define mitigation measures for identified risks and establish a risk management plan. Areas with no or little risk that have been identified give opportunity to adapt traditional trial oversight and management approaches. Implement the actions identified.

(c) Risk review: on-going reassessment of the risks by review of new information emerging during the conduct of the trial (e.g. new pre-clinical data, new safety data, updated Investigator Brochure, Protocol Amendment) and the outputs of trial management activities (e.g. Monitoring output, Data management, Data Monitoring Committee Meeting Output, Audit Reports), assess impact on risk management plan and tolerance limits.

(d) Risk management tools: can be paper based or built with the use of information technology. The tools can allow detection, identification, prediction, tracking, analysing with the generation of metrics. Broadly the tools support the risk management system and the decision making.

(e) Risk communication: distribution of the documents related to the risk review to all stakeholders and decision makers, communication of risk mitigation/acceptance measures.

All quality management processes are dynamic. Thus, continuous improvement is only ensured, when quality management processes are constantly adapted by collecting and using information on an on-going basis, and when changes are routinely evaluated to make sure they are effective. It is an essential part of the risk based quality management system that review takes place as additional information becomes available.

4. Risk assessment

4.1. Information gathering for risk identification

There are two levels to consider when gathering information for risk identification in clinical trials. At the first level, system risk, the information associated with the environment and its systems should be analysed to identify potential risks that could affect organisations, their technology and their data and products. These risks would indirectly affect a clinical trial. For the second level, project risk, the information directly linked with the trial should be analysed to identify the risks that are trial specific:

1. Information gathered at system level

The globalisation and fragmentation of clinical trial management across and within numerous organisations/departments can produce areas where risks can be envisaged, often at interfaces of quality systems or movements of information/data. Those system related risk factors may have impact across projects and or clinical trials. It is essential that systematic use of information on the quality management system of the sponsor organisation as well as of involved collaborators is obtained and evaluated to identify risks. This would include:

- organisation structures and responsibilities (e.g. organograms, communication plans, contractual partners);
- quality systems and processes (e.g. standardised procedures);
- facilities and computerised systems (e.g. Information technology infrastructure, document management system, data management system, IVRS, eCRF system);
- human resources including training and qualifications of personnel (e.g. job descriptions, training plans, performance management);
- compliance metrics, performance measurements, quality audit and/or inspection outcomes;
- regulatory and ethical framework (e.g. knowledge of national and local approvals and notification required and their timelines).

2. Information gathered at project level

A project may describe a single clinical trial to a full clinical development programme. Information gathering at the project level is to identify potential risks linked with a specific trial/clinical programme. The information to review is specifically related to the trial and would include the following areas: the investigational medicinal product(s), trial design and protocol specific requirements, the project

management, the resources and the training, the equipment and procedures/methods for this specific trial.

- IMP related risk area: any available information about the physico-chemical properties of the active ingredient(s), the manufacturing process of the active ingredient(s) as well as of the investigational medicinal product(s), and the pharmacokinetic, pharmacological and toxicological properties of the investigational medicinal product(s), derived (on-going) from preclinical and clinical trials, including the concerned trial, the requirements for the labelling and packaging of the IMP.
- Trial design related risk area: complexity of trial design, trial population (e.g. vulnerability, morbidity), therapeutic area (e.g. difficult recruitment associated with rare disease), sample size calculation, practicability and adequateness of the eligibility criteria, non-medicinal protocol related activities (e.g. risk associated with biopsies).
- Operational risk area: study budget (e.g. inadequate planning for resourcing monitoring or other trial activities), development deadlines, staff resource level and study specific training (e.g. lack of GCP experience at a trial site), study management team and responsibilities (e.g. lack of revision of documents), clinical trial site selection and management, contract research organisation involvement, clinical trial supply processes and management, clinical site set up and infrastructure, laboratory setup, setup of trial databases (e.g. trial specific IVRS, eCRF with controlled access of the study eCRF and specific site training), site monitoring and central monitoring, management of clinical data including adapted safety monitoring (e.g. lack of SUSARS reporting), reporting and/or communication lines.

4.2. Establishing priorities for risk evaluation

The first step is to clearly understand the processes and outcomes which really matter in order to achieve the objectives of the study protocol and good clinical practice. After the systematic identification of risks and before the definition of mitigation actions, it is first necessary to identify the risks that really matter and to establish priorities. Prioritisation should be oriented to meet the objectives of good clinical practice (assurance that the rights, safety and well-being of trial subjects are protected, and that the results of the clinical trials are credible) and the scientific objectives of the clinical trial.

The priorities need first to be established at the time of planning and preparation (design) of the clinical trial, including the corresponding documents, trial specific plan, data collection tools and all processes that will be used at the different stages of the trial. They should be carefully set out so that risk analysis is carried out and control measures are designed in a way that is continuously adapted to them.

The priorities should then be reflected in the trial related documents, in the assignment of resources and control procedures, in particular the focus of the data collection and monitoring and data management activities.

The establishment of priorities will guide the analysis and evaluation of risks. Qualitative or quantitative process methodologies based on risk categories can be used. Well established methods, like fishbone diagrams or Failure Mode and Effects Analysis (FMEA), take into account likelihood of occurrence, impact, and detectability of risks and can be useful tools.

The establishment of priorities will contribute to the identification of the risks that need to be mitigated and which should be the object of the risk based quality management process. Their analysis and evaluation can proceed with the knowledge that these risks are the ones that really matter.

Priorities should be continuously reviewed and adapted as deemed necessary during trial conduct.

5. Risk control

Risk control includes the process of decision making to reduce and/or accept risks (see for example ICH Q9[2] chapter 4.4). The purpose of risk control is to reduce the risk to an acceptable level. During risk control, a mitigation plan should be prepared and implemented. The amount of effort used for risk control should be proportional to the significance of the risk and the importance of the process or outcome exposed to identified risk.

Risk control might focus on the following questions:

- Is the risk above an acceptable level?
- What can be done to reduce or eliminate risks?
- What is the appropriate balance among benefits, risks and resources?
- Are new risks introduced as a result of the identified risks being mitigated or accepted?

5.1. Risk mitigation / risk acceptance

Risks might be acceptable if they have limited impact on subject's safety and rights as well as data integrity and reliability.

If a risk is not acceptable, it needs to be reduced by appropriate risk mitigation actions. Those need to be specified in a risk management plan. The latter needs to be reviewed and adapted accordingly.

Mitigation actions should be implemented to address identified risks with respect to the system and could include:

- documented procedures to formally link quality systems of organisation;
- detailed contracts between parties clearly defining roles, responsibilities and tasks to be undertaken;
- measures of oversight of delegated/contracted tasks;
- determination of communication plans, encompassing communication partners, objectives, goals, timetables and tools for all communications;
- tailored training in processes/procedures that may be new and/or unfamiliar;
- use existing data in different databases for risk assessment and risk mitigation, e.g. develop IT-tools and automatic data interfaces;
- quality performance measurement for internal and external service providers, linked to flexibility in plans for oversight and monitoring etc.

Mitigation actions to be implemented to address identified risks with respect to the project and could include:

- protocol design process with collaboration of expert functions including feasibility aspects;
- designing of training material, trial specific plans for monitoring, audit, data management etc. taking into account the identified priorities and risks;

- safety monitoring procedure adapted to each project and stage of the project e.g. post-approval trials where the safety profile for a product is known, such adaptation is most likely to be an efficiency gain of low risk to the patients;
- trial specific adaptation of extent and nature of monitoring, for example, adaptation of on-site monitoring visits, SDV (Source Data Verification) focused on particular data, (complementary) central monitoring processes etc. (subject to appropriate metrics being captured to determine when/if escalation in monitoring would be appropriate), data handling, and evaluation as well as reporting.

5.2. Quality tolerance limits

Having established the priorities and the processes for risk mitigation/acceptance, it is important to define the initial acceptable variation or tolerance limits for the clinical trial data and procedural metrics involved. It is important to recognise that tolerance limits do not need to be established for all variables or procedural metrics. It is envisaged that the limits may be readily deducted or may require an in-depth scrutiny of the objectives and endpoints (e.g. complex, larger and longer trials).

The acceptable variation of clinical trial data, predefined by the tolerance limits, should be established bearing in mind the current state of medical and statistical knowledge about the variables to be analysed as well as the statistical design of the trial. Measurements within the protocol tolerance range would therefore not be “protocol deviations”. The introduction of a tolerance range/limit for specific clinical trial data parameters, at an early stage, defined within the protocol, would allow better focus of the data measurement, collection and reporting. Tolerance limits can also be set for procedural metrics from trial management systems (e.g. deliverables for monitoring reports), these could be defined in other appropriate documents (e.g. SOPs, Monitoring plans etc.). The parameters for which a tolerance limit is appropriate should be decided as part of the risk assessment.

One of the benefits of setting tolerance limits early at the time of risk identification or prior to the start of the trial is to allow detection of the deviations from the tolerance range. This would be conducive to rectify or modify the processes to improve the conduct of the study. The other benefit of introducing quality tolerance limits is that it directs the oversight and the monitoring on the parameters that matter to the study objectives and help to design more risk based oversight, management and monitoring strategies. The tolerance limits can be set for a specific trial or some appropriate parameters could be general limits applied to all the sponsor’s trials and defined in the sponsor’s quality system.

The following are examples of areas for which variation or tolerance limits could be established:

1. Trial data

Consider the precision, the accuracy and the timing of clinical measurements. In particular in relation to the importance of the variable in terms of the trial objectives including safety monitoring (e.g. the occasional omission of some measurements, or early or late performance of some study visits may be in some cases less critical than in others).

With the knowledge of the tolerance limits, attention is only focussed on those situations where these established tolerance limits are exceeded, or exceeded by more than a set frequency or amount. In addition, especially with direct electronic data capture, the measurement and tracking of data within these limits is more easily achieved, reported and where needed acted on.

For example it may be important in some cases to very accurately time a procedure 60 minutes post administration of a dose of medicine for pharmacokinetic purposes and a tolerance of 60 minutes plus

or minus 1-3 minutes may be acceptable, based on the predicted or known PK profile of the drug. In other cases a one hour post dose safety monitoring of blood pressure or heart rate may be equally valid if performed plus or minus 15 minutes from the hour.

Consider the process for data recording/transcription and its accuracy. This would provide information for setting tolerance limits on source data verification requirements.

2. Trial protocol procedures and GCP

Monitor the compliance/deviation from protocols.

Effective mechanisms should be in place to capture protocol and/or GCP deviations and assess their impact on the objectives of the trial and the welfare of trial subjects. Tolerance limits could be set such that detected issues may trigger escalation of monitoring (e.g. additional site visits, additional training).

3. Trial management procedures

Define the metrics that will allow oversight of the trial.

Establish the oversight/management/monitoring strategy.

Define the timing of reporting/retrieval of data.

For example, a monitoring plan could include more emphasis on central monitoring and audit and targeted source data verification on those variables that have been identified as important for meeting the trial objectives, with no or reduced SDV on others. The use of eCRF systems facilitates the use of central monitoring activities and metrics could be developed such that triggers are set for targeted monitoring/audit activities.

An example metric that may trigger targeted activities could identify site with excessive delays in data being entered on to the eCRF system or in serious adverse event (SAE) reporting. The lack of variability in data can also trigger further monitoring, e.g. one digit preference for blood pressure measurements in hypertension trials.

There is potential to develop central monitoring systems using statistical methodology to monitor the quality of the trial conduct and data, with regular metrics reports and records produced that demonstrate the checks/activities that are being undertaken and that they are compliant with the defined monitoring strategy and procedures. This could lead to targeted on-site visits to address the issues that such visits are better placed to detect.

6. Risk review and reporting quality

6.1. Risk review cycle

The concept of risk based quality management in clinical research revolves around the following cycle (as presented in Figure 1):

- risk assessment with information gathering, the establishment of priorities and the identification of risks associated with the study;
- risk control which encompasses setting tolerance limits mitigation and acceptance of risks;
- risk review which necessitates knowledge of the previous steps with the integration of the risk management tools and the communication on the review of the results and data associated to the risk identified and the documentation of the actions needed.

6.2. Reporting quality

The feedback from the risk review cycle should be analysed and summarised. This will include measures of variability of measurements and their timing, assessment of deviations from tolerance limits or protocol requirements, and missing data. Additional information can be achieved by well-designed intra and inter site variance analysis on single or multiple variables. Any analysis of trends should be done in relation to the overall impact on the scientific merits and usability of the generated data as established through priority setting and identification of risks. Such analysis can be supplemented with information on process compliance derived from monitoring/data management reports.

At the end of a trial it should be possible, in a clear qualitative and/or quantitative way, to report on the extent to which a trial has operated within the tolerance limits established and maintained during the trial and whether it has been conducted to acceptable level of quality as assessed by a predetermined methodology. Such a report could be included in the clinical study report[4] (in section 9.6 Data Quality Assurance) and could describe actions, where possible, that were implemented to correct and prevent deviations from tolerance limits during the trial conduct. Audit outcomes will add to and serve to validate the quality report of a trial.

7. Proposed approaches

Clearly, the implementation of risk management methodology including the design of clinical trial tools requires the coordination and the integration of information from a broad range of sources. The issues giving rise to the problems presented in this paper are multifactorial. Clinical trials themselves cover a large range of objectives and vary enormously from phase 1 to large post authorisation clinical trials. No single tool or approach will address these issues. The references 5-11 provided in section 8 of this paper include a number of tools and discussions of these.

A “stratified approach” concerns categorisation of the trial risk based upon the marketing authorisation status of the investigational products and in relation to its use in the trial as per normal clinical practice. There is increasing consensus that this may not be sufficient on its own and that a “trial specific” or “customised approach” to risk assessment is also required. This would assess risks from the clinical trial protocol, which would be dependent upon, for example, the protocol complexity, subject population, therapeutic indication and nature of endpoints, clinical trial setting, administration of the product and complexity of study procedures and measurement.

It is suggested that there is a separation of prioritisation and risk mitigation approaches according to several dimensions, covering the design, conduct and trial reporting phases of the trial. These should always be aimed at protecting trial subjects’ rights, well being, integrity and safety and the assurance of quality of data and the trial results.

The identification of priorities and potential risks should commence at a very early stage in the preparation of a trial, as part of the basic design process. The concerns with trial and protocol design, design of data collection tools/instruments, the design of the monitoring and data management strategies and plans, including the relative role of centralised versus on-site activities and the data quality tolerances, and the design of record keeping for the study should be addressed within the framework of these dimensions, implementing a quality by design approach. Risk assessment and mitigation plans should be appropriately disseminated within the organisation, regularly reviewed and updated when new information becomes available.

In case of a clinical development programme, risk based approaches should ideally be established at the programme level and then protocol by protocol throughout clinical development, building on the

experience achieved with each study and general technical, regulatory and other advances made during the time period involved.

This should allow for periodic interaction and discussion of the approaches taken between the sponsor and the regulators involved in both the clinical trial authorisation and supervision and the marketing authorisation process[13].

Although approaches including tools have already been proposed and published, this is an evolving area and the concept as presented in this paper will benefit from information sharing and transparency. In building quality into the design and operation of clinical trials, we gain a more efficient and effective management to benefit the data quality and the safety and wellbeing of subjects and the development of medicines. Putting into practice the concept of risk based quality management to clinical trials will benefit the advancement and development of medicines and therapeutics strategies and overall health and well-being of subjects.

8. References

[1] ICH E6 Good Clinical Practice

[2] ICH Q9 Quality Risk Management

[3] ICH Q10 Pharmaceutical Quality System

[4] ICH E3 Structure and Content of Clinical Study Reports

[5] Clinical Trials 2009; 6: 585–596; O. Brosteanu, P. Houben, K. Ihrig, C. Ohmann, U. Paulus, B.Pfistner, G. Schwarz, A. Strenge-Hesse and U. Zettelmeyer; Risk analysis and risk adapted on-site monitoring in non commercial clinical trials

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[7] Contemporary Clinical Trials, Volume 32, Issue 1, January 2011, Pages 16-24; V. Journot, J-P. Pignon, C. Gaultier, V. Daurat, A. Bouxin-Métro, B. Giraudeau, P-M. Preux, J-M. Tréluyer, S. Chevret, V. Plättner, C. Thalamas, S. Clisant, P. Ravaud, G. Chêne and on behalf of the Optimon Collaborative Group; Validation of a risk-assessment scale and a risk-adapted monitoring plan for academic clinical research studies — The Pre-Optimon study

[8] MRC/DH/MHRA joint project; Risk-adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products

[9] OECD Recommendation on the Governance of Clinical Trials

[10] CTTI initiatives on developing effective quality systems in clinical trials: Effective and Efficient Monitoring as a Component of Quality in the Conduct of Clinical Trials

[11] FDA Guidance for Industry Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring

[12] ICH Q8 Pharmaceutical Development

[13] Jonathan R. Davis, Vivian P. Nolan, Janet Woodcock, and Ronald W. Estabrook; Roundtable on Research and Development of Drugs, Biologics, and Medical Devices, Institute of Medicine; Assuring Data Quality and Validity in Clinical Trials for Regulatory Decision Making: Workshop Report; National Academies Press (1 July 1999)

Appendix D: FDA Guidance – *Part 11, Electronic Records; Electronic Signatures – Scope and Application*

Guidance for Industry

Part 11, Electronic Records; Electronic Signatures — Scope and Application

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
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August 2003
Pharmaceutical CGMPs

Guidance for Industry

Part 11, Electronic Records; Electronic Signatures — Scope and Application

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or
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Center for Food Safety and Applied Nutrition (CFSAN)
http://www.cfsan.fda.gov/~dms/guidance.html.

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August 2003
Pharmaceutical CGMPs

TABLE OF CONTENTS

Guidance for Industry[1]
Part 11, Electronic Records; Electronic Signatures — Scope and Application

I. INTRODUCTION

This guidance is intended to describe the Food and Drug Administration's (FDA's) current thinking regarding the scope and application of part 11 of Title 21 of the Code of Federal Regulations; Electronic Records; Electronic Signatures (21 CFR Part 11).[2]

This document provides guidance to persons who, in fulfillment of a requirement in a statute or another part of FDA's regulations to maintain records or submit information to FDA,[3] have chosen to maintain the records or submit designated information electronically and, as a result, have become subject to part 11. Part 11 applies to records in electronic form that are created, modified, maintained, archived, retrieved, or transmitted under any records requirements set forth in Agency regulations. Part 11 also applies to electronic records submitted to the Agency under the Federal Food, Drug, and Cosmetic Act (the Act) and the Public Health Service Act (the PHS Act), even if such records are not specifically identified in Agency regulations (§ 11.1). The underlying requirements set forth in the Act, PHS Act, and FDA regulations (other than part 11) are referred to in this guidance document as *predicate rules.*

[1] This guidance has been prepared by the Office of Compliance in the Center for Drug Evaluation and Research (CDER) in consultation with the other Agency centers and the Office of Regulatory Affairs at the Food and Drug Administration.

[2] 62 FR 13430

[3] These requirements include, for example, certain provisions of the Current Good Manufacturing Practice regulations (21 CFR Part 211), the Quality System regulation (21 CFR Part 820), and the Good Laboratory Practice for Nonclinical Laboratory Studies regulations (21 CFR Part 58).

As an outgrowth of its current good manufacturing practice (CGMP) initiative for human and animal drugs and biologics,[4] FDA is re-examining part 11 as it applies to all FDA regulated products. We anticipate initiating rulemaking to change part 11 as a result of that re-examination. This guidance explains that we will narrowly interpret the scope of part 11. While the re-examination of part 11 is under way, we intend to exercise enforcement discretion with respect to certain part 11 requirements. That is, we do not intend to take enforcement action to enforce compliance with the validation, audit trail, record retention, and record copying requirements of part 11 as explained in this guidance. However, records must still be maintained or submitted in accordance with the underlying predicate rules, and the Agency can take regulatory action for noncompliance with such predicate rules.

In addition, we intend to exercise enforcement discretion and do not intend to take (or recommend) action to enforce any part 11 requirements with regard to systems that were operational before August 20, 1997, the effective date of part 11 (commonly known as legacy systems) under the circumstances described in section III.C.3 of this guidance.

Note that part 11 remains in effect and that this exercise of enforcement discretion applies only as identified in this guidance.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

In March of 1997, FDA issued final part 11 regulations that provide criteria for acceptance by FDA, under certain circumstances, of electronic records, electronic signatures, and handwritten signatures executed to electronic records as equivalent to paper records and handwritten signatures executed on paper. These regulations, which apply to all FDA program areas, were intended to permit the widest possible use of electronic technology, compatible with FDA's responsibility to protect the public health.

After part 11 became effective in August 1997, significant discussions ensued among industry, contractors, and the Agency concerning the interpretation and implementation of the regulations. FDA has (1) spoken about part 11 at many conferences and met numerous times with an industry coalition and other interested parties in an effort to hear more about potential part 11 issues; (2) published a compliance policy guide, CPG 7153.17: Enforcement Policy: 21 CFR Part 11; Electronic Records; Electronic Signatures; and (3) published numerous draft guidance documents including the following:

[4] See *Pharmaceutical CGMPs for the 21st Century: A Risk-Based Approach; A Science and Risk-Based Approach to Product Quality Regulation Incorporating an Integrated Quality Systems Approach* at www.fda.gov/oc/guidance/gmp.html.

- *21 CFR Part 11; Electronic Records; Electronic Signatures, Validation*
- *21 CFR Part 11; Electronic Records; Electronic Signatures, Glossary of Terms*
- *21 CFR Part 11; Electronic Records; Electronic Signatures, Time Stamps*
- *21 CFR Part 11; Electronic Records; Electronic Signatures, Maintenance of Electronic Records*
- *21 CFR Part 11; Electronic Records; Electronic Signatures, Electronic Copies of Electronic Records*

Throughout all of these communications, concerns have been raised that some interpretations of the part 11 requirements would (1) unnecessarily restrict the use of electronic technology in a manner that is inconsistent with FDA's stated intent in issuing the rule, (2) significantly increase the costs of compliance to an extent that was not contemplated at the time the rule was drafted, and (3) discourage innovation and technological advances without providing a significant public health benefit. These concerns have been raised particularly in the areas of part 11 requirements for validation, audit trails, record retention, record copying, and legacy systems.

As a result of these concerns, we decided to review the part 11 documents and related issues, particularly in light of the Agency's CGMP initiative. In the *Federal Register* of February 4, 2003 (68 FR 5645), we announced the withdrawal of the draft guidance for industry, *21 CFR Part 11; Electronic Records; Electronic Signatures, Electronic Copies of Electronic Records*. We had decided we wanted to minimize industry time spent reviewing and commenting on the draft guidance when that draft guidance may no longer represent our approach under the CGMP initiative. Then, in the *Federal Register* of February 25, 2003 (68 FR 8775), we announced the withdrawal of the part 11 draft guidance documents on validation, glossary of terms, time stamps,[5] maintenance of electronic records, and CPG 7153.17. We received valuable public comments on these draft guidances, and we plan to use that information to help with future decision-making with respect to part 11. We do not intend to re-issue these draft guidance documents or the CPG.

We are now re-examining part 11, and we anticipate initiating rulemaking to revise provisions of that regulation. To avoid unnecessary resource expenditures to comply with part 11 requirements, we are issuing this guidance to describe how we intend to exercise enforcement discretion with regard to certain part 11 requirements during the re-examination of part 11. As mentioned previously, part 11 remains in effect during this re-examination period.

III. DISCUSSION

A. Overall Approach to Part 11 Requirements

[5] Although we withdrew the draft guidance on time stamps, our current thinking has not changed in that when using time stamps for systems that span different time zones, we do not expect you to record the signer's local time. When using time stamps, they should be implemented with a clear understanding of the time zone reference used. In such instances, system documentation should explain time zone references as well as zone acronyms or other naming conventions.

As described in more detail below, the approach outlined in this guidance is based on three main elements:

- Part 11 will be interpreted narrowly; we are now clarifying that fewer records will be considered subject to part 11.
- For those records that remain subject to part 11, we intend to exercise enforcement discretion with regard to part 11 requirements for validation, audit trails, record retention, and record copying in the manner described in this guidance and with regard to all part 11 requirements for systems that were operational before the effective date of part 11 (also known as legacy systems).
- We will enforce all predicate rule requirements, including predicate rule record and recordkeeping requirements.

It is important to note that FDA's exercise of enforcement discretion as described in this guidance is limited to specified part 11 requirements (setting aside legacy systems, as to which the extent of enforcement discretion, under certain circumstances, will be more broad). We intend to enforce all other provisions of part 11 including, but not limited to, certain controls for closed systems in § 11.10. For example, we intend to enforce provisions related to the following controls and requirements:

- limiting system access to authorized individuals
- use of operational system checks
- use of authority checks
- use of device checks
- determination that persons who develop, maintain, or use electronic systems have the education, training, and experience to perform their assigned tasks
- establishment of and adherence to written policies that hold individuals accountable for actions initiated under their electronic signatures
- appropriate controls over systems documentation
- controls for open systems corresponding to controls for closed systems bulleted above (§ 11.30)
- requirements related to electronic signatures (e.g., §§ 11.50, 11.70, 11.100, 11.200, and 11.300)

We expect continued compliance with these provisions, and we will continue to enforce them. Furthermore, persons must comply with applicable predicate rules, and records that are required to be maintained or submitted must remain secure and reliable in accordance with the predicate rules.

B. Details of Approach – Scope of Part 11

1. Narrow Interpretation of Scope

We understand that there is some confusion about the scope of part 11. Some have understood the scope of part 11 to be very broad. We believe that some of those broad interpretations could

lead to unnecessary controls and costs and could discourage innovation and technological advances without providing added benefit to the public health. As a result, we want to clarify that the Agency intends to interpret the scope of part 11 narrowly.

Under the narrow interpretation of the scope of part 11, with respect to records required to be maintained under predicate rules or submitted to FDA, when persons choose to use records in electronic format in place of paper format, part 11 would apply. On the other hand, when persons use computers to generate paper printouts of electronic records, and those paper records meet all the requirements of the applicable predicate rules and persons rely on the paper records to perform their regulated activities, FDA would generally not consider persons to be "using electronic records in lieu of paper records" under §§ 11.2(a) and 11.2(b). In these instances, the use of computer systems in the generation of paper records would not trigger part 11.

2. Definition of Part 11 Records

Under this narrow interpretation, FDA considers part 11 to be applicable to the following records or signatures in electronic format (part 11 records or signatures):

- Records that are required to be maintained under predicate rule requirements and that are maintained in electronic format *in place of paper format*. On the other hand, records (and any associated signatures) that are not required to be retained under predicate rules, but that are nonetheless maintained in electronic format, are not part 11 records.

  We recommend that you determine, based on the predicate rules, whether specific records are part 11 records. We recommend that you document such decisions.

- Records that are required to be maintained under predicate rules, that are maintained in electronic format *in addition to paper format*, and that *are relied on to perform regulated activities*.

  In some cases, actual business practices may dictate whether you are *using* electronic records instead of paper records under § 11.2(a). For example, if a record is required to be maintained under a predicate rule and you use a computer to generate a paper printout of the electronic records, but you nonetheless rely on the electronic record to perform regulated activities, the Agency may consider you to be *using* the electronic record instead of the paper record. That is, the Agency may take your business practices into account in determining whether part 11 applies.

  Accordingly, we recommend that, for each record required to be maintained under predicate rules, you determine in advance whether you plan to rely on the electronic record or paper record to perform regulated activities. We recommend that you document this decision (e.g., in a Standard Operating Procedure (SOP), or specification document).

- Records submitted to FDA, under predicate rules (even if such records are not specifically identified in Agency regulations) in electronic format (assuming the records have been identified in docket number 92S-0251 as the types of submissions the Agency accepts in electronic format). However, a record that is not itself submitted, but is used

in generating a submission, is not a part 11 record unless it is otherwise required to be maintained under a predicate rule and it is maintained in electronic format.

- Electronic signatures that are intended to be the equivalent of handwritten signatures, initials, and other general signings required by predicate rules. Part 11 signatures include electronic signatures that are used, for example, to document the fact that certain events or actions occurred in accordance with the predicate rule (e.g. *approved*, *reviewed*, and *verified*).

C. Approach to Specific Part 11 Requirements

1. Validation

The Agency intends to exercise enforcement discretion regarding specific part 11 requirements for validation of computerized systems (§ 11.10(a) and corresponding requirements in § 11.30). Although persons must still comply with all applicable predicate rule requirements for validation (e.g., 21 CFR 820.70(i)), this guidance should not be read to impose any additional requirements for validation.

We suggest that your decision to validate computerized systems, and the extent of the validation, take into account the impact the systems have on your ability to meet predicate rule requirements. You should also consider the impact those systems might have on the accuracy, reliability, integrity, availability, and authenticity of required records and signatures. Even if there is no predicate rule requirement to validate a system, in some instances it may still be important to validate the system.

We recommend that you base your approach on a justified and documented risk assessment and a determination of the potential of the system to affect product quality and safety, and record integrity. For instance, validation would not be important for a word processor used only to generate SOPs.

For further guidance on validation of computerized systems, see FDA's guidance for industry and FDA staff *General Principles of Software Validation* and also industry guidance such as the *GAMP 4 Guide* (See References).

2. Audit Trail

The Agency intends to exercise enforcement discretion regarding specific part 11 requirements related to computer-generated, time-stamped audit trails (§ 11.10 (e), (k)(2) and any corresponding requirement in §11.30). Persons must still comply with all applicable predicate rule requirements related to documentation of, for example, date (e.g., § 58.130(e)), time, or sequencing of events, as well as any requirements for ensuring that changes to records do not obscure previous entries.

Even if there are no predicate rule requirements to document, for example, date, time, or sequence of events in a particular instance, it may nonetheless be important to have audit trails or other physical, logical, or procedural security measures in place to ensure the trustworthiness and

reliability of the records.[6] We recommend that you base your decision on whether to apply audit trails, or other appropriate measures, on the need to comply with predicate rule requirements, a justified and documented risk assessment, and a determination of the potential effect on product quality and safety and record integrity. We suggest that you apply appropriate controls based on such an assessment. Audit trails can be particularly appropriate when users are expected to create, modify, or delete regulated records during normal operation.

3. Legacy Systems[7]

The Agency intends to exercise enforcement discretion with respect to all part 11 requirements for systems that otherwise were operational prior to August 20, 1997, the effective date of part 11, under the circumstances specified below.

This means that the Agency does not intend to take enforcement action to enforce compliance with any part 11 requirements if all the following criteria are met for a specific system:

- The system was operational before the effective date.
- The system met all applicable predicate rule requirements before the effective date.
- The system currently meets all applicable predicate rule requirements.
- You have documented evidence and justification that the system is fit for its intended use (including having an acceptable level of record security and integrity, if applicable).

If a system has been changed since August 20, 1997, and if the changes would prevent the system from meeting predicate rule requirements, Part 11 controls should be applied to Part 11 records and signatures pursuant to the enforcement policy expressed in this guidance.

4. Copies of Records

The Agency intends to exercise enforcement discretion with regard to specific part 11 requirements for generating copies of records (§ 11.10 (b) and any corresponding requirement in §11.30). You should provide an investigator with reasonable and useful access to records during an inspection. All records held by you are subject to inspection in accordance with predicate rules (e.g., §§ 211.180(c), (d), and 108.35(c)(3)(ii)).

We recommend that you supply copies of electronic records by:

- Producing copies of records held in common portable formats when records are maintained in these formats
- Using established automated conversion or export methods, where available, to make copies in a more common format (examples of such formats include, but are not limited to, PDF, XML, or SGML)

[6] Various guidance documents on information security are available (see References).

[7] In this guidance document, we use the term *legacy system* to describe systems already in operation before the effective date of part 11.

In each case, we recommend that the copying process used produces copies that preserve the content and meaning of the record. If you have the ability to search, sort, or trend part 11 records, copies given to the Agency should provide the same capability if it is reasonable and technically feasible. You should allow inspection, review, and copying of records in a human readable form at your site using your hardware and following your established procedures and techniques for accessing records.

5. Record Retention

The Agency intends to exercise enforcement discretion with regard to the part 11 requirements for the protection of records to enable their accurate and ready retrieval throughout the records retention period (§ 11.10 (c) and any corresponding requirement in §11.30). Persons must still comply with all applicable predicate rule requirements for record retention and availability (e.g., §§ 211.180(c),(d), 108.25(g), and 108.35(h)).

We suggest that your decision on how to maintain records be based on predicate rule requirements and that you base your decision on a justified and documented risk assessment and a determination of the value of the records over time.

FDA does not intend to object if you decide to archive required records in electronic format to nonelectronic media such as microfilm, microfiche, and paper, or to a standard electronic file format (examples of such formats include, but are not limited to, PDF, XML, or SGML). Persons must still comply with all predicate rule requirements, and the records themselves and any copies of the required records should preserve their content and meaning. As long as predicate rule requirements are fully satisfied and the content and meaning of the records are preserved and archived, you can delete the electronic version of the records. In addition, paper and electronic record and signature components can co-exist (i.e., a hybrid[8] situation) as long as predicate rule requirements are met and the content and meaning of those records are preserved.

[8] Examples of hybrid situations include combinations of paper records (or other nonelectronic media) and electronic records, paper records and electronic signatures, or handwritten signatures executed to electronic records.

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2. *General Principles of Software Validation; Final Guidance for Industry and FDA Staff* (FDA, Center for Devices and Radiological Health, Center for Biologics Evaluation and Research, 2002) (http://www.fda.gov/cdrh/comp/guidance/938.html)

3. *Guidance for Industry, FDA Reviewers, and Compliance on Off-The-Shelf Software Use in Medical Devices* (FDA, Center for Devices and Radiological Health, 1999) (http://www.fda.gov/cdrh/ode/guidance/585.html)

4. *Pharmaceutical CGMPs for the 21st Century: A Risk-Based Approach; A Science and Risk-Based Approach to Product Quality Regulation Incorporating an Integrated Quality Systems Approach* (FDA 2002) (http://www.fda.gov/oc/guidance/gmp.html)

Industry References

1. *The Good Automated Manufacturing Practice (GAMP) Guide for Validation of Automated Systems, GAMP 4* (ISPE/GAMP Forum, 2001) (http://www.ispe.org/gamp/)

2. ISO/IEC 17799:2000 (BS 7799:2000) Information technology – Code of practice for information security management (ISO/IEC, 2000)

3. ISO 14971:2002 Medical Devices- Application of risk management to medical devices (ISO, 2001)

Appendix E: FDA Guidance – Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring

Guidance for Industry

Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
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Guidance for Industry

Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring

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Food and Drug Administration

August 2013
Procedural

Contains Nonbinding Recommendations

TABLE OF CONTENTS

Contains Nonbinding Recommendations

Guidance for Industry[1] Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance assists sponsors of clinical investigations in developing risk-based monitoring strategies and plans for investigational studies of medical products, including human drug and biological products, medical devices, and combinations thereof. The overarching goal of this guidance is to enhance human subject protection and the quality of clinical trial data by focusing sponsor oversight on the most important aspects of study conduct and reporting.

This guidance makes clear that sponsors can use a variety of approaches to fulfill their responsibilities for monitoring clinical investigator (CI) conduct and performance in investigational new drug (IND) studies conducted under 21 CFR part 312 or investigational device exemption (IDE) studies conducted under 21 CFR part 812. The guidance describes strategies for monitoring activities that reflect a modern, risk-based approach that focuses on critical study parameters and relies on a combination of monitoring activities to oversee a study effectively. For example, the guidance specifically encourages greater use of centralized monitoring methods where appropriate.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Rather, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

[1] This guidance has been prepared by the Office of Medical Policy in the Center for Drug Evaluation and Research (CDER) in cooperation with CDER's Office of Scientific Investigations in the Office of Compliance, CBER's Office of Compliance and Biologics Quality, CDRH's Office of Compliance, Office of the Commissioner's Office of Good Clinical Practice, and the Office of Regulatory Affairs (ORA).

II. BACKGROUND

Effective monitoring of clinical investigations by sponsors is critical to the protection of human subjects and the conduct of high-quality studies. Sponsors of clinical investigations involving human drugs, biological products, medical devices, and combinations thereof are required to provide oversight to ensure adequate protection of the rights, welfare, and safety of human subjects and the quality of the clinical trial data submitted to FDA.[2] FDA's regulations require sponsors to monitor the conduct and progress of their clinical investigations.[3,4] The regulations are not specific about how sponsors are to conduct such monitoring and are therefore compatible with a range of approaches to monitoring (see section III) that will vary depending on multiple factors (see section IV.C).

During the past two decades, the number and complexity of clinical trials have grown dramatically. These changes create new challenges to clinical trial oversight, particularly increased variability in clinical investigator experience, site infrastructure, treatment choices, and standards of health care,[5] as well as challenges related to geographic dispersion. At the same time, increasing use of electronic systems and records and improvements in statistical assessments, present opportunities for alternative monitoring approaches (e.g., centralized monitoring) that can improve the quality and efficiency of sponsor oversight of clinical investigations. FDA encourages sponsors to develop monitoring plans that manage important risks to human subjects and data quality and address the challenges of oversight in part by taking advantage of the innovations in modern clinical trials. A risk-based approach to monitoring does not suggest any less vigilance in oversight of clinical investigations. Rather, it focuses sponsor oversight activities on preventing or mitigating important and likely risks to data quality and to processes critical to human subject protection and trial integrity. Moreover, a risk-based approach is dynamic, more readily facilitating continual improvement in trial conduct and oversight. For example, monitoring findings should be evaluated to determine whether additional actions (e.g., training of clinical investigator and site staff, clarification of protocol requirements) are necessary to ensure human subject protection and data quality across sites.

This guidance focuses principally on monitoring, which is one aspect of the processes and procedures needed to ensure clinical trial quality and subject safety. Monitoring is a quality control tool for determining whether study activities are being carried out as planned, so that deficiencies can be identified and corrected. Monitoring, or oversight, alone cannot ensure quality. Rather, quality is an overarching objective that must be built into the clinical trial enterprise. FDA recommends a *quality risk management* approach to clinical trials and is considering the need for additional guidance describing this approach.

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[2] 21 CFR part 312, subpart D generally (Responsibilities of Sponsors and Investigators) and 21 CFR part 812, subpart C generally (Responsibilities of Sponsors).

[3] 21 CFR 312.50 requires a sponsor to, among other things, ensure "proper monitoring of the investigation(s)" and "that the investigation(s) is conducted in accordance with the general investigational plan and protocols contained in the IND." 21 CFR 812.40 states that sponsors are responsible for, among other things, "ensuring proper monitoring of the investigation, …"

[4] See also 21 CFR 312.53(d), 312.56(a), 812.43(d), and 812.46.

[5] Glickman et al. Ethical and Scientific Implications of the Globalization of Clinical Research. NEJM. 360: 816-823 (2009).

We are aware that the term *monitoring* is used in different ways in the clinical trial context. It can refer to the assessment of CI conduct, oversight, and reporting of findings of a clinical trial; to the ongoing evaluation of safety data and the emerging benefit-risk profile of an investigational product; and to the monitoring of internal sponsor and contract research organization (CRO) processes and systems integral to proposing, designing, performing, recording, supervising, reviewing, or reporting clinical investigations.

For purposes of this guidance, *monitoring* refers to the methods used by sponsors of investigational studies, or CROs delegated responsibilities for the conduct of IND studies, to oversee the conduct of, and reporting of data from, clinical investigations, including appropriate CI supervision of study site staff and third party contractors. Monitoring activities include communication with the CI and study site staff; review of the study site's processes, procedures, and records; and verification of the accuracy of data submitted to the sponsor.

A. Current Monitoring Practices and FDA Guidance

A survey conducted through the Clinical Trials Transformation Initiative (CTTI)[6] indicated that a range of practices has been used to monitor the conduct of clinical trials. These practices vary in intensity, focus, and methodology and include centralized monitoring of clinical data by statistical and data management personnel; targeted on-site visits to higher risk CIs (e.g., where centralized monitoring suggests problems at a site); and frequent, comprehensive on-site visits to all CI sites by sponsor personnel or representatives (e.g., clinical monitors or clinical research associates).[7] See definitions of on-site and centralized monitoring in section III.A.

Although survey participants reported a range of monitoring methods, periodic, frequent visits to each CI site to evaluate study conduct and review data for each enrolled subject remain the predominant mechanism by which pharmaceutical, biotechnology, and medical device companies monitor the progress of clinical investigations. For major efficacy trials, companies typically conduct on-site monitoring visits at approximately 4- to 8-week intervals,[8] at least partly because of the perception that the frequent on-site monitoring visit model, with 100% verification of all data, historically has been FDA's preferred way for sponsors to meet their monitoring obligations. In contrast, academic coordinating centers, cooperative groups, and government organizations use on-site monitoring less extensively. For example, some government agencies and oncology cooperative groups typically visit sites only once every 2 or 3 years to qualify or certify clinical study sites[9] to ensure they have the resources, training, and safeguards to conduct clinical trials. FDA also recognizes that regulators and practitioners have relied on data from critical outcome studies (e.g., many National Institutes of Health-sponsored trials, Medical Research Council-sponsored trials in the United Kingdom, ISIS (International

[6] CTTI is a public-private partnership involving FDA, academia, industry representatives, patient and consumer representatives, professional societies, investigator groups, and other government agencies, initiated in 2008. CTTI's mission is to identify practices that will increase the quality and efficiency of clinical trials.
[7] Morrison et al. Monitoring the Quality of Conduct of Clinical Trials: A Survey of Current Practices. Clin Trials. 8: 342-349 (2011).
[8] Usher, R. PhRMA BioResearch Monitoring Committee Perspective on Acceptable Approaches for Clinical Trial Monitoring. Drug Inf J. 44: 477-483 (2010).
[9] *Id.*

Study of Infarct Survival) trials,[10] and GISSI[11]), which had no regular on-site monitoring and used primarily centralized and other alternative monitoring methods.[12] These examples suggest that use of alternative monitoring approaches should be considered by all sponsors, including commercial sponsors, when developing risk-based monitoring strategies and plans.

The 1996 International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidance on good clinical practice (ICH E6) and the 2011 International Standards Organization (ISO) Clinical investigation of medical devices for human subjects – good clinical practice (ISO 14155:2011) address monitoring. Both ICH E6 and ISO 14155:2011 specifically provide for flexibility in how trials are monitored. ICH E6 and ISO 14155:2011 advise sponsors to consider the objective, design, complexity, size, and endpoints of a trial in determining the extent and nature of monitoring for a given trial.[13,14] The ISO standard further states that a sponsor's assessment of these factors should be used to develop a monitoring plan, a recommendation consistent with FDA's recommendation for monitoring plan development in this guidance. Although the ICH guidance and ISO standard specifically provide for the possibility of reduced, or even no, on-site monitoring, they also make clear that it would be appropriate to rely entirely on centralized monitoring only in exceptional circumstances.

FDA has communicated the goals of, and recommendations for, risk-based monitoring to FDA staff in review, inspection, and compliance functions. FDA's bioresearch monitoring compliance program guidance manuals (CPGMs) for sponsors, CROs, and monitors (CPGM 7348.810)[15] and for CIs and sponsor-investigators (CPGM 7348.811)[16] are compatible with the approaches described in this guidance. For example, CPGM 7348.810 informs FDA field staff that the regulations do not prescribe a specific monitoring technique. While CPGM 7348.810 refers to site visits and does not discuss centralized monitoring, the focus is on the review of monitoring activities through documentation and whether these activities were carried out in accordance with the sponsor's (or CRO's) monitoring procedures.

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[10] Califf et al. Developing Systems for Cost-Effective Auditing of Clinical Trials. Controlled Clinical Trials. 18: 651-660 (1997).

[11] Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico-Italian group for the study of the survival of myocardial infarction.

[12] Temple, R. Policy Developments in Regulatory Approval. Statistics in Medicine. 21: 2939-2948 (2002).

[13] Guidance for industry, E6 Good Clinical Practice: Consolidated Guidance, 1996, section 5.18.3. We update guidances periodically. To make sure you have the most recent version of a guidance, check the guidance Web site. CDER guidance documents can be found at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. CBER guidance documents can be found at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. CDRH guidance documents can be found at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/default.htm.

[14] ISO 14155:2011, Clinical investigation of medical devices for human subjects – Good clinical practice, sections 5.7 and 6.3.

[15] CPGM 7348.810: Sponsors, Contract Research Organizations and Monitors (March 11, 2011), available at: http://www.fda.gov/ICECI/EnforcementActions/BioresearchMonitoring/ucm133777.htm.

[16] CPGM 7348.811: Clinical Investigators and Sponsor-Investigators (December 8, 2008), available at: http://www.fda.gov/ICECI/EnforcementActions/BioresearchMonitoring/ucm133562.htm.

B. FDA's Rationale for Risk-Based Monitoring

FDA is issuing this guidance to provide FDA's current recommendations regarding monitoring practices and to encourage sponsors to consider a change in approach to monitoring. FDA believes that risk-based monitoring could improve sponsor oversight of clinical investigations. This guidance is therefore intended to make it clear that risk-based monitoring, including the appropriate use of centralized monitoring (see section III.A.2 for discussion of centralized monitoring) and reliance on technological advances (e.g., e-mail, webcasts, online training modules), can meet statutory and regulatory requirements under appropriate circumstances.

There is a growing consensus that risk-based approaches to monitoring, focused on risks to the most critical data elements and processes necessary to achieve study objectives, are more likely than routine visits to all clinical sites and 100% data verification to ensure subject protection and overall study quality.[17,18,19,20] For example, incorporation of centralized monitoring practices, where appropriate, should improve a sponsor's ability to ensure the quality of clinical trial data. Several publications suggest that certain data anomalies (e.g., fraud, including fabrication of data, and other non-random data distributions) may be more readily detected by centralized monitoring techniques than by on-site monitoring.[21, 22, 23] It has been suggested that a statistical approach to central monitoring can "help improve the effectiveness of on-site monitoring by prioritizing site visits and by guiding site visits with central statistical data checks," an approach that is supported by illustrative examples using actual trial datasets.[24] A recent review of on-site monitoring findings collected during a multi-center international trial also suggests that centralized monitoring can identify the great majority of on-site monitoring findings. The review determined that centralized monitoring activities could have identified more than 90% of the findings identified during on-site monitoring visits.[25]

FDA encourages sponsors to tailor monitoring plans to the needs of the trial (see section IV). FDA recognizes that this guidance places greater emphasis on centralized monitoring than appeared feasible at the time ICH E6 was finalized. However, FDA considers the approach to monitoring described in this guidance to be consistent with ICH E6 and ISO 14155:2011. FDA

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[17] Usher, R. PhRMA BioResearch Monitoring Committee Perspective on Acceptable Approaches for Clinical Trial Monitoring. Drug Inf J. 44: 477-483 (2010).
[18] FDA, Concept Paper: Quality in FDA-Regulated Clinical Research; Background to HSP/BIMO Workshop 5/10-5/11/07, (4/26/07).
[19] Brosteanu et al. Risk Analysis and Risk Adapted On-Site Monitoring in Noncommercial Clinical Trials. Clin Trials. 6: 585-595 (2009).
[20] Tantsyura et al. Risk-Based Source Data Verification Approaches: Pros and Cons. Drug Inf J. 44: 745-756 (2010).
[21] Usher, R. PhRMA BioResearch Monitoring Committee Perspective on Acceptable Approaches for Clinical Trial Monitoring. Drug Inf J. 44: 477-483 (2010).
[22] Baigent et al. Ensuring Trial Validity by Data Quality Assurance and Diversification of Monitoring Methods. Clin Trials. 5: 49-55 (2008).
[23] Buyse et al. The Role of Biostatistics in the Prevention, Detection and Treatment of Fraud in Clinical Trials. Statistics in Medicine. 18: 3435-51 (1999).
[24] Venet et al. A Statistical Approach to Central Monitoring of Data Quality in Clinical Trials. Clin Trials. 0: 1-9 (2012).
[25] Bakobaki et al. The Potential for Central Monitoring Techniques to Replace On-Site Monitoring: Findings from an International Multi-Centre Clinical Trial. Clin Trials. 9: 257-264 (2012).

believes it is reasonable to conclude that the flexibility described in ICH E6 and ISO 14155:2011 was intended to permit innovative approaches to improve the effectiveness of monitoring. Notably, the advancement in electronic systems and increasing use of electronic records (i.e., electronic data capture (EDC) systems) facilitate remote access to electronic data and, increasingly, to some source data (see section III.B.2.b for further discussion of access to electronic source data). Additionally, statistical assessments using data submitted on paper CRFs or via EDC may permit timely identification of clinical sites that require additional training, monitoring, or both. We expect that the pharmaceutical and device industries will, for the foreseeable future, continue to use some amount of on-site monitoring, but we anticipate decreased use of on-site monitoring with evolving monitoring methods and technological capabilities.

The following sections reflect FDA's current thinking on monitoring and include recommendations on how to develop and implement a study-specific monitoring plan as well as how to document monitoring activities. FDA acknowledges that there are limited empirical data to support the utility of the various methods employed to monitor clinical investigations (e.g., superiority of one method versus another), including data to support on-site monitoring.[26] As a result, the recommendations are based, in part, on FDA's experience from the review of protocols during the IND or IDE phase, data submitted in pre-approval applications, results of inspections conducted to ensure human subject protection and data integrity, and information obtained from public outreach efforts conducted under the auspices of the CTTI.

III. OVERVIEW OF MONITORING METHODS

A. On-Site and Centralized Monitoring

This section is intended to assist sponsors in identifying and designing monitoring practices appropriate to a given clinical trial. It describes some of the capabilities of on-site and centralized monitoring processes and factors to consider in determining which monitoring practices may be appropriate for a given clinical trial. See section IV.C for a discussion of factors to consider when determining the types, frequency, and extent of monitoring activities and section IV.D.1 for examples of events or results that would trigger a change in planned monitoring activities.

1. On-Site Monitoring

On-site monitoring is an in-person evaluation carried out by sponsor personnel or representatives at the sites at which the clinical investigation is being conducted. On-site monitoring can identify data entry errors (e.g., discrepancies between source records and case report forms (CRFs)) and missing data in source records or CRFs; provide assurance that study documentation exists; assess the familiarity of the site's study staff with the protocol and required procedures; and assess compliance with the protocol and investigational product

[26] Two studies are on-going as of June 2013 that compare the effectiveness of on-site to alternative (e.g., centralized) monitoring methods (OPTIMON study (https://ssl2.isped.u-bordeaux2.fr/optimon/Default.aspx) and ADAMON study (http://ctj.sagepub.com/content/6/6/585.full.pdf+html)).

accountability. On-site monitoring can also provide a sense of the quality of the overall conduct of the trial at a site (e.g., attention to detail, thoroughness of study documentation, appropriate delegation of study tasks, appropriate CI supervision of site staff performing critical study functions). On-site monitoring can therefore be particularly helpful early in a study, especially if the protocol is complex and includes novel procedures with which CIs may be unfamiliar. Findings at the site may lead to training efforts at both the site visited and elsewhere (see section VI.B).

2. Centralized Monitoring

Centralized monitoring is a remote evaluation carried out by sponsor personnel or representatives (e.g., clinical monitors, data management personnel, or statisticians) at a location other than the sites at which the clinical investigation is being conducted. Centralized monitoring processes can provide many of the capabilities of on-site monitoring as well as additional capabilities.

FDA encourages greater use of centralized monitoring practices, where appropriate, than has been the case historically, with correspondingly less emphasis on on-site monitoring. The types of monitoring activities and the extent to which centralized monitoring practices can be employed depend on various factors, including the sponsor's use of electronic systems; the sponsor's access to subjects' electronic records, if applicable; the timeliness of data entry from paper CRF, if applicable; and communication tools available to the sponsor and study site. These may vary by study and by site. Sponsors who plan to use centralized monitoring processes should ensure that the processes and expectations for site record keeping, data entry, and reporting are well-defined and ensure timely access to clinical trial data and supporting documentation.[27] If sponsors intend to rely heavily on centralized monitoring practices, they should identify, in the monitoring plan, when one or more on-site monitoring visits would be indicated.

B. Examples of Alternative Monitoring Techniques

As discussed in section II, monitoring activities broadly include communication with the CI and study site staff; review of the study site's processes, procedures, and records; and verification of the accuracy of data submitted to the sponsor. This section highlights areas for which centralized monitoring techniques could be considered. For certain monitoring activities, centralized monitoring techniques can be considered in place of, or to complement, traditional monitoring techniques. Specific techniques used should be prospectively included in the monitoring plan and should be informed by the risk assessment (see section IV.B for discussion of risk assessment).

Centralized monitoring techniques should be used to the extent appropriate and feasible to:

[27] See guidances for industry: Part 11, Electronic Records; Electronic Signatures – Scope and Application and Computerized Systems Used in Clinical Investigations.

- Supplement or reduce the frequency and extent of on-site monitoring with monitoring activities that can be done as well or better remotely or with monitoring activities that can be accomplished using centralized processes only. Examples include:
    - Monitor data quality through routine review of submitted data to identify and follow-up on missing data, inconsistent data, data outliers, and potential protocol deviations that may be indicative of systemic or significant errors in data collection and reporting at a site
    - Conduct statistical analyses to identify data trends not easily detected by on-site monitoring, such as
        - Standard checks of range, consistency, and completeness of data
        - Checks for unusual distribution of data within and between study sites, such as too little variance[28]
    - Analyze site characteristics, performance metrics (e.g., high screen failure or withdrawal rates, high frequency of eligibility violations, delays in reporting data), and clinical data to identify trial sites with characteristics correlated with poor performance or noncompliance
    - Verify critical source data remotely as described in the monitoring plan, in cases where such source data are accessible, or where CRF data are, according to the protocol, source data
    - Complete administrative and regulatory tasks. Such tasks include, for example, verifying continuous institutional review board (IRB) approval by reviewing electronic IRB correspondence, if available; performing portions of investigational product accountability, such as comparison of randomization and CRF data, to preliminarily assess whether the subject was administered or dispensed the assigned product and to evaluate consistency between investigational product receipt, use, and disposition records; and verifying whether previously requested CRF corrections were made.

  Centralized techniques, including routine review of submitted data and statistical and other analyses, may also be used to identify significant concerns (e.g., need for clarification of a protocol procedure, indications of data fabrication) with non-critical data that may not have otherwise been a focus of monitoring (e.g., source document verification).
- Target on-site monitoring by identifying higher risk clinical sites (e.g., sites with data anomalies or a higher frequency of errors, protocol violations, or dropouts relative to other sites), through the activities described above. Such findings, whether related to critical or non-critical data, may warrant more intensive and consideration of on-site monitoring.

The following sections provide additional descriptions of alternative monitoring techniques.

[28] Collins, Rory. (2010, October) Quality Design of Clinical Trials. Presentation at CTTI work stream 3 expert meeting. Available at: https://www.ctti-clinicaltrials.org/files/monitoring-collins_quality_design_of_clinical_trials_final.pdf.

1. Communication with Study Site Staff

Communication between the monitor and the study site staff is an essential component of monitoring. Various modes of communication (e.g., teleconferences, videoconferencing, email) could be considered for specific study time points (e.g., study initiation) and activities (e.g., to discuss findings of a monitor's eCRF review, training of new site staff).

2. Review of Site's Processes, Procedures, and Records

Techniques for monitoring informed consent and site records are included here as examples of approaches to monitoring site's processes, procedures, and records.

a. Informed Consent

Verification of subjects' informed consent is a critical activity that should be monitored (see section IV.A). Alternatives to the traditional approach (monitors verifying the original signature on the consent form for each subject at the site) may be more effective in identifying inadequacies in the consent process and may be more efficient. For example, the study site electronically sends (e.g., fax, e-mail) the signed page(s) of consent forms to the monitor, or the monitor performs remote comparison of dates of study procedures and documentation of informed consent on CRFs. An internet portal that enables the site staff to upload signed consent forms and enables access by designated monitors is a tool that can be considered. Use of electronic informed consent may also facilitate sponsor oversight of human subject protection. We recognize that sponsors must attend to privacy and confidentiality concerns when considering techniques for monitoring informed consent remotely.

b. Site's Records

A growing portion of source documents (e.g., laboratory and radiology reports, source documents submitted by the CI for other purposes such as health records documenting serious adverse events or adjudicated events) are electronic and may be available to the sponsor remotely. Furthermore, consistent with ICH E6 and ISO 14155:2011, original observations can be entered directly into the eCRF or transmitted to the eCRF from various locations, devices, or instruments.[29] We recognize that sponsors may not have remote access to electronic health records maintained by hospitals, universities, and other institutions because of data privacy and security concerns as well as technological challenges. Sponsors should consider risk-based approaches to monitoring using the format of study information (i.e., electronic, paper, or combination of electronic and paper), tools, and other resources available to them.

As discussed in this guidance, a variety of centralized monitoring techniques can be used to replace, supplement, and target on-site monitoring activities. The majority of these techniques

[29] Section 6.4.9 of ICH E6 provides that the trial design description should include "The identification of any data to be recorded directly on the CRFs (i.e., no prior written or electronic record of data), and to be considered to be source data." ISO 14155:2011, section 6.8.2, provides that the clinical investigation plan "shall specify which data can be recorded directly in the CRFs."

(e.g., checks for completeness of data, sites with a higher frequency of protocol violations relative to other sites, sites with high screen failure rates) can be performed regardless of the extent of use of electronic records in the study. For example, the majority of these techniques can be performed using CRF data collected either using electronic data capture systems or entered into a database from a paper CRF collected by the sponsor. A recent publication discusses statistical techniques for identifying various types of data errors.[30] We recognize that the statistical techniques described in this guidance may not be routinely used by all sponsors and may not be appropriate for every trial, but they are included in this guidance as examples of monitoring techniques that may be considered by sponsors.

Additional monitoring techniques, such as routine review of data as they are submitted, are possible for studies that use electronic CRFs. Although not a monitoring technique, another method of ensuring data quality routinely implemented in eCRFs is the use of electronic prompts in the eCRF to minimize errors and omissions at the time of data entry, particularly if data are entered directly into the eCRF.

3. Source Data Verification and Corroboration

The sponsor should consider the quantity and types of source data that need to be verified against CRFs or corroborated against other records (e.g., review of medical record to corroborate a subject's response of "no hospitalizations" since the previous visit on a CRF) during the sponsor's identification of critical data and processes or in the risk assessment, or both. The sponsor should include a description of the quantity and types of source records to verify or corroborate in the monitoring plan. The sponsor should consider which source records are likely to provide the most meaningful information about a subject's participation and the CI's conduct and oversight. For example, for a particular study, there may be minimal benefit in comparing 100% of the source data for each subject to the CRFs for each study visit. Rather, it may be sufficient to compare the most critical data points for a sample of subjects and study visits as an indicator of data accuracy. Similarly, for a particular study, although collection of all concomitant medications, body temperature, and body weight are required by the protocol and are documented in the medical record and transcribed to a CRF, they may not be identified by the sponsor as critical data, because a small error rate in those variables would not affect the outcome of the trial. In the absence of information indicating potential concerns with the data (e.g., sites with data anomalies, inconsistent data), source document verification or corroboration of these non-critical data may not provide significantly useful information to the sponsor.

IV. RISK-BASED MONITORING

No single approach to monitoring is appropriate or necessary for every clinical trial. FDA recommends that each sponsor design a monitoring plan that is tailored to the specific human subject protection and data integrity risks of the trial. Ordinarily, such a risk-based plan would

[30] Venet et al. A Statistical Approach to Central Monitoring of Data Quality in Clinical Trials. Clin Trials. 0: 1-9 (2012).

include a mix of centralized and on-site monitoring practices. The monitoring plan should identify the various methods intended to be used and the rationale for their use (see section IV.D for recommendations on the components of a monitoring plan).

Monitoring activities should focus on preventing or mitigating important and likely sources of error in the conduct, collection, and reporting of critical data and processes necessary for human subject protection and trial integrity. Sponsors should prospectively identify critical data and processes, then perform a risk assessment to identify and understand the risks that could affect the collection of critical data or the performance of critical processes, and then develop a monitoring plan that focuses on the important and likely risks to critical data and processes.

A. Identify Critical Data and Processes to be Monitored

Sponsors should prospectively identify critical data and processes that if inaccurate, not performed, or performed incorrectly, would threaten the protection of human subjects or the integrity of the study results. As examples, the following types of data and processes should ordinarily be identified as critical:

- Verification that informed consent was obtained appropriately
- Adherence to protocol eligibility criteria designed to exclude individuals for whom the investigational product may be less safe than the protocol intended and to include only subjects from the targeted study population for whom the test article is most appropriate
- Procedures for documenting appropriate accountability and administration of the investigational product (e.g., ensuring the integrity of randomization at the site level, where appropriate)
- Conduct and documentation of procedures and assessments related to
  - study endpoints
  - protocol-required safety assessments
  - evaluating, documenting, and reporting serious adverse events and unanticipated adverse device effects, subject deaths, and withdrawals, especially when a withdrawal may be related to an adverse event
- Conduct and documentation of procedures essential to trial integrity, such as ensuring the study blind is maintained, both at the site level and at the sponsor level, as appropriate, referring specified events for adjudication, and allocation concealment

Other types of data (e.g., covariates such as concomitant treatments or demographic characteristics, routine laboratory tests performed as part of subject monitoring that do not address protocol specified safety or efficacy endpoints) and processes (e.g., a hospital pharmacy's storage of an investigational product with no specific critical handling instructions) identified by the sponsor as non-critical often may be monitored less intensively.

There is increasing recognition that some types of errors in a clinical trial are more important than others.[31] For example, a low, but non-zero rate of errors in capturing certain baseline characteristics of enrolled subjects (e.g., age, concomitant treatment, or concomitant illness) will not, in general, have a significant effect on study results if the errors are distributed randomly. In contrast, a small number of errors related to study endpoints (e.g., not following protocol-specified definitions) can profoundly affect study results, as could failure to report rare but important adverse events. Based on FDA's inspection and review experience, infrequent errors in non-critical data are unlikely to alter FDA's conclusions about whether a product is safe and effective and whether participants' safety was appropriately monitored.

B. Risk Assessment

This guidance discusses the risk assessment, a component of risk management, as applied in the context of clinical monitoring. Risk assessment generally involves identifying risks, analyzing risks, and then determining whether risks need to be modified by implementing controls (e.g., processes, policies, or practices). The risk assessment recommended in this guidance to inform development of a monitoring plan may also support efforts to manage risks across a clinical trial (e.g., through modifying the protocol design or implementation) or development program. This guidance does not provide comprehensive detail on how to perform a risk assessment. There are many risk assessment methodologies and tools from a variety of industries that can be applied to clinical trials. [32,33]

Following the identification of critical data and processes (section IV.A), sponsors should perform a risk assessment to identify and understand the nature, sources, and potential causes of risks that could affect the collection of critical data or the performance of critical processes. Risks to critical data and processes most merit consideration during risk assessment, to ensure that monitoring efforts are focused on preventing or mitigating important and likely sources of error in their conduct, collection and reporting.

Risk identification for monitoring purposes should generally consider the types of data to be collected, the specific activities required to collect these data, and the range of potential safety and other human subject protection concerns that are inherent to the clinical investigation (e.g., based on trial design or investigational product).

[31] Baigent et al. Ensuring Trial Validity by Data Quality Assurance and Diversification of Monitoring Methods. Clin Trials. 5: 49-55 (2008).
[32] Guidance for industry, Q9 Quality Risk Management, June 2006.
[33] ISO 31010:2009 Risk Management – Risk Assessment Techniques.

The identified risks should be assessed and prioritized by considering the following:

- the likelihood of errors occurring
- the impact of such errors on human subject protection and trial integrity
- the extent to which such errors would be detectable

Sponsors should use the results of the risk assessment in developing the monitoring plan (e.g., determining which risks may be addressed through monitoring, determining the types and intensity of monitoring activities best suited to addressing these risks). Sponsors may also determine that some risks are better managed through activities other than monitoring, for example, modifying the protocol to remove the source of the risk. Sponsors should periodically evaluate emerging risks and whether monitoring activities require modification to effectively oversee the risks.

C. Factors to Consider when Developing a Monitoring Plan

A monitoring plan ordinarily should focus on preventing or mitigating important and likely risks, identified by the risk assessment, to critical data and processes. The types (e.g., on-site, centralized), frequency (e.g., early, for initial assessment and training versus throughout the study), and extent (e.g., comprehensive (100% data verification) versus targeted or random review of certain data (less than 100% data verification)) of monitoring activities will depend to some degree on a range of factors, considered during the risk assessment, including the following:

- Complexity of the study design

More intensive monitoring (e.g., increased frequency and extent of review) may be necessary as study design complexity increases. Examples may include studies with adaptive designs, stratified designs, complex dose titrations, or multiple device placement studies.

- Types of study endpoints

Endpoints that are more interpretative or subjective may require on-site visits to assess the totality of subject records and to review application of protocol definitions with the CI. More objective endpoints (e.g., death, hospitalization, or clinical laboratory values and standard measurements) may be more suitable for remote verification. Endpoints for which inappropriate subject withdrawal or lack of follow-up may impede study evaluation are likely to need more intensive monitoring to identify the reason(s) subjects are withdrawing and to determine whether follow-up can be improved.

- Clinical complexity of the study population

A study that involves a population that is seriously ill or vulnerable may require more intensive monitoring and consideration of on-site monitoring visits to be sure appropriate protection is being provided.

- Geography

Sites in geographic areas where there are differences in standards of medical practice or subject demographics, or where there is a less established clinical trial infrastructure may require more intensive monitoring and consideration of on-site monitoring visits.

- Relative experience of the CI and of the sponsor with the CI

CIs who lack significant experience in conducting and overseeing investigations, using a novel or innovative medical device, or with the surgical procedure associated with medical device use may benefit from more intensive monitoring and frequent communication to ensure CI understanding of responsibilities. In addition, the relative experience of a sponsor with the CI may be a factor in determining an appropriate monitoring plan.

- Electronic data capture

Use of EDC systems with the capability to assess quality metrics (e.g., missing data, data error rates, protocol violations) in real-time could help identify potentially higher risk sites for the purpose of targeting sites in need of more intensive monitoring.

- Relative safety of the investigational product

A study of a product that has significant safety concerns or for which there is no prior experience in human clinical trials (e.g., a phase 1 pharmaceutical investigation or a device feasibility study) may require more intensive monitoring and consideration of on-site monitoring visits to ensure appropriate CI oversight of subject safety.

- Stage of the study

A tapered approach to monitoring may be used where appropriate, with more intensive monitoring at initiation and during early stages of a trial. For example, a tapered approach could be used for a complex study where more intensive and on-site monitoring might be required early, but where, once procedures are established, less intensive monitoring might suffice. Similarly, a tapered approach could be used for relatively inexperienced CIs.

- Quantity of data

Some centralized monitoring tools may be more useful as the quantity of data (e.g., size or duration of trial, number of sites) collected increases.

D. Monitoring Plan

For each clinical trial, the sponsor should develop a monitoring plan that describes the monitoring methods, responsibilities, and requirements for the trial. The monitoring plan should include a brief description of the study, its objectives, and the critical data and study procedures, with particular attention to data and procedures that are unusual in relation to clinical routine and require training of study site staff. The plan should also communicate the specific risks to be addressed by monitoring and should provide those involved in monitoring with adequate information to effectively carry out their duties. A monitoring plan may reference existing policies and procedures (e.g., standard operating procedure describing general monitoring processes or issue investigation and resolution). All sponsor and CRO personnel involved with monitoring, including those who review or determine appropriate action regarding potential issues identified through monitoring, should review the monitoring plan and associated documents (e.g., standard operating procedures or other documents referenced in the monitoring plan).

Sponsors of device studies wishing to solicit feedback on their monitoring procedures prior to the submission of the application may either submit a Pre-Submission,[34] or contact CDRH's Division of Bioresearch Monitoring.[35]

Sponsors of drug studies may include specific questions about a monitoring plan in a request for a formal meeting with FDA (e.g., end of phase 2 meeting).

The components of a monitoring plan might include the following:

1. Description of Monitoring Approaches

- A description of each monitoring method to be employed during the study and how it will be used to address important risks and ensure the validity of critical data
- Criteria for determining the timing, frequency, and extent of planned monitoring activities
- Specific activities required for each monitoring method employed during the study, including reference to required tools, logs, or templates
- Definitions of events or results (e.g., findings from central monitoring activities) that would trigger changes in planned monitoring activities for a particular CI

  For example, if it is determined that a CI differs markedly from other CIs in making safety-related findings or other key safety metrics, in rate of enrollment, in the number of protocol deviations, or in the rate of missing CRFs, the CI's site should be considered for targeted on-site visits. The establishment of acceptable variation for particular critical data and processes would facilitate identification of significant deviations.
- Identification of possible deviations or failures that would be critical to study integrity and how these are to be recorded and reported

  For example, sponsors may wish to establish a specific mechanism for tracking and notifying key study personnel of deviations related to collection or reporting of data necessary to interpret the primary endpoint, regardless of which monitoring method identified a concern.

The study monitoring plan should also describe how various monitoring activities will be documented, regardless of whether they are conducted on-site or centrally (see section V).

2. Communication of Monitoring Results

- Format, content, timing, and archiving requirements for reports and other documentation of monitoring activities (see section V)
- Process for appropriate communication

[34] For more information, see FDA's draft guidance Medical Devices: The Pre-Submission Program and Meetings with FDA Staff. When final, this guidance will represent the FDA's current thinking on this topic.
[35] IDE regulations (21 CFR 812.25(e)) require that written monitoring procedures be submitted as part of the IDE application.

- of routine monitoring results to management and other stakeholders (e.g., CRO, data management)
- of immediate reporting of significant monitoring issues to appropriate parties (e.g., sponsor management, CI and site staff, IRB, FDA), as necessary
- from study management and other stakeholders to monitors

For example, data management personnel may provide monitors with routine reports of outstanding CRFs or of common data queries at or across sites that may enable effective targeting of monitoring activities.

3. Management of Noncompliance

- Processes for addressing unresolved or significant issues (e.g., significant non-compliance with the investigational plan, suspected or confirmed data falsification) identified by monitoring, whether at a particular site or across study sites
- Processes to ensure that root cause analyses are conducted where important deviations are discovered and that appropriate corrective and preventive actions (e.g., additional training on a study or site level) are implemented to address issues identified by monitoring
- Other quality management practices applicable to the clinical investigation (e.g., reference to any other written documents describing appropriate actions regarding non-compliance)

4. Ensuring Quality Monitoring

- Description of any specific training required for personnel carrying out monitoring activities, including personnel conducting internal data monitoring, statistical monitoring, or other centralized review activities. Training should include principles of clinical investigations and human subject protection. In addition, study-specific training should include discussion of the trial design, protocol requirements, the study monitoring plan, applicable standard operating procedures, appropriate monitoring techniques, and applicable electronic systems.
- Planned audits of monitoring to ensure that sponsor and CRO staff conduct monitoring activities in accordance with the monitoring plan, applicable regulations, guidance, and sponsor policies, procedures, templates, and other study plans. Auditing is a quality assurance tool that can be used to evaluate the effectiveness of monitoring to ensure human subject protection and data integrity.[36]
- Many sponsors have successfully implemented on-site co-monitoring visits (i.e., monitoring visits performed by both a study monitor and the monitor's supervisor or another evaluator designated by the sponsor or CRO) to evaluate whether monitors are effectively carrying out visit activities, in compliance with the study monitoring plan. These visits may be conducted either for randomly selected monitors or may be targeted to specific monitors, based upon questions arising from review of monitoring visit documentation.

[36] See ICH E6, section 5.19 and ISO 14155:2011, section 6.11 for additional information on audits.

5. Monitoring Plan Amendments

Sponsors should consider what events would indicate a need for review and revision of the monitoring plan and establish processes to permit timely updates where necessary. For example, a protocol amendment, change in the definition of significant protocol deviations, or identification of new risks to study integrity could result in a change to the monitoring plan.

V. DOCUMENTING MONITORING ACTIVITIES

Documentation of monitoring activities should generally include the following:

- The date of the activity and the individual(s) conducting and participating in it
- A summary of the data or activities reviewed
- A description of any noncompliance, potential noncompliance, data irregularities, or other deficiencies identified
- A description of any actions taken, to be taken, or recommended, including the person responsible for completing actions and the anticipated date of completion

Documentation of monitoring should include sufficient detail to allow verification that the monitoring plan was followed.

Monitoring documentation should be provided to appropriate management in a timely manner for review and follow-up, as indicated.

VI. ADDITIONAL STRATEGIES TO ENSURE STUDY QUALITY

Although the focus of this guidance is on monitoring the oversight and conduct of, and reporting of data from, clinical investigations, FDA considers monitoring to be just one component of a multi-factor approach to ensuring the quality of clinical investigations. Many other factors contribute to the quality of a clinical investigation. This section highlights additional areas that complement monitoring and can affect study quality.

A fundamental component of ensuring quality monitoring is a sponsor's compliance with monitoring plans and any accompanying procedures.

A. Protocol and Case Report Form Design

The most important tool for ensuring human subject protection and high-quality data is a well-designed and articulated protocol. A poorly designed or ambiguous protocol may introduce systemic errors that can render a clinical investigation unreliable despite rigorous monitoring. Additionally, the complexity of the trial design and the type and amount of data collected may influence data quality.[37] The CRF, which captures the data required by the protocol, is another

[37] Sponsors are encouraged to consult the appropriate review division within FDA's medical product centers with questions about quality aspects of clinical trial design.

critical tool for which design directly affects the quality of trial data. Care should be taken to ensure that the CRF captures data accurately (e.g., as required by the protocol) and that the CRF design and instructions facilitate consistent data collection across CI sites.

B. Clinical Investigator Training and Communication

Clinical trial monitors conducting on-site visits have historically played an important role in training the CI and site staff during a study. On-site visits also have served as a primary means of providing feedback to CIs and study personnel on study conduct. Without meaningful training prior to the conduct of a study and of appropriate instruction during the study (e.g., when changes are made to the protocol), CIs and their staff may have difficulty carrying out a trial correctly. Sponsors who plan less frequent or limited on-site monitoring should consider the following:

- Monitoring activities should include sufficient time for discussion of CI's and site staff's responsibilities, feedback, and additional training, if needed, during the conduct of the study.
- It may be necessary to implement alternative training (e.g., teleconferences, webcasts, online training modules) and communication methods (see section III.B.1) for providing and documenting ongoing, timely training and feedback, as well as to provide notification of significant changes to study conduct or other important information.

C. Delegation of Monitoring Responsibilities to a CRO

If a sponsor of an IND study delegates the responsibility for ensuring proper monitoring to a CRO, FDA regulations (21 CFR 312.52) require the written transfer of any obligations from a sponsor to a CRO and require the CRO to comply with the regulations.[38] Although sponsors can transfer responsibilities for monitoring to a CRO(s), they retain responsibility for oversight of the work completed by the CRO(s) that assume this responsibility. Sponsors should evaluate CRO compliance with regulatory requirements and contractual obligations in an ongoing manner. For example, sponsor oversight of monitoring performed by a CRO may include the sponsor's periodic review of monitoring reports and vendor performance or quality metrics and documented communication between the sponsor and CRO regarding monitoring progress and findings.

Sponsors and CROs should consider additional factors when a sponsor transfers responsibilities for monitoring to a CRO. Sponsors and CROs should prospectively establish a clear understanding of both parties' responsibilities and of the expectations for the conduct of the transferred obligations. Sponsors should share information with a CRO that may inform decisions a CRO may make regarding the monitoring practices for a trial (e.g., findings of a risk assessment). Sponsors should prospectively evaluate monitoring procedures and monitoring plans developed by a CRO to ensure the monitoring approach is consistent with applicable aspects of the trial. In addition, sponsors and CROs should have processes in place for timely

[38] The regulations for investigational device exemptions (21 CFR part 812) do not contain a provision for delegation to a contract research organization.

exchange of relevant information (e.g., significant monitoring findings, significant changes in risk for a trial).

D. Clinical Investigator and Site Selection and Initiation

In addition to regulatory requirements for CI selection, sponsors should consider factors such as sponsor's previous experience with the CI or site, workload of the CI and study staff, and resource availability at the study site during CI and site selection.

Site initiation is a critical study activity that often involves sponsor personnel from a range of disciplines, including monitors. Key components of site initiation include ensuring the CIs and site staff understand their responsibilities, including applicable regulatory requirements as well as study processes and procedures, including the sponsor's processes for monitoring the investigation. Communication and documentation tools for monitoring discussed in this guidance can also be used for site selection and initiation activities.

VII. PAPERWORK REDUCTION ACT OF 1995

This guidance contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520).

The time required to complete this information collection is estimated to average 4 hours per response, including the time to review instructions, search existing data resources, gather the data needed, and complete and review the information collection. Send comments regarding this burden estimate or suggestions for reducing this burden to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy
10903 New Hampshire Avenue, Bldg. 51, rm. 6337
Silver Spring, MD 20993-0002

This guidance also refers to previously approved collections of information found in FDA regulations. The collections of information in part 312, including certain provisions under subpart D, and part 812 have been approved under OMB control numbers 0910-0014 and 0910-0078.

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. The OMB control number for this information collection is 0910-0733 (expires 06/30/2019) (Note: Expiration date updated 07/15/2016).

Appendix F: ICH Reflection on “GCP Renovation”: Modernization of ICH E8 and Subsequent Renovation of ICH E6

ICH Reflection on "GCP Renovation": Modernization of ICH E8 and Subsequent Renovation of ICH E6

January 2017

Introduction

This paper outlines an approach to potential renovation of the ICH Guidelines related to clinical trial design, planning, management, and conduct. The scope of the renovation would include the current *E8 General Considerations for Clinical Trials* and the *E6 Guideline for Good Clinical Practice.* The goal is to provide updated guidance that is both appropriate and flexible enough to address the increasing diversity of clinical trial designs and data sources that are being employed to support regulatory and other health policy decisions. The underlying principles of human subject protection and data quality would remain.

ICH believes that the proposal outlined in this reflection paper would largely address concerns recently expressed by some research organizations and an international consortium of health researchers.[1] In a February 2016 letter to ICH, these stakeholders conveyed concerns that the current ICH E6 guideline fails to sufficiently recognize variations in the level of risk for participants in different types of trials and allow corresponding flexibility in managing the risks. Another major concern was related to E6's limited scope. It was felt that a guideline entitled "good clinical practice" should more holistically address the planning and conduct of clinical trials.

The proposed renovation would address these broad and important concerns through targeted revisions made to two current ICH guidelines.

- First, ICH would propose to address the broader concern about the principles of study design and planning for an appropriate level of data quality through revision to the current *ICH E8 General Considerations for Clinical Trials*. This is based on the recognition that data quality fundamentally depends on the quality of the study that generates the data, and that many aspects of study design affect the reliability of the study conclusions. The proposed revision would include a well-organized and fairly comprehensive review of the issues and questions that are most critical to clinical trial quality. This may include "critical to quality" factors that should be considered by sponsors when planning a study. Among the ICH Efficacy guidelines, the focus of ICH E8 also provides a logical place for an updated comprehensive guide or cross-referencing of all the other relevant ICH guidelines that sponsors should refer to when planning and executing development program-related studies.
- Subsequently, ICH would propose to address the flexibility concern via further renovation of *ICH E6 Good Clinical Practices* to anticipate and address a broader range of study types and data sources, while retaining the current E6 focus on good clinical *investigative site* practices.

This reflection paper begins with a background discussion of the role and value of the current E6 guideline, the range of regulatory and other health research questions that need to be addressed, and data sources in addition to traditional interventional trials that might be used to address them. The paper then outlines how E8 might be revised to enhance its utility in supporting clinical trial design and planning for data

[1] Updated open Letter to EMA & ICH: From 5 research organizations and an international consortium of 119 health researchers in 22 countries, 26th February, 2016: Co-ordinated response to the consultation by the International Council for Harmonisation (ICH) on its proposed E6(R2) "Integrated Addendum" to the ICH E6 Guideline for "Good Clinical Practice".

quality. This is followed by a discussion of the proposed structure for a future "renovated" E6 guideline that might better address the range of possible studies and data sources of interest, applying a risk-based approach to site monitoring. The final section of this paper discusses a proposed plan for how this renovation work could be sequenced and undertaken.

1. Background

The goals and scope of the current E6 include: a) assurance of human subject protection; b) assurance of data quality; c) limited to clinical research performed with regulatory intent; and d) to provide a standard guide so that clinical researchers (drug developers and clinical research staff) know what they need to do both to comply with the regulations and document compliance. E6 is primarily a procedural document that stipulates processes that should be followed both in study conduct and in documentation. E6 has provided critical guidance for both international regulators and clinical researchers who conduct trials to explore the safety and effectiveness of investigational new drugs. Investigational new drugs pose the greatest potential risks to study participants because of the limited safety and effectiveness information available at the time of the study. There is significant cost associated with obtaining the clinical trial data necessary to establish safety and effectiveness for regulatory review. Therefore, the sponsor of this research desires assurance that the planned trial conduct will be acceptable to the regulators. The regulator needs to be able to confirm the veracity of the data because regulatory actions rely upon conclusions drawn from the study results.

E6 was developed in the mid-1990s as the international guideline to be followed when generating clinical data intended to be submitted to regulatory authorities. Moreover, E6 aimed to provide enough specificity so as to minimize potential ambiguity and resulting inconsistency in the interpretation of the guideline across different global regions where approaches to health care delivery and regulatory practice might be expected to vary. The specificity was thus intended to minimize the potential for E6 interpretation to be yet another source of variability across investigational sites in multiregional clinical trials. Over the past twenty years, E6 has played an essential role in enabling the continued growth and success of multiregional clinical trials of investigational new drugs, including critical guidance related to training, responsibilities, and expectations of investigators, sponsors and IRBs. It has thereby supported the earlier submission of new drug applications (with data collected in conformance with the harmonized guidelines adopted by regulators in multiple regions), enabling earlier access to new medicines for patients who need them. E6 is applicable to all clinical trials performed with regulatory intent during the entire life-cycle of product development. In addition to the clinical trials supporting a new drug or biologic marketing application, it includes clinical trials performed to support a new indication of an already approved drug and clinical trials performed to fulfill post-marketing commitments or requirements.

In 2014, ICH endorsed the development of E6(R2) to supplement E6 with "additional recommendations to facilitate innovative approaches to GCP to better ensure data quality and human subject protection in an environment of highly complex multinational trials".[2] E6(R2) is intended "to encourage implementation of improved and more efficient approaches to clinical trial design, conduct, oversight, recording and reporting while continuing to ensure human subject protection and reliability of trial results. Standards regarding

[2] http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2_Concept_Paper_July_2014.pdf

electronic records and essential documents intended to increase clinical trial quality and efficiency have also been updated".[3] E6(R2) reached step 4 in November 2016.

Emerging Data Sources for Drug Regulatory Decisions

In the two decades since E6 was first drafted, the ways in which clinical trials are conducted and the corresponding aspects of good clinical practice have evolved. For example, clinical trials initially were often conducted in only a few clinical sites, often of a single type (e.g., academic medical practices) in a highly controlled setting. Over time, that has evolved to include multiple sites, often including sites from multiple countries. Accordingly, regulatory agencies have embraced a more flexible risk-based approach to the monitoring of clinical trials. This is based in part on the recognition of challenges of the increasing number and complexity of clinical trials and opportunities to use electronic systems with improved statistical assessments for centralized monitoring of clinical sites. A risk-based approach can enable the sponsor to focus oversight activities on preventing or mitigating important and likely risks to data quality and to processes critical to human subject protection and trial integrity.[4] The most recent E6(R2) has made important steps in this direction.

Recently, there has been a further shift to leverage the large amounts of available data from the "real world" (e.g., electronic health records, hospital discharge summaries, claims data, patient/disease registries, etc.), collected and stored for other purposes, that could inform regulatory decision-making. A patient registry has been defined as an organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves a predetermined scientific, clinical, or policy purpose(s).[5] Other possible sources of real world data include electronic medical records (EMRs) sometimes referred to as electronic health records (EHRs) generated by ongoing patient care, as well as health care administrative data sources. However, it should be noted that there are no universally accepted standards currently in use for formatting data from these different real-world sources, and this is probably the single biggest impediment to large-scale use of existing health care records in clinical trials. The adoption of standardized electronic formats for health care administrative data, and patient EMRs will greatly improve the ability of researchers to use these data to address health care and policy questions.

There have also been efforts to better integrate clinical studies into regular health care delivery by interfacing the electronic case report form with EMRs to minimize duplicative collection of patient/study participant data. This could facilitate performance of pragmatic clinical trials conducted under everyday clinical conditions and designed to test two or more treatments using more flexible study protocols and local customization, with less strict eligibility criteria, with less collection of data beyond the norm in routine clinical practice.[6]

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[3] http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Addendum_Step2.pdf

[4] http://www.fda.gov/downloads/Drugs/.../Guidances/UCM269919.pdf

[5] http://www.pcori.org/assets/11-Gliklich-Slides-Registries.pdf

[6] See for example: Use of Electronic Health Record Data in Clinical Investigations Guidance for Industry – May 2016 - http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm501068.pdf

Other Research Questions for Health Authorities

At the same time that E6 enabled global gains in patients' access to drugs, other technology, policy, and market drivers have been working to expand the set of research questions that health authorities need to address. In addition to the conduct of clinical trials to generate information needed to inform regulatory decision-making for marketing, other potential applications of E6 may include clinical research to assess the value and cost of drugs, comparative effectiveness research (CER), development of clinical practice guidelines, and academic research. Although the principles of human subject protection and data integrity apply in all circumstances, some flexibility in the application of these principles may be appropriate for different trial designs and contexts. For instance, observational studies of two approved therapies used to generate CER may not require the same level of documentation of informed consent, or it may be waived, as compared to a randomized controlled trial (RCT) of an investigational agent. Likewise, the level of resources and costs associated with the processes to document data integrity for an RCT being performed to support drug approval may not be justified for an academic research trial.

The aim of CER is to improve decisions by other players in the health care system and affect medical care at the levels of both policy and the individual. The key elements of CER are (a) head-to-head comparisons of active treatments, (b) study conditions and populations typical of routine clinical practice, and (c) a focus on evidence to inform care tailored to the characteristics of individual patients. Observational studies and randomized trials are often employed in the conduct of CER[7].

Questions concerning the value and cost associated with medical technology are being addressed by health technology assessment (HTA), as well as individual health care payers such as private insurance. HTA refers to the systematic evaluation of properties, effects, and/or impacts of health technology. It is a multidisciplinary process to evaluate the social, economic, organizational and ethical issues of a health intervention or health technology. The main purpose of conducting an assessment is to inform a policy decision making.[8]

The number of other health research questions has grown along with the urgency of need to address them. This is fueled by the rising complexity and cost of health care driven by scientific and medical technology innovation, expansion of health care benefits, and patient needs given significant increases in the number of patients with serious chronic disease, including the elderly with multiple chronic conditions.

The Issue to Address in Future E6 Renovation

As noted previously, the original objective of E6 was "to provide a unified standard for the European Union (EU), Japan and the United States to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions [and]…should be followed when generating clinical trial data that are intended to be submitted to regulatory authorities". E6 thus considers clinical trial designs that are typical of such regulatory submissions, namely the RCT in a controlled trial setting where data are collected or acquired prospectively through patient-clinician interactions (e.g., observed, self-reported, measured, or tested), and stipulates procedures for such studies. However, it is recognized that the emerging clinical trial environment may increasingly serve as an important adjunct to traditional interventional trials to support regulatory decisions, and would ideally be addressed more explicitly in ICH guidelines.

[7] Sox HC, Goodman, SN, The methods of comparative effectiveness research*, Ann Rev Public Health.* 2012 Apr; 33:425-45, doi: 10.1146/annurev-publhealth-031811-124610. Epub 2012 Jan 3.

[8] http://www.who.int/medical_devices/assessment/en/

Furthermore, although E6 was not designed with alternative study types or data sources in mind, absent a GCP guideline tailored to the varying human subject risk and data quality considerations posed by these other types of studies and data sources, some researchers, referring to some of the provisions of the current E6, have recently shared concerns about the lack of a good fit.

2. Proposed Structure for a Modernized ICH E8 Guideline and a Future Renovated ICH E6 Guideline

E8 General Considerations for Clinical Trials was finished in 1997 and has not been updated subsequently. E8 is a high level guidance that serves as a general roadmap to other ICH Guidelines concerning clinical trials. For example, it contains a Table classifying clinical studies according to objective, and also an Annex cross-referencing other relevant ICH guidelines. The Table includes examples of large simple trials, comparative effectiveness studies, and pharmacoeconomic studies, but the rest of the guidance is focused on studies intended to support regulatory submissions and does not further address differences in design and conduct that might be encountered in these different types of studies. Section 3.2 of the E8 Guideline, "Considerations for Individual Clinical Trials", has very high level descriptions of trial objectives and design, and does not address design or planning considerations for data quality (i.e., the quality of the study that generates, and determines the quality of, the data). In fact, the 1997 concepts of data quality were more procedural in nature and did not encompass the current goal of "quality by design", that is, explicitly stating the data quality parameters that need to be achieved in the trial, and planning the trial conduct, based on an assessment of risk, in order to achieve these parameters.

ICH is proposing that E8 would be revised and modernized to address these critically important aspects of study quality. This would include the need to identify 1) aspects of a trial that are critical to generating reliable data (e.g., relevant critical-to-quality (CTQ) factors) and 2) the strategies and actions that could effectively and efficiently support quality in these critical areas. The document could identify a basic set of CTQ factors generally relevant to the integrity and reliability of study conclusions and patient safety that sponsors should consider, to determine which factors stand out as critical and need to be explicitly addressed in a risk-based management and monitoring plan. Recent literature can provide resources to support development of this revised text, as well as the work by collaborative groups such as the Clinical Trials Transformation Initiative (CTTI)[9]. This type of prospective planning feeds directly into ICH E6, where the procedures implemented and followed should flow from the prospective identification of the desired data quality parameters for various types of data. ICH is proposing a modernization of ICH E8 in order to incorporate the most current concepts achieving fit-for-purpose data quality as one of the essential considerations for all clinical trials.

ICH is proposing a subsequent renovation of the current ICH E6 guideline that would preserve a key role for the current focus on traditional interventional trials conducted in a clinical trial setting while also addressing the other types of data sources or decision contexts. Thus the revised guideline would remain consistent with the assertion in the introduction of the current E6 guideline that "The principles established in this guideline may also be applied to other clinical investigations that may have an impact on the safety and well-being of human subjects." Following the approach taken in the development of the ICH E6 R2 addendum, the proposed revision to the overarching E6 guideline and the proposed annexes would

[9] E.g., the *CTTI Quality by Design Project Critical To Quality Factors Principles* document https://www.ctti-clinicaltrials.org/files/principles_document_finaldraft_19may15_1.pdf

similarly maintain a focus on essential guidance rather than general, long discussion of topics. Proposed revisions of E6 include the following:

1. The renovated E6 guideline would retain the focus of the current E6 on good clinical site practices and other key considerations in the current document.[10] However, recognizing that the most important tool for ensuring human subject protection and high-quality data[11] is a well-designed and well-articulated protocol, the renovated E6 would also refer to the *proposed-to-be-revised* E8 guideline for a more comprehensive discussion of study quality considerations and relevant discussion and guidance in other ICH E guidelines.

2. It is also being considered that the main body of the renovated E6 guideline would be revised to focus on overarching principles including key elements of human subject protection and data quality, using a risk-based approach to study oversight and monitoring. A number of available reference documents could be used to inform the development of these basic principles and list of candidate CTQ factors including, for example, *FDA Guidance to industry: Oversight of Clinical Investigations—A Risk-Based Approach to Monitoring*[12], the *EMA Reflection paper on risk based quality management in clinical trials*[13], and MHLW administrative notice on Basic Principles of Risk-based Monitoring[14]. The overarching principles document would further recognize that trial design and study objectives will strongly influence the criticality of different factors.

A set of annexes would be developed to be attached to the new E6 guideline. Each annex would address in more detail a particular type of study and/or data source to which E6 could be applied, and provide a more detailed workup of the CTQ factors that should be considered. This approach would allow flexibility to ensure that the principles remained the same regardless of the study's objectives or setting, but the application of those principles would be specific to the type of study and data source. While the scope of these proposed annexes would be further clarified following the renovation work on ICH E8, it is currently envisioned that the initial study types proposed for future development include:

1. <u>Proposed Annex 1: Traditional Interventional Trials of investigational unapproved or approved drugs</u> This would encompass trials of unapproved drugs or of approved drugs for a new indication or use in a controlled setting with prospective collection of trial data. The current E6 document is focused on traditional interventional trials conducted for regulatory purposes in a clinical trial

[10] ICH E6 also includes e.g. a detailed chapter which describe standards for Ethics Committees/ Institutional Review Boards, a chapter describing in detail standards for sponsors when designing, conducting, evaluating and reporting clinical trials, and chapter describing the structure and content of Investigator Brochures and Clinical Trial Protocol. These need revision but should be maintained. Reference to the activities of regulatory authorities for clinical trials should also be included as in many cases these complement the role of the ethics committee, for instance in areas of safety reporting and oversight.

[11] Including electronic health records (EHRs)

[12] http://www.fda.gov/downloads/Drugs/.../Guidances/UCM269919.pdf

[13] http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/11/WC500155491.pdf

[14] http://www.pmda.go.jp/files/000215858.pdf

setting, with data collected primarily through traditional case report forms and trial monitoring requirements consistent with the regulatory requirements for studies of investigational products. This document would become the first annex to the new overarching principles document, with revisions, as needed to reflect current risk-based approaches and practices and remove any inconsistencies. It is anticipated that this annex would include the updates and risk-based approaches addressed in the current E6(R2).

2. Proposed Annex 2: Non-Traditional Interventional Trials and/or data sources. Trial designs such as pragmatic clinical trials would be included in this annex, as would real world data sources to supplement or possibly replace new data collection within the trial itself. The study objectives could include evidence generation for regulatory review of approved products as well as for broader research questions, as appropriate. Principles for protocol compliance and trial monitoring would reflect the fact that approved, marketed products with better-documented and better-known safety profiles are being studied.

3. Proposed Annex 3: Non-Traditional Trial Designs. This annex would include designs other than RCTs and may include observational studies, patient registries, and other non-traditional trial designs that rely heavily on alternative data sources (e.g., EHRs, claims data, etc.). The studies may be designed to generate findings for important research objectives regarding health care practice and policy but could also be used to address regulatory questions (e.g., concerning product safety post-marketing). Principles for protocol compliance and trial monitoring laid out in this annex would be consistent with the data source and also, as in proposed annex 2, reflect the fact that marketed products with better-known safety profiles are being studied.

ICH anticipates that ICH EWGs would lead and undertake first the development of the revised E8, next the new E6 overarching principles document, and later undertake the development of the proposed annexes. In view of the inter-relationship of issues and considerations that will be addressed in E8 and E6, with ICH *E9 Statistical Principles for Clinical Trials*, including concepts of randomization, power and data/safety monitoring committees, plans would be made for cross-consultation and coordination of any parallel ongoing work of WG experts for these guidelines. Recognizing the broader application of the types of studies included in the third proposed annex ICH would also anticipate engaging others with expertise in the conduct of such studies, which may include government health researchers as well as academic researchers, perhaps working in collaboration in development of the proposed guideline annex for these types of studies.

3. Proposed Plan for "Renovation" Work

ICH proposes that the renovation work would be organized into a series of guideline efforts conducted by EWGs.

A. ICH proposes that the first effort would focus on modernization of E8 per the approach described above. This revision would include the addition of quality by design as a key consideration in the planning and design of clinical trials. The revision could also include an updating of the current E8 cross-referencing of the other ICH guidelines that should be referred to when planning clinical studies. The cross-referencing could be provided, for example, in a table or chart that lists the CTQ factors identified in the revised E8 guideline and shows where the CTQ factors included in this list may be addressed in other ICH E guidelines. Such an updated reference chart, with an appropriate level of explanation could be quite helpful to prospective users of the ICH guidelines. For the E8 renovation

work, the EWGs could be comprised of experts from a mix of relevant disciplines including clinical, statistical, data science, patient-reported outcome/clinical outcome assessment experts, and potentially others. This work might proceed as follows:

I. **Guideline effort 1**: Develop a revised ICH E8 guideline – potentially starting in the late 2017 or in 2018.

B. For the E6 renovation work, the EWGs would be comprised of experts in clinical trial conduct and GCP compliance, and for the development of a particular annex, experts in the study types identified for that annex. The work might proceed as follows:

I. **Guideline effort 2**: Develop new ICH E6 Overarching Principles guideline. This work might start after the proposed Guideline effort 1 work on ICH E8 reaches at least Step 2b. An appropriate subset of the elements for study quality and CTQ factors identified in the revised E8, that would be relevant to E6, could then be carried over and referenced in the overarching principles of a revised E6.

II. **Guideline effort 3**: Develop E6 Annex 1 focused on *traditional interventional* trials of investigational unapproved or approved drugs (i.e., trials of unapproved drugs or of approved drugs for a new indication or use) in a controlled setting with prospective collection of trial data. This work would start after the proposed Guideline effort 2 work on the ICH E6 Overarching Principles has reached at least Step 2b.

III. **Guideline effort 4**: Develop ICH E6 Annex 2 focused on *non-traditional interventional* trials and/or data sources. This work would be expected to start after the proposed Guideline effort 3 had reached at least Step 2b.

IV. **Guideline effort 5**: Develop ICH E6 Annex 3 focused on *non-traditional* trial designs. This work would be expected to start after the proposed Guideline effort 4 had reached at least Step 2b. It is also being proposed that ICH incorporate a process of engagement taking the approach outlined below.

ICH Step Process Enhancement for the GCP Renovation

In recognition of the considerable stake and significant GCP expertise of parties outside ICH in the academic research community, ICH also proposes specific enhancements to the public consultation process for the revision of ICH E8 and E6.

As a first component of expanded consultation, ICH is seeking stakeholder comment on the overall GCP Renovation proposal herein. To begin obtaining stakeholder input, ICH is therefore posting this proposal on its website, in conjunction with issuance of a press release to provide public notice of our interest in hearing the views of public stakeholders. A 60-day comment period is being provided to enable time for the stakeholder review and response, while still allowing time following the close of the comment period for ICH analysis of the input received, to determine if major revisions should be considered to the current proposal based on the public input. The aim is to proceed with initiating needed renovation work as soon as practical, for example, within the next year.

Additional components of the proposed enhancements include the following recommendations for information sharing, consultation and interaction:

1. Seek outside stakeholder comment on the Concept Paper and Business Plan associated with the Guideline efforts outlined above. These work products are developed prior to the initiation of Step 1 of the five-step Formal ICH Procedure, at the time when work on those documents is being planned and scoped in preparation for getting Working Group efforts under way. ICH is considering providing a 30-day public comment period to receive timely comments at this early and formative stage while avoiding delays in the start of work.
2. Hold meetings with outside stakeholders at key guideline development milestones. ICH is proposing to hold a meeting with public stakeholders to present, get input, and discuss work to date and planned next steps at one or more points in the proposed guideline development. ICH is considering holding these meetings at the following key points in the process:
    a. Before the completion of Step1 – to get input on the Step 1 draft before completion.
    b. At Step 3 to have a face-to-face meeting and in-depth discussion and consultation on the Step 3 document.
    c. After Step 4 to review and discuss the final resulting version and get input on design of training materials for guideline implementation.

Conclusion

Over the past twenty years, the ICH E6 and E8 guidelines, ICH E6 in particular, have played an essential role in enabling the continued growth and success of multiregional clinical trials of investigational new drugs, including critical guidance related to training, responsibilities, and expectations of investigators, sponsors and IRBs. ICH believes that the proposed approach to renovation of the ICH Guidelines related to clinical trial design, planning, management, and conduct of studies outlined in this paper would address important concerns recently expressed by some of our external stakeholders, but also bring critical modernization to these foundational guidelines. The proposed renovation work will build on the important work of ICH E6 R2 and expand it, and bring even greater cohesiveness to the critical interplay of factors addressed in various E guidelines including but not limited to the topics of quality by design and related study quality considerations, statistical principles, and good clinical practices.

Appendix G: ICH E8 – *General Considerations for Clinical Trials*

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

GENERAL CONSIDERATIONS FOR CLINICAL TRIALS
E8

Current *Step 4* version

dated 17 July 1997

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

E8
Document History

First Codification	History	Date	New Codification **November 2005**
E8	Approval by the Steering Committee under *Step 2* and release for public consultation.	7 November 1996	E8

Current *Step 4* version

E8	Approval by the Steering Committee under *Step 4* and recommendation for adoption to the three ICH regulatory bodies.	17 July 1997	E8

GENERAL CONSIDERATIONS FOR CLINICAL TRIALS

ICH Harmonised Tripartite Guideline

Having reached *Step 4* of the ICH Process at the ICH Steering Committee meeting on 17 July 1997, this guideline is recommended for adoption to the three regulatory parties to ICH

TABLE OF CONTENTS

GENERAL CONSIDERATIONS FOR CLINICAL TRIALS

1. OBJECTIVES OF THIS DOCUMENT

In the three ICH regions, the evolution of drug development strategies and evaluation processes has led to the establishment of regional guidances on general considerations for clinical trials and the process of clinical development of pharmaceuticals for human use. This harmonised guideline is derived from those regional documents as well as from ICH Guidelines.

The ICH document "General Considerations for Clinical Trials" is intended to:

(a) describe internationally accepted principles and practices in the conduct of both individual clinical trials and overall development strategy for new medicinal products.

(b) facilitate the evaluation and acceptance of foreign clinical trial data by promoting common understanding of general principles, general approaches and the definition of relevant terms.

c) present an overview of the ICH clinical safety and efficacy documents and facilitate the user's access to guidance pertinent to clinical trials within these documents. The relevant ICH documents are listed in Annex 1.

(d) provide a separate glossary of terms used in the ICH clinical safety and efficacy related documents that pertain to clinical trials and indicate which documents contain them.

For the sake of brevity, the term "drug" has been used in this document. It should be considered synonymous with "investigational (medicinal) product", "medicinal product" and "pharmaceutical" including vaccines and other biological products. The principles established in this guideline may also be applied to other clinical investigations (e.g. radiotherapy, psychotherapy, surgery, medical devices and alternative therapies).

2. GENERAL PRINCIPLES

2.1 Protection of clinical trial subjects

The principles and practices concerning protection of trial subjects are stated in the ICH Guideline on Good Clinical Practice (ICH E6). These principles have their origins in The Declaration of Helsinki and should be observed in the conduct of all human drug investigations.

Before any clinical trial is carried out, results of non-clinical investigations or previous human studies should be sufficient to indicate that the drug is acceptably safe for the proposed investigation in humans. The purpose and timing of animal pharmacology and toxicology studies intended to support studies of a given duration are discussed in ICH M3. The role of such studies for biotechnology products is cited in ICH S6.

Throughout drug development, emerging animal toxicological and clinical data should be reviewed and evaluated by qualified experts to assess their implications for the safety of the trial subjects. In response to such findings, future studies and, when necessary, those in progress should be appropriately modified in a timely fashion to maintain the safety of trial participants. The investigator and sponsor share responsibility for the protection of clinical trial subjects together with the

Institutional Review Board/Independent Ethics Committee. The responsibilities of these parties are described in ICH E6.

2.2 Scientific approach in design and analysis

Clinical trials should be designed, conducted and analysed according to sound scientific principles to achieve their objectives; and should be reported appropriately. The essence of rational drug development is to ask important questions and answer them with appropriate studies. The primary objectives of any study should be clear and explicitly stated.

Clinical studies can be classified according to when the study occurs during clinical development or as shown in Table 1 by their objectives. (The illustrative examples are not intended to be exhaustive). The cardinal logic behind serially conducted studies of a medicinal product is that the results of prior studies should influence the plan of later studies. Emerging data will frequently prompt a modification of the development strategy. For example, results of a therapeutic confirmatory study may suggest a need for additional human pharmacology studies.

The availability of foreign clinical data should obviate the need to generate similar data in an ICH region if the ICH E5 and ICH E6 guidelines are followed. (see ICH E5).

Table 1 - An Approach to Classifying Clinical Studies According to Objective

Type of Study	*Objective of Study*	*Study Examples*
Human Pharmacology	• Assess tolerance • Define/describe PK[1] and PD[2] • Explore drug metabolism and drug interactions • Estimate activity	• Dose-tolerance studies • Single and multiple dose PK and/or PD studies • Drug interaction studies
Therapeutic Exploratory	• Explore use for the targeted indication • Estimate dosage for subsequent studies • Provide basis for confirmatory study design, endpoints, methodologies	• Earliest trials of relatively short duration in well- defined narrow patient populations, using surrogate or pharmacological endpoints or clinical measures • Dose-response exploration studies
Therapeutic Confirmatory	• Demonstrate/confirm efficacy • Establish safety profile • Provide an adequate basis for assessing the benefit/risk relationship to support licensing • Establish dose-response relationship	• Adequate, and well controlled studies to establish efficacy • Randomised parallel dose-response studies • Clinical safety studies • Studies of mortality/ morbidity outcomes • Large simple trials • Comparative studies
Therapeutic Use	• Refine understanding of benefit/risk relationship in general or special populations and/or environments • Identify less common adverse reactions • Refine dosing recommendation	• Comparative effectiveness studies • Studies of mortality/morbidity outcomes • Studies of additional endpoints • Large simple trials • Pharmacoeconomic studies

[1]Pharmacokinetics
[2]Pharmacodynamics

3. DEVELOPMENT METHODOLOGY

This section covers issues and considerations relating to the development plan and to its individual component studies.

3.1 Considerations for the Development Plan

3.1.1 Non-Clinical Studies

Important considerations for determining the nature of non-clinical studies and their timing with respect to clinical trials include:

a) duration and total exposure proposed in individual patients

b) characteristics of the drug (e.g. long half life, biotechnology products)

c) disease or condition targeted for treatment

d) use in special populations (e.g. women of childbearing potential)

e) route of administration

The need for non-clinical information including toxicology, pharmacology and pharmacokinetics to support clinical trials is addressed in the ICH M3 and S6 documents.

3.1.1.1 Safety Studies

For the first studies in humans, the dose that is administered should be determined by careful examination of the prerequisite non-clinical pharmacokinetic, pharmacological and toxicological evaluations (see ICH M3). Early non-clinical studies should provide sufficient information to support selection of the initial human dose and safe duration of exposure, and to provide information about physiological and toxicological effects of a new drug.

3.1.1.2 Pharmacological and Pharmacokinetic Studies

The basis and direction of the clinical exploration and development rests on the non-clinical pharmacokinetic and pharmacology profile, which includes information such as:

a) Pharmacological basis of principal effects (mechanism of action).

b) Dose-response or concentration-response relationships and duration of action

c) Study of the potential clinical routes of administration

d) Systemic general pharmacology, including pharmacological effects on major organ systems and physiological responses

e) Studies of absorption, distribution, metabolism and excretion

3.1.2 Quality of Investigational Medicinal Products

Formulations used in clinical trials should be well characterised, including information on bioavailability wherever feasible. The formulation should be appropriate for the stage of drug development. Ideally, the supply of a formulation will be adequate to allow testing in a series of studies that examine a range of doses. During drug development different formulations of a drug may be tested. Links between formulations, established by bioequivalence studies or other means are important in interpreting clinical study results across the development program.

3.1.3 Phases of Clinical Development

Clinical drug development is often described as consisting of four temporal phases (Phase I-IV). It is important to recognise that the phase of development provides an inadequate basis for classification of clinical trials because one type of trial may occur in several phases (see Fig 1.). A classification system using study objectives as discussed in section 2.2 is preferable. It is important to appreciate that the phase concept is a description, not a set of requirements. It is also important to realise that the temporal phases do not imply a fixed order of studies since for some drugs in a development plan the typical sequence will not be appropriate or necessary. For example, although human pharmacology studies are typically conducted during Phase I, many such studies are conducted at each of the other three stages, but nonetheless sometimes labelled as Phase I studies. Figure 1 demonstrates this close but variable correlation between the two classification systems. The distribution of the points of the graph shows that the types of study are not synonymous with the phases of development.

Correlation between Development Phases and Types of Study

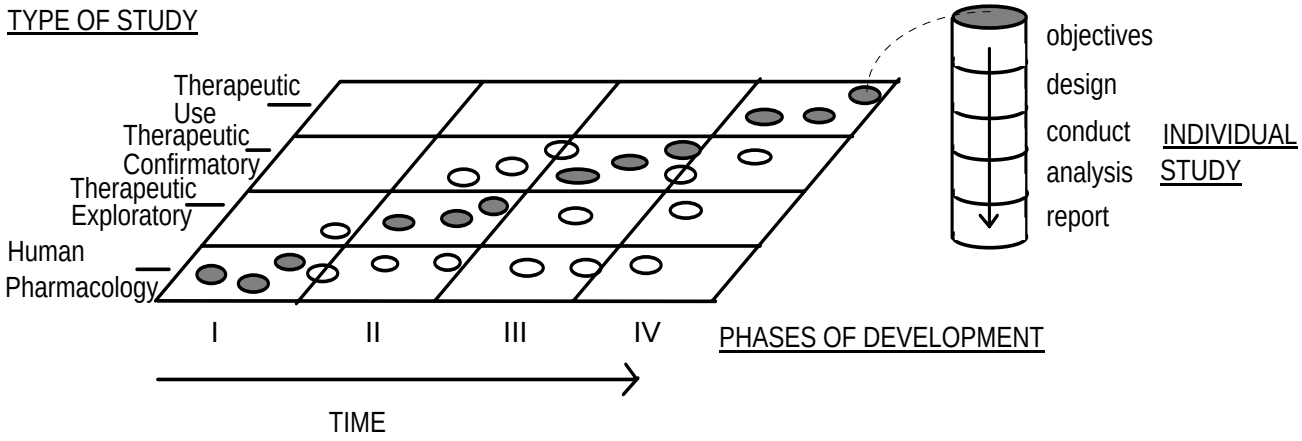

Figure 1 *- This matrix graph illustrates the relationship between the phases of development and types of study by objective that may be conducted during each clinical development of a new medicinal product. The shaded circles show the types of study most usually conducted in a certain phase of development, the open circles show certain types of study that may be conducted in that phase of development but are less usual. Each circle represents an individual study. To illustrate the development of a single study, one circle is joined by a dotted line to an inset column that depicts the elements and sequence of an individual study.*

Drug development is ideally a logical, step-wise procedure in which information from small early studies is used to support and plan later larger, more definitive studies. To develop new drugs efficiently, it is essential to identify characteristics of the investigational medicine in the early stages of development and to plan an appropriate development based on this profile.

Initial trials provide an early evaluation of short-term safety and tolerability and can provide pharmacodynamic and pharmacokinetic information needed to choose a suitable dosage range and administration schedule for initial exploratory therapeutic trials. Later confirmatory studies are generally larger and longer and include a more

diverse patient population. Dose-response information should be obtained at all stages of development, from early tolerance studies, to studies of short-term pharmacodynamic effect, to large efficacy studies (see ICH E4). Throughout development, new data may suggest the need for additional studies that are typically part of an earlier phase. For example, blood level data in a late trial may suggest a need for a drug-drug interaction study, or adverse effects may suggest the need for further dose finding and/or additional non-clinical studies. In addition, to support a new marketing application approval for the same drug e.g. for a new indication, pharmacokinetic or therapeutic exploratory studies are considered to be in Phase I or Phase II of development.

3.1.3.1 Phase I (Most typical kind of study: Human Pharmacology)

Phase I starts with the initial administration of an investigational new drug into humans.

Although human pharmacology studies are typically identified with Phase I, they may also be indicated at other points in the development sequence. Studies in this phase of development usually have non-therapeutic objectives and may be conducted in healthy volunteer subjects or certain types of patients, e.g. patients with mild hypertension. Drugs with significant potential toxicity, e.g. cytotoxic drugs, are usually studied in patients. Studies in this phase can be open, baseline controlled or may use randomisation and blinding, to improve the validity of observations.

Studies conducted in Phase I typically involve one or a combination of the following aspects:

a) Estimation of Initial Safety and Tolerability

The initial and subsequent administration of an investigational new drug into humans is usually intended to determine the tolerability of the dose range expected to be needed for later clinical studies and to determine the nature of adverse reactions that can be expected. These studies typically include both single and multiple dose administration.

b) Pharmacokinetics

Characterisation of a drug's absorption, distribution, metabolism, and excretion continues throughout the development plan**.** Their preliminary characterisation is an important goal of Phase I. Pharmacokinetics may be assessed via separate studies or as a part of efficacy, safety and tolerance studies. Pharmacokinetic studies are particularly important to assess the clearance of the drug and to anticipate possible accumulation of parent drug or metabolites and potential drug-drug interactions. Some pharmacokinetic studies are commonly conducted in later phases to answer more specialised questions. For many orally administered drugs, especially modified release products, the study of food effects on bioavailability is important. Obtaining pharmacokinetic information in sub-populations such as patients with impaired elimination (renal or hepatic failure), the elderly, children, women and ethnic subgroups should be considered. Drug-drug interaction studies are important for many drugs; these are generally performed in phases beyond Phase I but studies in animals and in vitro studies of metabolism and potential interactions may lead to doing such studies earlier.

c) Assessment of Pharmacodynamics

Depending on the drug and the endpoint studied, pharmacodynamic studies and studies relating drug blood levels to response (PK/PD studies) may be conducted in

healthy volunteer subjects or in patients with the target disease. In patients, if there is an appropriate measure, pharmacodynamic data can provide early estimates of activity and potential efficacy and may guide the dosage and dose regimen in later studies.

d) Early Measurement of Drug Activity

Preliminary studies of activity or potential therapeutic benefit may be conducted in Phase I as a secondary objective. Such studies are generally performed in later phases but may be appropriate when drug activity is readily measurable with a short duration of drug exposure in patients at this early stage.

3.1.3.2 Phase II (Most typical kind of study: Therapeutic Exploratory)

Phase II is usually considered to start with the initiation of studies in which the primary objective is to explore therapeutic efficacy in patients.

Initial therapeutic exploratory studies may use a variety of study designs, including concurrent controls and comparisons with baseline status. Subsequent trials are usually randomised and concurrently controlled to evaluate the efficacy of the drug and its safety for a particular therapeutic indication. Studies in Phase II are typically conducted in a group of patients who are selected by relatively narrow criteria**,** leading to a relatively homogeneous population and are closely monitored.

An important goal for this phase is to determine the dose(s) and regimen for Phase III trials. Early studies in this phase often utilise dose escalation designs (see ICH E4) to give an early estimate of dose response and later studies may confirm the dose response relationship for the indication in question by using recognised parallel dose-response designs (could also be deferred to phase III). Confirmatory dose response studies may be conducted in Phase II or left for Phase III. Doses used in Phase II are usually but not always less than the highest doses used in Phase I.

Additional objectives of clinical trials conducted in Phase II may include evaluation of potential study endpoints, therapeutic regimens (including concomitant medications) and target populations (e.g. mild versus severe disease) for further study in Phase II or III. These objectives may be served by exploratory analyses, examining subsets of data and by including multiple endpoints in trials.

3.1.3.3 Phase III (Most typical kind of study: Therapeutic Confirmatory)

Phase III usually is considered to begin with the initiation of studies in which the primary objective is to demonstrate, or confirm therapeutic benefit.

Studies in Phase III are designed to confirm the preliminary evidence accumulated in Phase II that a drug is safe and effective for use in the intended indication and recipient population. These studies are intended to provide an adequate basis for marketing approval. Studies in Phase III may also further explore the dose-response relationship, or explore the drug's use in wider populations, in different stages of disease, or in combination with another drug. For drugs intended to be administered for long periods, trials involving extended exposure to the drug are ordinarily conducted in Phase III, although they may be started in Phase II (see ICH E1). ICH E1 and ICH E7 describe the overall clinical safety database considerations for chronically administered drugs and drugs used in the elderly. These studies carried out in Phase III complete the information needed to support adequate instructions for use of the drug (official product information).

3.1.3.4 Phase IV (Variety of Studies: - Therapeutic Use)

Phase IV begins after drug approval. Therapeutic use studies go beyond the prior demonstration of the drug's safety, efficacy and dose definition.

Studies in Phase IV are all studies (other than routine surveillance) performed after drug approval and related to the approved indication. They are studies that were not considered necessary for approval but are often important for optimising the drug's use. They may be of any type but should have valid scientific objectives. Commonly conducted studies include additional drug-drug interaction, dose-response or safety studies and studies designed to support use under the approved indication, e.g. mortality/morbidity studies, epidemiological studies.

3.1.3.5 Development of an application unrelated to original approved use

After initial approval, drug development may continue with studies of new or modified indications, new dosage regimens, new routes of administration or additional patient populations. If a new dose, formulation or combination is studied, additional human pharmacology studies may be indicated, necessitating a new development plan.

The need for some studies may be obviated by the availability of data from the original development plan or from therapeutic use.

3.1.4 Special Considerations

A number of special circumstances and populations require consideration on their own when they are part of the development plan.

3.1.4.1 Studies of Drug Metabolites

Major active metabolite(s) should be identified and deserve detailed pharmacokinetic study. Timing of the metabolic assessment studies within the development plan depends on the characteristics of the individual drug.

3.1.4.2 Drug-Drug Interactions

If a potential for drug-drug interaction is suggested by metabolic profile, by the results of non-clinical studies or by information on similar drugs, studies on drug interaction during clinical development are highly recommended. For drugs that are frequently co-administered it is usually important that drug-drug interaction studies be performed in non-clinical and, if appropriate in human studies. This is particularly true for drugs that are known to alter the absorption or metabolism of other drugs (see ICH E7), or whose metabolism or excretion can be altered by effects by other drugs.

3.1.4.3 Special Populations

Some groups in the general population may require special study because they have unique risk/benefit considerations that need to be taken into account during drug development, or because they can be anticipated to need modification of use of the dose or schedule of a drug compared to general adult use. Pharmacokinetic studies in patients with renal and hepatic dysfunction are important to assess the impact of potentially altered drug metabolism or excretion. Other ICH documents address such issues for geriatric patients (ICH E7) and patients from different ethnic groups (ICH E5). The need for non-clinical safety studies to support human clinical trials in special populations is addressed in the ICH M3 document.

Particular attention should be paid to the ethical considerations related to informed consent from vulnerable populations and the procedures scrupulously followed.(see ICH E6)

a) Investigations in pregnant women

In general, pregnant women should be excluded from clinical trials where the drug is not intended for use in pregnancy. If a patient becomes pregnant during administration of the drug, treatment should generally be discontinued if this can be done safely. Follow-up evaluation of the pregnancy, foetus, and child is very important . Similarly, for clinical trials that include pregnant women because the medicinal product is intended for use during pregnancy, follow-up of the pregnancy, foetus, and child is very important.

b) Investigations in nursing women

Excretion of the drug or its metabolites into human milk should be examined where applicable. When nursing mothers are enrolled in clinical studies their babies should be monitored for the effects of the drug.

c) Investigations in children.

The extent of the studies needed depends on the current knowledge of the drug and the possibility of extrapolation from adults and children of other age groups. Some drugs may be used in children from the early stages of drug development (see ICH M3).

For a drug expected to be used in children, evaluation should be made in the appropriate age group. When clinical development is to include studies in children, it is usually appropriate to begin with older children before extending the trial to younger children and then infants.

3.2 Considerations for Individual Clinical Trials

The following important principles should be followed in planning the objectives, design, conduct, analysis and reporting of a clinical trial (see ICH guidelines in Annex 1). Each part should be defined in a written protocol before the study starts (see ICH E6).

3.2.1 Objectives

The objective(s) of the study should be clearly stated and may include exploratory or confirmatory characterisation of safety and/or efficacy and/or assessment of pharmacokinetic parameters and pharmacological, physiological, biochemical effects.

3.2.2 Design

The appropriate study design should be chosen to provide the desired information. Examples of study design include parallel group, cross-over, factorial, dose escalation, and fixed dose-dose response. (See ICH E4, E6, E9 and E10). Appropriate comparators should be utilised and adequate numbers of subjects included to achieve the study objectives. Primary and secondary endpoints and plans for their analyses should be clearly stated (see ICH E9). The methods of monitoring adverse events by changes in clinical signs and symptoms and laboratory studies should be described (see ICH E3). The protocol should specify procedures for the follow-up of patients who stop treatment prematurely.

3.2.2.1 Selection of subjects

The stage of development and the indication to be studied and should be taken into account in selecting the subject population (e.g. normal healthy subjects, cancer patients or other special populations in early phase development) as should prior non-clinical and clinical knowledge. The variability of groups of patients or healthy volunteers studied in early trials may be limited to a narrow range by strict selection criteria, but as drug development proceeds, the populations tested should be broadened to reflect the target population.

Depending on the stage of development and level of concern for safety, it may be necessary to conduct studies in a closely monitored (i.e., inpatient) environment.

As a general principle trial subjects should not participate concurrently in more than one clinical trial but there can be justified exceptions. Subjects should not be enrolled repetitively in clinical trials without time off treatment adequate to protect safety and exclude carry-over effects.

In general, women of childbearing potential should be using highly effective contraception to participate in clinical trials (see ICH M3).

For male subjects, potential hazards of drug exposure in the trial to their sexual partners or resulting progeny should be considered. When indicated (e.g. trials involving drugs which are potentially mutagenic, or toxic to the reproductive system), an appropriate contraception provision should be included in the trial.

3.2.2.2 Selection of Control Group

Trials should have an adequate control group. Comparisons may be made with placebo, no treatment, active controls or of different doses of the drug under investigation. The choice of the comparator depends, among other things, on the objective of the trial (see ICH E9 and E10). Historical (external) controls can be justified in some cases but particular care is important to minimise the likelihood of erroneous inference.

3.2.2.3 Number of subjects

The size of a trial is influenced by the disease to be investigated, the objective of the study and the study endpoints. Statistical assessments of sample size should be based on the expected magnitude of the treatment effect, the variability of the data, the specified (small) probability of error (see ICH E9) and the desire for information or subsets of the population or secondary endpoints.. In some circumstances a larger database may be needed to establish the safety of a drug. ICH E1 and ICH E7 suggest a minimum experience to assess safety for a registrational database for a new indication. These numbers should not be considered as absolute and may be insufficient in some cases (e.g. where long-term use in healthy individuals is expected).

3.2.2.4 Response Variables

Response variables should be defined prospectively, giving descriptions of methods of observation and quantification. Objective methods of observation should be used where possible and when appropriate (see ICH E9).

Study endpoints are the response variables that are chosen to assess drug effects that are related to pharmacokinetic parameters, pharmacodynamic measures, efficacy and safety. A primary endpoint(s) should reflect clinically relevant effects and is typically selected based on the principal objective of the study. Secondary endpoints assess

other drug effects that may or may not be related to the primary endpoint. Endpoints and the plan for their analysis should be prospectively specified in the protocol.

A surrogate endpoint is an endpoint that is intended to relate to a clinically important outcome but does not in itself measure a clinical benefit. Surrogate endpoints may be used as primary endpoints when appropriate (when the surrogate is reasonably likely or well known to predict clinical outcome).

The methods used to make the measurements of the endpoints, both subjective and objective, should be validated and meet appropriate standards for accuracy, precision, reproducibility, reliability, and responsiveness (sensitivity to change over time).

3.2.2.5 Methods to Minimise or Assess Bias

The protocol should specify methods of allocation to treatment groups and blinding (see ICH E9 and E10).

a) Randomisation

In conducting a controlled trial**,** randomised allocation is the preferred means of assuring comparability of test groups and minimising the possibility of selection bias.

b) Blinding

Blinding is an important means of reducing or minimising the risk of biased study outcomes. A trial where the treatment assignment is not known by the study participant because of the use of placebo or other methods of masking the intervention, is referred to as a single blind study. When the investigator and sponsor staff who are involved in the treatment or clinical evaluation of the subjects and analysis of data are also unaware of the treatment assignments, the study is double blind.

c) Compliance

Methods used to evaluate patient usage of the test drug should be specified in the protocol and the actual usage documented.

3.2.3 Conduct

The study should be conducted according to the principles described in this guideline and in accordance with other pertinent elements outlined in ICH E6 and other relevant ICH guidelines (see Annex 1). Adherence to the study protocol is essential. If modification of the protocol becomes necessary a clear description of the rationale for the modification should be provided in a protocol amendment (see ICH E6). Timely adverse event reporting during a study is essential and should be documented. Guidance is available on expedited reporting of safety data to appropriate officials and on the content of safety reports and on privacy and confidentiality of data (see ICH E2A and E2B and ICH E6).

3.2.4 Analysis

The study protocol should have a specified analysis plan that is appropriate for the objectives and design of the study, taking into account the method of subject allocation, the measurement methods of response variables, specific hypotheses to be tested, and analytical approaches to common problems including early study withdrawal and protocol violations. A description of the statistical methods to be employed, including timing of any planned interim analysis(es) should be included in the protocol (see ICH E3**,** ICH E6 and ICH E9).

The results of a clinical trial should be analysed in accordance with the plan prospectively stated in the protocol and all deviations from the plan should be indicated in the study report. Detailed guidance is available in other ICH guidelines on planning of the protocol (ICH E6), on the analysis plan and statistical analysis of results (ICH E9) and on study reports (ICH E3).

Studies are normally expected to run to completion, although in some studies the possibility of early stopping is formally recognised. In such cases this should be clearly described in the protocol with due statistical attention to the overall levels of statistical significance and to the need to adjust the estimates of the size of treatment effects (ICH E9).

Safety data should be collected for all clinical trials, appropriately tabulated and with adverse events classified according to their seriousness and their likely causal relationship (see ICH E2A).

3.2.5 Reporting

Clinical study reports should be adequately documented following the approaches outlined in other ICH guidelines (see E3 and E6).

ANNEX

LIST OF RELEVANT ICH GUIDELINES AND TOPICS

Code	***Topic***
E1	The Extent of Population Exposure to Assess Clinical Safety for Drug Intended for Long-term Treatment of Non-Life-Threatening Conditions
E2A	Clinical Safety Data Management: Definitions and Standards for expedited Reporting
E2B	Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports
E2C	Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs
E3	Structure and Content of Clinical Study Reports
E4	Dose-Response Information to Support Drug Registration
E5	Ethnic Factors in the Acceptability of Foreign Clinical Data
E6	Good Clinical Practice: Consolidated Guideline
E7	Studies in Support of Special Populations: Geriatrics
E8	General Considerations for Clinical Trials
E9	Statistical Considerations in the Design of Clinical Trials
E10	Choice of Control Group in Clinical Trials
M3	Non-Clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals
S6	Safety Studies for Biotechnology-Derived Products