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OVERSIGHT AND MONITORING IN CLINICAL TRIALS

This guideline assists sponsors of clinical investigations in developing monitoring strategies and plans for investigational studies of medical products, including human medicine and biological products, medical devices, and combinations thereof. The overarching goal is to enhance human participant protection and the quality of clinical trial data by focusing sponsor oversight on the most important aspects of study conduct and reporting. While this guideline makes it clear that sponsors, and clinical research organisations (CROs) acting on their behalf, can use a variety of approaches to fulfil their responsibilities for monitoring Principal investigator (PI) conduct and performance in investigational studies. It must be highlighted that the responsibility for adequate oversight of the conduct of a clinical trial, including the justification for and selection of monitoring methods, remains that of the sponsor solely. SAHPRA reserves the right to request any additional information and may make amendments in keeping with the knowledge which is current at the time of consideration.

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Contents

Glossary

Abbreviation/ Term	Meaning
CRFs	Case Report Forms
CROs	Clinical Research Organisations
EDC	Electronic Data Capture
IRB	Institutional Review Board
ICH	International Conference on Harmonisation
ISO	International Standards Organization
PI	Principal Investigator
RBM	Risk-based monitoring
SDV	Source Data Verification
SAHPRA	South African Health Products Regulatory Authority

1. INTRODUCTION

This guideline assists sponsors of clinical investigations in developing monitoring strategies and plans for investigational studies of medical products, including human medicine and biological products, medical devices, and combinations thereof. The overarching goal is to enhance human participant protection and the quality of clinical trial data by focusing sponsor oversight on the most important aspects of study conduct and reporting.

While this guideline makes it clear that sponsors, and clinical research organisations (CROs) acting on their behalf, can use a variety of approaches to fulfil their responsibilities for monitoring Principal Investigator (PI) conduct and performance in investigational studies. It must be highlighted that the responsibility for adequate oversight of the conduct of a clinical trial, including the justification for and selection of monitoring methods, remains that of the sponsor solely. The consequences of inadequate monitoring are the sole responsibility of the sponsor or its representative.

2. BACKGROUND

Effective monitoring of clinical trials by sponsors is critical to the protection of human participants and the conduct of high-quality studies. Sponsors of clinical trials involving human medicines, biological products, medical devices, and combinations thereof are required to provide oversight to ensure adequate protection of the rights, welfare, and safety of human participants and the quality of the clinical trial data submitted to the South African Health Products Regulatory Authority (SAHPRA). The SAHPRA requires sponsors to monitor the conduct and progress of their clinical trials.

During the past decade, 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, as well as challenges related to geographic dispersion. At the same time, increasing use of electronic systems and records, as well as improvements in statistical assessments and pharmacovigilance, present opportunities for alternative monitoring approaches that can improve the quality and efficiency of sponsor oversight of clinical trials.

SAHPRA encourages sponsors to develop monitoring plans that manage important risks to human participants and data quality and address the challenges of oversight, in part by taking advantage of the innovations in modern clinical trials.

This guideline focuses principally on monitoring, which is one aspect of the processes and procedures needed to ensure clinical trial quality and participant safety. Monitoring is a quality control tool for determining whether study activities are being carried out as required 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.

The term *monitoring* is used in different ways in the clinical trial context. It can refer to the assessment of Principal Investigator (PI) 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 (IP); and to the monitoring of internal sponsor and CRO processes and systems integral to proposing, designing, performing, recording, supervising, reviewing, or reporting clinical investigations.

For purposes of this guideline, monitoring refers to the methods used by sponsors of investigational studies, or CRO's delegated responsibilities for the conduct of studies, to oversee the conduct of, and reporting of data from clinical investigations, including appropriate PI supervision of study site staff and third party contractors. Monitoring activities include communication with the PI 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.

2.1 Definitions

Risk-based monitoring (RBM) is a monitoring technique that involves the use of validated tools in the evaluation and assessment of risk in the oversight of the quality of data and using the risk assessment to increase or decrease on site monitoring and/or Source Data Verification (SDV).

Remote monitoring is the technique of monitoring sites offsite by involving the site in verification of source data for example asking the site to confirm the time of consenting. It implies the reliance on the site itself to augment or replace onsite monitoring. This may involve the use of digital platforms to monitor the site.

Centralised or central monitoring is the use of data generated on site which is used by the sponsor offsite to evaluate and assess risk and deviations from the protocol or the median and is not dependant on the site verifying the data. Centralised monitoring can be used to augment RBM or 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 is the tradition technique where a monitor reviews source on site to ensure compliance and data quality. On site monitoring may involve the use of centralised tools and remote access to facilitate efficiencies and streamline on site visits.

Remote access to data and even source can be facilitated by the advancement in electronic systems and the increasing use of electronic records. Remote access to source documents which meets all the ethical and legal requirements for participant protection and safety allows for review and monitoring offsite but is then essentially equivalent to onsite monitoring in many but not all aspects. Ideally, remote access should be used to augment and focus on-site monitoring along with RBM tools.

2.2 Current Monitoring Practices

Historically, a range of practices have been used to monitor the conduct of clinical trials. These practices vary in intensity, focus, and methodology and include centralised monitoring of clinical data by statistical and data management personnel; targeted on-site visits to higher risk sites (e.g. where centralised monitoring suggests problems at a site), and frequent, comprehensive on-site visits to all sites by sponsor personnel or representatives (e.g. clinical monitors or clinical research associates).

Periodic, frequent visits to each site to evaluate study conduct and review data for each enrolled participant 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. This type of traditional frequent on-site monitoring visit model, with 100 % verification of all data, historically has been the SAHPRA's preferred way for sponsors to meet their monitoring obligations.

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. Both 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. 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 centralised monitoring only in exceptional circumstances.

2.3 Approach to Risk-Based Monitoring

A risk-based approach to monitoring (RBM) by definition involves the use of validated tools in the evaluation and assessment of risk in the oversight in the quality of data. It does not imply nor is equivalent to remote or off-site monitoring, and must be distinguished from this.

While it does not suggest any less vigilance in the oversight of clinical investigations, there is the danger that the risk-based monitoring may offer less oversight than the traditional monitoring approaches. RBM focuses sponsor oversight activities on preventing or mitigating important and likely risks to data quality and to processes critical to human participant protection and trial data 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 participant protection and data quality across sites. Sponsors should be prepared to augment RBM if necessary as it is an imperative of the concept of RBM.

The SAHPRA believes that RBM could improve sponsor oversight of clinical investigations if understood and executed correctly. RBM and the reliance on technological advances (e.g. remote risk and quality management tools and processes), can meet statutory and regulatory requirements under appropriate circumstances.

The incorporation of centralised monitoring practices, where appropriate, should improve a sponsor's ability to ensure the quality of clinical trial data. While 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 centralised monitoring techniques than by on-site monitoring, there is also confusion around both terminology and implementation. While adequate training may address some of these issues, it has been suggested that a statistical approach to central monitoring can help improve the effectiveness of on-site monitoring by prioritising site visits and by guiding site visits with central statistical data checks.

The SAHPRA encourages sponsors to tailor monitoring plans to the needs of the trial. 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 although limited. Additionally, statistical assessments using data submitted on paper case report forms (CRFs) or via EDC may permit timely identification of clinical sites that require additional training, monitoring, or both.

The SAHPRA acknowledges that there is 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. As a result, the recommendations are based, in part, on the SAHPRA's experience from the review of protocols, data submitted in pre-approval applications, and the results of inspections conducted to ensure human participant protection and data integrity.

3. OVERVIEW OF MONITORING METHODS

3.1 On-site and Centralised 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 centralised monitoring processes and factors to consider in determining which monitoring practices may be appropriate for a given clinical trial.

3.1.1 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 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 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, and appropriate PI 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 PIs may be unfamiliar. Findings at the site may lead to training efforts at both the site visited and elsewhere.

3.1.2 Centralised Monitoring

Centralised 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. Centralised monitoring processes can provide some of the capabilities of on-site monitoring as well as additional capabilities.

The types of monitoring activities and the extent to which centralised monitoring practices can be employed depend on various factors, including the sponsor's use of electronic systems; the sponsor's access to participants' 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 centralised 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.

If sponsors intend to rely heavily on centralised monitoring practices, they should identify, in the monitoring plan, the limitations of this plan, and when more on-site monitoring visits would be indicated, noting that monitoring remains a sole responsibility of the sponsor.

3.2 Examples of monitoring practices and activities

Monitoring activities broadly include communication with the PI 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.

Centralised monitoring techniques should be used to the extent appropriate and feasible to:

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 centralised 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 the ranges, consistency, and completeness of data
  - Checks for unusual distribution of data within and between study sites, such as data with too little variance
- Analyse 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 randomisation and CRF data, to preliminarily assess whether the participant 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.

Centralised 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.

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 on-site visits or more intensive and consideration of further on-site monitoring.

The following sections provide additional descriptions of various monitoring approaches.

3.2.1 Communication with study site staff

Communication between the monitor and the study site staff is an essential component of the clinical trial. Various modes of communication (*e.g*. teleconferences, videoconferencing, e-mail) 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). Communication with sites does not involve evaluation or review of data by sponsor personnel or representatives.

3.2.2 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 participants' informed consent is a critical activity that should be monitored. Alternatives to the traditional approach (monitors verifying the original signature on the consent form for each participant at the site) may be effective in identifying inadequacies in the consent process.

The study site sending documents electronically (*e.g*. fax, e-mail) to the monitor off-site may not be appropriate. The monitor may perform remote comparison of dates of study procedures and documentation of informed consent on CRFs. A secure 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 participant protection. Sponsors must attend to privacy and confidentiality concerns when considering techniques for monitoring informed consent.

b) Site's records

A growing portion of source documents (*e.g*. laboratory and radiology reports, source documents submitted by the PI for other purposes such as health records documenting serious adverse events or adjudicated events) are electronic and may be available to the sponsor remotely. 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.

3.2.3 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 participant's response of "no hospitalisations" 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 participant's participation and the PI's conduct and oversight. For example, for a particular study, there may be minimal benefit in comparing 100 % of the source data for each participant to the CRFs for each study visit. Rather, it may be sufficient to compare the most critical data points for a sample of participants 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.

4. RISK-BASED MONITORING

No single approach to monitoring is appropriate for every clinical trial. The SAHPRA recommends that each sponsor design a monitoring plan that is tailored to the specific human participant protection and data integrity risks of the trial. Ordinarily, such a risk-based plan would include a mix of centralised and on-site monitoring practices. The monitoring plan should identify the various methods intended to be used and the rationale for their use.

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 participant 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.

4.1 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 participants 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 participants 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 randomisation 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, participant 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 participant 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. For example, a low, but non-zero rate of errors in capturing certain baseline characteristics of enrolled participants (*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.

4.2 Risk assessment

This guideline also discusses risk assessment, a component of risk management, as applied in the context of clinical monitoring. Risk assessment generally involves identifying risks, analysing 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 guideline 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 guideline 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. These should be validated.

Following the identification of critical data and processes, 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 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 participant protection concerns that are inherent to the clinical investigation (*e.g*. based on trial design or investigational product).

The identified risks should be assessed and prioritised by considering the likelihood of errors occurring and the impact of such errors on human participant 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.

4.3 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, centralised), 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.

- Types of study endpoints

Endpoints that are more interpretative or participative may require on-site visits to assess the totality of participant records and to review application of protocol definitions with the PI. More objective endpoints (*e.g*. death, hospitalisation, or clinical laboratory values and standard measurements) may be more suitable for remote verification. Endpoints for which inappropriate participant withdrawal or lack of follow-up may impede study evaluation are likely to need more intensive monitoring to identify the reason(s) participants 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 participant 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 PI and of the sponsor with the PI

  PIs 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 PI understanding of responsibilities. In addition, the relative experience of a sponsor with the PI 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 PI oversight of participant 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 PIs.

- Quantity of data

  Some centralised monitoring tools may be more useful as the quantity of data (*e.g*. size or duration of trial, number of sites) collected increases.

4.4 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 and appropriately trained in the conduct of the study (*e.g*. standard operating procedures or other documents referenced in the monitoring plan).

The components of a monitoring plan might include the following:

4.4.1 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 PI.

For example, if it is determined that a PI differs markedly from other PIs in making safety-related findings or other key safety metrics, in rate of enrolment, in the number of protocol deviations, or in the rate of missing CRFs, the PI'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.

4.4.2 Communication of Monitoring Results

Format, content, timing, and archiving requirements for reports and other documentation of monitoring activities.

Process for appropriate communication:

- 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, PI 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.

4.4.3 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).

4.4.4 Ensuring Quality Monitoring

It is the sponsor's responsibility to ensure that the monitor is both trained and qualified to undertake the monitoring of a specific trial. Description of any specific training required for personnel carrying out monitoring activities, including personnel conducting internal data monitoring, statistical monitoring, or other centralised review activities should be provided.

Training should include Good Clinical Practice, principles of clinical investigations and human participant protection. In addition, study-specific training should include training on the disease under study, study trial design, protocol requirements, study monitoring plan, applicable standard operating procedures (SOPs), 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 participant protection and data integrity.

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, centralised data review or PI feedback.

4.4.5 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.

4.5 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.

5. ADDITIONAL STRATEGIES TO ENSURE STUDY QUALITY

Although the focus of this guideline is on monitoring the oversight and conduct of, and reporting of data from, clinical investigations, the SAHPRA 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.

5.1 Protocol and Case Report Form design

The most important tool for ensuring human participant 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. The CRF, which captures the data required by the protocol, is another 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 PI sites.

5.2 Principal Investigator training and communication

Clinical trial monitors conducting on-site visits have historically played an important role in training the PI and site staff during a study. On-site visits also have served as a primary means of providing feedback to PIs 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), PIs 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 PI'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, on-line training modules) and communication methods 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. It must be considered that many of the factors that necessitate onsite monitoring may be relevant and this should be considered.

5.3 Delegation of monitoring responsibilities to a CRO

If a sponsor of a study delegates the responsibility for ensuring proper monitoring to a CRO, the SAHPRA would require the written transfer of any obligations from a sponsor to a CRO and require the CRO to comply with the regulations. 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 exchange of relevant information (e.*g*. significant monitoring findings, significant changes in risk for a trial).

5.4 Principal Investigator and site selection and initiation

In addition to regulatory requirements for PI selection, sponsors should consider factors such as sponsor's previous experience with the PI or site, workload of the PI and study staff, and resource availability at the study site during PI and site selection.

Site training and 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 PIs and site staff understands 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 guideline can also be used for site selection and initiation activities.

6. REFERENCES

Guidance for Industry. 2013. Oversight of Clinical Investigations - A Risk-Based Approach to Monitoring. FDA. August.

International Standard. 2011. Clinical investigation of medical devices for human subjects-Good Clinical Practice. ISO14155. 2nd edition.

International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. (1996) ICH Harmonised Tripartite Guideline. Guideline for Good Clinical Practice. Current Step 4 version dated 10 June 1996 (including the Post Step 4 corrections).

7. VALIDITY

This guideline is valid for a period of 5 years from the effective date of revision and replaces Oversight and Monitoring in Clinical Trials, old document number 2.43. It will be reviewed on this timeframe or as and when required.