Smarter Clinical Solutions

WHITE PAPER

Risk-Based Monitoring: The Path Forward

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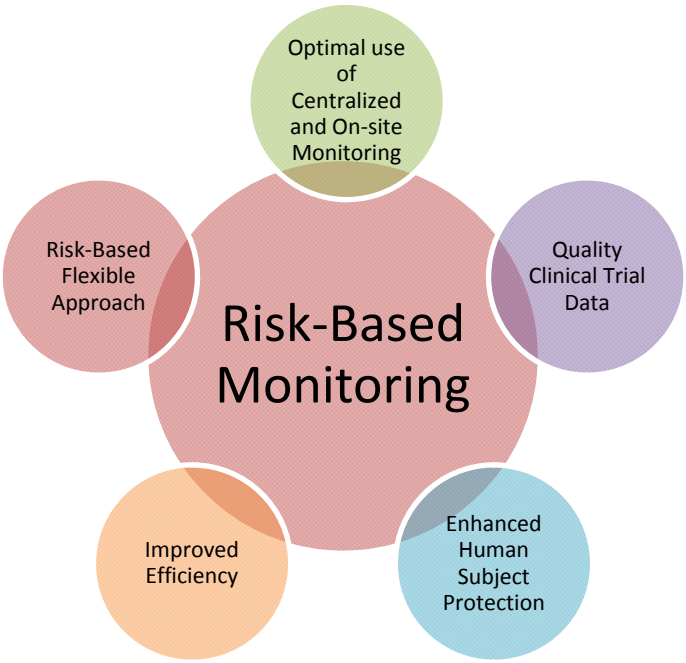
Effective monitoring of clinical trial is critical to protection of human subject as well as high quality credible data. Traditionally, it was believed that Regulators like US Food and Drug Administration (FDA) and European Medicines Agency (EMA) insist on 100% source-document verification (SDV) through on-site monitoring. However, recent guidance like FDA draft guidance on Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring issued in August 2011 and EMA Reflection Paper on risk based quality management in clinical trials issued around same time have altered the widespread impression on Regulators expectation, opened the path for a flexible risk-based monitoring approach through implementation of risk-based study specific strategies with a balance of remote and onsite monitoring aimed at maximizing monitoring effectiveness with judicious use of resources.



Monitoring ranges from on-site SDV to centralized monitoring using various technologies:

On-Site Monitoring: In person evaluation is carried out by sponsor/CRO personnel (usually known as Clinical Monitor or Clinical Research Associate) at the site. The objectives of on-site monitoring are to identify data entry errors and missing data in source records and case report forms to assess compliance with protocol and study drug accountability and to assess investigator supervision.

Centralized Monitoring (also known as remote monitoring): Remote evaluation carried out by sponsor personnel or representatives at a location other than the site. Centralized monitoring consists of standard checks of range, consistency, completeness of data aimed at identifying unusual distribution of data, higher risk sites to target on-site monitoring. Routine review of data in real time is possible through centralized monitoring. Increase in efficiency and reduction in cost are in large part from the reduction of non-monitoring time (e.g., travel, document retrieval). Even after implementation of centralized monitoring, an initial site visit would be necessary to confirm that the site is prepared to initiate the study and that staff are properly trained. A follow-up visit may be required to ensure that clinical trial is conducted and documented as per the protocol and applicable regulations. Centralized monitoring is usually performed by

a multidisciplinary team consists of Clinical Research Associates, Clinical Data Manager and Medical Monitor.

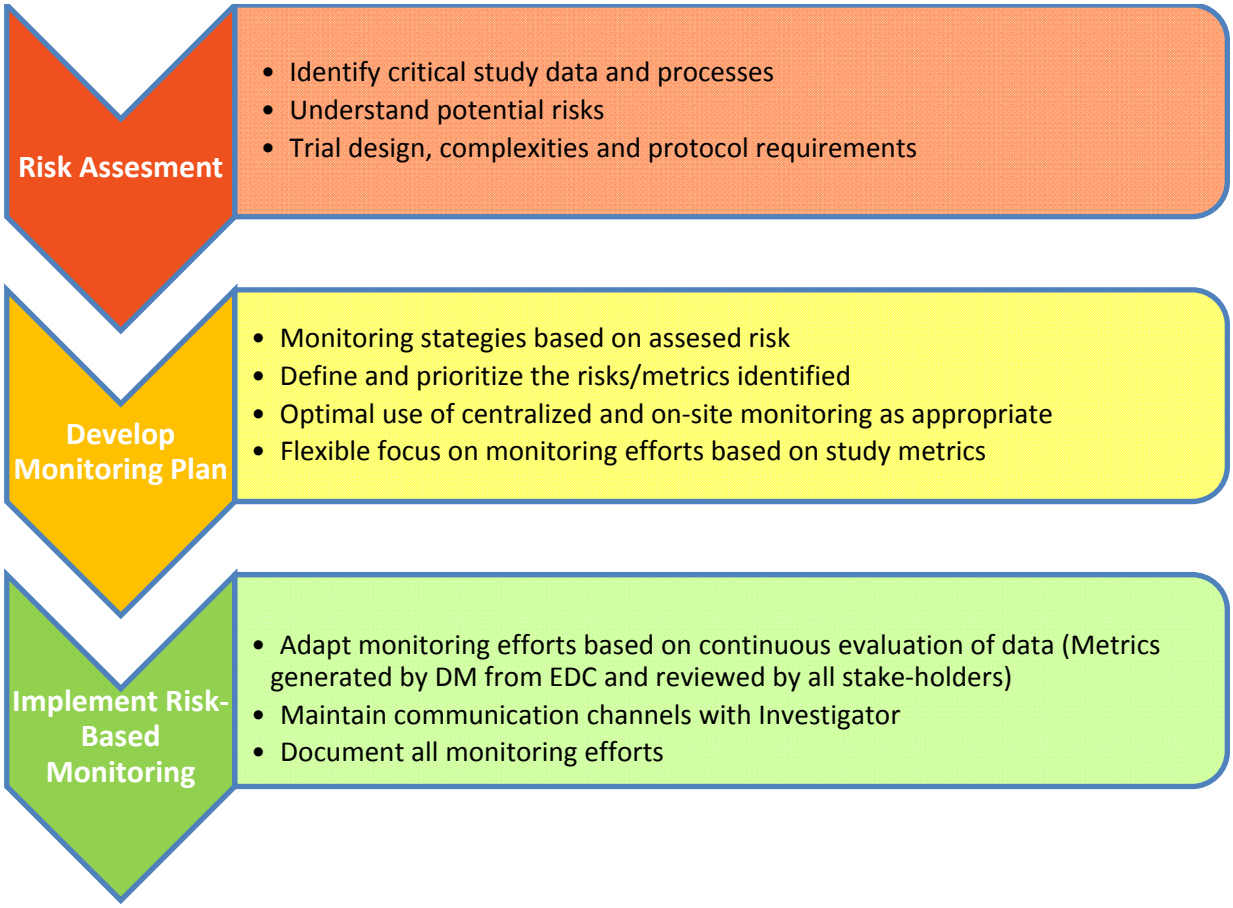
Use of Various Technological innovations Enabling Centralized Monitoring (EDC, CTMS, DDE): On-site source-data verification is a costly, time-consuming process. Use of various technologies can substitute on-site SDV without compromising data quality and integrity, significantly reducing cost by decreasing need of on-site monitoring. As early as 2007, the FDA acknowledged acceptability of original data recorded by direct entry into a computerized system as well as accept certified copies of original data, defined as a copy of original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original. Electronic Data Capture or use of eCRF is rapidly replacing paper CRF globally not only reducing the cost but also improving data quality by use of in-built edit checks which can substantially reduce inconsistencies across data fields. Use of EDC along with Clinical Trial Management System (CTMS) also enabled companies to perform real time centralized data monitoring and focus on critical data points during on-site monitoring. Direct data entry (DDE) allows electronic collection of data at the time of evaluation of study subject. DDE also allows for the acceptance by regulators of electronic source data as original data, rather than requiring subject data to be first transcribed on a piece of paper. Essentially, electronic source then becomes the eClinical trial record (eCTR). This ensures that electronic source records are original records controlled by the clinical research sites, and that a write protected copy of the eCRF for the study archives are available following review and sign-off.

Current monitoring practices in the pharmaceutical industry vary from frequent on-site 100% source data verification to reactive monitoring based on retrospective detection of errors. For major efficacy trials, companies typically conduct on-site monitoring visits at approximately four- to eight-week intervals. Often, oversight efforts are not proportionate with risks and may not optimally address significant risks to trial integrity, particularly systemic error.

Risk-based Approach:

A risk-based approach of monitoring is emerging with the aim of improving monitoring effectiveness which should improve quality and integrity of data, enhance human subject protection and utilize available resources more appropriately. It is increasingly recognized that no single approach to monitoring is appropriate or necessary for every clinical trial (not one size fits all!). Risk-based monitoring strategies and plans should be tailored to the specific human subject protection and data integrity risks of the trial, focuses on critical study parameters and encourages use of a combination of monitoring activities with a greater reliance on centralized monitoring whenever appropriate. Use of EDC systems with the capability to generate quality metrics (e.g., data error rates and protocol violations) in real-time could help identify potentially higher risk sites for the purpose of targeting sites in need of more intensive monitoring (e.g., an on-site monitoring visit). It is especially useful to analyze the data in aggregate manners looking at the trends and outliers and then look closer into the details of the outliers to identify the risks and develop monitoring strategies. As a result, more time would be available for focusing on review of critical data as well as mentoring, feedback, and additional training, if needed, during on-site monitoring visits.

Steps of Risk-based Monitoring:



First, a systematic risk assessment should be performed at the clinical study planning stage to identify and evaluate risks to critical study data and processes. Based on this initial risk assessment, a monitoring plan should be written that is tailored to address important and likely risks identified during risk assessment. A risk assessment should be performed by sponsor/CRO to assess the risk based on the types of data to be collected in a clinical trial, the specific activities required to collect these data, and the range of potential safety risks that are inherent to the clinical study. Findings of this risk assessment should be considered when writing the monitoring plan for the study. For obvious reasons some types of data errors in a clinical trial are more significant than others. For example, not following protocol specific definitions while considering the study endpoints is definitely more critical than errors while capturing subject's baseline demographic data (age, race etc.). Errors while capturing critical data points might profoundly affect study results.

Risk Assessment

At first, it is important to identify critical study data and processes including the following:

- Study endpoints (Data those are critical to the reliability of the study findings, specifically those data that support primary and secondary endpoints)
- Serious adverse events and events leading to discontinuation
- Randomization
- Informed consent
- Maintenance of study blind at site and sponsor level
- Eligibility of study subjects

Ideally, a multi-disciplinary team consists of various stakeholders (Medical Monitor, Clinical Operations, Data Management, Quality Representative, Statistician along with Project management team) should brain-storm on identifying risks to these critical data and processes (What could go wrong? What would be the impact? How these can be detected and rectified in real time?).

A risk assessment should contemplate the pros and cons of various monitoring approach (centralized monitoring or on-site monitoring or adjudication) for different types of data. The study specific factors to determine appropriate monitoring measures [monitoring type, frequency, intensity (100% SDV vs. targeted or random review of a subset of data)] should include the following:

- ***Subjective vs. objective study endpoints*:** Study endpoints that are more subjective or interpretative may require on-site visits to assess the totality of subject records and to review application of protocol definitions with the clinical investigator. More objective endpoints (e.g., death, hospitalization) may be more suitable for remote verification.
- ***Study design complexity*:** More rigorous monitoring approaches (e.g., increased frequency of review irrespective of the type of monitoring approach selected and/or use of multiple monitoring approaches) may be necessary as study design complexity increases. Examples may include studies with adaptive designs, stratified designs, complex dose titrations, or multiple device placements
- ***Health status of the study population*:** Seriously ill (e.g. Myocardial Infarction) and/or vulnerable should require more intensive on-site monitoring to be sure appropriate protection is being provided compared to study population which is suffering from minor illness (e.g. Chronic constipation)
- ***Safety profile of the study drug/investigational product***
- ***Phase of the study***
- ***Site specific factors:***
    - ***Geographical distribution of study sites*:** Different standards of care or less established clinical trial infrastructure may require more intensive monitoring, including some level of on-site monitoring
    - ***Experience of the Clinical Investigator:*** Relatively inexperienced study site may require a more intensive monitoring and early mentoring. A tapered approach to monitoring may be used with more intensive monitoring at the study initiation stage.

Well-designed protocol and Case Record Form (CRF)

One of the most important tool for ensuring human subject protection and high quality data is a well-designed and articulated protocol which prospectively incorporates the mitigation or management of the important risks associated with subject safety and data reliability. Monitoring is one tool in a quality

toolbox designed to mitigate and/or manage risks. A poorly designed or ambiguous protocol or Case Report Form may introduce systemic errors that can reduce credibility of data in a clinical investigation regardless of rigorous monitoring.

Development and Implementation of Monitoring Plan

Critical data and processes identified by the risk assessment should be addressed in a well-documented monitoring plan. The monitoring plan should have specifics of types of monitoring to be used and checks performed during these, responsibilities and requirements for the study. The timing, frequency and scope of planned monitoring activities need to be included. The plan should be flexible to focus on monitoring efforts based on continuous evaluation of study data. The triggers of such change in focus should be well-defined. All personal performing the monitoring tasks must be trained on the monitoring plan as well as all the applicable Procedures and Instructions required for performing these tasks.

Handling of possible deviations or failures critical to study integrity including documentation and communication process must be established in the monitoring plan. Centralized monitoring also must be documented as on-site monitoring. The process of such documentation including templates and logs should be part of the monitoring plan. If a substantial new risk is identified during the study, monitoring plan must be promptly amended by including appropriate monitoring strategies mitigating such risks.

Conclusion:

Risk-based approach of monitoring is unequivocally a significant advancement in clinical trial oversight process. Technological innovations like EDC definitely armed us to perform real time centralized monitoring which is proven to be a cost-effective solution. Risk-based monitoring is the path forward as it will also ensure protection of human subjects, increase credibility of study data along with optimal use of resources. No single plan fits all study scenarios. Hence, developing study specific monitoring plan following a systematic risk-assessment is critical to success of this new approach. A timely recognition of need from Regulators is welcomed by the Industry. Few aspects must be kept in mind while implementing more centralized monitoring process resulting less frequent site visits. Regular communication channels must be established in-between clinical investigator and sponsor/CRO. Sponsor/CRO should provide appropriate feedback to the Investigator regarding conduct of the study. Initial and ongoing site training must continue using remote training modes using technological innovations.

References:

1. Food and Drug Administration (2011) Guidance for Industry Oversight of Clinical Investigations – A risk Based Approach to Monitoring (Draft Guidance) http://www.fda.gov/downloads/Drugs/GuidanceCompliance%20RegulatoryInformation/Guidances/UCM269919.pdf

2. European Medicines Agency (2011) Reflection Paper on Risk Based Quality Management in Clinical Trials (Draft dated 05/08/2011) http://www.ema.europa.eu/ema/doc_index.jsp?curl=pages/includes/document/document_detail.jsp?webContentId=WC500110059&murl=menus/document_library/document_library.jsp&mid=0b01ac058009a3dc