Position Paper: Risk-Based Monitoring Methodology

1. Abstract

Current On-site Monitoring practices are frequency-based, conform to a prescribed monitoring visit schedule, and provide generalized quality control at investigational sites. Although this practice does provide a level of control, advances in risk-based approaches and technology provide an opportunity for a more holistic and proactive approach through Off-site and Central Monitoring and a targeted approach to On-site Monitoring. By building quality and risk management approaches into the scientific design and operational conduct of clinical trials, risks can be mitigated and issues can be detected early or prevented entirely. TransCelerate BioPharma Inc. (TransCelerate) developed a methodology that shifts monitoring processes from an excessive concentration on Source Data Verification to comprehensive risk-driven monitoring. This philosophical shift in monitoring processes employs Centralized and Off-site mechanisms to monitor important study parameters holistically and uses adaptive On-site Monitoring to further support site processes, subject safety, and data quality.

2. Introduction

Over the last decade, the complexity and cost of clinical trials has increased dramatically. Despite advances in the digital revolution, the pharmaceutical industry's productivity has dropped.[1] Current operational practices used in clinical trials are expensive and do not guarantee data quality. Through modernization, including use of technology enablers, efficiencies can be gained without impacting subject safety by implementing quality risk management approaches to clinical trial oversight.[2]

The pharmaceutical industry has traditionally relied heavily on On-site Monitoring approaches, including significant amounts of Source Data Verification (SDV) to help ensure subject safety and generate quality data. It is a reactive approach, limited in its ability to quickly identify issues and prevent them from recurring. Further, this resource-intensive approach is applied uniformly throughout a trial rather than proportionate to risks. Since intense On-site Monitoring does not guarantee identification of all subject safety or data quality issues, the associated high costs are disproportionate with the value gained. Therefore, there is movement within the industry (eClinical Forum[3]) driven by health authorities (HSP/BIMO Concept Paper 2007[4]; Food and Drug Administration [FDA], FDA Draft Guidance 2011[5]; European Medical Agency [EMA], EMA Reflection Paper 2011[6]; MHRA Risk Adapted Approaches[7]) to transition to Risk-Based Monitoring.

Several initiatives are underway to promote Risk-Based Monitoring (RBM) paradigms. The Clinical Trials Transformation Initiative (CTTI) identified practices to increase the quality and efficiency of clinical trials.[8] CTTI advocates building Quality by Design (QbD) into clinical trials, starting with protocol development and extending across all aspects of a trial. Quality refers to the ability to effectively and efficiently answer the intended question about benefits and risks, while assuring subject safety.

Decisions are supported by quality data which is not considered error-free data, but rather fit-for-purpose data that sufficiently supports conclusions equivalent to those derived from error-free data.[2] QbD includes a focus on key risks to subject safety and data quality, developing a quality risk management plan that focuses on factors that are at high risk for generating errors, and applying an efficient monitoring approach to rapidly detect and correct issues while the study is ongoing. A quality risk management plan should be created during study planning, and be reviewed and amended throughout the trial to mitigate risks. Monitoring strategies, tailored to risks, should permit timely oversight and be focused on Critical Processes and Critical Data. Notably, Investigators are responsible for their site's data quality and are expected to partner with the Sponsor to address, resolve, and prevent issues.

TransCelerate BioPharma Inc. (TransCelerate) is a non-profit organization comprised of pharmaceutical and biotechnology companies collaborating to create transformational process improvements that will help ensure safe and effective therapies are brought to market more efficiently. TransCelerate developed a standard approach for RBM that can be adopted for any type, phase (Phase 1 through Phase 4), and stage of trial. The TransCelerate RBM methodology improves efficiency by changing the focus to Central or Off-site Monitoring activities that are intended to identify potential issues sooner than a monitoring strategy that relies primarily on site monitoring visits. TransCelerate member companies are piloting the methodology on various types of trials. Lessons from these pilots will inform and evolve the RBM methodology, as needed.

TransCelerate's RBM methodology uses quality risk management as a foundation in ensuring subject safety and data quality through the implementation of the following: (1) building QbD into trials, (2) early and ongoing risk assessment, (3) a focus on Critical Processes and Critical Data, (4) use of Risk Indicators and Thresholds, and (5) adjustment of monitoring activities based on the issues and risks identified throughout the study. By monitoring available data Off-site or Centrally, On-site Monitoring can be targeted to activities that cannot be assessed remotely. Additionally, TransCelerate has adopted the term Source Data Review (SDR) that describes review of source data for protocol compliance, quality of documentation, as well as site processes in contrast to transcription checking, referred to as Source Data Verification (SDV).

The TransCelerate RBM methodology is aligned with the QbD paradigm, and with the monitoring and study oversight expectations of health authorities. When RBM methods are used, applicable ethical standards, subject rights, laws and regulations are expected to be followed. Further, TransCelerate's methodology is being developed concurrent with the transition to risk-based inspection processes by health authorities.[5,6]

2.1. Retrospective Analysis of Monitoring and SDV

To better understand the impact of existing SDV approaches on overall data quality, TransCelerate member companies evaluated data discrepancies for completed studies to determine the rate of queries identified via SDV as compared to all queries for a study, and then further assessed those queries to determine what percentage of SDV-generated queries were found in Critical Data.

Nine sample studies from 6 member companies were analyzed [Retrospective Analysis of Monitoring and SDV]. Despite variability in the way companies manage their data review activities, all companies were similar in the low rate of SDV-generated queries. The average percentage of SDV queries generated was 7.8% of the total number of queries generated. The average percentage of SDV queries that were generated in Critical Data as represented as a part of the total number of queries was 2.4%.

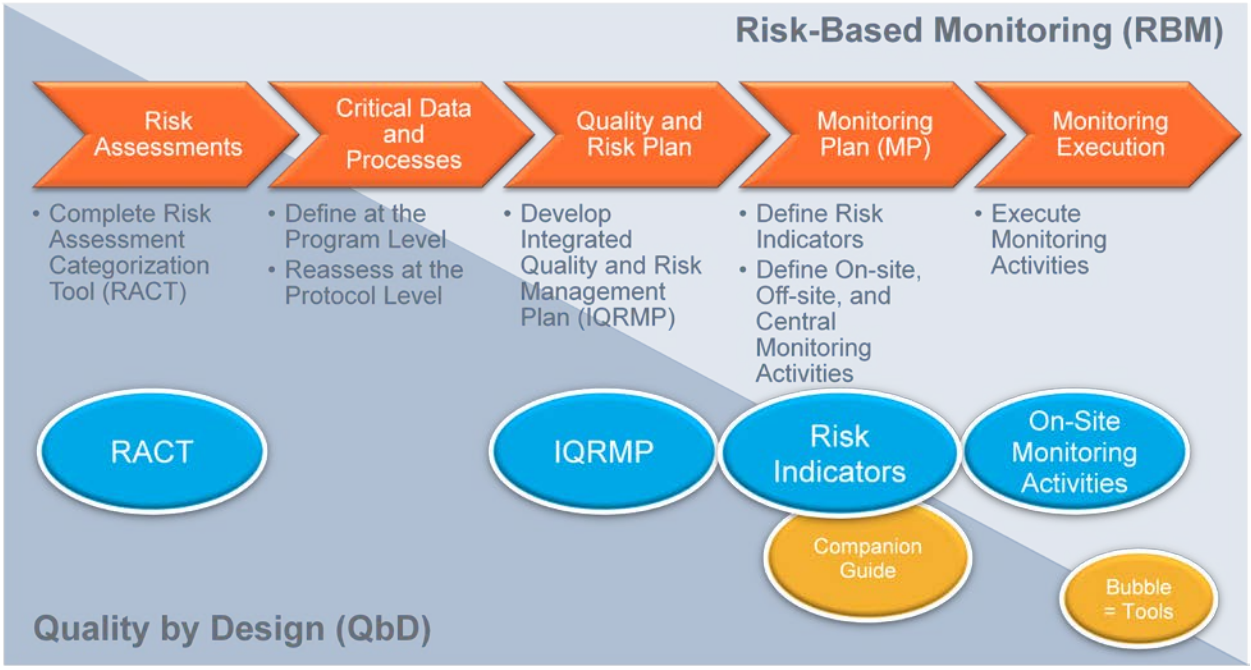
The rate of SDV-only discrepancies in Critical Data (2.4%) suggests that SDV has a negligible effect on data quality. These data help support the TransCelerate methodology which recommends shifting the focus from On-site Monitoring (including 100% SDV) to a risk-driven tailored approach to monitoring. This shift is consistent with regulatory guidance.[5,6,7]

3. Methodology for Risk-Based Monitoring

TransCelerate's RBM methodology describes the steps taken to assess risk, to determine Critical Data and Processes, and to mitigate those risks through the utilization of the Integrated Quality Risk Management Plan (IQRMP). Well-designed protocols and case report forms (CRFs) are considered important foundational influencers with an impact on quality and efficient monitoring.

Figure 1 shows an overview of TransCelerate's methodology and the fundamental connection between QbD and RBM.

Figure 1 TransCelerate Methodology for Risk-Based Monitoring – High Level Process and Associated Tools



3.1. Risk Assessment

The first step in application of the methodology requires a cross-functional risk assessment at the program level. Program-level risks are not specific to a particular protocol, but rather are common across all studies in the program (e.g. Investigational Product, or IP, is first in class). The program-level risk assessment includes identification of the initial list of data which are to be treated as Critical Data across all protocols in the program.

Moving next from program-level to protocol-level risk assessment, the initial list of Critical Data is expanded as risks are assessed in greater detail during protocol development. The Risk Assessment and Categorization Tool (RACT) can be used to facilitate risk assessment by helping to identify various risks and establish any associated mitigation plans [Risk Assessment Categorization Tool (RACT)]. Protocol-level risks and mitigations are documented in the various components of the IQRMP [Integrated Quality Risk Management Plan (IQRMP)]. The individual plans contained in the IQRMP (e.g. Monitoring Plan) should be developed based on a risk assessment that takes into consideration the impact and likelihood of error, mitigation plan and the extent to which the error would be detectable. All data (critical and data not qualifying as critical) should be managed, as appropriate, through standard data processing using edit checks, analytical, and statistical methods as outlined in the appropriate functional plan in the IQRMP. There are various strategies to monitor Critical Data (e.g. On-site, Off-site, or Central). To some extent, the choice depends on the data collection technology employed.

Next, each study is assigned a high, medium or low Overall Risk Level. The assigned Overall Risk Level may vary across the various stages of the study (e.g. assigned as high during recruitment, medium during the active stage, and low during long-term follow-up). The baseline type and amount of monitoring activities varies depending on the assigned Overall Risk Level.

3.2. Critical Data and Processes

When defining Critical Data, cross-functional collaboration is necessary to ensure appropriate identification and monitoring of the data and to avoid duplication of efforts across functions. Emphasis should be placed on the quality of data required to meet the trial objectives and to obtain reliable results. Critical Data includes data that will be used to make decisions about the IP's safety and efficacy profile. Examples of Critical Data and Processes include:

- Data that support primary and key secondary objectives
- Data critical to subject safety (e.g. serious adverse events, other events leading to discontinuation of treatment)
- Processes that underpin subject safety and ethical treatment (e.g. seeking appropriate medical consultation or scheduling extra visits/procedures in the event of significant clinical or laboratory findings)
- Processes that underpin data quality (e.g. blinding, referring events for adjudication, controlling inter-rater variability)

Once defined, Critical Data and Processes should be monitored accordingly.

3.3. Risk Indicators

The next step involves the creation of potential Risk Indicators [Risk Indicators]. Risk Indicators should be assigned with Thresholds which once reached, are designed to trigger an action such as increased data scrutiny or site follow-up (e.g. telephone call or visit to the site). Risk Indicators and associated Thresholds and actions are also documented in the IQRMP [Integrated Quality Risk Management Plan (IQRMP) and Risk Indicators]. As with all other components of the IQRMP, Risk Indicators should be developed and finalized in a timely manner (i.e. during study planning), using cross-functional collaboration. To support the use of Risk Indicators, a companion guide has been prepared that describes how to implement Thresholds and weightings associated with each risk [Companion Guide to Risk Indicators]. Feedback is being collected on how well these Risk Indictors perform in RBM.

Note that site-level risks are initially assessed during site selection and qualification and are not specifically addressed in the completion of the risk assessment at the protocol level. The method of identifying and managing site-level risks may be documented in either a process document or in a monitoring plan.

3.4. Monitoring Approach

TransCelerate accepts the ICH GCP description of monitoring which refers to 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), GCP, and the applicable regulatory requirements (ICH-E6 definitions). The primary assumptions involved with this approach are listed in Table 1 (following page).

TransCelerate describes RBM approaches that are carried out by various roles (e.g. Statisticians, Data Managers, Monitors). When other functions not traditionally labeled as Monitors are performing RBM activities (e.g. Statisticians), these functions should describe their monitoring activities using a plan (e.g. Statistical Analysis Plan). The IQRMP ensures proper mapping between various plans. Documents contained therein should be amended (e.g. to reflect new information, issues, risks) as needed at any point in the study.

Table 1 Assumptions for the TransCelerate Risk-Based Monitoring Methodology

1	Central and Off-site Monitoring Activities serve as the foundation of monitoring efforts and are complemented by targeted On-site Monitoring Activities based on a defined risk level, critical process and data, ongoing assessment of Risk Indicators and instructions within the Monitoring Plan.
2	Regardless of the monitoring approach established in the MP, monitoring activities can be increased in response to issues and risks identified (whether identified by other functions e.g. Statisticians or during the Monitor's Off-site or On-site Activities). Increases in monitoring activities should be done in a temporary, targeted manner with the goal of returning to the standard level of monitoring as described in the MP. To prevent the issue from recurring, it is important to identify and address the root cause of the issue.
3	The methodology is tailored to the available technology. For example, if electronic medical records are available for remote monitoring, the Monitor can perform certain activities (e.g. SDV, informed consent review) off-site (remotely).
4	Central and Off-site Monitoring is dependent on the timely entry of data and query resolution. Sponsors should set expectations for data entry and query response timeliness in their contracts with sites.
5	Functional oversight and associated quality documents within the IQRMP may be amended at any point in the study in response to changing risks or identified issues (e.g. in response to a protocol amendment; instructions for monitoring a new safety signal).
6	Risk-based monitoring expectations can be documented as a standard process (e.g. SOP) rather than in a functional plan in the IQRMP, as appropriate.
7	The methodology may be applied to all phases (Phase 1 through Phase 4), types, and stages of trials.
8	Routes of communication should be tailored to what is most effective in ensuring successful conduct of the study.
9	Risk Assessments should be initiated prior to the finalization of protocols and CRFs to minimize risks in advance of starting the trial. Monitoring strategies are adapted to ensure oversight to what is not prevented via protocol or CRF design.

3.4.1. Monitoring Plan (MP) Requirements

The trial-specific Monitoring Plan (MP), a plan within the IQRMP, typically is created by the clinical monitoring group. The MP includes trial-specific instructions for Monitors including monitoring activities that are conducted to mitigate risks associated with a particular study. The MP should guide Monitors beginning after site activation until close-out and should address any changes to the way that the trial is monitored during various stages (e.g. recruitment, conduct, follow-up) of the study.

Based on the defined Overall Risk Level (high/medium/low), a standard monitoring approach is defined in the MP. Monitoring activities are aligned with the Overall Risk Level assigned at the protocol level; as risk level decreases, the level of monitoring should decrease, except as needed to address issues.

Similarly, if the Overall Risk Level changes at various stages of the study (e.g. moving from active IP to follow-up stage), the monitoring level changes. The MP should be driven by risk and include plans for risk mitigation. Even in a low-risk study, there may be aspects of the study that might be considered high-risk. In these cases, the MP should include directions on how to mitigate those risks.

The MP should include those activities conducted Centrally, Off-site, and those that must be performed On-site [Definitions]. On-site Monitoring Activities are conducted based on (1) timing of study activities (e.g. Site Initiation Visit), (2) workload (e.g. SDV), or (3) interventions to address issues or risks (e.g. by targeted Risk Indicators). On-site Monitoring visits are not conducted on a predetermined timeframe (e.g. every 4-6 weeks). Off-site and Central Monitoring is ongoing and such activities can be targeted or can occur at fixed intervals.

3.4.2. Off-site and Central Monitoring Activities

Off-site Monitoring Activities are performed by Monitors and can be distinguished from Central Monitoring which could also be performed by Monitors or other roles within clinical operations or by other functions (e.g. Statistics, Data Management, Safety). Off-site and Central Monitoring include various types of data review activities.

3.4.3. On-site Monitoring Activities

On-site Monitoring Activities are described in the Appendix [On-site Monitoring Activities]. Two areas of particular interest are detailed below.

3.4.3.1. Source Data Verification (SDV) and Source Data Review (SDR)

TransCelerate draws a distinction between Source Data Verification (SDV) and Source Data Review (SDR). SDV is the process by which data within the CRF or other data collection systems are compared to the original source of information (and vice versa) to confirm that the data were transcribed accurately (i.e. data from source matches data in the CRF or other system and vice versa). SDR involves review of source documentation to check quality of source, review protocol compliance, ensure the Critical Processes and source documentation (e.g. accurate, legible, complete, timely, dated) are adequate, to ascertain Investigator involvement and appropriate delegation, and assess compliance to other areas (e.g. SOPs, ICH GCPs). SDR is not a comparison of source data against CRF data. SDR is necessary to evaluate areas that do not have an associated data field in the CRF or system available for more timely remote review.

The rationale for the SDV-SDR distinction is two-fold. First, it enables companies to prioritize the high-value task of compliance checks and de-prioritize the low-value task of checking for transcription errors. Transcription errors identified by SDV are typically infrequent, insignificant, and do not lead to study data being unusable. In contrast, issues with compliance (i.e. protocol violations) are one of the reasons for study data being excluded from the final efficacy analysis. Based on risk level, as well as available technology, different levels of SDV and SDR may be specified in the MP. Second, the SDV-SDR distinction permits a more focused response to errors identified in each category.

For example, if the Monitor identifies a potential issue with lack of Investigator involvement, there is no need to escalate the amount of SDV since it is not a transcription issue. Instead, the Monitor could evaluate other areas (e.g. staff meeting minutes) to assess Investigator involvement.

Since the defined SDV task is considered low-risk and low-value, routine SDV (i.e. the baseline amount of SDV that must be conducted at each site) is reduced to a percentage of Critical Data (or a percentage of subject visits if available technology does not facilitate efficient flagging of Critical Data within the CRF) described further in section 3.4.4. This SDV definition and priority (per low-risk and low-value) also means that SDV does not need to be conducted prior to other functions completing their data review activities.

Sponsors should consider the following with respect to SDR and SDV:

- SDV and SDR do not need to be performed on the same sample
- SDV and SDR may be assigned different percentages as a starting point
- SDV and/or SDR can be temporarily increased or decreased depending on the type of issues and risks noted at the site, country/region, or study (during On-site, Central or Off-site reviews). For example, if a site is identified as an outlier based on a lower than average number of reported adverse events, consider increasing SDV of visits for those subjects that have no AEs reported.

3.4.3.2. Documentation of On-site Monitoring Activities

Monitoring reports should serve as tools for the Monitor to communicate a concise, high-level summary of monitoring activities, issues and associated actions. While monitoring reports traditionally capture a summary of activities as a snap-shot in time, other approaches (e.g. review of issue listings) are also acceptable where technology permits (e.g. electronic audit trails showing CRF pages opened, availability of study- or site-level listings of issues). While there is generally not a need to document every monitoring activity, appropriate documentation, which includes documentation of the management and resolution of issues is necessary. Written follow-up to the site is necessary to document issues in which the Investigator must be informed and/or needs to take action.

3.4.4. Utilization of the Overall Risk Level to Establish Baseline Monitoring Levels

Utilization of the Overall Risk Level (high/medium/low) and the Risk Indicators [Risk Indicators] drive monitoring activities and actions throughout the study. Those actions might include an On-site Monitoring visit or other Off-site actions which could be employed to investigate or mitigate potential issues [On-site Monitoring Activities]. Table 2 (following page) illustrates how the study's Overall Risk Level impacts on some of the common monitoring activities. These ranges are recommendations; higher or lower percentages can be applied for a given study or site. Depending on available technology or innovative processes, the activities described in Table 2 may be performed Centrally or Off-site.

Table 2 Risk Categorization and Application to Monitoring Activities

Monitoring Activity*	High Risk	Medium Risk	Low Risk
Validation and Review of Data (Central/Off-site^)	100%	100%	100%
SDV of Critical Data for First Randomized Subject	>75 - 100%	>50 - 75%	0 - 50%
SDV of Critical Data for Subsequent Randomized Subjects	>15 - 25%	>5 - 15%	0 - 5%
SDR of Critical Data for First Randomized Subject	>75 - 100%	>25 - 75%	0 - 25%
SDR of Critical Data for Subsequent Randomized Subjects	>25 - 40%	>10 - 25%	0 - 10%
Informed Consent Review	>75 - 100%	>50 - 75%	20 - 50%

* As the risk level may vary across the various ***stages*** of the study, the type, amount, and location of monitoring activities may also vary

^ Centralized or Off-site review may guide specific interventions

The Informed Consent process is critical in ensuring that the rights of the patient have been considered prior to enrollment in a clinical trial. The level of risk associated with the informed consent process can also be assessed for a study/site on an ongoing basis throughout the clinical trial life-cycle as there may be situations where it is not necessary to perform the suggested levels of review of the Informed Consent Forms (e.g. updates to safety information within long term follow-up studies where patients have been in the trial for several years and may no longer be receiving IP). In these cases alternative methods can be considered to ensure that the informed consent process has been appropriately considered and patients informed appropriately.

4. Implementation Considerations

4.1. Measures

The following metrics are examples intended to assess the impact of the proposed methodology. Collectively, they measure changes in quality, timeliness of data collection and issue resolution, and efficiency of trial operations affected by Risk-Based Monitoring, on an ongoing basis or after the closure of a study.

Table 3 Suggested Measures for Evaluating TransCelerate's Risk-Based Monitoring Methodology

Dimension	Metric Examples
Quality	• Number and classification of major/critical audit/inspections findings per audited site • Number of significant protocol deviations per site • Number of unreported, confirmed SAEs as discovered through any method
Timeliness/Cycle Time	• Average number of days from data entry to initial monitoring • Median number of days from visit to CRF data entry • Median number of days from query open to close
Efficiency	• Average monitoring (all types) cost per site • Average interval between On-site Monitoring visits per site

4.2. Technology

Technology, data integration, and analytics are all key enablers for efficient implementation of the proposed methodology. A significant but achievable challenge to enable efficient remote monitoring is the effective integration of disparate data sources and formats. Additionally, relevant analytics must be developed to enable rapid identification of outliers and trends in large volumes of data. Key elements that enable data integration and analytics should be considered by companies implementing the proposed methodology [System Requirements and Preferred System Attributes]. TransCelerate will refine these system requirements while piloting the methodology.

Looking ahead, the continued digitization of clinical research data will enable further expansion of Off-site and Central Monitoring Activities. As all clinical trial data – including Informed Consent – becomes digital, a major shift to Off-site and Central Monitoring is possible.

4.3. Capabilities and Organizational Change Management

It is important to consider resourcing capabilities, as well as the organizational change management required to implement risk-based methodology. Training, coaching, and ongoing communication will be necessary at all levels of the sponsor organization, associated third-party providers, and at the investigational sites. Off-site and Central Monitoring Activities might require a different set of skills than required to perform On-site Monitoring Activities (e.g. the Off-site and Central Monitoring might require data-focused, analytical skills to help manage risks and identify issues across a site and/or study).

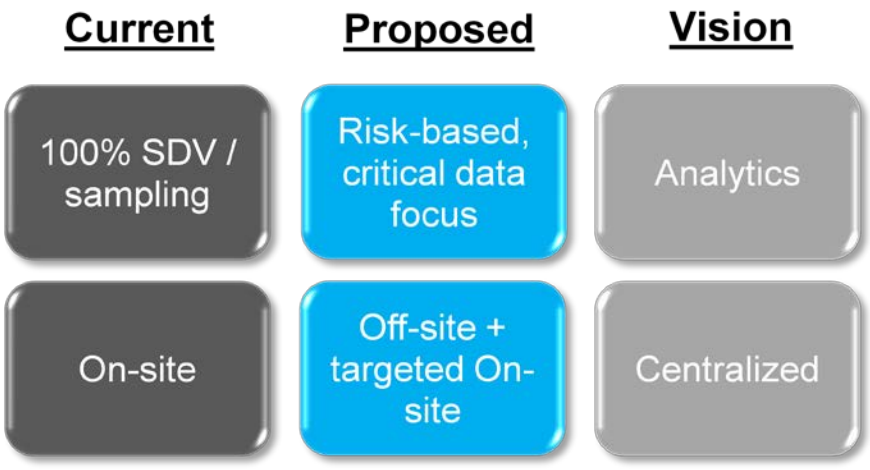
Additionally, sponsors and third-party providers must consider the degree of organizational change necessary to implement this methodology. There are dynamic business process and technology implications that affect sponsors, third-party providers, and technology vendors.

As pilot trials are conducted using the RBM methodology described herein, lessons from these pilots will be included in a future TransCelerate RBM paper centered on resourcing capabilities and organizational change management.

5. Conclusion

TransCelerate's RBM methodology described throughout this document is positioned as an ongoing progression in the evolution of clinical trial monitoring processes depicted below.

Figure 2 Evolution of TransCelerate Methodology for Risk-Based Monitoring



The approach includes early and recurrent risk assessment, identification of Critical Data to be monitored for risk mitigation, Off-site and Central Monitoring as the foundation, and targeting of On-site Monitoring visits. The approach brings QbD and risk-based methodology to the forefront of efforts to ensure data quality and subject safety by leveraging available technology and improved processes.

It can benefit subjects, Investigators, regulators, third-party providers, and sponsors: In short, this methodology benefits the entire clinical trial ecosystem.

5.1. Looking Ahead

As previously mentioned, clinical research data is becoming increasingly digitized. As this trend continues and data standardization is realized, a transition to centralized, analytics-enabled monitoring will become a reality. Centralized analytics are used extensively in other industries (e.g. process control in manufacturing, banking, etc.), at great benefit including improved quality with an associated lower cost. The same principles - *digitize; centralize; analyze; predict; and prevent* – can soon be effectively applied to pharmaceutical development and collectively comprise our vision for the next evolutionary step in clinical trial monitoring.

6. References

1. Scannell JW, Blanckley A, Boldon H, Warrington B. Diagnosing the decline in pharmaceutical R&D efficiency. *Nature Reviews Drug Discovery*. 2012;11:191-200.
2. Meeker-O'Connell A, Ball L. Current trends in FDA inspections assessing clinical trial quality: an analysis of CDER's experience. The Food and Drug Law Institute Update. March/April 2011.
3. eClinical Forum. Risk-based approaches – best practices for ensuring clinical data quality. Available at: http://eclinicalforum.org/en-gb/knowledge.aspx. Published September 2012.
4. HSP/BIMO Concept Paper: Quality in FDA-Regulated Clinical Research. Human Subject Protection (HSP)/Bioresearch Monitoring (BIMO) Initiative Workshop April 2007.
5. FDA. Guidance for industry oversight of clinical investigations – a risk-based approach to monitoring [draft]. Available at: http://www.fda.gov/downloads/Drugs/guidanceComplianceRegulatoryInformation/Guidances/UCM269919.pdf. Accessed May 20, 2013.
6. EMA. Reflection paper on risk based quality management in clinical trials (EMA/INS/GCP/394194/2011). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/08/WC500110059.pdf. Accessed May 20. 2013.
7. MHRA. Risk-adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products. Available at: http://www.mhra.gov.uk/home/groups/l-ctu/documents/websiteresources/con111784.pdf. Accessed May 20, 2013.
8. Clinical Trials Transformation Initiative. Effective and efficient monitoring as a component of quality. Available at: https://www.ctti-clinicaltrials.org/project-topics/study-quality/effective-and-efficient-monitoring-as-a-component-of-quality. Accessed May 20, 2013.

7. Definitions

Term	Definition
Critical Data	Data that are critical to the reliability of the study findings, specifically those data that support primary and key secondary endpoints. Other Critical Data include data related to subject safety, such as serious adverse events and events leading to discontinuation of treatment.
Critical Processes	Processes that are critical to the reliability of the study findings. Other Critical Processes include those related to ensuring subject safety and compliance with ICH-GCP and regulations.
Integrated Quality and Risk Management Plan (IQRMP)	A tailored and integrated plan for a specific clinical trial that aligns associated quality management plans (e.g. Monitoring Plan) across identified risks and defined Critical Data and Processes to ensure cross-functional teams focus on the risks that are most important to subject safety, data quality and regulatory compliance.
Monitoring	
Central Monitoring	A "remote evaluation carried out by sponsor personnel or representatives (e.g. Data Manager, Statistician, or Monitor)" (FDA Draft Guidance).
Off-site Monitoring	Includes monitoring activities as defined either within process documents or in the MP that occur away from the study site location (e.g. at a Monitor's home or in a sponsor representative's office). This is also commonly known as remote monitoring.
On-site Monitoring	"An in-person evaluation carried out by sponsor personnel or representative(s) at the site(s) at which the clinical investigation is being conducted" (FDA Draft Guidance).

Term	Definition
Overall Risk Level	An estimate of the level of risk described as high/medium/low that guides the application of a baseline monitoring approach.
Quality by Design (QbD)	Systematically building quality into clinical trial design to ensure that processes are focused on what is critical and are performed in a way that mitigates errors which have the greatest impact on subject safety and data quality.
Risk Indicator	Critical Data and other study variables to be assessed (in many cases by comparing across program / protocol / country / site).
Risk-Based Monitoring	An adaptive approach to clinical trial monitoring that directs monitoring focus and activities to the evolving areas of greatest need which have the most potential to impact subject safety and data quality.
Source Data Verification (SDV)	Commonly known as 'transcription checking', the process by which data within the CRF or other data collection systems are compared to the original source of information (and vice versa) to confirm that the data were transcribed accurately (i.e. data from source matches data in the CRF or other system and vice versa).
Source Data Review (SDR)	Review of source documentation to check quality of source, review protocol compliance, ensure the Critical Processes and source documentation (e.g. accurate, legible, contemporaneous, original, attributable) are adequate, to ascertain Investigator involvement and appropriate delegation, and assess compliance to other areas (e.g. SOPs, ICH GCPs). SDR is not a comparison of source data against CRF data.
Thresholds	The level, point, or value associated with a Risk Indicator that will trigger an action.

8. Appendices

8.1. Appendix 1 – Toolkit

8.1.1 Risk Assessment Categorization Tool (RACT)

Risk Assessment Categorization Tool (RACT)

Purpose

The purpose of the Risk Assessment and Categorization Tool (RACT) is to facilitate risk assessment and risk mitigation by the following:

- Determine the risks that could affect subject safety, data quality or regulatory compliance
- Identify how and by which function(s) the risks will be managed
- Document risk mitigations in the individual functional plans which form the study's overall Integrated Quality Risk Management Plan (IQRMP) (e.g. Data Review Plan, Statistical Analytical Plan, Safety Plan)

Categories of monitoring activity risk will be ranked as high (red), medium (yellow) or low (green), based on discussions with appropriate functions (potential questions are provided as guides and are not considered all inclusive). Using the agreed risk categorizations and application to Monitoring Plan activities, an Overall Risk Level for monitoring activities will be determined. This Overall Risk Level (high/medium/low) will determine the baseline level of Monitoring Activities described in the Monitoring Plan table (Table 2).

Instructions for Use

A list of potential categories for risk assessment (e.g. Study Phase, Subject Population) is provided in the RACT (download here). Risk Categories that would likely impact the assignment of Monitoring Activities shown in Table 1 are noted accordingly. The Risk Categories should be reviewed, adjusted, and any deemed to affect the study's Monitoring Activities should be documented as such. All Risk Categories should be assessed for risks and their impact on functional plans housed within the IQRMP should be documented. Each Risk Category has an objective, a list of potential questions and considerations or examples that should be considered when determining risks. After team discussion, each Risk Category should be ranked as high, medium or low. The risks, Overall Risk Level, as well as the individual functional plans for risk mitigation (e.g. Monitoring Plan, Safety Plan, Medical Monitor Plan, etc.), should be documented accordingly.

Assignment of Overall Risk Level

The final RACT output is part of the Integrated Quality Risk Management Plan (IQRMP). Risks identified during the risk assessment process should be documented within the IQRMP.

Upon completion of the RACT (see Excel RACT Tool embedded below), assign the Overall Risk Level as it relates to monitoring activities: <<*high/medium/low*>>, and document it in the appropriate risk plan (e.g. Monitoring Plan). The Overall Risk Level may vary by stage of the study.

Justification

Document the rationale for the assigned Overall Risk Level. Examples could include weighting certain categories according to their risk impact as illustrated below.

Example for Overall Risk Level Scoring

Category (Weighting %)	**Study A** **Phase III, endpoint/mortality study**	**Study B** **Phase IV, some remote data entry by subjects**	**Study C** **Phase II, well-known population, well-categorized disease state**
Safety (xx%)	high	low	high
Study Phase (xx%)	med	low	high
Complexity (xx%)	med	low	med
Technology (xx%)	low	med	low
Subject Population (xx%)	high	low	med
Data Collection (xx%)	low	low	low
Endpoints (xx%)	high	low	med
Overall Risk Level	**high**	**low**	**med**

Excel RACT Tool

The RACT can be downloaded for use here.

Integrated Quality and Risk Management Plan (IQRMP)

Purpose

Study quality is a shared responsibility across all functions involved in collecting, analyzing and reporting clinical trial data.

The IQRMP provides a tailored and integrated plan for a specific clinical trial that will:

- Include the clinical and medical risks identified at the program level
- Define the actions that each function will take to proactively identify, assess, and manage risk throughout the life of a clinical trial
- Define the Critical Data identified by cross-functional representatives (e.g. elements that impact primary efficacy endpoint and critical safety parameters)
- Align associated quality management plans (including the Monitoring Plan) across identified risks and defined Critical Data and Processes to ensure cross-functional teams focus on the risks that are most important to subject safety, data quality and regulatory compliance
- Describe the process that each function will follow to review and revise the IQRMP throughout the life of the clinical trial

The IQRMP is not intended to duplicate the content of existing functional plans; these are linked or referenced within the IQRMP and accountability for each plan remains with the relevant function.

Content

Examples of inputs to the IQRMP include:

- Clinical Development Plan
- Regulatory Strategy
- Risk Assessment and Categorization Tool
- Critical Data
- Any existing program or product risk management plans

The IQRMP is graphically depicted below. The procedures and activities described within the IQRMP should not duplicate instructions contained in Standard Operating Procedures. The IQRMP should describe the trial-specific actions/processes that will be implemented to address identified risks and focus on Critical Data.

The overall accountability for the development and maintenance of the IQRMP should be assigned to a centralized function such as project or program management to ensure that the key elements are aligned across all functions.

The IQRMP including the RACT, Critical Data, Risk Indicators, and Various Functional Plans

Recommended / Potential Risk Elements within the IQRMP

Key Elements of the IQRMP	Description	Location (*Provide link to document*)
Approval Section	Documents agreement and sign off by all relevant functions.	
Revision History	Provides version control and tracking.	
Critical Data	Defines and documents the Critical Data for the study. Critical Data is data that is critical to the reliability of the study findings, specifically those data that support primary and key secondary endpoints. Other Critical Data includes data critical to subject safety, such as serious adverse events and events leading to discontinuation of treatment.	
Medical Monitoring Plan	Describes clinical science/medical monitoring data review and cleaning activities.	
Safety Plan	Describes how pharmacovigilance/drug safety will manage safety risks related to a product.	
Data Plan	Describes the procedures for data collection/review/cleaning.	
Statistical Analysis Plan	Describes the procedures for executing the statistical analysis of the primary and secondary variables and other Critical Data.	
Monitoring Plan	Describes the remote/Off-site and On-site Monitoring Activities based on the identified risks. Includes Risk Indicators (triggers) that will help to drive decisions on the type of monitoring to be conducted.	
Training Plan	Describes the trial-specific training required of each party involved in the clinical trial, (e.g. Study Management teams, Monitors, Investigator Site Staff and Vendors).	
Quality Plan	Describes quality assurance/management activities. Provides tools and materials to ensure compliance to regulatory requirements and inspection readiness.	
Other Functional Plans		
Risk Management Log	A tool used by the cross-functional team to track and monitor risk management, including the progress and actions relating to identified risks.	
Communication Plan	Describes the pathway for communicating and escalating issues.	

Note: Elements contained within this table are examples. Each company will select which plans are appropriate for its clinical trial.

Risk Assessment Categorization Tool (RACT)

The baseline RACT output and any revisions should be maintained and documented. For example, the Overall Risk Level may be documented in the final RACT output as an appendix. Changes to RACT may be tracked using revision history of IQRMP.

Critical Data

The identified Critical Data should be documented. An example of how to capture Critical Data is shown below.

Example Critical Data Table

CRF Module Name	Critical Data	Instructions (optional)

Revision History and Approval History

IQRMP Revision and approval histories should be maintained. Below are examples of documentation.

Example Revision History

Version Number	Version Date	Key Changes

Example Approval History

Version Number	Version Date	Approved by

Appendices (to the IQRMP)

Risk Assessment and Categorization Tool

Risk Indicators with Thresholds

Optional: Risk Management Log

Optional: Decision/Issue Log

8.1.3. Risk Indicators

CLINICAL TRIAL EXECUTION PROJECTS: RISK-BASED MONITORING	
Risk Indicators	
Categories	**Variables to be Assessed (with comparability across program / protocol / country / site, as outlined in the Integrated Quality and Risk Management Plan)**
Safety	***Suspected Unexpected Serious Adverse Reactions*** Concerns regarding processing of safety information ▪ PI/designee receipt/accessing of safety documents ▪ Timeliness of reporting of safety information to site's local IRB/IEC (as applicable
	Non-serious Adverse Events ▪ Outliers / trends in number of events per subject or per site
	Serious Adverse Events ▪ Outliers / trends in number of events per subject or per site ▪ Timeliness of reporting (e.g. date of event compared to date of data entry) ▪ Incidence of potentially unreported SAEs based on information from data review
Investigational Product	**Concerns regarding accountability, dosing, administration, or compliance** ▪ Receipt at site (e.g. timeliness of acknowledgement in IVRS) ▪ Dispensation (e.g. compare CRF entries to IVRS assignments); bar code scan errors (e.g. error rate based on comparison of IVRS container number assigned vs. IP dispensed numbers as documented in CRF) ▪ Compliance (e.g. amount assigned versus administered) ▪ Number of IP interruptions compared to average across sites ▪ Incidence of temperature excursions
Subject Recruitment and Discontinuation	***Subject Recruitment*** Outliers in screen failure rate / enrollment rate ▪ Number of screen failures compared to average across sites – protocol dependent ▪ Planned versus actual enrollment ▪ Inconsistent recruitment
	Subject Discontinuation Outliers / trends in ratio of subjects discontinued to subjects randomized ▪ Reason for discontinuation (e.g. number per each category vs. total number of discontinuations)

CLINICAL TRIAL EXECUTION PROJECTS: RISK-BASED MONITORING	
Risk Indicators	
Categories	**Variables to be Assessed (with comparability across program / protocol / country / site, as outlined in the Integrated Quality and Risk Management Plan)**
Issue Management	***Protocol Compliance*** Outliers / trends in number or type of deviations ▪ Number of deviations (e.g. per subject/site and compared to average across sites) ▪ Type of deviations (e.g. significant/non-significant)
	General Issues Concerns about number and/or severity of Issues ▪ Number of issues (e.g. overall, by category, by severity) ▪ Number of unresolved issues
Data Quality	***Abnormal Trends in Data*** Abnormal trend or lack of variability in data, for example ▪ Duplicates ▪ Visits ▪ Risk score too low for high enrolling site
	CRF Completion Concerns about overdue data entry, number of incomplete pages ▪ Visit date to CRF completion date ▪ Missing pages ▪ Timeliness of eCRF Approval (PI)
	Discrepancy Management Concerns about: ▪ Number of queries ▪ Number of overdue queries ▪ Number of queries requiring re-addressing ▪ Query response time
On-site Workload-Based Triggers	**Workload-Based Triggers Per Monitoring Plan** (e.g. the amount of data pending SDV or review requirements On-site)
Essential Documents	**Concerns about processing or storage of essential documents** ▪ Number of overdue or missing documents (e.g. IRB approval of protocol amendment) ▪ Number of documents
Staffing, Facilities, and Supplies	**Concerns about staffing or supplies / equipment** ▪ Amount of staff turn-over ▪ Staff training needs ▪ Inappropriate delegation of responsibilities ▪ Adequacy, maintenance, calibration, storage of supplies/equipment

8.1.4. Companion Guide to Risk Indicators

Companion Guide to Risk Indicators

Purpose

To ensure that there is a consistent approach to the application of Risk Indicators and associated Thresholds.

General Principles

TransCelerate created a collection of Risk Indicators that are intended to be monitored Centrally or Off-site on an ongoing basis. In the absence of technology that enables continual monitoring of Risk Indicators, monitoring the Risk Indicators at specific intervals or time points is recommended to ensure key risks are managed throughout the study. Monitoring Risk Indicators Centrally or Off-site allows for more rapid detection of possible issues and conduct of targeted actions to either further investigate or mitigate an issue. Those investigations can determine whether a problem is real and requires a solution or whether it isn't and just requires continued monitoring.

Thresholds can aid in decision-making and can positively impact subject safety, data quality and GCP compliance. This guide describes how Thresholds are determined and how they are viewed, including specific examples.

a. Determination of Thresholds for a specific Risk Indicator

When deciding on a specific Threshold for a Risk Indicator, an expected value (e.g. rate, number, or range) must be ascertained. As an example, perhaps query responses are expected to be entered into the CRF within five working days of generation. Once the expected value is established, consider the risk to subject safety and data quality if the Threshold is exceeded. If the risk is relatively high as documented in the IQRMP, then the Threshold should be relatively small. For example, blood pressure measurements are usually identified as Critical Data in hypertension studies. The Threshold for triggering attention to anomalous blood pressure measurements could be as little as a 1% variation when compared across sites. For an oncology study where blood pressure values are unlikely to impact the primary endpoint, the allowable variation may be much higher, for example, 5%. More variation may be permitted when the impact of the Risk Indicator is lower.

Thresholds can be adjusted depending on the needs of the study to be either more stringent (e.g. for risks impacting subject safety) or less stringent (e.g. for risks that are considered low or with minimal impact to a given study). When establishing a value for a Threshold, consider whether to assign a relative weighting to each Risk Indicator. Certain risks (and therefore Risk Indicators) could be deemed more important than others and could be documented as such during the development of the IQRMP.

For example, perhaps Subject Recruitment and Discontinuation risks carry a greater importance (greater weight value) than issues related to Data Quality. Subject Recruitment and Discontinuation Thresholds might then carry a greater weighting and require more immediate attention than Data Quality Thresholds. Relative weighting could be useful in supporting decisions on the type of actions to take in response to a Threshold being exceeded. The recommended time to assign the Threshold values should be done after risks are determined but before risk mitigation plans (e.g. Monitoring Plan) are finalized.

b. Attention to Risk Indicators

Though not required, a visual system (e.g. dashboard) based on a traffic light metaphor is a simple method that can represent whether a value is within an acceptable range (green), an awareness range (yellow), or a warning range (red). A red light indicator should require more immediate attention.

System attributes are listed in the technology requirements appendix [System Requirements and Preferred System Attributes]. At a minimum, the Risk Indicator system or tool should be able to display information that allows comparison of subject-level data across a site, comparison of a site against its peer sites within a country or within a protocol, and facilitates the detection of problems that require further investigation. If sites are participating in multiple protocols, the system should allow for comparison of those protocols against peer sites. A dashboard should be able to provide the right level of information to the function/role performing a monitoring activity (e.g. a person with study-level responsibilities should be able to assess risk across all sites for a given protocol).

c. Responses to Thresholds

When a given Threshold is reached, a decision needs to be made regarding the appropriate action to take. The choice, depending on the issue, may simply be to continue Central or Off-site Monitoring for potential trends. If the issue is more serious, immediate investigation may be warranted. Determine whether to be prescriptive and assign a specific response or action to each Threshold. For example, if a Safety Risk Indicator shows that a site has 50% fewer AEs reported than the average number reported across sites; the prescribed action may be to contact the site. Examples of actions include:

- Assess other types of data remotely
- Contact the site to gather additional information
- Collect site documentation
- Visit the site to assess documentation that is only available on-site and cannot be made available remotely through electronic means

A decision tree approach may also be useful. For example,

1. Assess other types of data remotely; if still unresolved then:
2. Contact the site to gather additional information; if still unresolved then:
3. Arrange an on-site visit or include on the agenda for the next planned visit

Once it is determined that a risk requires some form of mitigation, a decision should be made as to whether the solution may be accomplished remotely. Successful solutions do not necessarily require an on-site visit. Also remote actions can be accomplished sooner and thus may lead to a more timely resolution. For example, training may be conducted remotely with current technologies.

d. Availability of Data

The effectiveness of Off-site or Centralized Monitoring requires that data is entered in a timely manner and is available remotely.

e. Acceptable Error Rates

For the purposes of this document, decisions on what constitutes acceptable error rates are not described. This information may be added later following the pilot stage.

Application Examples of Thresholds and Actions

Provided below are examples of Risk Indicators, including pre-determined Thresholds and the possible actions once a specific Threshold is exceeded.

Scenario 1

Risk Indicator Category: Safety

Per the IQRMP, the risk level for the Safety category is high

Risk Indicator: Outlier / trend in number of Adverse Events (AEs) per subject or per site

Threshold:

Threshold	Examples of Action(s)
+/- 5% more/less than the average reported AE rate (Green)	No action
+/- 5.1 to 15% more/less than the average reported AE rate (Yellow)	No action Assess data remotely (e.g. determine if AE symptoms were listed as separate AEs versus entered as one diagnosis, consider if the site's subject population is associated with a higher than average number of AEs) Call the site Visit the site
Greater than 15% of the average reported AE rate (Red)	Assess data remotely Call the site Visit the site

Why is this Risk Indicator important?

- Possible over or under reporting of safety information can impact subject safety
- Possible over or under reporting of safety information can impact the final study report

If site is contacted or an on-site visit conducted, consider the following:

- How does the site assess and document AEs?
- Does the site have qualified resources assessing AEs?
- If an on-site visit is conducted, review source documentation for unreported AEs.

Scenario 2

Risk Indicator Category: Subject Recruitment and Discontinuation

Per IQRMP, the risk level for this category is high

Risk Indicator: Subject Discontinuation (outliers / trends in ratio of subjects discontinued to subjects randomized)

Threshold:

Threshold	Examples of Action(s)
5 to15% more/less than the expected ratio and at least 3 subjects discontinued (Green)	No action
15.1 to 30% more/less than the expected ratio and at least 3 subjects discontinued (Yellow)	No action Assess data remotely (e.g. check against the average discontinuation rate across sites) Call the site Visit the site
Greater than 30% more/less than the expected ratio and at least 4 subjects discontinued (Red)	Assess data remotely (e.g. review the reasons for discontinuation, determine if risk Thresholds were exceeded for other Risk Indicators) Call the site Visit the site

Why is this Risk Indicator important?

- Possible safety signal
- Lack of sufficient data for statistical analysis and potential failure of the primary objective

If site is contacted or visited, determine the following:

- What are the reasons for discontinuation?
- Assess the site's screening procedures to ensure they are adequate to select appropriate subjects.
- How does this Risk Indicator compare to another Risk Indicator (e.g. number of Investigational Product interruptions compared to average across sites)?

Scenario 3

Risk Indicator Category: Data Quality

Per IQRMP, the risk level for this category is high

Risk Indicator: Discrepancy Management – Query response time

Threshold:

Threshold	Examples of Action(s)
< 5 days (Green)	No action
5 to 30 days (Yellow)	No action Assess data remotely (e.g. check against Risk Indicator for 'Visit date to CRF completion date') Call the site Visit the site
Greater than 30 days (Red)	Assess data remotely (e.g. determine if other risk Thresholds were exceeded, compare against the rate for other sites) Call the site Visit the site

Why is this Risk Indicator important?

- Quality of query response may be lower when the response is late
- Delay in data analysis
- Possible failure to meet regulatory disclosure requirements
- Delay in final study report

If site is contacted or visited, consider the following:

- Is the site aware of the expected timelines for responding to queries and the risks associated with response delay?
- Does the site have adequate and sufficient resources?
- Does the clarity of the query contribute to the response delay?

Conclusion

Thresholds add value to the decision-making process during the Central or Off-site review of data against Risk Indicators. The present document provides examples of how to apply Thresholds in a simple manner. Following pilot implementation, it may be of value to create standard Thresholds for each Risk Indicator.

8.1.5. On-site Monitoring Activities

CLINICAL TRIAL EXECUTION PROJECTS: RISK-BASED MONITORING	
On-site Monitoring Activities (Outlined in Monitoring Plan, SOPs or other Guideline Documents)	
On-site Monitoring Activities	
Baseline Approach to On-site Activity	**Information obtained from the Off-site Monitoring review and Central data review should be utilized to ensure that necessary on-site follow-up is focused (e.g. workload, safety concerns). Monitoring activities may occur Centrally or Off-site for any of the areas described below where the capability (e.g. technology, innovative processes) exists.**
	Source Documentation – Approach applied based on risk (described in Monitoring Plan) ▪ Ranges to consider when deciding what source data on site is verified or reviewed may vary based on both the initial risk assessment for a given study or site, and may be modified based on an ongoing basis throughout the study (Table 2). – Note that the same sample of source documentation could be used as the starting point for both SDV and SDR. – The approach to sampling needs to be simple and randomized. Sampling approaches are determined by the company. ▪ Alterations to either SDV or SDR may be based on either observations made on-site or by Central/Off-site (triggers) assessment. – A high query rate of a given data field for multiple sites may lead to a decision to increase the level of SDV for that data field across all sites (if suggestive of a common transcription error). – If a Monitor cannot confirm Investigator oversight from the sample reviewed, additional site documentation may be reviewed. ▪ The review of subject-level safety information follows the sampling methodology above. Additional review on-site is based on issues and risks identified on-site or through anomalies detected through Off-site or Centralized review of data. – If an unreported SAE was identified in the sample checked, then a decision to check more source data is a possible action to this finding.
	Consent Forms ▪ Consent forms may not require 100% review but the size of sample should be based on risk and on the types of issues identified off-site or on-site (e.g. unauthorized person obtaining consent) (Table 2).
	Investigational Product (IP) – Drug accountability and reconciliation activities include the following: ▪ Verify protection of the blind (and if broken, check appropriate reporting). ▪ Ensure that correct subject assignments have been made against IVRS (or other) treatment assignments. ▪ Ensure product use dates are suitable. ▪ Ensure IP logs are up-to-date. Note: Counting of individual pills returned by subjects is not required.
	Essential Documents On-site File – On-site review should be based on issues/risks identified for the site (GCP/regulatory related). Unless part of issue/risk management, there should not be a requirement to perform a detailed on-site regulatory file review nor on-site reconciliation with the TMF. Review of Essential Documents can occur remotely. Periodically, the Monitor can conduct a cursory evaluation of the site file for general appearance while on-site to ensure there are no obvious issues (e.g. an empty or missing binder/box).

Note: Address other activities on-site *as needed* (e.g. site relationship building, discussion of upcoming studies of interest, recruitment/retention concerns for current study, training).

8.1.6. System Requirements and Preferred System Attributes

	System Requirements	Preferred System Attributes
Planning		▪ Ability to apply a risk assessment algorithm (high/medium/low) ▪ Ability to extract data directly from forms (e.g., protocols)
Data Capture		▪ Accommodates direct digital data capture (e-source)
Data Aggregation	▪ Ability to access/aggregate data from disparate systems ▪ Ability to standardize data to enable analysis ▪ Flexible to accommodate multiple source systems and formats	▪ Near real-time data access
Analytics		▪ Ability to apply analytics to aggregated data (virtual or actual) in order to identify outliers, trends ▪ Ability to apply Thresholds relative to outliers; prefer dynamic Threshold definition ▪ Ability to indicate potential quality risk ▪ Automated reporting
Reporting and Visualization	▪ Ability to report on outliers and trends ▪ Reporting driven via issues (creation/resolution) format	▪ Ability to visualize (preferred) outliers and trends ▪ Role-specific views (Study Manager, Site Manager, functional, etc.) ▪ Customizable consumption ▪ Ability to push (v. pull) information
Miscellaneous		▪ Portable, applicable to any sourcing model/partner ▪ Flexible navigation (to other applications)

8.2 Appendix 2 – Retrospective Analysis of Monitoring and SDV

	Queries Processed (N)	Queries Identified by SDV (n)	SDV Query Rate (n/N)	Critical SDV-Only Queries (c)	Critical Data SDV-Only Query Rate (c/N)
Neuroscience Study (Phase 2)	26264	5795	22.06%	1742	6.63%
Diabetes Study (Phase 3)	79273	5711	7.20%	870	1.10%
Pain Study (Phase 2)	8566	617	7.20%	106	1.24%
Diabetes Study (Phase 3)	18193	2691	14.79%	444	2.44%
Alzheimer's Study (Phase 2)	16221	1385	8.54%	895	5.52%
Hidradenitis Study (Phase 2)	12060	1280	10.61%	545	4.52%
Cardiovascular Study (Phase 3)	130843	10397	7.95%	2967	2.27%
Oncology Study (Phase 3)	45741	2565	5.61%	805	1.76%
Overactive Bladder Study (Phase 3)	44860	239	0.53%	27	0.06%
Mean Rates			**7.80%**		**2.36%**