What Does a Risk-Based Approach Really Mean? Summary of the TMF RM Risk Initiative

Joanne Malia, TMF Reference Model Steering Committee
Sr. Director, Development Records Management, Regeneron Pharmaceuticals

Meet the Speaker

Joanne Malia

Representing: TMF Reference Model Steering Committee

Title: Sr. Director

Organization: Regeneron Pharmaceuticals

Joanne Malia as a member of the TMF Reference Model Steering committee recently led the Risk Initiative with a great group of talented volunteers. For her day job, she drives operational excellence activities related to the implementation and management of eTMF and Record Management processes. In this capacity she interacts with international senior level management, external vendors, collaboration partners, clinical study and other internal personnel to ensure compliance with regulations, Regeneron business practices and clinical research program objectives. Prior to Regeneron, Joanne served in a variety of roles in pharma, biotech and CRO companies where she has been responsible for research quality, risk management, data integrity and inspection readiness in clinical research. She has been a member of the industry Reference Model for many years.

Disclaimer and Disclosures

- *The views and opinions expressed in this presentation are those of the author(s) and do not necessarily reflect the official policy or position of CDISC or Regeneron Pharmaceuticals.*

Agenda

1. What is the Risk Initiative
2. What is a Risk Based Approach
3. Considerations for the TMF
4. Summary

Purpose

To encourage:

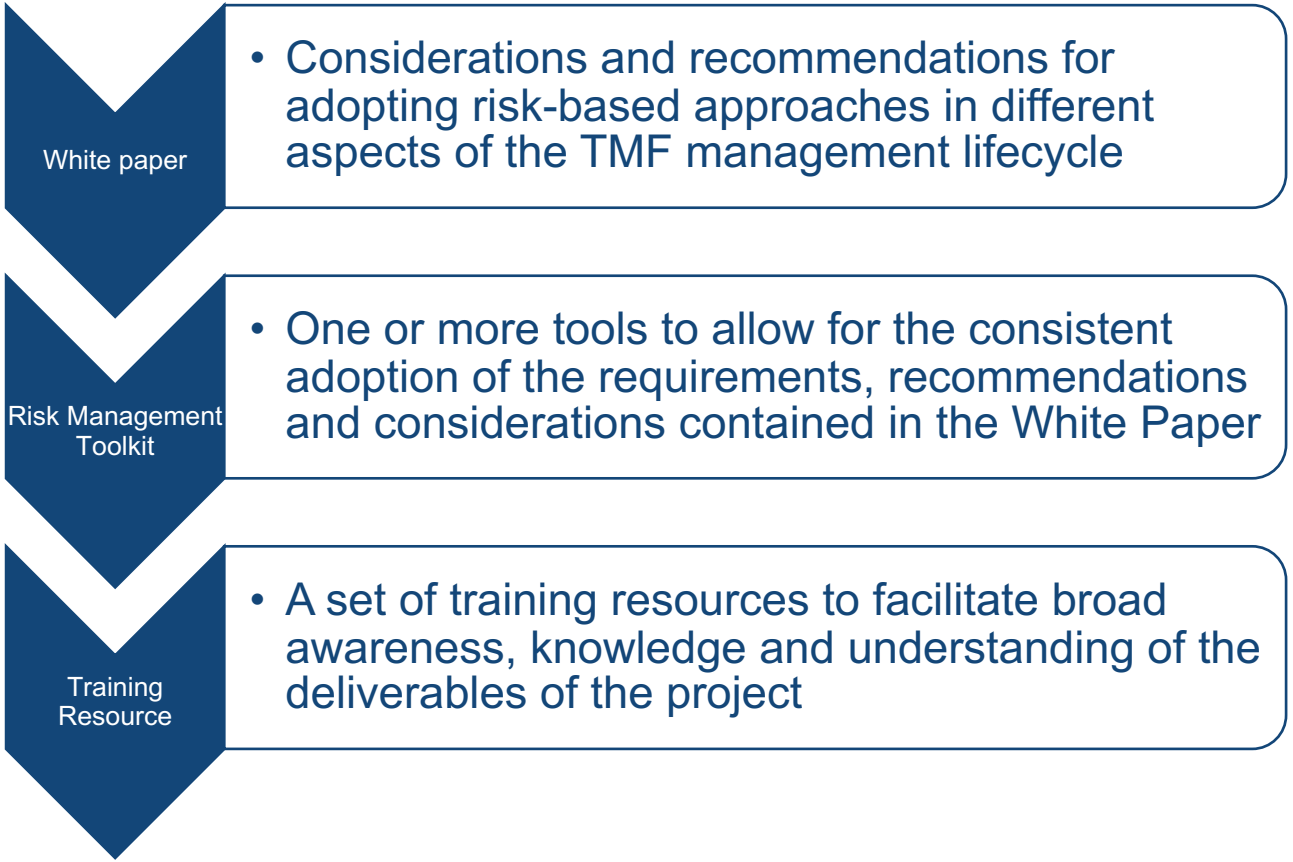
- Greater understanding of the term, “Risk based approach”
- More consistent risk-based approach to TMF management

Consider opportunities for taking a risk-based approach across the whole TMF management lifecycle

Specifically identify solutions and/or recommendations for the application of risk-based approaches for:

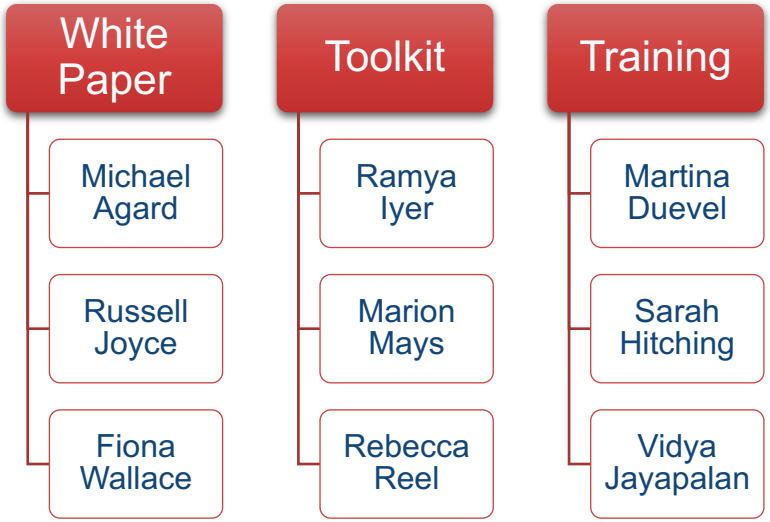
- Defining the required content of a TMF
- Quality control activities to ensure quality and completeness
- Documentation requirements for supporting systems/vendors

Deliverables



Volunteers

- 70 individuals volunteered
- Divided into 3 workstreams, each headed by a leadership team of 3.
- Met independently
- Leadership met regularly to address challenges & stay aligned
- Reviews: Workstreams, Steering Committee, Regulator volunteers
- Pilots



Risk

Risk defined as: a probability or threat of damage, injury, loss, or any other negative occurrence that is caused by external or internal vulnerabilities, and that may be avoided through preemptive action. - *www.stakeholdermap.com*

- Risk is multifactorial and contingent on many variables, among them
  - trial design/complexity;
  - technology maturity/complexity; and
  - operating model.
- Each organization is responsible to construct its risk-based approaches
  - its understanding of risk,
  - its appetite for risk,
  - its ability to justify its approach, and
  - any associated limiting factors such as available organizational resources.

TMF Considerations

- Protocol sets the stage for risk approach
- Defines what records are essential
  - Phase of study
  - Countries / Sites
  - Computerized systems
  - Service providers
  - Processes

Not about taking risks but identifying and managing potential risks

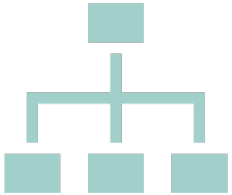
TMF Risk-Based Approach

- Risk-based approaches: some TMF elements are subject to more scrutiny than others.
- Baseline TMF controls should be increased or decreased relative to the potential threats identified in relation to impacts on
  - patient rights, well-being, safety or dignity;
  - regulatory expectations for data integrity;
  - “essentiality” as stipulated in ICH GCP E6 (R3);
  - the evidential value and quality of records; and
  - the completeness of the TMF.
- Risk management activities should establish the proper correlation between risk and criticality leading to:
  - appropriate resource planning,
  - timely detection of issues or errors in TMF records,
  - and proactivity.

ICH GCP (R3) Risk Management

- Risk Management cycle
- Define what is critical for each study
- Needs team approach
- Must be done periodically

TMF Risks



Risks to TMF processes should be identified and assessed at organizational, trial, country, and site levels and should support

* implementation of controls,
* risk monitoring,
* communication, and
* reporting.

When identifying and evaluating TMF risks, a sponsor should consider

* clinical trial type;
* its resources, processes, and procedures;
* its planned use of the trial results; and
* best practice in relation to risk management.

Virtual TMF

Important note: TMF comprises essential records in **all repositories** that collectively permit the evaluation of a clinical trial and provide evidence of compliance with the protocol, and regulatory / ethical guidance.

These other repositories should have QC and oversight activities to ensure the completeness and quality of the essential records.

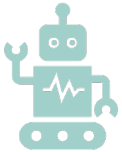
People Process Technology

People

- Roles and responsibilities clarity
- Training
- Actions on issues and metrics

Process

- TMF processes should be logical, simple and user-friendly
- Thresholds for KPIs
- Cross functional reviews
- Escalation



Technology

- Expected records
- AI / Automation / Reporting
- Alerts & notifications

Risk Mitigation

- Some things to consider
  - Predicate and regulatory rule requirement review
  - Define locations of the virtual TMF – ensure all measured for quality and reconciled for completeness
  - Develop correspondence guidance

Risk Monitoring

- Effective risk-based approaches to TMF management and oversight includes monitoring of tolerance limits and other identified risks.
- Monitoring should occur periodically and be documented e.g. on risk log.
- Risk-based approaches to record level quality control may allow reduction from 100% (excessive) to a more appropriate level (e.g. 10%) without reducing quality targets.
  - If sample is less than or meets the tolerance level, then no additional action is required
  - If the threshold is exceeded, then additional actions are required (additional sampling and testing)

Summary

Regulatory Authorities actively encourage the adoption of risk-based approaches to TMF management. **This paper**:

- highlights **benefits of risk-based approaches**, primarily the ability to ensure the ready availability of “essential” TMF records, compliance with regulatory requirements, and enhancements in TMF management and quality;
- discusses **critical & essential TMF records** and processes that should be considered, as well as the risks and mitigations associated with TMF management;
- advocates for **flexible, agile, and resource-efficient approaches to TMF management** that accommodate the varying capacities of organizations, while also leveraging technology to improve quality and integrity in record management processes; and
- emphasizes necessity of **evaluating trends from findings to prevent larger issues** and to verify effectiveness of preventative actions and mitigation plans.

Next Steps

- Read and consider recommendations
- Incorporate as appropriate for your organization
- Overcome resistance to change
- Assess risk using tool
- Continuous monitoring and improvement

Thank you!