QMS Risk Management

RISK LIBRARY

TransCelerate BIOPHARMA INC.

ACCELERATING THE DEVELOPMENT OF NEW MEDICINES

QMS RISK MANAGEMENT RISK LIBRARY

To support efficient execution of risk management activities, organizations may develop a risk library framework, which groups risk statements into manageable categories. A risk library provides a framework and repository for consistent risk information to be captured. It summarizes and defines those risks to which the company/ area/ subject is exposed. The library helps to facilitate discussions of risks and their definitions, and it promotes both consistency and a culture of risk awareness. The considerations for implementation or improvement of a quality risk management program vary based on the maturity of an organization's risk management program. The following table (Table 1) provides guidance on how such a risk library can be developed and maintained. It describes further the relevant activities for setting up the framework and key elements (Figure 1). Details on Quality Risk Management for Clinical Development can be found in the TransCelerate paper: Risk Management Framework Guidance for Successful Implementation of Risk Management in Clinical Development.

Table 1. Developing and Maintaining a Risk Library

Process Step	Description
Identify your risks	**The first task in developing a risk library is identifying risks.** Whilst risks may be identified at any time, there may be specific opportunities to consider new risks for example: • Initiation of a new clinical program, or of a new region/country • Clinical protocol development, • New process or changes to existing processes, • Regulations and Guidelines, • Industry intelligence, • Changes in stakeholders/ patient populations, or emergence of new behaviours (e.g. massive use of a concomitant medication, wide use of social networks in some patient networks, influencing safety reporting) • In response to any of the below clinical Quality Management System (QMS) elements. – *Inspection experience* – *Assessment of the QMS (ACQMS)* – *Process Management* – *Issue Management (Realized risk)* – *Audit observations* – *Monitoring observations (i.e. reported by CRAs ?)* – *Analytics could you please specify what do you mean by analytics* – *Knowledge Management (any example?)* ***Note: The risk identification process needs to preserve space for open thinking about unique or previously-unidentified risks to the QMS or clinical trial quality beyond those listed in the library.***

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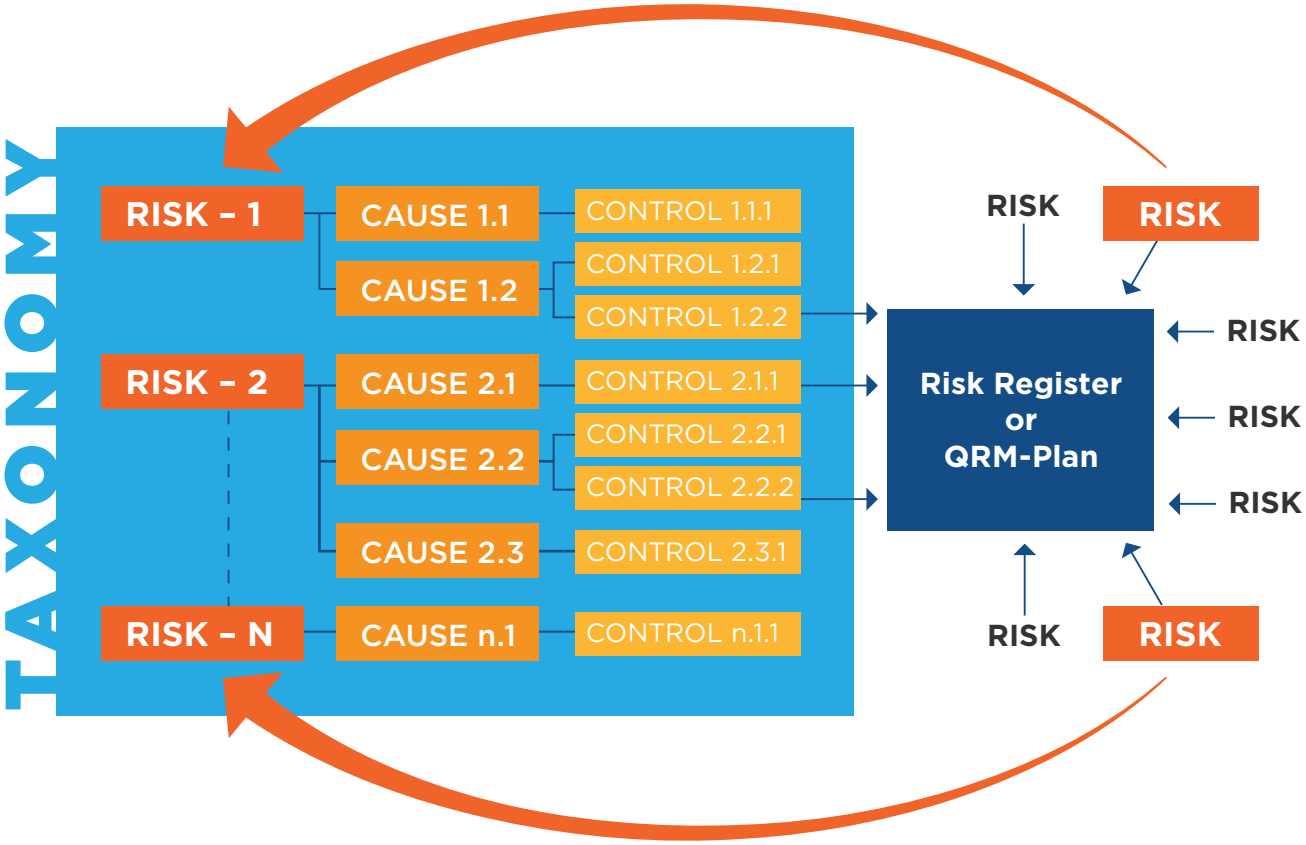
Table 1. Developing and Maintaining a Risk Library *continued*

Process Step	Description
Create a risk library	• Once risks have been identified and in order to support effective risk management, it is helpful to order risks in a structured framework. • The framework may be built around relevant risk attributes and should be fit for purpose. These attributes may provide appropriate differentiation of risks into useful groupings. (For example, the framework may include the mapping of risk attributes to elements of the cQMS). • Attributes may be arranged in a hierarchy or other structure to provide taxonomy of risks. The number of attributes and complexity of the framework is driven by how an organization wishes to categorize and view risks. • Where taxonomy exists for categorizing issues it may be beneficial to adopt the same taxonomy for risks enabling consistency in reporting and linking risk management to issues. • As risks are added they should be mapped to the relevant attributes in the library. • The library should include a description of the risk and relevant information to help in risk evaluation and review, for example the cause(s) and potential controls. The description of the risk should clearly outline the scope and potential negative outcome. The description should avoid statements of impact; this is assessed separately in risk scoring. • All risks submitted should have a risk owner assigned. Risk owners are usually the most appropriate person to monitor and manage those risks. The risk owner is responsible for assessing risks and identifying associated controls. • Known (or potential) causes of the risk may be included to help inform the development of risk controls.
Use of the Risk Library	Once the risk library has been established it may be used to provide a framework for ongoing risk management activities. • Risk identification (as new risks are identified consideration should be given to adding these to the library). • Risk evaluation (the library may be used for historical evaluation, comparing relative risk. Risk evaluation results may be documented as additional information). • Risk control (Quality Risk Management-Plan) • Working with the risk owners, identify current controls that are in place to mitigate and/or reduce risk. Each control should also be assigned an owner or responsible party. This can be a functional responsibility, instead of an individual or specific person. • Risk review • All risks should be periodically reviewed to consider whether the risk remains under control. The frequency of review may change if there has been a substantial change in risk profile.
Maintaining the Risk Library	A process should be defined for maintaining the risk library in a controlled manner. It is a valuable exercise to re-visit the risk library periodically as risks and definitions may develop and change over time. The periodic review should consider changes in the known risks from across all the elements of clinical QMS. There may be a need to react to event-driven triggers (for example, changes in organizations or operating environment or repeat/ persistent issues).

Figure 1. Risk Library – Key Elements



Light Blue Box: Risk Library and key content elements (Taxonomy, risk collection, linked causes and potential control)

Dark Blue Arrows: use of Risk Library to identify relevant risks

A risk library provides the basis for the risk assessment process. It should not be a list of all risks ever identified, only the ones that may have broad applicability. The risks within the library should be general and not specific. A risk library helps facilitate risk discussion and identification, and supports a consistent approach to the risk assessment process as well as promoting a risk management culture.

Table 2 provides a few examples of risks that might be included in a library for informational purposes only. These examples do not constitute an exclusive list of possible relevant examples. Nothing in the examples is intended to imply that the issues identified as risks should or must be considered or managed in the way identified in the examples. Each company is solely responsible for determining which risks should be considered, how they should be considered, and how to appropriately address any identified risks.

Table 2. Examples of Risks Across QMS Elements

Processes		
Risk	**Cause**	**Control**
Storage requirements not met for investigational product	Storage requirement not met during shipment Storage requirement not met at depot Storage requirement not met at site	Ship the investigational product in insulated containers. Falls below risk threshold so no controls put in place. Strict requirements for site storage capabilities during site selection.
Safety reporting fails to meet regulatory requirements	Protocol inadequately addresses the safety reporting process and trial specific safety events Sites do not report safety issues in a timely manner	Update protocol template to include standard safety language and a placeholder for identification of study-specific safety events. Understand the technology capability of each site
Blinded personnel receive unblinded data	Trial data is emailed from site to study team	Verify site capability to use approved systems for data sharing during site selection/ initiation Confirm site awareness of acceptable processes for data transfer and maintaining the blind prior to first subject first visit

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Table 2. Examples of Risks Across QMS Elements *continued*

Resources, Roles & Responsibilities		
Risk	**Cause**	**Control**
A study requires clinical trial naïve investigators.	The study is in a rare disease space or there is high competition in the disease state for experienced sites.	Ensure effective, GCP training, protocol-specific training and investigator qualification. Specific monitoring plans are developed for these sites.
Rater variability for a key primary endpoint.	(1) The endpoint is subjective. (2) Sites may have different experiences in assessing the endpoint.	Determine if an objective endpoint is a viable alternative. Establish a Centralized endpoint assessment committee (EAC) to reduce assessment bias and potentially increase assessment precision and accuracy
Partnering		
Risk	**Cause**	**Control**
Vendor delays in transfer of data and query resolution may impact interim analysis /DBL timelines	(1) Inappropriate resource allocation at vendor for timely query resolution. (2) Query resolution time not defined in Master Service Agreement/Monitoring/Data Analysis Plan	(1) Extrapolation of expected mean of queries per data point based on historical data/previous studies. (2) Immediate action: allocate resource for query resolution/ prioritize queries based on time needs to be closed; preventive: query resolution time to be added into template MSA/ Monitoring/DA Plan
Multiple vendors participating in a trial can lead to oversight deficits.	(1) service(s) package to be outsourced to vendors were incompletely defined at start of vendor selection process (2) inappropriate interface mapping (sponsor/vendor and vendor/vendor) was done to secure timely oversight on activities/data flow (3) global trial required contracting of different vendors for same service (biomarker analysis/laboratory) in different location (China, West Africa, Europe)	(1) add interdisciplinary meeting to define service packages as a first step of the vendor selection process (2) perform interface analysis and compile map on process and system level before study start (3) ensure alignment of laboratory analysis/standards (validation, etc.) in between local labs to achieve comparable results

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Table 2. Examples of Risks Across QMS Elements *continued*

Risk Management		
Risk	**Cause**	**Control**
Proactive risk management is deprioritized over aggressive study timelines	Aggressive timelines do not allow for effective risk management planning Lack of follow up on determining if issues alter the risk profile of a study	Implement SOP for proactive quality risk management in alignment with ICH E6 R2
Issue Management		
Risk	**Cause**	**Control**
Investigator sites or internal staff underreporting issues	New employees at sites or the organization are not aware of their reporting responsibilities	Ensure training in issue reporting is a mandatory requirement for all new employees
Inconsistency in identifying or triaging issues that matter	Different colleagues applying different subjective standards to triage process	Ensure triage process is objective. Check consistency of process execution by colleagues performing the triage role, using the same examples
Knowledge Management		
Risk	**Cause**	**Control**
Turnover of experienced colleagues	Natural career progression Average trial timelines exceed expected time at level	Ensure adequate training available Succession planning
Individuals involved in clinical development inadequately trained	Lack of availability of training system	Ensure business continuity practice is in place (i.e. back-up system or paper training records)
Documentation Supporting Achievement of Quality		
Risk	**Cause**	**Control**
Incomplete TMF	TMF index is not complete	SOP-driven review of TMF documentation process
SOPs overly complex	CAPA-driven approach to SOP revision	Risk management approach to determining issues that matter