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Managing Risks for Medical Device Clinical Trials and Medical Devices

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Abstract: *Medical device clinical trial managers must manage risks in their clinical trials and may also be involved in the product risk management process for the device under evaluation. This article provides an overview of the project risk management process of the Project Management Institute® and how it can be executed to achieve clinical trial objectives; the ISO 14971 product risk management process and how it can be executed; and the clinical trial manager's role in the product risk management process.*

INTRODUCTION TO RISK

According to the Merriam-Webster Dictionary, risk is the "possibility of loss or injury" or "Someone or something creating or suggesting a hazard."[1] According to Murphy's Law and its corollaries:

> If something can go wrong, it will.
> If anything simply cannot go wrong, it will anyway.
> Left to themselves, things tend to go from bad to worse.

Most people hear the word "risk" and want to run away or not deal with it. Charles Robert Tremper, an author on a variety of risk management topics, said:

> "The first step in the risk management process is to acknowledge the reality of risk. Denial is a common tactic that substitutes deliberate ignorance for thoughtful planning."

Risk must be acknowledged, and plans must be developed to deal with risk. Things will always go wrong; however, planning for risks makes dealing with them easier.

RISK MANAGEMENT

Risk management for medical devices and IVDs is conducted according to the harmonized standard ISO 14971 (2019. Medical devices — Application of risk management to medical devices).

"Risk management" is the process of identifying, evaluating, and prioritizing potential hazards (risks, i.e., things that may go wrong), followed by the application of plans and resources (people and more) to minimize, monitor, and control the likelihood (probability) of risks occurring and minimize the impact of issues (risks that have occurred). Risk management is a life cycle effort that is conducted from beginning to end of any entity, project, or project outcome such as a medical device.

We all do risk management, whether we realize it or not. A logical thought process used in daily life is a form of risk management. For example, during the drive to work, a person would identify a hazard and its cause (e.g., a traffic delay due to an accident) and analyze the situation (being late for work). Then, the person would check real-time traffic

on a smart phone's app and see that the route is red. This is risk analysis. Next, the person would choose a detour route on a navigation app. This is risk mitigation. Taking the detour to get to work on time verifies the risk mitigation appropriately addressed the risk.

This innate thought process can be translated into a general risk management framework. Planning, the first step in the risk management framework, defines how the risk management process will be executed. It includes defining the roles and responsibilities of each participant, including who has decision-making authority and the tools, techniques, and strategies to be used. The plan must be developed ahead of time so that staff members know how the risk management process will be executed.

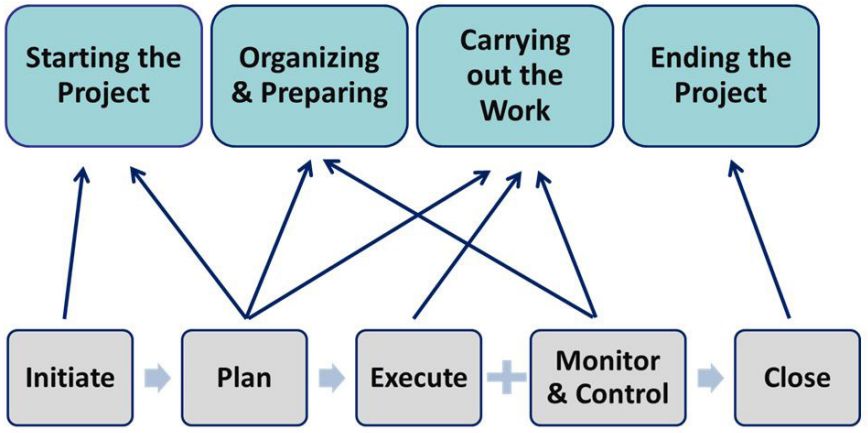
The next step in the risk management framework is identifying hazards that can lead to negative risks and their sources or triggers. Once risks are identified, they are analyzed to understand their characteristics and to prioritize them. Ranking risks enables staff members to prioritize each risk and develop actions that will be taken to respond to each risk. Actions will be based upon the potential effect of the risk. They include eliminating, mitigating, reducing, or accepting a risk. Negligible risks may be accepted with a rationale.

If actions are taken, verification is necessary to ensure that the actions are doing what they are supposed to do. If the actions taken are not effective in reducing the risk, additional actions must be taken.

Some risks can be identified ahead of time – these are called "known unknowns." Other risks, the "unknown unknowns," cannot be identified ahead of time. The processes of monitoring and controlling risks enables staff members to prepare for both types of risks and to identify changes in known risks and new risks. Changes in risk include finding out that risks that were thought to be high are low, or risks that were thought to have a low impact may have a more severe impact. New risks may also need to be considered and entered into the process. During the process and after the process is completed, outcomes must be reported, and continuous improvement activities must be conducted to learn from the process as executed and make improvements going forward ("lessons learned").

This general risk management life cycle framework - an iterative and ongoing process (Table 1) - serves as the foundation for the life cycle risk management processes used for projects and medical device products.

Diagram 1: Project Life Cycle



Five (5) Project Management Processes

RISK MANAGEMENT FOR PROJECTS AND MEDICAL DEVICES – A HOLISTIC VIEW

Clinical trials are projects. The Project Management Institute's best practices for project risk management can be applied to clinical trials.[2] The project life cycle goes from the beginning to the end of the clinical trial: start the project, organize and prepare the project, carry out the work, and end the project. Five management processes are foundational for the project life cycle:

- Initiate
- Plan
- Execute
- Monitor and control
- Close.

These processes are a systematic series of activities directed toward causing an end result - the project's outcome - and consist of a logical

TABLE 1
RISK MANAGEMENT LIFE CYCLE FRAMEWORK

Plan:
- How the risk management effort will be planned and managed?
- Roles and authorities
- Risk tools, techniques, and strategies

Identify:
- Hazards that can lead to negative risks
- Sources and triggers of risk

Estimate/analyze:
- Evaluate likelihood (probability) of risks occurring
- Evaluate the potential effect of the risks (situation and impact)
- Identify changes in risks and identify new risks

Respond/verify:
- Determine actions to take (controls) to reduce likelihood of negative risks
- Verify that implemented controls reduce or eliminate the risks, and do not create new risks

Monitor and control
- Identify changes in risks and new risks

Report

Repeat throughout the life cycle

grouping of a series of inputs, outputs, tools, and techniques. These processes can easily be mapped to the project life cycle. Initiation can be mapped to starting the project. Planning is conducted throughout the project life cycle and maps from initiation, through organizing, preparing, and carrying out the work. The plan may need to be changed and adapted during the project, which comprises executing, monitoring, and controlling the work, which maps to carry out the work. Based on actual project performance, things may need to be changed or fixed during the project. Closing the project life cycle ends the project.

Five (5) Project Management Processes can be seen in Diagram 1:

1. Initate
2. Plan
3. Execute
4. Monitor + Control
5. Close

These five management processes encompass the following ten knowledge areas of project management:

1. Integration
2. Scope
3. Risk
4. Quality
5. Schedule
6. Cost
7. Resources
8. Stakeholders
9. Communications
10. Procurement.

The knowledge areas are defined by their own knowledge requirements and can be considered subprocesses with their own inputs, outputs, and activities. All or nearly all

of these are applicable to all projects, including clinical trials.

The medical device total product life cycle[3] also goes from beginning to end, i.e., from the product's concept to its obsolescence. The medical device total product life cycle can be divided into three major areas: premarket, post-market, and end of life. Risk management, grounded in clinical evidence, is conducted throughout the entire medical device life cycle.

Premarket activities cover the conceptualization, design, development, verification, and validation of the product, transfer to manufacturing, and the regulatory filings and authorizations necessary to commercialize the product. Once the medical device is released to the market, post-market activities are conducted. These include supporting the device and conducting surveillance. When a medical device is no longer able to serve the market or can no longer maintain its safety/risk profile, end-of-life activities are conducted. In this event, the device will be removed from the market, whether this is an individual device or an entire product line.

Table 2 highlights the holistic view of life cycle risk management for all medical device projects and their outcomes, whether premarket or postmarket. The holistic view includes understanding the risks associated with both the medical devices and their projects as well as how they relate to each other.

Project risk includes considering both negative and positive impacts. Negative risks are threats to project success. Positive risks, a difficult term to understand, refers to benefits or opportunities that could increase the chances of project success and benefit project objectives, such as shortening the schedule or reducing costs.

Device risk focuses strictly on harm, the potential negative impact of the device to patients or users. ISO 14971 defines harm as physical injury/damage to the health of people, or damage to property or the environment, and it defines risk as the combination of the probability of occurrence of harm and severity of that harm.[4] Risks must be managed to ensure that the medical device operates within its safety/risk profile throughout its entire life cycle.

THE PROJECT RISK MANAGEMENT PROCESS

The project risk management process is grounded in the general risk management framework with specific project aspects. Planning is done at the start of the project. For clinical trial projects, the project risk management plan may be part of the general program or quality plan for the device, or it may be part of the clinical trial plan. The planning process should be documented to serve as a tool for the team.

The plan defines how the risk management effort will be planned and executed for the trial. It includes the pathway for escalating issues, and who should be notified and the information needed for decision-making when a risk occurs. The plan also covers the way in which changes will be managed.

TABLE 2
HOLISTIC VIEW OF LIFE CYCLE RISK MANAGEMENT

Project:
- Identify risks not addressed by other project management processes:
  - Harms (negative)
  - Benefits (positive)
- Manage risks throughout the life cycle to increase chances of project success

Device:
- Harm:
  - Physical injury/damage to health of people, or damage to property or environment
- Manage risks throughout life cycle to ensure device operates within its safety/risk profile

Risk analysis includes understanding risks from the clinical trial as well as the triggers and sources of those risks. Triggers should be monitored throughout the clinical trial. Analyzing and estimating identified risks includes understanding their characteristics and ranking them by likelihood of occurrence and impact on the clinical trial. Ranking is necessary in order to prioritize risks and to plan actions and responses to reduce or eliminate negative risks or to exploit/enhance positive risks.

During project execution, monitoring and controlling is performed. This involves monitoring the identified risks and the entire process in order to understand any new risks or new information that must be entered into the process. At the project's end, staff members report on the completeness and effectiveness of the risk management effort.

SCENARIO: IVD CLINICAL TRIAL

In this scenario, a clinical trial of a new *in vitro* diagnostic (IVD) device product in development will be conducted. The purpose of the clinical trial is to obtain clinical data to complete validation for regulatory filings, whether this is for a U.S. Food and Drug Administration 510(k) submission or a European Union Technical File. The clinical trial project manager must consider many risk management aspects for the project (Table 3).

The first risk management consideration is the project scope. The project manager must define the requirements, including quality and the work deliverables. For a clinical trial, the deliverables are the data, reports with the analysis of the data, and any safety data that need to be fed back into the process.

In order to avoid additional work, it is important to define what is in and out of scope for the clinical trial. In-scope work is based upon the intended use of the device, label claims for the first commercialization, and the ability to leverage the scope for the United States and the European Union. Out-of-scope work adds time and cost to the project outside of agreed-to allocations.

Project scope also includes escalation and change control pathways. Sometimes changes must be made during clinical trials. Those changes must be made using a process that includes reviewing, justifying, and approving the changes.

Quality requires managing the project's key success factors. Most of the device's quality requirements come from applicable Regulations and Standards, which must be incorporated into the project's scope. Sponsor requirements should also be considered. Metrics for conducting the clinical trial and the risks of not fulfilling these metrics must be considered. Metrics include adequacy of the protocol, data analysis, protection of patient data, handling of data discrepancies, and escalation paths for data that do not meet the specifications.

The schedule defines the clinical trial timeline; however, it is common for the plan for contracting with clinical research sites and enrolling participants to fall behind schedule. Sites may take longer than expected to complete the contracting process, and then they often cannot find enough participants to meet the inclusion/exclusion criteria. Risks to the schedule based on past experience should be identified, and a potential mitigation plan should be put in place in order to meet timelines for providing data for regulatory filings. For example, the sponsor or contract research organization may have a second tier of sites that can be added to the clinical trial if necessary.

All of these risks can impact the clinical trial budget, including not having the right resources available at the right time. Resources include personnel and materials, equipment, services, and the supply chain. If resources are in-house, other priorities may be competing for their time. If resources must be contracted, a process for doing this is necessary, including quality requirements.

Products are shipped to clinical research sites in the United States and internationally. Considerations include requirements for investigational devices, customs requirements, and labeling and packaging requirements. All of these things must be planned ahead of time in order to map mitigation strategies that can be put in place.

Stakeholders are people who can be influenced or

TABLE 3
PROJECT RISK MANAGEMENT CONSIDERATIONS

Scope:
- Requirements
- Work deliverables
- Examples:
    - In-scope and out-of-scope
    - Change control

Quality:
- Key success factors
- Examples:
    - Metrics
    - Acceptance criteria
    - Tools
    - Escalation pathways

Time (Schedule):
- Examples:
    - Site engagement and training, patient enrollment, and more
    - Data readiness to meet regulatory filing dates

Cost (Budget):
- Examples:
    - Risks impacting the budget

Resources and procurement:
- People and other resources
- Examples:
    - Right skill sets at the right time
    - Right materials, equipment, services, and supply chain at the right time

Communications:
- Examples:
    - Who, what, when, and how?
    - Effectiveness

Stakeholders:
- Examples:
    - Who needs to be engaged for each purpose (e.g., decisions or escalations)

Integration:
- Examples:
    - Managing everything together

impacted by the project or who can influence or impact the project. It is necessary to identify stakeholders and their roles (e.g., decision making). Communications involve understanding the information that stakeholders need and when they need it, the type of communications, and monitoring the effectiveness of the communications. The clinical trial project manager must also provide stakeholders with requirements for their deliverables. Two-way communication must be planned ahead.

The clinical trial project manager must then integrate all of this in order to manage everything together for the life cycle of the clinical trial. Clinical trial project managers need both hard and soft skills to do this.

PROJECT RISK ANALYSIS

When conducing a risk analysis process, the clinical trial project manager and trial team identify the possible causes of hazards or risks in the clinical trial. The effect of each risk (harm or benefit) is also identified. Using a tool such as a risk register helps the clinical trial project manager conduct the risk analysis process with the team.

It is crucial to document the risks and the analysis process. Documenting the process includes a qualitative analysis of the most severe threats and the best opportunities, and it identifies the impact of each risk on scope, schedule, budget, resources, and quality. It also includes a response approach, which is used to develop the response plan. The risk analysis must be reviewed regularly and updated based on changes in the clinical trial. Projectmanagement.com offers a risk analysis template.

Another tool is a color-coded risk ranking table; an example of a negative risk ranking table is shown in Diagram 2.

The two scales used are: a) probability (likelihood) of risks occurring (ranking example: high = 3, medium = 2, or low = 1), and b) risk impact (ranking example: minor = 1, serious = 2, or critical = 3). The numbers are multiplied and compared against criteria. For this example, any rankings ≤ 2 are considered low negative project risk (green), rankings between 3 and 5 are considered medium negative project risk (yellow), and any rankings ≥ 6 are considered high negative project risk (red). These risk ranking scales can be easily adapted to the needs of the project. Use of a tool like this helps the team visualize the risk evaluation outcomes.

Less effort, resources, and time will be allocated to low risks than to high risks. Red risks are catastrophic. They must be dealt with and eliminated, or at least mitigated to a medium level. The risk rankings must also be monitored, as risk level and probability can change. These are ongoing life cycle tools to use throughout the clinical trial.

Table 4 provides tips on project risk analysis.

People who are new to risk management should try one concept, such as a risk register, and see how it works. All of these tools are easy to adapt to a specific clinical trial. If the team is struggling with risk management as a whole, try taking a holistic approach and discussing both clinical trial and product risks together and their relationships. This provides a fuller understanding of how product risks could impact trial objectives and vice versa.

The plan sets a solid foundation for the clinical trial and should be used as an ongoing tool throughout the clinical trial. Planning is often not initiated or completed due to schedule demands in starting a project. The clinical trial project manager should schedule specific planning time or brainstorm planning methods

Diagram 2

	Risk Impact		
Probability*	**Minor (1)**	**Serious (2)**	**Critical (3)**
High (3)	Medium (3)	High (6)	High (9)
Medium (2)	Low (2)	Medium (4)	High (9)
Low (1)	Low (1)	Low (2)	Medium (3)

TABLE 4
TIPS ON PROJECT RISK ANALYSIS

Keep it simple:
- Choose and try one concept

Take a holistic approach to risk analysis:
- Discuss the clinical trial and product risks together

Initiate and complete planning:
- Schedule specific planning time or brainstorm planning methods with team and stakeholders

Remember to plan for positive risks

Document the plan as per:
- Sponsor requirements
- Applicable Regulations and Standards

Document in-scope and out-of-scope work and adhere to the change control process

Issue escalation:
- Ensure that the team knows to how to analyze and develop recommended actions/mitigations with rationales
- Reframe this as problem solving if this process seems too complicated

Communicate risk status to stakeholders using easy-to-understand methods

with the team and stakeholders. It is necessary to understand the sponsor's requirements and applicable regulations and standards as part of planning. As negative impacts can often be exhausting, the clinical trial project manager should also work with the team on potential benefits or opportunities (the positive risks).

The clinical trial project manager should ensure that the plan addresses in-scope and out-of-scope work. To avoid scope creep, adhere to the documented change control process. Ask for justifications for requested changes.

For issue escalation, the clinical trial project manager should ensure that team members know how to analyze and develop recommended actions/mitigations with rationales for decision-making. It may be necessary to help team members understand how to solve problems, for example, through root cause investigations. The clinical trial project manager needs to bring the information to the program manager, who will bring it to leadership for decision-making.

When communicating risk status to stakeholders, the clinical trial project manager should use easy-to-understand methods. Making the information more visual, for example, by using dashboards, helps people understand risk and facilitates faster and more manageable reviews.

THE MEDICAL DEVICE RISK MANAGEMENT PROCESS

Like clinical trial project risk management, the medical device product risk management process is grounded in the general risk management framework and life cycle process. Risk management for devices is an integral part of determining safety and efficacy

for devices along with design control and the other quality management system processes.

There are specific documentation requirements for the risk management process for medical devices per ISO 14971 and associated regulations and standards. The risk management file serves as the home for all of the inputs and outputs of the risk management process for the medical device. ISO 14971 provides guidance for the risk management file and its constituent parts.

The first item in the risk management file is the risk management plan, which documents how risk management will be conducted throughout the entire device life cycle including roles and responsibilities, verification and validation including clinical evidence, criteria for risk evaluation and risk acceptability, and more.

There are many possible sources of risk for medical devices, starting with the device's intended use and its safety characteristics (Table 5). Risks include all aspects of the design, including materials, hardware, software, electrical, and reagents. Usability and human factors, the manufacturing and testing processes, instructions for use, labeling, packaging and biocompatibility must also be considered in managing risks for the device.

Risk assessment consists of identifying a device element, the potential source of harm from the element, the resulting hazard (risk), the hazardous situation that could occur, and the potential harm (Table 6). Potential risks posed by the device to the patient and user (which can be the patient, lay caregiver, or healthcare provider), property, equipment, or the environment must be evaluated. For example, if the company has an instrument with a housing, the element being evaluated is the housing. Say that the housing has a sharp edge - this is a potential source of harm. In handling the device in a particular way, the user could be cut - this is the hazardous situation. The potential harm is the cut, which in many cases will be a minor injury.

Criteria must be established for risk evaluation. The company will develop severity, probability, and detectability tables based on guidance from ISO 14971 and other standards, the medical device's intended use, and information from similar devices of the company or other companies. A risk priority number (RPN) is typically used to estimate the hazards and risks. This combines a ranking for severity (a measure of possible consequences of the harm) with the probability (likelihood that the harm will/may occur). In the device housing example, harm would be determined based on whether the injury is minor or requires medical intervention, is serious, or can cause death. These are the general categories for severity. Other categories may be added as necessary, depending on the device and its intended use. Detectability of the hazard may also be included. A dashboard format can be used to rank the risks identified from the medical device's assessment.

After the risks are assessed, risk controls must be identified in the design and its processes. Reducing or eliminating risks starts with safety by design. If risk cannot be completely eliminated by the medical device's design, other mitigations such as protective measures should be determined to reduce risk.
As risk controls are implemented and the design is developed, the risk controls must be verified and validated. Verification ensures that the

TABLE 5
TYPES OF MEDICAL DEVICE RISK

- Processes
- Usability/human factors
- Design
- Instructions for use, labeling, and packaging
- Software, hardware, cybersecurity, etc.
- Biocompatibility
- Materials – chemical, biologic, animal
- More

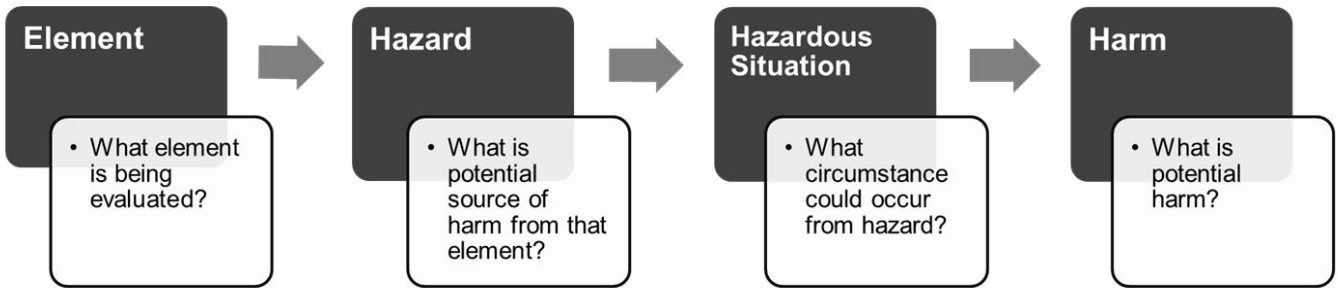
TABLE 6
MEDICAL DEVICE RISK ASSESSMENT

Element (cause):
- Product or process element failure, user error, etc.

Hazard:
- Potential source of harm:
  - Is there a flaw in the element?
  - Is there another issue that could create a hazard?

Hazardous situation:
- The circumstance in which people, property, or the environment are exposed to hazard(s)

Harm:
- Physical injury or damage to the health of people
- Damage to property or the environment



device as designed meets requirements, including risk controls. Validating the design ensures that it fulfills its intended use, including risk mitigation.

The medical device's risks remaining after verification and validation are the residual risks. The residual risks – individual and overall - are evaluated in comparison to the device's clinical benefits for determination of risk acceptability. Residual risks must also be documented in the instructions for use and in the device's labeling and packaging.

Reviews must be conducted and documented throughout the life cycle process. Iterative reporting throughout the process covers the completeness of the risk management effort for the device and the product risk management process as proceduralized. This product risk management process does not stop once the medical device is commercialized. It continues for the remainder of the device's post-market life. Production and post-production information is fed into the risk management file, including complaints, reportable adverse events, recalls, information from clinical studies regardless of the sponsor, and information from similar devices. The risk management file is constantly reviewed and updated to add and utilize post-market information.

There have been some nuances regarding risk reduction in the versions of ISO 14971 recognized by regulatory bodies. In the United States, the U.S. Food and Drug Administration (FDA) recognized the 2007 version of ISO 14971, which referred to the concept of reducing risk "as low as reasonably possible" (ALARP). Within and outside the European Union, the 2012 version of ISO 14971 was used. This referred

to reducing risk "as far as possible" (AFAP). This revised wording was implemented to emphasize that a company cannot use lack of money or resources as an excuse to not mitigate risk, and must utilize all efforts to mitigate risk as far as possible until the device's safety profile can no longer be improved. As of January 2020, FDA recognized the 2019 Edition of ISO 14971 as its consensus standard. Going forward, reducing risks "AFAP" per the associated intent in ISO 14971, should be used for all assessments.

CLINICAL'S ROLE IN RISK MANAGEMENT

Clinical relationships are part of the device's life cycle risk management. Premarket, during the concept feasibility phases, the risk management file is initiated and planning and the initial risk assessment is performed. Data from pre-clinical and early clinical studies are fed into the process early in the pre-market phase and clinical trials are planned. Clinical data from the state-of-the-art, i.e., similar medical devices on the market, are also evaluated. All of this information is used to start to plan risk control before the design and development phase, when it is less expensive and easiest to implement.

Moving into design and development, verification and validation testing, and prior to preparation of regulatory filings, risk controls are implemented and data are obtained from clinical and safety studies. Clinical study and validation data are used to support the risk/benefit analysis, which is part of evaluating residual risk acceptability. In preparation for commercialization, all of this information will be summarized in the risk management report.

During post-marketing surveillance, production, support and change information are integrated into the risk management process. All clinical studies must be fed into the risk management file. The continuing evaluation of risk acceptability and the evaluation of clinical risk versus benefit will use postmarket data. These data will incorporate clinical data from both the company's medical device and similar devices. When the device can no longer serve the market, or when it can no longer maintain its safety/risk profile, these data will support the end of life evaluation.

Criteria for risk acceptability must be established, and is increasingly being grounded in clinical evidence, as per the European Union medical device regulations and FDA guidance documents. A body of data must be used to substantiate the acceptability of device risks as well as the benefits versus the risk.

The clinical subject matter expert plays a key role in medical device risk management. He/she should partner with the program manager, team, and medical advisors to ensure that clinical risks are properly incorporated into the risk assessment and the entire risk management file as well as to ensure that the clinical benefits are supported with evidence. The clinical subject matter expert should also actively participate and provide expertise on the device's clinical and functional performance and how device elements could cause potential clinical harms. This will ensure that the clinical voice is heard and incorporated.

TAKEAWAYS

Risk is a reality and should be embraced. Clinical trial project managers spend most of their time on communication and risk management. Risk management is a best practice strategy for achieving objectives for medical device clinical trial projects and the medical device products.

Clinical trial project managers working on medical device studies should use a logical, step-by step approach to risk management and regularly communicate risks, actions, and progress. New clinical trial project managers should focus on keeping it simple and should partner with the device's risk subject matter expert, who could be the program manager, a research and development engineer, or a regulatory staff member. For those new to the ISO 14971 process, there are many free training tools available on-line.

Table 7 highlights references used in this article and additional resources.

Acknowledgement*: This presentation is based on an article written by C. Campbell-Matland via 3Sixty Pharma Solutions LLC and published in MedDevice Online.*

TABLE 7
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