Risk-Based Inspection Readiness: Reducing Headaches with Advanced Preparation

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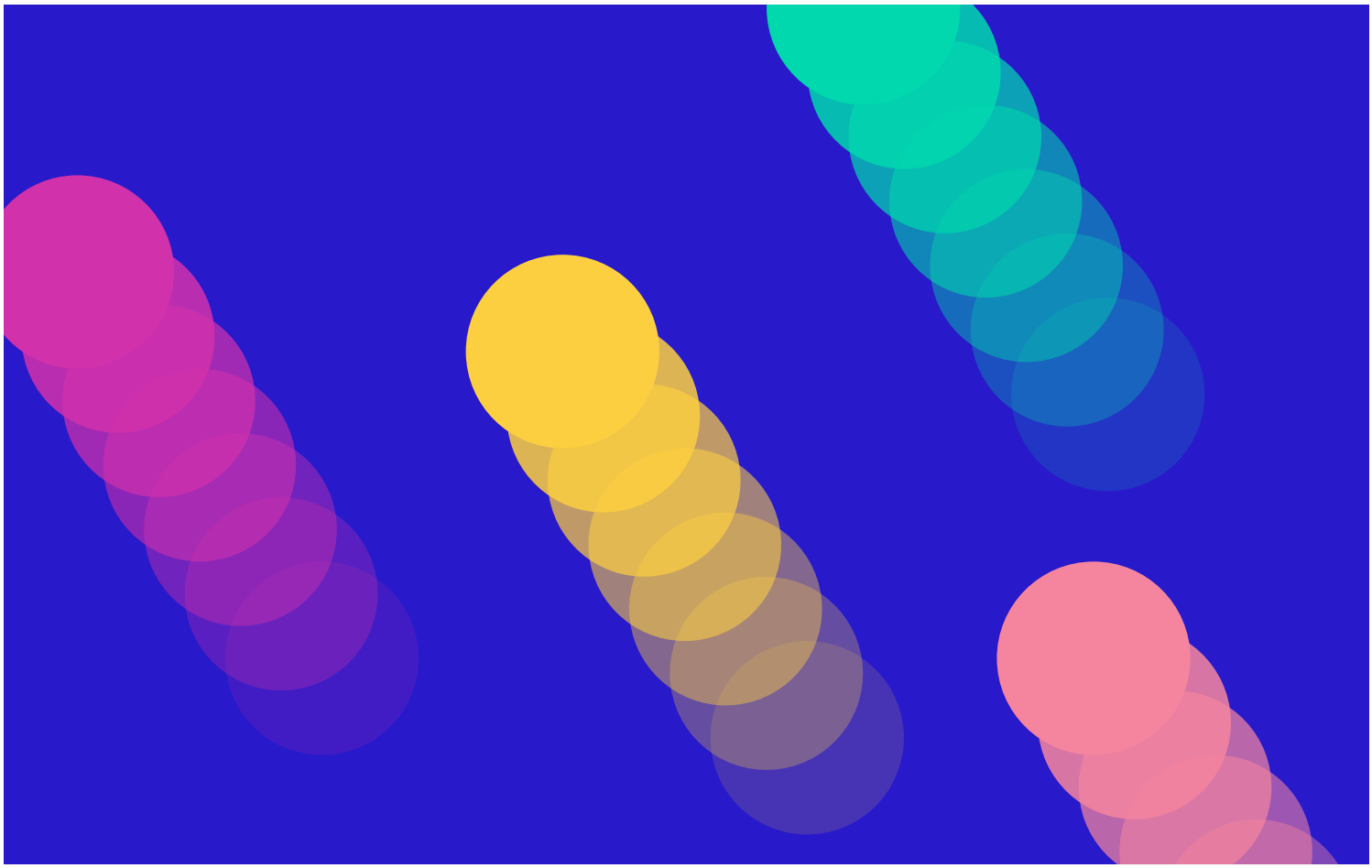

So often, inspections are a major source of stress in the clinical trial environment. This is especially true when processes involved in preparing for an inspection are reactive. But, it doesn't have to be that way. Using industry-leading practices and resources enables a proactive approach to mitigate—or even eliminate—the pain points associated with preparing for inspections.

WHAT IS A RISK-BASED APPROACH TO INSPECTION READINESS?

The term "risk-based approach" encompasses all activities related to risk-based quality management (RBQM). RBQM is defined as a "systematic process put in place to identify, assess, control, communicate, and review the risks associated with the clinical trial during its lifecycle."[1]

The International Council on Harmonisation ICH E6 (R2) guidance, now adopted into legislation in many regions (including the USA and countries across Europe), promotes a risk-based approach to all aspects of clinical research **(Figure 1)**, including inspection readiness. For this reason, it's essential that sponsors, providers, and clinical research sites proactively prepare for inspections from all regulatory bodies, with a particular focus on the regions in which sponsors are seeking market authorization approval.

A risk-based approach to inspection readiness can be thought of as a demonstration of intentional, thoughtful, and systematic assessment and analysis of the risks. This applies not only to study planning and conduct, but also to inspection preparation and keeping abreast of the specific

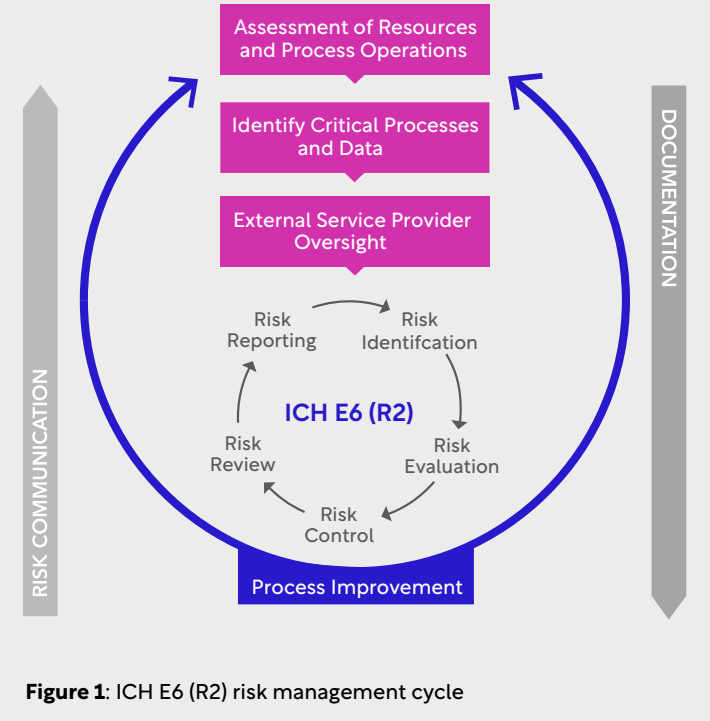

Figure 1: ICH E6 (R2) risk management cycle

As with other risk-based approaches, risk-based inspection readiness involves the identification, evaluation, control, review, reporting, and communicating of risks, and especially those risks pertaining to inspections. The aim is to always evaluate risks and focus on managing and mitigating those that will likely have the greatest impact should they manifest.

WHERE TO BEGIN?

While some might think that inspection readiness applies when getting ready for a regulatory submission, to be actively inspection-ready, it's important to use risk-based approaches from the beginning of the trial throughout the planning phases, study conduct, and study closeout—as well as in preparation for the inspection itself.

Each of these stages has different activities and therefore different risks, so the focus of the quality activities will change throughout the study. For example, at the start of a study, the focus should be on identifying risks related to study-critical data and processes. If the study will involve use of a service provider, a quality agreement must be established and should include the risk measures (e.g., Key Quality Indicators and Key Risk Indicators) that the sponsor and service provider agree to capture, evaluate, and communicate; targets and thresholds to trigger actions to address risks; and the planned actions. During study conduct, focus will shift to the quality assessment outputs and to managing and re-evaluating predicted and/or emerging risks. Closer to the time of inspection, attention will need to focus primarily on inspection preparation activities to ensure sites are prepared, such as providing inspection logistics and interview training of subject matter experts (SMEs) and staff who will be involved in the inspection.

"Risk-based inspection readiness involves an intentional, thoughtful, and systematic assessment and analysis of risks from the start of study, throughout the study conduct, and in the lead-up to an inspection."

BUILD, SHARE, AND LEARN

Often, we go into risk management feeling overwhelmed about how to identify the relevant risks in the first place. However, the risk identification process doesn't have to be challenging. You can build on what's already known within your organization and leverage the collective knowledge of industry consortia such as the Avoca Quality Consortium (AQC). Industry consortia provide a wide range of tools, templates, position papers, and educational materials that can be used to help identify and subsequently manage risks related to provider selection, performance oversight, and inspection preparation—essentially throughout the clinical trial lifecycle.

Utilizing these resources and prior experiences with clinical trials, in general (and often with the specific focus of your clinical trial), you can establish a framework of risks that require attention at all levels: system, clinical trial program, and study/trial execution **(Figure 2).**

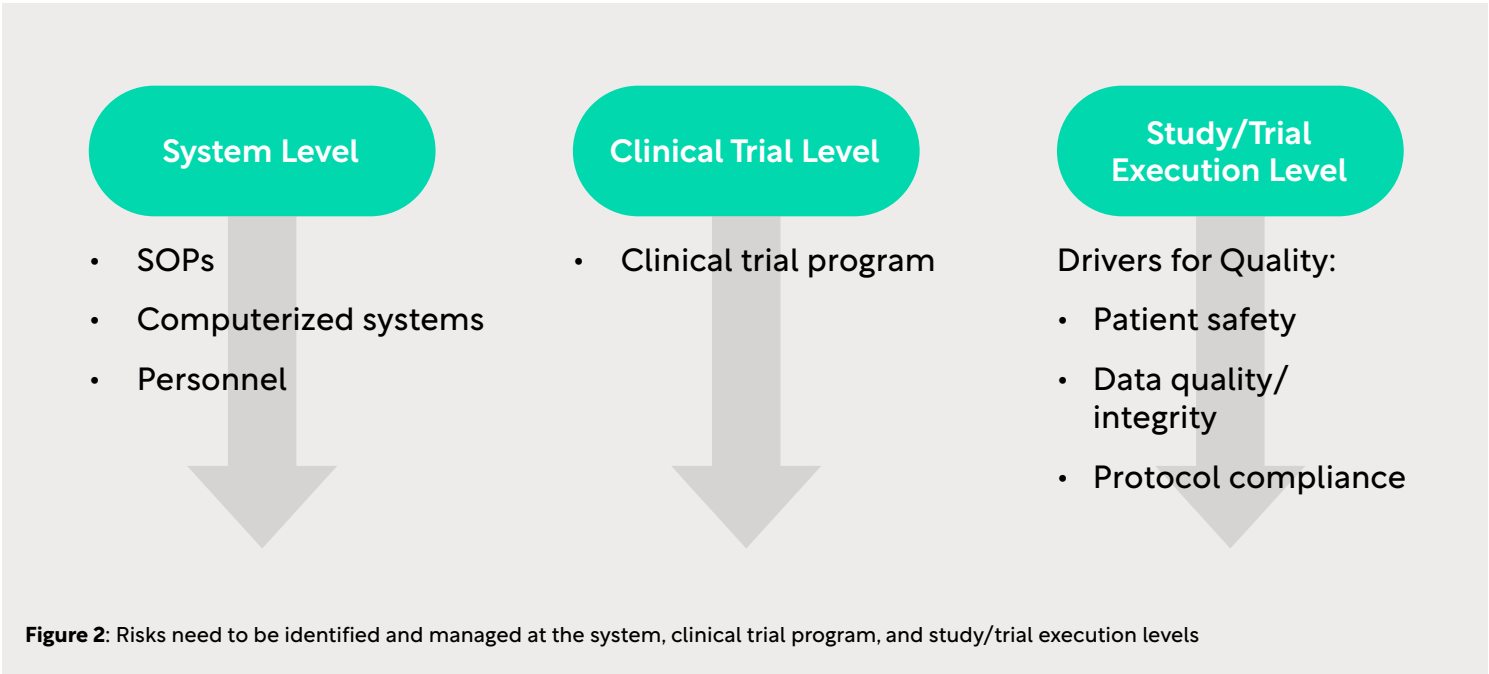

Figure 2: Risks need to be identified and managed at the system, clinical trial program, and study/trial execution levels

One leading practice is to follow an "Active Lessons Learned" process whereby experiences and learnings from each study team are shared with other teams as well as with the rest of the organization **(Figure 3)**. The management of identified or emerging risks during one study can be used to inform the risk management of subsequent studies. This is important because it's almost impossible to "reverse engineer" quality. Inspection management teams are often brought in at the very end stages and are expected to clear up issues, even though many of those issues may have been encountered previously in related contexts (e.g., in another study), and therefore could have been monitored and prevented.

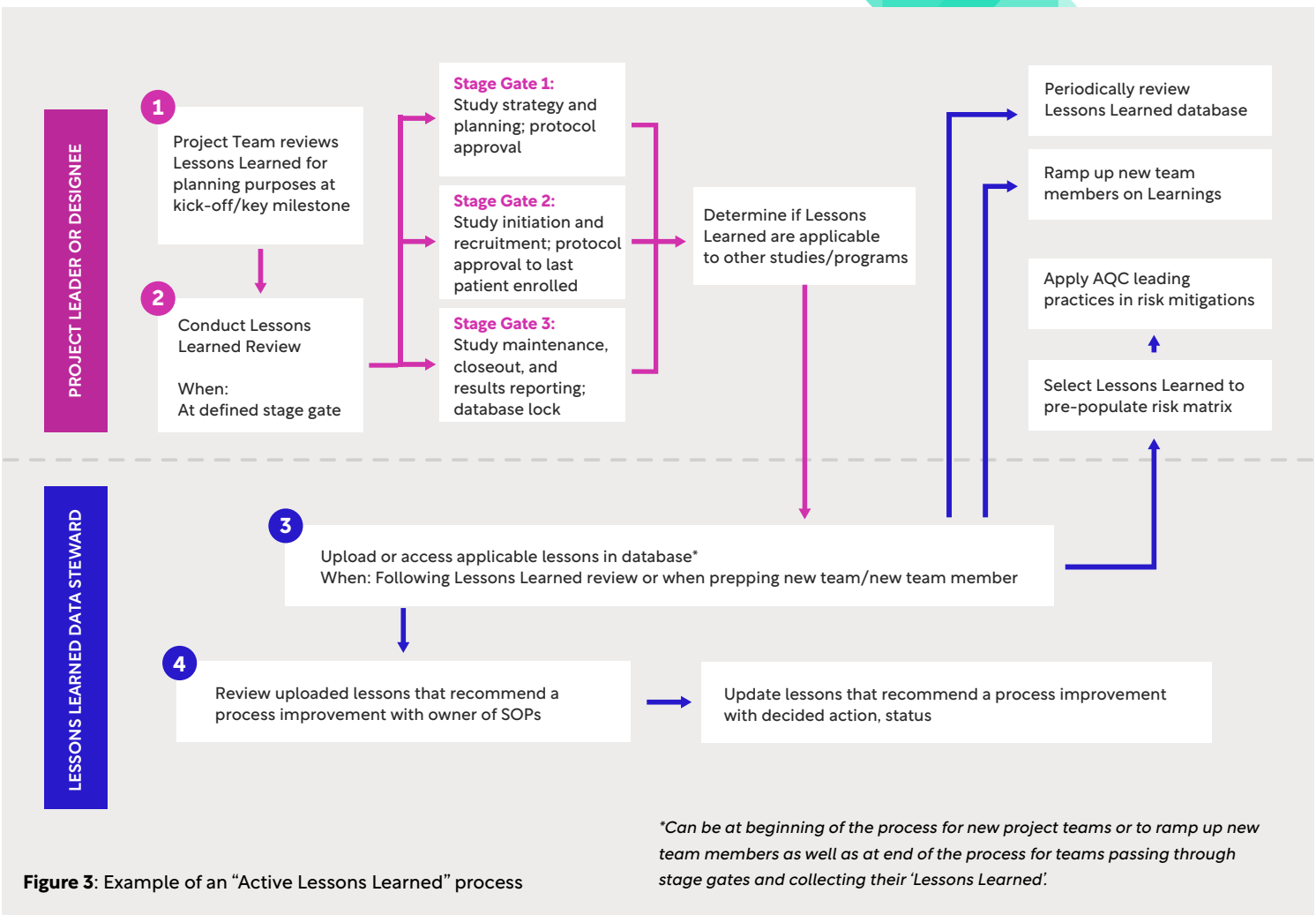

Figure 3: Example of an "Active Lessons Learned" process

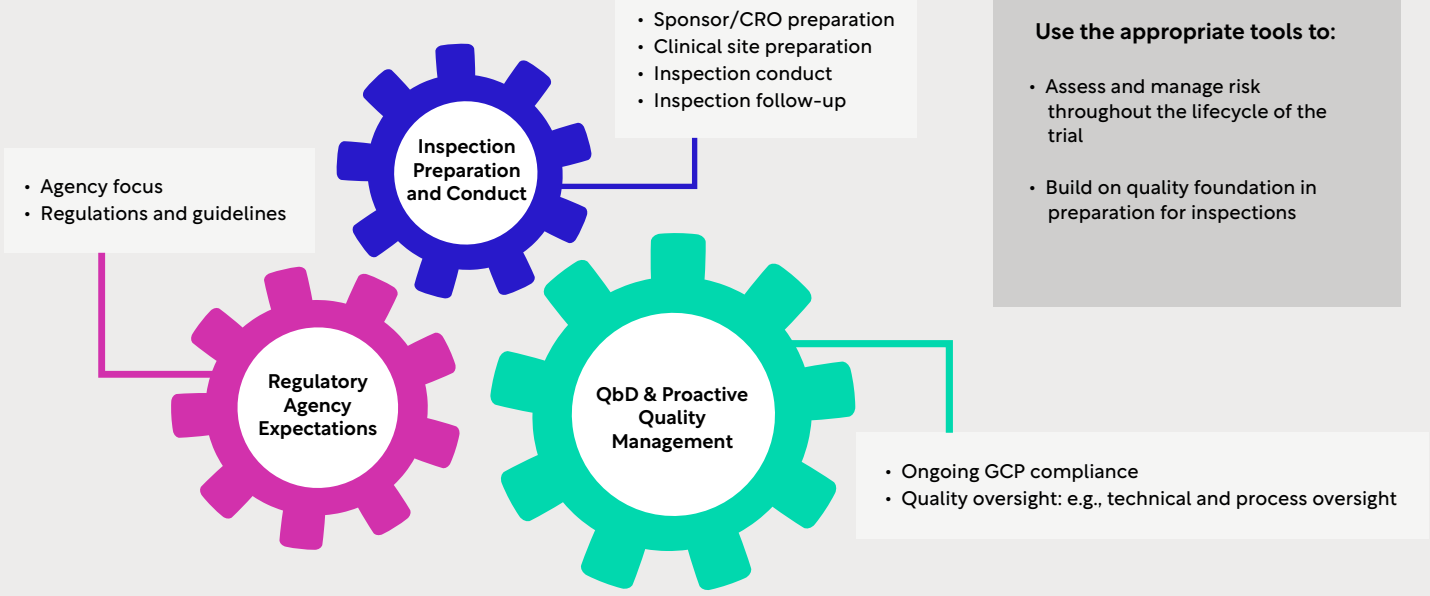

Figure 4: Use of appropriate tools can help manage the risk throughout the clinical trial lifecycle

Take a particular look at data quality and patient safety. These areas are always at the forefront of inspection attention and should be managed carefully. In alignment with ICH E6 (R2), it is important that all staff members are well aware of, intentionally look out for, and apply the criteria critical for data quality and the associated documentation (e.g., the ALCOA+C standards: attributable, legible, contemporaneous, original, accurate, and complete). It is also important to set appropriate quality tolerance limits and take targeted actions as needed to make sure that you are not only doing due diligence for your patients and study success but are also providing inspectors with no cause for concern in these areas.

Finally, it is important to establish a culture of quality and continuous learning throughout your organization. Too often, it is the staff called upon to put out fires during inspections who are rewarded. Instead, to promote a quality culture, leadership needs to reward those who are preparing in advance, providing notification when new risks arise, and implementing appropriate mitigation strategies. Inspection readiness needs to be part of everyone's goals and at the core of day-to-day work activities.

CONDUCT AND ACT ON QUALITY ASSESSMENTS

To identify areas of high risk within all aspects of a Quality Management System (QMS) **(Table 1)** and to prepare for an inspection, it's important to conduct regular quality assessments. For this purpose, functional checklists and inspection readiness dashboards may be used to help teams focus on the areas requiring the most attention.

Using outputs from the QMS assessments and functional checklists, thoroughly prepare explanations for any deficiencies and/or areas of complexity and risk. These could be documented, preferably in real-time, in the form of storyboards that will support SMEs when preparing for inspections. For example, a storyboard may be developed to proactively address strategies and rationale for a decision that may not be in the required documentation but may provide valuable insight and background to the inspector.

Quality Agreements	Clarity and documentation of mutually-aligned quality expectations and definitions of quality by the use of leading practice templates
Quality Metrics Taxonomy	Predefined approach to focus on quality outcomes of clinical programs, predictive metrics that lead to desired quality outcomes, and clarity of decision-making roles and processes for utilizing quality metrics
KPIs and KQIs	Active identification, monitoring, and reporting of performance, quality, and risk indicators
Policies/Procedures	Documentation of quality expectations into operational documents that are aligned to clear business drivers
Vendor Management/Oversight	Processes and documentation to oversee outsourced clinical trial activities; including guidelines and tools
Training	Adequate training of staff, contractors, and vendors
Clinical Risk Management	Strategies/tools to proactively manage risk throughout GCP activities
Knowledge Management	Getting the right information to the right people at the right time
Quality Culture	Developed and proven culture of quality across company components and through to partner organizations where quality is proactively built into programs
Inspection/Audit Management	Risk-based audit planning, audit management, and trend analysis tools
Issue Management and CAPA	Processes and tools for issues escalation, root cause assessment, impact analysis, resolution, and prevention
Documentation and TMF/eTMF	Processes and tools used in managing clinical trial documentation

Table 1: Key components of a Quality Management System (QMS)

Study teams can also prepare storyboards to address the high-level aspects of their deliverables, especially for large trials. Such storyboards can be used to clearly and concisely address expected areas of inspection focus and controversial topics. For example, if high staff turnover is highlighted as a risk, the names and roles of staff working on the trial can be documented in a storyboard trial at all times. Through the exercise of compiling such documents, there are benefits from proactively addressing potential issues that could occur further down the line.

DEVELOP KNOWLEDGE OF YOUR TARGET MARKET

Keeping abreast of the diverse inspection requirements, new approaches, and evolving focus of the different global regulatory agencies is critical when preparing for target markets in other countries. For this purpose, it is important to dedicate the time and resources to understand the global regulatory requirements and ensure that staff are appropriately trained on processes that meet regulatory expectations. Building this knowledge from the beginning of the study supports study conduct as well as inspection preparation.

SIMULATE INSPECTION LOGISTICS AND CONDUCT

Not knowing how to coordinate an inspection is a risk of its own, but one that can be easily managed up front. For example, to ensure that everyone who will be involved with inspections is aware of the overall process that occurs during an inspection, training is essential.

Provide inspection preparation support for your SMEs by performing mock inspections and providing interview training with a focus on the identified risks. Storyboards can be used as part of a mock interview process and then refined based on feedback and need.

Inspections are inherently stressful and can be disruptive to clinical trial teams when they are supported by reactive processes. However, by implementing a proactive, risk-based approach, organizations can move toward a steady state of inspection readiness that is supported by confident, knowledgeable staff. Leveraging the collective knowledge and industry-leading tools and practices of consortia, such as the Avoca Quality Consortium, and at collaborative industry meetings, like Avoca's annual Summit, makes the transition to a proactive state smoother and more time efficient **(Figure 5).**

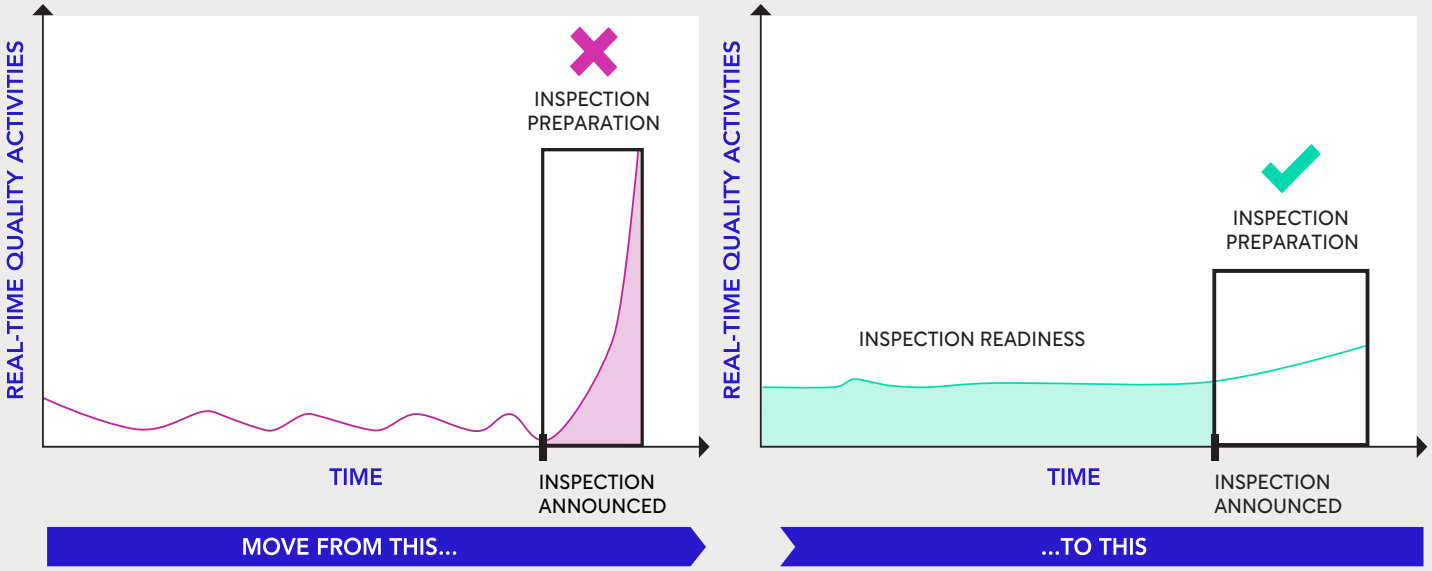

Figure 5: Moving from reactive to proactive inspection readiness ensures successful outcomes

REFERENCES

1. EMA Reflection paper on risk-based quality management in clinical trials, November 2013

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