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Review Article

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A Practical Approach and Framework to Quality Management for Smaller Sponsor Companies

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ABSTRACT

Sponsor companies engaged in clinical trials are to design quality into clinical studies upfront as outlined in ICH E8 R1, General Considerations for Clinical Studies, and ICH E6 R3, Guideline for Good Clinical Practice. The establishment of core quality management system elements and identification of what is critical to quality should be done as early as possible to facilitate the assessment of risks to participants and data integrity. Sponsors should develop systems to manage quality throughout all stages of the trial process, in accordance with regulations and ICH E6 R3, and ensure that oversight is commensurate with the risks associated with the clinical development programs to support informed decision-making. Quality system core elements should be established to facilitate compliance, be flexible enough to accommodate shifting priorities, and mature to scale with growth. For smaller start-ups or mid-size organizations, the same requirements apply as they would for the research and development of any other drug, biologic, or device developed by large pharmaceutical companies. Funding campaigns should include quality management related costs as early as possible to enable regulatory compliance.

Introduction

Whether you are a one-asset company in the startup environment, a mid-size biotech with multiple programs in the pipeline, a sponsor of a new device company, or embarking on the approval of a novel psychedelic therapy, the establishment of a quality management system (QMS) is critical to ensuring effective, efficient, and regulatory compliant operations. Although a small biotech company with one asset in development would not produce the same volume of data generated by larger pharmaceutical companies with multiple products in the pipeline, the quality principles and core elements that comprise a QMS to manage and oversee a clinical program applies the same to ensure participant safety, and data integrity. The QMS should be designed in alignment with the International Council for Harmonization (ICH) E8 General Considerations for Clinical Research, ICH E6, Guideline for Good Clinical Practice, and where devices apply, in accordance with the Quality Management System Regulation, with a focus on risk-based quality management and continuous improvement cycles [1-3]. Regulations and guidance provide a framework for sponsors to follow but rarely dictate how the requirements can be achieved. Quality management that is fit for purpose within the context of the operating environment does not require sophisticated tools or elaborate web platforms and can be designed effectively by leveraging fundamental principles and core elements. Initial funding campaigns should include provisions for quality management activities as soon as the company is established and the target profile product is identified.

Quality Principles

There are various definitions of the word "quality," ranging from those specific to a degree of excellence or meeting customer expectations or specifications, to others that focus on the absence of errors. All these definitions apply to a clinical development program in its various forms as part of quality management. Quality management, as executed through a quality management system or QMS for short, is the set of objectives and expectations set by an organization to drive efficient and effective operations across people, process, and technology to ensure the quality of output, goods, or services produced. Most critically, the QMS for a drug development company functions as an enabler to regulatory compliance as it applies to participant safety and data reliability for clinical development programs and regulatory submissions.

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Quality assurance, typically thought of as an independent department, is key to quality management and can be considered a tool in the arsenal of ways in which quality can be maintained. A quality assurance function will typically create and manage a robust audit program to demonstrate oversight both within an organization and as part of vendor oversight. ICH E6 notes the differences between quality control and quality assurance in that QC is performed in real time as part of ongoing reviews (e.g., site monitoring) vs. a more holistic retrospective assessment (e.g., audits). The results of both tend to produce lagging indicators of issues; therefore, it is important to leverage quality control checks and audits as early as possible in the lifecycle of a drug development program and implement risk assessment to identify what is critical to quality upfront during protocol design.

Start-up organizations with funding constraints may choose to delay contracting or hiring quality assurance experts until they have progressed further into the drug development process. Minimal elements of quality may be implemented from a manufacturing perspective, but often the QMS is not fully developed until later or is implemented de facto through an acquisition by or merger with a larger company. The risk in delaying quality management is often rationalized commensurate with the risk tolerance of the organization, but this can be problematic, leading to costly errors, resource waste, and delayed submissions. Additionally, the development and implementation of a QMS may seem cost prohibitive when compared to those developed by larger pharmaceutical companies, but it does not have to be when reduced to the fundamental principles and core elements that have served many companies, including those outside of the pharmaceutical and biotechnology industries. The principles referenced herein date back to the teachings of Joseph Juran, author of the first "Quality Handbook" published in 1951, which remains applicable across multiple industries to present day [4]. Known as the "Juran Trilogy," the three principles of quality planning, quality control, and continuous improvement may be applied to all types of industries producing products and services. Although some may consider risk identification as part of planning, risk management has evolved considerably with the pace of technologies and thus has been incorporated into many regulations and guidance, such as ICH Quality (Q9, Q10, Q12) and Efficacy (E6, E8). In determining where to begin in the development of a QMS for smaller sponsors or mid-size organizations, the Juran Trilogy can be adapted to any organization, including sponsor investigators in academic environment, as the fundamental quality principles in support of a risk-based quality management framework, as viewed in Figure 1.

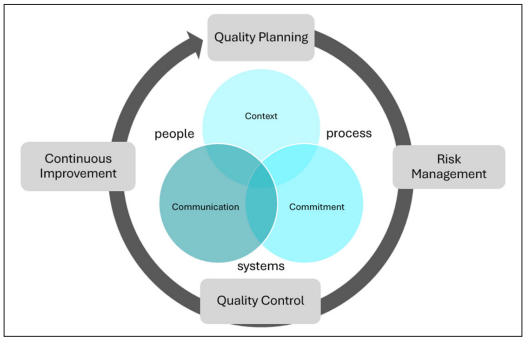

Figure 1: Quality Principles

While foundational, successful application of the quality principles cannot be achieved without the addition of three components or the "three Cs" necessary to build and sustain a strong quality-minded culture of a given organization. The components or "three C's" include - Context, Commitment, and Communication. As noted in Figure 1, an organization must know and understand the Context of the business environment in which they work, both internal and external to ensure business and quality objectives are in alignment with regulatory requirements. Understanding context is also considered a foundational element of the clinical quality management system as described in the TransCelerate Whitepaper to allow for tailored development, refinement, and implementation of a clinical QMS [5]. To understand the context of the environment, information from external parties such as patients, advocacy groups, key opinion leaders (KOLs), and medical associations, as applicable to the disease and population under study, is critical input into the design and execution of a protocol. Costs can be minimized by leveraging associations, consortia, advocacy programs, and the FDA's Patient Focused Drug Development (PFDD) pathway prior to phase 3 trials. Additionally, when clinical evidence from a limited number of patients will be available to support the individualized product's safety or efficacy in the intended patient population, FDA anticipates that substantial evidence of effectiveness for individualized therapies could be established based on a single adequate and well-controlled clinical investigation with confirmatory evidence, as described in the Considerations for the use of the Plausible Mechanism Framework to Develop Individualized Therapies that Target Specific Genetic Conditions with Known Biological Cause draft guidance for industry [6]. Though this pathway may reduce costs associated with a second well- controlled randomized clinical trial (RCT), it does not negate the need for quality oversight as it applies to all sources of data being included in a submission.

Context alone is not enough to cultivate a quality mindset across the organization. Employees at all levels must also Commit to quality and continuous improvement through training and education, and adherence to regulations, procedures. This commitment transcends reporting hierarchies and should serve as a baseline requirement as part of the code of conduct or compliance policy for any organization. Staff should be hired with appropriate expertise for their role, and where outsourcing models apply, reference to quality and compliance requirements should be incorporated into contracts and agreements. Those who do not commit to quality may prioritize speed or cost over quality, and/or choose to exclude quality representatives from key activities thus missing an opportunity to fully embrace the importance of quality by design (QbD) as it applies to the industry. When commitment to quality is minimized or secondary, it often leads to increased deviations, compliance issues, chaos, and a reactive state vs. one that is less error-prone, more stable, proactive, and efficient.

Clinical development programs are fraught with variation, which can challenge one-size-fits-all standards or box-checking approaches. While helpful for certain types of tasks, box checking can create gaps across different therapeutic areas, clinical investigator sites, and trial models (e.g., decentralized). Higher-level critical thinking is required to identify what is critical to

quality for a given clinical development program as part of risk assessment. Employees working in clinical development roles should be trained to leverage critical thinking, and sponsors should ensure there is open Communication between all relevant stakeholders. As indicated in ICH E8, creating a culture that values and rewards critical thinking and open, proactive dialogue about what is critical to quality for a particular study, going beyond sole reliance on tools and checklists, is encouraged [4]. Robust training in root cause analysis (RCA) can support critical thinking so that all stakeholders, regardless of their role or function, can understand and contribute to the development of effective solutions. Emphasis on reporting issues when they happen can help to ensure they are caught early and rectified before they become a larger problem with material impact to participant safety and/or data reliability. Ongoing communication with quality leads and stakeholders, inclusive of patients, patient advocacy groups, key opinion leaders, and medical associations, is necessary to support proactive QbD approaches as described in ICH E8.

Quality Management System Core Elements

Once fundamental principles have been established, core elements are necessary to execute the QMS as seen in Figure 2. ICH E8 clarifies that the quality of a clinical study should be fit for purpose, meaning the quality of the information generated should be sufficient to support good decision-making. The QMS enables a QbD approach in support of any clinical development program through a lattice of policies and procedures, training, risk management, vendor oversight, audits, CAPA tracking, and governance as the minimum core elements, like how nucleotides support the helical structure of DNA.

The "three Cs" *Context*, *Commitment*, and *Communication*, facilitate the practical application of quality planning, risk assessment, quality control, and continuous improvement and are fundamental for all quality management systems, in support of a quality by design approach regardless of the size of a sponsor organization or company. Like the sugar phosphate backbone that forms the helical structure of DNA, the "three Cs' are fundamental to the quality principles. Core quality system elements comprised of SOPs, Training, Vendor Oversight, Inspections, Audits, CAPA Management, and Governance may be considered analogous to the nucleotide bases of the DNA double helix.

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Policies/SOP	Training	Vendor Management	Risk Management	Audits & Inspections	CAPA Management	Governance/ Oversight
Policies	Curriculum Development	RFP/Vendor Selection	Protocol design	Audit planning: investigator sites, vendors, CDMOs, Systems, Internal	Gap Assessments/RCA	Data Analytics/Trend Reports
Procedures	Training Delivery	Quality Agreements	CTQ identification	Inspection Readiness: Documents, Mock Interviews, Storyboards, PAI	Audits/Inspection	Compliance Investigations
Work Instructions/ Forms/ Templates	Training Compliance	Inventory Management	Risk assessment	Inspection hosting - regulatory authority engagement	Quality Events	Escalation
Regulatory surveillance	Quality Outreach: - Support study risk assessment - Education	Qualification	Mitigation	Reports/response coordination and review	Deviations/ Serious Breach	External Reporting
Lifecycle Management		Audit Cycle/Tracking	Documentation		Complaints	Enterprise Risk Management
Change Control		Quality to Quality Engagements -KPI/KQI review	Communication of risks		Effectiveness Checks	Committee/Board Reporting
			Routine review			

Figure 2: Core Quality Management System Elements

The core elements apply to all size development companies yet there can be some flexibility across the sub-elements. As an example, a small start up with ~25 employees will not require the same level of communication pathways and escalation procedures as a large organization may need to ensure regulatory reporting timelines are met for safety related or serious breach reporting. There may also

be one committee that handles quality governance and oversight (e.g., training compliance, risk management, change control, etc.) in tandem with corporate compliance activities in a small company vs. these being delegated across different functional areas in a large global company.

The development of standard operating procedures, polices, and training programs can vary by company, again under the guise of what is fit for purpose in the context of business objectives. At a minimum, policies should include a declaration of acceptable codes of conduct and general principles for compliance with regulations as applicable. SOPs should include purpose, scope, roles, and responsibilities, and be written clearly to facilitate compliance, not hinder it. Work instructions and forms can include more detailed "how to" instruction, and all procedures should be subject to document lifecycle management to ensure ongoing reviews for feasibility, compliance, change control, and impact assessment for compliance with current regulatory requirements. SOPs should reflect the actual process at an appropriate level of detail and not represent a carbon copy purchased from a vendor or consultant, whereby there may be misalignment or compliance gaps. What is fit for purpose for a large pharmaceutical company may not be fit for purpose or feasible for mid-size or smaller companies. It is recommended that process mapping be done first to ensure the SOP reflects the actual work being done and specific roles involved. Consultants can be extremely helpful, but a gap analysis alone is not enough to develop the procedures for a given function or regulated activity. In smaller companies, poor compliance is often the result when consultants with good intentions bring a suite of pre-written SOPs that have been tailored for a different type of organization. SOPs should be customized to align with the context of the business (e.g., one drug in development vs. multiple, solid dosage form vs. device, U.S. vs. global submission, etc.). Quality system elements should be flexible enough to mature and scale with the growth of the company (e.g., SOPs may increase as internal hires, global footprint, and system applications grow).

Training programs are a critical necessity from a regulatory perspective and should include job role-specific curricula, competency testing, and monitoring for compliance. Even for smaller companies, it is wise to invest in a formal learning management system (LMS) to reduce the manual effort involved in documenting training and monitoring compliance metrics for internal and external training courses as applicable (e.g., third party GDPR or GCP certifications). Even for smaller companies, ongoing education should be a mainstay in training programs wherever possible as best practice and in support of career development.

As is typical for smaller companies, a full or partial outsourcing model can be leveraged over internal hiring, but vendor oversight related costs will apply. The list of contractors and vendors to whom services are outsourced will be requested during inspections to assess the services provided. FDA investigators will also document the physical location, point of contact, and contact information (address, phone number, and email address) of these contracted parties as instructed in the Bioresearch Monitoring Program Compliance Manual [7]. Under BIMO, focus is given to how vendors are qualified for the services being provided and how performance is monitored on an ongoing basis. Routine sponsor-to-vendor engagement is required to review KPIs, and quality-to-quality engagement should be implemented to ensure KPIs include quality related measures, as well as those that are milestone driven such as enrollment. Tracking of all vendor awards, engagements, audits, and performance should be embedded within quality management and governance activities and documented in meeting minutes. All forms of outsourcing such as outcome measure assessments that may be performed by a qualified third party to control bias or video review as part of study monitoring must be documented and retained as essential sponsor documentation. Although accountability for all decisions and oversight lies with the sponsor, roles and responsibilities should be documented in service level agreements and language should be clear regarding disclosure, oversight, and communication of issues as applicable to any sub-contracted entities by the vendor.

When the effort is made to establish a robust and fit-for-purpose quality management program upfront (e.g., at the time of protocol design), inspection readiness activities will be less resource-intensive, less costly, and more efficient. Storyboards for pertinent issues should be created in real time, vs. long after an issue has occurred, and routine QC checks of the trial master file (TMF) can significantly reduce backlogs. Keeping the end in mind may take more time to arrange upfront but can significantly reduce time and costs associated with end-of-trial file clean-up. It is advised to have an SOP to manage and facilitate inspections. The more prepared an organization is with defined roles and tasks to cover front and back-room activities, the more calm staff and inspectors will be, which can facilitate a smooth inspection. Leverage message boards and internal trackers to monitor inspection document requests and questions, build in QC reviews before anything is handed over to an inspector, and remember to conduct mock interviews in advance. Regulators share the same "north star" as every sponsor regarding patient safety and data integrity and acknowledge that errors can happen in clinical research. Perfection should not be the goal if a quality system is truly risk-based, and in fact, ICH E8 states that perfection in every aspect of an activity is rarely achievable or can only be achieved by use of resources that are out of proportion to the benefit obtained [2]. Inspection procedures should include support that can be provided to clinical investigator sites, similar to preparations done for internal sponsor inspections, for both file organization and mock interviews. Full transparency is best when dealing with regulatory authorities who may be questioning gaps in process steps or documentation.

An integral core element of the quality system is the audit program. Audits are key to demonstrating sponsor oversight and involve management of corrective and preventative action plans (CAPAs). Audit programs can be risk-based, leveraging data obtained through centralized monitoring to target specific investigator sites for audit visits and must also include routine audits of vendor partners. Contracted audit firms overseen by an internal quality function can offer an independent review under a flexible model for smaller companies. It is advised to perform internal audits and gap assessments of critical functions and activities such as adverse event reporting and study monitoring. The quality principle of continuous improvement cannot be fully realized without investigations into RCA to create CAPA plans that allow for effective and sustained improvement. A proactive,

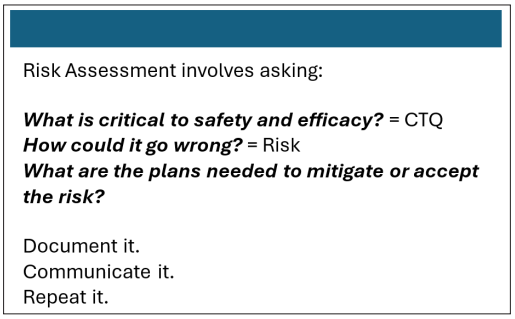
risk-based quality management program can help organizations avoid "death by CAPA" that can result in a highly reactive environment. This is where the benefit of adopting a culture of quality and QbD is maximized, as study teams can communicate freely to ensure appropriate escalation of issues early, in the spirit of continuous improvement, and before they become a systemic problem with material consequence.

One way to continuously monitor and assess the effectiveness of the quality system is through managerial review and of quality data for training compliance, SOP lifecycle reviews, quality events reported, audit and inspection results, and CAPA tracking. Quality is an enabler to compliance; therefore, the quality outcomes should be summarized and reviewed as part of routine governance and quality oversight meetings (e.g., executive and board levels). For smaller companies, this committee may also serve as the change control committee to document impact assessments and perform risk assessments. Sophisticated technology and systems exist across the industry to manage quality and compliance outputs, some with elaborate dashboards, predictive analytics, and artificial intelligence (AI) capabilities. While these systems can offer efficiency, they can be costly with licenses and resources needed to maintain them, and systems routinely used for larger pharmaceutical companies may not be fit for purpose for smaller companies. If utilizing artificial intelligence (AI) to supplement development program-related work, a risk assessment and compliance oversight should be incorporated into governance reviews and quality plans. System SOPs should be created for the curation and versioning of AI models used, algorithm training and validation, continuous monitoring for model drift and bias detection. Life science companies are leveraging AI for patient recruitment, medical writing, TMF checks, and consistent delivery of safety information updates across regions. Other uses for AI in clinical development are being explored, and this will continue to be an evolving space. Use of AI in capacity requires validation, and where global marketing strategies apply, the European Commission (EU) GMP New Annex 22 requires that AI systems be static and deterministic, not generative if used for manufacturing purposes [8]. Additionally, if the program involves grant funding through the National Institutes of Health (NIH) and/or the Department of Defense, additional requirements and risk management frameworks may apply under the U.S. Department of Commerce, National Institute of Standards and Technology (NIST) [9].

Risk Management

Just as a tear or break in a strand of DNA can result in a block to genetic replication, a defect within the core quality system elements can lead to an under-performing QMS. Risk assessment, as required under ICH, both at the study and corporate level, cannot be understated. The first step in assessing risk at the clinical trial level is to identify what is critical to quality, as described in ICH E8 and E6, which provides an outline for conducting risk assessment. Large companies may generate internal tools or leverage more sophisticated systems, but for smaller companies, there are free tools available. The TransCelerate Risk Assessment and Catagorization Tool (RACT) and the Clinical Trials Transformation Initiative (CTTI) Quality by Design Tool Kit are two examples of free tools available to the industry [10,11]. The process of performing risk assessment can take multiple meetings with various stakeholders, but as stated previously, the time spent upfront pays dividends in the end. For manufacturing, quality risk management is managed similarly as required under ICH Q9 and Q10.

Figure 3 below demonstrates how a sponsor should proceed with risk assessment as defined in ICH E6. In the most practical approach, risk assessment begins by asking basic questions, such as "what is critical," "what could go wrong," and "how can it be mitigated?" The risks and mitigations must be communicated to development teams and relevant parties, and the process is repeated annually, or at a prespecified enrollment milestones for shorter studies.



Risk Assessment Steps	Step Description	How to proceed?
Step 1 – CTQ	Identify Critical to Quality study parameters and activities	Ask what is most critical to the success of your trial in ensuring participant safety and data integrity.
Step 2 – Risks	Identify risks as they pertain to the CTQs identified in step 1 above	Ask what could go wrong? In addition to ensuring sound science, are there limitations to enrollment capabilities or operational risks such as using a centralized vendor or pharmacy, or multiple sites?
Step 3 – Evaluate	Determine the likelihood for error, detectability, and impact of identified risks	What is the likelihood of risks happening? Are they detectable? What is the impact of errors on human subject protection and reliability of results?
Step 4 – Control	Determine what risks may be accepted vs. those that should be reduced or mitigated	Document how risk may be reduced or mitigated. Ensure appropriate monitoring is in place to detect errors and reduce risks early on in the trial. Consider setting quality tolerance limits upfront to monitor risks from study start and facilitate when action is needed.

Step 5 – Communicate	Discuss the risks during study team meetings, during routine huddles. Consider sharing risks with other study teams doing similar research.	Document the risk assessment and maintain in the TMF to demonstrate quality management activities for the study. Inform all who are involved in study activities, to facilitate risk review and continuous improvement during clinical trial execution.
Step 6 – Review	Risk assessment is iterative. Revisions may be necessary with protocol modifications or when new risks are identified	Periodically review risk control measures to ascertain whether the implemented quality management activities remain effective and relevant, taking into account emerging knowledge and experience. Update at least annually or at specified milestones as appropriate for shorter studies.
Step 7 – Report	Requires including quality management activities in study reports. Also includes reporting deviations and updates based on any new risks identified	Describe the quality management approach implemented in the trial and summarize important deviations from the predefined quality tolerance limits and remedial actions taken in the clinical study report.

Figure 3: Risk Assessment Process

Identification of what is critical to quality (CTQs) to facilitate the assessment of risks should be done at the time of protocol development, with risk assessment continuing throughout the execution of the study. Examples of CTQ parameters may include participant safety endpoints, enrollment to drop out ratios, blinding controls, proper administration of investigational product, and proper study data access and permissions. Sponsors should develop systems to manage quality throughout all stages of the trial process, as required by ICH, and ensure that quality oversight is commensurate with the risks associated with the clinical development program to support informed decision-making. Where outsourcing models apply, procedures to demonstrate proper oversight such as vendor qualification questionnaires, quality agreements, routine audits/audit trail reviews, and governance meetings are necessary. For example, routine meetings to review status of manufacturing, distribution, and on-going review of all drug accountability logs from suppliers to sites through to return is critical to quality to demonstrate proper chain of custody for a study using cold chain or controlled substances. Special considerations should be given to data for endpoint measurements associated with patient reported outcomes or quality of life scales to control bias. Data capture specifications or where necessary for paper, certified copy practices, should be established upfront before a trial begins and monitored routinely per the monitoring plan during the trial to ensure data integrity of endpoint measures.

Through the 21st Century Cures Act, the FDA formally created a program to evaluate the potential use of Real-World Data (RWD) which may be analyzed for submission as Real-World Evidence (RWE) in support of new indications for previously approved drugs. It is important to ensure risk assessments include mitigations for the management of data coming from external sources to the clinical development program. Reviews and data checks are necessary to ensure accuracy in data collection that aligns with the objectives of the study, and to ensure privacy and security controls. Retrospective review of existing data also requires IRB/Ethics committee review for consent requirements and approval.

Discussion

The quality by design approach can be realized in any size company or organization when quality principles and core elements of the QMS have been established, people are trained, processes and system applications are outlined clearly and refined commensurate with the risks of a given clinical program. It is important to note that the adoption of a quality by design approach may not be possible if efforts to establish the foundational principles, QMS core elements, and quality culture are delayed. It is the people who execute day-to-day quality management activities and a culture of beliefs and behaviors that can enhance or detract from the value of the clinical quality management enterprise [12]. This applies to all key functions such as clinical program operations, study teams, product manufacturing, regulatory, and medical affairs. It also applies to commercialization and marketing groups where pharmacovigilance regulations apply (e.g., patient support programs). While the fundamental quality principles and core elements drive the quality management system forward, diversity, equity, inclusion, and regulatory compliance remain central to patient/participant safety and data integrity, as seen in the example QMS construct depicted in Figure 4 below. Studies designed without consideration of diverse patient populations, or those that exclude patients due to economic limitations (e.g., lack of access to internet) may result in gaps in the robustness of the data necessary to fully characterize the safety profile of the investigational product under study. For support in addressing diversity, equity, and inclusion in clinical trials, reference the Achieving Diversity, Equity, and Inclusion in Clinical Research Guidance Document, published by the Multi-Regional Clinical Trials Center [13].

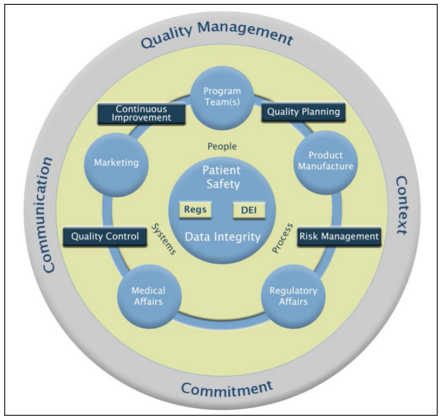


Figure 4: Example QMS

Establishing quality upfront and as early as possible enables a proactive approach to regulatory compliance for any clinical development program. The quality culture cannot be established effectively without the "three C's" serving to provide an understanding of the context of the business environment, a commitment to quality by all employees, and ongoing communication between all functions and departments. The "three C's" remain fundamental to driving behaviors in support of a quality mind-set and culture, which facilitates continuous improvement. This framework aligns with ICH E6 and ICH E8 expectations and serves to enable regulatory compliance for any size organization.

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