WEBINAR

The BIMO Guide Update:

How these expectations impact a Sponsor's Quality Management System

March 9, 2022

Today's Facilitators

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Introductions – WCG Avoca Quality Consortium (AQC)

wcg Avoca QUALITY CONSORTIUM™

180+ AQC Member Companies

Sponsors, CROs, clinical service providers, sites, and other organizations engaged in clinical trial execution

Avoca Research

Quantitative and qualitative data from across the industry on key topic areas

Leading Practices

Access to ~500 guidelines, tools, approaches, standards, and templates focused on proactive quality and risk management

Collaboration

Leadership advisory boards, annual global Summit, working sessions, regional networking events, educational webinars, and online community, *Aha!*

WCG Avoca Quality Consortium Member Companies

As of 3/2/2022

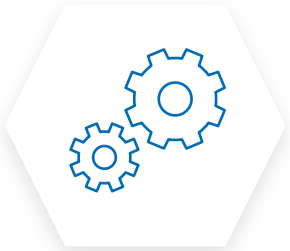
Today's Objectives

1

BIMO Updates

2

Quality Management Systems



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Leveraging the QMS

How familiar are you with the updated BIMO Guide (9/2021)?

- Very familiar
- Slightly familiar
- Not very familiar
- Haven’t heard of it

When was your last FDA Inspection?

- >5 years ago
- 3-5 years ago
- 1-3 years ago
- Within the past year
- Upcoming within the year

BIMO Update

(9/15/2021)

BIMO Changes

BIMO

FDA Bioresearch Monitoring (BIMO) program ensures the protection of the rights, safety, and welfare of human research subjects involved in FDA-regulated clinical studies; to verify the accuracy and reliability of study data submitted to FDA in support of research or marketing applications; and to assess compliance with statutory requirements and FDA's regulations.

Key Updates

INCREASED FOCUS ON:

- Selection and monitoring of Clinical Investigators
- Sponsor's oversight of CROs and other vendors
- Selection of monitors, monitoring procedures and activities
- Data collection and handling
- Electronic records and Electronic signatures

NEW SECTIONS:

- Outsourced services
- Safety Oversight
- Data and safety monitoring board/data monitoring committee

These areas of focus align closely with some of the most common inspection findings, found in the 2021 BIMO report (https://www.fda.gov/media/156517/download).

https://www.fda.gov/media/75916/download

Inspection Items Added

Selection and Monitoring of Clinical Investigators

- Check if an investigator conducted a non-IND trial outside the US
- List of investigators placed on enrolment hold and the reason
- List of changes to the investigator and reason
- Criteria for selection of investigators, including if the sponsor considers the FDA Debarment List and previous administrative and regulatory actions against the investigator
- Sponsor's provision of adequate training to the investigator prior to initiation of and during the clinical trial and that it's documented (e.g., protocol, electronic systems, labelling or Investigator's Brochure, etc.)

Monitoring Procedures and Activities

- A risk-based approach to selecting monitoring activities means that methods may differ between clinical trials. Some changes to the new CPGM include:
  - Increased focus on written monitoring plan (before mentioned guidelines and SOPs), if it was followed, and if it had to be modified
  - Expanded the review to remote monitoring processes
  - Increased scrutiny of monitoring activities, including specifically mentioning assurances that IRB approval and informed consent were obtained
  - Focus on how remote monitoring accesses site files and assures the security and confidentiality of the records (e.g., direct access to EMR)

https://www.fda.gov/media/75916/download

Inspection Items Added

Safety Oversight

- Determine:
  - If the sponsor had a risk management plan and if it was followed
  - Processes and procedures for use of safety data
  - If any SAEs were endpoints or safety events per the protocol

Electronic Records and Electronic Signatures

- Inspection of:
  - Electronic systems that are used to manage critical data and study procedures as well as processes or methods for electronically signing documents

https://www.fda.gov/media/75916/download

Inspection Items Added

Data Collection and Handling

- Inspection of:
  - Data Management plans and SOPs for data collection, handling, and management procedures
  - If there are processes and procedures for data modifications or corrections that they create an audit trail
  - Electronic systems data integrity, security controls, validation, and their documentation
  - Whether the sponsor or vendor provides the electronic system
  - Data flow (creation to reporting) and transmission procedures
  - Assurance that only authorized users have access
  - Training on the systems was provided by qualified individuals
  - Data retention procedures and disaster recovery plans.

https://www.fda.gov/media/75916/download

Inspection Items Added

Outsourced Services

- Review or Determine:
  - If the sponsor has processes and procedures in place for selection of a CRO including determining that the CRO will follow GCP and regulations and that processes of oversight focus on outsourced services that played a significant role in the clinical trial
- Written agreements between the sponsor and CRO, including:
  - where roles, tasks, and responsibilities of the sponsor and CRO are defined
  - where who has the decision-making authority for study activities is documented
- Qualifications of the CRO personnel
- SOPs for audits, communication plans, escalation plans, and contingency plans
  - if there were deviations, what impact assessment and CAPA were performed
- Sponsor communication with the CRO in terms of frequency, purpose, and if they were documented
- Protocol-specific training provided to the CRO
- Oversight plans and any audits that occurred, including their scope

https://www.fda.gov/media/75916/download

How do we ensure all of this is covered?

A Clinical Quality Management System

The BIMO guides outlining how inspectors will ensure regulations are being followed.

Section 5.0 of ICH E6 (R2) notes that the Sponsor is responsible to:

- Implement a **system to manage quality** throughout all stages of the trial process.
- Focus on trial activities essential to ensuring human subject protection and the reliability of trial results.
- Use methods to assure risk and quality control of the trial that are proportionate to the risks.

Quality Management Systems

Does your organization leverage a holistic Clinical Quality Management System?

- Yes, and it is frequently updated to align with regulatory expectations
- Yes, but it is out of date and not up to date with regulatory expectations
- No, but we are working on putting one in place
- No, we are not leveraging a clinical quality management system

What component of Clinical Quality Management does your organization find most difficult?

- Metrics Frameworks
- Vendor Oversight
- Policy/Procedure Development
- Training
- Risk Management
- Quality Culture
- Inspection Management
- TMF/Documentation
- CAPA/Issue Management

WCG Avoca's Components of a Leading Practice CQMS

Quality Agreements	Clarity and documentation of mutually aligned quality expectations and definitions of quality by the use of leading practice templates
Quality Metrics Strategic Framework	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, tools, and documentation to oversee outsourced clinical trial activities; including guidelines and tools
Training	Adequate training of staff, contractors, and vendors
Clinical Risk Management	Strategies and tools to manage risk on a proactive level 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 issue escalation, root cause assessment, impact analysis, resolution, and prevention
Documentation and TMF/eTMF	Processes and tools used in managing clinical trial documentation

Note: Capabilities such as Organizational Change Management, Leadership, Roles/Responsibilities and Compliance Assessment serve as umbrella activities for the CQMS components.

Policies and Procedures

Key Insights

- Policies and procedures serve as a documentation of quality expectations into operational documents that are aligned to clear business drivers and regulatory requirements.
- An organization’s policies and procedures assist in ensuring consistency in execution across the organization and to guide employees to ensure that the documentation that is needed to re-create a clinical trial is completed and filed accordingly.
- Sponsors should implement a CQMS and SOP system to manage quality throughout the design, conduct, recording, evaluation, reporting and archiving of trials.
- Sponsors should focus on essential trial activities (e.g., SAE reporting, CFR Part 11 Compliance, ICH E6 R2 requirements, vendor oversight), and ensure appropriate SOPs, WIs, Templates and Forms are in place.

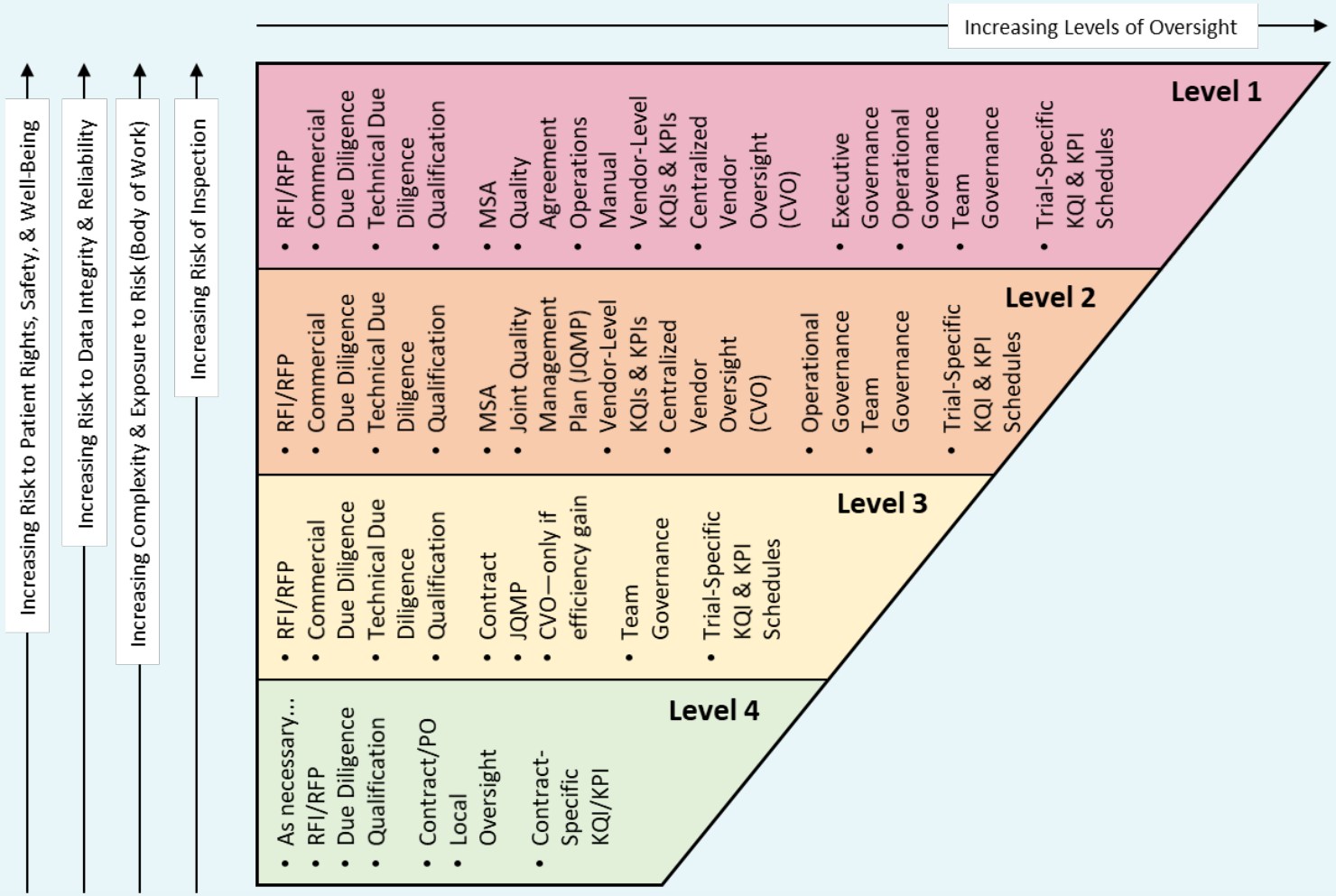
Vendor Oversight

Key Insights

- ICH E6 (R2) has increased regulatory expectations for Sponsor oversight and documentation requirements that are reiterated in the BIMO guide.
- Via networking with the AQC member companies, an eight-component construct has been developed for leading practice oversight of vendors. Sponsors should effectively implement select leading practices from each of the eight components.
- Determine vendor risk categorization to inform the risk of each vendor's activities to ensure human subject protection and reliability of trial results, especially for important efficacy and safety endpoints.

Vendor Oversight

Vendor Risk Categorization



Vendor Oversight

Key Insights

- During regulatory inspections, inspectors will keenly evaluate employee job descriptions, CVs and training plans/records to assess if employees, contractors or investigators are qualified for the activities they perform.
- Job descriptions will be compared to the job titles referenced within the SOPs.
- Regulators will also assess if training is in place to ensure appropriate use of IT systems, the ability to be CFR Part 11 compliant, and to ensure that SAE reporting and other processes impacting patient safety and data integrity are compliant.

Key Insights

- The increased focus on investigator selection and training opens the door for increased need for Sponsors to take risk-based approaches to site monitoring and oversight.

Sponsors need to identify and prepare all sites that they feel could be identified as "high risk"

High risk can include:

- High or low dropout rate
- High or low screening failure rate
- Low or high AE and SAE reporting
- High number of protocol deviations
- Low use of concomitant medications
- Low medical history reporting
- High enrolling sites
- Sites with investigator change

Additional risk areas include:

- Sites with a low or high number of data queries
- Sites with high resolution time/open duration for data queries
- Sites with unusually high or low volume of monitoring issues in MVRs
- Sites with high duration of monitoring issues remaining open in a trial

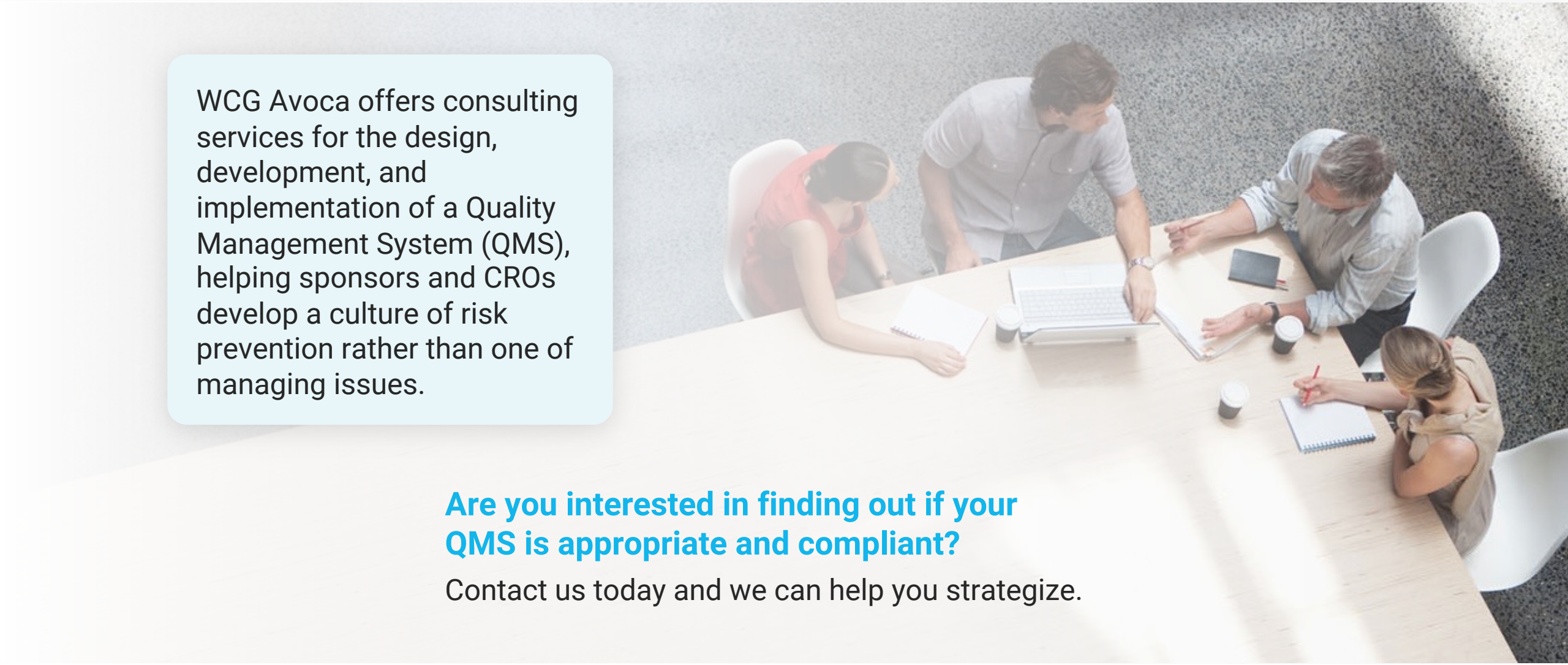
Leveraging your QMS for Successful Inspections

Industry Challenges and Opportunities Relative to CQMS and Inspections

- Understanding and adapting to evolving regulatory landscape, including **ICH E6(R2)**
  - **How will inspections occur relative to prospectively documented risk-based CQMS?**
- Identifying and being prepared for some **common** and some **different** expectations across global agencies
- Coordinating **joint inspections** seamlessly
- Learning from and applying **inspection experiences** from within an organization and across the industry
- Engaging across **complex partnership constructs** to ensure all stakeholders are ready for inspections
- Creating and maintaining **leading practice processes, tools, and behaviors** for a culture of proactive inspection preparedness

Any Questions?

WCG Avoca offers consulting services for the design, development, and implementation of a Quality Management System (QMS), helping sponsors and CROs develop a culture of risk prevention rather than one of managing issues.



Are you interested in finding out if your QMS is appropriate and compliant?

Contact us today and we can help you strategize.

Thank you

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