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# WEBINAR

## *Pass Your Inspections With a Risk-Based Approach in Accord With Trends and Anticipated Ramifications of ICH E6 (R2)*


**PRESENTED BY:**

**Grace Crawford**
*VP Clinical Quality and Compliance*, MedImmune

**Steve Whittaker**
*Senior Consultant*, The Avoca Group


**July 25, 2018**

**HOSTED BY:**

eXL events

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# Topics

- Compare inspections from different regulatory authorities
- Foci of inspectors
  - What they inspected and didn't inspect to determine compliance
- First-hand experiences of sponsors to uncover common pitfalls
- MHRA's emphasis on conducting a risk-based analysis
  - Study case examples
- Comply with ICH E6 (R2) changes by adapting risk-based tools and methods
- Effect a risk-based approach to inspection readiness with tried and tested strategies

# The Avoca Group®

Transforming clinical trial execution by **driving efficiency**, **increasing quality**, and **mitigating risk**.


**Pharma Industry Focus: Quality and Compliance in Clinical Research**

# Avoca Quality Consortium® (AQC)

Driving efficiency, increasing quality, and mitigating risk in clinical trial execution.


**90+ Member Companies** (Sponsors, CROs, Clinical Service Providers)

- **Avoca Research:** Gathering of quantitative and qualitative data from Members; provision of aggregate data and individual benchmarking reports.
- **Leading Practices:** Development of guidelines, tools, approaches, standards, and templates focused on proactive quality management.

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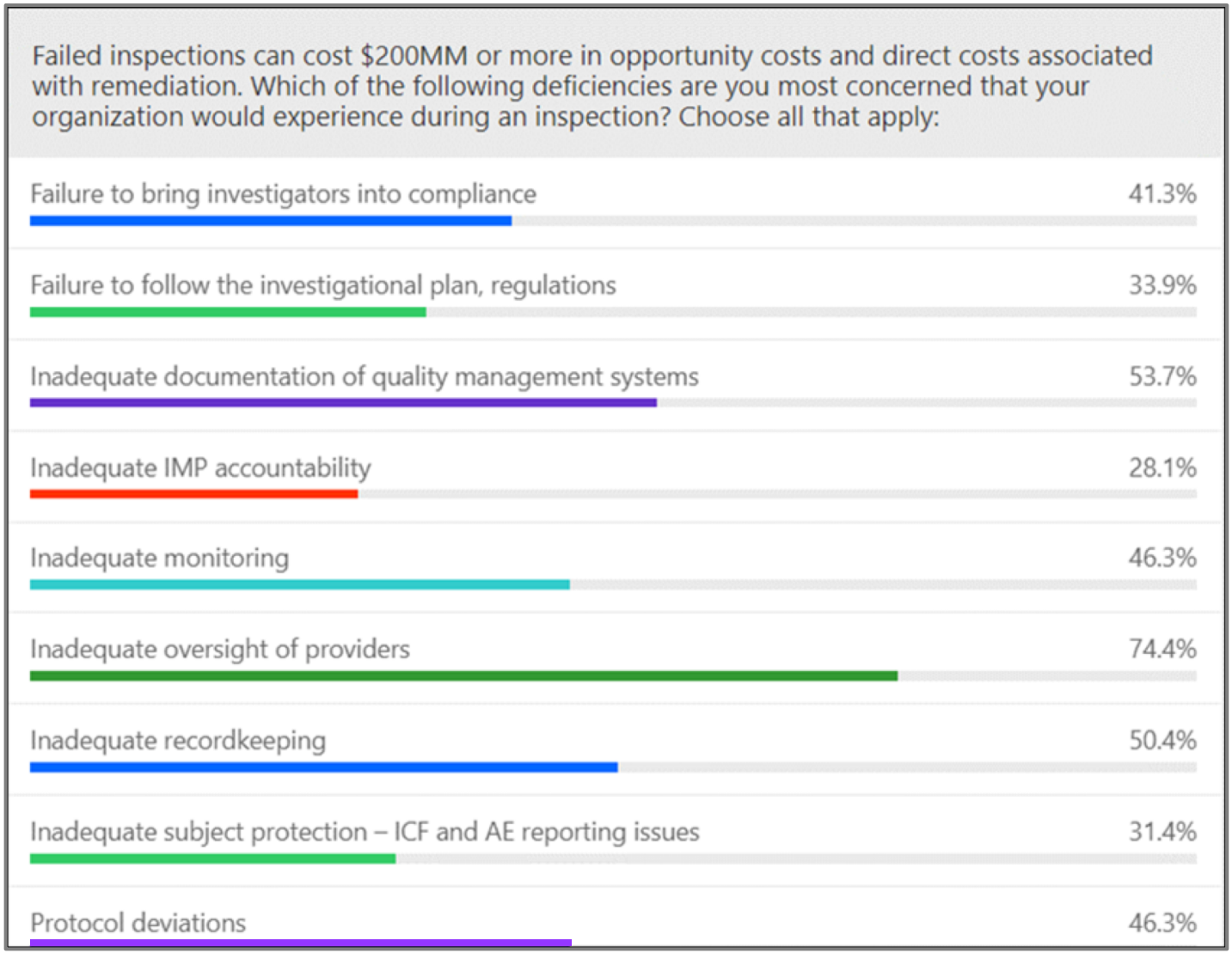
# Current AQC® Members

as of 07/12/2018

# Polling Question

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# Knowledge Grid Construct

## Four Layer Grid

1) Agency Overview / Agency Focus / Member Experiences & Tips / Pharmacovigilance
2) FDA / EMA / MHRA / PMDA / CFDA / Health Canada
3) Specific Categories

| Agency Overview | FDA | EMA | MHRA | PMDA | CFDA | Health Canada |
|---|---|---|---|---|---|---|
| Types of Inspect | | | | | | |
| Inspect | | | | | | |
| Areas o | | | | | | |
| Inspect Approa | | | | | | |
| Finding | | | | | | |

| Agency Focus | FDA | EMA | MHRA | PMDA | CFDA | Health Canada |
|---|---|---|---|---|---|---|
| TMF | | | | | | |
| Monito | | | | | | |
| System | | | | | | |
| Site Per | | | | | | |
| Docum | | | | | | |
| Protocc | | | | | | |
| Provide Oversig | | | | | | |

| Member Experiences & Tips | FDA | EMA | MHRA | PMDA | CFDA | Health Canada |
|---|---|---|---|---|---|---|
| Logistics | | | | | | |
| TMF | | | | | | |
| Monito | | | | | | |
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| Provide Oversig | | | | | | |
| Pharma | | | | | | |
| Genera | | | | | | |

| Pharmacovigilance | FDA | EMA | MHRA | PMDA | CFDA | Health Canada |
|---|---|---|---|---|---|---|
| Logistics | | | | | | |
| TMF | | | | | | |
| Monitoring | | | | | | |
| Systems & Data | | | | | | |
| Site Performance | | | | | | |
| Documentation | | | | | | |
| Protocol | | | | | | |
| Provider Selection, Qualification, & Oversight | | | | | | |
| Pharmacovigilance | | | | | | |
| General | | | | | | |

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# Compare Inspections from Different Regulatory Authorities

## Example agency overview categories (1 of 2)

| Agency Overview | FDA | EMA | MHRA |
|---|---|---|---|
| Types of Inspections | • Marketing Application<br>• For Cause | • Marketing Application<br>• For Cause<br>• National Programs | • IMP in UK<br>• Serious Breach<br>• Risk-based Compliance |
| Inspection Triggers | • Marketing Application<br>• For Cause | • Marketing Application<br>• For Cause<br>• Identified Programs | • Serious Breach<br>• Identified by Risk<br>• Completed Trials |
| Areas of Focus | • Data<br>• Documentation | • TMF<br>• Systems | • TMF<br>• Systems |
| Inspection Approach | • District-based<br>• Announced<br>• CTTI Risks | • Notification<br>• TMF | • Notification<br>• TMF<br>• Grey Guide |
| Findings | • Clinical Investigators<br>• IRBs<br>• Sponsor/Monitor/CRO | • Investigational Site<br>• Sponsor/Monitor/CRO | • Sponsor<br>• CRO<br>• Clinical Research Units |

# Compare Inspections from Different Regulatory Authorities

## Example agency overview categories (2 of 2)

| Agency Overview | PMDA | CFDA | Health Canada |
|---|---|---|---|
| Types of Inspections | • Marketing Application (New or Partial Change)<br>• Good Post Marketing Study Practice (GPSP) | • Marketing Application<br>• For Cause<br>• Routine for Clinical Research Institutions | • Clinical Trial Compliance Program |
| Inspection Triggers | • Marketing Application<br>• Post-marketing every 5 yrs.<br>• For Cause | • Marketing Application<br>• For Cause<br>• Renewal of GCP certification | • Sites for Ongoing Trials |
| Areas of Focus | • Checklists – GCP and Document Conformity | • Clinical Trial Conditions<br>• Regulatory Compliance | • GCP<br>• ICH E6 |
| Inspection Approach | • GCP and Document Conformity in Parallel<br>• Announced in Advance | • CDE Determines Products and Targets<br>• Self Assessment Forms then On-site Inspections | • Scheduled and Announced in Advance<br>• Pre-inspection Checklist |
| Findings | • Data Inconsistencies<br>• Safety Information Provision to Sites | • Data Traceability<br>• Protocol Deviations<br>• IMP Handling | • Systems and Procedures<br>• Records<br>• Training |

# Foci of Inspectors

## Examples of what they inspected and didn't inspect to determine compliance (1 of 2)

| Agency Focus | FDA | EMA | MHRA |
|---|---|---|---|
| TMF | • TMF Available<br>• Inspector Requests Docs | • Primary Focus<br>• Direct Access | • Primary Focus<br>• Direct Access<br>• Provide All Answers |
| Monitoring | • BIMO<br>• System, Trial, Site Levels | • System, Trial, Site Levels through to CSR | • System, Trial, Site Levels<br>• Follow SOPs |
| Systems & Data | • Data are primary focus | • Preliminary assessment with specific questions | • Not primary focus |
| Site Performance | • Algorithm to select sites | • High-risk sites | • High-risk sites |
| Documentation | • May request documents in advance; no dossier | • EMA dossier requirements in advance | • MHRA dossier requirements in advance |
| Protocol | • Protocol deviations | • Protocol deviations | • Protocol deviations |
| Provider Selection, Qualification, & Oversight | • Contracts<br>• Documented selection, qualification, oversight<br>• TORO, Quality Agreement | • Contracts<br>• Oversight | • Contracts<br>• Oversight |

# Foci of Inspectors

## Examples of what they inspected and didn't inspect to determine compliance (2 of 2)

| Agency Focus | PMDA | CFDA | Health Canada |
|---|---|---|---|
| TMF | • Documents from TMF Available<br>• Compares Documents against Checklist | • Documents from TMF or LIMS available<br>• Facility Certifications | • Systems and Procedures with some Sent in Advance |
| Monitoring | • Monitoring SOP and Documentation<br>• Trial, Site and Subject Levels | • Oversight of CRO Conducting Monitoring | • Evidence of Risk-based Approach<br>• Monitoring SOP |
| Systems & Data | • Process and Data Oriented<br>• Data Discrepancies | • Focus on Data Integrity and Potential Fraud | • Focus on ICH E6 Section 5.5.3 |
| Site Performance | • Annex 8 of PMDA Procedure | • Site Conditions and Compliance | • Focus on Inspection Document Checklist |
| Documentation | • Documents Requested in Advance – Annex 8 | • Document Reviews | • Document Reviews |
| Protocol | • Protocol deviations | • Concomitant Drug Use | • Protocol Documentation |
| Provider Selection, Qualification, & Oversight | • Contracts Compliance to JCP Article 12 | • Compliance to Contracts, GCPs and Protocol | • Contracts<br>• Delegation of Activities |

# First-hand Experiences of Sponsors to Uncover Common Pitfalls

## Glimpse* of AQC Member company experiences and tips

(1 of 2)

| Member Experiences & Tips | FDA | EMA | MHRA |
|---|---|---|---|
| Logistics | • Multiple Days on Site | • Multiple Days on Site | • Multiple Days on Site |
| TMF | • Documents to be Provided | • eTMF Access | • Extensive eTMF Access |
| Monitoring | • Monitoring Plan<br>• Issue Resolution | • Monitoring Plan<br>• Issue Resolution | • Monitoring Plan<br>• Issue Resolution |
| Systems & Data | • Validation<br>• Analytics | • Data Integrity Relative to time Entered | • Quality Metrics |
| Site Performance | • Qualification, Training | • Systems and Procedures | • Data Queries |
| Documentation | • BIMO Required Docs Available | • Contracts and Proof of Insurance | • Relevant Persons Present to Discuss |
| Protocol | • CSR Reportable Violations | • Monitor Reports to CSR | • Deviations |
| Provider Selection, Qual., & Oversight | • Credibly Speak to Inspectors about oversight | • Demonstrate Effective Oversight Process | • Prospective Oversight for trial Management |
| Pharmacovigilance | • Late Reports | • Assessments w/i Trials | • Process, Timeline, Quality |
| General | • Proactively Prepare Sites | • Present to Inspectors | • GCP Inspection Dossier |

*Time only permits sharing a glimpse during today's session.

# First-hand Experiences of Sponsors to Uncover Common Pitfalls

## Glimpse* of AQC Member company experiences and tips

(2 of 2)

| Member Experiences & Tips | PMDA | CFDA | Health Canada |
|---|---|---|---|
| Logistics | • Follow Checklists Closely | • 4 – 5 Sites for 6- 8 Days | • Risk-based Compliance Program |
| TMF | • Documents to be Provided | • Documents to be Provided | • Documents to be Provided |
| Monitoring | • Monitoring plan<br>• Sponsor Follow-up to Issues | • Monitoring plan | • Monitoring plan<br>• Visit Reports |
| Systems & Data | • Compliance and Consistency of Data in EDC | • Data Integrity for Specific Subjects | • Systems Deep Dive |
| Site Performance | • PI Interviews Important | • Systems and procedures | • Site Process and Performance |
| Documentation | • Published Inspection Checklists | • Focus on Documentation | • Documentation to Follow SOPs |
| Protocol | • Evidence of Draft Protocols with Functional Inputs | • Compliance to Protocol | • Compliance to Protocol |
| Provider Selection, Qual., & Oversight | • Compliance to JCP Article 12 | • Focus on Financial Information | • Focus on Oversight |
| Pharmacovigilance | • Good Post-Marketing Study Practice (GPSP) | • AE and PSUR Reporting | • Compliance to SOPs |
| General | • Focus on Management of IMP | • 3 Day Site Response | • Focus on Management of IMP |

*Time only permits sharing a glimpse during today's session.

# First-hand Experiences of Sponsors to Uncover Common Pitfalls

## Example Pharmacovigilance Insights (1 of 2)

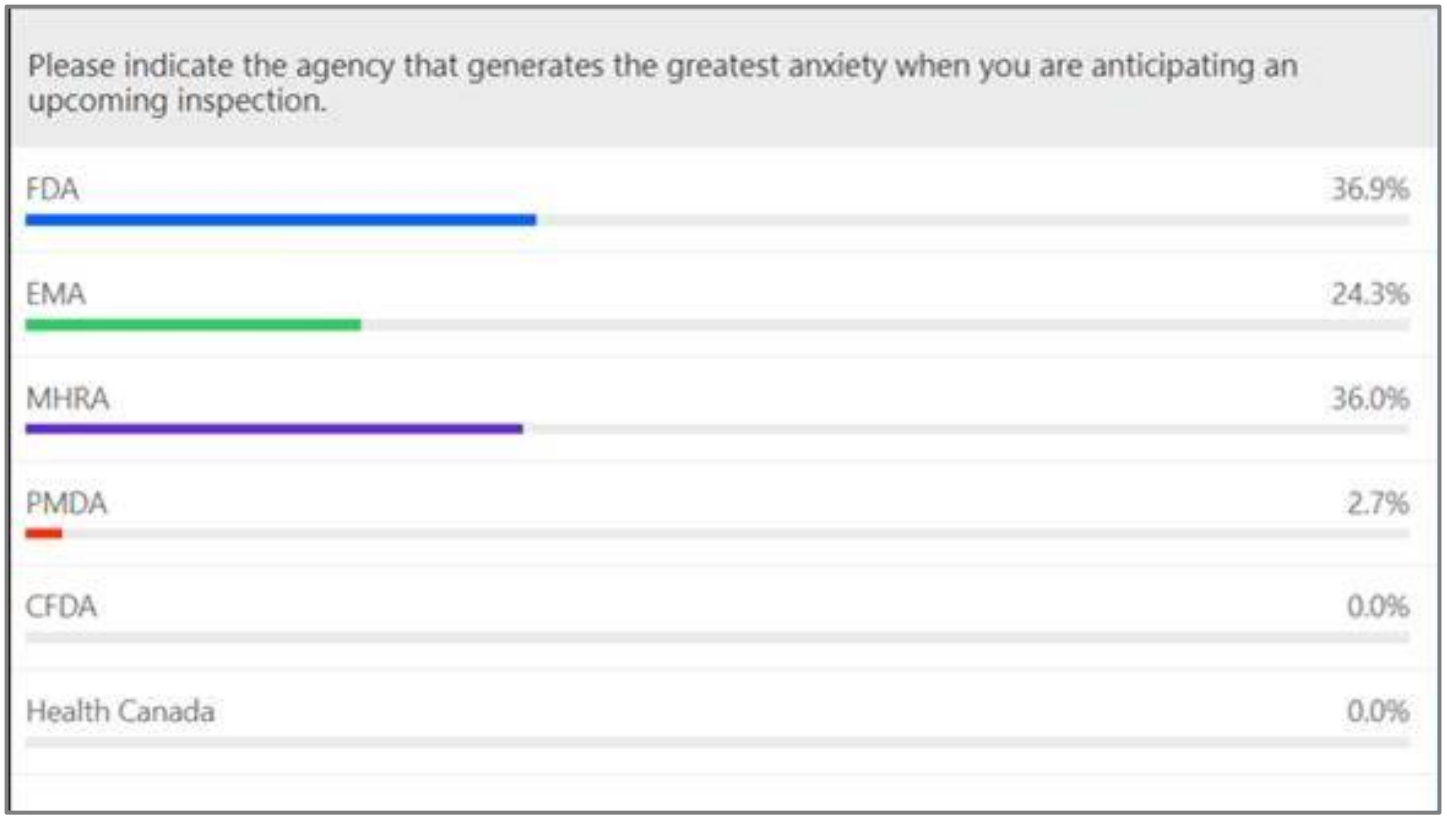
| Pharmacovigilance | FDA | EMA | MHRA |
|---|---|---|---|
| Supporting References | • FDA Compliance Manual | • GVP Module III<br>• Annual PV Report | • GPvP<br>• PV Metrics |
| Types of Inspections | • CT Inspections<br>• Post-Marketing Drug Experience (PADE)<br>• Risk Evaluation and Mitigation Strategies (REMS) | • CT Inspections<br>• Routine PV Inspections<br>• "For Cause" PV Inspections<br>• PV Systems<br>• Product Related | • CT Inspections<br>• Routine PV Inspections<br>• "For Cause" PV Inspections |
| Inspection Triggers | • Market Application<br>• PADE Directed | • Market Application<br>• QPPV Qualification<br>• Adequacy of PV System | • Market Application<br>• GPvP Breach |
| Inspection Approach | • Focus on Products with Greatest Safety Risks | • Request for Pharmacovigilance System Master File (PSMF) | • Request for PSMF |
| Inspection Findings | • Inadequate Subject Protection<br>• Failure to Report AEs, including on time | • Failure to Report AEs, including on time<br>• Quality Management System | • Inadequate Resolution of Prior Findings<br>• Quality Management System |
| Areas of Focus | • Safety Reports | • Safety Reports | • Safety Reports |

# First-hand Experiences of Sponsors to Uncover Common Pitfalls

## Example Pharmacovigilance Insights (2 of 2)

| Pharmacovigilance | PMDA | CFDA | Health Canada |
|---|---|---|---|
| Supporting References | • PMDA Webpage<br>• PMDA Safety Online | • CFDA Circular | • GVP Guidelines<br>• Compliance and Enforcement Policy |
| Types of Inspections | • CT Inspections<br>• GVP Compliance<br>• Reliability Assurance | • CT Inspections<br>• Routine PV Inspections<br>• "For Cause" PV Inspections | • CT Inspections<br>• Post-Marketing |
| Inspection Triggers | • Market Application<br>• Good Post-Marketing Surveillance Practice (GPMSP) | • Market Application<br>• Routine Inspections<br>• "For Cause" Inspections | • Facility Compliance<br>• ADRs |
| Inspection Approach | • On-site Surveys and Document Review | • Locations Where Drug Manufacturers Participate in ADR | • Advance Notice and Inspection Duration Vary |
| Inspection Findings | • May be Accessed from Japan Society of QA | • Not Publicly Available | • Serious Adverse Drug Reporting (SADR) Reports |
| Areas of Focus | • Safety Reports | • Cluster AEs<br>• SAEs | • Safety Reports |

# Polling Question



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# Study Case Examples – Inspection Experiences

## TMF

- Completeness of the TMF
- Directly accessible by inspectors
- Review Original/Certified copy documents
- Record/Data Integrity (audit trails)
- Inspector Access to Unblinded content (and measures to protect)

## CRO Oversight - Data quality/integrity findings

- Data critical to quality (inc/exl criteria, 1$^{o}$ Efficacy, Endpoints, etc.)
- Audit trails from vendor systems in xls format

# Study Case Examples – Inspection Experiences

**Risk Based Monitoring**

- Encouraging adoption of this approach
- Training of monitors (site and central)
- Sufficient time to do the work
- Delivers in accordance with established plans
- Governance & Controls

# MHRA's Emphasis on Conducting a Risk-based Analysis

## 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

# Adapted Risk-based Tool: Example Weighted Decision Grid

**Avoca Quality Consortium Quality Oversight Module:**
**Governance Tool- Decision Scorecard**

**DECISION SCORECARD**

**INSTRUCTIONS**

1. Engage relevant team members during development to ensure decisions represent a balanced viewpoint.
2. High Level: Try to keep the number of categories to < 7 so it does not dilute critical concerns.
3. Add additional comments or smaller concerns as 'comments'.

**DECISION DETAILS**

| | |
|---|---|
| WHAT? Decision needs to be made | |
| WHY? Decision needs to be made | |
| WHEN? Decision needs to be made | |
| WHO? Makes the decision/recommendation | Responsible:<br>Accountable:<br>Consulted: |
| COMMUNICATION Who is informed about the decision? | Informed:<br>Meeting updates required: |

| KEY DECISION FACTORS | | ALTERNATIVE OPTIONS | | | |
|---|---|---|---|---|---|
| | | 1) OPTION 1 . . . . | | OPTION 2 . . . . . | |
| Factor | Factor Weight (1-10) | Score* | Comments | Score* | Comments |
| Factor 1: | | | | | |
| Factor 2 | | | | | |
| Factor 3 | | | | | |
| Factor 4 | | | | | |
| Factor 5 | | | | | |
| Factor 6 | | | | | |
| Factor 7 | | | | | |
| TOTAL (highest score = best alternative) | | 0 | | 0 | |

*SCORING LEGEND

| | |
|---|---|
| Strong Positive | Score = 10 |
| Neutral | Score = 5 |
| Strong Negative | Score = 1 |



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# Effect a Risk-based Approach to Inspection Readiness

## Tried and Tested Strategies

**ICH E6 (R2) Elements**

**Quality Management System**

- Design
- Conduct
- Recording
- Evaluation
- Reporting
- Archiving

**Risk-based Approach**

- Critical Process and Data Identification
- Risk Identification
- Risk Evaluation
- Risk Control
- Risk Communication
- Risk Review
- Risk Reporting

**21 CFR 820**

Quality System ***Regulation***

System **Requirements**

- Management Responsibility
- Quality Audit
- Personnel

**Controls**

- Design
- Document
- Purchasing
- Identification & Traceability
- Production and Processing
- Acceptance Activities
- Nonconforming Product
- CAPA
- Labeling & Packaging
- Handling, Storage and Distribution
- Maintain Records
- Records

**ISO 13485:2016**

Quality Management System – **International Standard**

**QMS Requirements**

- Quality Manual
- Medical Device File
- Control of Documents
- Control of Records

**Management Responsibility**

- Planning
- Responsibility, authority, communication
- Management Review

**Resource Management**

- Human Resources
- Infrastructure
- Work environment

**Product Realization**

- Planning
- Customer-related processes
- Design and development
- Purchasing
- Production and Service Provision

**Measurement, Analysis and Improvement**

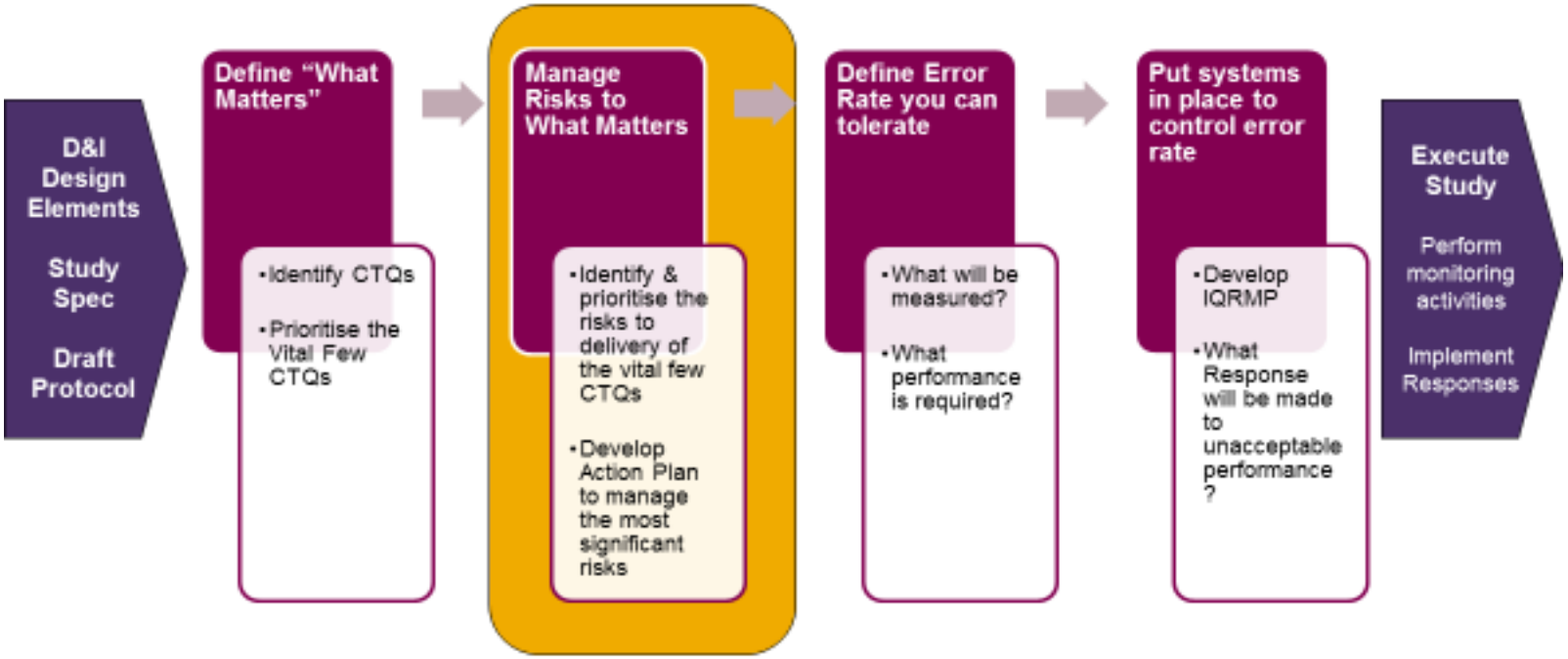
- Monitoring and measurement
- Control of nonconforming product
- Analysis of data
- Improvement

# Example Approach

## Identify Potential Risks, Assess, & Focus on What Matters

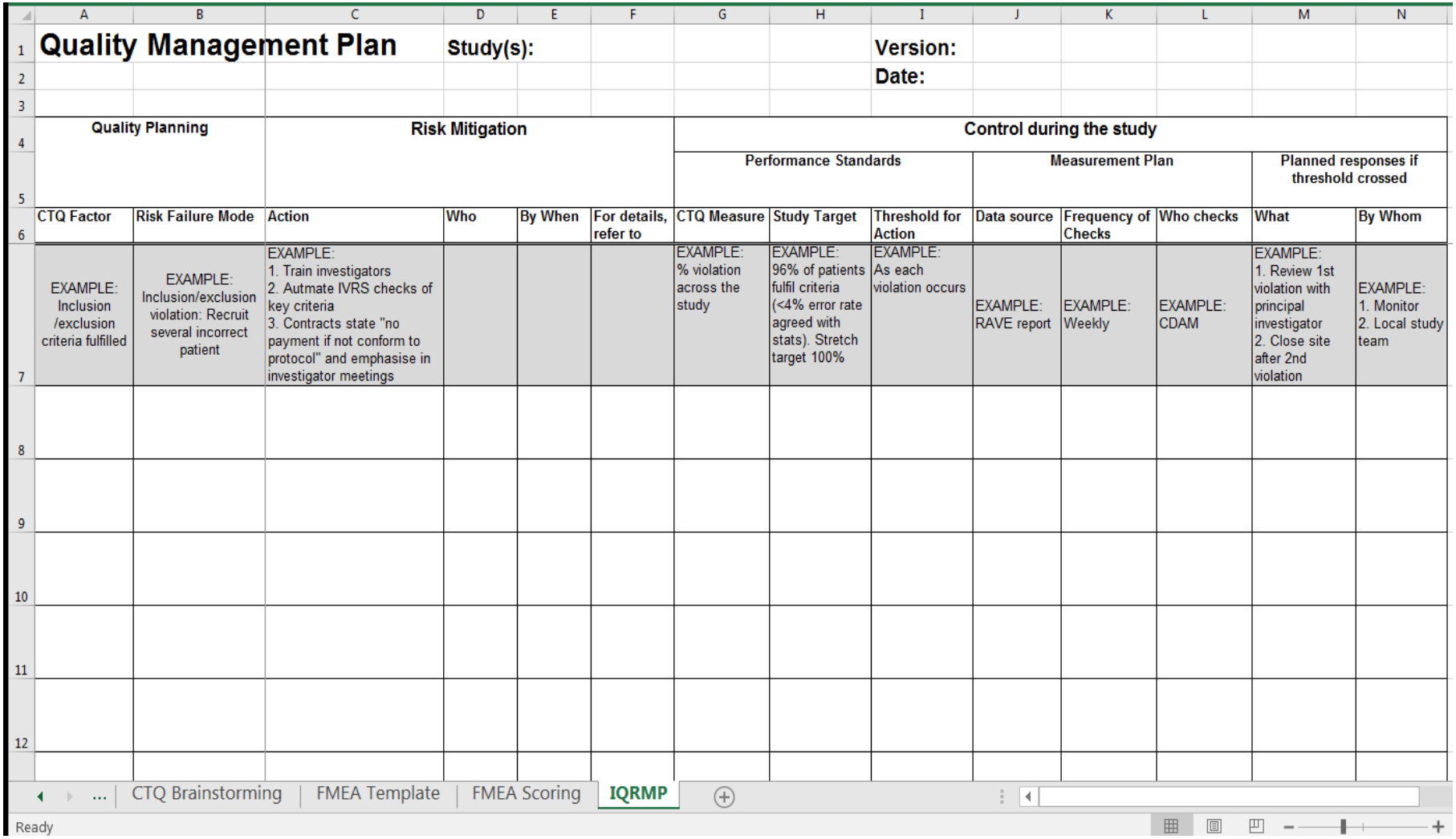
### Quality Planning: Deliverables

**Failure Mode & Effect Analysis (FMEA) is a structured way to identify the few critical quality risks where mitigation needs to be carried out**




CTQ-Critical To Quality
IQRMP- Integrated Quality Risk Management Plan

# Integrated Quality Risk Management Plan (IQRMP)



| Quality Management Plan | | | Study(s): | | | | | Version: | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Date: | | | | | |
| Quality Planning | | Risk Mitigation | | | | Control during the study | | | | | | | |
| | | | | | | Performance Standards | | | Measurement Plan | | | Planned responses if threshold crossed | |
| CTQ Factor | Risk Failure Mode | Action | Who | By When | For details, refer to | CTQ Measure | Study Target | Threshold for Action | Data source | Frequency of Checks | Who checks | What | By Whom |
| EXAMPLE: Inclusion /exclusion criteria fulfilled | EXAMPLE: Inclusion/exclusion violation: Recruit several incorrect patient | EXAMPLE: 1. Train investigators 2. Autmate IVRS checks of key criteria 3. Contracts state "no payment if not conform to protocol" and emphasise in investigator meetings | | | | EXAMPLE: % violation across the study | EXAMPLE: 96% of patients fulfil criteria (<4% error rate agreed with stats). Stretch target 100% | EXAMPLE: As each violation occurs | EXAMPLE: RAVE report | EXAMPLE: Weekly | EXAMPLE: CDAM | EXAMPLE: 1. Review 1st violation with principal investigator 2. Close site after 2nd violation | EXAMPLE: 1. Monitor 2. Local study team |
| | | | | | | | | | | | | | |
| | | | | | | | | | | | | | |
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# Effect a Risk-based Approach to Inspection Readiness

## Tried and Tested Strategies

### Documentation of plans and strategies:

- Risk Based Auditing
- Vendor Selection Process
- Vendor Oversight Plan(s)
- Integrated Quality Management Plans
  - Trial Oversight
  - Risk Based Monitoring (and links to all other plans)
  - Monitor, Review, Re-assess risk, and Update plans throughout study
  - Quality Summary report

### Examples of tiered approach based on risk:

- Vendor Due Diligence
- Exploratory analysis & reporting
  - White Paper if risk changes (document how quality was built in)
- Legacy Study TMFs
- Mergers/Acquisitions/Spin Offs
- Inspection Preparations

# ICH E6 (R2) and Risk Management


## LEVELS

**SYSTEM LEVEL**

- SOPs
- Computerized Systems
- Personnel

**CLINICAL TRIAL LEVEL**

**Program**

**Study (Trial Level)**

**Common Drivers for Quality**

- Patient safety
- Data quality/integrity
- Protocol compliance

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# QUESTIONS?

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# Other Upcoming Events

**ExL's 7th Clinical Trials Inspection Readiness Summit,** August 13-14, 2018 | Philadelphia, PA

- Monday, August 13 | 1:45pm

  **Comparing how agencies (FDA, EMA, MHRA, Health Canada, PMDA, and CFDA) conduct inspections. What are the implications of ICH E6 (R2), based on recent inspection experiences?** *Presented by Steve Whittaker, Senior Consultant, The Avoca Group*

- Monday, August 13 | 11:00am

  **Case Study: Challenges Of Quality Oversight With Business Stakeholders: Vendor Management** *Presented by Grace Crawford, VP Clinical Quality and Compliance, and Gerry Grove, Director, Clinical Operations, Respiratory, Inflammatory and Autoimmunity, MedImmune*

**Webinar: AQC Knowledge Center Monthly Demo**

August 14, 2018 | 11:00am – 12:00pm EDT

**ExL's 9th Clinical Quality Oversight Forum,** October 10-12, 2018 | Philadelphia, PA

- Friday, October 12 | 11:15am

  **The Impact of (R2) on Sites** *Presented by Steve Whittaker, Senior Consultant, The Avoca Group*

- Friday, October 12 | 1:45 pm

  **Panel Discussion: Inspection of Oversight Activities** *Led by Steve Whittaker, Senior Consultant, The Avoca Group*

# Thank You!

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