

Risk Evaluation and Control - Meeting the Requirements of ICH E6 (R2)



A worked example with Keith Dorricott, Metrics
Champion Consortium Ambassador

kdorricott@metricschampion.org

Metrics Champion Consortium

Mission: Bring clinical research stakeholders together, including **sponsors**, **CROs**, **partners** and **investigational sites**, to collaboratively develop standardized performance metrics and associated tools that help organizations oversee, manage and optimize clinical trial execution.

Metric Toolkits: Library of > **300** consensus-based portfolio, study and site level time-quality-cost **performance metrics** grouped into 20 functional area metric toolkits.

Risk and Quality Management Tools: Suite of **tools** that enable and support implementation of **risk-based quality management** and **quality-by-design** programs, including a risk assessment and mitigation management tool, protocol operational complexity scoring tool and cost of poor quality estimator tool.



MCC Collaborative Groups



Best Practice Communities

- Study Quality Trailblazers
- Centralized Monitoring
 - Small Sponsor Community of Practice

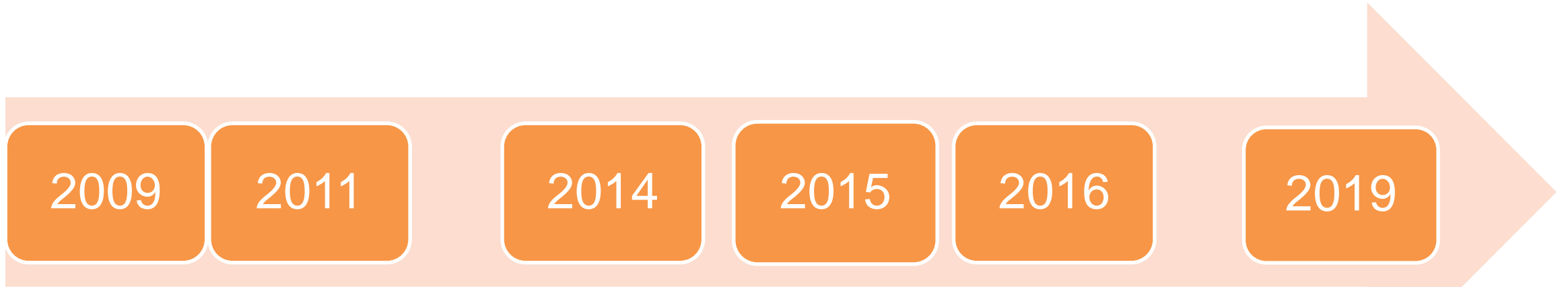
Implementation Q&A

- Cardiac Safety
- Central Lab
- Data Mgmt, Biostats, Medical Writing
 - eCOA
 - RAMMT 2.0
- Site Contracting
- Trial Master File

Metric Development

- Imaging Metrics
- Vendor Oversight Metrics
- NEW: Centralized & Site Monitoring Metrics
- NEW: Site Selection & Start-Up Metrics

Evolving View of Risk-based Quality Management



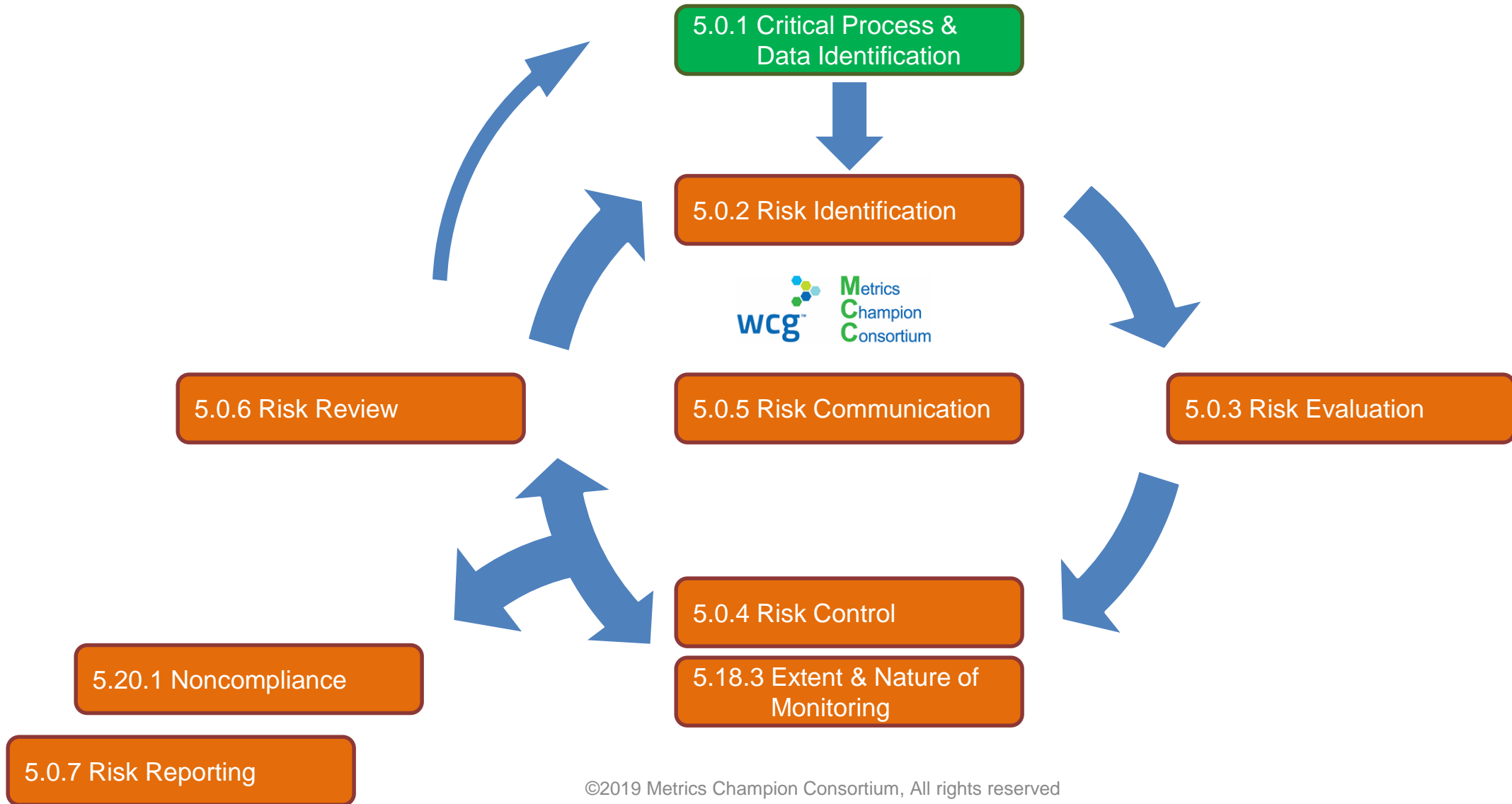
Redefining Quality: Errors that matter & Issues that matter –
Human Subject Protection & Reliability of Trial Results



ICH E6 (R2)



MCC Quality Risk Management Diagram – ICH E6 (R2)



Critical Data – Critical Process

5.0.1 Critical Process and Data Identification

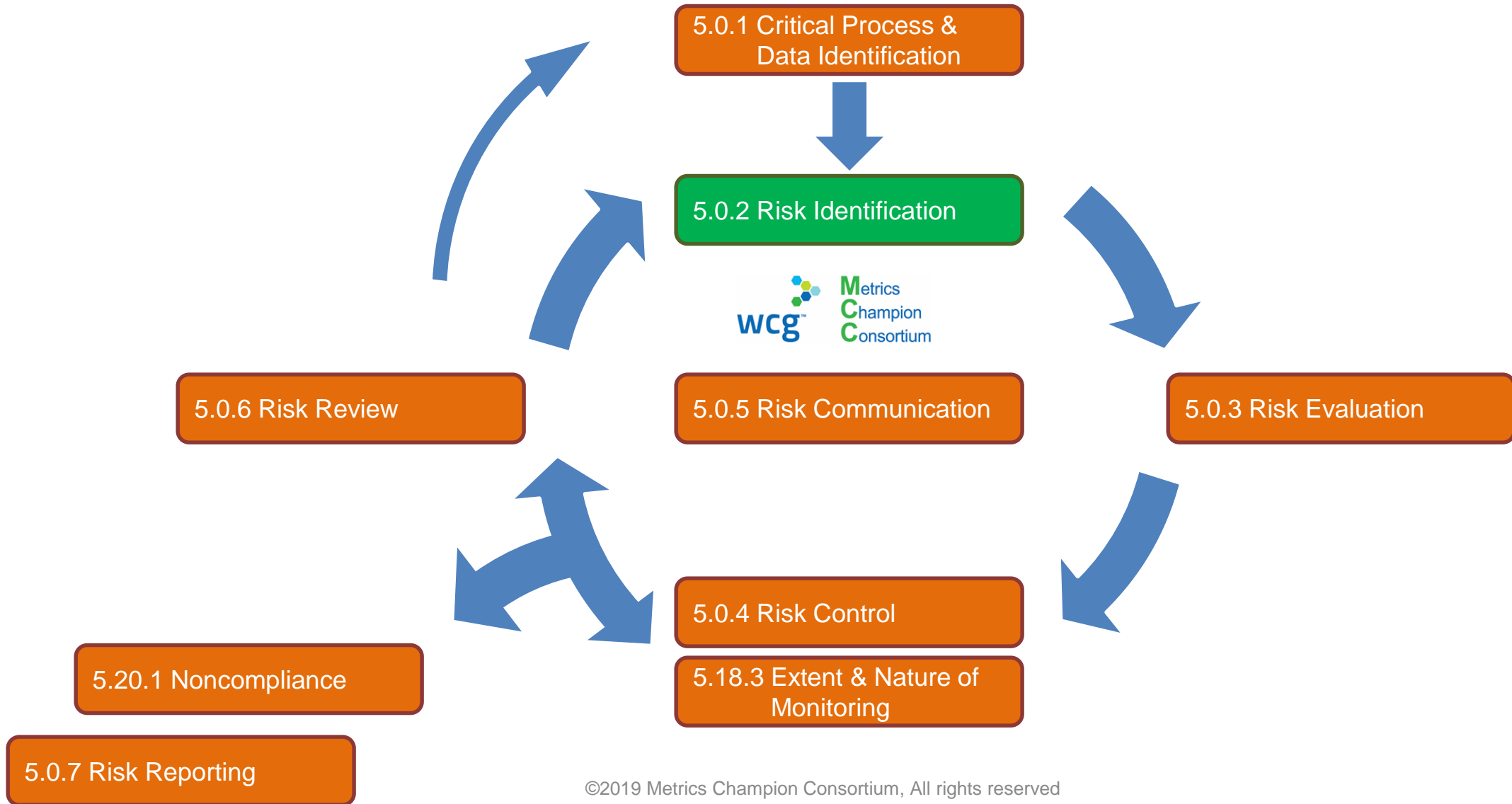
During protocol development, the sponsor should identify those processes and data that are critical to ensure human subject protection and the reliability of trial results.

- We can't focus on everything
- Prioritise by focusing on critical processes and data
- Data is critical when it relates to:
 - Human subject protection
 - Reliability of trial results



- Primary endpoints
- Secondary endpoints
- Anything unique or unusual e.g.
 - Unique study conduct practices e.g. IP mgmt., lab tests, eIC
 - New country

MCC Quality Risk Management Diagram – ICH E6 (R2)



ICH E6 (R2) says ...

5.0.2 *Risk Identification*

The sponsor should identify risks to critical trial processes and data. Risks should be considered at both the system level (e.g., standard operating procedures, computerized systems, personnel) and clinical trial level (e.g., trial design, data collection, informed consent process).

Identify risks by considering:

- What might go wrong in the critical processes
- Previous knowledge / data

Risk Statement

Not
This!



Risk area	Risk Event examples
Lab data	Lab samples incorrectly handled
Research-naïve sites in India	High level of protocol deviations

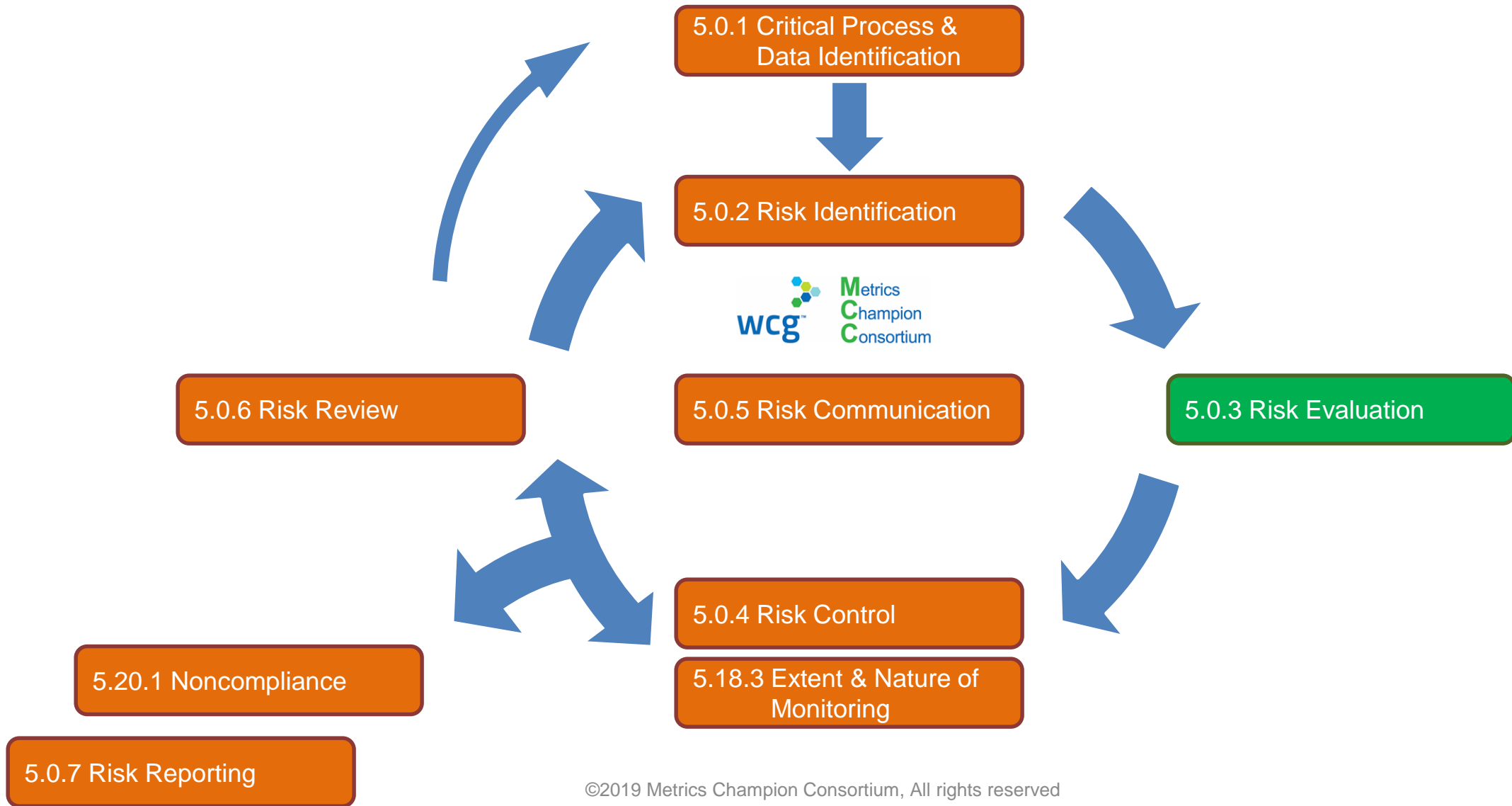
Risk Statements

If the lab samples are incorrectly handled by sites due to the unique handling and packing requirements, then there may be lab test errors and missing critical endpoint data

If there is a higher level of protocol deviations due to using research-naïve sites in India then there may be increased risk to patient safety and trial results

If [Event] occurs (due to [Cause]) then [Negative Impact] may result

MCC Quality Risk Management Diagram – ICH E6 (R2)



ICH E6 (R2) says ...

5.0.3 Risk Evaluation

The sponsor should evaluate the identified risks, against existing risk controls by considering:

- (a) The **likelihood** of errors occurring.
- (b) The extent to which such errors would be **detectable**.
- (c) The **impact** of such errors on human subject protection and reliability of trial results.

Likelihood: Relates to the Event / Cause in the Risk Statement

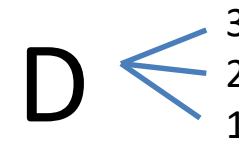
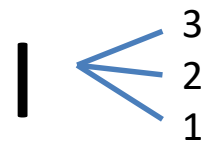
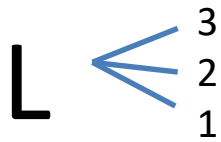
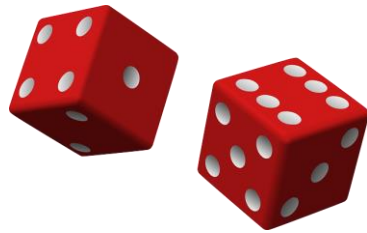
Impact: Relates to the Negative Impact in the Risk Statement

Detectable: Is there a signal early enough to take action?

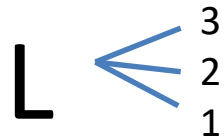
Evaluate Risks Using: L – I – D

Risk Scores and the Risk Statement

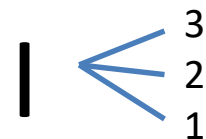
If [Event] occurs (due to [Cause]) then [Negative Impact] may result



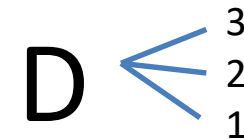
Risk Scores



X



X

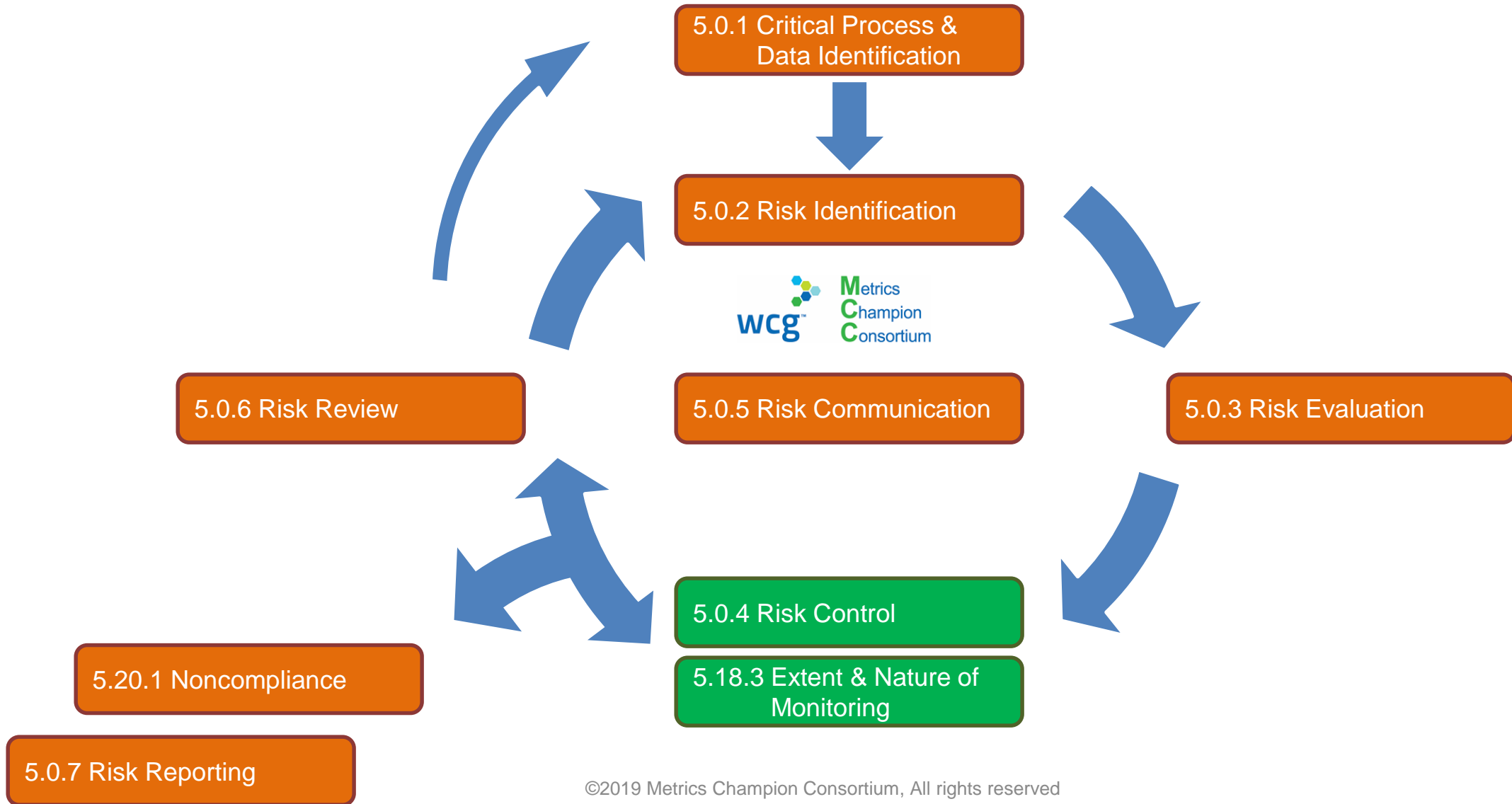


Detectability:

- How clear is the signal in relation to the risk?
- Do you have experience in using the detection method?
- Can it detect the emerging issue in time for you to act?

Risk Score =
 $L \times I \times D =$
Risk Prioritization Number

MCC Quality Risk Management Diagram – ICH E6 (R2)

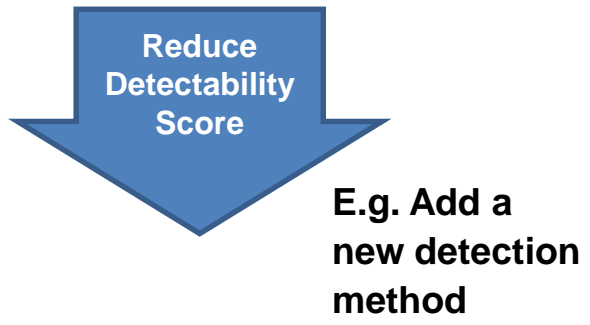
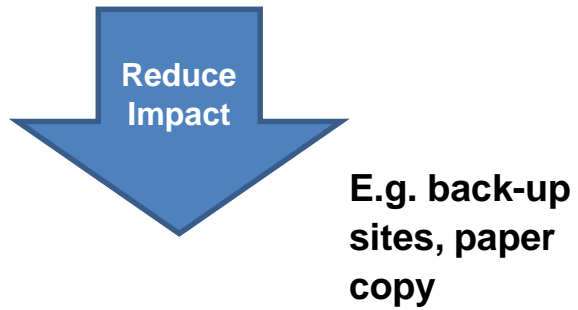
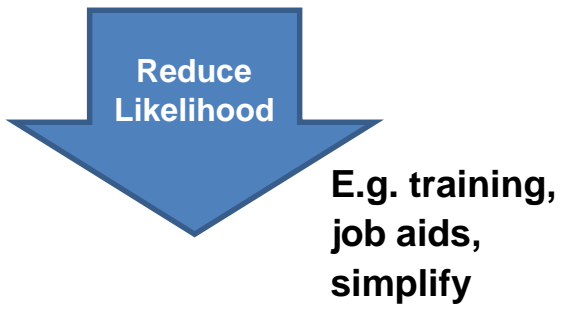
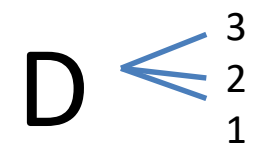
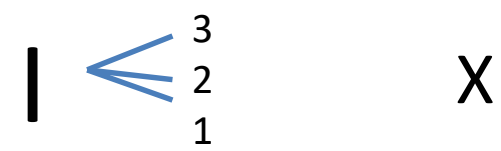
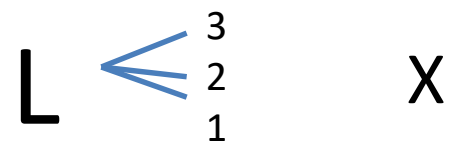


5.0.4 *Risk Control*

The sponsor should decide which risks to reduce and/or which risks to accept. The approach used to reduce risk to an acceptable level should be proportionate to the significance of the risk. Risk reduction activities may be incorporated in protocol design and implementation, monitoring plans, agreements between parties defining roles and responsibilities, systematic safeguards to ensure adherence to standard operating procedures, and training in processes and procedures.

Predefined quality tolerance limits should be established, taking into consideration the medical and statistical characteristics of the variables as well as the statistical design of the trial, to identify systematic issues that can impact subject safety or reliability of trial results. Detection of deviations from the predefined quality tolerance limits should trigger an evaluation to determine if action is needed.

Reducing Risk



ICH E6 (R2) says ...

5.18.3 Extent and Nature of Monitoring

ADDENDUM

The sponsor should develop a systematic, prioritized, risk-based approach to monitoring clinical trials. The flexibility in the extent and nature of monitoring described in this section is intended to permit varied approaches that improve the effectiveness and efficiency of monitoring. The sponsor may choose on-site monitoring, a combination of on-site and centralized monitoring, or, where justified, centralized monitoring. The sponsor should document the rationale for the chosen monitoring strategy (e.g., in the monitoring plan).

On-site monitoring is performed at the sites at which the clinical trial is being conducted. Centralized monitoring is a remote evaluation of accumulating data, performed in a timely manner, supported by appropriately qualified and trained persons (e.g., data managers, biostatisticians).

Centralized monitoring processes provide additional monitoring capabilities that can complement and reduce the extent and/or frequency of on-site monitoring and help distinguish between reliable data and potentially unreliable data.

Review, that may include statistical analyses, of accumulating data from centralized monitoring can be used to:

- (a) identify missing data, inconsistent data, data outliers, unexpected lack of variability and protocol deviations.
- (b) examine data trends such as the range, consistency, and variability of data within and across sites.
- (c) evaluate for systematic or significant errors in data collection and reporting at a site or across sites; or potential data manipulation or data integrity problems.
- (d) analyze site characteristics and performance metrics.
- (e) select sites and/or processes for targeted on-site monitoring.

Example Key Risk Indicators (KRIs)

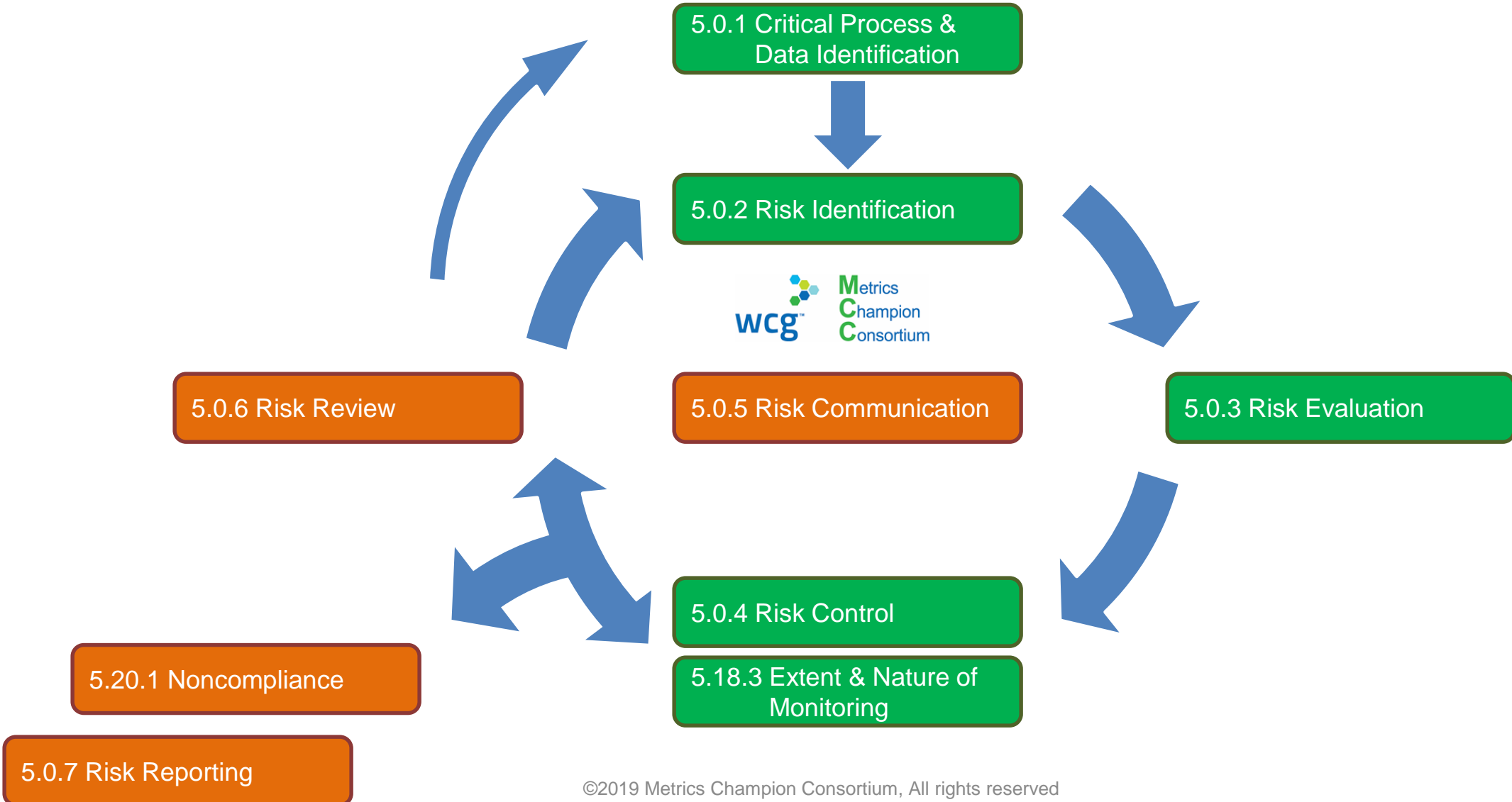
- SAE Reporting Rate
- AE Reporting Rate
- Query Rate
- Data Entry Timeliness
- Screen Failure Rate
- Protocol Deviation Rate
- % Images Evaluable



Additional Risk-based Quality Management Resources

1. Mastering Risk Management – MCC eLearning Program (2019) – available at metricschampion.org
2. MCC Risk Assessment & Mitigation Management Tool 2.0 (RAMMT) (2018) – available to member organizations at metricschampion.org
3. ICH E6 (R2) (2016) and ICH E8 (R1) draft (2019) – available at www.ich.org
4. MHRA Risk-adapted Approaches to the Management of Clinical Trials of IMP (2011) – available at www.gov.uk
5. EMA Reflection Paper on Risk Based Quality Management in Clinical Trials (2013) – available at www.ema.europa.eu
6. FDA Guidance: Oversight of Clinical Investigations – a Risk-Based Approach to Monitoring (2013) – available at www.fda.gov
7. FDA Guidance: A Risk-Based Approach to monitoring of Clinical Investigations Questions and Answers (draft) (2019)– available at www.fda.gov

Now – Let's Try It!



Now – Let's Try It!

Resources

- Definitions of likelihood, Impact and Detectability Scores
- Risk Assessment and Control Worksheet

Situation

- You are the operational team leading a phase 2 oncology study
- Planned enrolment is 50 patients in USA, France and Japan
- Study includes lab data from a Central Lab and Imaging data
- You are tasked with assessing and controlling risk. The study has not launched.

Task

- Make whatever assumptions you like about the study design
- Develop a list of risks using risk statements (5-10)
- Evaluate and prioritise the risks
- Determine how you will control the priority risks – if you plan to monitor the risk, how will you do that? Any measurements (KRIs)?
- Re-score the priority risks
- Prepare to feed back to all delegates: Summary, Challenges & Learnings

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