Using metrics to achieve inspection readiness

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Metrics Champion Consortium

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Agenda

- Setting the stage – metric background
- Trial Master File metrics
- Risk-based Quality Management & Centralized Monitoring KRIs and Metrics
- Vendor Oversight Metrics

The Metrics Champion Consortium (MCC) is dedicated to the development and adoption of standardized performance metrics and quality tools to improve clinical trials.

For more than a decade, individuals from more than 90 organizations have invested over 1,000,000 hours in the development of MCC standardized metric sets; risk management and quality scoring tools; and risk-based monitoring key risk indicators. Today, nearly 1500 individual users from approximately 80 organizations - including 9 out of 10 top pharmaceutical companies – participate in MCC work groups and access MCC tools, metric sets and education webinars.

Metric Sets

- Proprietary Metric Development Framework
- Extensive library of 200 consensus-based standardized time-quality-cost performance metrics (metric definition, performance targets, wiki, companion metric mapping)

Existing Metric Toolkits

- Clinical Trial Performance Metrics [sponsor/CRO/Site metrics] (v1.2)
- Protocol, Site Management & Compliance Quality Metrics (v1)
- Data Mgmt & Biostats Metrics (v2)*
- Lab Performance Metrics (v2)
- eCOA Performance Metrics (v1)*
- ECG, ABPM and Spirometry Performance Metrics (v2)
- Imaging Performance Metrics(v2)
- Clinical CAPA Metrics (v1)
- Risk-based monitoring
  - Site Key Risk Indicator Set
  - Pilot Success Factors
- Site Contracting Performance Metrics (v1)
- Site-generated Performance Metrics (v1)
- Trial Master File Metrics (v2)*
- Vendor Oversight Milestone and Relationship Assessment Metrics (v1)*

** = new metric sets with basic/advanced metrics*

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Types of Metrics

Metric Type:	Definition:
TIMELINESS	Measures whether a milestone was achieved on-time
CYCLE TIME	Measures how long it takes to complete a task
QUALITY	Measures the accuracy of completing a task or how closely aligned performance is to a set of requirements
EFFICIENCY/COST	Measures the resources required to complete a task

Metrics are:	Metric Results are used to:
LEADING →	identify opportunities to affect change in current study.
← LAGGING	identify opportunities to affect change in future studies only.

Use a combination and balance of metric types to produce a holistic view of what is being measured

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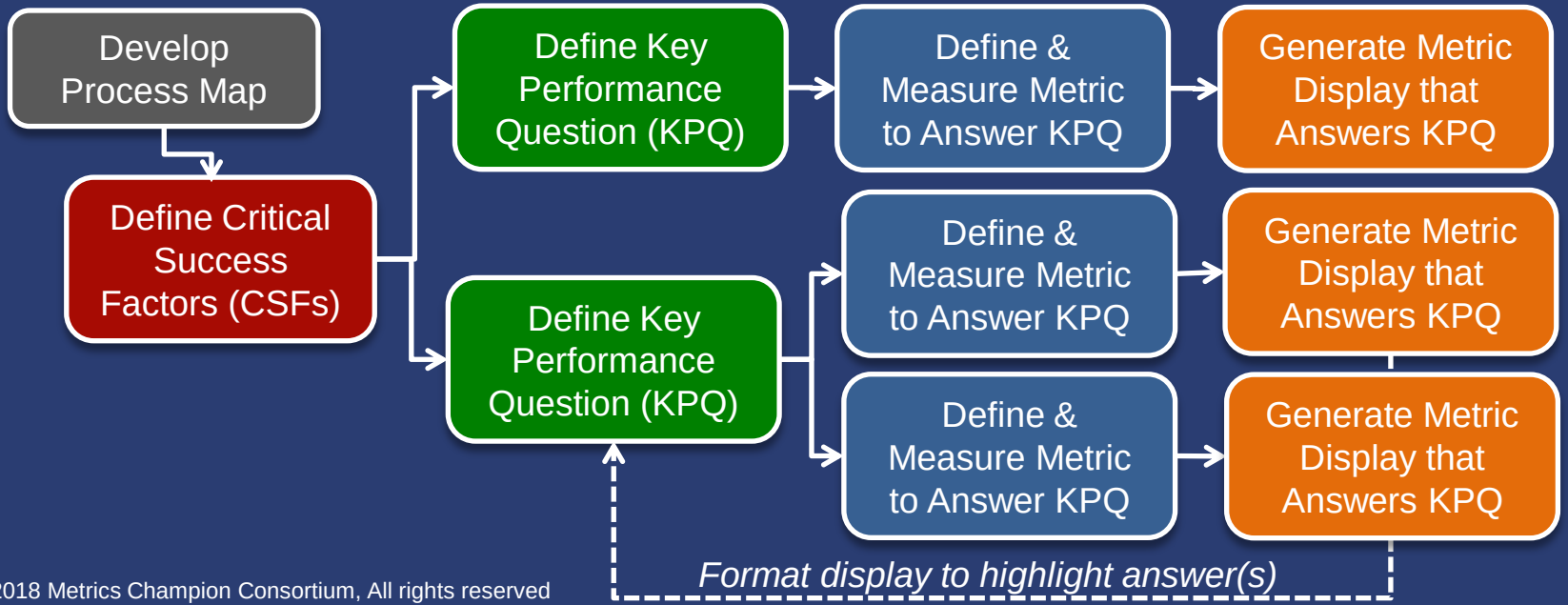
Adapted from Dave Zuckerman, Customized Improvement Strategies

Measure What Matters Most – Metrics That Answer Important Questions

MCC Metric Development Framework



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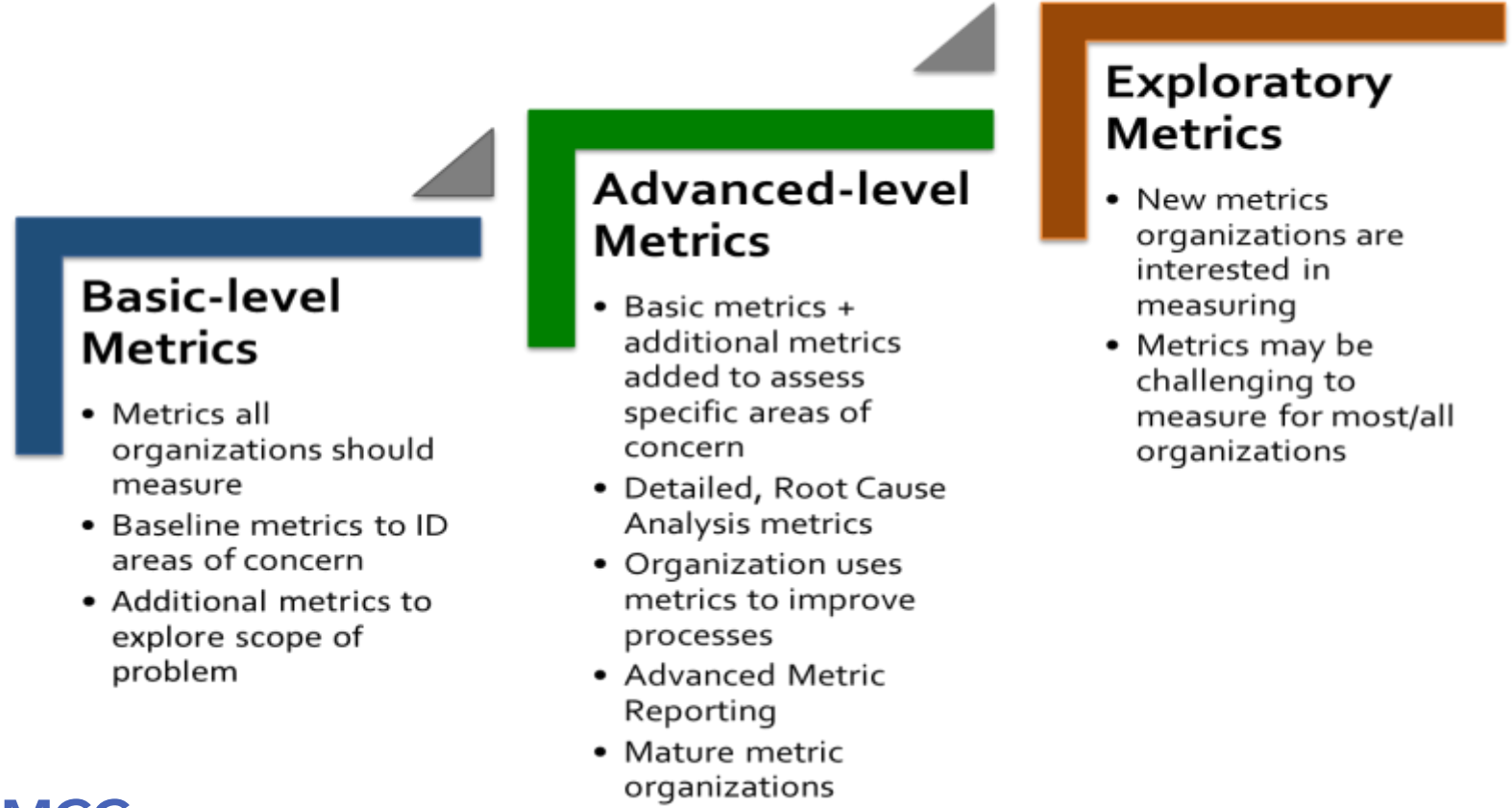
Metrics Segmented into 3 tiers



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MCC Metric Definition Template

Critical Success Factor:				
Metric Description		**Key Performance Question to be answered with metric**	**Why is the Key Performance Question important? What actions might be taken based upon results?**	**What the metric does not tell you**
Metric Type	**Reporting Level**	**Basic/Advanced**		

Formula / Example	**Performance Target (suggested)**	**Additional Analysis for Missed Target**	**Companion Metrics (Portfolio)**
			(Study)
	Reporting Frequency		
			(Country)
	Sub-process		
			(Site)

Glossary Terms (See Glossary Tab)	**Data Elements**

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Audience Poll

Has your organization had TMF-related findings in a recent inspection?

1. Yes
2. No
3. Don’t know

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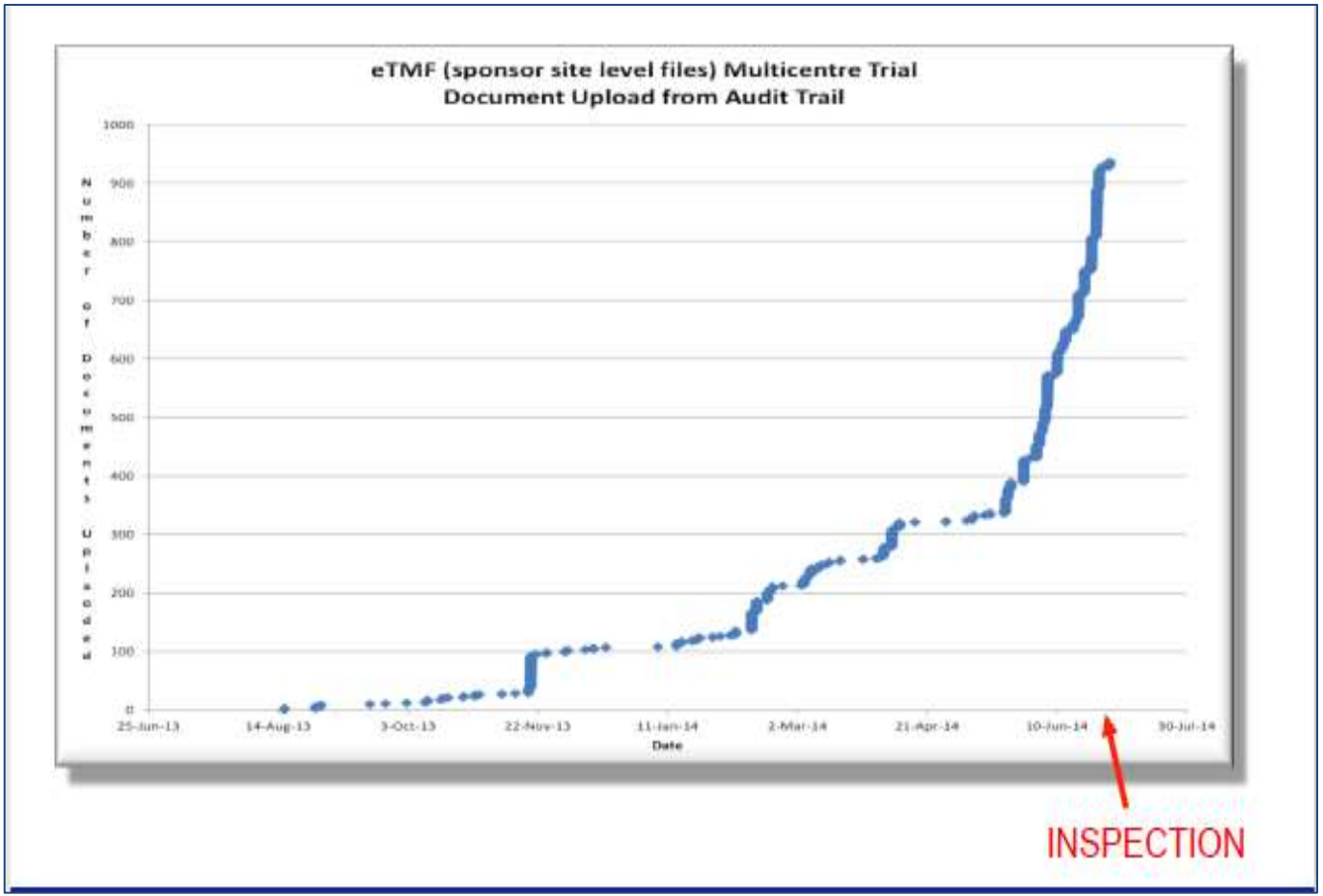

Source: Andy Fisher/TMF presentation - 4th Annual European Trial Master File Summit, 12-13 October 2015 in London, UK.

Industry Focus on TMF Due to Regulatory Updates

MHRA: GCP Inspection Findings Classifications*	EMA: Grading of Inspection Findings^
Critical C. Where provision of the Trial Master File (TMF) does not comply with Regulation 31A 1-3, as the TMF is not readily available or accessible, or the TMF is incomplete to such an extent that it cannot form the basis of inspection and therefore impedes or obstructs inspectors carrying out their duties in verifying compliance with the Regulations	**Critical** Conditions, practices or processes that adversely affect the rights, safety or well being of the subjects and/or the quality and integrity of data. Critical observations are considered totally unacceptable. Possible consequences: rejection of data and/or legal action required Remark: Observations classified as critical may include a pattern of deviations classified as major, bad quality of the data and/or absence of source documents.

* Source: SOP C006/11 “Reporting of GCP Inspections” Effective 15th April 2014

^ Source: Procedure for reporting of GCP inspections requested by the Committee for Medicinal Products for Human Use (CHMP) p19

"Directive 2005/28/EC Article 16 … defines ***essential documents*** as those which ***enable both the conduct of the clinical trial and the quality of the data to be evaluated.*** It further states that these documents must show whether the investigator and sponsor have complied with the principles and guidelines of good clinical practice and with the applicable regulatory requirements."

Source: EMA - Good Clinical Practice Inspectors Working Group (GCP IWG). *Reflection paper on GCP compliance in relation to trial master files (paper and/or electronic) for management, audit and inspection of clinical trials.* 15 June 2015.

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TMF Requirements

"The TMF must be sufficient to ***adequately reconstruct the trial activities undertaken*** … along with ***key decisions made concerning the trial*** and thus should be prepared and maintained appropriately."

"Consideration should be given to the ***TMF*** being a ***stand-alone set of documentation that does not require additional explanation*** from the associated sponsor or site staff."

Source: EMA - Good Clinical Practice Inspectors Working Group (GCP IWG). *Reflection paper on GCP compliance in relation to trial master files (paper and/or electronic) for management, audit and inspection of clinical trials.* 15 June 2015 .

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Contemporariness of TMF

"The TMF should to be up to date, with documents placed in the TMF in a timely manner with the aim to maintain the TMF "inspection ready".

"GCP inspectors would raise concerns if the TMF appeared out of date such that the ability to manage and oversee the trial conduct was questionable."

Source: EMA - Good Clinical Practice Inspectors Working Group (GCP IWG). *Reflection paper on GCP compliance in relation to trial master files (paper and/or electronic) for management, audit and inspection of clinical trials.* 15 June 2015 .

Contemporariness of TMF

"In trials that have more complex TMF arrangements with multiple parties involved it may be ***useful to define the timescales for submission and filing of documents to the TMF in procedural documents or TMF plans***."

Source: EMA - Good Clinical Practice Inspectors Working Group (GCP IWG). *Reflection paper on GCP compliance in relation to trial master files (paper and/or electronic) for management, audit and inspection of clinical trials.* 15 June 2015 .

Scanning or transfers to other media

"The QC of the scanning, as part of the validation or subsequent sample QC activities could assess, for each document reviewed, one or more of the following:

- accuracy of the metadata attributed to the document (it is recommended that the sponsor has defined the required metadata in a formal procedure);
- **quality of the image** (readability, reproduction of colour, the quality of wet ink signature or annotations and handwriting in general etc.);
- **whether it was the correct document (as expected)**;
- that the document had the correct number of pages;

Source: EMA - Good Clinical Practice Inspectors Working Group (GCP IWG). *Reflection paper on GCP compliance in relation to trial master files (paper and/or electronic) for management, audit and inspection of clinical trials.* 15 June 2015 .

Scanning or transfers to other media

"The QC of the scanning, as part of the validation or subsequent sample QC activities could assess, for each document reviewed, one or more of the following: (continued)

- the **eTMF audit trail** associated with the document;
- chain of records transfer documentation;
- approval process (where applicable);
- scanned images should be at appropriate resolution so that when viewed at actual size on the screen (as per the original) the image is clear and legible."

Source: EMA - Good Clinical Practice Inspectors Working Group (GCP IWG). *Reflection paper on GCP compliance in relation to trial master files (paper and/or electronic) for management, audit and inspection of clinical trials.* 15 June 2015 .

CRO TMF – Outline Expectations

The contract or other document or procedure is recommended to outline the arrangement for the TMF in some detail address:

- which party holds the official TMF (or which parts of the TMF each party holds when this is divided);
- the process for filing documentation in the TMF;
- the access arrangements for both parties;
- the structure and indexing of the TMF;
- where an eTMF is being used, the details of the system;
- lists of applicable procedures to be followed and training requirements; documents that both parties must retain;

Source: EMA - Good Clinical Practice Inspectors Working Group (GCP IWG). *Reflection paper on GCP compliance in relation to trial master files (paper and/or electronic) for management, audit and inspection of clinical trials.* 15 June 2015 .

CRO TMF – Outline Expectations

The contract or other document or procedure is recommended to outline the arrangement for the TMF in some detail address: (continued)

- arrangements for managing correspondence;
- how the TMF would be made available if either party was inspected;
- arrangements for when the trial is completed (the CRO may archive the TMF [or parts thereof] on behalf of the sponsor);
- arrangements for oversight of the quality control/quality assurance of the TMF by the sponsor and how this would be documented (e.g. audit reports, QC8 reports).

Source: EMA - Good Clinical Practice Inspectors Working Group (GCP IWG). *Reflection paper on GCP compliance in relation to trial master files (paper and/or electronic) for management, audit and inspection of clinical trials.* 15 June 2015 .

CRO TMF – Outline Expectations

It is important the documentation generated by the CRO from following its internal procedures is retained and sponsors must consider this part of the TMF (Directive 2005/28/EC Article 2[4] and 16).

Source: EMA - Good Clinical Practice Inspectors Working Group (GCP IWG). *Reflection paper on GCP compliance in relation to trial master files (paper and/or electronic) for management, audit and inspection of clinical trials.* 15 June 2015 .

Risk-based Approach to QC Checks

"Where the transfer of documents is undertaken using a validated process, ***a formal process is recommended to be in place for regular checks of documents in the eTMF.*** This would usually be undertaken on a ***sampling basis, including escalation procedures where errors occur beyond a pre-defined acceptable error rate.*** The sponsor is responsible for deciding this value and it may vary, and the ***QC levels vary for different sets of documentation on a risk based approach***."

Source: EMA - Good Clinical Practice Inspectors Working Group (GCP IWG). *Reflection paper on GCP compliance in relation to trial master files (paper and/or electronic) for management, audit and inspection of clinical trials.* 15 June 2015 .

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What is your organization measuring around TMF timeliness, quality and completeness?

Can selecting the right performance metrics improve your TMF?

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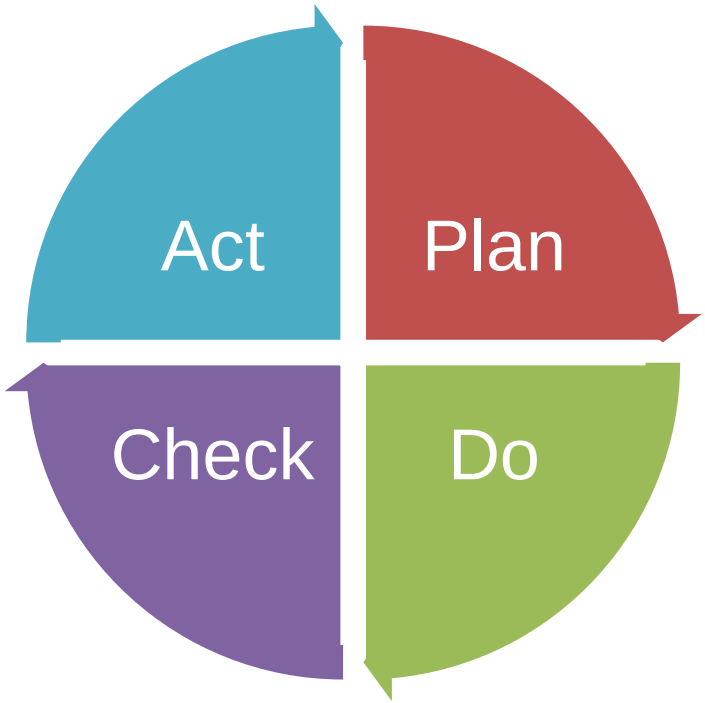
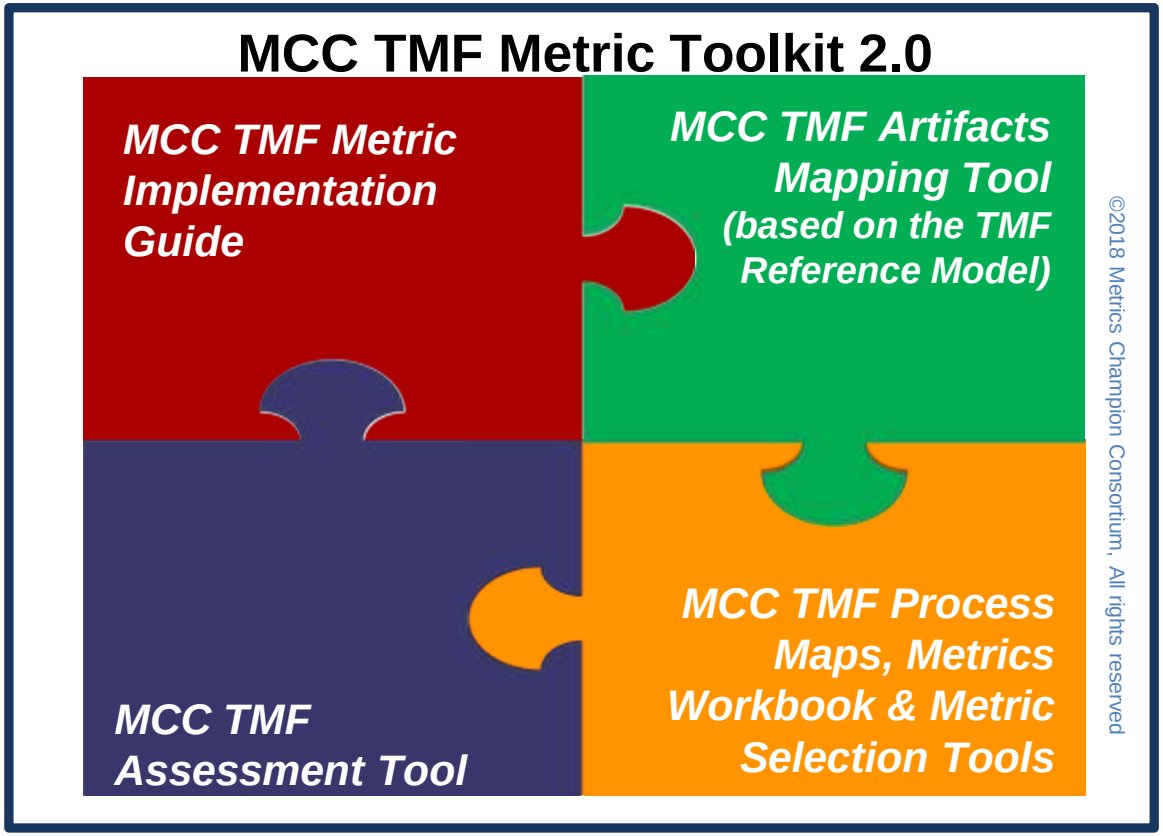


- **T**ake time to establish expectations (Plan)
- Process and file artifacts (Do)
- **M**easure (Check)
- **F**ix Problems (Act)

Key Performance Question	Metric Type	Metric Level
Is the TMF set up in a timely manner?	Timeliness	Basic
Do the artifacts submitted to the TMF meet the quality standard?	Quality	Basic
Are artifacts being provided, processed and published/filed in the TMF in a timely manner?	Cycle Time	Basic
Are artifacts being published in the TMF in a timely manner?	Timeliness	Advanced
Do the artifacts in the TMF meet the quality standard	Quality	Basic
Does the TMF contain all the required expected artifacts at the time of the assessment?	Timeliness	Basic
Are TMF quality issues being resolved in a timely manner?	Cycle Time	Basic
What proportion of placeholder due dates are accurate?	Quality	Advanced



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MCC TMF Metrics Toolkit v2.0

Component	Webinar	Purpose
At-A-Glance		Short document to describe the purpose of the MCC TMF Metrics Toolkit v2.0 and updates since v1.0
MCC TMF Metrics Toolkit 2.0 Overview Webinar - Slides	Recording (13 min.)	To provide an overview of purpose of the metrics and how to use the toolkit
MCC TMF Metric Implementation Guide		To provide guidance on how to implement and use the MCC TMF metrics
MCC TMF Artifact Mapping Tool	Recording (9 min.)	To capture expectations of who is responsible for uploading/filing artifacts and when they are due
MCC TMF Assessment Tool	Recording (11 min.)	To capture TMF assessment results, calculate metrics and track numbers of queries
MCC TMF Metrics and Process Maps Workbook	Recording (6 min.)	To define each metric. Includes purpose, recommended usage, target glossary and process maps
Metric Selection Tools:		
Tool 1: Metrics to Data Elements	Recording (4 min.)	To determine data elements needed to calculate specific metrics
Tool 2: Data Elements to Metrics	Recording (4 min.)	To determine metrics available with a given set of data elements
Tool 3: Issues to Metrics	Recording (4 min.)	To determine recommended metrics and data elements for particular issues

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Audience Poll

Has your organization been through an inspection that reviewed risk-based quality management?

1. Yes
2. No
3. Don’t know

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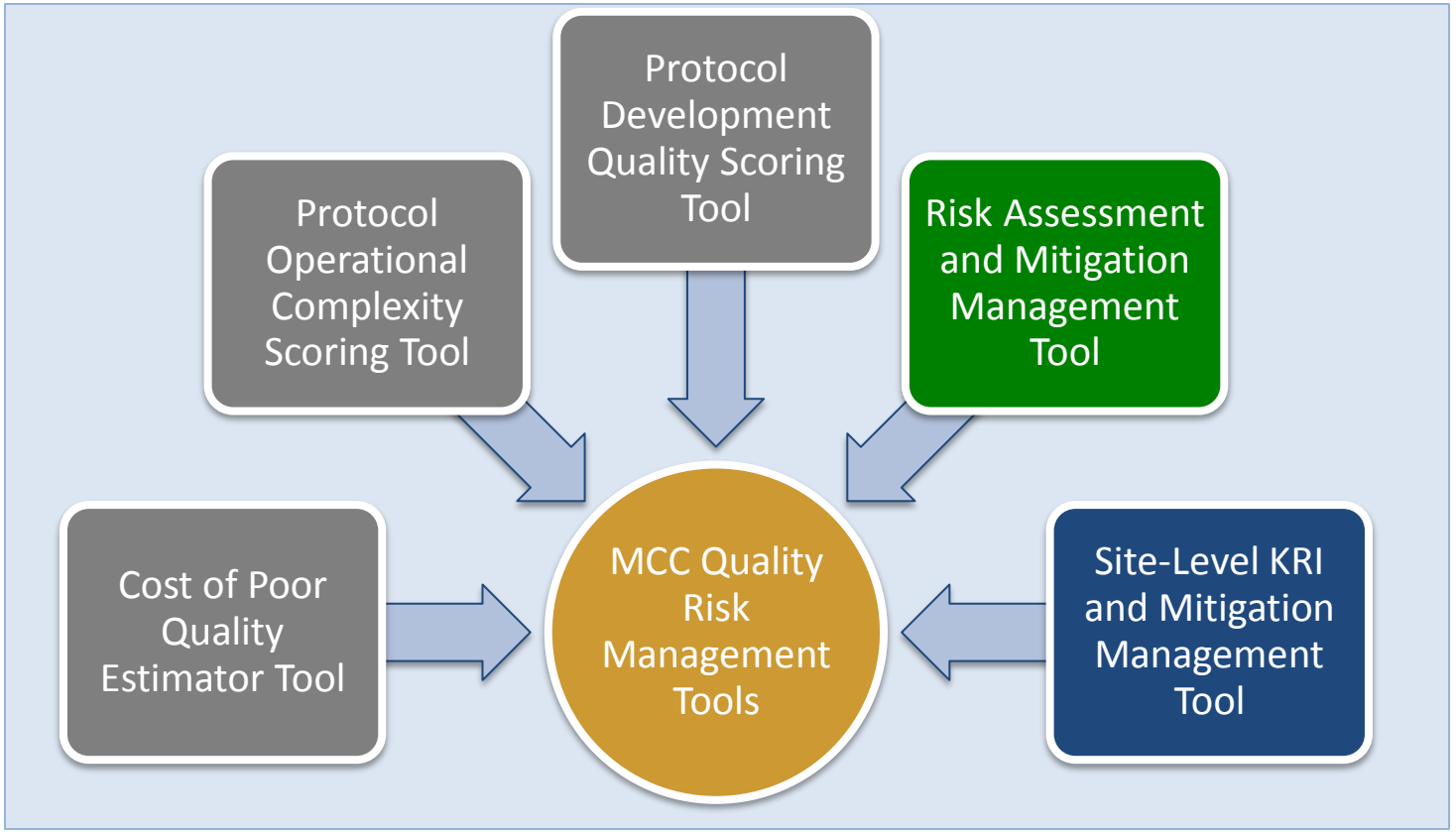

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Evolving View of Quality Risk Management and Protocol Operational Complexity

ICH E6 (R2)

MCC Study Quality Trailblazers

Risk Assessment & Mitigation

- 5.0.1 Critical Process & Data Identification
- 5.0.2 Risk Identification
- 5.0.3 Risk Evaluation
- 5.0.4 Risk Control
- 5.0.5 Risk Communication
- 5.0.6 Risk Review
- 5.0.7 Risk Reporting
- 5.18.3 Extent & Nature of Monitoring

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KRI & Data Monitoring

5.0 “The Quality Management System should use a risk-based approach…”

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ICH E6 (R2) – It's Not Linear!

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Risk Scores

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

L < High / Medium / Low

I < High / Medium / Low

Risk Scores

L < 3 2 1 X I < 3 2 1 X D < 3 2 1

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 x I x D

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Reducing Risk

5.0.4 Risk Control

L < 3 2 1 X I < 3 2 1 X D < 3 2 1

Reduce Likelihood

E.g. training, simplify

Reduce Impact

E.g. back-up sites, paper copy

Reduce Detectability Score

E.g. KRIs

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ICH E6 (R2) says…

5.0.3 Risk Evaluation

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

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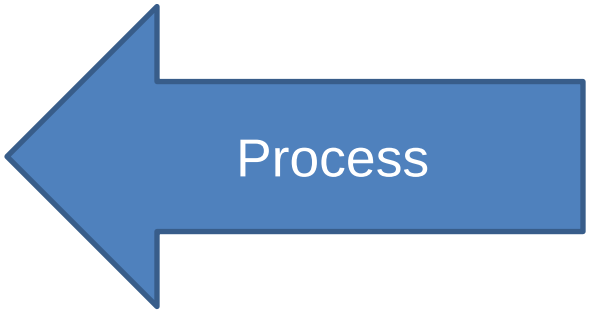
Comparing The Tools

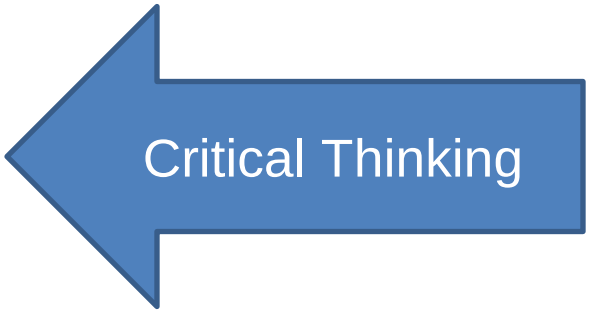
	RACT 2.0	RA&MMT 1.0	RA&MMT 2.0
70+ potential risks	☑	☑	☑
Risk score by combining Likelihood, Impact, Detection	☑	☑	☑
Suggested mitigations for potential risks	☑	☑	☑
Prioritization by individual risk rather than risk category		☑	☑
Use of a risk statement to assist with scoring		☑	☑
Clear definitions of Likelihood, Impact, Detection		☑	☑
List of potential MCC metrics to use for Detection		☑	☑
Collection of risk reduction actions		☑	☑
Encourage critical thinking by avoiding checklist approach			☑
Aligns with ICH E6 (R2) - Critical data/processes followed by risks			☑
Enhanced definition of Detection			☑
Aligns with ICH E6 (R2) - Quality Tolerance Limits			☑
Allows rescoring of risk based on risk reduction actions			☑
List of possible MCC KRIs to use for Detection			☑

Some Challenges

- Timing of initial Risk Assessment
- Timing of subsequent Risk Assessments
- Who to involve e.g. CROs, Vendors
- **Communication, tracking decisions & actions**



- Knowing the right point to stop
- Understanding detectability
- **Implementing detection methods**
- Managing the unknown



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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).

5.18.3 Extent and Nature of Monitoring

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ADDENDUM

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.

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5.18.6 Monitoring Report

5.18.6 Monitoring Report

ADDENDUM

(e) Reports of on-site and/or centralized monitoring should be provided to the sponsor (including appropriate management and staff responsible for trial and site oversight) in a timely manner for review and follow up. Results of monitoring activities should be documented in sufficient detail to allow verification of compliance with the monitoring plan. **Reporting of centralized monitoring activities should be regular and may be independent from site visits.**

Centralized Monitoring

5.18.3 Extent & Nature of Monitoring

- Centralized Monitoring Guidance Document
  - What is the scope of Centralized Monitoring?
  - **From Risk Assessment to Centralized Monitoring**
  - **Data flow diagrams**
  - Outsourcing considerations
  - Developing a Centralized Monitoring Plan
  - Different approaches to data analysis
  - KRIs & QTLs: definition and use
  - Need for critical thinking
- 2018 MCC-CenterWatch Survey
  - How is the industry executing centralized monitoring?
  - 80 respondents

MCC Centralized Monitoring WG

KRI & Data Monitoring

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5.2.2 Any trial-related duty and function that is transferred to and assumed by a CRO should be specified in writing

ADDENDUM The sponsor should ensure oversight of any trial-related duties and functions carried out on its behalf, including trial-related duties and functions that are subcontracted to another party by the sponsor's contracted CRO(s).

MCC Metric Toolkits

- Clinical Trial Performance Metrics [sponsor/CRO/Site metrics] (v1.2)
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- **Lab Performance Metrics (v2)**
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- Risk-based monitoring
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- Site-generated Performance Metrics (v1)
- Trial Master File Metrics (v2)*
- **Vendor Oversight Milestone and Relationship Assessment Metrics (v1)***

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Critical Thinking – What is it?

Exercising judgement

Not just reacting

Beyond the check-box

Problem solving

Enquiring Mind

Not always going with the flow

Root cause analysis

Asking why

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Summary

- What your organization chooses to measure sends a signal to stakeholders about what is important - what behavior do your metrics support?
- Inspectors will look at what you measure and how you react when results do not align with expectations – are you documenting the risk-based quality management process? (ICHE6(R2) section 5)
- Does your staff have the critical thinking skills to interpret metric results?

Metrics don’t fix problems – people do!

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Questions?

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