

Metrics 101

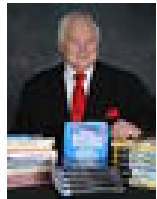
Produced by the TMF
Reference Model
Metrics and Reporting
Sub-team

1 August 2014

Agenda

- Why a metrics program?
- Goals of a metrics program
- Types of metrics
- Further analytics on metrics
- Metrics program design
- Metrics program implementation
- Final thoughts

Why a Metrics Program?



“Measurement is the first step that leads to control and eventually to improvement. If you can’t measure something, you can’t understand it. If you can’t understand it, you can’t control it. If you can’t control it, you can’t improve it.”

— H. James Harrington

Perspective: Performance Measurements and Continuous Improvement

A formal Performance Metrics Program brings value because it.....

1. Provides a clear link and focus to strategy and strategy realization
2. Creates alignment, transparency, and accountability at all levels in the organization
3. Enables a focus on continuous improvement efforts where they have the most impact
4. Enables fact based decisions – not “gut feel” - You can't improve what you don't measure
5. Creates a common language to assess and improve performance

Industry Status: Demonstrating Value with Performance Metrics and Continuous Improvement
DIA EDM San Diego: Fall 2013
Steve Gens, Managing Partner, Gens and Associates, Inc.



GOALS OF A METRICS PROGRAM

Goals of a Metrics Program

1. Provide insight into the ongoing status and quality of a trial
2. Provide insight into overall trends to support process improvements
3. Allow a CRO to report statistics to their sponsor
4. Allow the comparison of a sponsor's CROs against their Service Level Agreements
5. Support planning for future studies (headcount, timeframes...)
6. Allow a sponsor or CRO to monitor performance of specific departments or groups
7. Allow a sponsor or CRO to monitor performance against the industry as a whole
8. Allow the comparison of a sponsor's CROs against each other

-- according to a recent informal survey



TYPES OF METRICS

Types of TMF Metrics

Type	Definition
Administration	Indication of whether TMFs have defined ownership and planning measures in place
Completeness	Extent to which a TMF/eTMF contains all documents that are expected at the current point in the study (usually based on last milestone date), or, for completed trials, at the end of the trial.
Quality	Measure of whether document content, metadata, and indexing are complete and accurate
Timeliness	Indication of whether documents are available when expected or needed, and of how long documents take to finalize
Use	Measure of how frequently an electronic TMF system is accessed
Volume	Measures of the types, numbers and sizes of documents in a TMF/eTMF

TMF Key Parameters for Metrics



- **Completeness:** so that the authorities can reconstruct the trial and ensure GCP compliance
- **Timeliness:** so that accurate decisions can be made based on close to real-time information
- **Quality:** so all parties can have confidence in the documented processes and data

Completeness: Challenges

“Procedures should be in place ... to assure that the TMF is complete and accurate.” - EMA Reflection paper on GCP compliance in relation to trial master files (paper and/or electronic) for management, audit and inspection of clinical trials

But... how do you measure completeness?

- To know what’s missing, you must know what is expected
- Different for every trial
- Changes of the course of the trial
- For paper TMFs, tracked in a highly manual way

TMF Completeness – what do you measure?

- TMF Completeness assesses if all anticipated documents are collected for trial.
 - Comparison of anticipated content index to filed content
 - Manual process for paper trials
- eTMF facilitates completeness metrics
 - Visual signals for audit / inspection readiness
 - Take action before milestones are missed
 - Real time course corrections and identification of trends
- TMFs completeness can also be measured across programs
 - are all TMFs accounted for and well controlled throughout their lifecycle?

Timeliness – What are You Measuring?

“The TMF should be up to date, with documents placed in the TMF in a timely manner with the aim to maintain the TMF “inspection ready”.” – EMA Reflection paper

- How do you know when documents are due?
 - Most documents can be tied to a milestone
 - Best case: monitor documents against due dates
 - Next best: monitor to ensure documents tied to milestone are received by milestone due dates
 - Better than nothing: all received before TMF can be closed out and archived



Timeliness – What Do You Measure?

- Compliance with protocol and study timeline
 - Is content created, finalized and filed in alignment with timeline and study processes?
- Timely availability of documents
 - Is a document collected and filed/uploaded in a timely manner so that it can be generally available by its due date?
- Effectiveness of processes
 - Is a document quality checked and finalized in a timely manner after receipt?
 - Do bottlenecks inhibit timely process flow?

Quality: What Can Go Wrong?

“Failure to fully document and perform effective QC checks on documents uploaded into eTMF – the result being that the inspectors had no confidence that the eTMF was accurate. Discrepancies were seen, as were missing pages, incorrect documents, poor quality scans.”

- reported in EMA Reflection paper

“... recommendation that there are regular reviews is to ensure that the documents remain accessible, readable, are filed/named appropriately, so that if there are any issues with the process, individuals utilising the system or the functioning of the system itself, they may be detected and managed. We have seen issues on inspection where scanned documents have not been readable, or not been complete.”

- Clarification provided in email by MHRA

TMF Quality Measurements

- Accuracy and completeness of documents
 - Missing signatures, inaccurate dates, incorrect annotations
- Accuracy of file location / eTMF indexing
 - Document filed in the correct location
 - Accuracy of metadata for eTMF – assigned to correct trial, site, doc type, etc.
- For scanned content, accuracy and completeness of visual image
 - Defects such as missing/extra pages, skewing, etc. must be detected

TMF Metrics

	A	B	C	D	E	F	
1	Metric Title	Metric Type	Definition	Metric Indicator	Part of Study	Business Driver / Benefit Statement	Form
2	TMF % Complete	Completeness (based on due date)	Percent of documents whose due date has passed that have undergone all necessary review, approval or QC processes and are considered final.	Leading	Conduct	Ensure that the TMF is complete for purpose of decision-making and audit readiness at all times.	Coun today final that date
3	Milestone % Complete	Completeness (based on events)	Percentage of documents associated with an event that have that have undergone all necessary review, approval or QC processes and are considered final. E.g., based on when recruitment is done, site selection is done, interim analysis, LPLV, CSR, etc. Documents are attached to the event, and at the point where event is being assessed for completeness then the status of associated docs are assessed. This metric does not take into account dates, but instead assessment for completeness before milestone can be declared as complete. Also may be associated with events such as Protocol Amendments or Safety Events rather than milestones.	Leading	Conduct	Ensure at major checkpoints that all documents needed have been received; prevent only detecting at end of study that things are missing. Inspection readiness can focus on only the more recent event if earlier out.	Coun with even / Tot assoc mile:
4	Archive Ready	Completeness (end of trial)	Percentage of expected documents that have undergone all necessary review, approval or QC processes and are considered final.	Lagging	Close-Out	Ensure that the TMF is ready for archive.	Coun coun expe close
5	Content Problems	Quality (content)	Percent of documents for which quality defects related to content (e.g., missing signatures, incorrect annotations, etc.) were identified during QC processes.	Leading	Conduct	Understand the extent to which documents have to be re-worked.	Coun one c rew
	Image Problems	Quality (visible image)	Percent of documents for which quality defects related to image quality (missing/extra pages, skewing, etc.) were detected during	Leading	Conduct	Understand the extent to which documents have to be re-worked	Coun one c

The Metrics Working Group has defined a total of 21 metrics for consideration

Metrics Definitions

- Each metric is defined with details to aid in understanding its business value, how it should be computed, etc.
- Standard metrics structures defined by the [Metrics Champion Consortium](#) were taken into consideration and augmented with TMF specific information

Defining Metrics (1 of 2)

- Metric Title
- Metric Type (completeness, quality, etc.)
- Definition
- Metric Indicator
 - Leading: shows opportunity for change within a current trial based on that reported metric. They are predictive and can provide forward-looking glimpses into the progression of a trial
 - Lagging: shows opportunity for change in a future trial based on results of previous trials. They are statements of what has already occurred, and are best looked at to evaluate performance for future trials. They are results instead of a prediction.

Defining Metrics (2 of 2)

- Part of Study (Start Up, Conduct, Close-Out)
- Business Driver / Benefit Statement
- Formula / Example
- Reporting Frequency: recommendation on how often metric should be measured and reported
- Notes on eTMF vs. Paper
- General Notes

Metrics Example: Completeness by Due Date

Metric #	Metric Type	Metric Title	Category	Metric Indicator	Part of Study
1	Completeness	TMF % Complete by Due Date	N/A	Lagging	Conduct
Definition			Formula / Example	Reporting Details	
Percent of documents whose due date has passed that have undergone all necessary review, approval or QC processes and are considered final.			Count of documents due by today's date that have been finalized / count of documents that were expected by today's date and	Study / Country / Site / Sponsor / CRO / Function (Zone) / Milestone / CRA / Process / Document Type	
				Unit of Measure	
Business Driver / Benefit Statement			Additional Analysis on a "for cause" basis	Reporting Frequency	Threshold Target
Ensure that the TMF is complete for purpose of decision-making and audit readiness at all times.				Monthly or in advance of milestones	Defined by organization
Companion Metrics	Quality metrics, as driving higher completeness could compromise quality.				
Notes (eTMF vs. Paper)	For paper TMFs, manually tracked in spreadsheet. For eTMFs, system should be able to determine as long as the system knows what is expected and when.				
Notes (General)	Do not count documents received by today's date but not yet due by today's date.				

Metrics Example: Quality: Content Problems

Metric #	Metric Type	Metric Title	Category	Metric Indicator	Part of Study
4	Quality	Content Problems	N/A	Lagging	Conduct, Retrospective
		Definition	Formula / Example	Reporting Details	
		Percent of documents for which quality defects related to content (e.g., missing signatures, incorrect annotations, etc.) were identified during QC processes.	Count of documents returned one or more times for content rework / total documents	Study / Country / Site / Sponsor / CRO / Function (Zone) / Milestone / Defect Type / Rework Time / User/Operator / Time Period	
				Unit of Measure	
				Percentage	
Business Driver / Benefit Statement			Additional Analysis on a "for cause" basis	Reporting Frequency	Threshold Target
Understand the extent to which documents have to be re-worked.					Defined by organization
Companion Metrics		Quality metrics, as driving higher completeness could compromise quality.			
Notes (eTMF vs. Paper)		Relevant for both paper TMFs and eTMFs.			
Notes (General)		Assume that this is mainly for scanned documents. Do you count the impact of documents re-worked multiple times?			

Paper TMF vs. eTMF Metrics

- eTMF data enables speed and ease with metrics
- Issues in paper TMF metrics
 - Some metrics do not apply (scanning quality)
 - Many may be labor-intensive
- For paper TMF, consider a risk-based approach to make metrics practical and cost-effective
 - Focus on a subset: high risk content, critical trial process, critical path trial, new personnel, signals from audits



FURTHER ANALYSIS ON METRICS

Further Analysis on Metrics

- Insight requires **relevant** information that reveals **actionable** details about a process
- For metrics to be meaningful and actionable, they often must be broken down to a more granular level
- The Working Group has provided a list of 17 types of analysis that may be useful in understanding trends and identifying issues

Metrics Analysis Example: Analysis by CRO

- For sponsor, determine performance of trials for a specific CROs or compare performance across CROs
- Purpose: Analyze performance of partners, compare against Service Level Agreements, compare against each other
- Examples:
 - TMF Completeness or number of misfiled documents for all studies run by a specific CRO
 - Comparison of time to process documents for all of a sponsor's CROs

Metrics Analysis Example: Analysis by Country

- Determine overall performance for documents related to a specific country or compare performance across countries (including site level documents)
 - Quality: to determine how units in the country are performing
 - Example: level of completeness in a specific country may reflect on responsible managers in that country
 - Study Knowledge: Improve knowledge of and forecasting for specific countries
 - Example: Average number of regulatory documents per country

Metrics Analysis Example: Analysis by Time Period

- Determine performance for one selected time period or by comparing multiple time periods
- Purpose: Analyze improvements, compute return on investment (e.g. adding more staff or increasing training).
- Example:
 - Average TMF Timeliness (Processing) time for each of the last 12 months
 - Average TMF Timeliness (Processing) time for Q1 of this year vs. Q1 of last year

Sample Reports

- The following reports are some examples that provide useful information about TMF health, content and processes
- These are just examples – not meant to imply that these are required or complete
- General Good Practices:
 - Provide an actionable level of detail
 - Properly label reports and ensure that what they represent is clear
 - Choose a report format that offers the most insight (bar, pie, scatter, etc.)
 - As always, if you are using an eTMF, review what your system can offer you

Example Report: TMF Completeness by Country

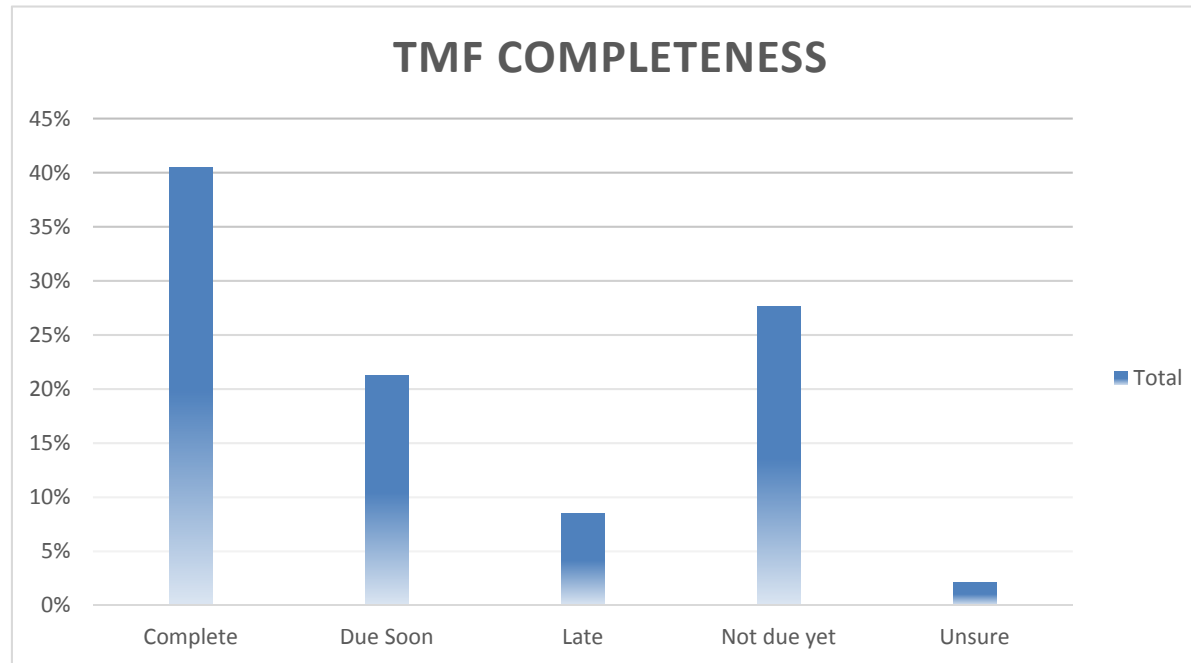


Country	Total Expected Docs	Final	Past Due	Nearly Due	Not Yet Due
	838	324	228	0	286
CANADA	501	149	96	28	228
MEXICO	601	68	86	32	415
FRANCE	608	114	73	78	343
UNITED STATES	553	212	64	22	255
SOUTH AFRICA	251	78	59	1	113
UNITED KINGDOM	198	61	59	10	68
SPAIN	309	56	44	18	191
ARGENTINA	225	98	5	27	95

This report represents a snapshot of the completeness of a single study at the current time decomposed by Country. It shows the number of final, overdue, coming due and not yet due documents for each country.

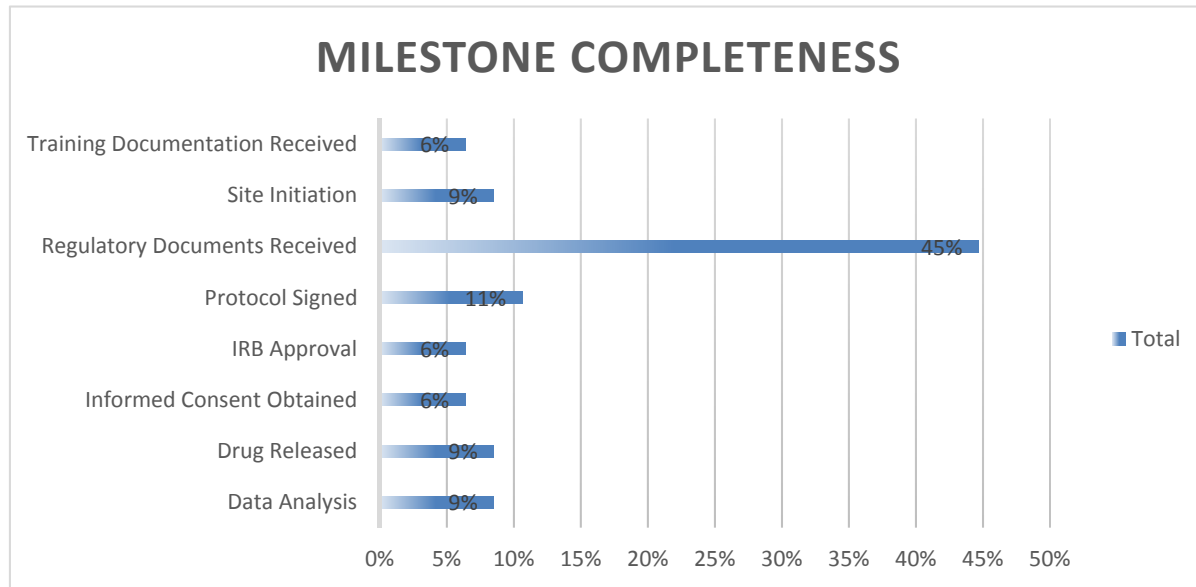
The same report could be generated by Organization, Business Unit, Category/Zone, Therapeutic Area, or Program.

Example Graphic: TMF Completeness by Status



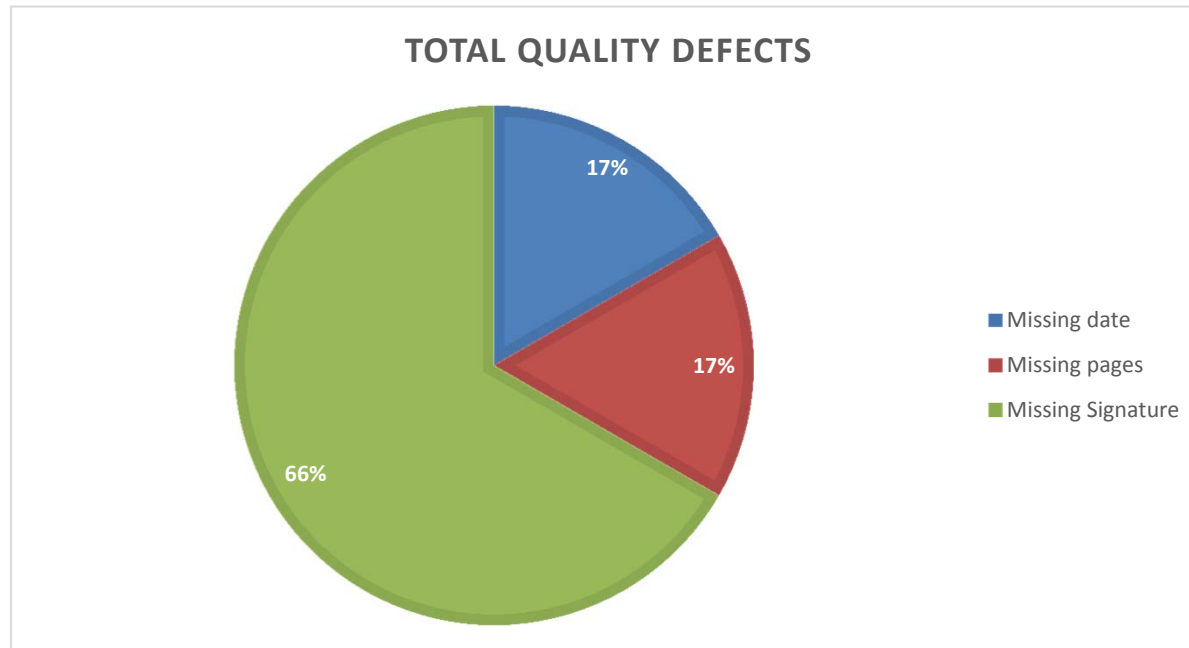
This chart represents a snapshot of the completeness of a single study at the current time.

Example Graphic: TMF Completeness by Status



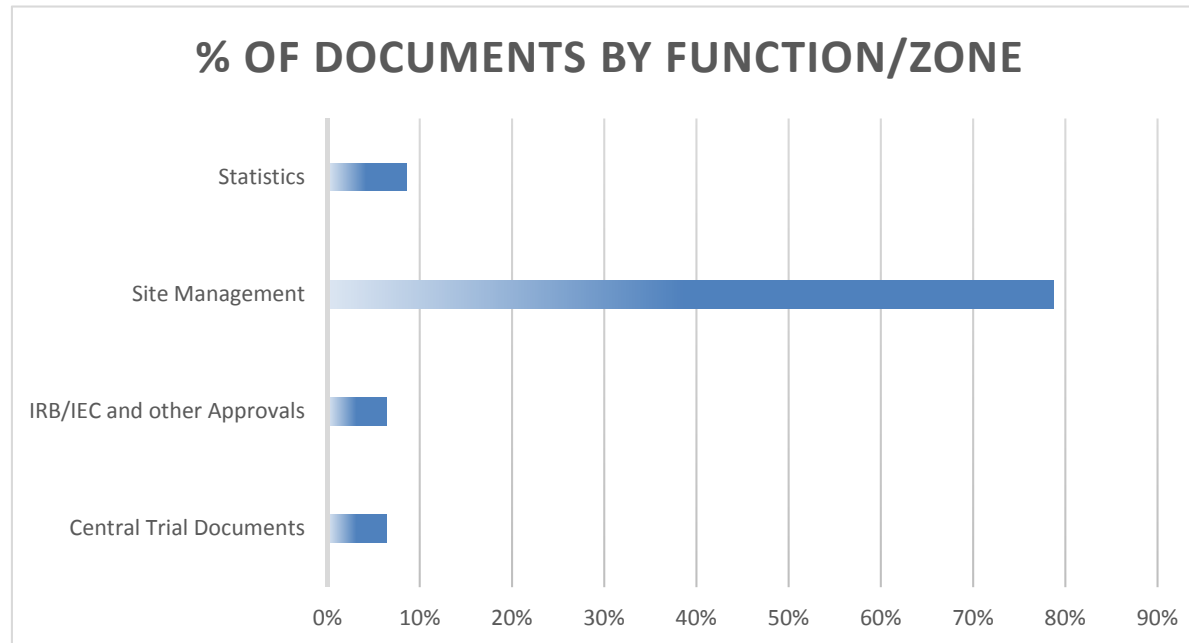
This chart represents average completeness for each milestone across a collection of studies at a given time, e.g., all oncology studies.

Example Graphic: Quality Defect Breakdown



This chart represents a collection of studies and quality defects found during a selected time period, e.g., Q4 2013.

Example Graphic: Received Documents by Zone



This chart represents the breakdown of documents by type for all studies.



METRICS PROGRAM DESIGN

Design of a Metrics Program

- Goal Selection
 - Quality by design
- Choosing metrics to support your goals
 - Cost – benefit analysis
 - Support for risk-based approaches

Quality by Design and TMF Metrics

Quality by Design (QbD): designing and developing processes to ensure that a **product** (TMF in this case) consistently attains a **predefined quality** at the end of the process.

When applied to eTMF, QbD involves identifying **key parameters** that affect quality and risk, and monitoring those parameters
... achievable only when a metrics program is in place

Defining Key Goals

- Goals supported by metrics may come out of QbD sessions, audit findings, or many other sources. Examples:
 - Audit readiness
 - Decreased processing time
 - Improved capacity planning
- Make sure metrics goals support and align with overall organizational goals

Achievable Goals

- Choose an achievable set of goals and determine which specific metrics best support them
- Consider a phased approach, i.e. introducing metrics gradually
 - Low hanging fruit could be targeted first
 - Once baseline metrics are available and understood, introduce escalation and personal responsibility, objectives and penalties

Example of QbD applied to eTMF

- An example of applying QbD to eTMF is documented in [“The New Gold Standard: Pfizer's Quality by Design Approach to Trial Management”](#), Pharmaceutical Executive, April 2013
 - Business Case
 - Solution Overview
 - Critical-To-Quality attributes

Cost vs. Benefit

- How important is the business driver?

Metric #	Metric Type	Metric Title	Category	Metric Indicator	Part of Study
1	Completeness	TMF % Complete by Due Date		Lagging	Conduct
		Definition	Formula / Example	Reporting Details	
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				Unit of Measure	
				Percentage	
		Business Driver / Benefit Statement	Additional Analysis on a "for cause"	Reporting Frequency	Threshold Target
		Ensure that the TMF is complete for purpose of decision-making and audit readiness at all times.		Monthly or in advance of milestones	Defined by organization

Quality: A Risk Based Approach

Ensuring quality is daunting... but what if you were managing a trial conducted in dozens of countries and over a thousand sites...

Defining a **risk based approach**
Is essential for success

Produced by TMF Reference Model

Applying a Risk Based Approach

- Identify which processes are more high risk.
Examples:
 - 100% QC checks might be required for IP Greenlight documents, a lesser percentage for other processes or milestones
 - Countries with more complex regulatory processes
 - Sites with a high number of screening failures or protocol deviations
 - Document types commonly examined by inspectors
 - Content that affects patient safety
- Take into account reliability of document source
 - E.g. validated pharmacovigilance system vs. desktop scanning
- Establish and monitor confidence levels



METRICS PROGRAM IMPLEMENTATION

Metrics Program Implementation - Principal Considerations

1. Logistics (data population)
2. Accountability
3. Frequency
4. Presentation
5. Triggered activity & escalation

1. Logistics

- For each metric; define how it will be populated and how it will be shared
- Consider the benefit of ‘self service reports’ vs circulation via email at scheduled frequencies
- For eTMFs, evaluate the use of pre-existing BI tools to supplement the eTMF toolset
- Remember to consider security and appropriateness of report vs audience

2. Accountability

- Remember the TMF includes documents from a multitude of functions; so a central, cross functional ‘Business Owner’ is advisable
- Consider generating a RACI (Responsible, Accountable, Consulted, Informed) to clarify who will be generating the metrics vs. who is accountable for their contents

Example of eTMF RACI

Activity (short description of interface /relevant task)	Sponsor	CRO	eTMF provider
Create & circulate SLA Report	I	I	R
Monitor Service Level Agreements (SLA) – Sponsor	A		
Monitor SLA – CRO	I	A	
Monitor SLA - eTMF provider	I		A
SLA Oversight	A	I	I
Create & circulate Close-out Timeline Report	I	I	R
Monitoring Close-Out Timeline /Milestones	A	R	I

3. Frequency

- Link frequency to the Business Benefit or Benefit Statement. What period of data and associated frequency is required?
- Do all users need the report at the same frequency and same view of data?
 - Study Managers might need a monthly report
 - CRO Account Manager may only need quarterly summary.

4. Presentation

- Most people find graphics easiest to interpret
- Consider different views for different time periods, e.g.
 - 6 month view cumulative graph of submissions
 - Summary table of monthly detail
- Systems that allow drill through or data expansion offer most flexibility
- Use colour & formatting (e.g. traffic lights) to enhance tabular reports
- If using a portal consider:
 - frequency of data archival
 - benefit of keeping comparator data available e.g. 2013 data vs 2014

5. Triggered activity & escalation

- You've distributed the metrics report – what next?
- How can you promote and measure compliance to reacting to the data?
 - Define Workflow
 - Define responsibilities in RACI
 - Personal objective tie-in
 - Management accountability
 - 'Metrics on metrics'

Business Processes – Role of Partners

- Depending on Metrics introduced partners can be metrics providers or report receivers or both
- Metrics can be linked to contracts and SLA and it's advisable to create template reports and specific CRO generation/review responsibilities within contracts
- Comparison between different CROs and CRO vs Sponsor users can aid future decision making and promote healthy competition

Metrics Program Implementation– Ongoing Program Review

- Define timelines for review at point of introduction
- Ensure the Business Drivers and/or Benefit Statements are valid and being met
- Some metrics may become redundant as your eTMF model matures; circulating superfluous information is pointless
- ‘Quality’ is key – do not lose sight of this

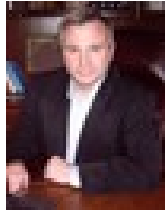


FINAL THOUGHTS AND SUMMARY

Available Materials

- This presentation
- Metrics Definition spreadsheet covering metrics definitions, analyses, roles and glossary

Using Metrics to Drive Decision-Making and Behavior



“If a measurement matters at all, it is because it must have some conceivable effect on decisions and behaviour. If we can't identify a decision that could be affected by a proposed measurement and how it could change those decisions, then the measurement simply has no value”

— [Douglas W. Hubbard, *How to Measure Anything: Finding the Value of "Intangibles" in Business*](#)

Opposing Forces in TMF Quality

- Law of Unintended Consequences: actions always have effects that are unanticipated or unintended
- Need to ensure that any effort to improve one of the key metrics doesn't result in degradation in other areas



Conclusions

- Metrics are needed to provide the insight to manage risk and to implement true process improvements
- Up-front investment in a well-designed metrics program can improve efficiency and increase compliance
- Implement a program that
 - Drives the behavior that you want
 - Provides the information needed to make good decisions
- Involve the business across your organization – don't start with technology but understand what technology can do for you

Thank you

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Join the LinkedIn group [TMF Metrics](#)



The full set of materials can be found on the TMF Reference
Model site: <http://tmfrefmodel.com/resources-2/>