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White Paper

Clinical Analytics: The Journey from Problem Identification to Solution

The Problem

Encouraged by Health Authorities, Life Sciences organizations have moved towards risk based approaches in almost all of their activities. Since 2002, the FDA has pursued an initiative entitled "Pharmaceutical CGMP Initiative for the 21st Century – a Risk Based Approach". This was followed in 2005 by ICH Q9 (Quality Risk Management), which focused on defining the principles by which risk management will be integrated into decisions by regulators and industry regarding quality. Later, clinical guidance documents were released, such as the 'FDA Guidance Oversight of Clinical Investigations: A Risk-Based Approach to Monitoring' and the 'EMA Reflection Paper on risk-based quality management in clinical trials.'

> "Quality" in clinical trials is defined as the absence of errors that matter to decision making—that is, errors which have a meaningful impact on the safety of trial participants or credibility of the results (and thereby the care of future patients) - CTTI

One key element of risk-based approaches is detectability - defined by ICH as "The ability to discover or determine the existence, presence, or fact of a hazard." Clearly, true risk-based approaches require near real-time data to anticipate, detect and mitigate risk.

Another important concept is quality. An excellent definition of quality is provided by the North Carolina Translational and Clinical Sciences Institute's Clinical Trials Transformation Initiative: "Quality" in clinical trials is defined as the absence of errors that matter to decision making—that is, errors which have a meaningful impact on the safety of trial participants or credibility of the results (and thereby the care of future patients) . This translates to identifying metrics which have a meaningful impact.

Information from a variety of sources must be unified and analyzed to present an accurate understanding of status, risk and progress. For example, risk-based clinical quality may require information from not only the Clinical Trial Management System) CTMS and Electronic Trial Master File (eTMF), but also Electronic Data Capture (EDC), Electronic Patient Reported Outcomes (ePRO), Randomization and Trial Supply (RTS), Regulatory Information Management System (RIMS) and Quality Management System (QMS). Without automation, the process of populating and analyzing data is both resource-intensive and error-prone.

Dashboards and analytics should enable users to reach conclusions and assess priorities easily. But there's a lot to think about before you can create analytics that truly aid in identifying risk, understanding status, uncovering and addressing inefficiencies and bottlenecks, and prioritizing work.

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Considerations for Defining Analytic

Defining meaningful and actionable analytics requires a series of steps.

Understanding the Purpose of Metrics

Analytics can be grouped into four major categories:

1. **Metrics**. These are usually Key Performance Indicators (KPIs) which are often reported periodically to upper management and often used, rightly or wrongly, as a measure of an organization's success. Metrics can often be thought of as information for the 1%.

2. **Risk analysis**. These analytics report against predefined risk factors, that is, the potential for adverse consequences. They include information on outliers and anomalies as well as out of specification conditions. They are often used by those responsible for managing processes or business units.

3. **Planning**. These analytics report on or estimate upcoming workload, by using awareness of known tasks and due dates, by projecting work based on known factors, or by using Artificial Intelligence algorithms to predict. These are truly analytics for the 99% since at some level they provide useful information to almost everyone in an organization.

4. **Status**. These analytics provide a snapshot of where an organization stands at a point in time by reporting on finished and unfinished business.

Defining Desired Metrics

Within this framework, an organization can identify specific sets of metrics that will support reaching organizational objectives. These metrics should answer the questions about what an associate needs to know to plan, manage or mitigate processes and risks in clinical trials.

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Sets of metrics can be grouped to fulfill specific business purposes. This aids in producing cohesive dashboards that present a consolidated set of information to fulfill user needs.

TransCelerate Risk Indicator Library

When identifying what metrics to analyze, considerable insight can be gained by studying TransCelerate's Risk Indicator Library. This is an extensive library of around 140 individual metrics proposed by industry to assist in uncovering and addressing risk. The Risk Indicator Library is part of a larger toolkit focusing on Risk-Based Monitoring that includes a framework, Risk Assessment and Categorization Tool (RACT), and Quality Tolerance Limits White Paper .

TransCelerate metrics cover many, but not all, aspects of clinical trials. Risks are organized into categories and identified by level of scrutiny, level of industry experience, etc., as shown in the snippet below.

Category	Sub-Category	Risk Indicator	Discussion/Details	Core KRI or Extended KRI *(Identification of Core vs Extended KRIs is intended to be completed by sponsor as appropriate)*	General or Specific	Level of Scrutiny
Data Quality	Discrepancy Management	Query count (critical DP)	Number of queries created (on critical data points only)		General	All levels apply
Data Quality	Discrepancy Management	Number of queries resulting in data change (critical DP)	Number of queries auto-closed (on critical data points only)		General	All levels apply
Data Quality	Discrepancy Management	Query aging (critical DP)	Average age of open queries (on critical data points only)		General	All levels apply
Data Quality	Discrepancy Management	Query aging (all DP)	Average days outstanding for open queries (all data points)		General	Protocol, Country, Site and Patient
Data Quality	Discrepancy Management	Reissued query count (critical DP)	Number of queries that have changed status from responded to		General	All levels apply
Data Quality	Data Trends	Query response time (critical DP)	Average days from open to respond (on critical data points		General	All levels apply
Data Quality	Data Trends	Query response time (all DP)	Average days from open to respond (all data points)		General	Site
Data Quality	Discrepancy Management	Query rate	Total queries created per data point		General	Protocol, Country, Site and Patient
Data Quality	Discrepancy Management	Manual query rate	Total manual queries created per data point		General	All levels apply
Data Quality	Discrepancy Management	Reissued manual query rate	Total manual queries reissued (query status from respond to		General	Protocol, Country, Site and Patient

Qualification of Proposed Metrics

Proposed metrics should be considered carefully.

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What is the purpose? Each metric should support a purpose that is clear to those who will consume it.

Who is the audience? The metric should fulfill the business objectives of the audience. If there are multiple audiences, they may require different versions or presentations of the same data.

What will be done with the data? Will it be used to make decisions, trigger actions, or reward individuals or groups? Where will this be documented?

Is the result meaningful? For example, the average time to close Corrective or Preventive Actions (CAPAs) is easily computed. However, it may not be meaningful since some CAPAs are intended to be closed promptly while others require multi-year follow-up.

Is accurate measurement possible? For example, TransCelerate metrics often recommend analysis that involves the number of critical data points in a protocol. If this information is not being collected, then the analysis cannot be done. There may also be a problem of availability (for example, if the EDC is not yet integrated with or unified with the CTMS). Finally, users may have low confidence in some data and consider it too "polluted" to use – whether perception or reality.

How should KPIs be established? If KPIs are to be used, how will thresholds be defined and what are the intended or unintended consequences? These can range from those responsible for establishing the metrics setting the bar so low that they will always be met, to failure to reach KPIs being used as a coercive force.

Validity of Comparisons

Finally, consider the value across programs, studies or sites, or at different times throughout the trial. There are often valid reasons why metrics are not comparable across trials, or have different thresholds in different types of trials. When comparing sites, the number of subjects and the amount of data (Case Report Form pages/data points) collected can be used to normalize results. In the example below, Site A has the fewest protocol deviations. When normalized by subject, Site C (a high-enrolling site) has the fewest deviations per subject. But when further normalized by the number of critical data points collected, Site B has the lowest incidence because they are at a later milestone in the trial and have collected more data.

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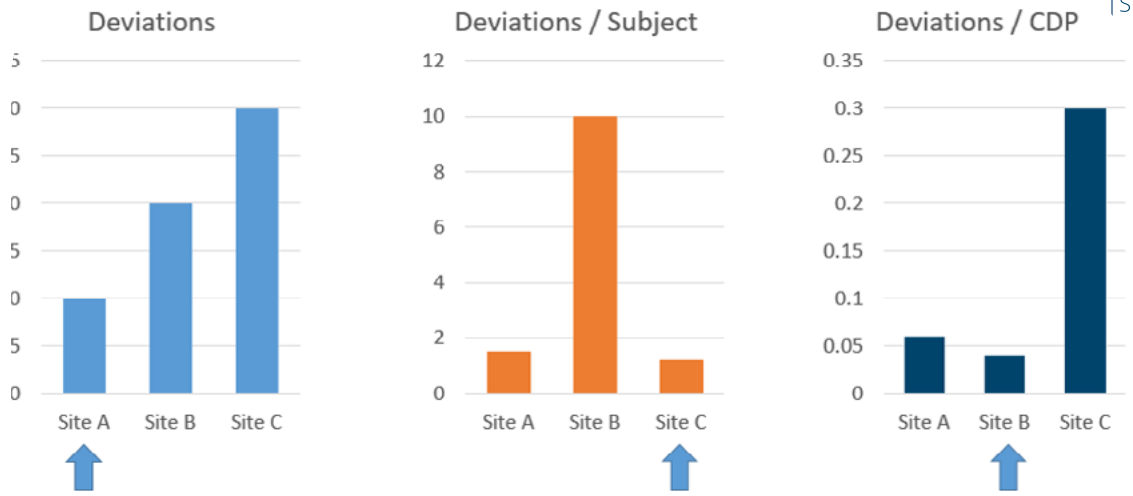

Managing R and Increasing Efficiency

Risk Metrics

Some sample metrics focused on risk appear below. Again, TransCelerate is a great source for CTMS metrics. It's worth noting that many of these metrics require at least some level of integration between EDC and CTMS in order to automate – for example, producing any metric related to the patient CRF would be onerous to attempt manually except in studies with very few patients.

There are no real published sources that recommend eTMF metrics related to risk. The proposed eTMF metrics are based on the general concept of ensuring data integrity and patient safety.

CTMS Metrics	eTMF Metrics
Timeliness of data entry	TMF Completeness
Number of open CRF queries/resolution time/data corrections	Average age, overdue documents
Number, severity, causality, etc. of AEs	TMF Correspondence %
Number of important protocol deviations	QC Backlog
Subject deaths, dropouts (reason, related to AEs)	Additional analysis by document risk/criticality
Missing CRF visits / pages	(US) status of IND submissions (protocols, investigators, etc.)
Timeliness of PI CRF approvals	Expired documents not replaced
eDiary compliance	
PI present at monitoring visits	
Informed consent issue rate	
% subject visits out of window	
AE/SAE rates	
AEs of special interest	
Compliance with Monitoring Plan (late visits)	
Site personnel or CRA turnover	

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Operational/Efficiency Metrics

Many metrics are more related to efficiency than risk, although they often have a risk element as well. The table below includes sample operational metrics.

CTMS Metrics	eTMF Metrics
Volume of site visits, SDR/SDV	TMF Timeliness
Monitoring Report approval timeliness	TMF Quality
Issue resolution time/volume	TMF Volume (per time period)
Time to report protocol deviations	TMF Submitter volume, rejection percentage, rejection reasons
Average site contract approval time	Document specialist volume and QC outcomes
Average times, consent->randomization, randomization -> first visit, …	TMF QC Rework cycles
Enrollment rates vs targets	Projected workload based on planned documents
Screen failure rate	
Site initiation time	
Health Authority authorization time (where applicable)	
IRB/IEC approval times and cycles	
1572 Submission times and status	
IRB/IEC expiration (upcoming/overdue)	

Measuring Associate Performance

Metrics related to associate performance can be valuable in many ways. They can be used to identify associates who need additional training, to reward high-performing employees, and to establish benchmarks for the workload associated with certain roles. Of course, these metrics need to be available only to those with a legitimate need to use them.

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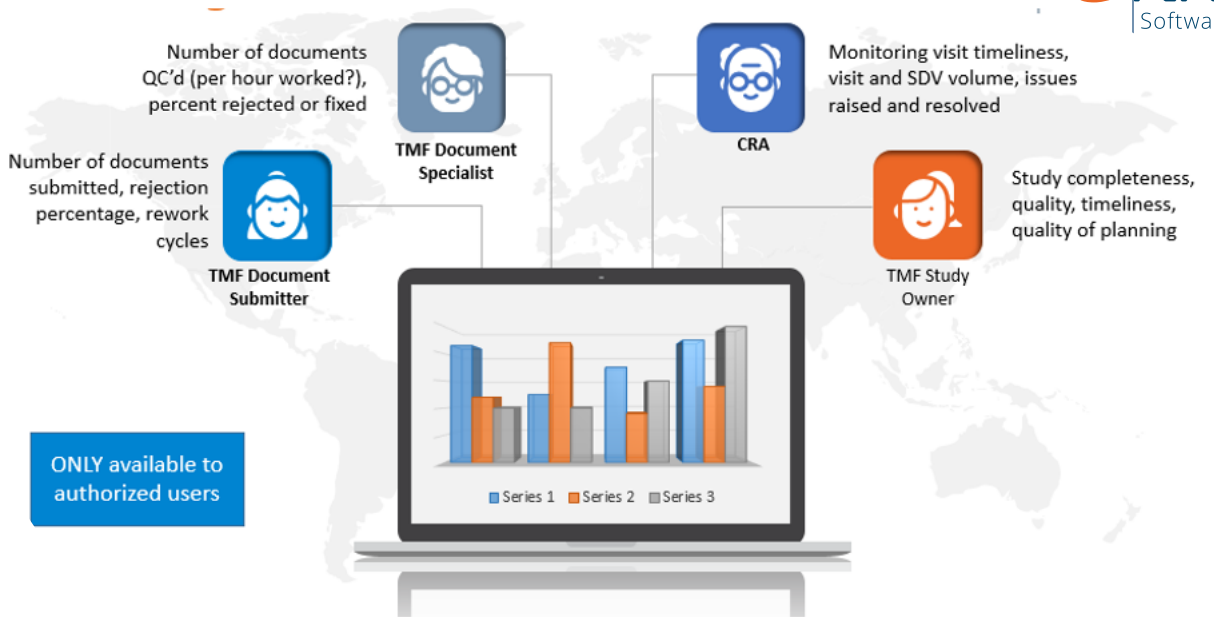

If associates have goals or bonuses based performance metrics, transparency on metrics and how they are determined is needed. Metrics may have to be normalized by relevant factors to be meaningful – such as the hours worked by Document Specialist performing QC, the number of patents at a CRA's sites, etc. In one example, Document Specialists were evaluated based on the number of documents QC'd. One Document Specialist was found to be selecting documents based on the number of pages in each, avoiding longer documents that too more time to check.

Defining and Presenting Data

Collecting the Right Data

After desired metrics are defined, the next step is to determine whether it is really feasible to collect them, and at what cost in terms of time and effort.

AVAILABILITY

- Do you have the data needed to provide your defined analytics?

EFFORT

- If not, do you need to add or update your clinical IT systems to collect it?
- Or to update your processes to measure it?
- What is the burden on the user and is it justified?

QUALITY

- Can the data be collected consistently and reliably?
- Will users have confidence in the results?
- Will the measurement actually support the defined purpose?
- Can users "game" the metrics?

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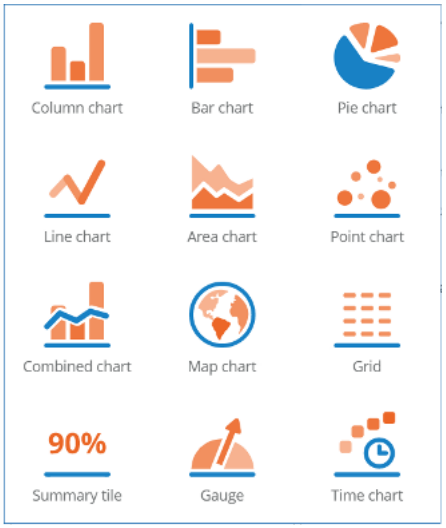
Data Visualization



Once the feasibility of collecting is determined and any necessary cost-benefit analysis is completed, the presentation of metrics in analysis dashboards can be defined.

Dashboards with well-chosen visualizations help users to identify and manage risk. Choosing the right data visualization is important. Some considerations:

- What can your system(s) provide? Can they do complex calculations or just report counts? (For example, can they just produce a count of subjects, or can they produce a count of subjects screened between certain dates but not randomized within two weeks?)
- Can you compare across studies, sites, associates…?
- Can you identify outliers? How will they be highlighted?
- What can you measure against KPIs?
- When is tabular data needed? Can it be sorted, grouped, filtered? Export to Excel?
- Can you provide attention-getting summary tiles (for example, the number of sites with ethics expirations in the next month, a count of important protocol deviations that have not been resolved)?

Data visualizations should be selected and organized into dashboards that trace back to the key goals of identifying risk, understanding status, planning work, and increasing efficiency.

Summary

Defining a set of useful metrics to support planning, monitoring and managing clinical studies using analytics requires making a set of sound decisions, not just using what a vendor offers. Sound practices include:

1. Understanding what you want to measure – consulting industry sources for ideas as well as working with the user community.
2. Defining metrics that support risk management, operational efficiency, status reporting, and workload management.
3. Ensuring that the purpose, use and audience for each is well-defined.
4. Thinking about whether data can truly be used to compare across studies, sites or associates.
5. Defining how meaningful data can be collected, and consider cost-benefit in choosing metrics.
6. Choosing effective ways to visualize and present data.

References

[I] ICH guideline Q9 on quality risk management, effective January 2006.

[II] North Carolina Translational and Clinical Sciences Institute CTTI RECOMMENDATIONS: QUALITY BY DESIGN, June 2015

[III] Risk Based Monitoring Solutions, TransCelerate, accessed 14 October 2021

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