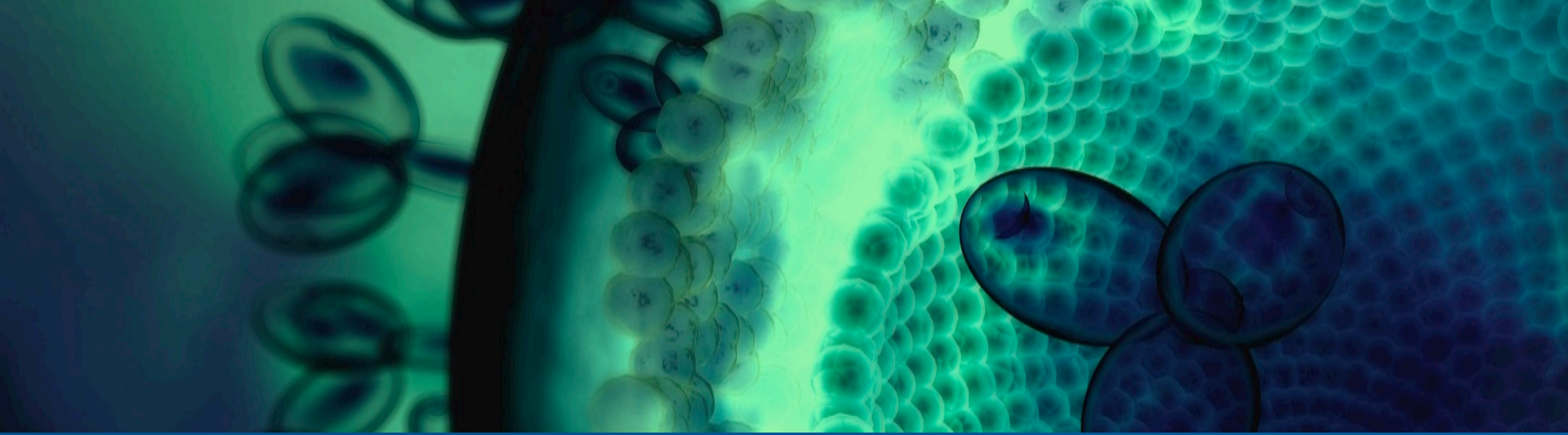


Analytical Risk Based Monitoring: A Deep Dive

Sina Djali
Head l Risk Management – Central Monitoring
Integrated Data Analytics and Reporting
Global Clinical Development Operations
Janssen R&D

Pictured above: The structure of HIV.

janssen | PHARMACEUTICAL COMPANIES OF Johnson&Johnson

Disclaimer

Presentations are intended for informational purposes only and do not replace independent professional judgment. Statements of fact and opinions expressed are those of the participants individually and, unless expressly stated to the contrary, are not the opinion or position of the Janssen Pharmaceuticals or its affiliates.

If you are in a shipwreck and all the boats are gone, a piano top buoyant enough to keep you afloat that comes along makes a fortuitous life preserver. But this is not to say that the best way to design a life preserver is in the form of a piano top.

I think that we are clinging to a great many piano tops in accepting yesterday's fortuitous contriving as constituting the only means for solving a given problem.....

Operating Manual for Spaceship Earth,* Buckminster Fuller;*1968

Clinical trials are essential to the evaluation of promising scientific discoveries, but they are becoming unsustainably burdensome, threatening to deprive patients and health-care providers of new therapies and new evidence to guide the use of existing treatments.

Impediments to Clinical Research in the United States; J M Kramer, P B Smith, R M Califf, *Clinical Pharmacology & Therapeutics* (2012); **91** 3, 535–541

Agenda

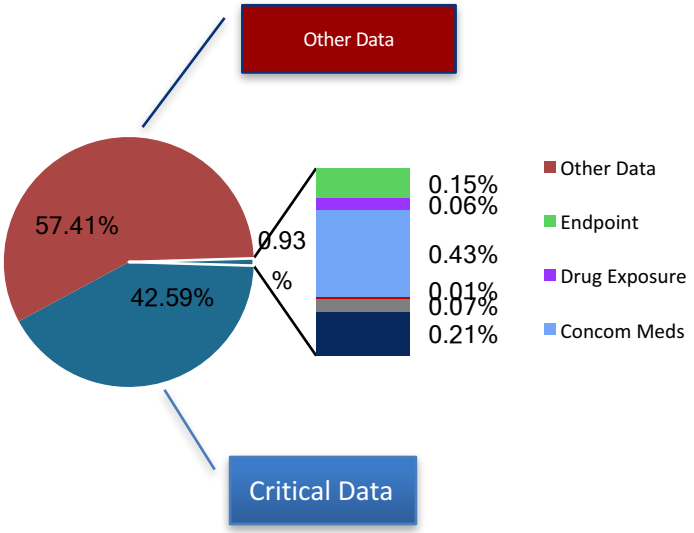
- Problem Statement
- Janssen Approach to Analytical Risk Based Monitoring (ARBM)
- Current metrics
- Integrated Analytics
- Future direction

Problem Statement

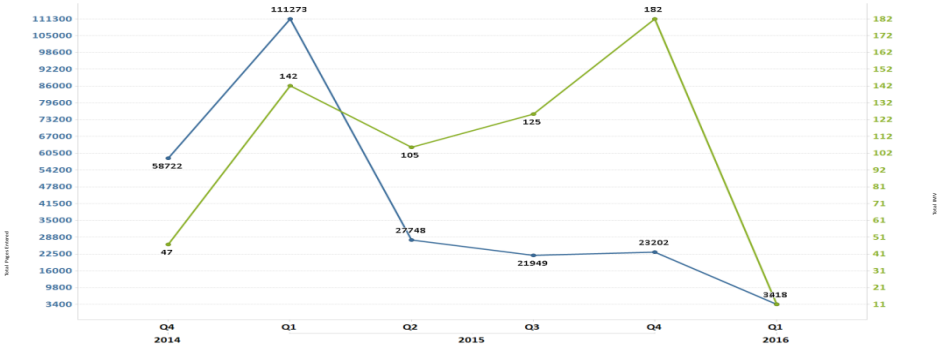
- Regulators are asking for more efficient ways of ensuring data quality.
- Requesting highest level of error free databases has a very high cost associated with it.
- However…

100% Source Data Verification will not always result in 100%

% CRA Associated Changes by Bucket on Critical Data - Overall



Monitoring Activity Do not Correspond to Activity at Investigator Sites



Janssen Approach to ARBM: Pro-active Risk Management

janssen | PHARMACEUTICAL COMPANIES OF Johnson & Johnson

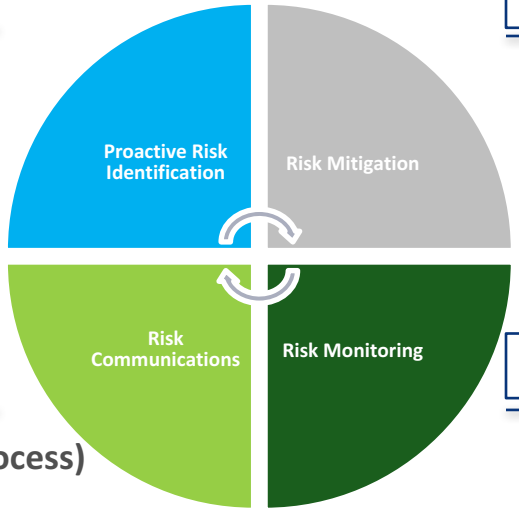
Risk Management – Central Monitoring

- Risk identification and mitigation during study set up and execution by focusing on key study objective around Critical to Quality (CtQ) data and their acquisition processes
- Support activities of central and local with focus on real time monitoring efficiencies related to CtQ data
- Enable efficient and early decision making by all relevant R&D stakeholders regarding data quality through use of analytics

Risk Management Process and Tools

Study Start Up

- Protocol Assessment **(Output)**
- Protocol De-risking **(Process)**



Study Start Up

- Integrated ARBM Plan **(Output)**
- Functional plans **(Output)**
- tSDV Specification **(Output)**
- Study Specific Report Intake **(Output)**

Study Execution

- Study Management Team Meetings **(Process)**
- CTM Team meetings **(Process)**
- Functional escalation **(Process)**
- Quality Working Group Meetings **(Process)**

Study Execution

- Study Specific Reports **(System)**
- Standard Key Risk Indicators/QRM Dashboard **(System)**
- Central Monitoring Working Group Meetings **(Process)**

Risk Management-Central Monitoring Core Capability

ARBM Study Set-Up Processes – All ARBM Studies

Protocol Assessment Tool

- High-level assessment of study completed by cross-functional team
- Outcome: ARBM type 1, 2, or 3
- ARBM type informs the monitoring approach
- The output should also be included in resource algorithms

Protocol derisking

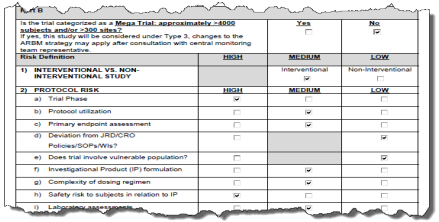
- In-depth discussions by cross-functional team on known/potential risks (protocol & operational)
- Where possible, fully mitigate these risks
- Identify residual risks impacting critical study data and/or critical study processes

Integrated ARBM Plan

- Document the residual risks from de-risking discussions
- Identifies functional group responsible for ongoing review of each risk, review frequency, & documentation
- Serves as a study 'road map' for study risk management and data oversight

tSDV Specs

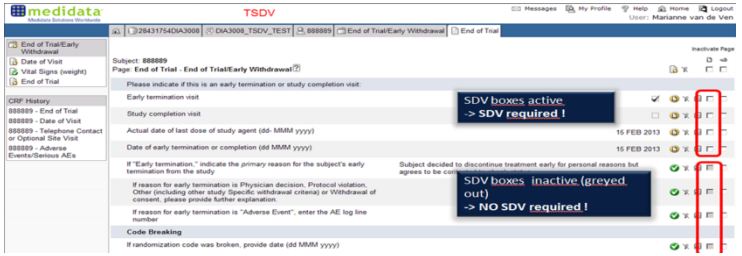
- Critical eCRF data fields defined by cross-functional team for SDV by the Site Managers
- *Note:* all data is still collected from sites
- *Note:* all eCRF data can still be reviewed centrally



Is the trial categorized as a Mega Trial: approximately >4000 subjects and/or >300 sites? If yes, this study will be considered under Type 3, changes to the ARBM strategy may apply after consultation with central monitoring team representative.		Yes	No
Risk Definition	**HIGH**	**MEDIUM**	**LOW**
1) INTERVENTIONAL VS. NON-INTERVENTIONAL STUDY		Interventional ☑	Non-Interventional ☐
2) PROTOCOL RISK	**HIGH**	**MEDIUM**	**LOW**
a) Trial Phase	☑	☐	☐
b) Protocol utilization	☐	☑	☐
c) Primary endpoint assessment	☐	☑	☐
d) Deviation from JRD/CRO Policies/SOPs/WIs?	☐		☑
e) Does trial involve vulnerable population?	☐		☑
f) Investigational Product (IP) formulation	☐	☑	☐
g) Complexity of dosing regimen	☐	☑	☐
h) Safety risk to subjects in relation to IP	☑	☐	☐
i) Laboratory assessments	☐	☑	☐

	Category	Identified Critical to Quality (CTQ) & Critical to Success (CTS) Factor(s)	Risk Assessment: Impact (1-3)	Probability (1-3)	Detectability (1-3)	Calculated Risk Level (Low, Medium, High)	Safety or Efficacy	Data Source	Data Source Vendor	Threshold	Mitigation & Contingency Strategies

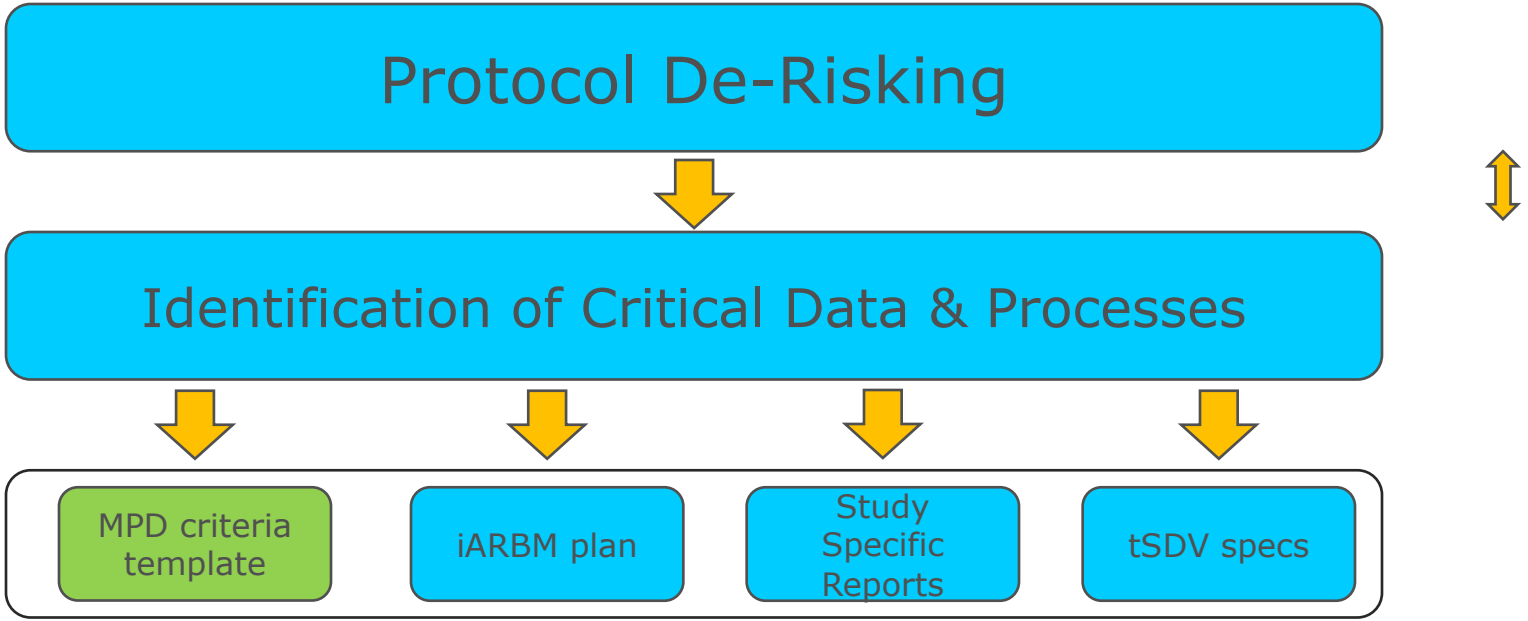
Mitigation & Contingency Strategies	Tracking-Reporting: Review Frequency	Tracking-Reporting: Documentation of Review	Functional Plan(s)	Responsible Person/Group



Examples of Critical Data/Critical Processes*

Therapeutic Area	Endpoint CTQ	Critical Data	Critical Processes
Metabolic	Change in baseline HbA1C at Week X	HbA1C	Collection, storage and shipment of labs
Cardiovascular	Number of CV events between treatment groups per adjudication committee	AEs of stroke, MI, death	Reporting and collection of AEs Collection and submission of source information to adjudication committee
IDV	SVR 12	HCV RNA	Collection, processing and shipment of labs
Oncology	Progression Free based on RECIST 1.1 criteria per Independent radiology review committee (IRRC)	Tumor measurements	Performance of scans to collect tumor measurements Assessment of RECIST 1.1 criteria Submission of scans and source information to IRRC

note these are only examples and may not be applicable to all studies in a therapeutic area



- Integrated ARBM plan has links to clinical operations including Data Management and medical Monitoring functional plans.
- As part of data flow project, there is ongoing discussion to align outcome of protocol de-risking with finalization of list of critical data/variables, front end edit checks, etc...

Risk Management - Central Monitoring During Execution

TRIAL EXECUTION

- Regular data reviews of potential study risks identified in integrated ARBM Plan by different functions.
- Routine Central Monitoring Working Group meetings to review the outcome of the reviews.
- Leveraging existing processes for review of Protocol Deviation /Issue Escalation, medical monitoring and Quality Working Group meetings
- Escalate significant findings to appropriate study team members and/or senior management if warranted.
- Follow up issues to closure.

Site Facing Elements – Janssen ARBM Today

- Implementation of risk-based review (QC sampling) – tSDV*

- Rationalize On site Frequency*
- Implement Formal Remote visits

- Focused Communication with sites on study specific risks

- Site Specific information to facilitate monitoring preparation, conduct and oversight – various reports today

*Note: tSDV % and on site visit frequency (prescribed intervals) set at study team level

Janssen ARBM – Impact on Roles

Site Managers/CRAs

- Remain primary site contact
- Monitoring frequency/focus changes
- Conduct formalized remote monitoring visits
- Follow up on central monitoring findings (site)

Local Trial Managers

- Remain secondary site contact
- Follow up on central monitoring findings (region, site)

Site Staff

- Less frequent SM visits
- Participate in remote monitoring visits
- Have more time to recruit/enroll/conduct study
- Continued responsibility for patients, trial conduct, data entry, filing, etc.

Integrated Analytics

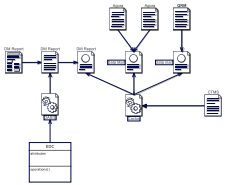
Problem Statements

- Current State of analytics in support of central and local reviews is segmented:
  - Multiple sources of reports and data making access to information both inefficient and ineffective
  - Outputs are not consolidated for easy access / review by either in–house functions or site facing staff
  - Techniques do not consistently support review / identify broader risks or issues across different functions
- On site QC activities, while reduced, are not at lowest industry levels
  - Opportunity for redirecting some of SM time

Analytics Maturity Model

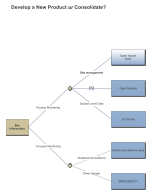
Stage 1

Data and Reporting



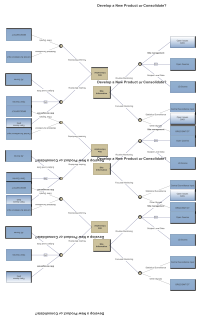
Stage 2

Predictive / optimization Modeling



Stage 3

Reproducibility / Scale up



Stage 4

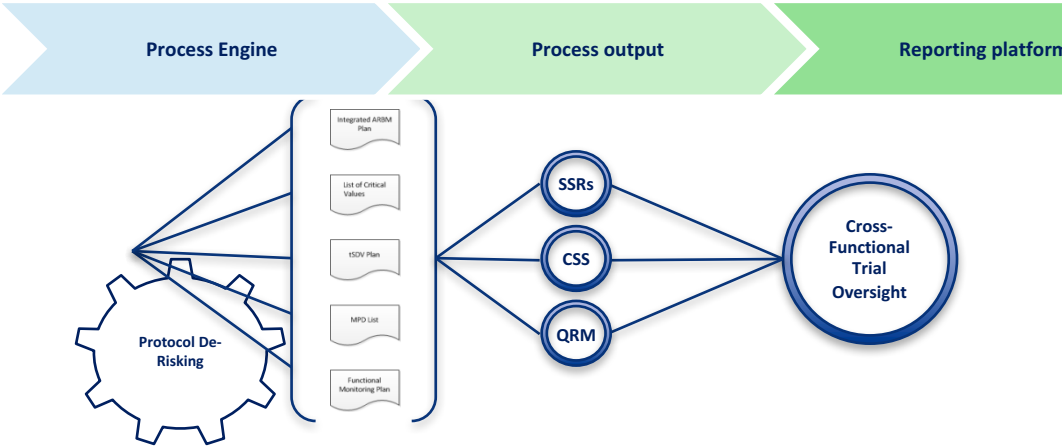
Enterprise Analytics

Stage 5

Analytic Driven Strategy

Analytical Core as an Enabler of Quality Oversight

- The objective of analytical core is to provide study support and oversight through use of programmed reports.
- This support includes programming of Study Specific Reports (SSR) and Central Statistical Surveillance (CSS).
- The team consists of small group of programmers, statisticians and informatics experts.



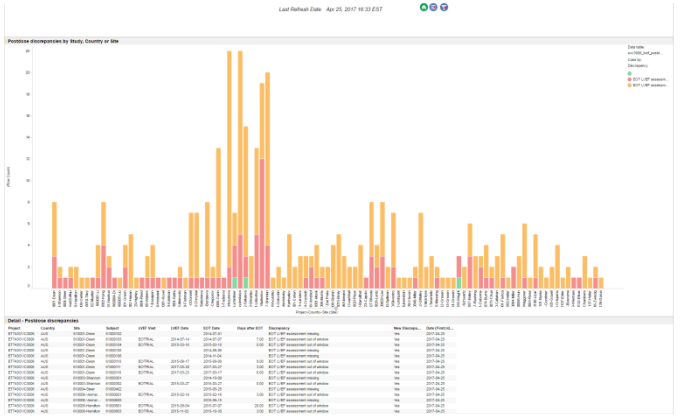
Study Specific Reporting as an Oversight Tool for Central Teams

- Study Specific Reports (SS-R) contain protocol specific information.
- SS-R content is determined as part of ARBM process and through de-risking.
- SS KRIs will have a direct link with DDA Critical Data Review and list of Major Protocol Deviations.
- In phase 1 RM-CM (ongoing) manually places data from different data sources in to SAS-Drug Development.
- In a second phase, data sets will be available through automated pull and conversions through data flow project.

Summary of Study Specific Report Implementation Across all TAs

Therapeutic Area	No Visualization	SpotFire	Grand Total
CV/Metabolism	1		1
Immunology	2	3	5
Infectious Diseases/Vaccines	3	2	5
Neuroscience		7	7
Oncology	5	7	12
Grand Total	**11**	**19**	**30**

Example of SSR: End of Treatment Left Ventricular Assessments "Not Done" or "Missing"

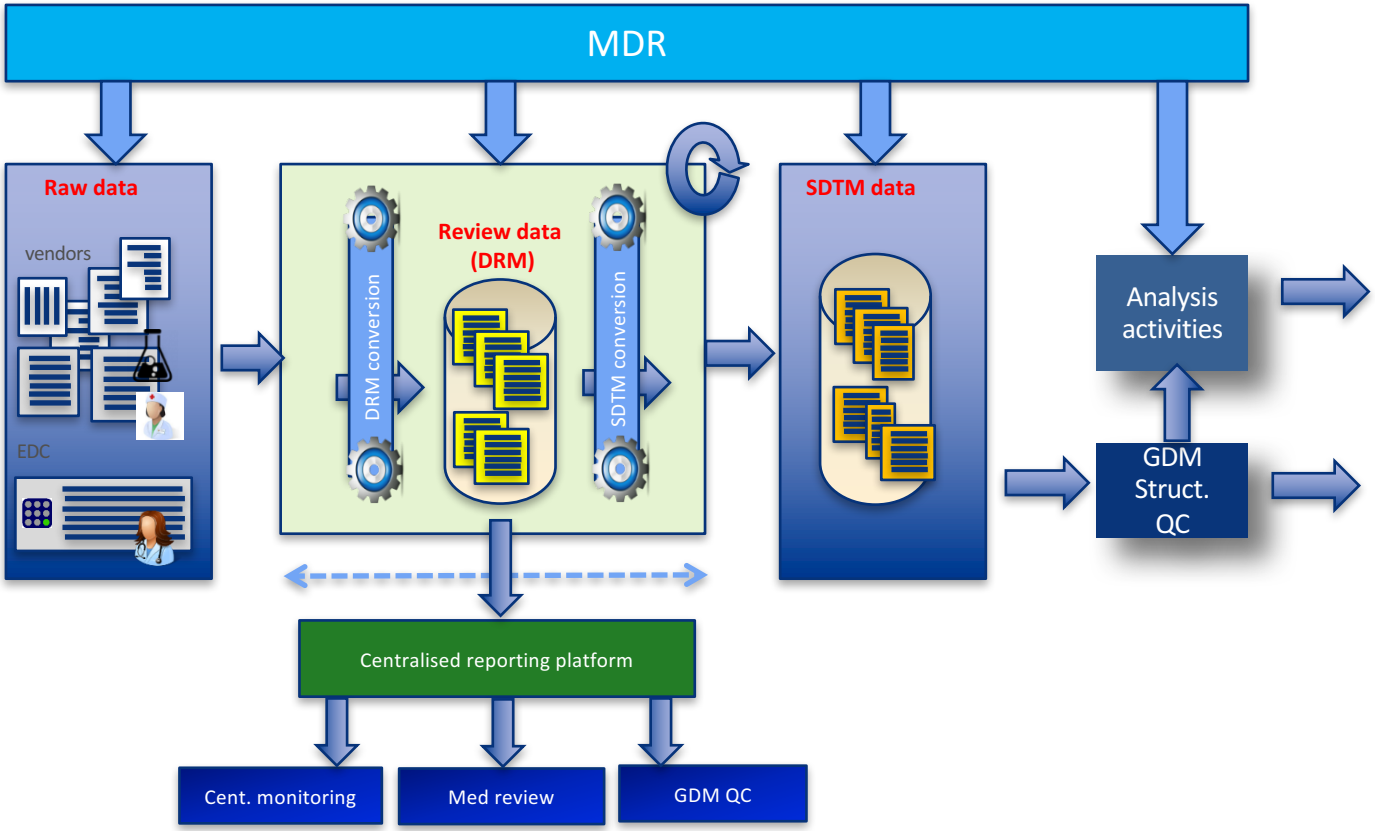


Future Direction

Future state capability: Advanced Use of Analytics

- Leverage Study and Site Specific Report to support Source Data Review as well as central reviews:
  - Focused oversight by utilizing data from multiple data streams including real-time inconsistency and quality checks
  - Single and efficient visualization platform for access to relevant information required for trial oversight by GCO
  - Fact-based determination of monitoring frequency
- Benefits:
  - Focus on critical data/trends and patient safety
  - Supports proper on-site monitoring frequencies by using data
  - Optimize future site engagement and reduce oversight time

Optimized Clinical Data Flow as an Engine for Analytics



In Closing: Enhanced Analytics / Visualizations Can Support Compliance and Trial Oversight

- Use of advanced analytics to manage to identify critical issues
- Provide consumable insights to the study / site staff – focus on support of SDR/ risk / issues
- Support a move from 100% QC of on site monitoring activities to a sample based verification activity, resulting in operational efficiency