acdm

association for **clinical data management**

A Practical Guide to Risk Based Data Management

Authors/Contributors: Adam Baumgart, Rich Davies, Mags Fraser, Pooja Ghorpade, Corinna Heide, Evaldas Lebedys, Naveen Kumar Kodavoor, Alicja Mark, Peggy Oni, Wibke Peylo, Tanya du Plessis, Peter Sec, Lynette Thomas, Achilleas Zaras

Date/Version: 18 September 2025 / 1.0

Disclaimer

The information presented in the paper draws upon the combined understanding and knowledge of the Association of Clinical Data Management (ACDM) Risk Based Quality Management (RBQM) Expert Group on this topic and is provided as an aid to understanding the environment around Risk Based Data Management (RBDM) in clinical research.

These recommendations are the opinion of the authors and do not necessarily reflect the position of individual companies. Readers should assess the content and recommendations considering their own knowledge, organisational needs and experience as well as interpretation of relevant guidance and regulations.

Purpose

This paper is intended as a guide to introduce risk based clinical data management practice into legacy processes. It is not intended as a menu or strict standard operating procedure to follow. The Risk Based Quality Management DMEG of the ACDM, has collected our best thinking in this area with a goal to support improvements in DM practice.

Part 1: Executive Summary

Introduction

Over 2024-25, the ACDM Risk Based Quality Management (RBQM) DMEG focussed on how RBQM is impacting Clinical Data Management (CDM). We have collected our experience and guidance into this document focussing on the topic of Risk Based Data Management (RBDM), as a subset of RBQM. We asked ourselves questions such as:

- How does RBQM impact Clinical Data Managers and CDM departments?
- If the new approach is "RBDM", what specifically is it and how should it be approached?
- The new RBQM functions e.g. central monitoring, analytics, medical & safety data review and statistical monitoring, how do they impact CDM?
- What is the best practise guidance for CDM, across these adjacent capabilities?
- Is there an opportunity for efficiencies in CDM or data collection modalities due to RBQM or RBDM?
- And finally, should RBQM and RBDM lead to an evolution of CDM or maybe a revolution?

The Problem and Opportunity

Problem Statement
Clinical Data Management has evolved around an increasingly complex ecosystem of data sources, systems, processes and roles over the last 30 years. Considering CDM started as lower-level tasks, that Biostatisticians preferred to delegate, we have developed into a formidable force of data managers, data scientists, analysts, programmers, coders, project managers and other adjacent disciplines e.g. central monitors, medical reviewers partially driven by ICH guidance such as ICH E8 R1 and E6 R2 and R3 .

Our CDM practices have been applied from one trial to the next, with limited critical or introspective assessment of meaningful value of such practices to the trial outcome.
CDM is collecting increasing data volumes, at faster speeds with continued quality requirements and yet somehow, we are broadly missing the opportunity to deliver fit-for-purpose quality database locks in faster timeframes. The amount of clinical data per trial has increased by 183% in the last decade.

The Opportunity
With the advent of Risk-Based Monitoring via ICH E6 R2, Quality by Design in ICH E8 R1, and RBQM through ICH E6 R3, Clinical Data Management can transition from striving for perceived perfection to implementing fit-for-purpose data strategies.

Clinical Data Management processes and methodologies can be enhanced to simplify the work of Clinical Data Managers and other clinical professionals. This includes minimizing multiple reviews and adopting a risk-based approach to prioritize CDM activities.

Additionally, there is considerable potential to improve efficiencies in study setup, increase site engagement, reduce the data query burden on sites, and significantly accelerate database lock timelines.

Part 2: RBQM Approach to Clinical Data Management

From review of the ICH E8 and E6 guidance, we identified the following key impacts on CDM.

Quality By Design

ICH E8 R1 guidance introduced Quality by Design principles including a foundational concept of "Critical to Quality" Factors (CtQs).

CDM should review the protocol as early as possible in the study design stage. This early involvement enables the Clinical Data Manager to contribute from a functional perspective to identification of Critical to Quality Factors and study risks prospectively.

CtQs are "attributes of a study whose integrity is fundamental to the protection of study participants, the reliability and interpretability of study results, and the decisions made on the

study results". The concept of CtQs is closely aligned with data and processes "that are critical to trial quality and risk" expressed in ICH E6 R3. Therefore, it is common practise now to identify critical processes and data as part of the QbD step.

Clinical Data Managers should play a key role in providing functional input to the definition of criticality of clinical data and process. In addition to CtQs can be measured through pre-specified acceptable ranges (e.g. Quality Tolerance Limits) in ICH E6 R3 3.10.1.3 (Risk Control).

Best practise has emerged over the last few years, which proposes the definition of:

Data Category	Proposed data components
Critical Data	Informed Consent, Investigational Product Compliance, Patient safety data, Primary Endpoint / estimand, and 'confirmatory' secondary endpoint, randomisation, blinding, eligibility, withdrawal and treatment discontinuation.
Supportive Data	Contributes to any secondary endpoints, contributes to safety endpoint, data being used in a table, figure with the Clinical Study Report.
Non-Critical Data	Contributes to an exploratory endpoint, data not being used in a table/ figure in CSR.

NB: The data categories above, have been enhanced with input from the ACDM RBQM DMEG.

Once critical and supportive data have been identified, CDM should drive the integration of these definitions into the design and function of the clinical data collection instruments, for example electronic data capture (EDC), data collected directly from participants (eDiary, eCOA, ePRO, Wearables), laboratory data and other clinical data sources.

The goal is to ensure a proactive and risk-informed setup that supports data quality and mitigates potential study risks from the outset. Criticality of data should also drive the focus of Audit Trial Review (ACDM whitepaper "Getting Started with Audit Trail Review in Clinical Trial Data An Essential Guide)

ICH E6 R3 section 3.16.1.(c) states "The sponsor should pre-specify data to be collected and the method of its collection in the protocol. Where necessary, additional details including a data flow diagram, should be contained in a protocol-related document (e.g. a data management plan." Therefore, CDM must critically consider all the potential data sources and domains within the sources of data, process related to its collection to ensure their data integrity, contemporaneous, validity, transformation and transfer mode as a precursor to any cross-functional risk assessment.

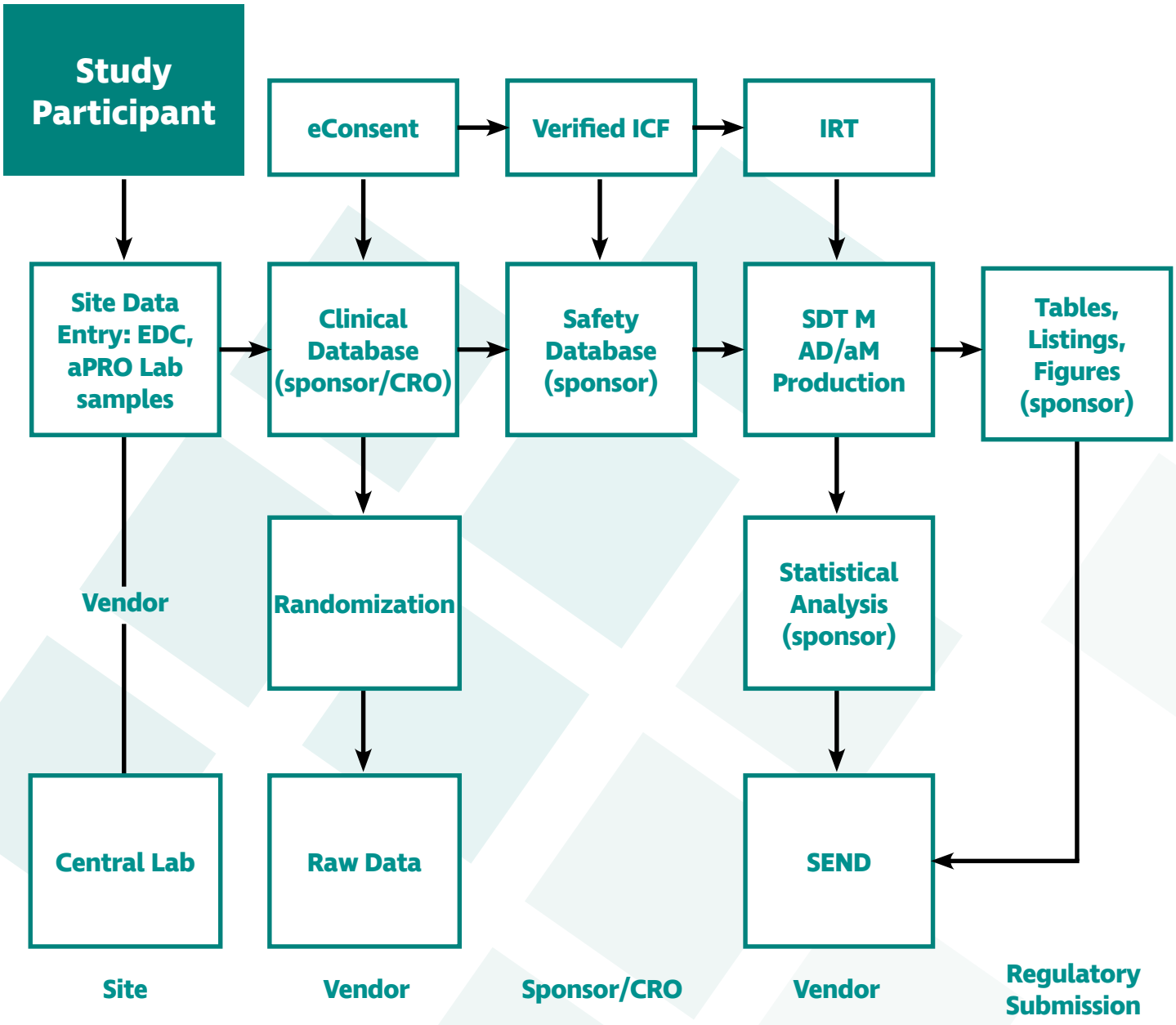


Image created by CoPilot Azure OpenAI ImageGen from analysing ICH E6 R3 guidance.

Emerging best practice is to document integrated end-to-end data review in a "Integrated Data Quality Review Plan". This IDQRP should record activities and responsibilities of all parties who review clinical data e.g. CDM, medical and scientific data reviewers, coders, programmers, biostatisticians and site monitors.

ICH E6 R3 section 3.11.4.2 refers to "Use of centralised data analytics can help identify systemic or site-specific issues, including protocol noncompliance and potentially unreliable data". CDM may already review data collection and quality Key Risk Indicators (KRIs). It is recommended that a single, integrated data source is used with clear functional responsibilities, for which KRI is reviewed. KRI Examples could include:

- High number of not complete eCRF forms
- High number of queries
- Late eCRF completion
- Late query response
- Late eCRF signature
- High rate of protocol deviations
- High rate of lost to follow-up subjects
- High rate of subjects withdrawing consent
- Low/high rate of adverse events

QbD is a principle that is applied throughout the clinical trial lifecycle. It is most impactful during the planning and design stages, but it is also continuously applied throughout execution, monitoring and data analysis.

Quality Risk Management

Quality Risk Management is described in ICH E6 R3 in section 3.10.1 with clear guidance for Risk Identification, Risk Evaluation, Risk Control in the planning and set up stages of a clinical trial and Risk Communication, Risk Review and Risk Reporting in the conduct and close out stages of a clinical trial.

The tasks required of CDM are clinical data management functional and study level risk identification, scoring (evaluation) and mitigation planning (control). CDM should be a key contributor to identifying any data related risks during the study risk assessment, this includes all risks identified while planning the study design with the focus on QbD. Risks related to all 3rd parties that impact the clinical data collection and handling e.g. CDM vendors, ePRO / eCOA, real world data, IVRS, CTMS and specialist data collection should also be included in risk assessments and logs.

Individual company's CDM processes may include a clinical data management specific risk assessment. CDM should be a key contributor for any data-related risks during the cross-functional study risk assessments performed during study conduct, thus taking ownership of risks in their functional area of expertise.

In addition, CDM should participate in other functional area risks that impact data integrity and trial results. All risks identified should go together with a plan on how to monitor these, when to flag risk activation as well as a mitigation plan on how to address the risk if needed.

Quality Control

This is affected by ICH E6 R3 sections 3.16.1 covering 'data handling' and section 4.0 Data Governance.

There are a series of emerging best practises that CDM should make themselves familiar with.

- Data Governance role: Own all the clinical data components collected and managed during the clinical trial, not only the data collected via EDC.
- Data collection and review need to be risk-focussed on Critical and Supportive Data with intentional thought being put into any plans/requests for the collection of non-critical data.
- Data flow diagrams are now proposed (ICH E6 R3 3.16.1.(c)), driving the ownership and accountability towards CDM in considering all type of clinical data and metadata in the study.
- Blinding safeguards continue to be required and should be clearly documented and executed in CDM processes.
- End-to-end data integration and review - CDM should set requirements for vendors but should keep oversight and ownership of data coming from all sources.
- Outlier surveillance - made easier through the techniques of Central Statistical Monitoring models and tools such as Artificial Intelligence models and Machine Learning.
- Automation of CDM tasks can significantly benefit manual data review steps such as coding, listing review and data reconciliation steps.
- The focus on participant safety through the essential role played by physicians and medical reviewers (in the medical and safety data review processes), emphasizing avoidance of duplicated tasks in participant data review.
- Biostatistical review of aggregated data in advance of tables, figures and listing production, or simulation of different aspects of trial results and review of central statistical monitoring outliers.
- Data flow management in the form of predicted volumes of data entry, queries, coding, reconciliation, medical and statistical review over time, based on planned and actual participant recruitment.

Quality Assurance

ICH E6 R3 sections 3.16.1 (data handling) and 4.2 (data lifecycle elements) impact CDM in this stage of RBQM.

Here it's important for CDM to participate in any Issue Management and Root Cause Analysis processes for emerging issues, that have a direct impact on any CDM processes and/or the clinical data.

CDM should lead the review of User Access Control in Data Acquisition Tools and all systems impacting the clinical data e.g. EDC, ePRO etc. In addition, audit trial reviews focused on data behaviour in these systems is likely to be best interpreted by CDM, whose knowledge of the clinical data, its sources and likely user groups is unparalleled. CDM advice and support may be needed to review audit trails in systems outside of CDM influence e.g. Clinical Trial Management Systems and Trial Master File.

Fraud detection is a joint responsibility together with the study Biostatistician, central monitor to look for trends from Central Statistical Monitoring (CSM) or statistical surveillance e.g. duplicate or professional participants, data propagation, holiday and weekend visit dates, outliers etc.

Proper control of a clinical trial's data flow is also essential, and clinical data management Key Risk Indicators must be reviewed by CDM. Any identified trends should be reported as mitigations for identified risks or as new issues requiring potential issue management and root cause analysis.

Part 3: Practical Deep-dive

Risk Based Data Management Guidance

Clinical Trial Stages and RBDM
If we now, consider the stages of a typical clinical trial and the perspective of Clinical Data Management we can organise these RBDM concepts into the following CDM task categories:

- Design, Planning and Set Up
- Data Review and Cleaning
- Database Lock, Analyses and Reporting

NOTE: The following sections are written in the form of a basic process guiding all personnel responsible for clinical data management in the best practise RBDM tasks.
Please refer to Appendix 1 for the RBDM Process Flow.

RBDM Design, Planning and Set Up Checklist

#	Checklist Item/Description
1.1	Contribute to protocol development and review
	Participate in protocol review and contribute from a data quality perspective. E.g. review Schedule of Assessments and visit windows to understand timing risks and implications for EDC or blinding protocol requirements.
1.2	Define pre-specified acceptable ranges for Critical to Quality Factors (CTQs)
	Use critical thinking to bring the CDM perspective to define Critical to Quality factors that protect participant safety and data integrity.
1.3	Support Identification of Critical Processes
	Consider all the identified CtQs and contribute to the identification of critical processes based on these factors.
1.4	Identify and Document: Critical, Supporting and Non-critical Data
	One of the most essential roles of CDM is to define Critical Data based on Critical Processes and CtQs and to lead this activity if possible. Coordinate and collaborate with study physicians, biostatistician, central monitoring and 3rd party CDM as appropriate. Aim for less than 20 individual datapoints and whole datasets (e.g. Adverse Events) that are defined as 'critical'. Use the Critical Data to identify and document the Supporting Data and finally determine the remainder of the clinical data as Non-Critical. Gain agreement with sponsor, CRO, 3rd party vendors and suppliers to ensure all are aligned on which data is collected where and how. NOTE: The order or priority of CtQs, critical process and critical data identification may differ according to company processes or study protocol.
1.5	Drive critical data focussed Data Acquisition Tools (DAT) and Targeted SDV build and testing
	Drive the risk-proportionate Data Acquisition Tools specification and testing approaches with all parties (3rd party CDM, vendors and suppliers). All study DATs should be built focussed on the defined critical and supportive data. Any in-built data validation or error checks should also focus on critical and supportive data. Any testing documentation should be reviewed for this risk-proportionate approach. Lead the EDC build by applying a risk-based approach, where appropriate, to mitigate operational complexity. Ensure that critical data elements and risk-informed edit checks are accurately incorporated into the EDC design and configure targeted Source Data Verification (tSDV) in alignment with the critical data specifications.

1.6	Participate in Study Risk Assessment and / or CDM specific risk assessment
	Participate in any initial study risk assessment during study planning, as ICH E6 R3 section 3.10.1 guidance proposes. Define CDM study risks based on the defined critical processes and critical data. Take ownership of study risks in the CDM area. Evaluate risks by scoring (Risk Priority Number = impact x likelihood x detectability) based off your experience. Control risks by implementing ways to monitor the associated risks as well as defining risk mitigations as per company procedures. Whenever possible prevent risks from occurring or reducing probability of occurrence.
1.7	Support Protocol Deviation Management / Plan
	Protocol deviation management and planning should form part of any data cleaning strategy. CDM is likely to participate in this activity together with study physicians and biostatisticians.
1.8	Define Participants Ready For Analysis Criteria
	May be known as "clean participant definition or criteria". Address the topic of what is defined as clean or fit-for-purpose data with study physicians and biostatisticians during planning. This proactively addresses downstream data quality expectations. Develop criteria for 'participants ready for analysis' definition and if possible higher-level groups e.g. 'clean site' etc. Finalise this definition as part of the CDM documentation. Note: ICH guidance does not require completely or 100% clean participant data. Data should be of sufficient quality to generate reliable results with a focus on review of data of higher criticality and relevant metadata (ICH E6 R3 3.16.1(b)).
1.9	Develop a Data Flow Diagram
	Develop a systems and data flow diagram to visualise all sources, delays, transfers and transformations of clinical data. This identifies any potential delays and data flow issues that needs to be accounted for in downstream data review and cleaning. (ICH E6 R3 3.16.1(c)). The Data Flow Diagram should be included in CDM planning documentation e.g. Data Management Plan etc.
1.10	Author an Integrated Data Quality Review Plan
	Develop an integrated data quality review plan. This may be an independent document to the Data Management Plan. The IDQRP should detail responsibilities for all parties involved in clinical data review and document who does what and when. This is an often-missing component of RBDM and reduces duplication of effort between functions. Clearly document the efficient delegation of data review across collaborating departments e.g. CDM, Centralised Monitoring, Statistical Surveillance and Medical and Safety Data Review, Clinical Monitoring. Ensure all parties are aligned with this approach. Note: This process may vary according to company specific processes and organisational structures.
1.11	Develop a Predicted and Actual Participant Data Status Tracker
	Work with biostatistics or data scientists to develop a robust predicted participant data status tracking model based on anticipated and actual participant recruitment and study visit schedule. Use this model to predict blockages and risks in clinical data flow in near real-time during the data review and cleaning.

RBDM Data Review Checklist

#	Checklist Item/Description
2.1	Review, Communicate and Mitigate CDM risks.
	Perform monitoring/review of CDM risks and re-score if required. Identify new risks and emerging CDM issues and trends. Communicate CDM risks to the data review community and team. Perform mitigation actions to reduce impact of previously identified CDM risks. Assess implemented mitigation actions for efficiency and effectiveness by re-evaluating the risk priority number (impact x detectability x likelihood), rescoring the risk, assessing the KRIs and examining site risk score.
2.2	Participate in ongoing Study Risk Review
	Continue to own CDM Risks, scoring and mitigations. Represent CDM in Study Risk Review activities and meetings summarising your changes and updates of CDM risks to the cross-functional study team. Provide input into other functional risks during this stage.
2.3	Monitor Protocol Deviation Management
	Responsibility for protocol deviation review and approval varies across organisations. However, it is encouraged that CDM play an important role in identification, review and labelling of Protocol Deviations (PD) and overall quality of this process. Final analysis datasets should have participants with important PDs clearly identified.
2.4	Ensure ongoing, contemporaneous and holistic Data Review
	Provide oversight of data review progress, comparing actual participant data status to the Predicted Participant or Participant Data Status Tracker. Address data entry and data flow backlogs, investigate and action to resolve e.g. external data often delays data review. Ensure there is ongoing integration of external clinical data into a holistic participant centric data repository. A holistic participant data review driven by the Integrated Data Quality Review Plan and Participants Ready for Analysis Criteria maximises the volume of participant data collected, integrated and reviewed and minimises unnecessary querying or edits of clinical data. Ensure data review dependencies are clearly identified to parties responsible for review, e.g. medical coders knowing when to perform medical coding or pharmacovigilance knowing when SAE reconciliation is required. Avoid additional complexity in these processes e.g. delaying physician participant data review.

2.5	Drive fit-for-purpose query process
	Apply risk-proportionate data querying for critical, supportive and non-critical data. For example: For critical data: query any missing, inconsistent, or illogical values; For supportive data: targeted query on trends and systemic issues rather than individual discrepancies; for non-critical data: minimal queries unless systemic errors. Targeted automated data validations and manual checks (outliers, targeted risk indicators) to flag discrepancies or missing data (comprehensive for selected critical data; minimal for supportive / exploratory data targeting significant or systemic issues only). Edit checks output can be reviewed for accuracy as the data review progresses to remove unnecessary edit checks and or reduce unnecessary queries to investigator sites.
2.6	Encourage ongoing declaration of clean / participants ready for analysis
	As the study progresses, ensure participants with few or no outstanding issues are prioritised for final review, then labelled as clean / ready for analysis. Flag, “freeze” or “lock” participants, sites and countries on an ongoing basis if possible, according to company-specific process, whilst avoiding unnecessary unlocking of site participant databases.
2.7	Drive Automation & Fraud Detection where possible
	Increase automation and intelligent review of clinical data. Data review steps can be automated through bots (e.g. SAE Reconciliation Listings, medical coding). In addition, Artificial Intelligence / Machine Learning can be used to make data cleaning more efficient through the automation of manual review tasks and the surfacing of issues for human review. Similarly statistical surveillance can occur across the clinical data set through central statistical monitoring (CSM) models to highlight outliers and identify systemic issues in the data.
2.8	Perform Dry Runs of Analysis Programs, Data Transformations and Pinnacle 21 findings
	Collaborate with Biostatistics and Statistical Programming to ensure analysis programs to produce Tables, Figures and Listings are run against the clinical data before database lock (preferably at regular intervals during study conduct). This reduces the risk of unanticipated analysis issues or errors after database locks. Ensure that data transformation programming is tested on clinical data before final transformations. Consider using Pinnacle21 to check the data fitness for Submission Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) transformation standards.

2.9	Review Audit Trails and User Access Control
	Perform audit trail review (ATR) and user access control (UAC) review at a frequency determined during the risk identification and assessment process, during the conduct of a clinical trial. For data sources within CDM control, do this directly and for data sources outside CDM control, require the responsible 3rd party to provide evidence this review. See ATR guidance* for details of Audit Trail Review. The audit trails should be interpretable and support review. If issues are identified, resolve directly or request resolution for any findings in ATR. If resolution is not possible, prevent new occurrences of the ATR issues. User access permissions and assignments should also be reviewed for clinical data systems. Users should be authorised to use clinical data systems, and their permissions should be aligned with the duties, functions and blinding requirements of their roles (ICH E6 R3 section 4.3.8(b). NOTE: This process may vary according to company specific processes and organisational structures. For example, the frequency of ATR review may be determined in the centralized monitoring plan and be performed by central monitoring role.
2.10	Initiate ongoing Investigator review and signature of clean / ready for analysis participants
	Recommend seeking Principal Investigator (PI) approval of reported data periodically to demonstrate PI oversight (see EMA GCP Q&A #13). Suggest risk-based approach to define timepoints when PI needs to sign data.

RBDM Database Close, Analysis & Reporting Checklist

#	Checklist Item/Description
3.1	Plan Database Lock Tasks
	Plan interim and final database closure activities using the CDM risk log to assess all potential risks are resolved and documented. Remediate any remaining risks through prompt direct action.
3.2	Execute Soft Lock or Database Freeze
	Notify 3rd parties in advance to align final transfers of external data and their review. Perform database freeze (or equivalent process step) and export data to biostatistics for final dry run of analysis programs. Resolve any final findings (e.g. final urgent queries or obvious database changes).
3.3	Transform clinical data to SDTM
	Ensure transformation to SDTM format is completed and Pinnacle 21 findings are resolved.
3.4	Execute Hard Lock of Database
	Finalise the investigator review and signature of clean participants. Perform database lock across partial or whole clinical database including communication to 3rd party vendors for finalisation of their data sources.
3.5	Export Interim / Final Clinical Database
	Ensure any labelling of participants and visit data (e.g. for interim analysis, per-protocol population, analysis population and Protocol Deviations etc.) is completed. Export interim or final clinical dataset to Biostatistics in preparation for analysis.
3.6	Manage and document database errors
	Respond to and investigate database errors identified after interim and final database locks, according to a risk-based approach, where potential corrections are assessed for impact on trial results and considering potential bias these corrections may introduce. Closely control any planned database unlocks as driven by internal Standard Operating Procedure. Ensure any valid findings and actions are documented in a final CDM report as errata. Ensure all authorised database errata are agreed by all data review parties.

Part 4 RBDM Case Studies

Case Study 1 – Critical Thinking in Data Management

A Phase II study to evaluate the effect of an Investigational Medical Product (IMP) on reducing overall symptom burden in participants suffering from late-stage cancer. The primary endpoint was based on changes in the Edmonton Symptom Assessment System (ESAS) Questionnaire scores. Primary endpoint data were to be collected via daily eDiary entries. Up to 60 subjects were to be enrolled across 10 sites.

RBDM and Critical Thinking
Clinical Data Management was involved at an early stage of protocol development. Following the definition of critical data and processes, discussions about data acquisition tools began. These discussions delved deep into the definition of the primary endpoint and the research question the study aimed to answer.

Problem Statement
The initial study concept defined the primary endpoint without properly considering standard clinical practice, participant burden and the data required to answer the research question. It focused too much on collecting data every day via daily eDiary, overlooking the participant-centric trial paradigm. As a result, original study plan had to be revised to align with standard practice and participant experience, shifting ESAS collection to every other week during site visits.

Key Considerations
1. Profile of a Typical Trial Participant: Understanding participants' perceptions of trial activities.
2. Optimal Frequency of ESAS Completion: Determining the best frequency to demonstrate treatment effect and answer the research question, considering factors like time to achieve stable effect, dose-response relationship, and fluctuations in effect.
3. Standard Clinical Practice: Aligning the study with common clinical practices.
4. Study Assumptions: Evaluating sites, subjects, study duration, and cost-benefit ratio.

Discussions and Findings
1. Frequency of ESAS Completion: In clinical practice, ESAS completion frequency varies (daily, weekly, or at each visit) based on participant health status and the questionnaire's purpose.
2. Comprehensive Assessment: ESAS is part of a broader assessment, and additional tools are recommended if participants report severe symptoms.
3. Self-Reporting Concerns: Issues with self-reporting, such as symptom reporting errors and difficulty understanding terms like "wellbeing," suggested that more reliable data could be obtained with site personnel assistance.
4. FDA Guidance on Participant-Reported Outcomes: Emphasizes balancing the need for frequent ESAS completion to demonstrate treatment effect with the burden on vulnerable participants.
5. Granular Data vs. Participant Burden: Daily ESAS completion provides detailed data for analysing daily symptom variations and closer monitoring but may be burdensome for severely ill participants.

6. Study's Primary Intention: To assess the IMP's impact at the end of the treatment period compared to baseline.

Conclusion
Critical thinking is a crucial component of risk-based data management. It supports designing a fit-for-purpose data collection process that targets the clinical research question and allows for a pragmatic and participant-centric data workflow.

Case Study 2 – Database Lock

Background
A Phase II neuroscience trial required an accelerated database lock, scheduled to occur just seven calendar days after the last participant's final visit. This expedited timeline was critical to enable early go/no-go decisions for an expanded Phase I and registrational Phase III program.

Challenges
- Vendor and CRO contracts lacked provisions for accelerated database lock timelines. Their SOPs also lacked accelerated DBL options.
- Significant data cleaning backlogs existed at the time of acceleration (across CRA and Clinical Data Management functions).
- Planned dry runs of Tables, Listings, and Figures (TLFs) were delayed.

Solutions
- Proactive Risk Management: Conducted an extensive cross-functional risk assessment and implemented mitigation plans to address potential delays.
- Prioritized Critical Data: Focused cleaning efforts on data impacting primary efficacy and safety endpoints.
- Contractual Adjustments: Amended vendor and CRO contracts to support accelerated timelines, including faster data transfers and issue resolution.
- Site-Level Risk Mitigation: Identified high-risk sites based on data entry and query delays; partnered with CRAs and site staff to resolve issues early.
- Adaptive SDV Strategy: Transitioned from 100% SDV to targeted SDV for critical variables or final visits to optimize resources.
- CRA Resourcing Strategy: Re-mapped monitoring visits and CRA activities based on backlog severity and site needs, with contractual updates to support intensified efforts.
- Sample Logistics Coordination: Collaborated with vendors and Clinical Operations to streamline sample management and prevent last-minute delays.
- Real-Time Data Review: Increased review cadence, aligned with CRA visits, and engaged cross-functional teams to collaboratively address backlogs. Implemented subset reviews and rolling locks.
- Iterative Dry Runs: Conducted continuous dry runs aligned with the subset data cleaning timelines to proactively resolve data issues, supported by enhanced validation listings.

- Risk-Based PI Signatures: Allowed post-lock PI signatures in low-risk cases to maintain timelines without compromising data integrity.
- Targeted Metric Reporting: Delivered frequent, actionable metric reports for study teams and high-level summaries for leadership to ensure visibility and timely escalation.
- Cross-Functional Communication: Maintained transparent, ongoing communication with all stakeholders to ensure alignment and accountability.

Conclusion

Through strategic prioritization, contractual agility, and intensive cross-functional collaboration, the study team successfully navigated the challenges of an accelerated database lock. Emphasizing real-time data cleaning, iterative analytics, and unified communication channels enabled the delivery of high-quality, decision-ready data within a condensed timeline—setting a precedent for operational excellence in future accelerated clinical trials.

Case Study 3 – Clinical Trial Unit Example of Risk-Proportionate Approach to Clinical Database Build

Background

To evaluate the efficacy of an investigational drug, the sponsor initiated a double-blind, randomized, parallel-group, multisite Phase III superiority trial targeting participants with severe Alcohol Use Disorder (AUD) in an academic setting.

Problem Statement

The study planned to enrol 280 participants over 24 months, with 3 months allocated from final protocol approval to EDC go-live in the beginning. Given the time constraints and complexity—72 Case Report Forms (CRFs), over 50% of them unique and the remaining standard forms were customised to fit the purpose of the indication—the Clinical Data Management team applied an agile, risk-based data management strategy to ensure efficient delivery.

Key considerations for Agile build:

- The Clinical Data Management team participated from the beginning of the protocol development. This early engagement allowed a deeper understanding of trial needs and supported proactive input on data collection strategy, CRF design, and questionnaire refinement. Clear approval workflows and expectations were defined early, and a build diary was maintained to track progress and decisions throughout.
- Identification and prioritization of critical data elements—including primary endpoints, safety fields, and key secondary endpoints—streamlined the design, build, and validation processes, ensuring the most important data received appropriate attention. Back-end testing and User Acceptance Testing (UAT) were meticulously planned around a critical data checklist, enabling a risk-based approach that optimized both quality and time efficiency.
- Statisticians were engaged early in the process, ensuring the database build aligned with the planned analysis. Their guidance helped identify potential data risks and informed the development of mitigation strategies well in advance.

- Documentation was developed iteratively, aligned with ongoing sprint work. Drafts were reviewed and finalized in parallel with other build activities, saving time and avoiding bottlenecks often caused by sequential workflows.
- The system build followed an agile sprint model. This allowed continuous feedback from statisticians and trial managers, with changes incorporated in real time. Edit checks and features related to the conduct phase were handled in the final sprint to minimize rebuilds and rework caused by cascading changes.
- Automated and mandatory queries were implemented selectively, focused on critical fields only. For non-essential fields, checks were added only where necessary to reduce clutter, avoid excessive query volumes, and streamline the data cleaning process.
- The data team collaborated closely with trial managers in drafting a comprehensive risk mitigation plan. This included anticipating expected risks and preparing structured responses to potential unknowns.
- Data review frequency and listing strategies were governed by Key Risk Indicators (KRIs) and Key Performance Indicators (KPIs), enabling ongoing, adaptive oversight that was responsive to data trends and site performance.

Conclusion

The agile, risk-based approach enabled the Clinical Data Management team to build a flexible, fit-for-purpose database within a constrained timeline while maintaining high quality. Proactive collaboration, early involvement of cross-functional team, prioritization of critical elements, and adaptive planning were essential to meeting both operational and scientific goals.

Conclusion

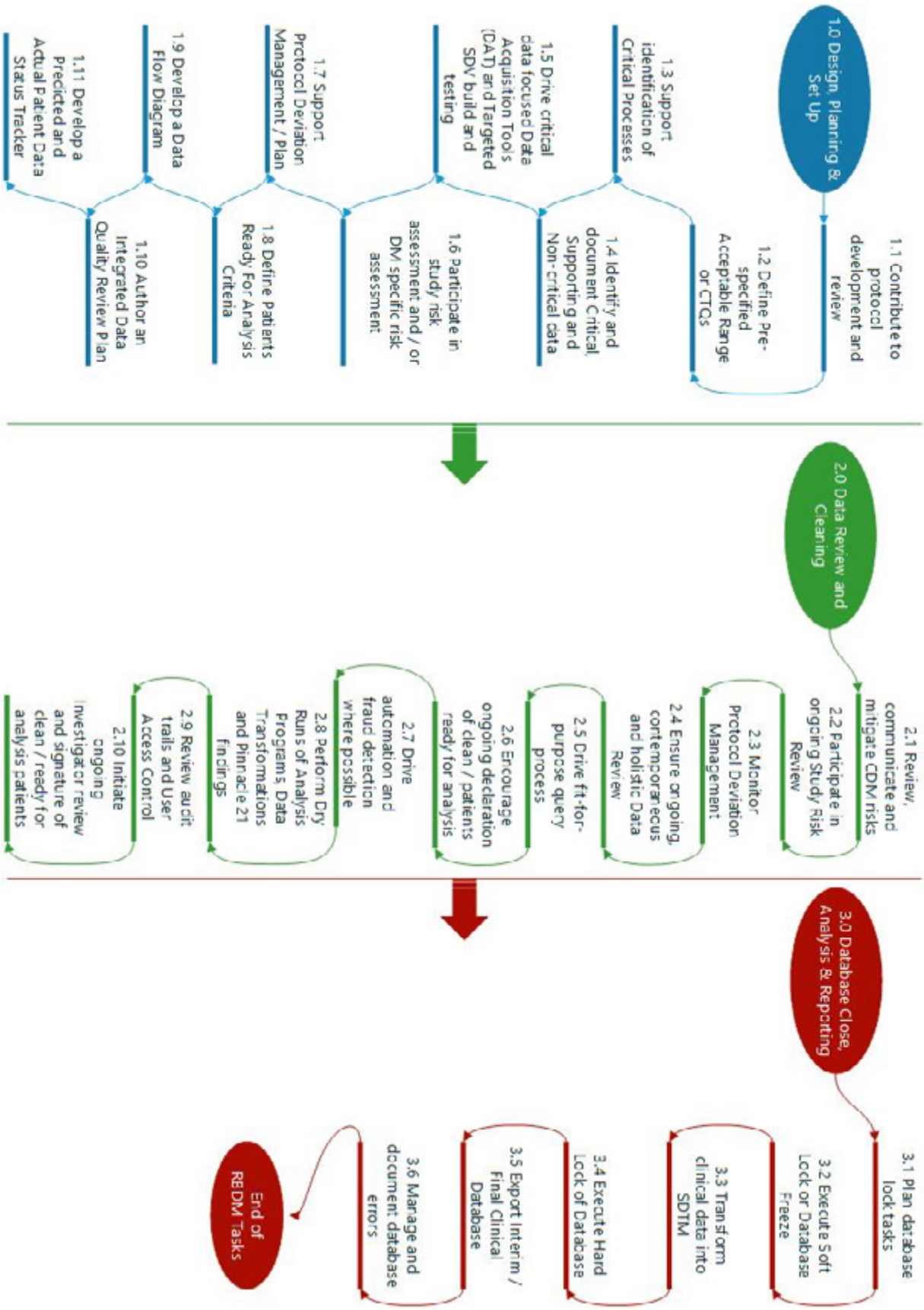
ACDM RBQM DMEG Recommendations

In this guidance the RBQM DMEG has summarised our collective thoughts and collective experience. However, we would like to recommend the following key actions:

- Cross-functional and aligned team approach from CtQs to data review including agreement on Source Data Verification.
- Ensure critical data are identified and managed through the whole Clinical Data Management lifecycle.
- Actively own Clinical Data Management risks.
- Control the flow of clinical data to ensure blockages and delays are dealt with before delaying database lock.
- Frontload Clinical Data Management tasks to ensure that blockages are minimised when approaching database lock.
- Plan database lock tasks and address critical issues prior to final lock. Any non-critical issues should be documented.

References

Getz, K, Anticipating the Impact of the Patient Engagement Movement on Clinical Operations, Presentation at CROWN conference, slide #9, January 202
Mian, S, (GSK), ACDM RBQM Symposium presentation, Nov 2023.
CTTI Quality by Design Project: CTTI QUALITY BY DESIGN PROJECT
ACDM whitepaper "Getting Started with Audit Trail Review in Clinical Trial Data An Essential Guide). https://www.google.com/url?sa=t&source=web&rct=j&opi=89978449&url=https://acdmglobal.org/wp-content/uploads/formidable/47/Getting-started-with-Audit-Trail-Review-in-Clinical-Trial-data-An-Essential-Guide.pdf
EMA GCP Q&A #13. https://www.ema.europa.eu/en/human-regulatory-overview/research-development/compliance-research-development/good-clinical-practice/qa-good-clinical-practice-gcp
ICH E8 R1: General Considerations for Clinical Trials. https://database.ich.org/sites/default/files/E8-R1_Guideline_Step4_2021_1006.pdf
ICH E6 R2: Good Clinical Practice. https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf
ICH E6 R3: Good Clinical Practice. https://database.ich.org/sites/default/files/ICH_E6%28R3%29_Step4_FinalGuideline_2025_0106.pdf
Appendix 1: RDBM Process Flow


1.0 Design, Planning & Set Up
1.1 Contribute to protocol development and review
1.2 Define Pre-specified Acceptable Range or CTQs
1.3 Support identification of Critical Processes
1.4 Identify and document Critical, Supporting and Non-critical data
1.5 Drive critical data focused Data Acquisition Tools (DAT) and Targeted SDV build and testing
1.6 Participate in study risk assessment and / or DM specific risk assessment
1.7 Support Protocol Deviation Management / Plan
1.8 Define Patients Ready For Analysis Criteria
1.9 Develop a Data Flow Diagram
1.10 Author an Integrated Data Quality Review Plan
1.11 Develop a Predicted and Actual Patient Data Status Tracker
2.0 Data Review and Cleaning
2.1 Review, communicate and mitigate CDM risks
2.2 Participate in ongoing Study Risk Review
2.3 Monitor Protocol Deviation Management
2.4 Ensure ongoing, contemporaneous and holistic Data Review
2.5 Drive fit-for-purpose query process
2.6 Encourage ongoing declaration of clean / patients ready for analysis
2.7 Drive automation and fraud detection where possible
2.8 Perform Dry Runs of Analysis Programs, Data Transformations and Pinnacle 21 findings
2.9 Review audit trails and User Access Control
2.10 Initiate ongoing Investigator review and signature of clean / ready for analysis patients
3.0 Database Close, Analysis & Reporting
3.1 Plan database lock tasks
3.2 Execute Soft Lock or Database Freeze
3.3 Transform clinical data into SDTM
3.4 Execute Hard Lock of Database
3.5 Export Interim / Final Clinical Database
3.6 Manage and document database errors
End of RBDM Tasks

www.acdmglobal.org