ICH GCP E8 (R1)
General Considerations for Clinical Studies
Impact on Data Management

ACDM DMEG: Regulatory

Introduction

- The key focus of the latest revision of ICH GCP documents (E6, E8) is embedding 'Quality by Design' into clinical research
  - Focus on critical to quality factors
  - Protection of subjects
  - Generation of reliable and meaningful results
  - Management of risks to the above
- The approach is supported by the establishment of an appropriate framework for the identification and review of critical to quality factors (Section 3.3) at the time of design and planning of the study, and throughout its conduct, analysis, and reporting
- "Activities such as document and data review and monitoring, where conducted retrospectively, are an important part of a quality assurance process; but, even when combined with audits, they are not sufficient to ensure quality of a clinical study" (ICH GCP R8(R1) 3.1)

Reflection paper on risk based quality management in clinical trials EMA/269011/2013

"The general problem can be summarised by stating that current practices in clinical research are not proportionate to risk nor well adapted to achieving the desired goals. The origins of the problem are multifactorial and include: …

- poor design of studies and study processes, often being much more complicated than necessary to achieve what is required, thus diminishing focus and resource available to achieve the quality necessary for the more important objectives;
- failure to identify priorities. Both study and process design is often cluttered by data collection requirements or quality control activities (e.g. monitoring etc.) of limited importance that distract greatly from the most important issues;
- poor risk identification and poor risk mitigation – a lack of use or understanding of risk- management tools and techniques, is often associated with a reactive, fire-fighting approach to problem management. This results in processes largely based on corrective rather than preventive action; "*

- *Reflection paper on risk based quality management in clinical trials EMA/269011/2013 - > https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-risk-based-quality-management-clinical-trials_en.pdf

The Paradigm Shift

Traditional Data Review and Cleaning	Risk Based Approach
Data checks driven by technical feasibility (if we can program it, we put it in the validation plan)	Data checks driven by category (critical, supportive, other)
Quality Checks:	Quality Assurance
Queries from edit checks	Quality by Design
Retrospective verifications on static data	Key Performance Indicators/Dashboards
Monitoring/SDV – point2point visual inspection	Continuous re-evaluation of KPIs, longitudinal analysis
Audits/Inspections (‘external’)	Integrated and Continuous Risk Management (‘self starting’)
Transactional:	Integrated:
Systems and processes for each department/function (seprate and disparate = siloed)	Data Visualisation systems with multiple roles and collaborative reviews. Cross functional processes and SOPs, enterprise level TMF documentation, no gaps and overlaps
Checklist driven, reactive, passive and segmented data reviews: importance on ‘How?’ and ‘By When?’	Conscious, validated and transparent evaluations. Clinical Study Team: importance on ‘Why?’ and ‘Event Driven/Proactive’

How does E8(R1) look to address this?

E8 (R1) Section 3
Designing Quality into Clinical Studies

- Section 3 has been dedicated to defining how to design quality into clinical studies

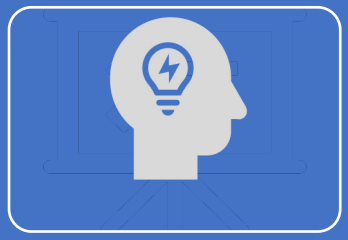
    - 3.1 Quality by Design of Clinical Studies
    - 3.2 Critical to Quality Factors
    - 3.3 Approach to identifying the Critical to Quality Factors
        - 3.3.1 Establishing a Culture that Supports Open Dialogue
        - 3.3.2 Focusing on Activities Essential to the Study
        - 3.3.3 Engaging Stakeholders in Study Design
        - 3.3.4 Reviewing Critical to Quality Factors

Identifying Critical to Quality factors (3.2 & 3.3)

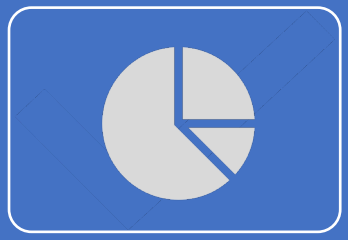
- A basic set of factors relevant to ensuring study quality should be identified for each study at the point of study design
- The risks that threaten their integrity should be determined and probability and impact assessed
- Pro-active communication of critical to quality factors and risk mitigation activities should be in place
- Proactive, cross functional discussions and decision making is required at the time of study planning

Establishing a culture (3.3.1)

Speak Up!! Open dialogue about quality



Create a culture that values and rewards critical thinking – lose the reliance on checklists (AGILE)



Choose quality measures and performance indicators that are aligned with proactive approach to design

Focus on activities essential to the study (3.3.2)

- Focus effort on activities that are essential to the reliability and meaningfulness of study outcomes and safe ethical conduct
  - Risk based methodologies will be applied to data cleaning to ensure that data cleaning approaches for critical data are interrogated to identify and mitigate risks
  - Non-critical data could be subject to reduced data cleaning ie; **Reducing low value queries**
- Evaluate the study design to verify that planned activities and choice of data to be collected are essential
  - Study designs should be operationally feasible
  - Avoid unnecessary complexity
  - Avoid unnecessary data collection

Engaging Stakeholders in Study Design (3.3.3)

- Clinical investigators and potential subjects have valuable insights into feasibility of a study
  - Are visits/procedures overly burdensome?
  - Are the end points relevant?
  - Value of the treatment within targeted population

- If there are novel elements early engagement with regulators should be considered

Reviewing Critical to Quality Factors (3.3.4)

- Periodic review of critical to quality factors is essential to determine if adjustment to risk controls are needed – new or unanticipated issues may arise once the study has started

- For adaptive design studies, interim decision points ensure proactive planning and ongoing review of critical to quality factors and risk management (ICH E9 Statistical Principles for Clinical Trials)

Other points of interest

Data Management

Understanding data classifications

- Primary Data Collection
  - Data collected for study purposes using processes that ensure a sufficient level of quality
- Secondary Data Collection
  - Use of data that was collected for other purposes and not collected just for the study
    - National Death Databases
    - Disease/drug registries
    - Medical and admin records from routine medical practice
    - Absence of affirmative info does not mean the condition is not present..

Data Standards

- Use of data standards supports the reliability of the data, facilitates correct analysis and proper interpretation of the data as well as promoting data sharing.
- International data standards exist for many sources of study data and should be used wherever possible.
  - Early identification of new data types/forms
  - Early identification of data sources

- For all data sources procedures to ensure the confidentiality of pt data should be followed
  - Ensure we know and follow the chain of custody for the study data

Data Management (6.1.3)

- Manner and timelines of data collection are critical components of overall study quality
- Operation checks and statistical surveillance can identify quality issues at a point where corrective action is feasible
  - Instream data collection
  - Ongoing review of KRIs
- Data management procedures should account for diversity of data sources
- Access to data: Inappropriate access to data during the conduct may compromise study integrity. Attention should be given to who has access to data and results (ICH GCP E6 6.1.4)

What's next…

- Reflection paper on modernisation of E8 and E6
  - ICH_Reflection_paper_GCP_Renovation_Jan_2017_Final.pdf
- ICH GCP E8 (R1) released this 06OCT2021 –
  - E8-R1_Guideline_Step4_2021_1006.pdf (ich.org)
- ICH E6 (R3) Undergoing revision
  - Alignment with E8 (R1) – release planned end 2022
  - Updates to data management sections to reflect changing landscape of technologies used in clinical trials