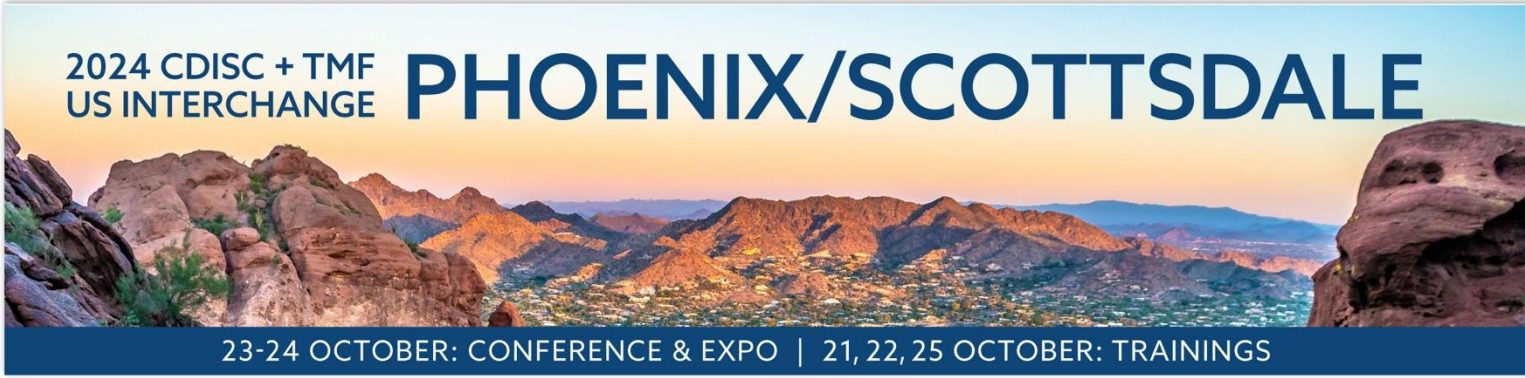

How to Use Current Regulations to Take TMF Risk-Based Approaches

Sarah Hitching, TMF Inspection Readiness Expert, Hedian Records Management

Meet the Speaker

Sarah Hitching

Title: TMF Inspection Readiness Expert

Organization: HEDIAN RECORDS MANAGEMENT

Worked in a GCP environment in the pharmaceutical industry for more than 30 years as a CRA, Project Manager, Line Manager and Project Director before specialising in TMFs and Records Management in 2005.

Hedian Records Management Ltd. was set up in 2018 providing TMF contract staff, particularly in relation to Inspection Readiness

Member of CDISC and the Health Sciences Records and Archives Association (HSRAA).

Currently taking part in the CDISC TMF Risk Initiative White Paper and co leading the Training.

Disclaimer and Disclosures

- *The views and opinions expressed in this presentation are those of the author(s) and do not necessarily reflect the official policy or position of CDISC.*
- *The author(s) have no real or apparent conflicts of interest to report.*

Poll – do you use TMF Risk based approaches?

- Yes, for most TMF tasks
- Yes, for TMF QC only
- No, but I'd like to
- No, I don't think it's a good idea

Agenda

1. Regulations Covering TMF Risk Based Approaches
2. What does the TMF community think?
3. What's next?

Regulations Covering TMF Risk Based Approaches

Yes, there are some…but not many…

TMF Risk Based Regulations etc.

No.	Document	Type	Date	Risk Stated
1	TMF Reference Model	Guidance	2010	N/A
2	Risk-adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products (MRC/DoH/MHRA)	Guidance	10Oct2011	184
3	Quality expectations and tolerance limits of TMF – Developing a risk- based approach for quality assessments of TMFs (German Medical Science)	Paper	10Dec2015	31
4	**Eudralex Volume 10** Chapter V Risk Proportionate Approaches in Clinical Trials	Guideline	25Apr2017	147
5	**ICH GCP E6 (R2)**	Guideline	14Jun2017	37
6	**EMA Guideline** on the content, management and archiving of the clinical trial master file (paper and/or electronic) EMA/INS/GCP/856758/2018	Guideline	06Dec2018	10
7	ICH GCP E8 (R1)	Guideline	14Apr2022	24
8	ANAB Implementing a Risk-Based Thinking Approach | ANAB Webinar (ansi.org)	Webinar	26May2022	N/A
9	Building a Risk-Based TMF Framework (Montrium)	Report	Dec2023	262
10	CDISC TMF Risk Based White Paper	Paper	TBC	TBC

General Concepts

- Core vs Recommended
- Lower risk studies, lower risk proportionate approach (MHRA, Eudralex)
- Risk adaptation (MRC/DoH/MHRA, Eudralex)
  - **Replacement** different document title but similar function
  - **Combining -** multi purpose document (also ICH GCP E6 (R2))
  - **Removal** – no longer applicable due to risk adaption measure e.g. RWE study
- Critical to Quality Factors (ICH E8 (R1))

ICH GCP E8 (R1) General Considerations for Clinical Studies

- Designing Quality into clinical studies
- Critical to Quality are attributes that -
  - Protect the rights, safety and wellbeing of study participants
  - Provide reliable and interpretable study results
  - Ensure decisions made on study results
- Identify ‘critical to quality’ factors at
  - Time of study design
  - During conduct
  - At Analysis and reporting

Considerations in Identifying Critical to Quality Factors (1)

- Adequate measures are used to **protect participants' rights, safety, and welfare** (informed consent process, Institutional Review Board/Ethics Committee review, investigator and clinical study site training, pseudonymisation).

- **Information provided to the study participants** should be clear and understandable.

- **Competencies and training** required for the study by sponsor and investigator staff, relevant to their role, should be identified.

- The **feasibility of the study** should be assessed to ensure the study is operationally viable.

- The number of participants included, the duration of the study, and the frequency of study visits are sufficient to support the study objective.

- The eligibility criteria should be reflective of the study objectives and be well documented in the clinical study protocol.

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Considerations in Identifying Critical to Quality Factors (2)

- The protocol specifies the collection of data needed to meet the study objectives, understand the benefit/risk of the drug, and monitor participant safety.
- The choice of response variables and the methods to assess them are well-defined and support evaluation of the effects of the drug.
- Clinical study procedures include adequate measures to minimise bias (e.g., randomisation, blinding).
- The statistical analysis plan is pre-specified and defines the analysis methods appropriate for the endpoints and the populations of interest.
- The extent and nature of study monitoring are tailored to the specific study design and objectives and the need to ensure participants' safety.
- The need for and appropriate role of a data monitoring committee is assessed.

In Summary – Risk Based Approaches So Far

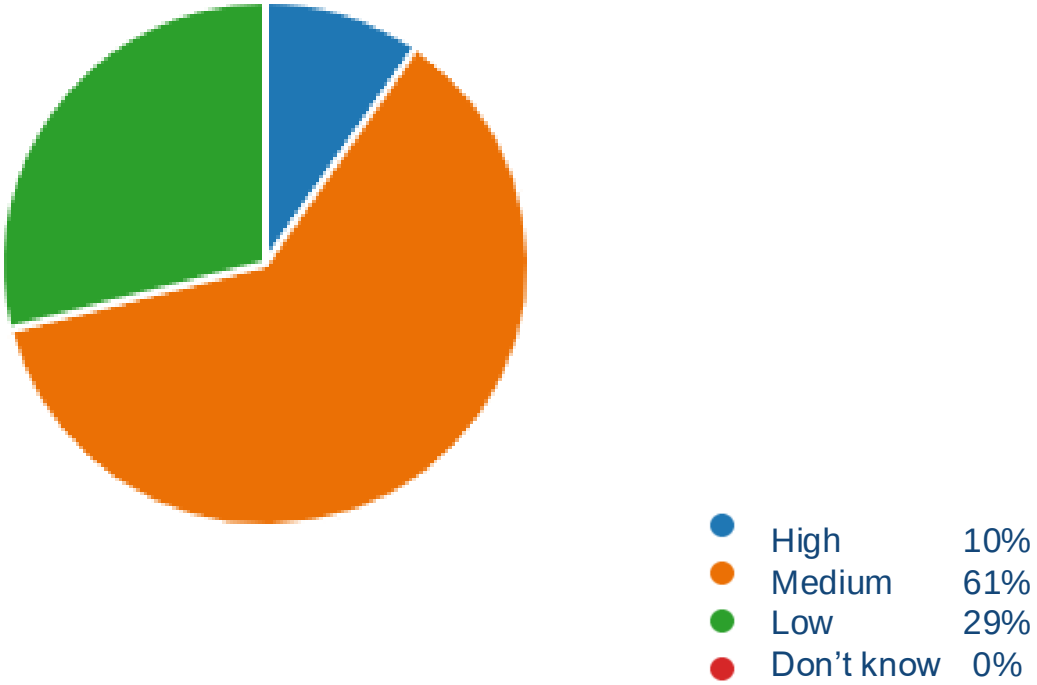
- Critical to Quality
- Adjust documents filed based on risk level of study
- Risk based TMF QC
- Awaited:
  - ICH GCP E6 R3
  - CDISC TMF Risk Initiative White Paper

TRIAL MASTER FILE

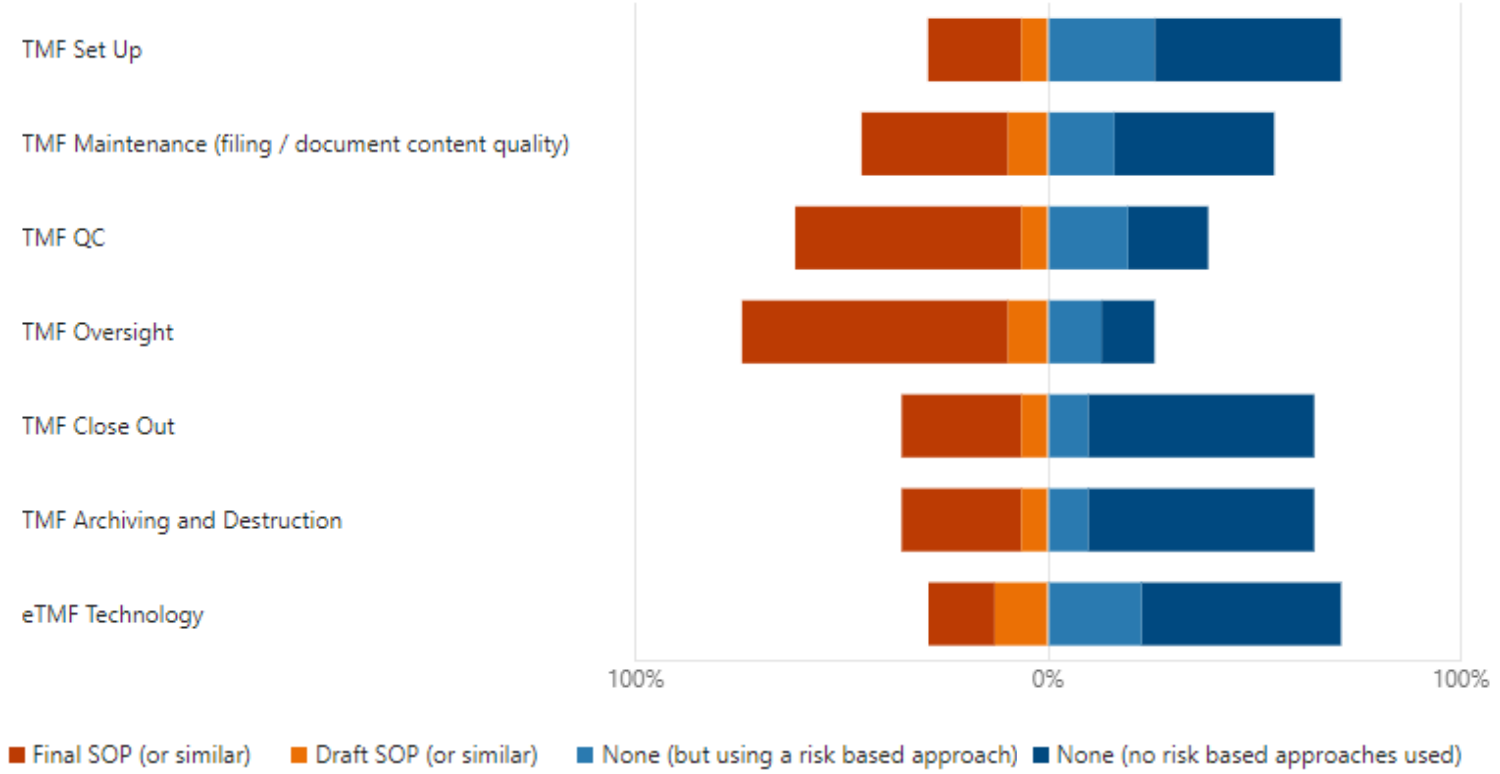
What does the TMF Community think?

…what did my survey say?

Respondents Attitude to TMF Risk

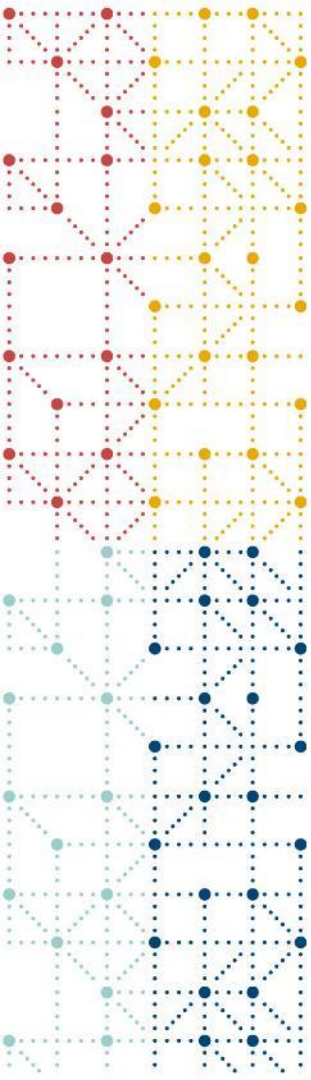


TMF SOPs Including Risk Based Approaches



Examples

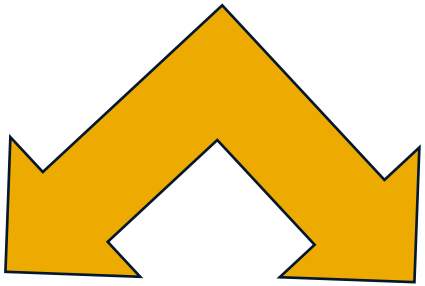
- TMF QC (decreasing percentage of high, medium low risk documents
- Completeness Reviews - define risk based classifications, review % of documents.
- Predefined artefact list for Quality Review
- Timeliness assessed on high risk documents only
- Risk Assessment Tool to evaluate criticality of each sub-artifact (Sponsor Oversight)
- QC based on error rates of classification
- Quarterly reviews – selected sites, one country, selected study level documents
- TMF QR using ISO/ANSI Method
- EDL Completeness check less than 100%
- High priority studies more checks than low priority study
- Document in TMF Plan



What's Next

There has to be something…

Awaited Regulations



ICH harmonisation for better health

Draft E6 (R3) Good Clinical Practise Guideline 19May2023

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Risk Based TMF Initiative

Draft ICH E6 (R3) 19May2023

- ICH Reflection on “GCP Renovation”: Modernization of ICH E8 and Subsequent Renovation of ICH E6 May 2021

- Appendix C. ESSENTIAL RECORDS FOR THE CONDUCT OF A CLINICAL TRIAL

- ‘Essentiality of Trial Records’
  - Essential Records for All Trials (Table 1) – 13 record categories (no exhaustive)
  - Potential Essential Records (Table 2) – 38 record categories

- ‘For other trial records, their presence and nature are dependent upon the trial design, its conduct and risk proportional management.’

Draft ICH E6 (R3) 19May2023

3.10 Quality Management

‘The sponsor should adopt a proportionate and risk-based approach to quality management, which involved incorporating quality into the design of the clinical trial (i.e. quality by design) and identifying those factors that are likely to have a meaningful impact on participant’s rights, safety and well-being and the reliability of the results (i.e. critical quality factors as described in ICH E8 (R1)

In Summary – What's Next

- Essentiality (draft ICH GCP E6 (R3))
- Consider critical quality factors (ICH 8 R1, draft ICH GCP E6 R3)
- CDISC TMF Risk Initiative
- What else would you like to see?

RISK BASED APPROACH

Thank You!

Any questions?