How Have the Regulations Influenced Risk Based TMF Strategies?

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 contracting 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, leading section 2 (Defining Risk Criteria) of the 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 and interviewee have no real or apparent conflicts of interest to report.*

Agenda

1. Regulations Covering TMF Risk Based Approaches
2. Survey Results
3. What's next?

Regulations Covering TMF Risk Based Approaches

Yes, there are some…but not many…

Meet the Speaker

Vittoria Sparacio

Title: Global Head, Clinical Document Governance & Management

Organization: Novartis

Leads a team of passionate leaders driving a company-wide transformation in a most challenging and business critical domain

Served as TMF reference model industry working group contributor, faculty member for TMF conferences, webinars as well as a master program in vaccinology & pharmaceutical clinical development since 2009

Currently lives in Basel, Switzerland!

What do the experts say - meet the expert

Louise Mawer

Title: TMF Inspection Readiness Expert

Organization: Mirabilitas

- Experienced Quality Assurance Auditor for more than 20 years
- Research, GCP, GLP and Pharmacovigilance
- Chair of EFGCP Quality Working Party
- RQA Research Practice Group Special Interest Group
- RQA Non-interventional Study Special Interest Group
- RQA Northern Regional Forum
- ISPE Mentoring Program
- CDISC TMF Risk Initiative White Paper

TMF Risk Based Regulations etc.

To recap…..

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	Guidance	10Oct2011	184
3	Quality expectations and tolerance limits of TMF – Developing a risk- based approach for quality assessments of TMFs	Paper	10Dec2015	31
4	**Eudralex Volume 10** Chapter V Risk Proportionate Approaches in Clinical Trials	Recommen-dations	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	Building a Risk-Based TMF Framework, Montrium	Report	Dec2023	262

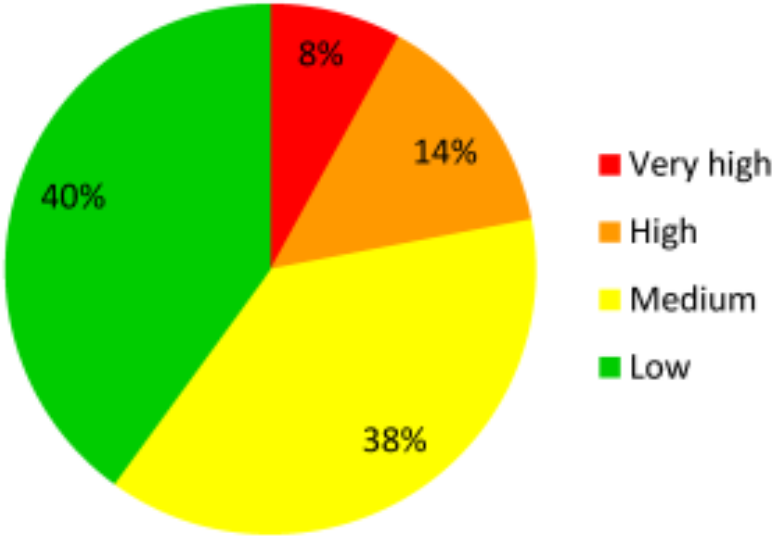
Risk-adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products (2011)

- **Level of Risk**
  - Type A = No higher than the risk of standard medical care
  - Type B = Somewhat higher than the risk of standard medical care
  - Type C = Markedly higher than the risk of standard medical care

- **Risk adaptation**
  - **Replacement** different document title but similar function
  - **Combining** **-** multi purpose document
  - **Removal** – no longer applicable as a result of implantation of other risk adaption measure

Quality expectations and tolerance limits of TMF – Developing a risk- based approach for quality assessments of TMFs (2015)

RPN Risk Categories



Tolerance Limits

Impact of missing process	Critical	Major	Minor	Stand-alone document
Tolerance limits	<1%	<3%	<5%	0%

Data for this article are available from the Dryad Repository: http://dx.doi.org/10.5061/dryad.t2f61 [8].

Eudralex Volume 10 Chapter V - Risk Proportionate Approaches in Clinical Trials (2017)

European Commission

4.5. Trial documentation

Content of the Trial Master File (TMF)

States) shall be kept by the sponsor and the investigator. Guidance on the content of the TMF is provided in the guideline on GCP compliance in relation to the trial master file (paper and/or electronic) for content, management, archiving, audit, and inspection of clinical trials and the ICH Guideline E6(R2) for Good Clinical Practice [iii] The latter guidance states that the essential documents listed should be supplemented or reduced where justified (in advance of the trial initiation). This justification should be based on the outcome of the risk assessment, which may identify where adaptations can be applied that would result in some of the documents no longer being relevant.

Article 57 of the Regulation states that the essential documentation in the TMF shall take into account all characteristics of the clinical trial including in particular whether the clinical trial is a low-intervention clinical trial.

Risk proportionate approaches applied to a trial therefore may affect the content of the TMF. The extent of these changes would be directly related to the type of clinical trial and the outcome of the trial risk assessment, with more adaptations likely to be possible for low intervention clinical trials.

Eudralex Volume 10 Chapter V - Risk Proportionate Approaches in Clinical Trials (2017)

Examples:

- Combining documents / multi purpose documents (also cited in ICH GCP E6 (R2)
  - Screen Log / Recruitment Log
  - Signature Log / Delegation Log
  - Site assessment / Site Initiation
- Absence of documents
  - SMPC vs IB
  - Medical journal publication vs CSR
  - IMP related documentation e.g. accountability, instructions for handling, shipping records, CoA, destruction of IMP, temperature monitoring, sample labels may not be required for IMP with MA
  - Hospital lab accreditation / reference ranges (if data is not critical)

Montrium Building a Risk-Based TMF Framework (2023)

Step 1 Existing Risks

Step 2 Core vs Recommended

Step 3 Patient safety and Data Integrity

Step 4 Non Compliance

Step 5 Additional Risk Factors

In Summary – Risk Based Approaches

- Supplement or reduce Essential Documents.
- Consider level of intervention
- Importance / relevance
- Combine documents
- Risk based TMF QC

TRIAL MASTER FILE

Impact on TMF Management

…what did my survey say?

The Survey - background

SECTOR

Pharma	48%
Biotech	23%
Provider / Supplier	13%
Consultant	10%
Other	6%

REGION

EU	35%
NA	52%
Asia	13%
Other	0%

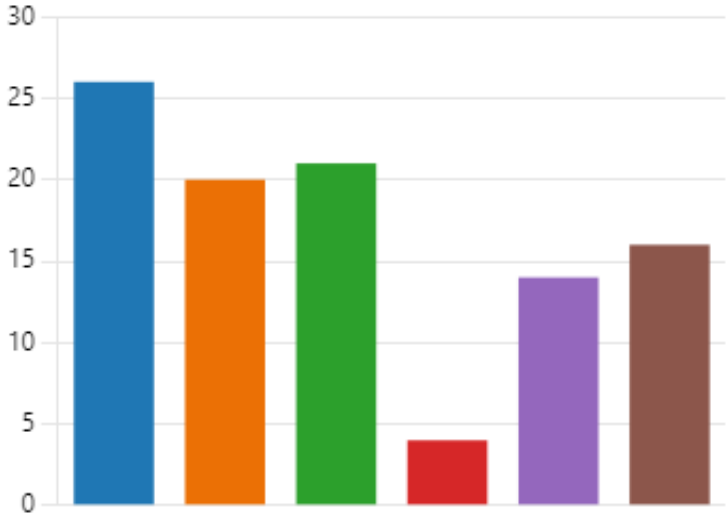
Respondents Attitude to TMF Risk

Poll to assess audiences attitude to risk

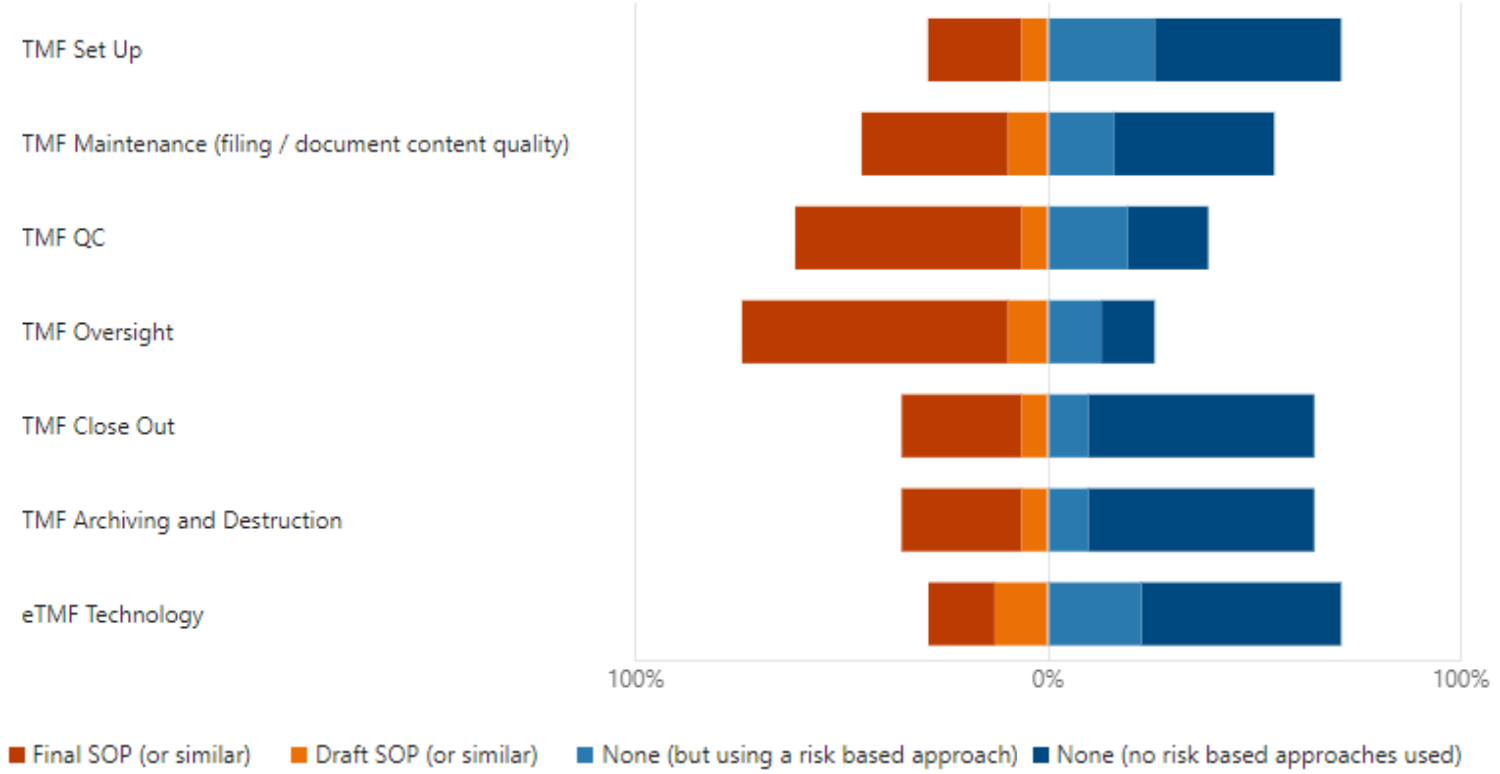
High	10%
Medium	61%
Low	29%
Don't know	0%

Regulations Respondents Knew

ICH GCP E6 (R2)	26
EMA Reflection paper on GCP c...	20
EMA Guideline on the content, ...	21
Eudralex Volume 10 Chapter V R...	4
Quality expectations and tolera...	14
Building a Risk-Based TMF Fram...	16

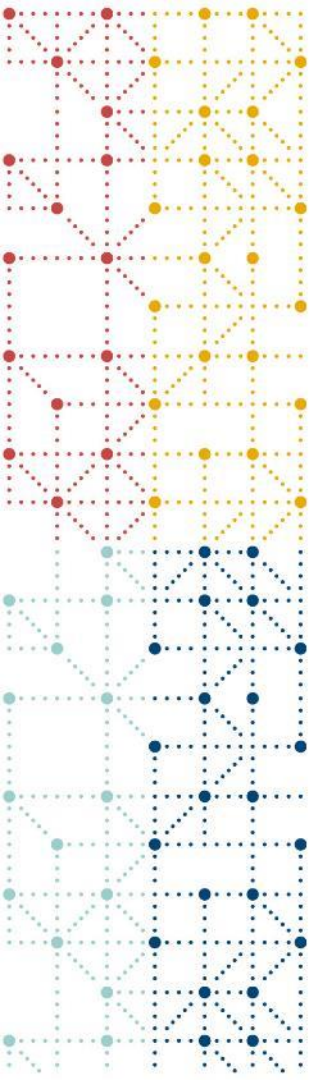


TMF SOPs Including Risk Based Approaches



Examples

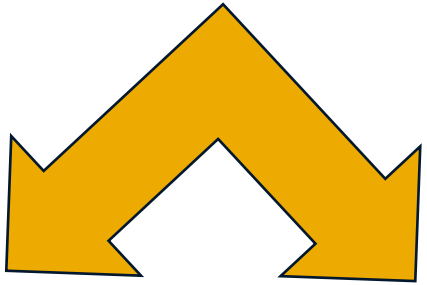
- TMF QC (decreasing percentage of high, medium low risk documents
- Completeness Reviews - define risk based classifications, review % of documents.
- Predefined artefact list for Quality Review
- Timeliness assessed on high risk documents only
- Risk Assessment Tool to evaluate criticality of each 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

cdisc

Risk Based TMF Initiative

Draft ICH E6 (R3) 19May2023

- 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?