Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

Trial Master Files

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Agenda

- GCP Findings for TMFs
- Critical Grading update by MHRA
- EU Legislation and Guidance News/Updates relating to TMF
- Essential Documents, Data, Processes….
- CRO/Sponsor Interaction & Sponsor Oversight

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Inspectors want to reconstruct the trial conduct so that it can be evaluated for compliance with legislation and GCP guidance such that patient rights/well being are/have been protected and the resulting data will be/are reliable. We want to review any documentation, data and metadata required to do this.

How much of a problem is it with commercial sponsors' TMFs?

2012-2013

(19 sponsor inspections)

84% had TMF findings (31% of those TMF findings were major

10% of inspections needed extra days

2013-2014

(22 sponsor inspections)

82% had TMF findings (78% of those TMF findings were major)

35% of inspections needed extra days

2014 - 2015

(11 sponsor inspections)

82% had TMF findings (22% of those TMF findings were critical** and 67% of those TMF findings were Major)

17% of inspections needed extra days

** MHRA definition of critical had been amended

"Where provision of the Trial Master File (TMF) does not comply with Regulation 31A 1-3, as the TMF is not readily available or accessible, or the TMF is incomplete to such an extent that it cannot form the basis of inspection and therefore impedes or obstructs inspectors carrying out their duties in verifying compliance with the Regulations"

Reference Documents

Recommendation on the content of the trial master file and archiving July 2006, Volume 10, Chapter V

EMA/INS/GCP/636736/2012: Reflection paper on GCP compliance in relation to trial master files (paper and/or electronic) for management, audit and inspection of clinical trials

EMA GCP INSPECTORS Questions and Answers

EU GCP Inspectors Working Group - Subgroup

NEW GUIDANCE
Q2 2016

Important note:

It has been decided that the revised version of the TMF document, based on the comments collected during the public consultation, will be incorporated into a guidance on TMF as part of the work related to the implementation of the new Clinical Trial Regulation (EU) 536/2014. **A public consultation on the new guidance will follow in due course**.

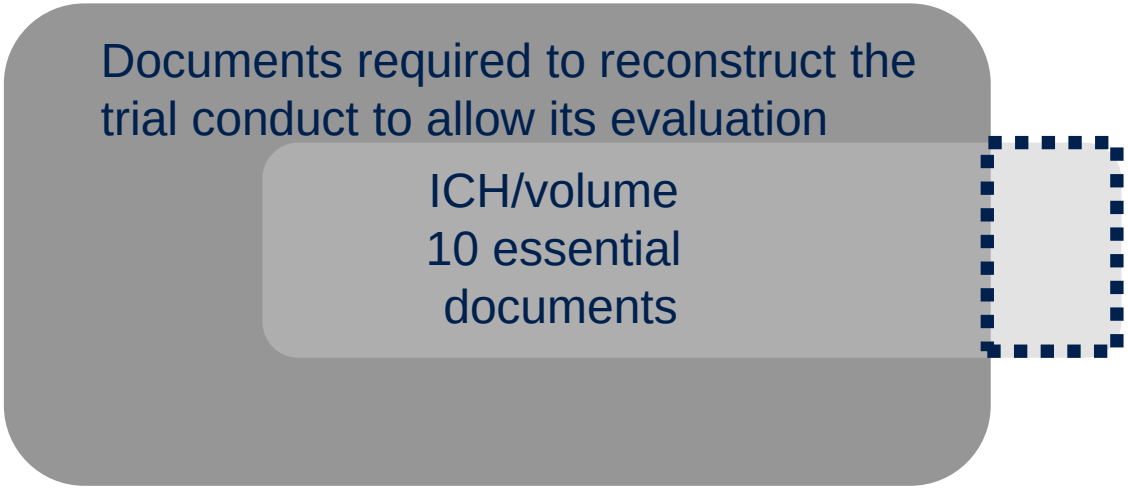
CPMP/ICH/135/95: “Note for Guidance on Good Clinical Practice” (ICH E6)

NEW ADDENDA

Essential Documents

Systems with procedures that assure the quality of every aspect of the trial should be implemented. 2.12

The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s). 5.1.1



Documents not applicable or not required for the trial

ICH - International Conference for Harmonisation

Documents and Data in the TMF

Sponsor at a UK inspection identified over 40 electronic systems that were “relevant to the TMF”

To decide….

- Is it part of the TMF?
- Will inspectors need aided or unaided direct access?

You need to evaluate what the system contains and what this could demonstrate with respect to GCP/SOP/Protocol compliance.

Documents or Data?

ICH GCP 1.9 Audit Trail: - **Documentation** that allows reconstruction of the course of events.

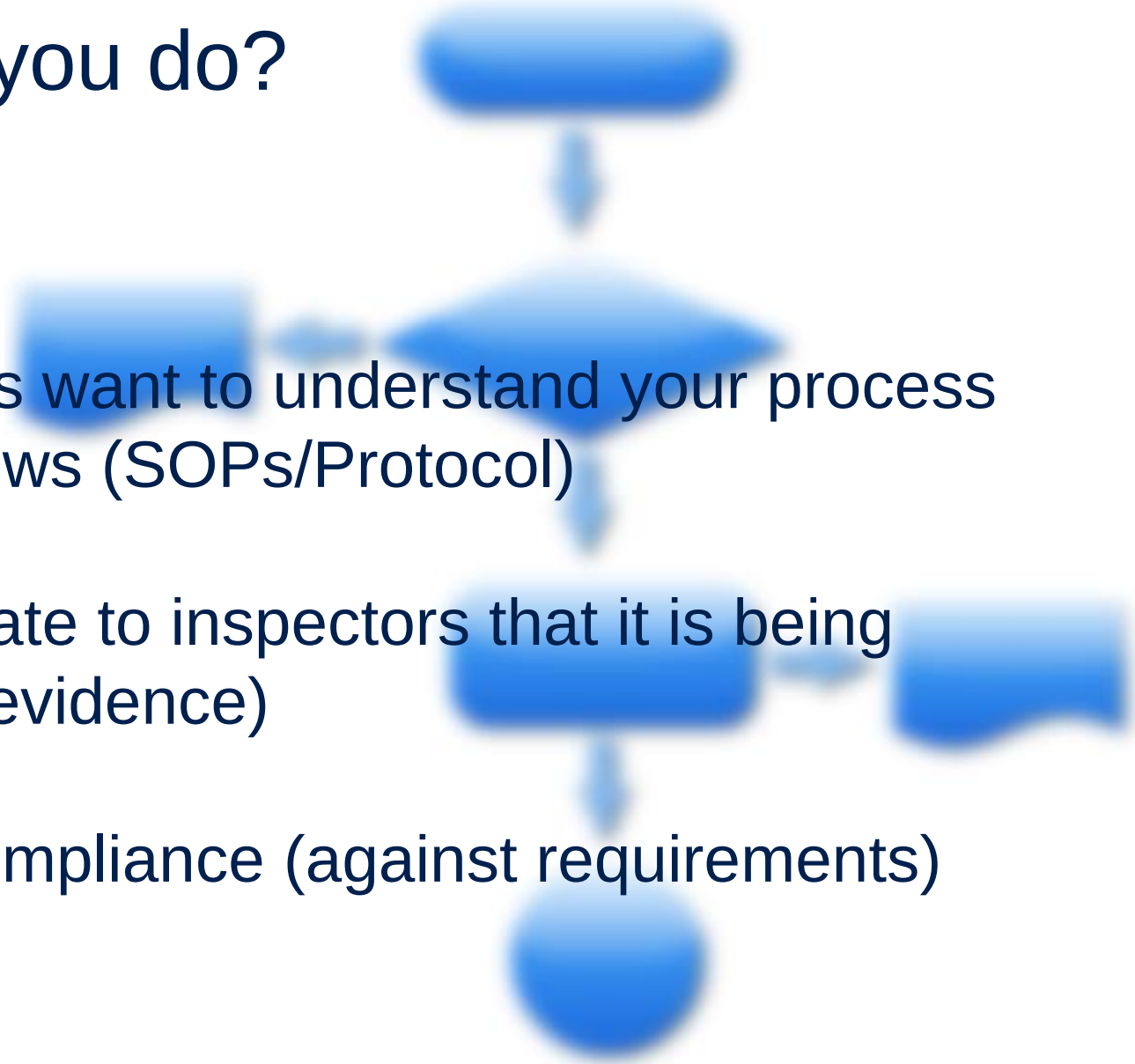
Sense Check

Is it sensible to convert everything to a pdf or move files into the eTMF system or can long term retention (archive) and direct access be maintained in current system?

For example:

- Output of a MVR pdf from the CTMS
- Printing of data to a pdf
- Moving SAS files (datasets, programs) into the eTMF

What do you do?



- Inspectors want to understand your process
  - Interviews (SOPs/Protocol)
- Demonstrate to inspectors that it is being followed (evidence)
- Assess compliance (against requirements)

Example – Some aspects of Monitoring

Monitor Visits Site

Conduct of Visit Report

Completes Data Fields in CTMS that can generate report

Report submitted for Review

Review completed and Report Signed

Example – Some aspects of Monitoring

Monitor Visits Site

Conduct of Visit Report

What was reviewed at site, who was interviewed, what SDV was undertaken etc.?

Completes Data Fields in CTMS that can generate report

Report submitted for Review

How are issues tracked, escalated and resolved?
How are protocol and GCP non-compliances logged and input into DM/Statistics/MW?

Review completed and Report Signed

Timeliness of reporting and review – compliant with SOP/Monitoring Plan?

What to look at?

- Visit reports
- Monitoring Plan
- SOP
- SDV records
- Deviation Logs
- Emails
- Audit trails (eCRF/CTMS)
- eCRF
- CTMS

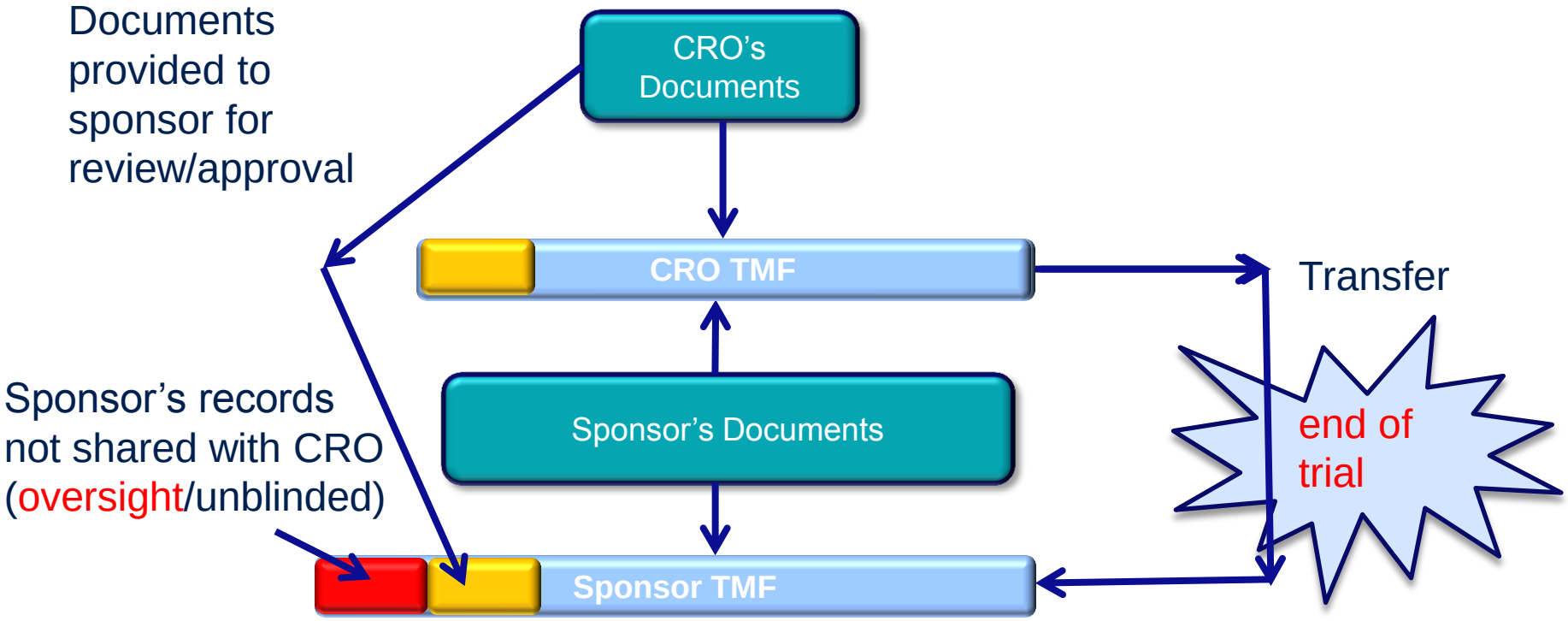
Documents (paper/PDFs), Spreadsheets, Database Field Clinical Data, Metadata (audit trails), Process Flows.

Guided access within an eSystem likely in addition to TMF system direct access

Who's Trial Master File is it?

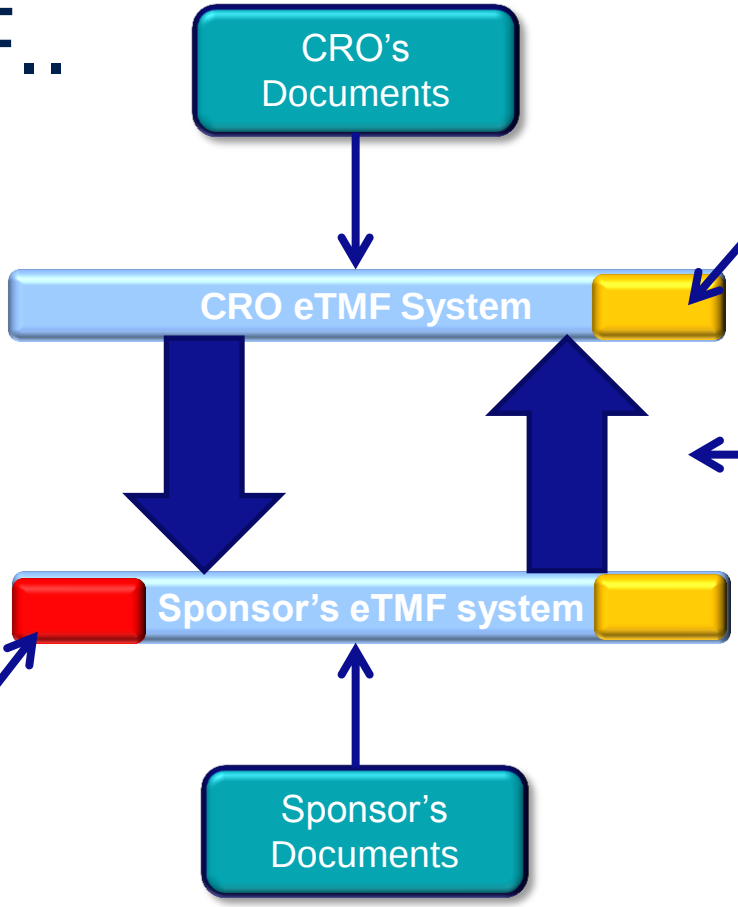
- Sponsor, Investigator, CRO, Laboratories, Vendors and the Sponsor-Investigator
- Complexity is increased with use of Contract Research Organisations and conducting Global Trials
  - The details of the documentation/data held by CROs/Investigators etc. should be clear
  - Contracts or other documentation (e.g. TMF plan) should be in place that details how the TMF will be managed (who, where, what, when) as any trial-related duty and function that is transferred to and assumed by a CRO should be specified in writing
  - There should be consistency with the actual tasks undertaken and those documented.
  - TMF contracts and plans may need amending during the trial

CRO/Sponsor interaction



What records does CRO keep? Does the CRO provide them all to sponsor? Does sponsor retain all the CRO records that are provided? What happens to sponsor's records (oversight ones)? Where are these kept? How is oversight demonstrated at trial end? What happens to documents in sponsor TMF when CRO TMF provided?

CRO/Sponsor interaction – using their own eTMF..



Documents provided to sponsor for review/approval

Uploading/copying of documents between systems – validation and 1:1 mapping

Sponsor's records not shared with CRO

End of Trial

Which is the TMF?

Reliability of the uploading/copying between systems needs to be demonstrated.

Any Questions?