How we are Navigating Global TMF Regulations and inspections: A Real example on How a Japanese Sponsor Address Diverse Regulatory TMF Requirements and Overcome Disparities

Presented by Yuto Kanda, TMF manager
Chugai Pharmaceutical co., ltd

Meet the Speaker

Yuto Kanda (神田 悠社)

Title: TMF manager

Organization: Contract and Record Management Group

-Joined Chugai in 2012 as a CRA

-prior clinical trial manager

in both Japan-domestic and global clinical trials.

- 3yr+ experience in Roche CTMS trainer.

#Open #Fair #Agile #English

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 and Chugai Pharmaceutical co., ltd.

- The author(s) have no real or apparent conflicts of interest to report.

Agenda

1. Self introduction
2. TMF in Japan
3. Chugai’s challenges
4. Closing

TMF and me

- Joined Chugai in 2012
- 2012~2014 : CRA/Study Manager

-I did not really understand how important TMF was…
-Not so engaged

- 2014~2019 : Process management / CTMS trainer
  - Chugai implemented IQVIA eTMF(Wingspan)
- 2019~2023 : Study Lead

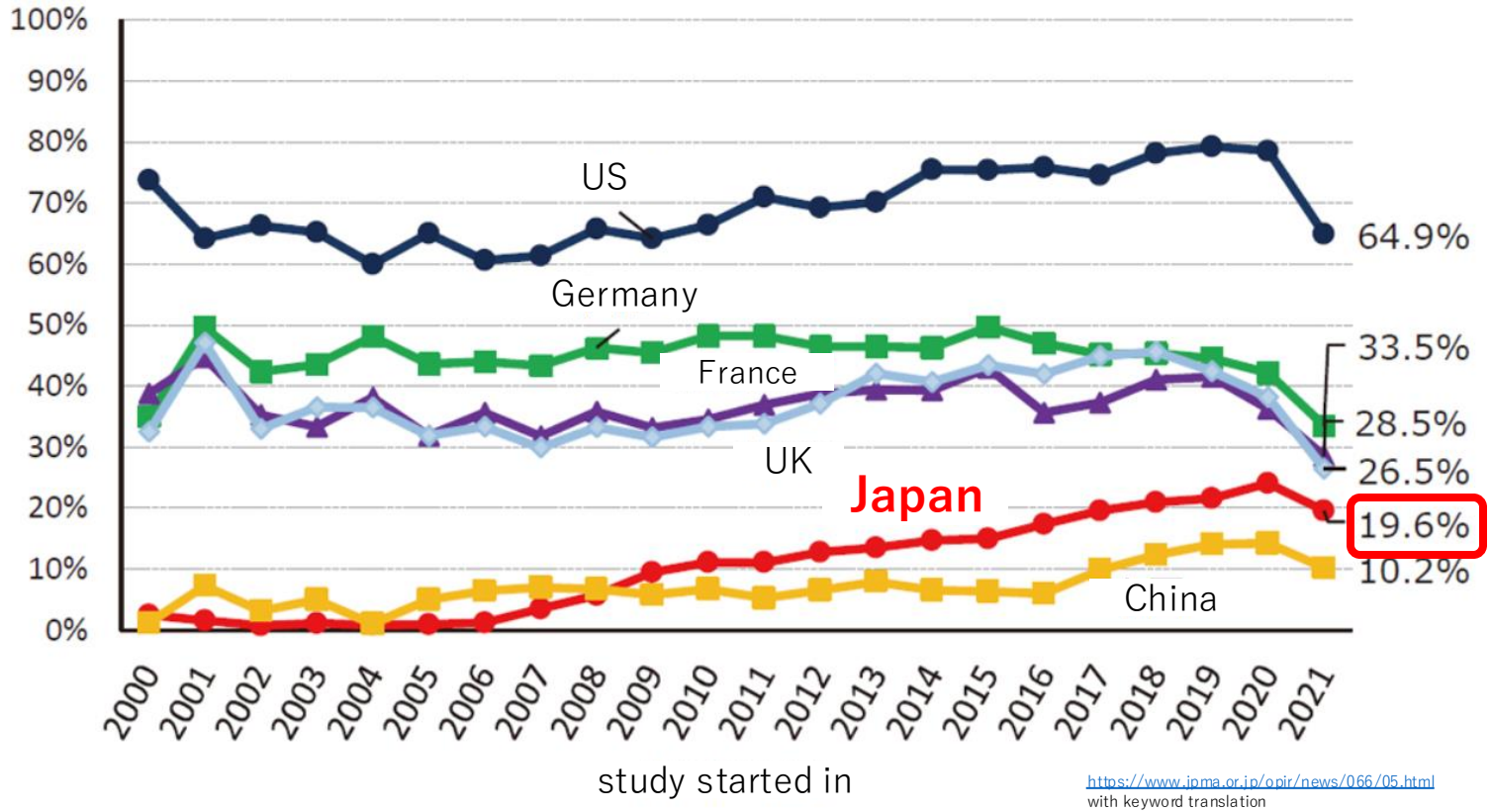
Filing location, naming convention, TMF review
"Timeliness, completeness and quality !"

TMF office

- **2 audits(vendor oversight and TMF) changed my mindset for TMF**
  - **I realized that TMF is a key for successful inspection !!!**
- **2023 until now : TMF management**

Global Trials in Japan

% of global clinical trials in each country



https://www.jpma.or.jp/opir/news/066/05.html
with keyword translation

TMF in Japan

- % of Global trials in Japan is still low
- eTMF launch was not in timely manner (Chugai implemented eTMF in 2017)

- Some JP pharma (including Chugai) need to **play TMF HQ role**, this require mutual understanding of TMF-related global regulations.
  - Lack of understanding may cause incomplete process
  - **Incomplete process may cause inspection finding in the end !**

- However, discussion/collaboration about TMF management is not very-active here…

Difference in Inspection management

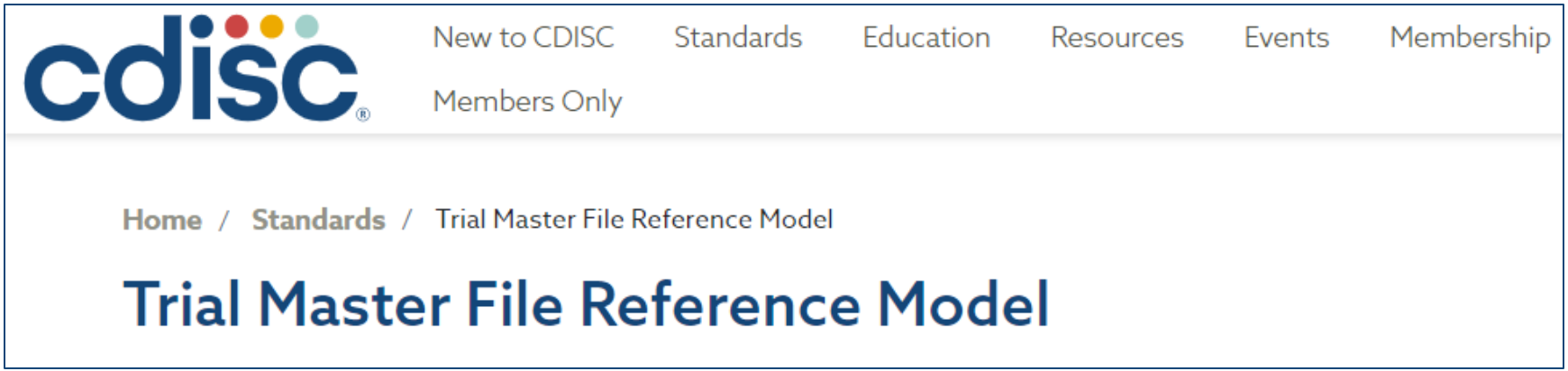
	PMDA(J-HA) inspection	European inspection	TMF Requirement
When	Post filing	May come in the **middle of trial**	
TMF access	Sponsor supplies requested TMF Docs to inspector	**Direct access by Inspector**	

3 Key challenges to present today

- TMF model overhaul
- TMF timeliness dashboard
- TMF workshop

CDISC TMF reference model

- Template for company specific TMF structure
- Now owned by **CDISC**, used to be managed by DIA (~2022)
- *The TMF Reference Model provides **standardized taxonomy and metadata** and outlines a **reference definition of TMF content** using standard nomenclature.*



https://www.cdisc.org/standards/trial-master-file-reference-model

TMF Reference Model

Version 3.3.1 | 11-AUG-2023

Zone	Zone Name	Section #	Section Name	Artifact	Artifact name	Definition / Purpose	Recommended Subartifacts - Documents/documentation recommended to be filed to the artifact.	Core or Recommended for inclusion	ICH Cod	ISO 14155 Reference (Device Studies	A ED
01	Trial Management	01.01	Trial Oversight	01.01.01	Trial Master File Plan	To describe how records for the trial will be managed and stored during and after the trial, including study-specific processes and documentation for archiving and destruction. To include TMF filing structure to be used. May include TMF content list, filing structure and chain of custody records. Artifact can include any evidence of plan execution including, but not limited to: plan, reports, checklists, etc.	Document Transfer Documentation Evidence of Quality Review Request to Lock TMF Trial Master File Plan Trial Master File Index Trial Master File Report	Recommended	5.5.7		
01	Trial Management	01.01	Trial Oversight	01.01.02	Trial Management Plan	To describe overall strategy for timelines, management and conduct of the trial and typically makes reference to other artifacts. Artifact can include details on contingency plan covering details for site start up planning.	Clinical Development Plan Project Management Plan Trial Management Plan	Recommended	2.2		
01											
01						themselves. May include SOP waivers to document and describe study-specific deviation from a named SOP or working procedure and the rationale for the deviation, when applicable.					
01	Trial Management	01.01	Trial Oversight	01.01.05	Operational Procedure Manual	To describe trial-related processes not covered by formal standard operating procedures. Includes manuals given to sites for ISFs and vendor study-specific manuals as well as any study related tools provided to investigator sites not subject to IRB/IEC approval. Artifact can include any evidence of plan	Operational Procedure Manual	Recommended	5.1.1		

In summary, the goal of the TMF Reference Model is to provide a single, unified interpretation of the regulations via document listing which would be accepted across the industry.

https://www.cdisc.org/standards/trial-master-file-reference-model

V 3.3.1 Clean | V 3.3.1 Markup | Model Overview | Milestones_Events & Description | Instructions and Glossary | Computer System Validation

#1 Chugai TMF Reference Model Overhaul

- TMF Audit in 2022 finding :
  "*TMF structure/document responsibility is not very clear*"

- As a CAPA, we conducted an overhaul of TMF model to achieve e.g.
  - More granularity of documents
    e.g. Data management plan, Data quality plan and Data transfer plan…
  - Clarification of Document ownership
  - Clarification of document level
    (in CDISC model multiple levels are compiled in 1 row)

- As a result, there is 750+ rows(items) listed in the latest version where as CDISC reference model V3.3.1 has 250 rows

Chugai Reference Model V14 outcome

Level	Enterprise	Program	Study	Country	Site	Total
#	37	96	440	88	111	**772**

More Clarity, as aimed !

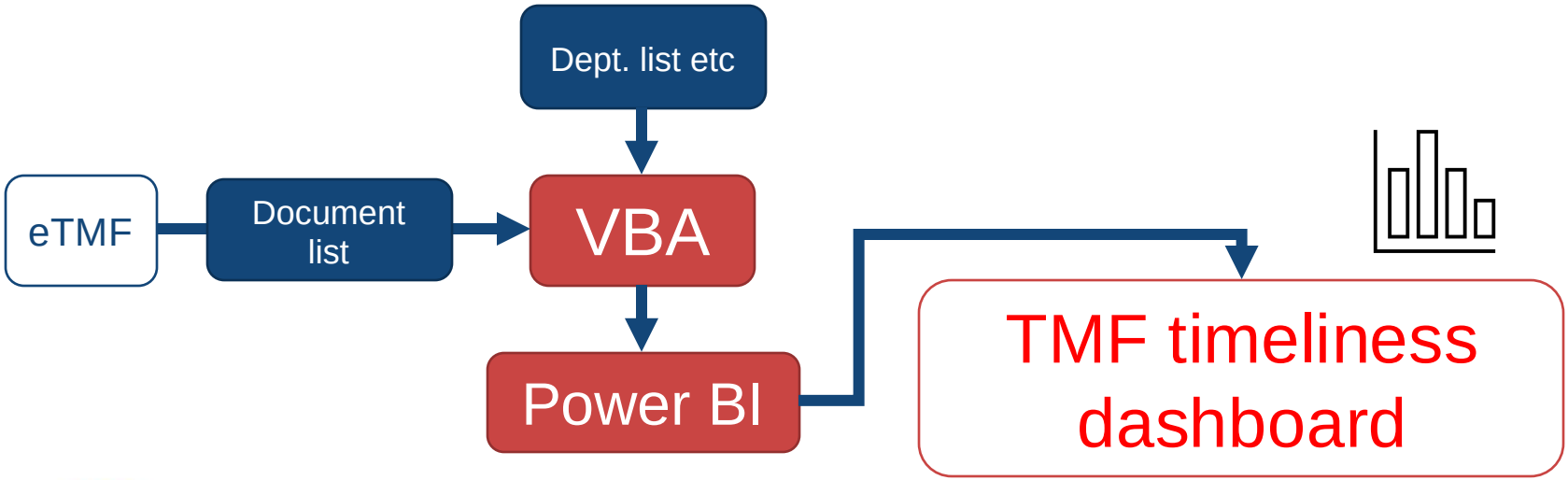
Huge spreadsheet
Maintenance workload

L&L

Balance between **Inspection readiness** and **UI/UX** are to be well considered

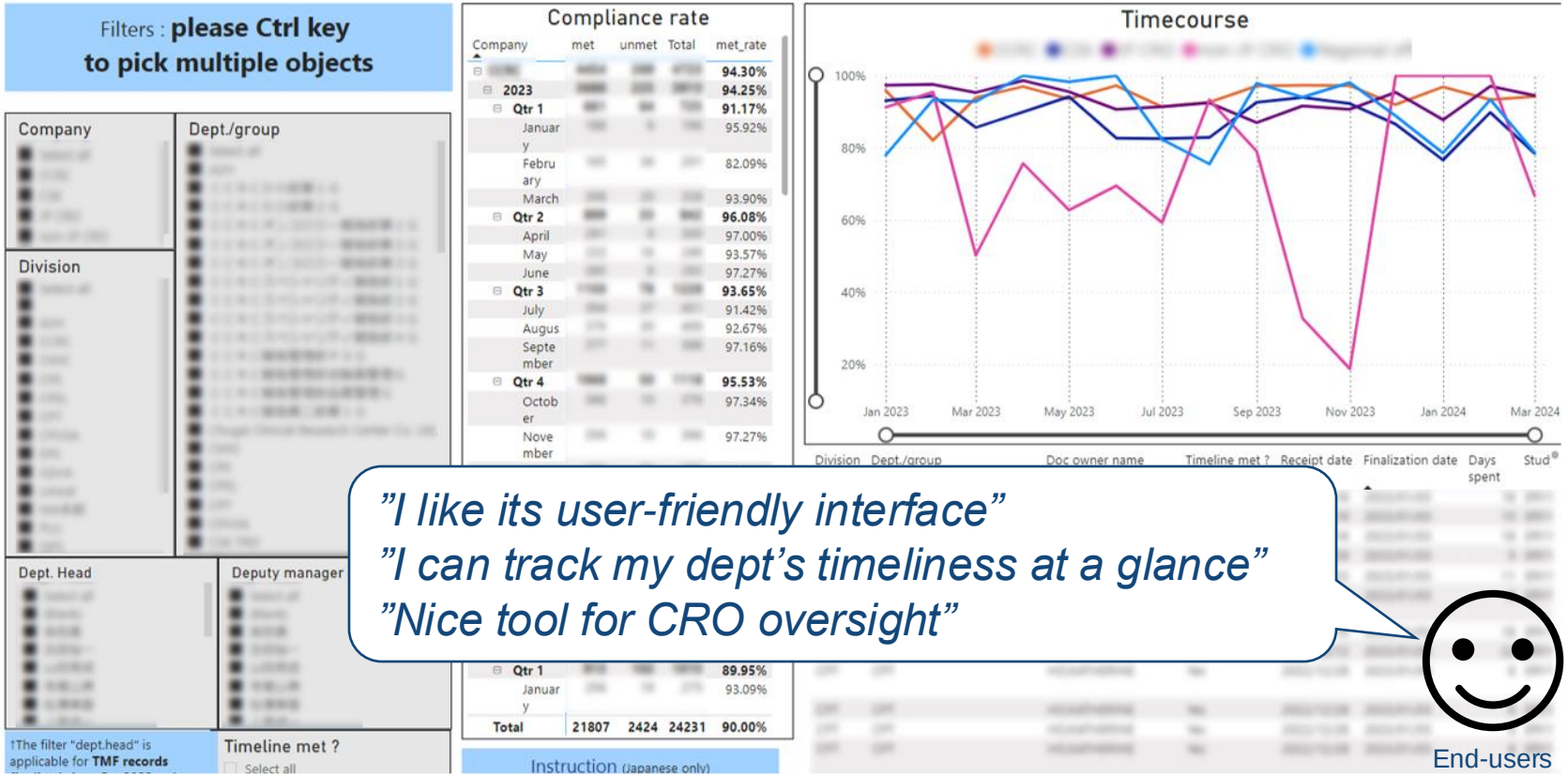
#2 TMF timeliness dashboard

- Reports/Metrics are available in eTMF to visualize TMF timelinessD, but it does not always fulfill Chugai's internal requirements. Such as…
  - **End users** want more **"easy to use"** platform
  - **Managers** would like to review **dept-level metrics**



VBA : Visual Basic for Applications

TMF Timeliness dashboard



#3 TMF workshop in Japan

- Franciska and I met in the EUTMF summit 2023
- We talked about…
  - Japanese pharma's potential challenges in TMF management
  - Importance to be global/united, transparent
  - Potential opportunity to keep collaboration
- **The F2F workshop was Held in Mar2024 having 14 attendees from 5 JP pharma companies.**

Assumption we had before the workshop:
"There would be Japan-specific challenges"

Challenges highlighted in the workshop

Inspection readiness	TMF Culture and Engagement
-How to track TMF Completeness -How to set up and manage EDLs (EDL = Expected Document List) -Balance of cost/workload vs TMF Health	-HQ need to engage end users -TMF importance needs further penetration -TMF is cross-functional , so we must manage various situations/opinions TMF champion : should be helpful
CRO collaboration and Oversight	**Risk-based TMF management**
-Who is responsible for the oversight ? -Education/training for CRO is critical	-What are “core” documents ? -TMF indicator could be risk-based -Blind/unblind : risky documents

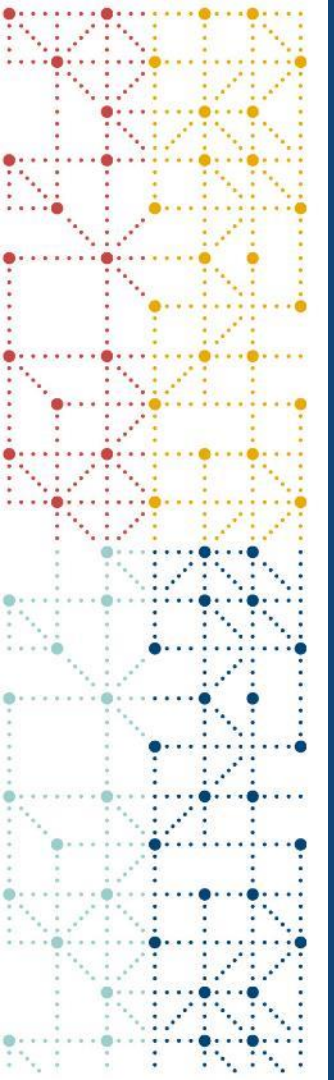
Workshop Summary : We are not alone !

- Key Challenges highlighted in the workshop did not look Japan-specific, they looked **very similar to global topics/challenges**.

Inspection readiness	TMF culture &Engagement	CRO collaboration and oversight	Risk based TMF management

<Attendees' consensus/comments>

- They would like to keep relationship with other pharma to discuss TMF issues.
- They'd like to **learn more about European TMF regulations.**



Closing

Recap/ Expected steps onwards

Chugai have made a lot of challenges to improve TMF management framework (and this must go on..)

TMF management has been Challenging in Japan, but no critical JP-specific issues have been highlighted

To arrange training for Japanese TMF managers to learn TMF-related regulations


Let’s have
#Too Much Fun !

Thank You!

Chugai's key challenges made so far

1. TMF plan template update to align with DIA TMF plan template
2. Close collaboration/daily communication with TMF team @ Chugai UK
3. Chugai TMF Reference Model Overhaul
4. TMF Timeliness dashboard
5. Assignment of "TMF lead" to each clinical trial team
6. TMF review (periodic review to ensure TMF health) : still struggling
7. TMF newsletters
8. Drop-in sessions
9. **Workshop with other Japanese Pharma**

TMF lead : assigned to each study team

1. To attend kick off meeting / regular study team meeting to announce TMF-related topics and to provide instruction/training.
2. **To lead and facilitate TMF plan creation and maintenance**
3. **To lead and oversee Sponsor's TMF review**
4. To manage TMF closure/TMF transfer
5. Inspection support (TMF perspective)
6. **To support study team for any TMF related questions/issues**
7. **To review CRO's RFP/SOW/SOP/TMF plan**
8. To oversee critical service providers' TMF review outputs
9. To be primary contact to service providers when it comes to TMF