Trial Master File Reference Model

General Meeting 27 February 2017
Agenda

- Welcome
- Update on the New members
- Version Control plans
- Refresher on past deliverables of the TMF Reference Model
- Subteam updates
- Survey update and reminder
- Date Conventions Subteam deliverables
- Summary of recent conferences
  - TMF Summit
  - DIA RSIDM
## New members

<table>
<thead>
<tr>
<th>Last name</th>
<th>First Name</th>
<th>Organisation</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bazile</td>
<td>Jacques</td>
<td>United Therapeutics</td>
<td>USA</td>
</tr>
<tr>
<td>Bhatt</td>
<td>Kamal</td>
<td>Inovio Pharmaceuticals</td>
<td>USA</td>
</tr>
<tr>
<td>Butler</td>
<td>Brandon</td>
<td>LMK Clinical Research</td>
<td>USA</td>
</tr>
<tr>
<td>Danage</td>
<td>Brianna</td>
<td>Parexel</td>
<td>USA</td>
</tr>
<tr>
<td>Bashford</td>
<td>Donna</td>
<td>Just in Time GCP</td>
<td>USA</td>
</tr>
<tr>
<td>Elliott</td>
<td>Stefanie</td>
<td>ICON Clinical</td>
<td>USA</td>
</tr>
<tr>
<td>Felsenstein</td>
<td>Ines</td>
<td>Ablynx</td>
<td>Belgium</td>
</tr>
<tr>
<td>Harada</td>
<td>Connor</td>
<td>MAPS Public Benefit Corporation</td>
<td>USA</td>
</tr>
<tr>
<td>Hawkins</td>
<td>Louise</td>
<td>Agios</td>
<td>USA</td>
</tr>
<tr>
<td>Kadakia</td>
<td>Ronak</td>
<td>J&amp;J</td>
<td>USA</td>
</tr>
<tr>
<td>Kongtong</td>
<td>Tipsuda</td>
<td>Eisai</td>
<td>USA</td>
</tr>
<tr>
<td>Lakin</td>
<td>Toni</td>
<td>Paragon Solutions Inc</td>
<td>USA</td>
</tr>
<tr>
<td>Lambert</td>
<td>Shayna</td>
<td>Janssen</td>
<td>Canada</td>
</tr>
<tr>
<td>Mauceri</td>
<td>Kelly</td>
<td>Rho</td>
<td>USA</td>
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</table>
# New members

<table>
<thead>
<tr>
<th>Last name</th>
<th>First Name</th>
<th>Organisation</th>
<th>Country</th>
</tr>
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<tbody>
<tr>
<td>Mills-Wilson</td>
<td>Marla</td>
<td>iNNO Clinical Outcomes</td>
<td>USA</td>
</tr>
<tr>
<td>Morris</td>
<td>Emily</td>
<td>Medicines360</td>
<td>USA</td>
</tr>
<tr>
<td>Nalepa</td>
<td>Slawomir</td>
<td>PPD</td>
<td>USA</td>
</tr>
<tr>
<td>O’Hern</td>
<td>Kelsey</td>
<td>Usona Institute</td>
<td>USA</td>
</tr>
<tr>
<td>Olszowy</td>
<td>Kara</td>
<td>TherapeuticsMD</td>
<td>USA</td>
</tr>
<tr>
<td>Owolabi</td>
<td>Abiola</td>
<td>Biogen</td>
<td>UK</td>
</tr>
<tr>
<td>Reed</td>
<td>Nic</td>
<td>Parexel</td>
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<tr>
<td>Shaffer</td>
<td>Debbie</td>
<td>Just in Time GCP</td>
<td>USA</td>
</tr>
<tr>
<td>Silk</td>
<td>David</td>
<td>The Kirby Institute</td>
<td>Australia</td>
</tr>
<tr>
<td>Smith</td>
<td>Alicia</td>
<td>Quintiles</td>
<td>USA</td>
</tr>
<tr>
<td>Tamblyn</td>
<td>Marjorie</td>
<td>Nant Bioscience</td>
<td>USA</td>
</tr>
<tr>
<td>Verdone</td>
<td>Alex</td>
<td>Roivant Sciences</td>
<td>USA</td>
</tr>
<tr>
<td>Williams</td>
<td>Karen</td>
<td>United Therapeutics</td>
<td>USA</td>
</tr>
<tr>
<td>Wolff</td>
<td>Thomas</td>
<td>Paragon Solutions</td>
<td>USA</td>
</tr>
</tbody>
</table>
Version Control

Proposal under review for 3-tier versioning

- Maintenance release e.g. v3.0.1
  - e.g. minor typographic changes, clarification, sub-artifacts

- Minor release e.g. v3.1
  - Substantial change in content but no compatibility issues e.g. additional optional column (milestones)

- Major release e.g. v4.0
  - Change likely to have compatibility issues with prior version e.g. addition/removal of artifacts
TMF RM Past Deliverables

Resources for Current Version of TMF Reference Model:

- TMF Reference Model v3.0, Released 16-JUN-2015, Excel Spreadsheet
- MindJet File for TMF-RM v3.o (.mmap format – requires MindJet licence to open file) – available to TMF Reference Model Project Team members via Yahoo!Group document library due to WordPress restrictions
- MindMap PDF File for TMF-RM v3.0 (.pdf format – requires Acrobat Reader and Adobe Flash)
- TMF Reference Model v3 Presentation – Overview of the Reference Model
- TMF Reference Model Process Maps: Used in development of Reference Model to align TMF artifacts to trial processes
- The Evolution of the TMF Reference Model v3.0: Recording of webinar delivered in July 2015
TMF RM Past Deliverables

**TMF Tools:**

- **TMF Quality Control:** Toolkit to help prepare a TMF quality control programme (Approved 12-Oct-2016)
- **TMF Quality Control Presentation:** Powerpoint slides presented to group meeting November 7, 2016
- **Inspection Readiness:** Toolkit to help prepare TMF for regulatory inspections (Approved 09-Nov-2016)
- **Inspection Readiness Presentation:** Powerpoint slides presented to group meeting January 9, 2017

- **Metrics 101** – How to Implement a TMF Metrics Program (PDF File)
- **Metrics 101** – How to Implement a TMF Metrics Program (PPT File)
- **Metrics Definitions** – Recommended Metrics for your TMF Metrics Program (XLS File)
TMF RM Past Deliverables

Miscellaneous Resources:

- 2016 Project Team Roadmap
- DIA Framework for the Destruction of Paper Originals v1.0 (24-JUN-2012)
- Presentation – Framework for Paper Destruction (May 2012)

Published Articles:

- TMF Reference Model Standard = Process Efficiency (published Applied Clinical Trials, May 2014)
- TMF Reference Model Presentation: Overview of the TMF Reference Model, Published August 2012

Project Team All-Hands Meetings:

- January 9, 2017
- February 27, 2017
- April 24, 2017
- June 12, 2017
## Activity Subgroups

<table>
<thead>
<tr>
<th>Group</th>
<th>Lead</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metadata</td>
<td>Todd Tullis</td>
</tr>
<tr>
<td>Implementation toolkit / Upgrade User Guide</td>
<td>Mike Czaplicki</td>
</tr>
<tr>
<td></td>
<td>Eric Rubinson</td>
</tr>
<tr>
<td>Dating conventions</td>
<td>Melissa Maberry – TODAY</td>
</tr>
<tr>
<td>Sub-artifacts</td>
<td>Karin Schneider</td>
</tr>
<tr>
<td>Inspection Preparation</td>
<td>Kathie Clark [✓]</td>
</tr>
<tr>
<td>TMF Quality</td>
<td>Sholeh Ehdaivand [✓]</td>
</tr>
<tr>
<td>Country specific artifacts</td>
<td>Eleanor Hewes</td>
</tr>
<tr>
<td>Milestones</td>
<td>Kathleen Kirby</td>
</tr>
<tr>
<td>Single Site Structure</td>
<td>Karen McCarthy Shau – OUTPUT DUE</td>
</tr>
<tr>
<td>Survey</td>
<td>Jane Twitchen – RELEASED</td>
</tr>
</tbody>
</table>
2017 Reference Model Survey Headlines so far!

- Survey Opened on Sunday 12th February
- It will remain open for 6 weeks (26 March 2017)
- To date, 151 people have responded
Why should I take part in the survey…? (1)

Because the data is shared with all participants, so you’ll gain fascinating industry insights and intelligence….

For example 1:
Q34: Please share some insight regarding the types of findings you have received following an Audit/Inspection using your eTMF or eISF (tick all that apply)

<table>
<thead>
<tr>
<th>Answer Choices</th>
<th>Responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>N/A (no findings or findings not yet received)</td>
<td>17.65% 6</td>
</tr>
<tr>
<td>Finding regarding TMF Completeness</td>
<td>61.76% 21</td>
</tr>
<tr>
<td>Finding regarding TMF Timeliness (i.e. non contemporaneous TMF)</td>
<td>47.06% 16</td>
</tr>
<tr>
<td>Finding regarding TMF Quality (document content)</td>
<td>26.47% 9</td>
</tr>
<tr>
<td>Finding regarding eTMF Quality (e.g. metadata or formatting)</td>
<td>23.53% 8</td>
</tr>
<tr>
<td>Finding regarding eTMF System navigation</td>
<td>20.59% 7</td>
</tr>
<tr>
<td>Finding regarding eTMF System access</td>
<td>11.76% 4</td>
</tr>
<tr>
<td>Finding regarding eTMF System training</td>
<td>5.89% 2</td>
</tr>
<tr>
<td>Finding regarding TMF Filing Structure used</td>
<td>14.71% 5</td>
</tr>
<tr>
<td>Finding regarding CRO Oversight</td>
<td>11.76% 4</td>
</tr>
<tr>
<td>Other (please comment)</td>
<td>8.82% 3</td>
</tr>
</tbody>
</table>

Total Respondents: 34
Why should I take part in the survey….? (2)

Because the data is shared with all participants, so you’ll gain fascinating industry insights and intelligence…. 

For example 2:

**Q33: When have you provided the Inspector/Auditor with their eTMF password?**

<table>
<thead>
<tr>
<th>Answer Choices</th>
<th>Responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior to the inspection, so they can start using straight away</td>
<td>18.18%</td>
</tr>
<tr>
<td>Prior to the inspection, but it only activates when they are onsite</td>
<td>12.12%</td>
</tr>
<tr>
<td>Once the inspection commences, but the password is only active whilst they’re on site</td>
<td>18.18%</td>
</tr>
<tr>
<td>Once the inspection commences, but the password is then active continually until the inspection is complete</td>
<td>33.33%</td>
</tr>
<tr>
<td>Other (please comment)</td>
<td>18.18%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>33</strong></td>
</tr>
</tbody>
</table>
Why should I take part in the survey….? (3)

Because this is your opportunity to give us feedback on what you need. The initiative's success is due to the breadth and depth of our volunteer participation across a wide spectrum of organizations involved in clinical trials, please take this opportunity to contribute your ideas and feedback.

Responses to date:

- Recommend trying to get more Japan input. PMDA is so unique in wanting to see paper records and this can be confusing for organization to understand how they use an eTMF and still meet needs of PMDA.
- Industry standard TMF plan. TMF RM needs more doc types / artefacts for Vendor oversight
- Need to add more guidance for functions other than Clinical to establish a more well rounded industry standard/ approach for the TMF management and oversight
- TMF metrics catalogue Inspection preparation and TMF training for inspectors signed documents – which documents in the TMF RM would be in scope for signatures and why TMF plan template
- It has really streamlined our filing process and I would not look to any other filing process unless a newer version was provided. I am truly impressed with the detailed and structure filing of the eTMF/TMF reference model. I also shared it with other companies that are in need of structure for their TMF and eTMF

The Steering Committee will take all feedback seriously, and use it to define the RM Roadmap and priorities for 2017 and beyond.
Date Conventions Subgroup

- Word guidance document and excel spreadsheet with suggested document dates
- Included in this guidance are definitions of key terms, recommendations for the date format, standard rules for ease of reference and suggestions for implementation.
# Document Types

<table>
<thead>
<tr>
<th>Document Type</th>
<th>Standard Rule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Functional Plans</td>
<td>Version Date* (not the template version date)</td>
</tr>
<tr>
<td>Manuals</td>
<td>Version Date*</td>
</tr>
<tr>
<td>Monitoring Visit Documents</td>
<td>Visit Start Date</td>
</tr>
<tr>
<td>Translated Documents</td>
<td>Date of document being translated</td>
</tr>
<tr>
<td>Tracking Information</td>
<td>Last Entry Date</td>
</tr>
<tr>
<td>Filenote</td>
<td>Filenote Date (not signature date)</td>
</tr>
<tr>
<td>Relevant Communications</td>
<td>Correspondence Date</td>
</tr>
<tr>
<td>Meeting Material</td>
<td>Meeting Start Date</td>
</tr>
</tbody>
</table>
# Ambiguous Dates

<table>
<thead>
<tr>
<th>Date Issue</th>
<th>Standard Rule</th>
</tr>
</thead>
<tbody>
<tr>
<td>No date</td>
<td>01-Jan-1900 – this has been selected to ensure it cannot be mistaken as a real date. It is only needed where a date in date format is mandated by an eTMF.</td>
</tr>
<tr>
<td>Month and year only, no day (e.g. May 2016)</td>
<td>01-MMM-YYYY</td>
</tr>
<tr>
<td>Day and month only, no year (e.g. May 18)</td>
<td>Try to interpret the year based on context, otherwise use 1900 (e.g. 18-MAY-1900)</td>
</tr>
<tr>
<td>Year only, no month or day</td>
<td>01-JAN-YYYY</td>
</tr>
<tr>
<td>Date Range</td>
<td>Start Date</td>
</tr>
<tr>
<td>Multiple Signatures</td>
<td>Last Signature Date</td>
</tr>
</tbody>
</table>
Implementation

- To achieve consistency, at a minimum, document your organization’s plans for:
  - The date format (e.g. DD–MMM–YYYY)
  - Standards for ambiguous dates (e.g. missing day)
  - Standards for common document types (e.g. functional plans)
Feb 6–8 2017 in Bethesda Maryland

FDA Plenary and Closing ’Ask the Regulators’

Session Tracks
- Regulatory Information Management Business
- Regulatory Information Management Technology
- Electronic Document Management
- Electronic Regulatory Submissions

Courses Offered
- Regulatory Content & Submissions Planning Primer
- Global Identification of Medicinal Products (IDMP)
- Achieving Regulatory Operations Excellence Through Outsourcing
Todd’s Highlights

- Identification of Medicinal Products (IDMP), parallels and potential impact to TMF RM

- ‘Structured Content Management’ – how far and how fast?

- An era of Regulatory Agency alignment?
Karin’s Highlights

Prescription Drug User Fee Act (PDUFA)
- PDUFA I enacted 1992; 5-year authorizations
  - Industry user fees for added staff and systems; Reduced average time to drug approval by almost 60%
  - PDUFA V sunsets September 30, 2017
    - First cycle approval rates at all-time highs

VI proposal in congress
- Combination product review
- Incorporating the Patient’s Voice in drug development and review
- Complex Novel Trial Designs
- Model Informed Drug Development
- Biomarker Qualification
- Use of Real World Evidence
Karin’s Highlights

- Data Standards
Karin’s Highlights

Some Submission Standards Will Be Required

**Study Data** started on Dec. 17, 2016

- **Commercial INDs**
  - Starting on Dec. 17, 2017
- **Noncommercial INDs**
  - exempt

Sponsors whose studies start after December 17, 2016 must use the data standards listed in the FDA Data Standards Catalog for NDAs, BLAs and ANDAs.

For Commercial INDs, the requirement starts after December 17, 2017.

**eCTD** starting on May 5, 2017

- **Commercial INDs**
  - Starting on May 5, 2018
- **Noncommercial INDs**
  - exempt

May 5, 2018: Commercial Investigational New Drug Applications (INDs) must be submitted using eCTD format.
Karin’s Highlights

- TA Standards Initiative, Players, Progress

Key Players

CDISC, C-Path, NIH, FDA, TransCelerate, and many other stakeholders

81%

Of the 54 TAs prioritized, 44 have begun, with 21 of those completed as of February 2017
Karin’s Highlights

**Industry Status:** Data Quality “Confidence” and Improvement Practices

- **Emerging Practices**
  - **Data Steward Role:** FTE investment versus remediation cost / compliance risk
  - **Sampling:** People based (audit) and System monitoring (e.g. timeliness)
  - **Culture:** Data Quality tied to rewards systems – “all in culture”

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**Graph:**

- **Global Authoritative Source Confidence Level**
  - N = 52
  - 33% High Confidence avg. for top 8 or 33% for all categories
Karin’s Highlights

Merged eCTD & TMF in Document Management

**Trial Master File (TMF)**
- 1.0 Trial Management
- 2.0 Central Trial Documents
- 3.0 Regulatory
- 4.0 IRB/IEC & Other Approvals
- 5.0 Site Management
- 6.0 IP & Trial Supplies
- 7.0 Safety Reporting
- 8.0 Centralized Testing
- 9.0 Third Parties
- 10.0 Data Management
- 11.0 Statistics

**EDM Ref Model**
- Regional US
- Regional EU
- Regional CA
- Quality-Drug Substance
- Quality-Drug Product
- Quality-Other
- Nonclinical - Study Reports
- Nonclinical - Other
- Clinical - Other

**eCTD**
- Module 1 - Regional
- Module II - Summaries
- Module III - Quality
- Module IV - Nonclinical
- Module V - Clinical
Karin’s Highlights

- Analytics
  - Semantic web technologies for text extraction and transformation
Karin’s Highlights

- Best Practices, one-size fits all

Evaluation Process – The Lemming Syndrome

JUST OUTSIDE THE BOX

Why’s he going in the opposite direction from us?

Don’t worry about him. He’s the black sheep in the family.

Sometimes being the black sheep has its advantages.
Karin’s Highlights

- EDM Future: BYOD, User Centric Design, AI

EDM EXPECTATIONS IN LIFE SCIENCE

- Consumerized IT
- Open Systems
Karin’s Highlights

What is RIM?

RIM Suite is the single source of truth

[Diagram showing the integration of Clinical, Medical, Submission Documents, Quality Manufacturing, Submissions Archive, Registrations, Regulatory, and Labeling]
Karin’s Highlights

- Integrated Regulatory Information and Submission Management

### Short and Long-Term Benefits

#### Planning and Operational Phase / Reduce hand-over
- Supports implementation of core regulatory dossiers
- Simplifies workshare between groups to balance workload

#### True Project Management Culture / KPIs
- Saves time, when it’s needed most
- Supports organization, management and control of offshore Reg. Ops. support

#### Built-in quality for continuous data quality measures
- Minimizes errors and re-work
- Reduces operational costs and improve productivity
- Offshore partners must rely on data ("single source of truth")

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TRIAL MASTER FILE TMF REFERENCE MODEL
Karin’s Highlights

- RFP’s

**Big Opportunity – Example in the US Government**

2015: 53,228 RFPs

**Assumptions**

- 4 weeks

- As of 2013, the average federal employee earns roughly $80,000.

- Each RFP then costs $12,307 to generate

**Grand total spent issuing RFPs in 2015 by the US Fed:**

$655,113,846
Other Highlights?
Ensure TMF Completeness Through SOP Creation, Data Management, Strong Partner Communication and Inspection Readiness
Co-Chairs

- Jamie Toth
  Daiichi-Sankyo
- Eric Rubinson
  Allergan
- Karen Roy
Over 200 Attendees
111 Sponsor Attendees – 57 Companies
28 CRO Attendees – 14 Companies
56 Vendor Attendees – 19 Companies
6 Site Attendees – 5 Companies
The TMF at Universal in 2017!!

• Major topics of discussion:
  • Moving off of Paper and into the eTMF realm
  • Managing change in process, technology and operating model
  • Building a culture of Inspection Readiness
  • Integrating with business partners and CROs
  • Using metrics to measure and improve the TMF
  • Ensuring TMF Quality regardless of format
  • Using TMF technology wisely
We need to evolve from the old ways of thinking and working!
We need to transform our processes and technologies!
We need to fearlessly solve the mysteries of Regulator Expectations!
We need to create a seamless society with partners and CROs!
We need to develop metrics to measure and improve our processes!
We need to focus on TMF quality, not appearance!
We need to embrace technology, but carefully!
We need to work together to improve our business!
eTMF Conferences coming up

- DIA Chicago, June
- DIA Operational Excellence Forum (in planning)
- EXL TMF Summit, Japan, September
- IQPC TMF Conference, September, Amsterdam?
- EXL TMF Summit, London, October
- Plus Inspection Readiness, Quality forums etc.
TMF RM General Meetings

- 24–Apr
- 12–Jun
Join the TMF Reference Model Yahoo! Group

http://tmfrefmodel.com/join

• Knowledge sharing
• Networking
• Too Much Fun!