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

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New members

Last name	First Name	Organisation	Country
Bazile	Jacques	United Therapautics	USA
Bhatt	Kamal	Inovio Pharmaceuticals	USA
Butler	Brandon	LMK Clinical Research	USA
Danage	Brianna	Parexel	USA
Bashford	Donna	Just in Time GCP	USA
Elliott	Stefanie	ICON Clinical	USA
Felsenstein	Ines	Ablynx	Belgium
Harada	Connor	MAPS Public Benefit Corporation	USA
Hawkins	Louise	Agios	USA
Kadakia	Ronak	J&J	USA
Kongtong	Tipsuda	Eisai	USA
Lakin	Toni	Paragon Solutions Inc	USA
Lambert	Shayna	Janssen	Canada
Mauceri	Kelly	Rho	USA

New members

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

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

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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 v3.0 (.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 User Guide – Guide for Implementing the TMF 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

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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)

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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

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Activity Subgroups

Group	Lead
Metadata	Todd Tullis
Implementation toolkit / Upgrade User Guide	Mike Czaplicki Eric Rubinson
Dating conventions	Melissa Maberry – TODAY
Sub-artifacts	Karin Schneider
Inspection Preparation	Kathie Clark ☑
TMF Quality	Sholeh Ehdaivand ☑
Country specific artifacts	Eleanor Hewes
Milestones	Kathleen Kirby
Single Site Structure	Karen McCarthy Shau – OUTPUT DUE
Survey	Jane Twitchen – RELEASED

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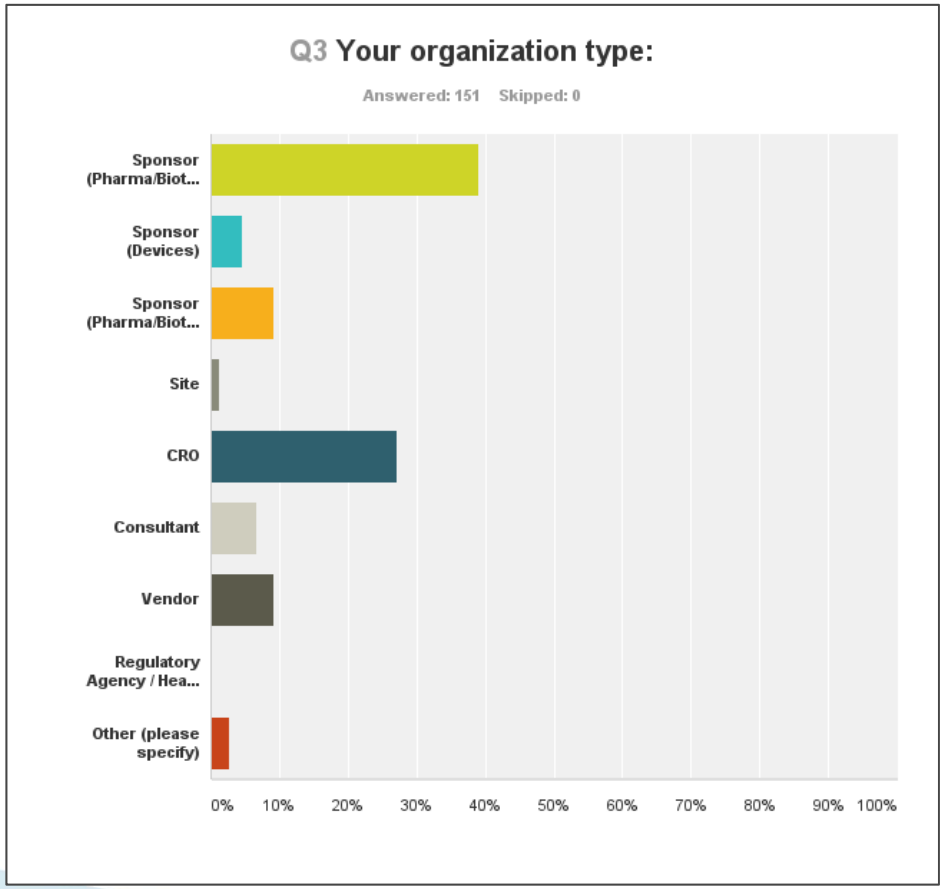
2017 Reference Model Survey Headlines so far!

- Survey Opened on Sunday 12th February
- It will remain open for 6 weeks (26 March 2017)
- To date, 151 people have responded



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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)

Answer Choices	Responses	
N/A (no findings or findings not yet received)	**17.65%**	6
Finding regarding TMF Completeness	**61.76%**	21
Finding regarding TMF Timeliness (i.e. non contemporaneous TMF)	**47.06%**	16
Finding regarding TMF Quality (document content)	**26.47%**	9
Finding regarding eTMF Quality (e.g. metadata or formatting)	**23.53%**	8
Finding regarding eTMF System navigation	**20.59%**	7
Finding regarding eTMF System access	**11.76%**	4
Finding regarding eTMF System training	**5.88%**	2
Finding regarding TMF Filing Structure used	**14.71%**	5
Finding regarding CRO Oversight	**11.76%**	4
Other (please comment)	**8.82%**	3
Total Respondents: 34		

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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?

Answer Choices	Responses	
Prior to the inspection, so they can start using straight away	**18.18%**	6
Prior to the inspection, but it only activates when they are onsite	**12.12%**	4
Once the inspection commences, but the password is only active whilst they're onsite	**18.18%**	6
Once the inspection commences, but the password is then active continually until the inspection is complete	**33.33%**	11
Other (please comment)	**18.18%**	6
Total		**33**

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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.

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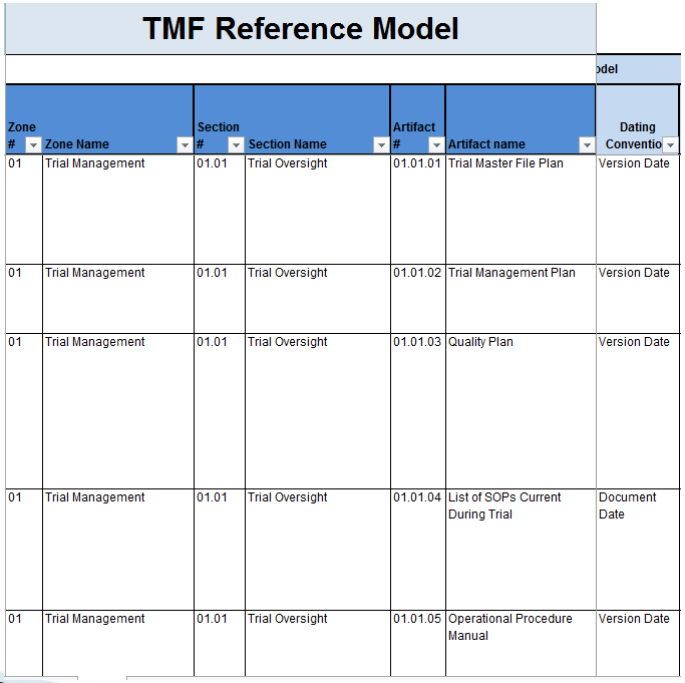
Date Conventions Subgroup

- 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.



TMF Reference Model

odel

Zone #	Zone Name	Section #	Section Name	Artifact #	Artifact name	Dating Conventio
01	Trial Management	01.01	Trial Oversight	01.01.01	Trial Master File Plan	Version Date
01	Trial Management	01.01	Trial Oversight	01.01.02	Trial Management Plan	Version Date
01	Trial Management	01.01	Trial Oversight	01.01.03	Quality Plan	Version Date
01	Trial Management	01.01	Trial Oversight	01.01.04	List of SOPs Current During Trial	Document Date
01	Trial Management	01.01	Trial Oversight	01.01.05	Operational Procedure Manual	Version Date

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Guidance for Date Conventions

<Approval Date dd-MON-YYYY>

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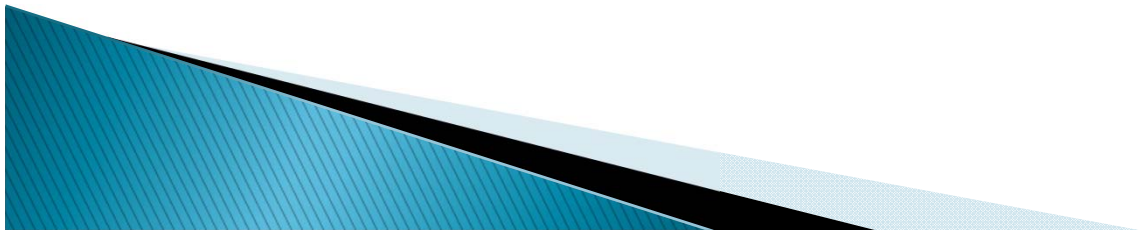
Document Types

Document Type	Standard Rule
Functional Plans	Version Date* (not the template version date)
Manuals	Version Date*
Monitoring Visit Documents	Visit Start Date
Translated Documents	Date of document being translated
Tracking Information	Last Entry Date
Filenote	Filenote Date (not signature date)
Relevant Communications	Correspondence Date
Meeting Material	Meeting Start Date



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Ambiguous Dates

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

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)

DIA RSIDM

Regulatory Submissions, Information, and Document Management Forum

- 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

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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?

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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

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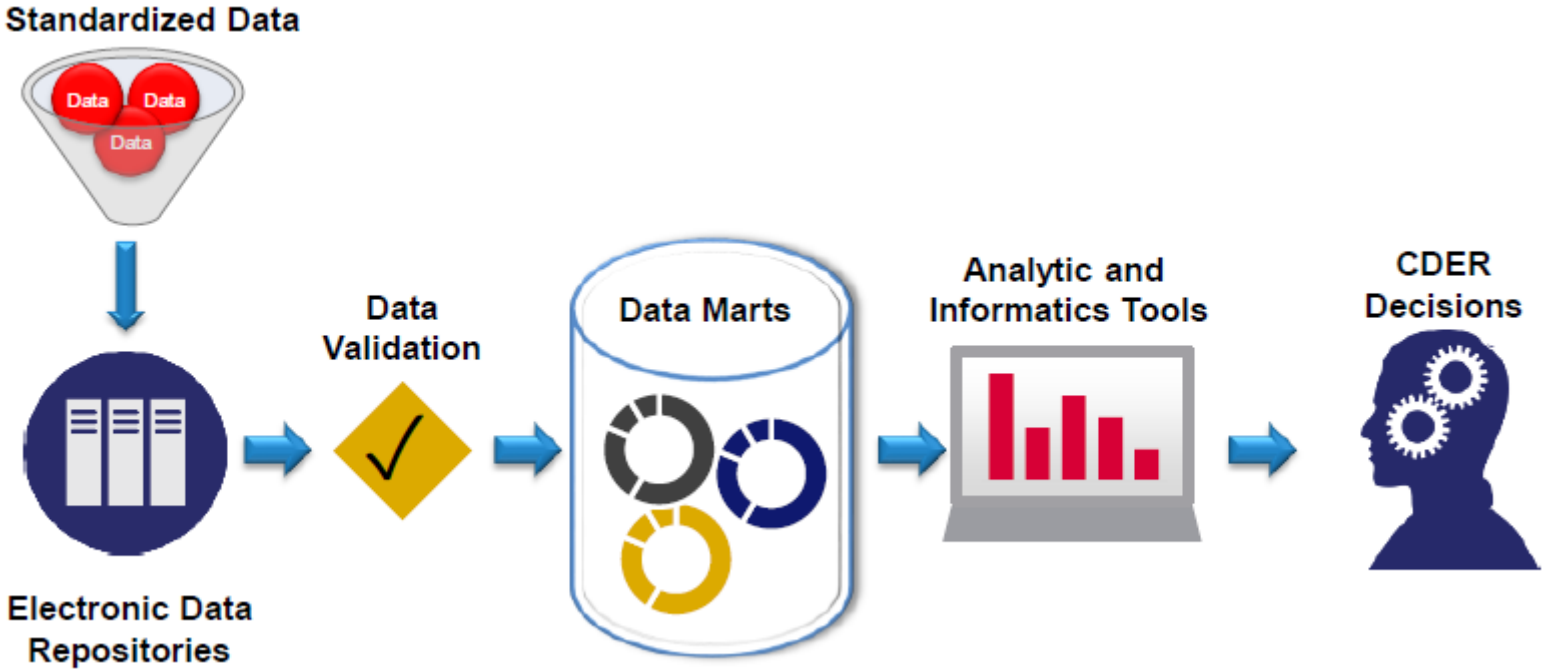
Karin's Highlights

- Data Standards



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Karin's Highlights

Some Submission Standards Will Be Required

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.

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

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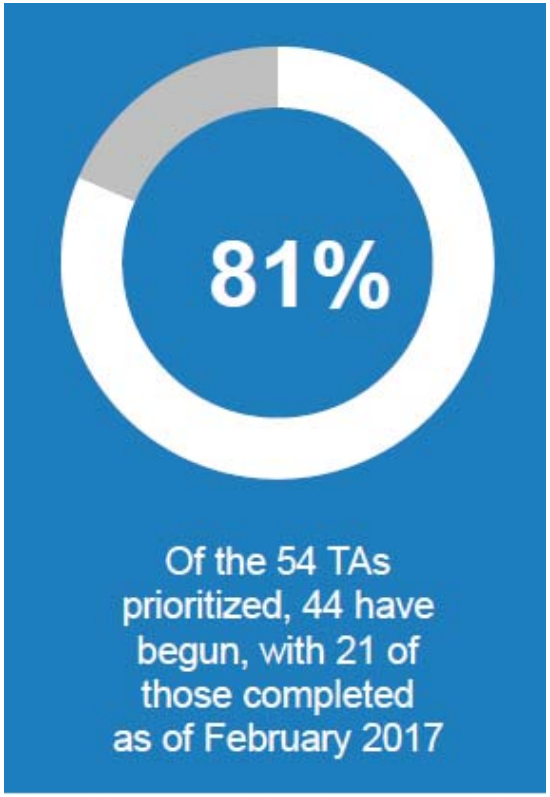
Karin's Highlights

- TA Standards Initiative, Players, Progress



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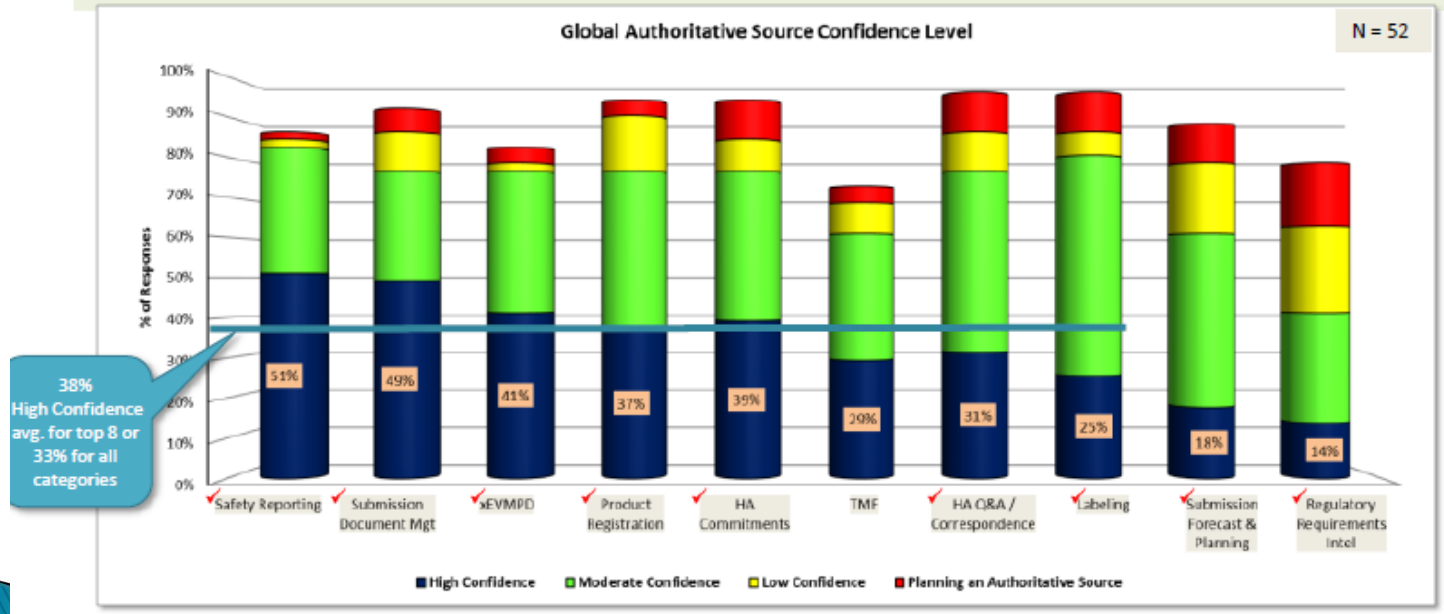
Karin's Highlights

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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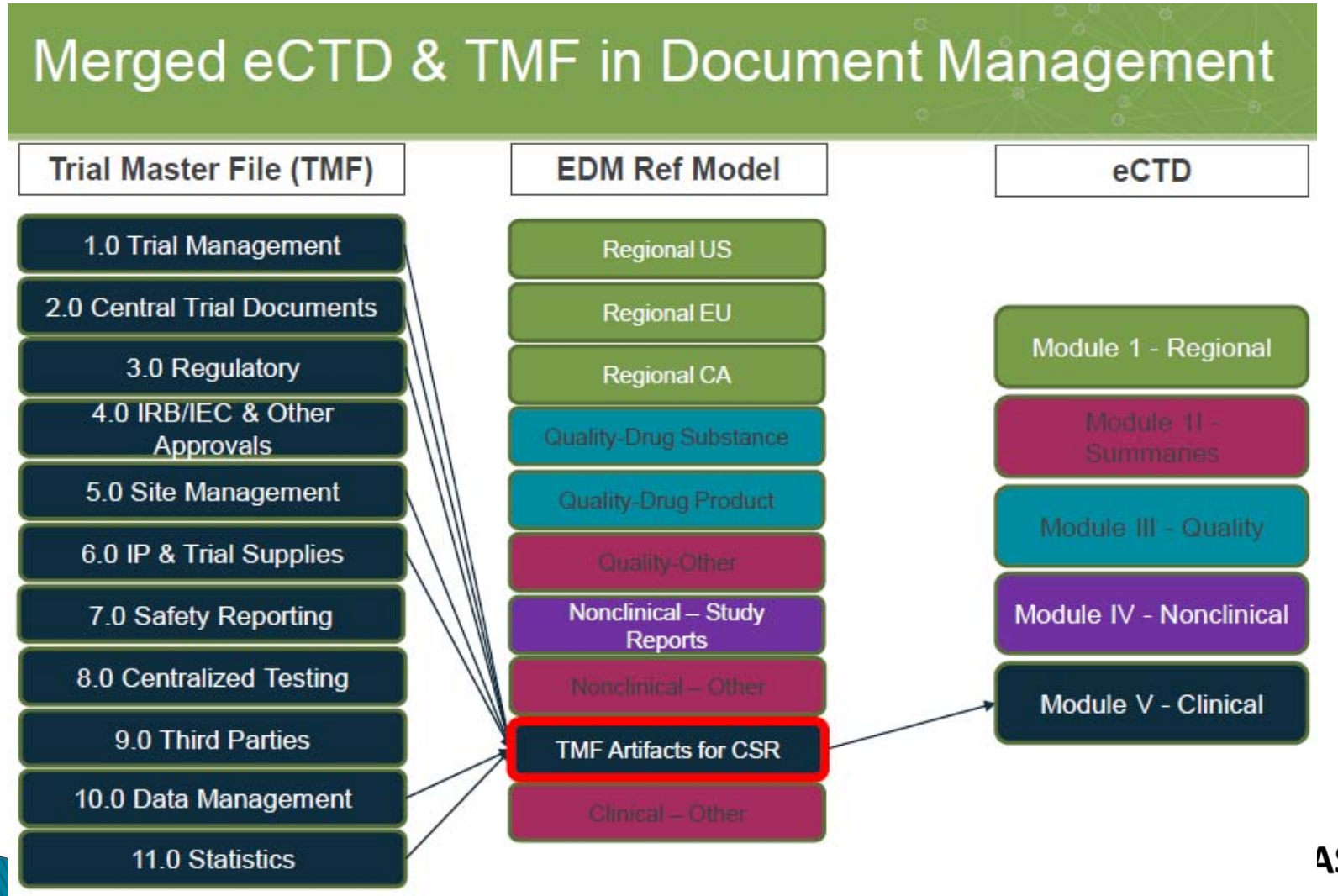
Karin's Highlights



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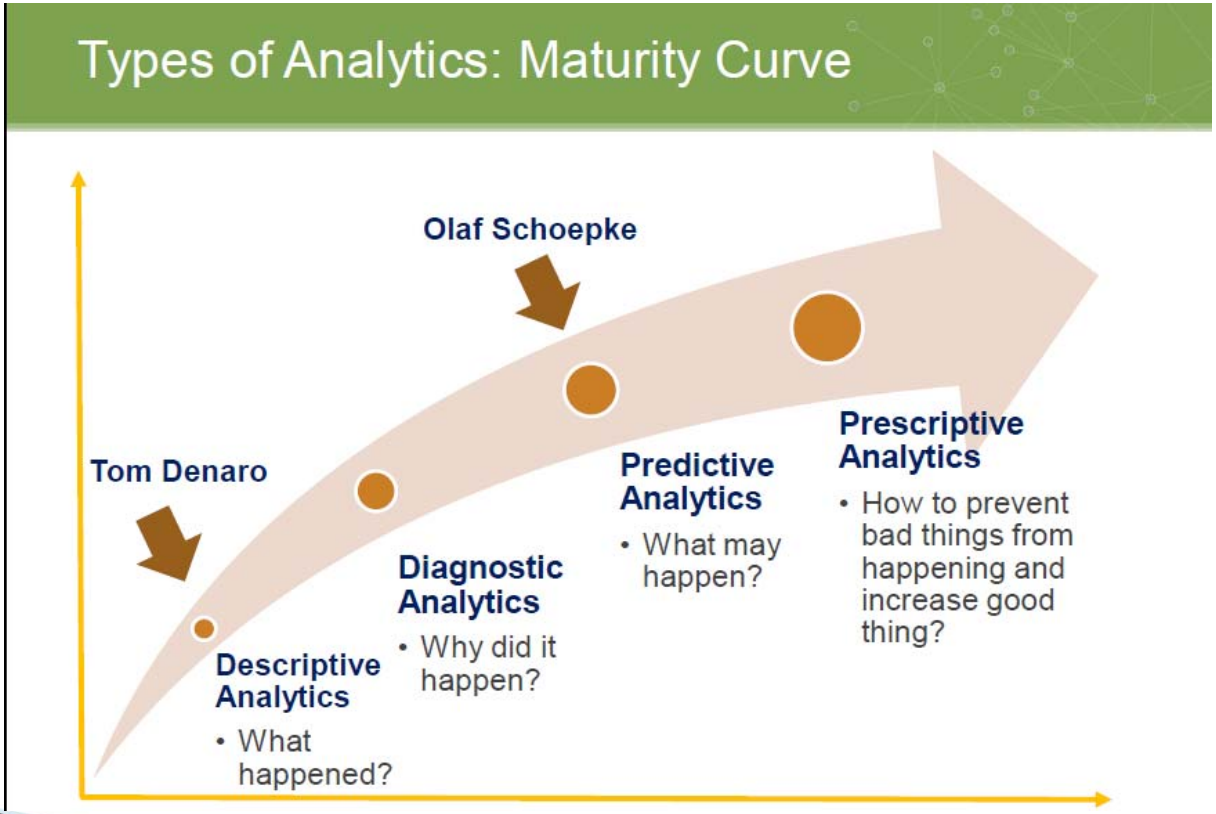
Karin's Highlights

- Analytics
  - Semantic web technologies for text extraction and transformation



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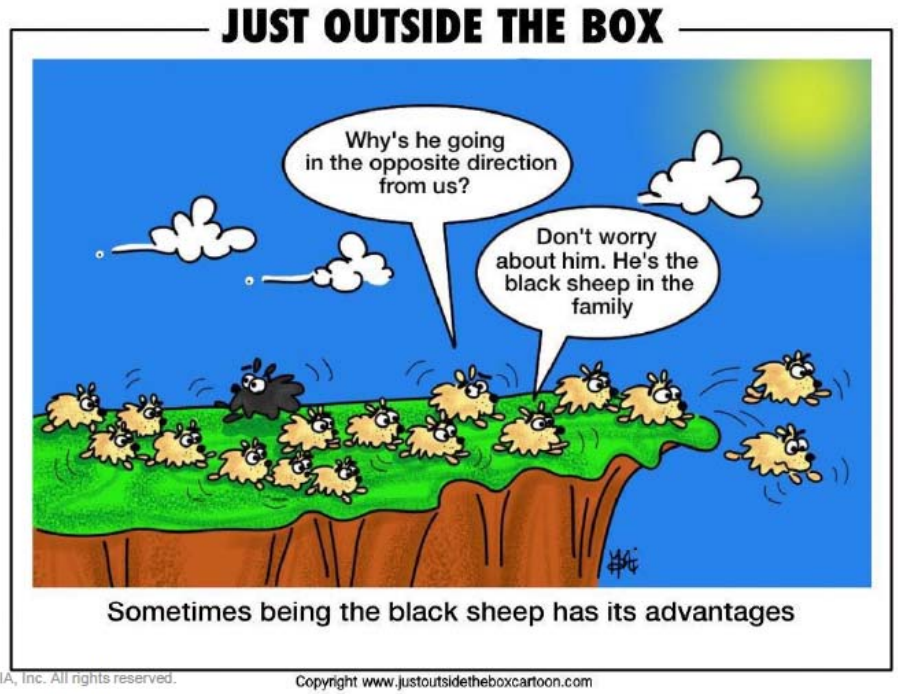
Karin's Highlights

- Best Practices, one-size fits all

Evaluation Process – The Lemming Syndrome



DIA

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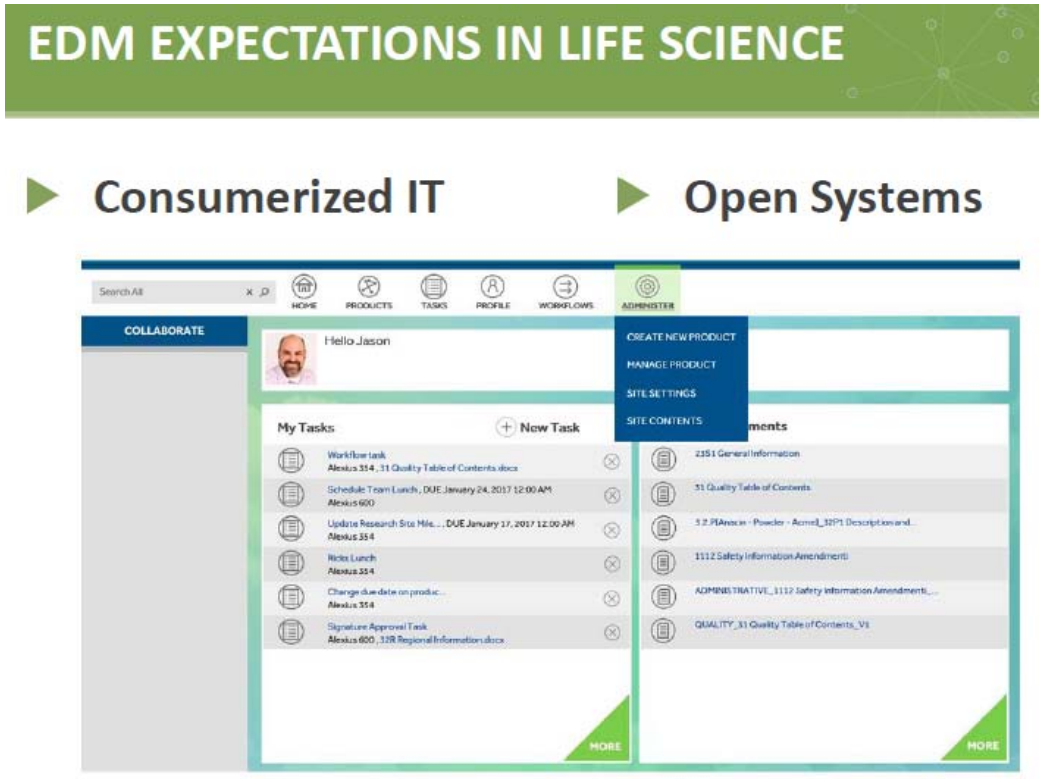
Karin's Highlights

- EDM Future: BYOD, User Centric Design, AI



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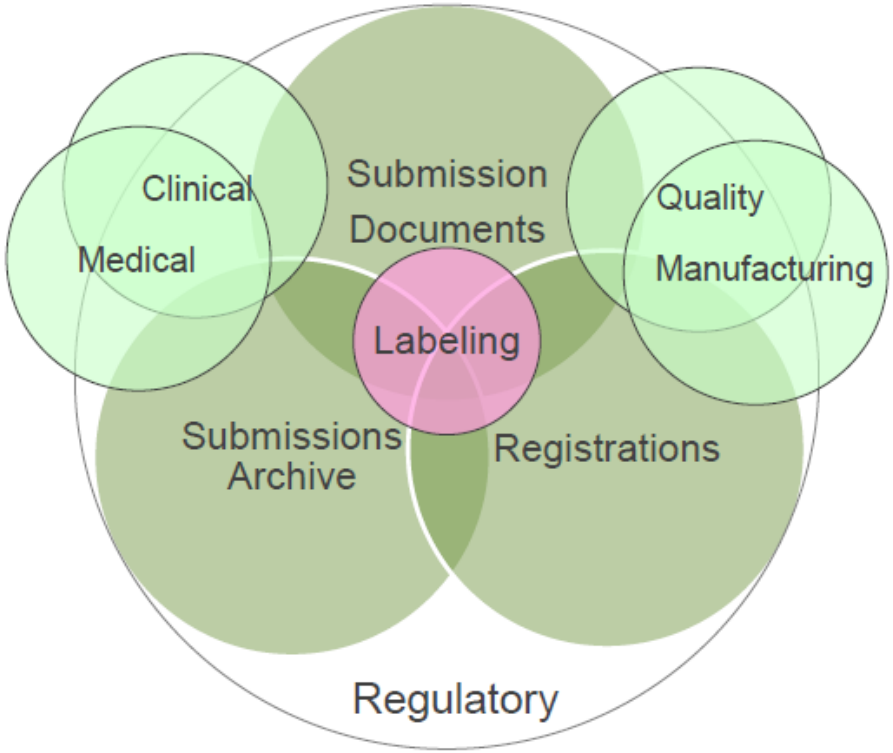
Karin's Highlights

What is RIM?

RIM Suite is the single source of truth



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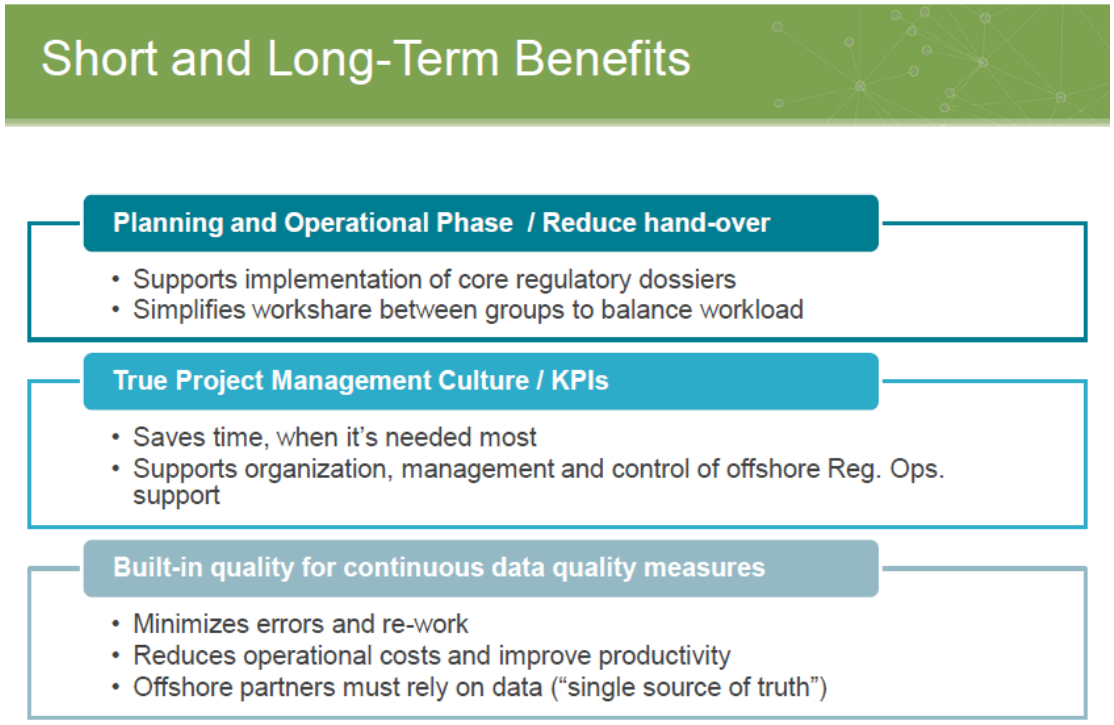
Karin's Highlights

- Integrated Regulatory Information and Submission Management



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Karin's Highlights

- RFP's

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Other Highlights?

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ExL Pharma's 6th US TRIAL MASTER FILE SUMMIT

Ensure TMF Completeness Through SOP Creation, Data Management, Strong Partner Communication and Inspection Readiness

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Co-Chairs

- **Jamie Toth**

Daiichi-Sankyo

- **Eric Rubinson**

Allergan

- **Karen Roy**

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Over 200 Attendees

111 Sponsor Attendees – 57 Companies

28 CRO Attendees – 14 Companies

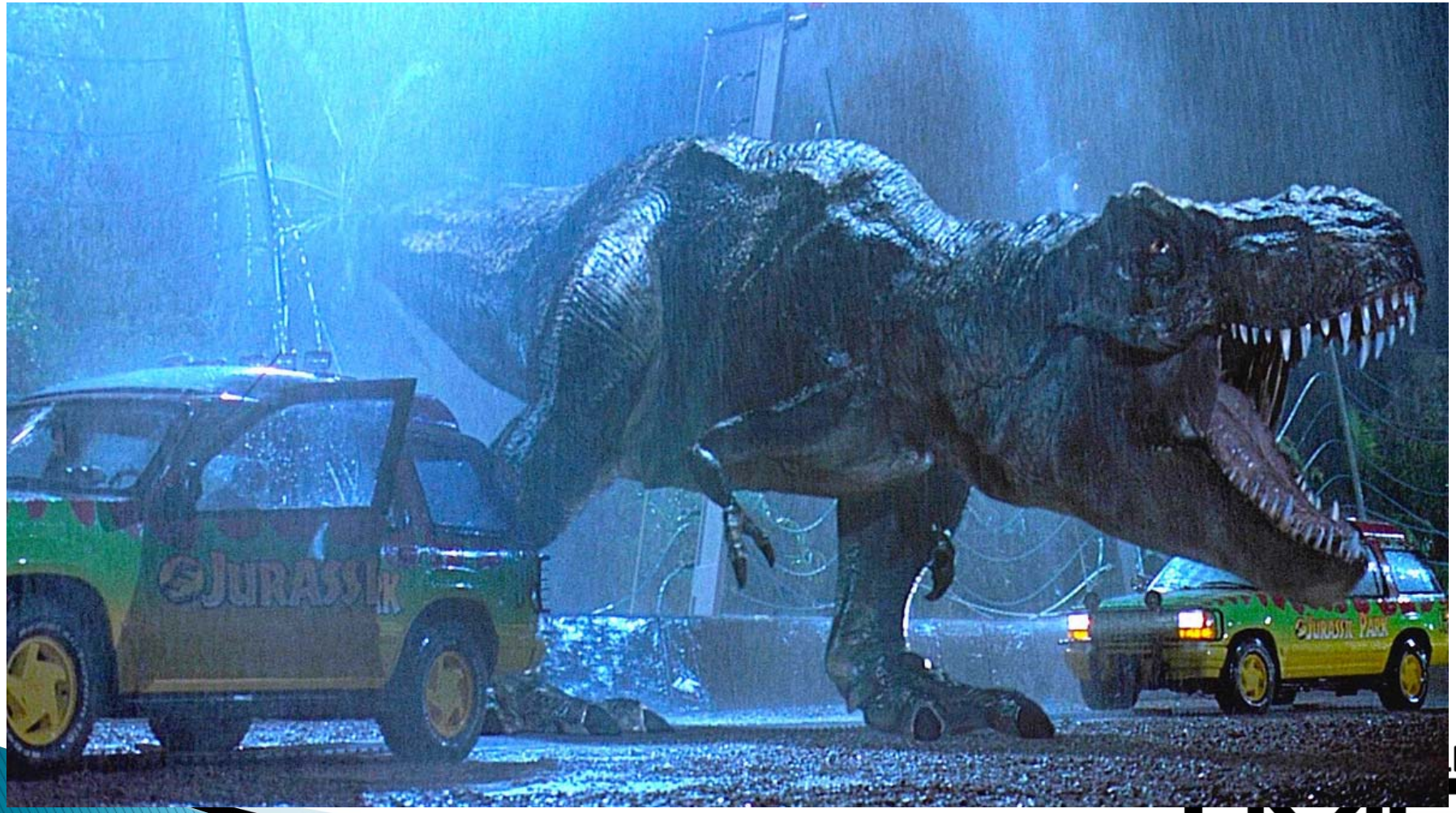
56 Vendor Attendees – 19 Companies

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.

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TMF RM General Meetings

- 24-Apr
- 12-Jun

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QUESTIONS?

Join the TMF Reference Model
Yahoo! Group

http://tmfrefmodel.com/join

- Knowledge sharing
- Networking
- Too Much Fun!

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