
Veeva

How to Build a TMF Strategy to be Inspection-ready

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VERTEX
THE SCIENCE of POSSIBILITY

TMF Process Owner and Clinical Documentation Head

Jason: How do you handle medical records at your office?
Mom: I print it out of <system1>, then I fax it into <system2>, then I classify it in <system3>, then I fax it to Bruce.

Jason: Can <system2> accept electronic documents?
Mom: Geez, I don't know.

Jason: Would you rather just fax it?
Mom: Yeah.

Jason: Why?
Mom: I don't know, but when I'm in Florida I just need to get it done.

Jason: You'll be able to do it, but you don't have to do it the way you do it now.
Mom: I don't know, I don't know this stuff (technology).

Jason: Just so I understand. You get the report electronically, and then you print it, then you fax it into a system, type some information into another system and then you fax it, again, to Bruce? The same report that you originally received electronically?
Mom: <Laughing> Give me a break!

Current Trends and Observations

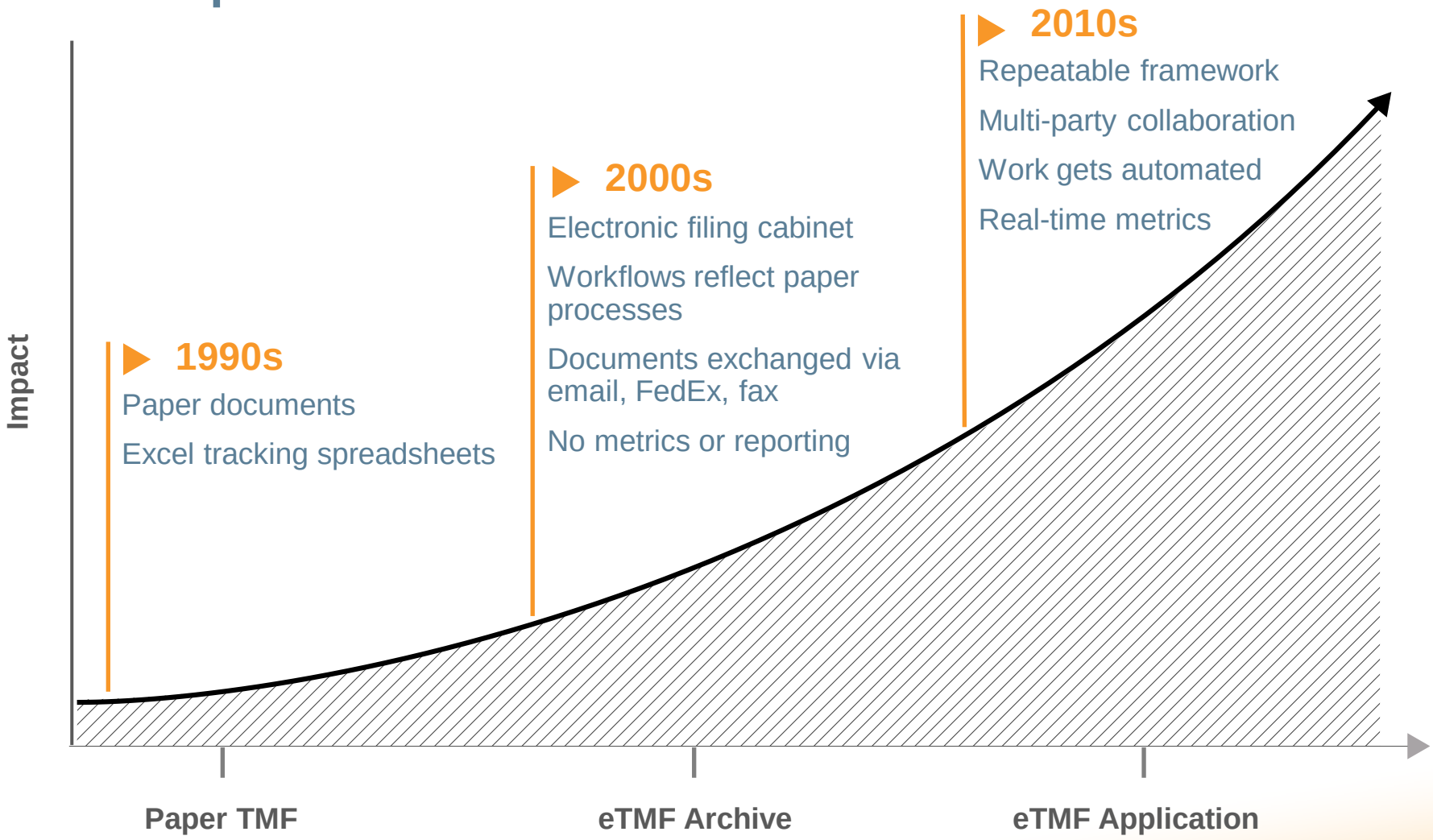
Updated definition of **CRITICAL** GCP inspection finding to include **incomplete TMFs**

35%

of inspections over the past year resulted in **extra days** to complete inspections where difficulties ensuring the TMF is complete and readily available.

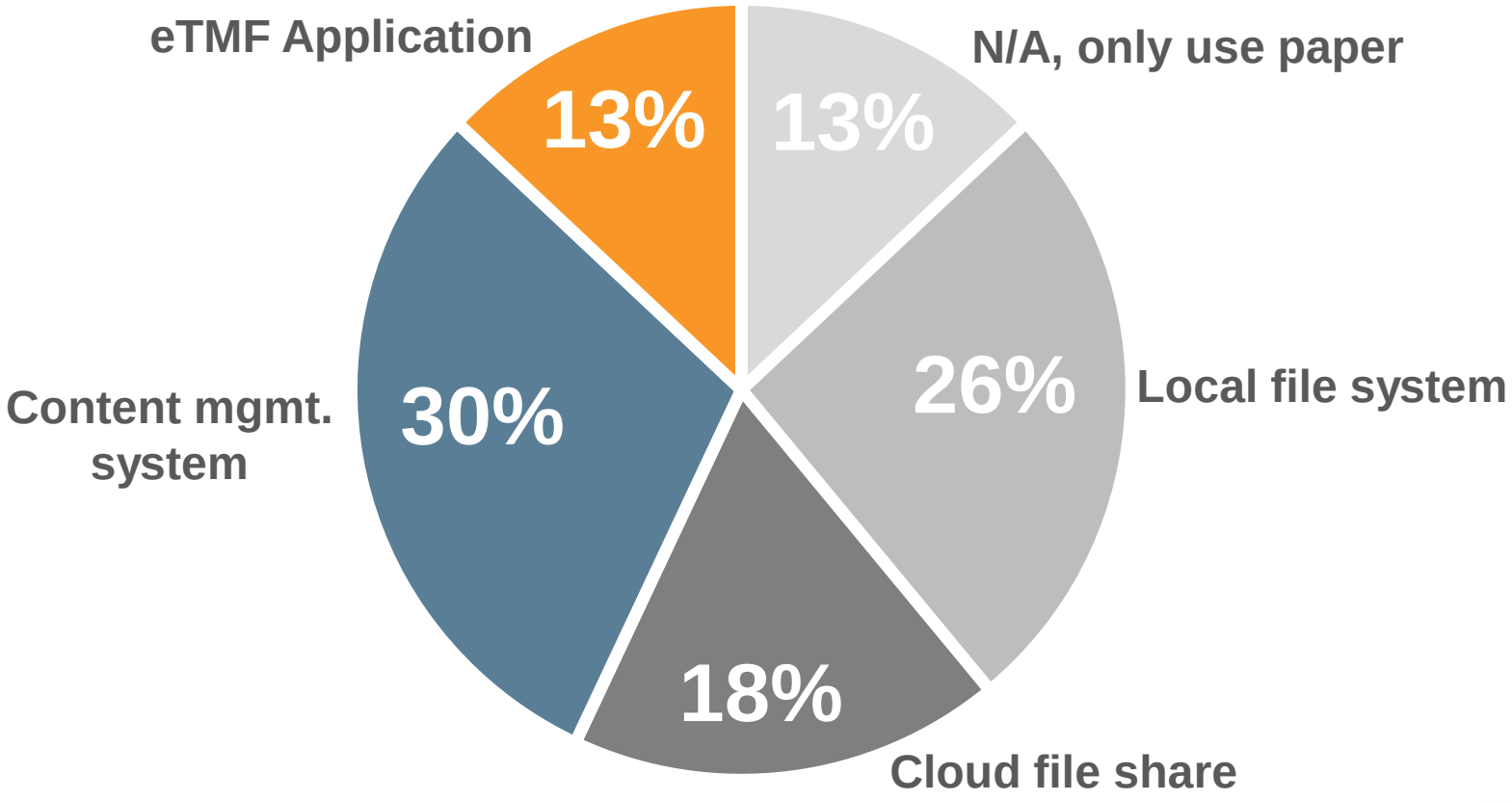
MHRA - April 2014

Paper Legacy Holds Back Productivity & Inspection Readiness



Significant Opportunity for the Industry

Only half of electronic models use eTMFs with advanced process management



Source: *Veeva 2015 Paperless TMF Survey*

What type of eTMF solution did you most recently use? (n=135, Q.9) ***Sponsor company responses only.***

Impact of Multiple Divergent Systems on Compliance

Multiple content copies

Greater compliance risk

More time spent on:

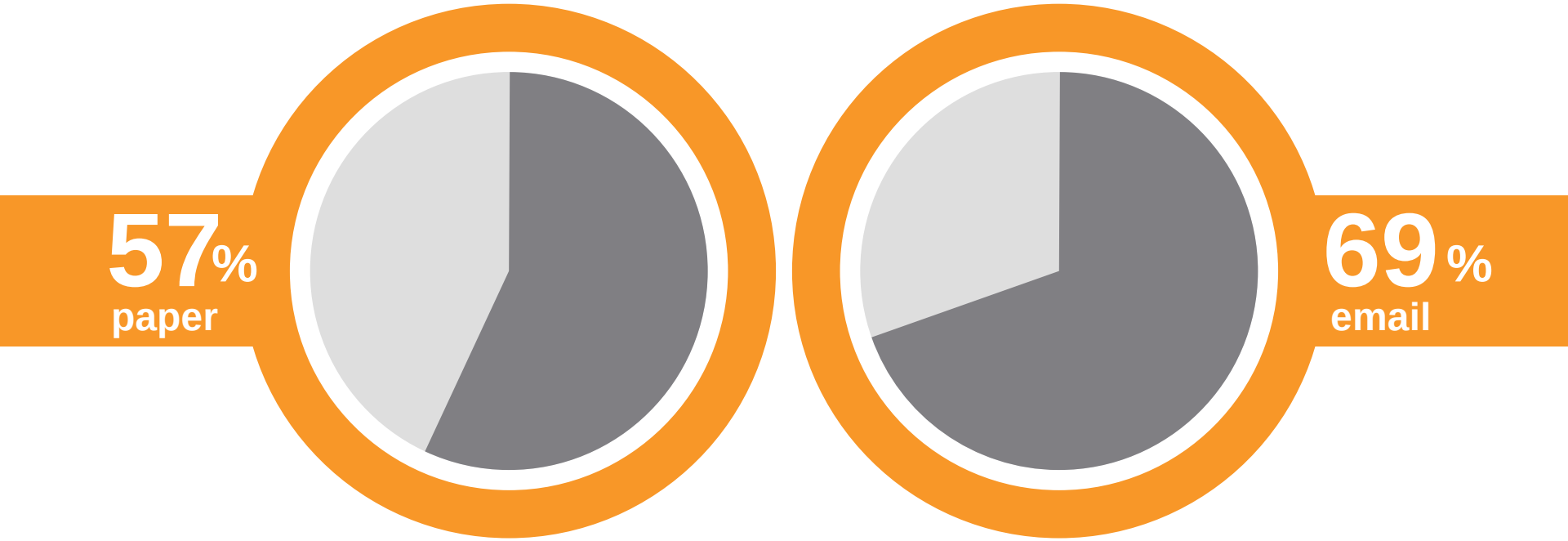
- Searching
- Reporting
- Updating
- Preparing for audits

Increased costs

Extended timelines

Manual Transactional Processes Persist

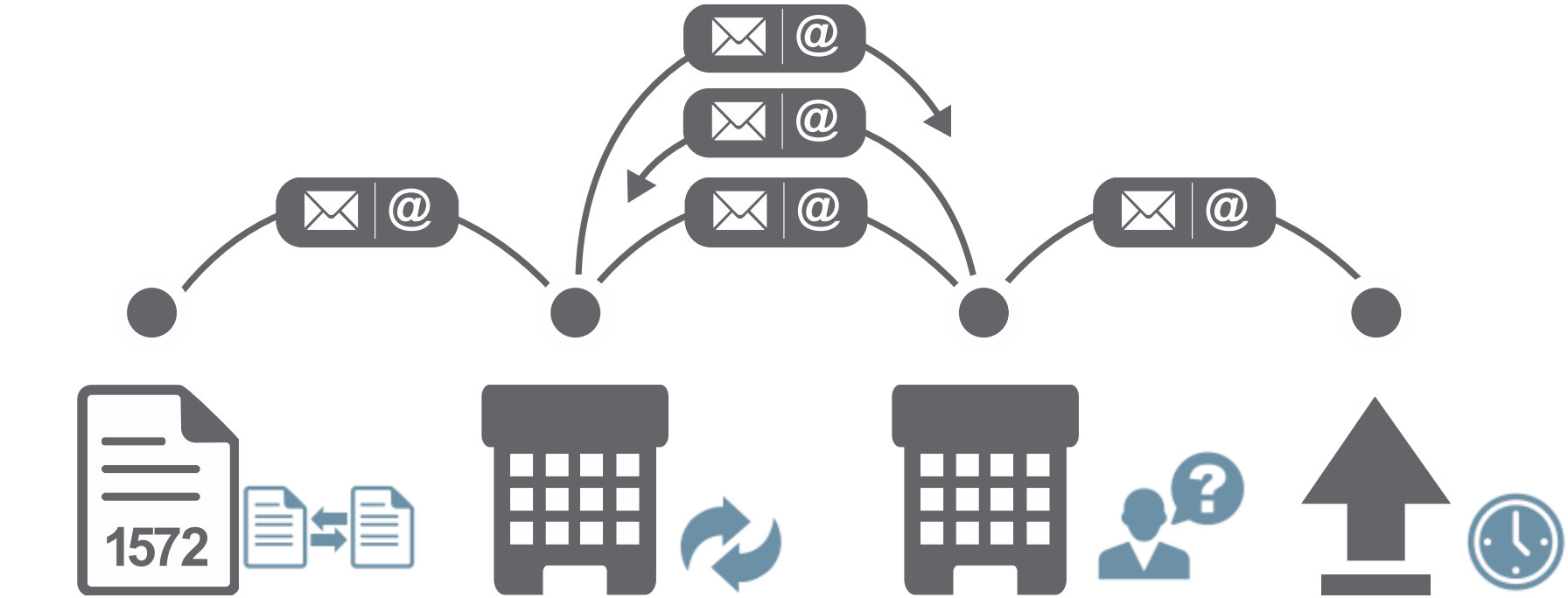
Manual exchange of TMF documents between sponsors and CROs



Source: *Veeva 2015 Paperless TMF Survey*

Traditional eTMF Archive Model

Electronic filing cabinet, workflows reflect paper processes, documents exchanged via email, FedEx and fax, limited reporting

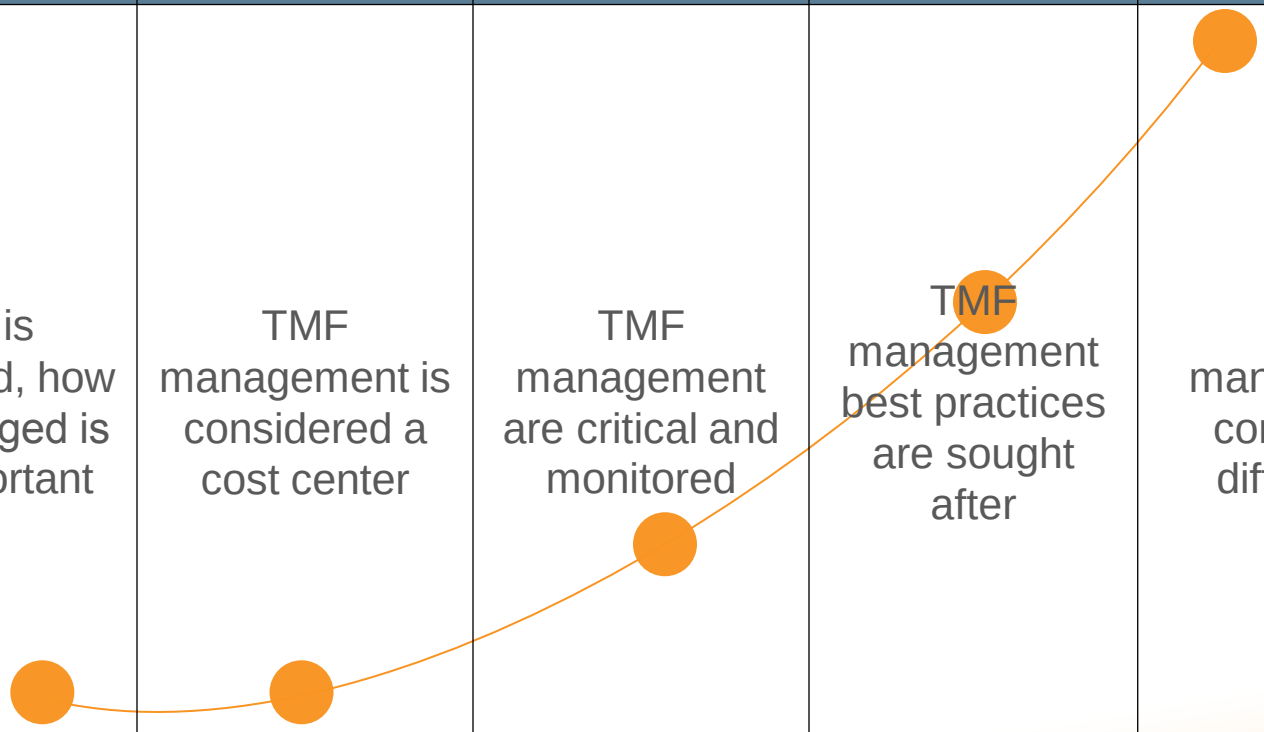


Controls to Ensure an Inspection Ready TMF

What is the TMF Maturity Model?

- **A model to evaluate TMF maturity levels of a life sciences company**

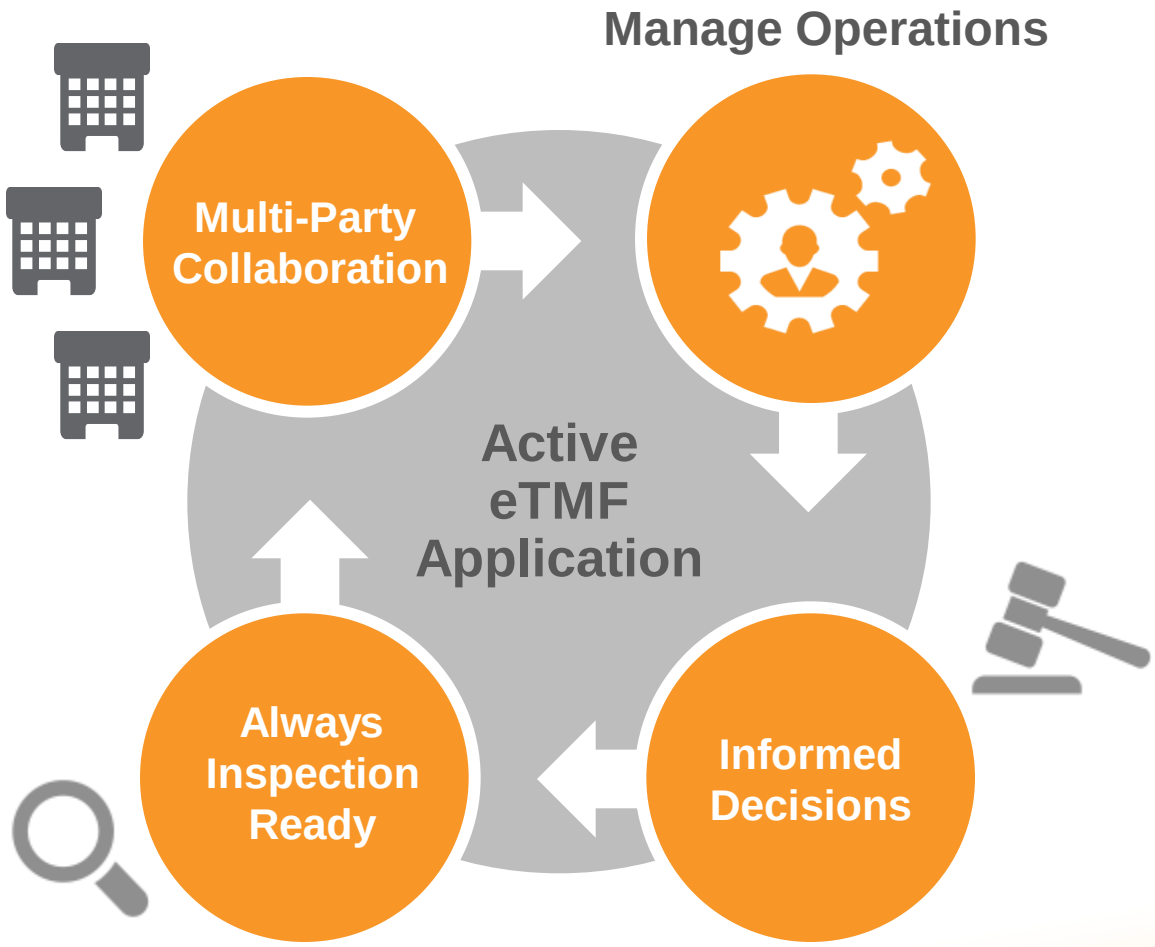
1. Required	2. Managed	3. Efficient	4. Optimized	5. Differentiator
TMF is mandated, how it's managed is not important	TMF management is considered a cost center	TMF management are critical and monitored	TMF management best practices are sought after	TMF management is considered a differentiator



How Does the TMF Maturity Model help our Clients?

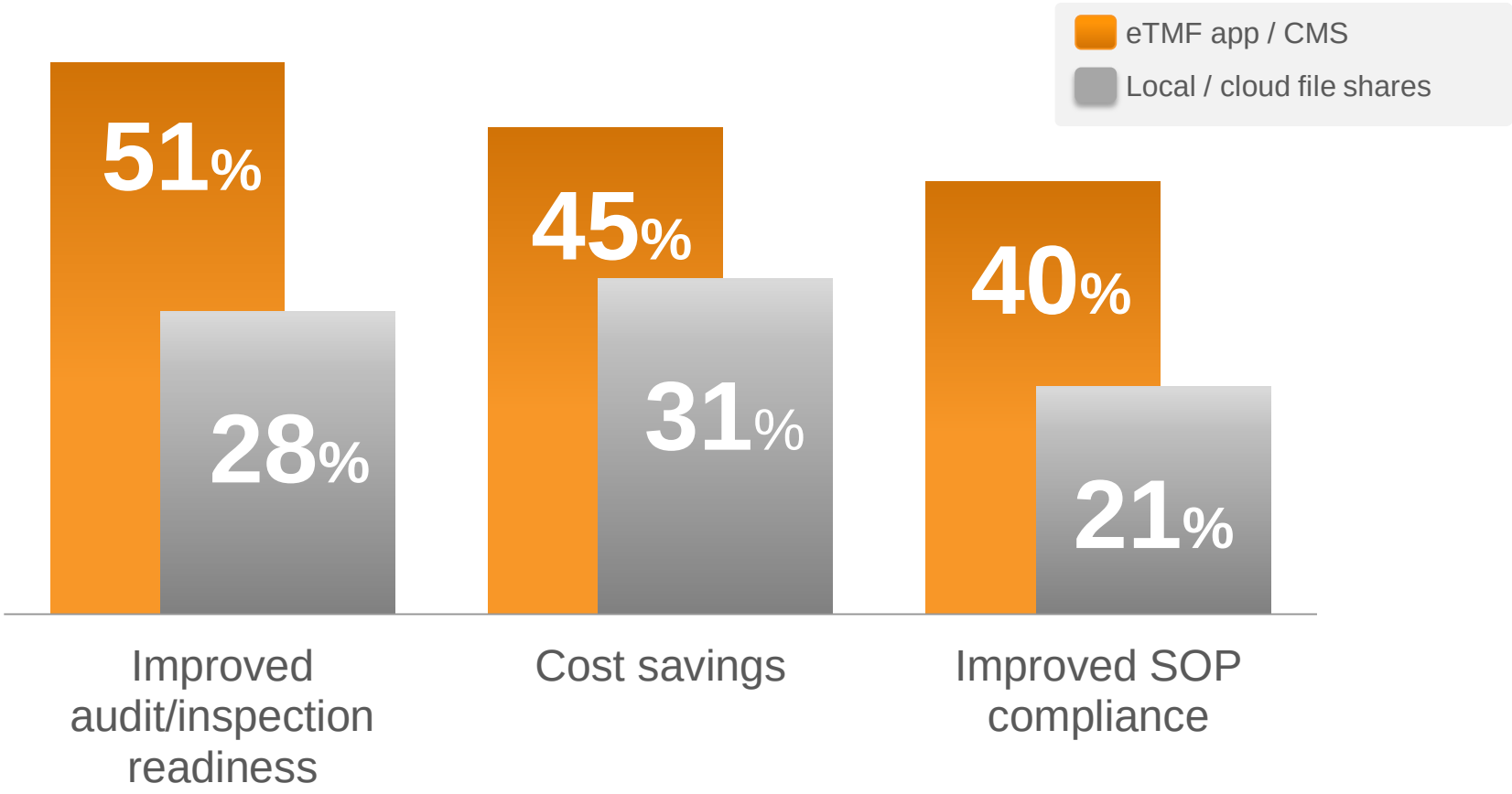
- **Path to Improvement**
  - Evaluate current state of TMF in the organization
  - Provide industry benchmarking
  - Determine the desired state
  - Understand capabilities required to reach the desired state
  - Provide a high-level roadmap to get there
- **Business Cases**
  - Illustrate qualitative benefits of good TMF management
  - Inform business case and quantitative ROI analysis

Leverage Technology to Bring Together Sponsors, CROs, and Sites



Benefits Achieved by Type of eTMF

Systems with advanced process management



Source: *Veeva 2015 Paperless TMF Survey*

What benefits were achieved with your organization's implementation of the eTMF solution specified in Question 9? (Q.10).

Conclusion

Creating an Inspection Ready Operating Model

Three major changes needed

1

Evaluate all aspects of TMF operations

2

Push towards single source of truth environment

3

Shift from passive eTMF Archive to active eTMF Application

Halloran

You Drive Innovation.
We'll Navigate.

Agenda

- Learning from Lessons: A Case Study to Inform What Not to do!
- Getting Prepared
  - What companies need to do to be ready
  - What the process is of getting ready
- Key lessons learned from IR projects
- How to work collaboratively with external parties to be prepared

Lessons Learned: Case Studies in Inspection Readiness

Agenda

- The Sponsor Composite
- Preparations
- Five Whos and a What
- In Conclusion

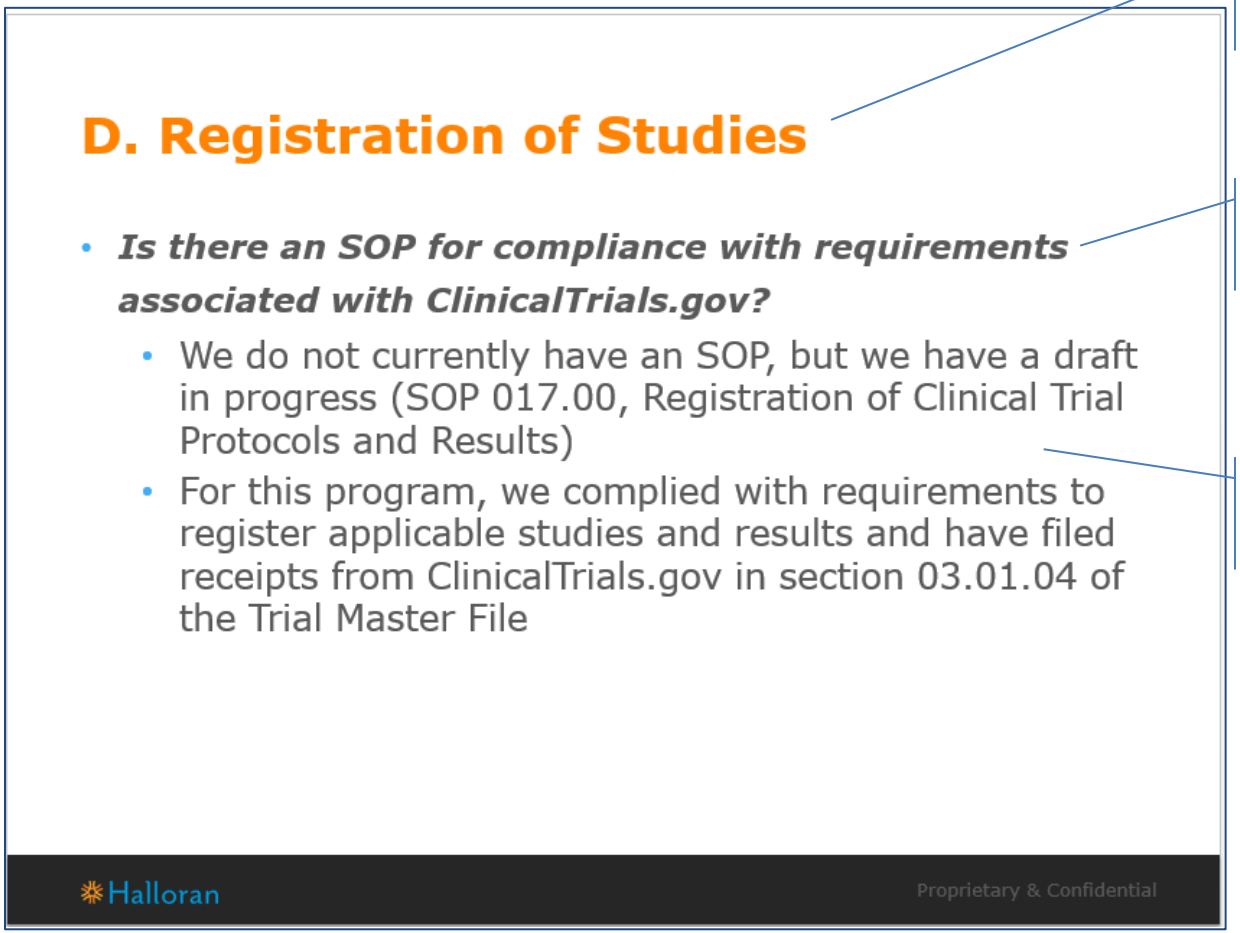
Sponsor Composite

- Small program
- Multiple vendors
- High turnover
- Late start

Preparations

- Reviewed pivotal Trial Master File + supportive studies
- Developed storyboard to capture history of program
- Trained inspection team on logistics
- Coached inspection team to respond to questions using storyboard
- Rehearsed inspection logistics

Storyboard



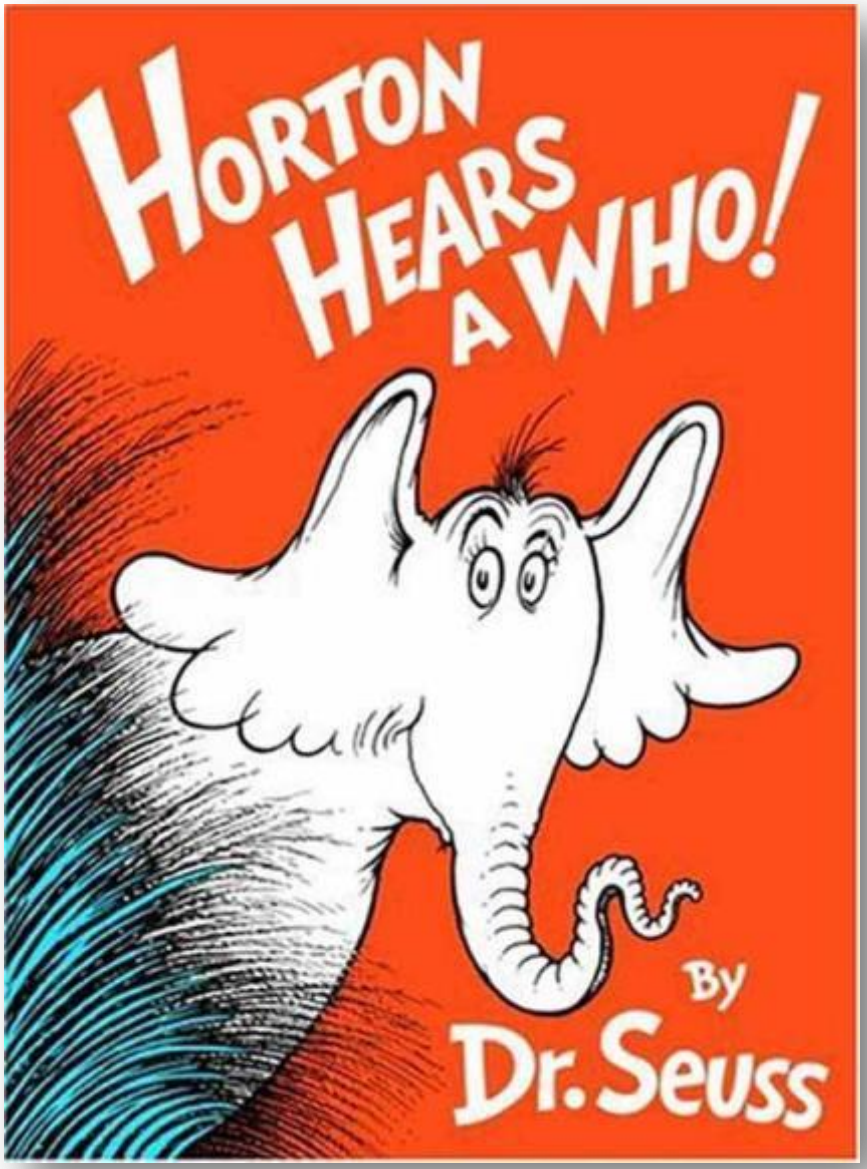
BIMO section

BIMO question

Facts and supporting documentation to be used in the question response

Five Whos and a What

- Who's who?
- Whose SOPs?
- Who's minding the store?
- Who's got the TMF?
- What's missing?
- Who is the FDA investigator?



Who's Who?

- Keep track of start/stop dates and responsibilities as you go along, rather than trying to reconstruct at the end:
  - Study team
  - Vendors
  - Site monitors
  - Systems

Whose SOPs?

- Define a mechanism for documenting whose SOPs are followed for each activity

Who's Minding the Store?

- Be prepared to answer questions about how the sponsor oversaw the vendor's work, including
  - Oversight plan
  - Evidence of oversight/adherence to plan
- (How do you know the vendor did a good job?)

Who's Got the TMF?

- Using the DIA TMF Reference Model, map out
  - The location of each document type ("artifact") during the study
  - The rendition (paper or electronic) of each document
- Loop in leaders from all locations that maintain TMF documents
  - QC documents in all locations
  - Practice retrieving documents from all locations

What's Missing?

- To facilitate TMF review, maintain trackers of documents that have multiple revisions, e.g.,
  - Protocol
  - Financial disclosures
  - CVs
  - Medical Licenses
  - 1572s, etc.
- Check documents against key stop/start dates to identify gaps
- Look for documentation of substantive issues in TMF

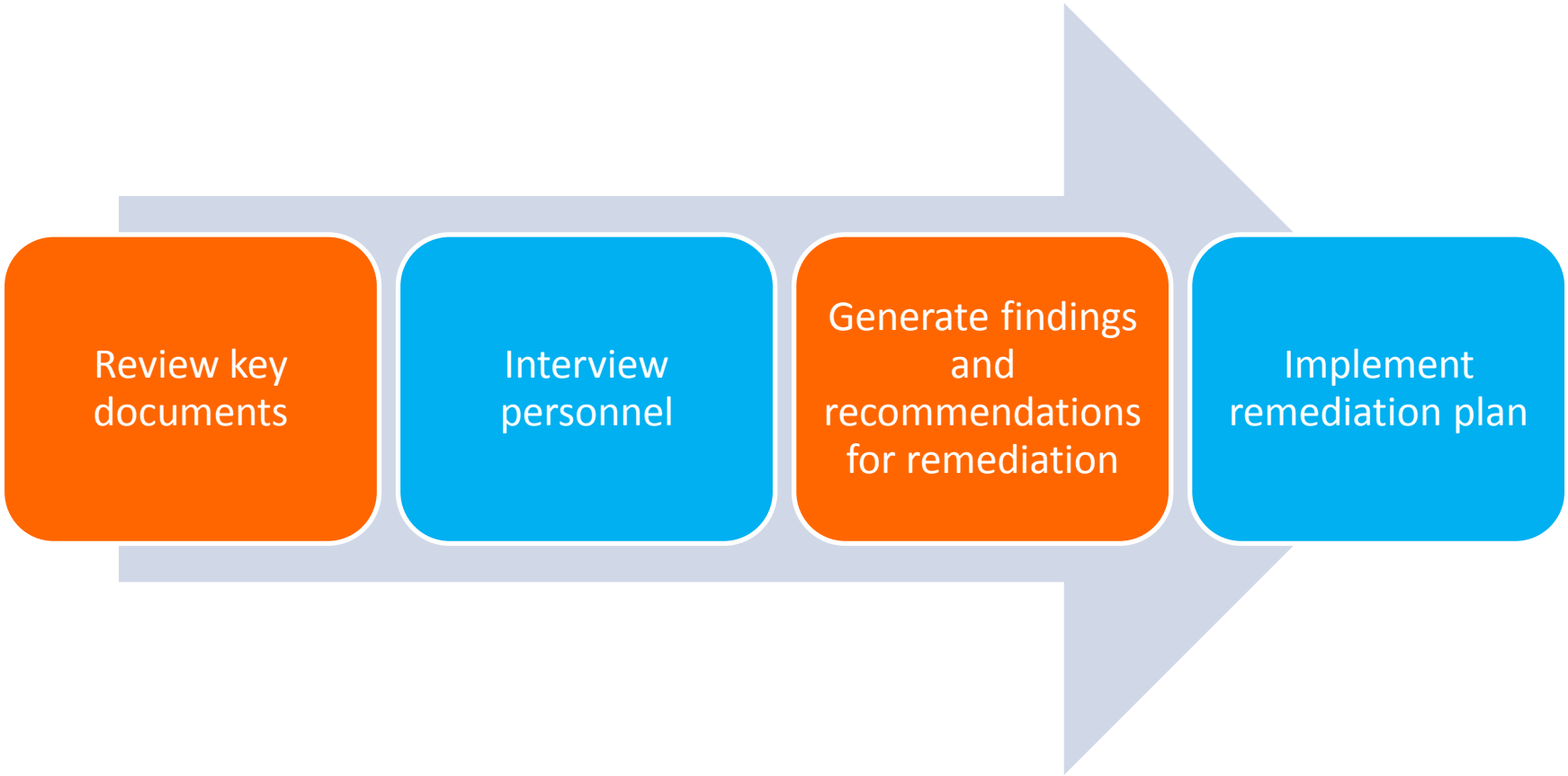
Who's the FDA Investigator?

- Once you have a name, consult Google
  - Background
  - Typical inspection assignments
  - Experience with clinical trials

A Stitch in Time Saves…….

Inspection Readiness Activities

Inspection Readiness Approach



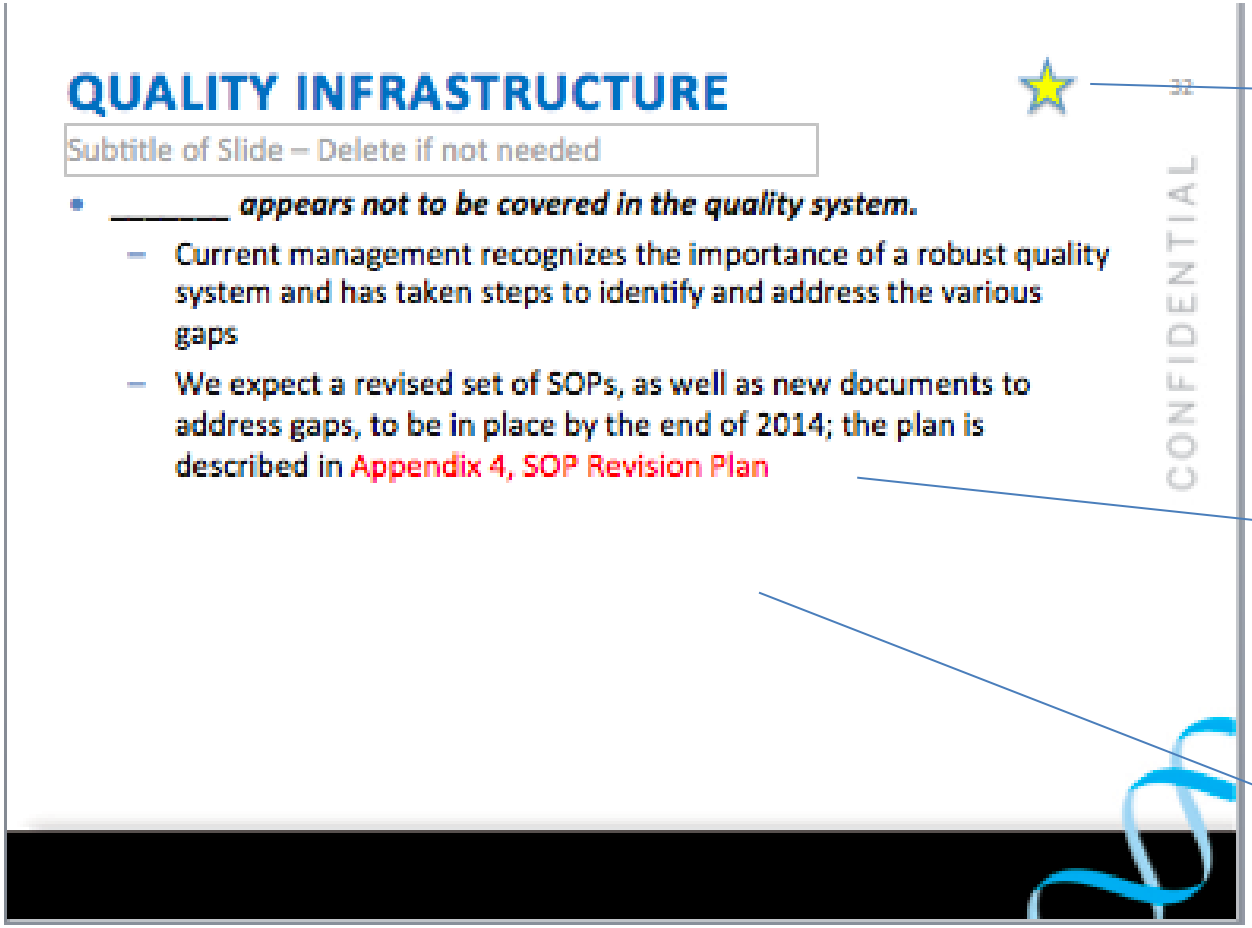
Remediation Activities

- Locate missing documents
- Identify SOPs in effect for each activity
- Develop “storyboard” to capture narrative history of the program
- Train inspection team on SOPs, Trial Master File, and storyboard
- Coach inspection team on how to respond to questions

Storyboard

- Provides answers to questions on BIMO CPM checklist
- Provides context
- Points to supporting documentation
- Highlights gaps to remediate
- Results in a document that is readily used to train the team

Storyboard structure



Indicates potential substantive issue; otherwise, it is a typical BIMO inspection guideline question

Appendix that is not currently part of the Trial Master File

Facts for responding to the question

Organization of the Story

- General Topics
- Organization and Personnel
- Quality Assurance
- Registration of Studies
- Key Clinical Operations Tasks
- Test Articles
- Safety/AE Reporting
- Data Collection and Handling
- Record Retention
- Electronic Systems

Sponsor X Organization

- ***What process was followed to ensure consistent transfer of responsibilities, given the significant turnover? Is there an SOP governing project transitions?***
  - A standard process is followed:
    - A transition meeting is held between the ongoing/incoming employee
    - The incoming employee is given access to all study communications
    - The incoming employee receives required training on SOPs, systems, and the protocol
    - The incoming employee reviews key plans and other study-specific documentation
    - The incoming employee is added to key meetings and begins to take over responsibilities under the supervision of his/her manager

Pivotal (YXZ 19)Study TOROs

- ***Were Transfers of Regulatory Obligation (TORO) appropriately completed and filed for YXZ-19?***
  - The original TORO, dated 18 Dec 2008, documents transfer of obligations from Biotech T to various vendors
  - An updated TORO, filed 19 January 2011 and submitted with _____, transfers/confirms transfer of the following obligations:
    - Study management, site monitoring and management from CRO1 to Sponsor X
    - ECG interpretation /analysis to CRO2
    - PK sample management and storage/PK analysis to CRO3
    - Independent Radiology Review to BioClinica (formerly RadPharm)
    - Central Pathology Review to BioClinica (formerly Radpharm)
    - Drug distribution and inventory for US to Almac
    - Drug distribution/inventory for EU, Canada, and ROW to Klifo
    - Oversight of drug distribution/inventory vendors to Sponsor X
  - In addition to the TOROs, Biotech T and Sponsor X completed a Delegation of Sponsorship Responsibilities on 13 April 2012

D. Registration of Studies

- ***Is there an SOP for compliance with requirements associated with ClinicalTrials.gov?***
  - We do not currently have an SOP, but we have a draft in progress (SOP 017.00, Registration of Clinical Trial Protocols and Results)
  - For this program, we complied with requirements to register applicable studies and results and have filed receipts from ClinicalTrials.gov in section 03.01.04 of the Trial Master File

Inspection Readiness on Multiple Fronts

Situation: A medium-sized pharma requested an inspection readiness assessment for a clinical program for which an NDA had recently been submitted for an expedited review. The program had seen almost 100% turnover – sponsor, CROs, and team members.

What We Did to Prepare for Inspection:

- Reviewed TMFs and interviewed team members, highlighting significant gaps in the quality system, TMF, and team's familiarity with the program
- Developed a storyboard to capture institutional memory and trained the inspection team to respond to BIMO questions consistently
- Deployed a team to obtain missing TMF documents and support the sponsor during the FDA inspection
- Redesigned the quality system to address gaps

Value: The Inspection received no 483s or Warning Letters. The product was approved and is now available for patients.

How Will eTMF Change Inspection Readiness Approach?

Impact of eTMF on Inspection Readiness

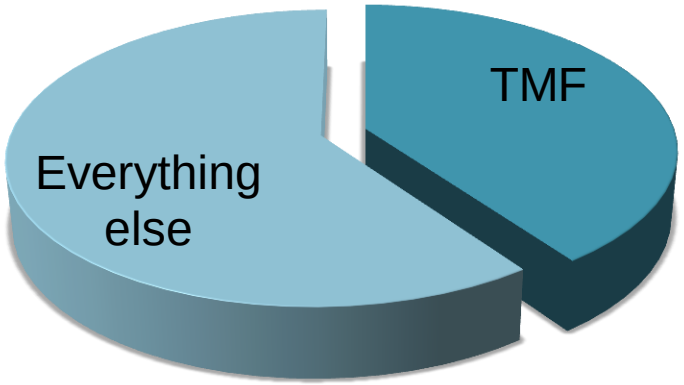
- More clarity on scope of TMF
- Reduces # of repositories
- Reduces risk of non-validated repositories
- Enables frequent remote reviews of TMF documents contributed by a variety of study team members and vendors
  - Frequent: Address quality issues while "fresh"
  - Remote: Save time and $ on travel for TMF audits
- Enables reporting of expected vs. uploaded documents

Working Collaboratively with External Parties

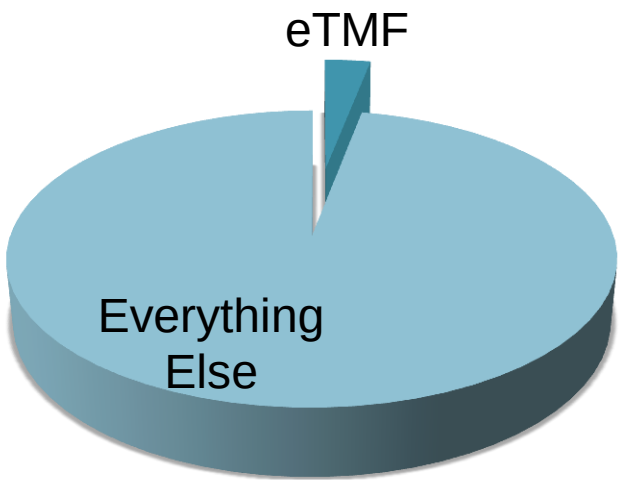
- Set clear expectations with vendors
- Build in ongoing QC vs. QA to avoid the firefighting
- Get your external view on potential gaps early so remediation can occur before the inspection
- Best practices can often be learned through the objective viewpoints of external consultants who prepare you for the inspection

In Conclusion

Before eTMF



After eTMF



Spend the time on preparing your team rather than searching for missing information!

ENSURE AN INSPECTION-READY TMF EVERY DAY

CLINICAL ROUNDTABLE BREAKFAST:

SPONSOR PERSPECTIVE

APRIL 30, 2015

SAGE THERAPEUTICS

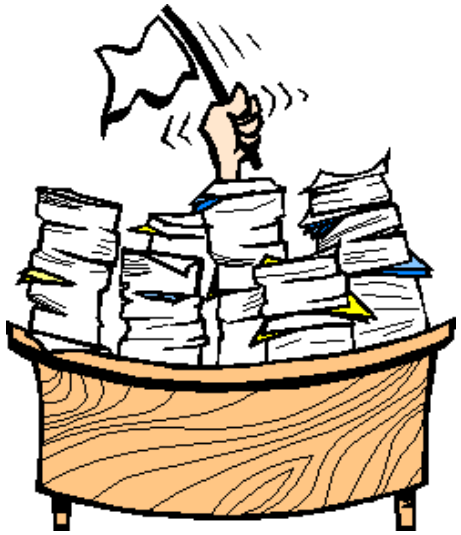
- Neuroscience-focused company discovering medicines to treat life-threatening, rare CNS disorders.
- Mission: to improve the lives of patients with nervous system disorders by discovering, developing, and delivering new medicines
- Growing company (~30 employees currently) founded in 2011
- Our lead program, SAGE-547, is in clinical development for super-refractory status epilepticus (SRSE)
- Currently starting Phase 3 studies

THREE TMF OPTIONS

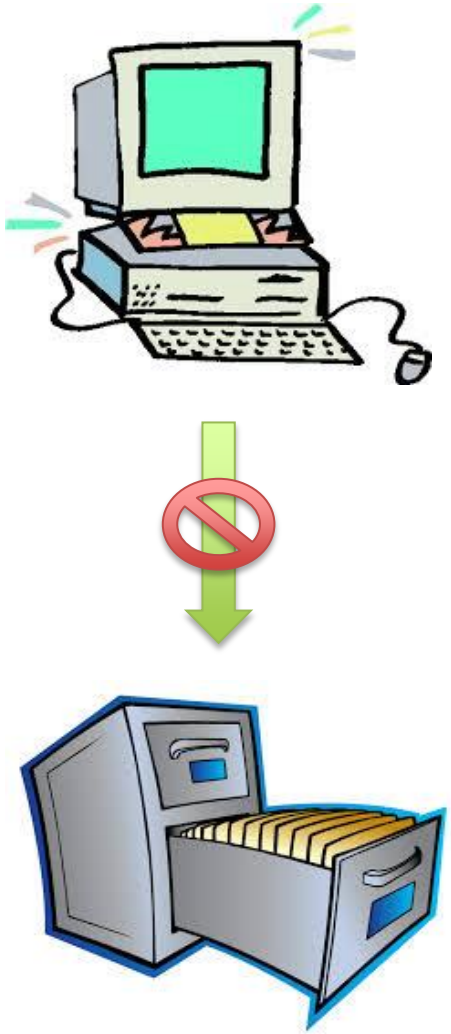
- Paper TMF
- “Hybrid” TMF (Paper/Electronic)
- Electronic TMF

PAPER TMF

- Infrastructure: Fire-Proof Room/ Cabinets
- Collection of Documents
  - Sites emailing/ mailing
  - CRAs collecting during monitoring visits
- Ongoing Reconciliation: Sponsor files vs. CRO files
- Archiving: Shipped from CRO to Sponsor, Long-term Storage
- Auditing for inspection readiness



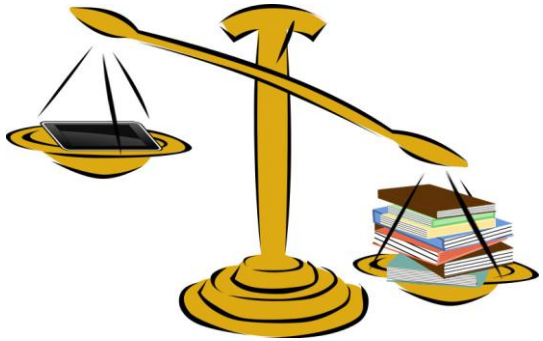
“HYBRID” TMF (PAPER/ELECTRONIC)



- Box, SharePoint or other file sharing
- Allows more team members to have access to document
- Still need to maintain paper TMF
- Many documents are scanned or sent electronically, but never printed and filed in the TMF
- Challenges of reconciliation

ELECTRONIC TMF

- Overall vision for the company, planning for success
- Critical to conducting clinical trials in the most efficient way possible
- Standardized structure
- Facilitate submission of documents from sites
- Global access to study documents by all team members
- Ensuring inspection readiness at all times
- Overall savings of time and resources



ELECTRONIC TMF IMPLEMENTATION AND MIGRATION STRATEGY

- 5-week implementation
- Small core group responsible for making decisions
- Utilized majority of the standard features
- Minimal process changes due to early implementation
- Migration of existing studies (~3,500 documents)
- Developed processes during migration
- Dedicated team for migration

SUMMARY

- Valuable to implements as early as possible
- Critical to streaming clinical development especially for smaller companies
- Investing now, saves both time and resources later
- Time preparing for inspections will be spent with the team and not on the TMF
- Additional benefits, such as to due diligence activities

QUESTIONS

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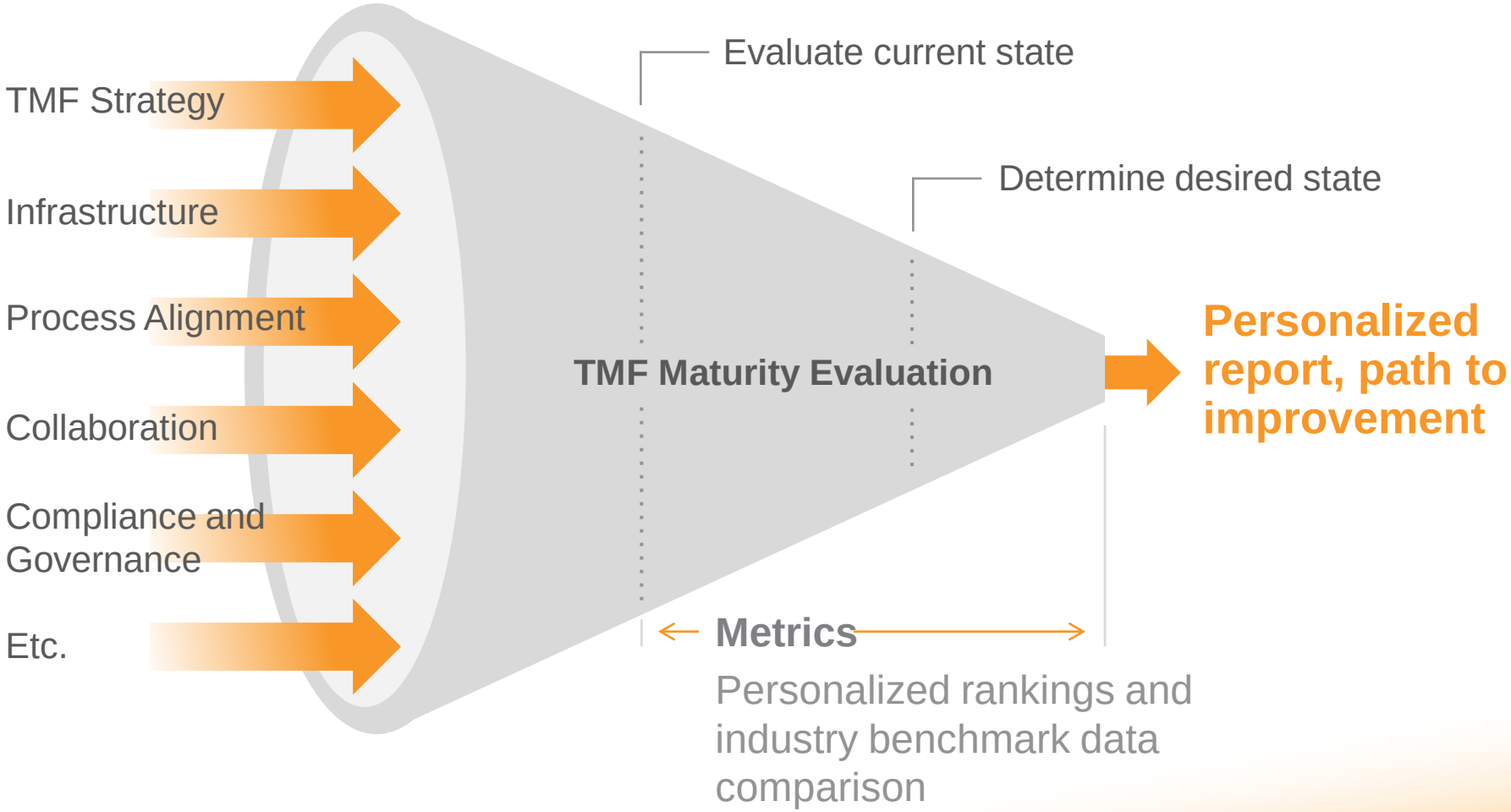
Thank You

Take the Veeva TMF Maturity Evaluation

Contact Jason Methia at jason.methia@veeva.com to schedule a meeting

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