Reducing the eTMF Operational Burden Using Risk-Based Approaches

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Agenda

+ Health Authority Expectations
+ The QC Burden – In Numbers
+ Risk Proportionate Approaches to TMF
+ Intelligent Use of Sampling
+ Eliminating QC Steps that Don’t Add Value
+ Summary and Checklist
Contributing Factors

- Failure to fully document and perform effective QC checks on documents uploaded into eTMF
  - The result being that inspectors had no confidence that the eTMF was accurate
- Incorrect documents located in the TMF and eTMF (e.g. from other trials)
- Poor, often repetitive & incorrect labelling of files

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

- Documents not filed consistently or correctly with documents at the inappropriate level of the TMF
- Incomplete and unreliable TMFs with emails incomplete, duplicate documents, etc.

MHRA GCP INSPECTIONS METRICS REPORT METRICS PERIOD: 1st April 2016 to 31st March 2017 [Critical Finding]
The Need for TMF Document QC

• Health Authorities clearly expect a quality control process in place
• For an electronic TMF, the process is usually for a document specialist to:
  - Open each submitted document
  - View each page and check the content
  - Check for the accuracy of all metadata

• Time-consuming process that can be complicated by the following:
  - The need to perform document type specific checks (e.g. for 1572)
  - The need to access external work instructions

Resource needs increase with every additional trial, and increase as you do more later phase trials
TMF QC Resource Growth

FTEs based on sample trial portfolio

How many documents can a person QC in a day?
- Industry average of 100 – 200
- Factors: experience, specialization, nature and number of checks

How many documents must be QCd?
- See above for estimates
- Factors: document sources, skipping QC, sampling
- Assume 10% rework

<table>
<thead>
<tr>
<th>Estimated Documents</th>
<th>Docs / Study</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1</td>
<td>1000</td>
<td>6</td>
<td>9</td>
<td>20</td>
<td>25</td>
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<tr>
<td>Phase 2</td>
<td>5000</td>
<td>2</td>
<td>4</td>
<td>7</td>
<td>11</td>
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<tr>
<td>Phase 3</td>
<td>20000</td>
<td>1</td>
<td>5</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Phase 4</td>
<td>5000</td>
<td></td>
<td></td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>8</td>
<td>24</td>
<td>32</td>
<td>47</td>
</tr>
</tbody>
</table>
Strategies to Control Exponential Growth

• Machine Learning / Artificial Intelligence
  - Automated document identification, metadata assignment, and document quality checks
  - Promising technology, but really not available today
  - When available, how much manual validation will be needed before we trust automatic filing?

• Until then, strategies can focus on:
  - Reducing the number of documents that need to be checked
  - Increasing quality of submitted documents
  - Reducing the extent and complexity of checks
# Tactics within Quality Control Strategies

## Goals
- Slow the increase staff needed to keep pace with the ever-increasing TMF operational burden
- Use resources to maximize quality

<table>
<thead>
<tr>
<th>Adjust QC Based on Trial Risk</th>
<th>Adjust QC Based on Artifact and User Risk</th>
</tr>
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</table>
| - Determine if TMF documentation can be reduced based on the low-intervention nature of the trial  
- Adjust scrutiny based on trial specific factors | - Implement sampling based on artifact risk  
- Enable users with proven track records to skip QC  
- Consider decreasing document QC and increasing TMF File Review |

<table>
<thead>
<tr>
<th>Eliminate Unneeded and Low Value Checks</th>
<th>Reduce the Need to Retain Paper</th>
</tr>
</thead>
</table>
| - Ensure QC not performed on documents uploaded by validated integrations  
- Ensure submitters are properly trained so QC personnel don’t have to repeat extensive, time-consuming content checks | - Use a validated process for certification of copies  
- Eliminate signatures wherever possible  
- Use electronic signatures instead of wet ink |
Low Intervention Trials vs. High Risk Trials

Low Intervention Trials allow for risk based approaches for TMF and are defined as:

- The IMPs, excluding placebos, are authorised;
- According to the protocol of the clinical trial…
  - The IMPs are used in accordance with the terms of the marketing authorisation; or
  - The use of the IMPs is evidence-based and supported by published scientific evidence
- The additional diagnostic or monitoring procedures only pose minimal additional risk to subjects

European Commission “Risk proportionate approaches in clinical trials” 25 April 2017

- Other trial factors that increase risk:
  - First in Human trials
  - Emerging regions
  - Vulnerable patient populations
  - Missing or overdue key documents
  - Site level factors: high enrollers, investigator turnover, CRA turnover, protocol deviations

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TMF Risk Adaptations for Low Intervention Trials

Guidance from Health Authorities

• Risk adaption of the Trial Master File documents may include:
  - Replacement by a document that serves a similar function
    › But does not carry the title presented in ICH GCP E6 Essential Documents
  - Combining of documents so that one document serves a number of purposes
  - Document removal, or document not present because it is no longer applicable
    › As a result of implementation of other risk adaption measures

• Many examples provided in the guidance

MRC/DH/MHRA Joint Project, “Risk-adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products”
Risk Per Artifact

Question
How do you concentrate limited resources to achieve the highest level of quality and lowest level of risk?

Answer
1) Have a good understanding of which portions of the file pose the highest risk if not filed accurately and in a timely manner
2) Use this risk information to focus Study Owner and QC resources on the documents that pose the highest risk
Artifact Risk Assessment

As a first step, a risk assessment was performed for all 148 required types of core documents included in the DIA TMF Reference model Version 2 (2012)... For each document type the impact with regard to “Safety, rights and wellbeing of patients” as well as “data integrity” was determined based on the assumption that a missing document would indicate that the underlying process was not performed (worst case scenario).

Research Article, “Quality expectations and tolerance limits of trial master files (TMF) – Developing a risk-based approach for quality assessments of TMFs”
Sampled QC Options

**Probationary Program For Document Submitters**

Example:
- Must submit at least 100 documents with no more than 5% rework
- Until then, 100% of the user’s documents must go through QC

**Automatic Sampling Percentage Based On Risk**

Example:
- 100% QC on high risk document types
- 70% QC med-high risk document types
- 50% QC on medium risk document types
- 10% QC on low risk document types
Research: Top Reasons for QC Failure

Analyzed across many eTMFs in use for a variety of global studies over multi-year periods

What do these have in common?

They are all indexing/metadata failures

<table>
<thead>
<tr>
<th>Incorrect Document Date</th>
<th>9% to 21% of all rework</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incorrect Document Type</td>
<td>9% to 14% of all rework</td>
</tr>
<tr>
<td>Incorrect Language</td>
<td>2% to 5% of all rework</td>
</tr>
<tr>
<td>Incorrect Subtype</td>
<td>10%</td>
</tr>
</tbody>
</table>

"Incomplete Indexing": one TMF used this general category 58%

Other metadata categories, system specific 2-9%

When used, up to 10% of failures
Failing QC for Problems with Content is Uncommon

(Percentage of all failures, not percentage of documents QC’d)

- Missing signature: 2% or less
- Pages skewed: 2% or less
- Missing pages: 1.7% or less
- Scanned documents not legible: 1% or less
- Blank pages: 1.2% or less
- Pages out of sequence: 0.4% or less
- Image not clean (streaks, etc.): 0.6% or less

Conclusion

- QC Specialists are looking at hundreds of thousands of pages with little impact on quality
- Consider reinforcing training of submitters and instead have QC specialists focus on metadata only
Quality Control – Defined by MHRA

It is recommended that there is a **formal process** in place for **regular checks** of documents in the eTMF, usually on a **sampling basis**, including escalation procedures where issues arise. This process could assess, for each document reviewed, one or more of the following:

- Accuracy of the metadata attributed to the document
- Quality of the image (for example, readability)
- Whether it was the correct document (as expected)
- The document had the correct number of pages
- The eTMF audit trail associated with the document (with a link to any changes)
- Chain of custody documentation and timeliness of uploading into the eTMF
- Approval process (where applicable)
The Role of Periodic TMF File Review

- Organizations are increasingly moving towards conducting periodic reviews of their TMFs using sampled processes
  - Periodically (e.g. every quarter) or at trial milestones
  - Examination of (for example) 10% of the content finalized during the review period
  - Extent of checks may be based on study and site risk factors
- Responsibility and criteria need to be clear and well-documented
- If you are going to do these reviews and make these checks anyway, can you relax other QC criteria?
Summary: Reducing the Burden

- **Fewer Documents**: Create and QC fewer documents based on risk-based approaches and wholistic file review.

- **Greater Efficiency**: Ensure that associates have clear at-hand instructions and are quickly available to make decisions about TMF readiness of documents.

- **Fewer Checks**: Ensure that associates don’t perform unnecessary or low-value checks.

- **Less Paper**: Put in place procedures that minimize the need for paper in the first place and don’t require it to be retained.

**Result**: Achieve similar quality levels with fewer resources and control resource needs as your organization expands.
Summary: Risk Based QC Checklist

Which Tactics are Appropriate for Your Organization?

- Number of documents decreased appropriately for low intervention studies
- Documents transferred from other validated systems do not undergo QC
- Submitters fully trained on requirements for submitting TMF Ready documents, reducing rework
- Required QC checks reviewed to eliminate those that do not contributing significantly to quality
- Consideration given to removing checks that duplicate those done by submitters
- Consideration given to sampled QC based on document risk level
- Consideration given to reducing QC levels in favor of File Review
- Rejection rates for submitters reviewed and follow-up guidance and education provided
- Document type specific indexing and QC instructions available in one or two clicks at most
- eTMF reconfigured to remove metadata that does not add value
- QC personnel trained to focus on specific document types to increase QC speed
- Complex cross-document checks done in File Review rather than as part of upload and QC process
- Signatures minimized and electronic signatures used wherever possible
- Certification process supports destruction of paper
Questions?
Thanks You

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