Strickland Quality Assurance

Protecting patients, data and reputations

EMA Trial Master File Guideline

Paul Strickland

27th November 2019

We've Been Waiting for This

"Good evening, Mr Bond, I've been expecting you"

Draft guideline ruled from 2013

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1 February 2013
EMA/INS/GCP/3636736/2012EMA/INS/GCP/636736/2012
Good Clinical Practice Inspectors Working Group (GCP IWG)

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

Draft

Final Version 06 Dec 2018

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

06 December 2018
EMA/INS/GCP/856758/2018
Good Clinical Practice Inspectors Working Group (GCP IWG)

Guideline on the content, management and archiving of the clinical trial master file (paper and/or electronic)

Draft adopted by GCP Inspectors Working Group (GCP IWG)	30 January 2017
Start of public consultation	12 April 2017
End of consultation (deadline for comments)	11 July 2017
Final revised document after comments received from public consultation adopted by GCP Inspectors Working Group (GCP IWG)	06 December 2018
Date of coming into effect	6 months after publication

It’s a Guideline

- Title indicates it is a guideline
- European inspectors can cite against guidelines
- Legislation contains strict requirements, guidelines and other document types give detail on how we must comply
- Considers the CTR already so will not need to be updated when CTR is issued

What Do We Have To Do?

- Define the structure of TMF and ISF from the start – overall index/ToC
- Availability, access, up to date
  - Including post-trial access to validation documents
- Assess CROs which will generate documents
- CRO responsibilities, including TMF access during inspections
- Know your repositories
- Risk-based QC for the contents of TMF

More Expectations

- Sponsor documents assessment of the ISF
- Periodic retrieval tests for primary eTMF
- Define and preserve metadata
- Validate your eTMF system
- Procedures if sponsor/CRO goes out of business
- Certified copies if originals to be destroyed

What Do We Have To Do?

- It’s not rocket science

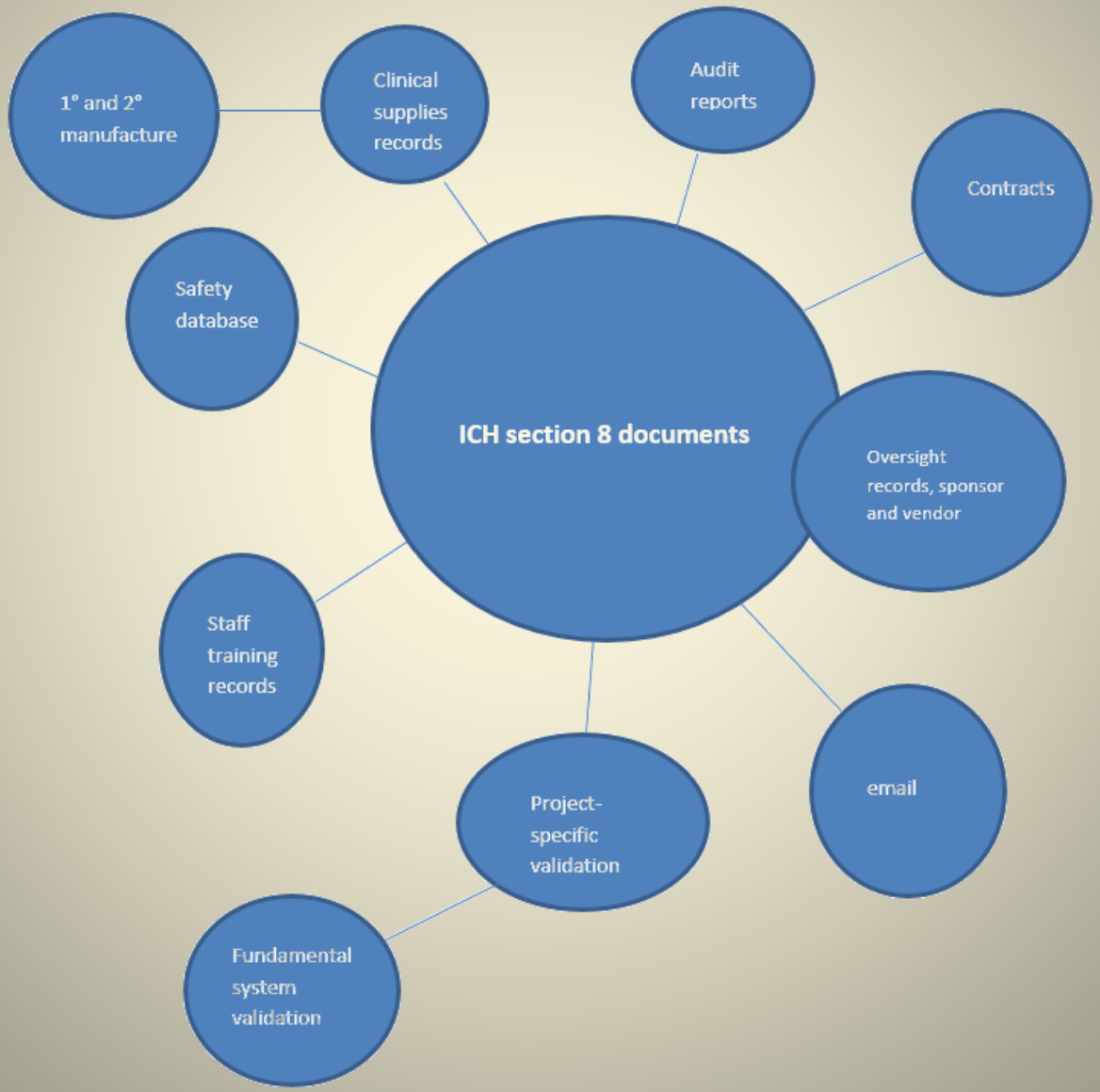
Availability

- "TMF readily available and directly accessible on request"
- MHRA tell us eTMFs are held in **14** separate systems on average
  - 44 at most (so far)
  - "Number of these systems should be minimised"
  - Including your SOP management system and email

Availability

- Have you a complete list of repositories holding your TMF documents?
- Identify them, map them, make sure they will be retained
- Don’t forget, the ISF is part of the TMF
- Sponsor TMF + ISF = Study TMF

Example TMF Map



The Forgotten Repository

- Records of vendor assessment and justification for selection
- Informal, hand-written, in a note book
- Held in a project manager's drawer
- Not to be retained
- But crucial

Procedures

- "Sponsor and CRO should have procedures in place for all aspects of the TMF"
  - Structure
    - Including all repositories
  - Access
  - Filing and naming conventions
  - Retention period
  - Maintenance of originals

Why pdf is Less Credible…

Paul Strickland

From:	Beyoncé Knowles <bknowles@stricklandqa.com
Sent:	Wednesday, 27 November 2019
To:	Paul Strickland
Cc:	Boris Johnson
Subject:	Re: Pizza time

Hey Paul,

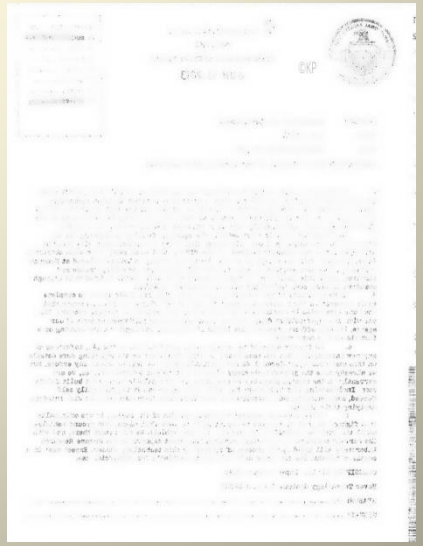
When you've finished the ICR presentation for today, come on over for a slice of my homemade pizza. I know you're a sucker for a Quattro Stagioni!

Love,

Beyoncé

Oversight

- “Arrangements for oversight and how they will be maintained”
- How is the sponsor aware of whether the TMF is up to date?
- Adequate risk-based document-level QC
- Who checks the quality?



Oversight 2

- With multiple CROs, set TMF expectations
  - Vendor/communication/TMF plan
- "Appropriate pre-qualification checks if a CRO is used to manage the TMF. Verify quality management during the trial"
- Will you be able to show records for this?

Access

- During one audit an additional e-repository was identified
- Need to be aware of all repositories as you create and file the records
- I did not have access
- So the project manager gave me access to her account
- Some of the best goals are own goals…

It’s a Lot of Work, But…

Why Inspectors Care So Much

- Not just the repository from which they retrieve documents for inspection
- It's a critical tool used by the sponsor, CROs and sites to keep up to date
- "Define timelines for document submission/ filing"
- Stay aware of the trial progress
- Particularly crucial where most of study is delegated

MHRA Position

- Change of definition for critical finding
- One of the three big areas of concern:
  - TMFs
  - RSI
  - Oversight
- Don't forget, it's also an area of criminal responsibility in SI 2006:1928
- Could the importance of the TMF possibly be emphasised more?

Yes

- Forbes magazine estimated the development costs per drug reaching the market
- From $3.7Bn to $12Bn
- At the point of regulatory submission, all that money is represented by the contents of your TMFs

Get it Right From the Start

- To rebuild a poor TMF can cost a fortune
  - And may be impossible
- You get one chance to do it right first time
- So…

Nail It!