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GCP Update Webinar

November 2021

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Objectives

- To provide a refresher on the regulations and guidelines to be followed.
- To provide information on recent changes in the regulations and guidelines.
- To consider some of the current hot topics.

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Agenda

- ICH Update
- EU Legislation Update
- Essential Documents
- Reference Safety Information
- Risk Assessment

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ICH

- International Council on Harmonisation
- US, EU and Japan
- Purpose:
  - Harmonise marketing authorisation requirements
  - Reduce timelines and cost
  - Reduce subject exposure to investigational products

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ICH GCP

1. Glossary
2. Principles

Responsibilities

3. Institutional Review Board/Independent Ethics Committee
4. Investigator
5. Sponsor

Documentation

6. Protocol / amendments
7. Investigator's Brochure
8. Essential Documents

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Update to ICH E6

- Proposals to facilitate
  - Implementation of new technologies
  - Risk Management
  - Risk Based Monitoring
  - Focus on critical study elements

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Ethics Committees

- Review trial for ethics
  - Appropriately constituted
  - Keep records for 3 years

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Investigator

- Trial conduct at site
- Welfare of participants
- Informed Consent
- Data collection and reporting
- Management of IMP at site

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Sponsor

- Design, management and funding
- Regulatory requirements and compliance
- Risk based quality management
- Monitoring and oversight
- Safety review and reporting
- Final study report

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- Ultimate responsibilities
  - Sponsor
    - Funding
    - Regulatory requirements
    - Ensuring Protocol, GCP and GMP compliance
  - Investigator
    - Trial Conduct at site
    - Subject safety and wellbeing
- Can delegate task but not responsibility
- Need very clear documentation

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ICH GCP Essential Documents

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- Protocol and Amendments
  - How the study is to be conducted
- Investigator's Brochure
  - All about the investigational product
- Trial Master File/ Investigator Site File
  - All documentation and correspondence
- Case Report Forms
  - Where all the study data are recorded

"If it's not documented it didn't happen!"

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ICH E8 and E6 "Renovation"

- ICH consulting on revision of E8 (General Considerations) and E6
- E8 (R1) Now final
- E6 also being revised
- More information on ICH website

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E8 (R1)

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1. Objectives of this document
2. General Principles
3. Designing Quality into Clinical Studies
4. Drug Development Planning
5. Design Elements and Data Sources for Clinical Studies
6. Conduct, Safety Monitoring and Reporting
7. Considerations in identifying Critical to Quality Factors

- Annex – Types of Clinical Studies

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ICH E6(R3)

- Draft principles document has been published
- Will form basis of new version
- Annex 1 – traditional RCTs
- Annex 2 – non-traditional designs

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Draft Principles – Key Points

- Participants not subjects
- QbD and CtQ
- Participant and physician involvement
- RBQM
- Use of tech in Informed Consent
- Feasibility and Simplicity
- Responsibility of Sponsor and Investigator
- Risk based approaches for supply and handling of IMP

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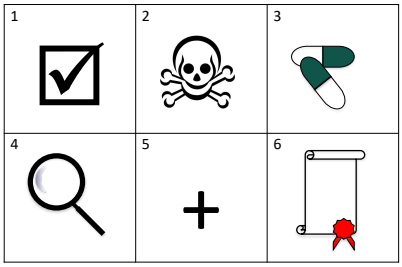
Eudralex Vol 10



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EU Clinical Trials Legislation

Current:
- Clinical Trials Directive
- GCP Directive
- GMP Directive

Future (Jan 2022):
- Clinical Trials Regulation
- GMP Regulation

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New EU Regulation

- Final version now published
- Implementation 6 months after database is finalised
- Latest estimate is late 2021/early 2022
- "will ensure that the rules for conducting clinical trials are identical throughout the EU"

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EU Regulation – Key Changes

- Clinical Trial Authorisation
  - Centralised review and decision
  - Approval in each member state
- Central Database – CTIS
- Transparency on trial status and results
- EMA inspection powers

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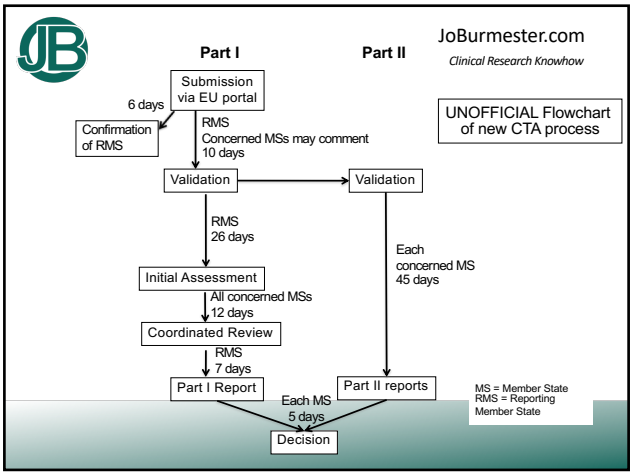

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Other changes

- Serious Breaches – 7 day reporting
- Urgent Safety Measures – 7 day reporting
- Any event affecting risk/benefit – 15 day reporting

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Other Changes

- Report to regulatory authority within 15 days of trial start (first subject recruited)
- Also within 15 days of end of recruitment
- Also within 15 days of end of trial in that state and then again and of trial overall.

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Post Trial

- Mandatory to post results within 12 months
- Lay persons summary also within 12 months
- TMF to be kept for 25 years

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Clinical Trial Information System

- New database
- Due to go live end 2021
- Everything will go in here!
- EMA and DIA working on training provision

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Clinical Trial Information System

- New database
- Due to go live end 2021
- Everything will go in here!
- EMA training provision
  - Sponsor Handbook and Reference materials
  - Online training materials
  - Master Trainer programme
  - Newsletters

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CTIS

- Sponsor Registration required
  - User Registration – EMA account
  - Sponsor Registration
    - Organisation
    - Sponsor Admin (at least 2 needed)

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CTIS

- Sponsor roles
  - Viewer
  - Preparer
  - Submitter
- Clinical Trial Administrator (Trial specific)
- Personas
  - Job function categories used to decide User Role

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New EU Guidances

- Inspections
- GMP for IMPs
- Ethical issues re clinical trials in children
- IMPs and AxMPs
- Summary of CT results for laypersons
- Risk proportionate approaches to clinical trial
- Serious Breaches

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Brexit

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Brexit

- EU Legal representative
- If no EU office outside UK will need to appoint a legal representative to run trials in the EU

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IMP Post Brexit

- QP certification from other EU countries will still be recognized, but UK QP review needed – 12 months to comply
- IMPs can be sent direct to investigational sites
- Import license will be required – 12 months to comply
- Will need EU QP release to export from UK

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Brexit

- CTA process
  - Now have to use UK system rather than EU system
  - cWoW will roll out this year
- Need to register trial and results in a public database e.g. clinicaltrials.gov
- UK will have its own portal and public database in due course

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Brexit

- Expedited safety reports
  - Cannot now use Eudravigilance for reports in UK
  - Must use MHRA online system

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The Future in the UK

- MHRA consulting on revised legislation
- First new legislation likely to come out later this year
- Second phase next year
- Many aspects of EU CTR and ICH E6(R3) will be implemented

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FDA Updates

- New guidances on:
  - Safety reporting (draft update)
  - Diversity in clinical trials (new - final)
  - 1572 (draft update)
  - Risk-Benefit Assessment (new – draft)
  - Real World Data 9(new – draft)

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Essential Documents

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Trial Master File

- Sponsor Files
- Investigator Site Files
- All relevant documentation and correspondence
- ICH E6 chapter 8

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Good Documentation Practice

- Authoring
- Review
- Approval
- Version Control
- Naming, filing and meta data
- Certified copies
- Archiving

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Example Inspection Finding

- MHRA Critical Finding (part of finding report):
- There were a number of essential documents for a trial retained by vendors which were not defined in the TMF plan or TMF index.
- The TMF index for a trial was at an artefact level and the quality system did not address an overview all the systems holding essential documents.
- There was a lack of effective oversight QC of an eTMF by the sponsor.
- Several issues were identified with the eTMF including examples of missing, misfiled, misnamed and duplicated documents.

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Archiving

- Up to 25 years
- Named person responsible for archives
- Separate files for Sponsor and Investigators
- Investigator to have independent copy of CRFs

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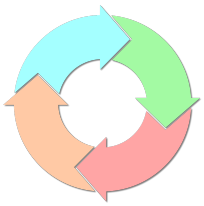
Risk Assessment

- RACT
- RAMP
- KRIs, QTLs and Thresholds



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Quality Tolerance Limits

- Defined at organization/programme/trial level
- Recommend 5-7 in total initially
- Apply to all trials/sites (generally)
- Different from KRIs but there is inevitably some overlap
- Reportable in CSR

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Elements to consider when establishing QTLs

- Parameter
- Definition
- Unit
- Expectation
- Tolerance limits (upper, lower, or both)
- Justifications
- Mitigations

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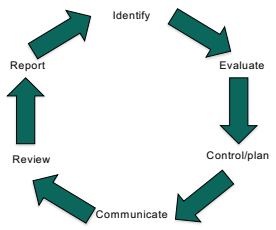
Risk Assessment Cycle



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Summary

- More change has happened
- More is coming
- Lots of guidance out there

Subject Safety **Data Quality**

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Thank you for coming!

- Certificates
- Feedback forms
- Post-course resources

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