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GCP Update for DIDACT

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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
- UK Update

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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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2016 update to ICH E6

- Changes 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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ICH GCP

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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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Principles

- Participant Protection
- Scientific Integrity
- Patient Input into Drug Development

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Quality by Design

- Quality is primary consideration
  - Objectives – clear and scientific
  - Participants – appropriate
  - Minimising Bias and control of confounding
  - Endpoints – defined, meaningful and relevant to patients
- Risk Proportionate approaches

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Critical to Quality Factors

- "attributes of a study whose integrity is fundamental to the protection of study participants, the reliability and interpretability of the study results, and the decisions made based on the study results"
- Approach to identifying CtQ factors:
  - Open dialogue
  - Focus on essential activities
  - Engaging Stakeholders
  - Review of CtQ factors
  - Feasibility in operational practice
- List of 18 considerations for CtQ factors

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Drug Development Planning

- Quality of IMP
- Non-clinical Studies
- Clinical Studies
  - Human Pharmacology
  - Exploratory
  - Confirmatory
  - Post-Approval
- Adaptive, Platform and Master Protocol Trials can combine stages

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Design Elements and Data Sources

- Different trial designs are described
- Design Elements:
  - Study Population
  - Treatment Description
  - Choice of Control Group
  - Response Variables
  - Methods to Reduce Bias
  - Statistical Analysis
  - Study Data – sources and Data Integrity

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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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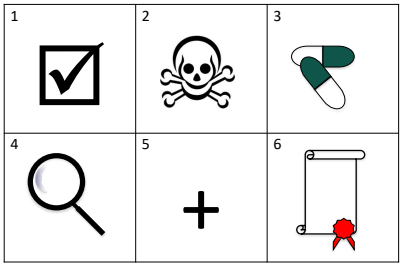
Eudralex Vol 10



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EU Clinical Trials Legislation

Option until Jan 23:
- Clinical Trials Directive
- GCP Directive
- GMP Directive

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

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EU CTR Application Timelines

EU CTR:
- Adopted in 2014
- Applied from January 31st 2022

Jan 2022
- New Clinical Trials: Optional CTD or CTR
- Transition of Ongoing Clinical Trials: Optional

Jan 2023
- New Clinical Trials: Required to follow CTR
  Transition of Ongoing Clinical Trials: Optional

Jan 2025
- All clinical trials to follow EU CTR

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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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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
- Also within 15 days of 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
- Now Live
- 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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Clinical Trials in the UK

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UK Clinical Trials Governance

- Medicines and Healthcare products Regulatory Agency (MHRA)
  - Regulatory Authority
  - CTA
  - Inspections
- Health Research Authority (HRA)
  - Ethics Committee review
  - Local (R&D committee) review
- Integrated Research Application System (IRAS)
  - Online application system

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UK Regional Differences

- Different Health Authorities cover the four different countries
- IRAS applications are automatically submitted where appropriate
- Scotland – differences wrt adults with mental incapacity
- Northern Ireland – differences wrt IMP and the Northern Ireland Protocol

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Current UK Legislation

- **SI 2004 No.1031**
- SI 2005 No. 2754 and 2759
- **SI 2006 No.1928** and 2984
- SI 2008 No. 941
- SI 2009 No. 1164

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- Medicines for Human Use (Clinical Trials) Regulations 2004
- Produced to implement the Clinical Trials Directive and GMP Directive
- Contains 9 parts and 12 schedules

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1031

- **Parts:**
  1. Introductory Provisions
  2. Ethics Committees
  3. Authorisation For Clinical Trials And Ethics Committee Opinion
  4. Good Clinical Practice And The Conduct Of Clinical Trials
  5. Pharmacovigilance
  6. Manufacture And Importation Of Investigational Medicinal Products
  7. Labelling Of Investigational Medicinal Products
  8. Enforcement And Related Provisions
  9. Miscellaneous Provisions

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1031

- Urgent Safety Measures – 3 day reporting timeline
- Requirements for UK QPs
- Requirements for UK Ethics Committees

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SI 2006 No. 1928

•Medicines for Human Use (Clinical Trials) Amendment Regulations 2006
•Produced to implement the GCP Directive
•Does not supersede 1031, but does make some amendments to it.

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- Many of the sections are correcting typos, making amendments which reflect the changes in the EU or including references to the GCP Directive
- Some new provisions and changes were significant

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- Inclusion of the sponsor's responsibility to validate and update the IB once per year.
- SmPC can be used instead of IB for Marketed Product
- Fee does not have to be sent with CTA if other arrangements have been made

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1928

- Notification of Serious Breaches
  - Sponsor to notify licensing authority in writing of serious breaches of GCP or the Protocol within **7 days** of becoming aware
  - Serious breach is one which is likely to significantly affect the wellbeing of subjects or the scientific value of the trial.

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- Trial master file
  - Sponsor to keep and maintain
  - To be kept for at least 5 years after end of trial
  - Medical files to be kept for same time
  - Named individual responsible for archives

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Clinical Trials Authorisation process - UK

- Combined review
- Uses IRAS

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CTA – MHRA Information

- From 1 Jan 2022 all CTIMPs to use Combined Review via IRAS
- Used to be called cWoW
- Sponsor to be established in UK or approved country
- Need legal rep if not
- HRA will automatically register trial on ISRCTN

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CTA – MHRA info on review timelines

- Validation 3 days
- Initial review 30 days
- If non-acceptance – 14 days to respond
- Final decision in 60 days (from application)
- 90 days for ATIMPs

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Common issues with CTA Applications

- Divided into categories:
  - Validation — Failure to provide information on the person authorised by the sponsor to correspond with the MHRA on behalf of the sponsor
  - Non-Clinical — Lack of information about pivotal safety studies that have been submitted in support of the application and the nature of the contraceptive advice as outlined within the protocol
  - Clinical — Lack of an acceptable Reference Safety Information (RSI) section and unacceptable recording and reporting of AEs/SAEs
  - Pharmaceutical — Characterisation data are frequently either missing from the dossier entirely, are deemed to be inadequate or insufficient interpretation of the data has been provided

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CTA – MHRA info on Risk Adapted Approaches

- Type A
  - No higher than the risk of standard medical care
  - IMP has MA and used On-label or established use
  - can use risk adapted assessment – Proportionate Review
- Type B
  - Somewhat higher than the risk of standard medical care
  - IMP has MA but used off label
- Type C
  - Markedly higher than the risk of standard medical care
  - IMP does not have MA

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MHRA GCP Inspection Metrics

Published annually – latest one 2018-2019

- Non-commercial Organisation Inspections – Critical findings
- 3 from 2 organisations

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MHRA GCP Inspection Metrics 2018-2019

Critical Findings from Non-Commercial Oranisations

- Pharmacovigilance
  - Issues with causality assessments and lack of follow up
- Oversight of CTIMP
  - Issues with PI suitability, delegation, protocol review and TMF
- Data Integrity
  - Issues with randomization and unblinding of monitor; no SAP

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MHRA - Example Critical Inspection Finding

- The protocol of a selected trial relied upon interpretation in order to understand the trial design. It consisted of two parts (known as two protocols) and within these parts there were a number of experiments that contained the objectives of the trial. However, the trial design was unclear and therefore difficult to reconstruct (e.g. randomisation process, data management etc).
- The sponsor representative and trial monitor confirmed that they did not understand the trial protocol and found it confusing.
- The Chief Investigator (CI) was inexperienced in running clinical trials however there were no mechanisms in place to ensure that they were properly qualified through experience, training and education or to provide support for their role as CI in order to mitigate this.
- There was no formal delegation of activities by the sponsor to the CI that clearly defined which activities were to be undertaken by the CI on behalf of the sponsor.

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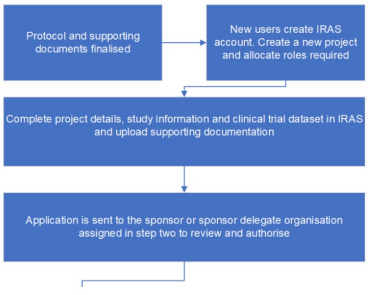
HRA Guidance on application

Overview of the application process



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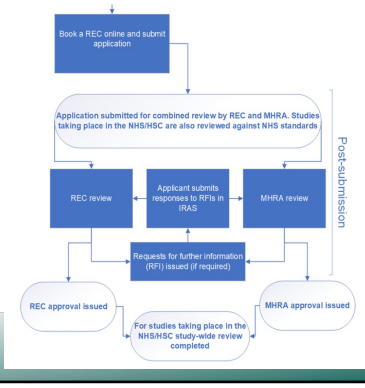
HRA Guidance on application (cont)



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IRAS application process

- Guidance provides information on process
- More guidance and training on IRAS website
- Sponsor or Sponsor Delegate Organisation must review and authorize the application
- REC booking then needs to be made
- Additional instructions for applications involved ionizing radiation or medical devices

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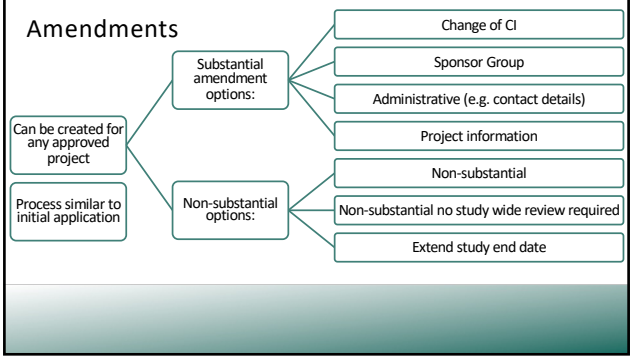
IRAS application process



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IRAS - Reporting

- Report options:

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Brexit

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Brexit

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- 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

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

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Brexit

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- CTA process
  - Now have to use UK system rather than EU system
  - Combined review now for all CTIMPs
- HRA will register trial on ISRCTN
- 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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MHRA recent Guidances

- Electronic Health Records
- Risk Adapted Approaches
- RWD / RWE
- Oversight and Monitoring of IMP trials

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The Future in the UK

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The Future in the UK

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- MHRA have consulted on revised legislation
- New Legislation will be issued at some point
- Many aspects of EU CTR and ICH E6(R3) will be implemented

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MHRA priorities for new legislation

- Patient focus
  - Involvement in research planning
  - Transparency
  - Diversity
- Streamlined processes
  - Combined Review
- Risk proportionality
  - Risk adapted approaches
  - Notification scheme for low interventional
- Agile
  - Flexibility – able to adapt to innovation
- International
  - In line with international standards

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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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• Certificates
• Feedback forms
• Post-course resources

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