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Clinical Trial Conduct

Course Tutor: Jo Burmester

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Agenda

- Protection of Participants
- Data Quality and Data Integrity
- Management of IMP

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Protection of Participants

- Participant Engagement, recruitment and retention
- Ethics and Informed Consent
- Safety Reporting and GPvP
- Transparency and the Lay Summary

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Participant Engagement, Recruitment and Retention

- Involvement of patients in trial design
- Patient centricity
  - Trial design
  - Remote vs onsite assessments
- Recruitment process
- Payments?
- Feedback and follow up

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Ethics Committee Approval

- IEC responsibility for participant protection
- Appropriately Constituted
- In UK regulated by HRA
- Review now combined with MHRA (CTA)

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Informed Consent

- It's a process not a document
  - Provide information
  - Time to consider
  - Opportunity to ask questions
  - ONLY THEN should they sign
- eConsent
- Ongoing consent/withdrawal

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Informed Consent

What would you want to know?

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SAFETY REPORTING

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Safety Review – Sponsor Responsibility

- Ongoing risk benefit
  - Animal toxicology
  - Adverse event reporting
  - Efficacy review
- Annual Report – DSUR
  - Within 60 days of IDBD
  - All research related events
  - ICH E2F

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Safety Reporting – Investigator Responsibility

- Report all AEs in the Case Report Form
- Report Serious AEs to sponsor within 24 hours
- Causality Assessment

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Adverse Event Reporting

- AE
- ADR
- SAE
- SSAR
- SUSAR
- DSUR

Adverse Event: Any untoward medical occurrence which happens to a participant in a clinical trial, regardless of relationship to test product

Adverse Drug Reaction: An AE which has a causal relationship to test product

Serious AE:
Fatal
Life threatening
Hospitalisation
Congenital anomaly
Disbabling/Incapacitating

Suspected Serious Adverse Reaction

Suspected Unexpected Serious Adverse Reaction
EXPEDITED REPORTING

Development Safety Update Report: Annual report of all safety information related to research

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Reference Safety Information

- Q&A document published by CTFG
- Came into force Jan 2019
- RSI should be a separate section in the IB

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RSI

- Purpose of RSI:
  - Identify SUSARs for expedited reporting
  - Categorise Events for DSUR

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RSI

- DO include:
  - Events classified using preferred terms (MEDDRA)
  - Events which are:
    - Serious
    - Reasonable evidence of causal relationship
    - Reported more than once
    - Has been OBSERVED with THIS product

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RSI

- "Expected" only if event appears at the same
  - Frequency
  - Specificity
  - Intensity

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Transparency and the Lay Summary

- Inclusion of Trial in a public database
- Publication of Final Study Report
- Publication of Summary of Results Understandable to the Lay Person
- Communication with participants post trial

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Data Monitoring and Management

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Data Integrity

- **A** Attributable
- **L** Legible
- **C** Contemporaneous
- **O** Original
- **A** Accurate

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Data Integrity (continued)

- Available
- Complete
- Consistent
- Enduring

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Monitoring and Query Resolution

- Monitoring Visits
  - ICH GCP 5.18.4
  - Monitor to visit before, during and after the trial
  - 3 reasons for monitoring:
    - Protection of subjects
    - Quality of data
    - Compliance with protocol and GCP

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Monitoring

- **Protection of Subjects**
  - Check informed consents
  - Check protocol compliance
  - Check adverse events
  - Check IMP
- **Quality of Data**
  - CRF review
  - SDV
  - Data query resolution
- **Compliance with protocol and GCP**

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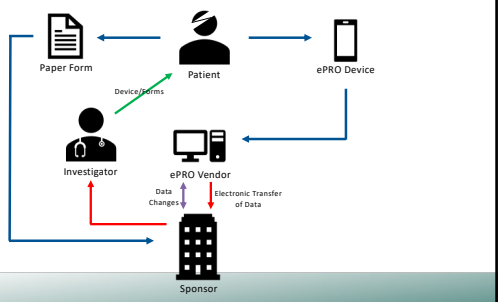
ePRO / Data Integrity Exercise – Data Flow



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Data Management Process

- Process between receiving the CRF data (paper or electronic) and releasing a clean database
- Terminologies:
  - Database
  - Data Entry
  - Data Validation

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Data Management Process

- Data Query (aka Data Clarification)
  - Document raised to ask for clarification or correction of a data point
- Coding
  - Applying a dictionary of terms (eg Medra) to text data to be able to group like terms, eg to adverse events
- Clean Data/Clean Database
  - Data that has been entered, validated, coded and all queries have been resolved
- Database Lock
  - Database that is considered clean and final and ready to be released to statistics for analysis

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Data Management Process

- Common challenges
  - Missing data and missing visits
  - Values outside of range
  - Inconsistency between adverse events and conmeds
- Common misunderstanding
  - Data management is an ongoing process throughout a trial
  - It is not just at the end of a trial
  - End-weighted recruitment can potentially cause large issues

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Final Study Report

- Required within one year of end of trial
- Content and format outlined in ICH E3
- Now need to include information on management of risk and breaches of Quality Tolerance Limits

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RBQM

- Risks
- Quality Tolerance Limits
- Key Risk Indicators
- Thresholds
- Mitigations

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What Might Affect Risk in a Clinical Trial?

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Drug Handling, Compliance and Accountability

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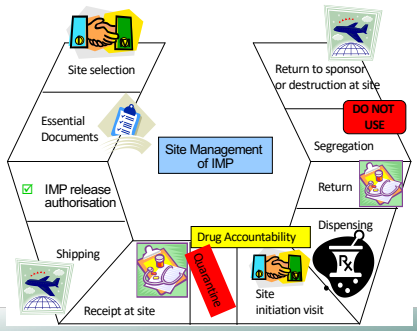
IMP Lifecycle



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IMP Release

- Release from Manufacture end
  - All batch release documentation in place
  - GMP release

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IMP Release

- IMP must not be sent to site until the site is ready.
  - Selection visit done
  - Receipt and storage arrangements made
  - Ideally initiation visit done or in progress
- Essential Documents must be on file
  - Ethics Committee approval
  - Regulatory approval
  - What else?

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Site Management of IMP

- Personnel
  - Pharmacist, Investigator, Nurses, Subjects
  - Trained in study procedures
  - Trained in drug storage, dispensing and accountability
- Who has responsibility at the site?
  - Investigator
  - Pharmacist
  - Monitor

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Site Management of IMP

- Storage
  - Temperature
  - Light
  - Humidity
- Access
  - Locked
  - Limited access
- Status
  - Quarantine
  - Returns – need to be in separate location and clearly marked

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Site Management of IMP

- Randomisation and blinding
  - Train staff and check randomisation
  - Check blinding at every visit
- Dispensing
  - Prescription process
  - How does it get from pharmacy to patient?
  - What QC checks for dispensing?
- Accountability
  - Risk proportionate
  - Keep up to date

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Site management of IMP

- Returns
  - Kept separate so not used for other patients
- Disposal
  - Returned to sponsor
  - Destroyed at site with written sponsor approval
  - Documentation
- Recall Procedure

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Site Management of IMP

Exercise

- What would you do if …..?
  - Temperature goes out of range
  - Drug given to wrong patients in study
  - Drug given to patients not in study
  - Drug gets lost in hospital
  - Patients do not return drug

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Summary

- Protection of Participants
- Data Quality and Data Integrity
- Management of IMP

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Thank you for coming!

- Quiz
- Certificates
- Additional resources

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ePRO / Data Integrity Exercise – Data Flow