What is necessary to provide good clinical data for a clinical trial?

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Is this a (typical) clinical trial?
Agenda

• Introduction (brief)

• So what is involved in a clinical trial?

• Clinical Trial Process

• Good Clinical Data
Introduction

- GCP – Good Clinical Practice, 1996

1. Ethical studies (Declaration of Helsinki, regulations)
2. Risk-benefit must be acceptable
3. Rights, safety and well-being of subjects are paramount and prevail over science and society
4. Data should support the study (pre-clinical, clinical)
5. Protocol needed – must be scientifically sound
6. Prior ethics committee approval of protocol
7. Qualified doctor (or dentist) is responsible for treatment and decisions
8. Staff must be adequately trained and qualified
9. Freely given informed consent before participation
10. Data should be properly recorded, handled and stored (5 years)
11. Confidentiality and privacy should be maintained
12. Drugs should be manufactured according to GMP and follow the protocol
13. Quality procedures should be applied throughout the trial process
Introduction
- Goal of Clinical Trials (NIH website)

• Develop knowledge

• Voluntary participation and right to withdraw

• By placing some people at risk of harm for the good of others, clinical research has the potential to exploit patient volunteers. The purpose of ethical guidelines is both to protect patient volunteers and to preserve the integrity of the science.

• Ethical guidelines in place today were primarily a response to past research abuses.
So what’s involved in a clinical trial?

- Directives
- National Legislation
- Regulations
- Sponsor SOPs / Working practices
- Guidelines
- Protocol
- Analysis
- Publication
- Data Management
- Budget
- Contracts
## So what’s involved in a clinical trial?

### Sponsor SOPs

<table>
<thead>
<tr>
<th>SOP nr.</th>
<th>SOP Title</th>
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<td>General</td>
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<td>Publication</td>
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So what’s involved in a clinical trial?
- Contracts

Courier  Funder  CRO

Trial sites

Collaborative Groups

Insurance  Central Lab

EBMT Contracts
So what’s involved in a clinical trial?
Clinical Trial Process
- Governance: CT2-EBMT

Timelines
Deadline = 17 April 2015
Board meeting = June 2015 – ratified
Clinical Trial Process
- Protocol and CRF

• The protocol needs to be:
  - Scientifically Relevant
  - Clear
  - Complete
  - Feasible
  - Agreed
  - Ethical

• A good protocol leads to a simple, clear CRF, built from a standard template:
  - Restrictive
  - Tested
  - Avoid duplication & potential for misinterpretation
• For a trial to provide good clinical data, it must be supported by adequate finance
  - Sufficient staff (including monitoring)
  - Centre payments

• Communication is key
  - Regular communication is vital
  - To allow proper risk management
  - To ensure the protocol is followed
Clinical Trial Process  
- Ethical Considerations

• The trial must be ethical
  - Rationale for trial (trial drug dosage, scientific novelty)
  - Patient population
  - Data collection
  - Data protection
  - Informed consent
  - EC and CA approval
• In 2016, the EU Clinical Trials Regulation will come into effect
  - It will supersede the CT directive (2001/20) and the GCP directive (2005/28)
  - It will provide a simplified coordinated approval process
  - It will depend upon an electronic portal for submissions and will therefore
    only take effect 6 months after the portal has been deemed fit for purpose
Clinical Trial Process
- Staff and Centres

• The trial management team staff need to:
  - Sufficiently trained
  - Support and oversight of centres
  - Select sites

• Centres need to:
  - Select trials
  - Ensure training
  - Ensure staff follow GCP, the protocol and SOPs and local rules
  - Submit (anonymised) data
  - Up-to-date delegation of authority log

• Communication
  - Meetings, TCs, newsletters, etc.
  - Update stakeholders
What effects Good Clinical Data?
# Good Clinical Data

- Data Quality during data collection

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<th>Believable</th>
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<td></td>
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*Good Clinical Data* is defined by the following characteristics:

- **Accessible**
  - Available
  - Efficient

- **Useful**
  - Interpretable
  - Timely
  - Relevant

- **Believable**
  - Complete
  - Credible
  - Consistent
  - Accurate
Good Clinical Data
- Monitoring

• Clear records (future understanding)
  – Good patient records at site
  – Complete and accurate ISF
  – “If it’s not written down, it didn’t happen!”

• The sponsor must have adequate oversight of the trial
  – Regular monitoring
    o SDV
    o ISF
    o Training
    o Pharmacy
    o Identify as yet unreported SAEs

  – Identification of protocol deviations and potential serious breaches

  – Issue identity and escalation to the sponsor
In addition to routine monitoring, auditing enables further confidence in the integrity of the data and ensures homogeneity between centres.

- Routine auditing

- ‘For-Cause’ auditing

- Competent Authorities can inspect centres
  - Part of GCP inspections for the Sponsor (e.g., MHRA GCP inspection)
  - To investigate serious breaches or fraud

- Good to be inspection ready
  - Files and data up to date
  - Training records complete
Good Clinical Data
- Data Integrity

Data Lifecycle
- Collection and corrections
- Processing
- Reporting
- Review
- Archiving

Data Governance
- Process and systems (SOPs)
- Ownership
- Monitoring / Audit
- Environment (Does everyone understand importance of integrity?)
- Training

Taken from MHRA guidance document on GMP data integrity

A quality management system is required
To ensure data integrity it is important that:

- Good documentation practices are followed for source data and records
- Systems are validated
- Process in place to ensure data quality and security
Good Clinical Data
- Data integrity – the data life cycle

- CRF completion at site

- In the data management department of EBMT:
  - Computer System Validation
  - Data entry
  - Data Validation Plan
  - Data query and data cleaning cycles (importance of audit trail)

- In the statistics department
  - Statistical Analysis Plan (SAP)

- In the CTO and centre
  - TMF and ISF – supports the data and shows data integrity
Good Clinical Data
- Why is CSV important?

• Can I trust the data generated?
  - Accuracy
  - Reliability
  - Integrity – can’t be modified
  - Availability – for staff and inspectors
  - Authenticity – is it from the correct person

• Does the system do what it is meant to do?
It is expected that systems are validated to accepted standards, additionally, principles of CSV should be applied to study specific builds/programs/applications, particularly:

- Specifications
- Testing against specifications
- Approval and release
- Change control
Good Clinical Data
- The CTO Quality system

- Quality Policy
- SOPs
- Work Instructions
- Standard Forms + Templates

All controlled
Good Clinical Data
- Data Validation Process

- Forms entered by data manager (or site)
- Data cleaning (automatic and manual queries)
- Database lock
- Queries to sites and corrections
- Interim analysis
- CTMS
- IDMC
- Statistical Analysis
- Close Out & Archiving
- Publication
Good Clinical Data
- Data Entry Process

- Check received CRF’s
  - Original
  - Version
  - Signature
  - Ink
- Date and Track
- Entry
- QC
Good Clinical Data
- Data Validation Plan development

• Draft DVP
• Review DVP (2\textsuperscript{nd} CTC, Stat’s, CI)
• Build edit checks in test database
• Check edit checks
• Implement edit checks in production database
• Documentation (of steps/activities and approvals)
Good Clinical Data
- Data query and data cleaning cycles

• Validation run
• Manual discrepancy check
• Query to site

FLOWCHART

• Answer provided (authorized)
• Answer processed
  - No change: accepted as is
  - Change: update of database
  - Query: still unclear or new question(s) have risen
• Validation run
• Documentation
Good Clinical Data
- Analyse and publish data

- All trials must be entered into a public register before the first patient is entered, to allow future publication
  - Clinicaltrials.gov
  - EudraCT register [https://eudract.ema.europa.eu](https://eudract.ema.europa.eu)

- During the trial, the data must be analysed as appropriate
  - IDMC
  - Interim analyses (stopping rules)
  - Continued assessment of risk
  - Pharmacovigilance

- After the end of the trial, the results must be uploaded onto a public database
  - Open access (as above)
  - Publications
Good Clinical Data
- End of trial

• End of trial notifications
  - EC and CA – Declaration of the end of a clinical trial Form – within 90 days of the end of the trial (define in the protocol – last subject, last visit)
  - Submit Clinical Study Report within 1 year

• Close centres

• Archive TMF and ISF (for 5 or 15 years – note 25 years in new CT Reg)

• Archive database
Good Clinical Data
- EBMT Data Management Activities

- From trial feasibility to clinical study report
- Coordination of review of:
  - Protocol Development
  - CRF, CRF completion guidelines
  - Data Management Plan
  - Data Validation Plan
  - Statistical Analysis Plan
  - CRF collection and Data Queries
  - Tables, figures and listings
  - Manuscript / Clinical Study Report
- Regular meetings
- Audits
Thank you!