Summary of Trial Management Systems Workstream 4 Document B

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MRC/DH joint project to codify good practice in publicly funded UK clinical trials with medicines

Trial Management

Trial management is the process of ensuring that a trial is run effectively and within budget. Within non-commercial organisations, this function is often undertaken by the Chief Investigator or a trial manager/coordinator. Alternatively, the sponsor may contract out many or all trial management functions to a Clinical Trial Unit or other third party.

Where functions are contracted out to third parties, the sponsor must ensure that there are formal processes in place to ensure oversight of delegated functions by:

1. Assessing that individuals or organisations taking on trial management functions are appropriately qualified and competent to perform those functions and have appropriate quality management systems in place.

2. Ensuring all parties are aware of their roles and responsibilities (for example by clearly defining them in contracts or agreements).
3. Maintaining lines of communication to ensure the obligations of all parties are being met (for example by receiving progress reports).

It is important that trial management systems are documented to define each step of the clinical trial process. This not only ensures that those performing the tasks have a clear plan of what, when and how trial activities are undertaken, but also enables auditors/inspectors to reconstruct how a trial was managed.

Trial management procedures/responsibilities that are common across all trials are usually defined in the sponsor's research standard operating procedures (SOPs)/policies and for less complex trials, trial management documentation may simply consist of an index of these SOPs with any trial-specific management described in sufficient detail in the protocol.

For more complex trials, the key activities associated with trial management (such as communication, monitoring and data management) are often described in separate trial-specific SOPs/plans.

The level of detail required will depend upon:

1. The clinical trial risk assessment*
2. The organisational structure within which the clinical trial is conducted, and
3. The design and methods of the clinical trial

*See MHRA Inspectorate Blog on Risk Adaption in Clinical Trials of Investigational Medicinal Products (CTIMPs).

Where institutional policies (such as those of the host University or NHS Trust/Health Board) prevail over the arrangements for a trial, these should be referenced within the trial management documentation.

The list below illustrates the key trial management considerations when conducting a large multi-site trial (reproduced with kind permission from the MHRA GCP Guide (ISBN 978 0 11 708107 9), page 42-44).

Project / Trial Management Considerations

Communication

Before:

- Project team set-up
- Project plan / milestones
- Communication plan

During:

- Project meetings and telephone / video conferences
- Progress / status reports
- Dissemination of key information / minutes etc.
- Changes to trial team

After:

- Trial debrief

Documentation

Before:

- Prepare trial master file
- Risk assessment
- Key trial documents (for example, protocol, investigator’s brochure, subject information sheet / consent forms, accountability records)
- Regulatory green-light check
- Trial manuals / plans (for example, pharmacy, laboratory manuals)
- Written procedures

During:

- Maintain trial master file
- Review / update / circulate risk assessment
- Review / update / circulate key trial documents, trial plans, written procedures etc.
- Amendments (including substantiality decision and implementation)
- Document and circulate any actions and decisions

After:

- Complete and archive trial master file
- Clinical study report

Regulatory and ethical correspondence

Before:

- Competent authority authorisation
- Favourable research ethics committee opinion

During:

- Substantial amendments
- Annual progress reports to research ethics committee
- Serious breaches
- Urgent safety measures
- Development safety update reports

After:

- End-of-trial notification
- Clinical trial summary report

Vendors

Before:

- Vendor selection
- Contracts and insurance
- Provision of required documentation
- Training

During:

- Oversight
- Review of contracts
- Ensure obligations of all parties are being met
- Status updates
- Visits / audits
- Management and escalation of issues

After:

- Vendor performance assessment

Investigational medicinal product

Before:

- Manufacture, packaging and labelling
- Qualified person certification
- Randomisation and blinding
- Release and distribution
- Investigational medicinal product dossier / summary of product characteristics

During:

- Ongoing supply
- Ongoing accountability
- Maintenance of blinding
- Temperature excursions
- Shelf-life changes

After:

- Complete accountability
- Return / destruction

Investigator site

Before:

- Monitoring plan
- Monitors assigned
- Site selection
- Initiation and training

During:

- Routine on-site / central monitoring
- Recruitment updates

- Issue identification and escalation
- Collection of case report form data
- Data query answering
- Additional investigator sites initiation and training

After:

- Notification of end of recruitment
- Close-out
- Complete and archive investigator site file

Pharmacovigilance

Before:

- Safety plan

During:

- Adverse event collection, assessment and reporting
- Ongoing safety updates
- Safety signal detection
- Data monitoring committee / data safety monitoring board
- Investigator’s brochure update / validation
- Development safety update reports preparation
- Reconciliation of safety and clinical databases

After:

- Final reconciliation of safety and clinical databases

Data management and analysis

Before:

- Case report form design and preparation
- Define major non-compliances
- Database build
- Computer system validation and validation of application builds

- Data management plan
- Statistical analysis plan

During:

- Data entry
- Protocol non-compliance collection and circulation
- Data queries
- Electronic data transfer
- Interim analyses (including dose escalation)

After:

- Final electronic data transfer
- Protocol non-compliance review for analysis
- Final analysis (for example, statistical and pharmacokinetic)

The content below provides examples of the systems, details and responsibilities that should be described in trial management documentation.

Key Details and Organisation

- Details of the trial protocol.
- Organisational structure, including relevant details of the identity and responsibilities of all involved; the sponsor, Chief Investigator, trial management team, host institution, Trial Steering Committee, Data Monitoring Committee, Endpoint Adjudication Committee, coordinating centre(s)and central laboratory(ies), as applicable.
- Details of care organisations, participating sites and investigators.
- Details of the relevant regulatory approvals (e.g. ethics committee, clinical trial authorisation) and documented systems to demonstrate there is appropriate input and review from those with relevant expertise (e.g. service departments such as pharmacy).
- The name of the individual who should be the first point of contact in the event of questions about the conduct of the trial (e.g. for audit/inspection purposes).

Trial Documentation

It should be clear who is responsible for overseeing the preparation of key trial documentation and details of the review and sign-off process. The procedure and responsibility for assessing the substantiality of amendments to key documents such as regulatory approvals, the protocol, patient information documentation etc. (and the subsequent change control procedures) should also be documented. Where the same information is contained in more than one document, (for example the protocol and participant information leaflet) there should be clear documentation to describe how consistency is ensured. In addition, these checks should extend to any documents produced by the investigator site (for example local pharmacy instructions/logs) to ensure they meet all protocol requirements. Details of and the responsibility for the regulatory green light processes, (for example ensuring all required documentation and approvals are in place before the release of trial supplies) should be defined.

Contracts and Financial Management

Details of any relevant information relating to budget management should be outlined.
The contractual framework should be clearly defined and should identify the individual or organisation responsible for:
a) Negotiating contracts/sub-contracts (if relevant)
b) Preparing and signing contracts/subcontracts
c) Dealing with invoices and payments
d) Ensuring all obligations are met

In many circumstances this role may be taken on by the host institution (e.g. University or NHS Trust/Health Board), in which case it is helpful to describe the role of the lead investigator at the research site(s) in the contractual process. For some trials (e.g. investigator-led single-site trials) where in-house agreements are in place to define roles and responsibilities, there may be little or no requirement for contracts or sub-contracts.

Insurance and Indemnity Arrangements

The arrangements for insurance and indemnity should be stated, including arrangements to address negligent harm to the participant (e.g. NHS indemnity) and adverse consequences of the interventions and trial procedures that are not due to clinical negligence (e.g. provision for ex gratia payment).
Where appropriate, the process for confirming that the trial is covered by the sponsor's insurance/indemnity, (i.e. no exclusions in the policy that may compromise cover) should be defined.

Quality Management

ICH GCP E6 (R2) Guidelines (.PDF) state that quality management systems should include, the design of efficient protocols and data collection tools and the collection of information that is essential to decision making. Mechanisms should be in place to provide assurance that all clinical trial activities are being performed in accordance with all regulatory and governance requirements. The approach to and level of quality assurance (both internal and external schemes) should be described.
Examples include: the evaluation of investigator sites to confirm suitability, the application of certified laboratory standards, validation procedures, protocols for imaging or histology reporting and central reviews of endpoints.
The rationale and details of the proposed audit plan should be stated.

Monitoring

The clinical trial risk assessment and the trial design should inform the approach taken to monitoring as well as the intensity and focus of the monitoring process (See Appendix 2 of the Risk-adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products (.PDF)).

Consideration should be given to the following aspects of the trial:
• Consent
• eligibility
• capturing and reporting safety information
• capturing, processing and coding of study endpoints

Comprehensive guidance on the approaches to monitoring and the documentation of monitoring activities can be found in the Monitoring Procedures Workstream Document.

Training

This should include the training delivered to all relevant personnel involved in the trial including coordinating centre staff and those at trial sites. The methods used to deliver training should be described (if applicable) and whether training on specific activities requires competency assessment. For example, training meetings, investigator meetings, arrangements for mentoring and supporting study staff and for encouraging continuing professional development, should be considered.
It is helpful to describe not only the methods for delivering training, but also how training is to be documented (e.g. personal training records, registers of attendance at training meetings or investigator meetings, or formal appraisal within an employer scheme).
Consideration should be given as to how the training and monitoring procedures interact, as each may usefully inform the other.

Trial Communication

Details relating to the communication of key trial information should be in place. For example: what needs to be communicated (including reports that will be required), the lines of communication, the frequency or timing of communication and the mode of communication such as phone/e-mail.
Regular project meetings to review trial progress should be recorded so that all actions, key decisions and timelines are clear.
Details of how the trial will be marketed should be defined including how the trial’s identity will be developed.
Details of any planned communication; for example, patient and public engagement activities, web-based information (if applicable, trial web site) and contact arrangements for participants with questions about the trial, should also be documented.

Pharmacovigilance

Definitions of Adverse Events (AEs), Serious Adverse Events (SAEs), Serious Adverse Reactions (SARs) and Suspected Unexpected Serious Adverse Reactions (SUSARs) relevant to the trial. Details of the reference safety information (Investigator Brochure or Summary of Product Characteristics) for the trial and

how any updates are to be managed should be defined. Procedures for capturing event information, processing reports, assessing safety signals and producing safety reports for regulatory agencies, data monitoring committees, ethics committees, investigators, etc. should be clear.
The protocol should state which adverse events do not need to be reported as SAEs, depending on the nature of the trial.
For trials involving advanced therapies, any additional arrangements for safety reporting should be described.
Other points to consider include trial-specific arrangements outlining out-of-hours cover with details of arrangements for trial team access in the event of an emergency and details of emergency code break if applicable.
The Pharmacovigilance Workstream Document provides comprehensive guidance on all aspects of the pharmacovigilance process.

Endpoint Assessment

This should outline the methods for assessing study endpoints, e.g. independent review, endpoint adjudication committee, procedures for assessing images, pathology samples, etc.

Writing of Reports and Publications

Arrangements for authorship and mechanisms for dissemination of results should be described.

Computer Systems

Computer systems used in clinical trials should be developed and maintained to a standard appropriate to their functionality within the trial. Particular attention should be paid to issues of confidentiality, validation*, security and access to data.

*ICH GCP E6 (R2) Guidelines (.PDF) electronic records and electronic signatures defines computer system validation as a process of establishing and documenting that the specified requirements of a computerised system can be consistently fulfilled. Validation should ensure accuracy, reliability and consistent intended performance, from design until decommissioning of the system or transition to a

new system. For some trials it may be necessary for computer systems to meet external standards such as the United States Code of Federal Regulations Chapter 21 Part 11 (21 CFR Pt. 11), although a risk adapted approach for the use of electronic records and electronic signatures (.PDF) is supported by the Food and Drugs Administration (FDA).

The procedure for developing and maintaining computer systems should be described in an appropriate level of detail, with reference to external standards if applicable. For example, sections on security, user specification, development process, validation methods, bug-reporting and disaster recovery may all be relevant. The change control process should be fully documented from the date of change request; date of release of amended version and any form of impact assessment associated with the changes where appropriate.
System validation should also be demonstrable for Interactive Voice/Web Response Systems used for activities such as randomisation, trial supply and blinding/unblinding.
For complex systems it is likely that these will need to be addressed in separate documents, which should be cross-referenced.

Data Management

The following should be defined:

- The identity and location of all source documents: For example, when the case report form (CRF) can be the source data and when a separate source document (often the subject's medical records) will be used.
- The CRF/database development process: The design of the CRF and trial database including who will be involved in the review and approval process. Further guidance on Developing a Case Report Form can be found on the CT Toolkit. It is often useful to include the 'end user' to help identify any problems with the design of the CRF and to ensure that the order in which data are captured aligns with clinical practice.

The location, change control and release procedures for all key data management documentation should be described.

- The data flow: How data will be integrated into the trial database (e.g. from paper or electronic CRFs, patient diaries, central laboratories).
- Data checking/query process: The level (percentage) and method of data entry checking should be defined (e.g. for logical consistency, missing or implausible data or protocol deviations). Methods could include data entry

printout comparison with the CRF, checking a sample of data, double data entry, range value checks, checks for missing data. - A predefined ‘acceptable error rate’ with actions to be taken if the error rate is exceeded, should be set.
    - Plans for making corrections (including self-evident corrections) and the tracking of queries so that additions and corrections made to the CRFs and the database can be tracked and explained in a clear audit trail.
    - It is important to specify the process for defining, capturing, and assessing GCP/protocol non-compliances so that any significant non-compliance can be identified for inclusion in the Clinical Study Report.
    - The process for confirming when the database is ‘clean’ and considered final and the confirmation of when/how it is formally locked must be clear.
    - How the database will be stored, accessed and protected (from editing or deletion), for example, the process for restricting or removing edit rights, should be described.

Investigational Medicinal Product Management

The following aspects may be relevant and are dealt with in more detail in the Trial Supplies station:

- Source of study drug (including comparator or placebo)
- Procedures for manufacture, packaging, labelling and distribution
- Accountability at site(s)
- Disposal of unused study treatment

Outline details of the management of the randomisation systems (telephone, web-based, fax, etc.) and blinding/unblinding procedures to be used.

Statistical Analysis

Identify those responsible for statistical analysis and documentation of the statistical analysis plan (see Statistical Data Analysis station).

Regulatory Submissions

If appropriate, describe who will be making the submission, and the arrangements for preparing data for submission and answering regulatory queries.

Archiving

Outline procedures for archiving all study documentation including the Trial Master File, case report forms and other essential documents and any arrangements with investigator sites for the archive of the Investigator Site File and source data to comply with relevant regulations. (see Archiving station). Outline procedures and timelines for storage/destruction of biopsies, tissue samples, genetic material, etc.

Additional Reading: A Guide to Efficient Trial Management - Trial Managers' Network (.PDF) (pdf).

Updated in October 2022: T Symons Associates Ltd