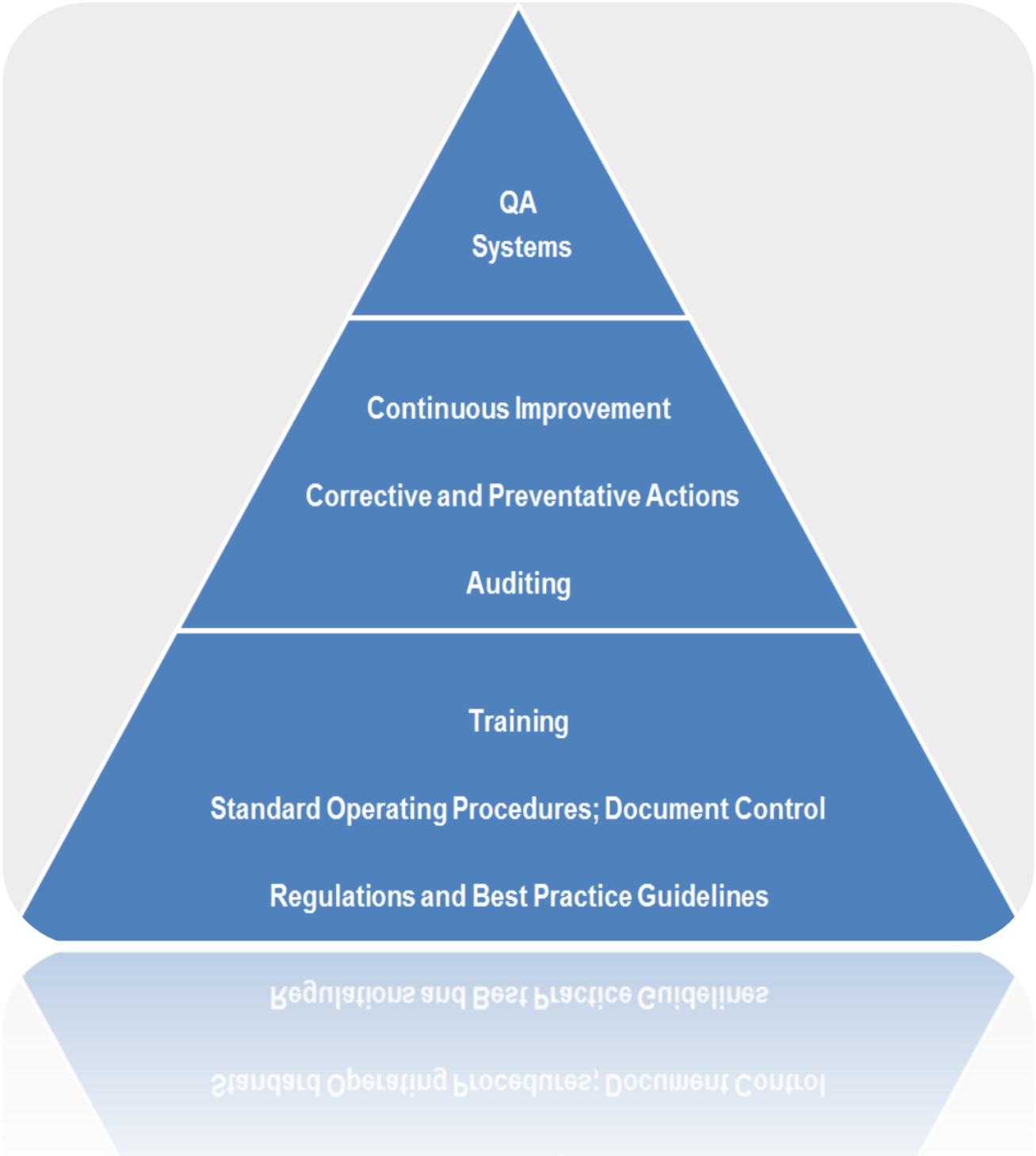
UKCRF
NETWORK

UK CRF QA Workstream Quality Manual Guidelines



Contents

General Introduction

These guidelines set out the core elements of a quality system in a clinical research setting and have been agreed by the members of the QA Workstream group of the UK CRF Network.

What is a Quality Manual?

The purpose of a Quality Manual is to provide a clear, high level overview of the quality management system, including the related policies and procedures that are in operation within a Clinical Research Facility. A Quality Manual demonstrates how the quality management systems of the CRF support the delivery of research projects to the highest standards of research and clinical governance, thus ensuring that quality and safety considerations are embedded throughout the Facility, and promoting a culture of continual quality improvement.

A Quality Manual also outlines responsibilities at both a managerial and operational level, in relation to the CRF's quality management systems, and hence can provide a useful introduction to the CRF's quality management systems for new starters, new investigators, inspectors and other external visitors

What is the purpose of these guidelines?

These guidelines detail the minimum requirements of a quality system in a clinical research facility setting. They are intended to be used a tool to which new CRFs can base their quality systems on, and one which more established CRFs can review their systems against.

How should I use these guidelines?

The scope of a quality management system, and hence of the Quality Manual, will vary between CRFs. This template is not intended to be prescriptive and has been designed as a guide covering some of the most common quality processes found in CRFs; users should add/ remove and modify sections in order to tailor the document to their own CRFs needs and requirements.

Sample wording is provided in each section to aid the user in the completion of each section and guidelines are provided in italics, these should be deleted prior to releasing the manual and where an SOP number is referred to in the text the user should include their own sites SOP number.

Note: Relevant policies and procedures should be signposted, rather than reproduced within the manual. Where local and trust polices exist they must be referred to when using these guidelines.

1 Introduction

<This section provides a brief overview of the Quality Manual including the scope of the manual, references and a definitions table to define any abbreviations used>

The Clinical Research Facility supports the delivery of research projects to the highest standards of research and clinical governance, ensuring that quality and safety considerations are embedded throughout the Facility, and promoting a culture of continual quality improvement. The Clinical Research Facility has documented and maintained a quality management system in accordance with the requirements of ICH GCP Guidelines and all applicable regulatory requirements.

1.1 Scope of the Quality Manual

This Quality Manual applies to all staff and investigators working within the CRF. It is every individual's responsibility to work within and adhere to current national legislation/ guidelines and local policies and procedures; these are referenced as relevant throughout the manual.

1.2 Definitions Section

<add to as required>

Abbreviation	Definition
CRF	Clinical Research Facility
ICH GCP	International Conference on Harmonisation Good Clinical Practice
SOP	Standard Operating Procedure
WI	Work Instructions
CAPA	Corrective Action Preventive Action
IMP/ NIMP	Investigation Medicinal Product/non-IMP
CTA	Clinical Trials Authorisation
MHRA	Medicines and Healthcare Products Regulatory Agency
QP	Qualified Person
CSV	Computer Software Validation
CTA	Clinical Trial Agreement

1.3 References

- ICH GCP Guideline (CPMP/ICH/135/95)
- EU Directive 2001/20/EC
- EU Directive 2003/94/EC
- EU Directive 2005/28/EC
- The Medicines for Human Use (Clinical Trials) Regulations 2004, as amended
- The Research Governance Framework for Health and Social Care, 2nd edition
- The Human Tissue Act 2004
- MHRAs guidelines: ‘Guidance on the maintenance of regulatory compliance in

laboratories that perform the analysis or evaluation of clinical trial samples'

- EudraLex volume 4, Annex 13: EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use.
- The clinical and research governance provisions of the <Insert Hospital Name> Hospital Trust/Governance.
- *<insert other relevant documents as required>*

2 Management Responsibility

<This section must detail the responsibility of management including management members, their responsibilities with regards to quality processes review and resource management>

2.1 Management Committee Members

<In this section it would be useful to provide an outline of the management committee structures (if you have more than one type of Committee. This might take the form of a flow chart showing the relationships between the CRF and the Trust / University. It would then be useful to provide a list of committee members for each committee (job titles – not names). Example committees might be: Medical Advisory Board, CRF Executive Committee, Senior Management Committee, SOP Committee, Faculty Executive Board etc.)>

2.2 Management Review

Management Committees take responsibility for the CRF's quality system by regularly including feedback opportunities through meeting agendas or by commissioning regular reports in various areas, some of these are:

- Follow-up actions from Previous Management Reviews
- Results of Internal Audits
- Customer Feedback and Complaints
- Status of Deviation Reports and CAPA projects.
- Recommendations for Improvement

All CRF staff have a responsibility to report any areas of concern they have relating to the quality system to their line managers or Heads of Department

2.3 Resources

The CRF and management are committed to resource the quality management system to meet regulatory requirements and to maintain and improve the effectiveness of the quality management system and its processes.

2.3.1 Premises

The CRF provides and maintains adequate infrastructure needed to provide service to our users and conform to required regulations including:

- Buildings, workspace and associated utilities
- Process equipment (both hardware and software)
- Support services (i.e. communication etc.)

2.3.2 Staff

- The CRF employs a team of core staff who have been rigorously selected to ensure that they have the right qualifications, skills and competencies to carry out their roles. All staff have clearly defined job descriptions (refer to SOP# *xxx* on Training File set up).
- Staff are actively encouraged to undertake professional development courses and attend conferences and seminars to ensure that their skills are continuously developed and updated.

2.3.3 Work environment

The CRF shall determine and manage the work environment ensuring that the workspace is suitable for all CRF staff.

2.3.4 Organisational Chart

An organisational chart providing generic details (i.e. job titles - not names) is attached to demonstrate reporting lines in the CRF. The organisational chart is maintained by the quality representative and approved by senior management, (refer to SOP# *xxx*). The chart is updated when required.

3 Document Control

<This section details the types of documents (SOPs and WIs) used and their control and how deviations from these documents are handled>

The quality management system has documented procedures to control and manage processes associated with the operational and administrative procedures within the CRF.

3.1 **Documents**

The quality management system includes the following documents:

- Documented statements of the CRFs Quality Policy and objectives.
- Documented standard operating procedures (SOPs) to ensure the effective planning, operation and control of the processes of the CRF.
- Documented Work Instructions (WIs) to detail how specified work should be carried out to ensure a systematic approach.
- Any other records required to demonstrate conformity to the requirements listed in section 1.3 above.

The CRF has an approved index of all SOPs and WI governing its processes.

<Add in a statement to detail where SOPs are stored in your institution>

3.2 **Change Control**

A system is in place to ensure that the latest copies of all documents are available readily to ensure effective functioning of the CRF quality management system. There is also a documented process used to ensure that changes to a system are introduced in a controlled and coordinated manner and to ensure that changes are appropriately controlled, documented and approved by designated functions, refer to SOP# xxx

<Add in a statement to detail where SOPs are stored in your institution>

3.3 Retention of Records

<This section details how quality records like training files etc. are stored and archived>

Records are maintained in order to provide evidence of conformity to the requirements listed in section 1.3 above, and of the effective operation of the quality management system. SOP# xxx details the storage, protection, retrieval, retention time and disposition of the CRFs quality records.

3.4 Deviation Reporting and CAPA

<A deviation is any non-conformance to documented requirements. This section details how deviations are documented and corrected. Refer to the NCR Guidelines in the QA Workstream Portal for more guidance on how to structure this process>

The CRF takes action to eliminate the cause of non-conformities and deviations in order to prevent recurrence, refer to SOP# xxx. Line Managers are responsible for the quality of the work carried out within their team and for escalating raising any quality issues to senior management and, if applicable, the quality representative.

The CRF should have a documented procedure which defines the requirements for:

- Reporting deviations.
- Determining the causes of deviations
- Recording the results of any investigation carried out to get to the root cause of the deviation.
- Correcting deviations
- Completing corrective actions.
- Determining and implementing preventative actions.
- Reviewing the effectiveness of the corrective and preventative actions taken.
- Reviewing deviations regularly to address unfavourable trends.

4 Risk Management

4.1 Risk assessment procedure

<Each CRF should have procedures in place to ensure that risk is assessed as part of their quality system and according to local policy, this should be detailed in this section>

4.2 Study approval process

<Each CRF should have a procedure in place to ensure all required approvals are in place prior to a study opening, this should be detailed in this section>

5 Equipment

<This section details how equipment is handled within the CRF>

All equipment is purchased and commissioned according to SOP # *xxx*, and where appropriate, SOPs are implemented for the use of equipment. Only suitably trained personnel have access to equipment, and this training/competency assessment is

documented.

5.1 Equipment Introduction

Where applicable this equipment is:

- Subject to risk assessment
- Given an unique identifier for traceability and record keeping
- Validated
- Calibrated against traceable international or national standards
- Maintained
- Safeguarded from adjustments that would invalidate results
- Protected from damage and deterioration during handling, maintenance and storage
- Kept clean and fit for use
- Decontaminated and decommissioned

5.2 Risk Assessment

5.2.1 Where applicable, equipment within the facility is subject to a risk assessment, as per Trust/local policy to assess impact on patients and trial data.

5.2.2 Potential safety issues are identified and suitable procedures are implemented and documented to mitigate these risks.

5.3 Fridges and Freezers

5.3.1 Fridges and freezers within the facility are temperature monitored according to SOP/WI# *xxx*.

5.3.2 Fridges and freezers are lockable and access to keys are restricted to authorised personnel only.

5.3.3 A schedule for fridge and freezer defrosting is set according to SOP # *xxx*.

5.4 Calibration and Preventative Maintenance

5.4.1 All equipment is subject to mandatory testing (for example PAT testing) according to Trust/local policy.

5.4.2 Where appropriate, equipment must be calibrated and regularly maintained to ensure it is fit for use. Ordinarily, the schedule for maintenance and calibration will be according to the manufacturer's instructions.

5.4.3 Evidence of maintenance and calibration visits must be maintained.

5.5 Validation and CSV

<Validation is the provision of evidence that a system works correctly and gives expected results. The term CSV covers validation of computer systems including software.>

5.5.1 All equipment is demonstrably fit for purpose, and as a minimum this requires records of installation and regular maintenance by a qualified person.

5.5.2 For specialist equipment, a process of validation must take place according to

SOP# xxx.

5.5.3 Laboratory equipment should be maintained according to the MHRA's requirements: 'Guidance on the maintenance of regulatory compliance in laboratories that perform the analysis or evaluation of clinical trial samples.'

5.5.4 All computerised systems used to support the conduct of clinical trials must be fully validated according to SOP# xxx.

5.6 **Identification and Traceability**

5.6.1 All equipment must be allocated a unique identifier and this must be displayed on the equipment.

5.6.2 A comprehensive log of all equipment in the facility must be maintained, including details of the supplier, date received, serial numbers, as well as calibration and maintenance details.

5.7 **Decommissioning of Equipment**

Any equipment that is no longer required or is faulty must be decommissioned according to Trust/local policy.

5.8 **Patient Safety Alerts and Medical Devices**

<Detail here how medical device alerts from the MHRA are handled in the CRF>

6 Training

< The below sections document the minimum requirements of the training system in the CRF. The sample title and descriptions and may be documented under different terms in each CRF so should be formatted as required.>

The CRF ensures that all staff working in the CRF are appropriately qualified and have received adequate training to enable them to carry out their duties and the duties delegated to them by the PI.

6.1 **Staff Induction**

Staff are appropriately inducted following the guidelines and checklists included in SOP# *xxx*. Qualifications are checked and training needs assessed. Staff will also be provided with the list of SOPs / WIs that they must be trained before they can start work on their duties and studies.

6.2 **Training File Maintenance**

Individual staff are required to keep a training file that includes their CV, job description, training certificates etc. in line with SOP# *xxx.*

6.3 **Training Competency**

Each manager in the CRF is responsible for ensuring that training and resources are available to enable staff to be competent for their specified role. Staff training in some areas (e.g. cannulation) will require a competency assessment to provide evidence of

competency. Competency assessments will be completed in line with the SOPs / WIs describing the procedure being undertaken.

6.4 Quality System Training

All staff are required to read and record the fact that they have read and understand this manual and the associated SOP's that relate to the Quality System.

6.5 GCP Training

Certified GCP training is essential for all staff working on trials – this training must be refreshed according to local/trust policy. Staff are responsible for ensuring that details of GCP and other essential training are recorded on their CVs and the associated certificates kept in individual training files.

6.6 External personnel

Where relevant expertise is not available in-house the CRF employs out-sourced, external personnel to support its activities. The CRF also has external users. The CRF is responsible for ensuring that any external personnel working with/in the CRF comply with relevant regulations whilst working for the facility, refer to SOP# *xxx*

6.7 Emergency Scenarios

Staff will have their life support skills tested regularly with Emergency Scenarios.

7 Investigational Agents

<This section details how all investigational agents, both IMP and N-IMP, are handled in the CRF; this section will differ depending on the structure of the CRF e.g. whether there is dedicated Pharmacy support, and so should be amended appropriately>

The use of all IMPs in a clinical trial are covered by a CTA issued by the MHRA. All clinical trials will have full R&D approval prior to IMPs being received from the Sponsor.

7.1 IMP Receipt

As per MHRA guidance, the receipt and storage of IMP is delegated to the Pharmacy Department. This is clearly stated in Trust Policy (insert policy title and number). Pharmacy *<or other delegated responsible person>* are responsible for ensuring that IMP have been manufactured, handled and stored according to GMP (EU Directive 2003/94/EC), that each batch has been certified by the Sponsor's QP and that labelling adheres to Eudralex, volume 4, annex 13. Refer to the Pharmacy SOPs for further details.

7.2 Temperature Mapping and Monitoring

All IMPs have instructions for storage with specified temperature ranges. All IMPs are stored in secure, temperature monitored locations to ensure that the temperature range specified is not breached (refer to *<insert SOPs relating to temperature monitoring>).*

In the event of a temperature deviation, the following SOPs are in place and are

followed: refer to SOP# *xxx* which details the actions required in the case of temperature deviations, and arrangements for out of hours action/ quarantine.

7.3 Accountability

Accountability of all IMP (and NIMP) is recorded at all times, ensuring that adequate reconstruction of IMP and NIMP movement is documented. This is achieved by following SOP #*xxx*.

7.4 Handling of non-conforming IMP

Any non-conforming IMP is quarantined or returned immediately to the Pharmacy Department, as per SOP # *xxx <insert details of SOP relating to non-conforming IMP>* ensuring that no product is used. The Sponsor and research team is notified of the non-conformance and the non-conformance is logged and followed up by following SOP# *xxx <insert details of SOP relating to non-conformance management>.*

8 Audit

<This section details the internal audit programme and how external, third party audits are handled. Refer to the QA Workstream section in the UK CRF portal for guidance on internal audits, including checklists>

8.1 Internal Audits

8.1.1 Internal audits should be conducted to verify that each CRF quality system is in compliance with the established CRF and regulatory requirements and to verify the effectiveness of each system. The internal audit process is documented in *<enter SOP details>*

8.1.2 The CRF QA representative should compile and administer an agreed internal audit programme in the CRF. This will include implementing, scheduling, communicating, maintaining and monitoring the programme.

8.1.3 An internal audit programme should be planned and maintained with audits conducted periodically to monitor compliance with CRF policies and procedures and regulatory requirements, refer to SOP# *xxx*.

8.1.4 Audits should be performed according to SOP *<enter number>*

8.1.5 Audit activities are selected according to the audit programme and CRF priorities and requirements and should be performed by persons who are not responsible for the area being audited. Each audit activity should be reported and acted upon as necessary.

8.2 Internal Audit Report

8.2.1 An internal audit report should be created to summarise audit findings - *<enter SOP reference>*.

8.2.2 This audit report should document the observations and findings of the components audited, with a comment and recommendations where appropriate. This report should then be issued to the personnel responsible for the area audited for review and action and for escalation to senior management as required.

8.2.3 Non compliance/ deviations will be managed according to section 3.4 and /or CRF policy *<enter details>*.

8.2.4 Findings and actions identified by audit should be documented and addressed in a timely manner with implementation of corrective and preventive actions verified and documented as per section 3.4.

8.2.5 It is important that continual review of audit findings and the management of associated corrective and preventive actions are performed to ensure continuous quality improvement.

8.3 Third Party Audits

8.3.1 A system should be maintained to manage regulatory inspections and third party audits and any associated responses and actions. Findings or observations identified during an inspection or audit must be responded to and resolved in a timely manner.

8.3.2 If the CRF conducts external audits of vendors or service providers, such as suppliers or laboratories etc., then an external audit programme will be required, refer to SOP# *xxx*.

9 Researcher, Participant, Sponsor and Staff Feedback

<This section details how feedback and complaints are handled>

9.1 Complaints

9.1.1 It is important that feedback from stakeholders is taken into account as part of the process for evaluating and continually improving the quality of the service provided by the CRF, refer to local policy on complaint handling and/ or SOP# *xxx*.

9.1.2 Positive comments are reported back to staff and constructive feedback is used to improve our users' experiences.

9.2 Complaint Handling

The CRF follows *<insert SOP or Trust policy>* for managing complaints. Formal complaints are directed to *<insert job title>* in the first instance, who investigates the issue and attempts to resolve it as quickly as possible. In the event that local resolution of a complaint is not possible, participants may be referred to the hospital's Patient Advice and Liaison Service (PALS).

References

- Emma Deenihan, Quality and Regulatory Affairs Manager, HRB CRF Galway, Ireland
- Judith Rucklidge, Quality Lead, NIHR/Wellcome Trust Manchester CRF
- Chris Blackwell, Senior QA Lead, NIHR/Wellcome Trust Southampton CRF
- Ann Ward, Head of Operations and Quality Systems, Surrey CRC
- Susan Shepherd, QA Manager, Wellcome Trust Edinburgh CRF
- Carolyn Sexton, QA Manager, NIHR/Wellcome Trust Cambridge CRF
- Terese Morley, CRF Nurse Manager, Cardiff CRF
- Alex MacLellan, QA Manager, Edinburgh ECMC
- Paul Cross, Quality Assurance Manager, NIHR Guy's and St Thomas CRF
- Ian Mackay, Research Study Manager, NIHR/Wellcome Trust Manchester CRF
- National Institute for Health Research (NIHR)