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Clinical Research (Support) Unit Quality Manual

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11 December 2020

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Chief Academic Officer UL Hospital Group & University of Limerick
As Chair and on behalf of the CRU Management Board

Clinical Research (Support) Unit Quality Manual

Note:
This is a controlled document. The original signed copy is located in the Clinical Research (Support) Unit at UHL. It is the responsibility of any person using a copy of this document to ensure that they are using the most up to date version, by checking with the Quality & Regulatory CRA

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Reviewed By	CRU Management Board
Approved by	Chair CRU Management Board
Approval date	11 December 2020
Effective date	11 December 2020
Review date	July 2022
Version	Version 2.0

Document History:

Version	Date	Reason for Change	Author
1.0	July 2018	Initial Release	Maria Ryan
2.0	September 2019	2 year review: 1. Changed from UL logo to UL HRI logo 2. Corrected name of CRSU Board of Management to CRU Management Board throughout 3. Updated CHO3 to new title 4. Removed reference to Steering committee which no longer exists & updated organogram 5. Included reference to Greenlight process in section 4 6. Added definition for CAPA in section 5 7. Added clarification on how long training files of old staff members will be kept in section 7 8. Condensed section 8 as no pharmacy facilities within the CR(S)U and these activities will be the responsibility of the individual PIs 9. Amended the internal audit schedule to take place every 2 years 10. Amended the Equipment log check to occur annually	Marie Therese Hayes Maria Ryan

Acknowledgements

This Quality Manual is based on a template developed by the UK CRF Network and from the Clinical Research Facility – Cork (CRF-C)

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Purpose

This Quality Manual is a summary document providing a clear, high level overview of the quality management system, including related policies and procedures that are in operation within the University of Limerick Health Research Institute Clinical Research (Support) Unit (CR(S)U). This manual includes a description of each element of the quality system, and their associated sub-systems.

The Quality Manual demonstrates how the quality management system of the CR(S)U supports the delivery of research projects to the appropriate standards of research and clinical governance, thus ensuring that quality and safety considerations are embedded throughout the Unit, and promoting a culture of continual quality improvement.

This Quality Manual also outlines responsibilities at both a managerial and operational level in relation to the organisation's Quality Management System (QMS) and hence can provide a useful overview of the quality management system for new starters, new investigators, inspectors and other external visitors.

The mission statement of the CR(S)U is to:

- Promote excellence in the design, conduct and analysis of Patient Focused Research,
- To protect the welfare of research participants,
- To mitigate all elements of risk associated with the conduct of research in human subjects.

1. Introduction

The CR(S)U supports the delivery of research projects to the highest standards of research and clinical governance, ensuring that the rights, safety and well-being of trial subjects are the overarching concern and that quality and safety considerations are embedded throughout the Unit and promote a culture of continual assessment and quality improvement. The CR(S)U has documented and maintained a quality management system in accordance with the requirements of ICH Good Clinical Practice (ICH-GCP) Guidelines and all applicable regulatory requirements.

1.1 Adherence to Hospital policies and procedures

The CR(S)U is located in the CERC Building of University Hospital Limerick (UHL) and can work out of any of the six clinical sites that form UL Hospitals Group – namely UHL, University Maternity Hospital, Croom Orthopaedic Hospital, Ennis Hospital, Nenagh Hospital and St. John's Hospital. CR(S)U research staff can also be required to perform their duties in HSE Mid-West Community Healthcare settings.

For research activities performed outside the Units dedicated research rooms (e.g. hospital wards, Out Patient Departments (OPDs), GP clinics, etc.) CR(S)U staff will adhere to HSE and local hospital policies and procedures for:

- Hand Hygiene
- Blood spillage
- Acute anaphylaxis
- Cardiac arrest
- Infection control
- Phlebotomy

1.2 Scope of the Quality Manual

This Quality Manual applies to all staff that fall under the remit of the CR(S)U QMS namely CR(S)U Core and affiliated staff. 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.

1.3 Glossary of terms

Abbreviation	***Term***
CAO	Chief Academic Officer
CAPA	Corrective & Preventative Action
CERC	Clinical Education Research Centre
CRA	Clinical Research Associate
CRCI	Clinical Research Co-ordination Ireland
CR(S)U	Clinical Research (Support) Unit
CRU	Clinical Research Unit
HPRA	Health Products Regulatory Authority
HRI	Health Research Institute
HSE	Health Service Executive
ICH-GCP	International Conference on Harmonisation Good Clinical Practice
IMP	Investigational Medicinal Product
MoU	Memorandum of Understanding
NCR	Non Compliance Report
OPD	Out Patient Department
PI	Principal Investigator
QMS	Quality Management System
SOP	Standard Operating Procedure
UHL	University Hospital Limerick

2. Management Responsibility

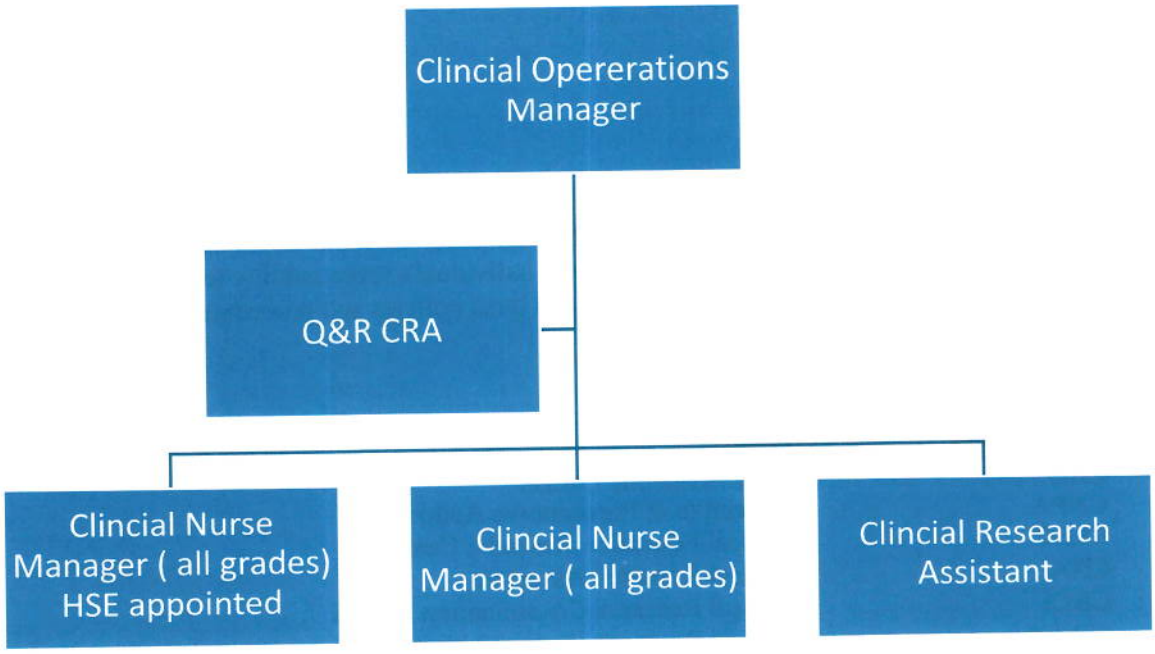
2.1 Overview of Management structure of CRSU

The Health Research Institute (HRI) Clinical Research (Support) Unit was established in 2014 as an integral part of the HRI to support its members in the conduct of clinical research projects. This included research nursing support for the planning, co-ordination and conduct of funded clinical research projects.

Partnership with UL Hospitals was agreed in 2015 through the signing of a Memorandum of Understanding (MoU) based on a detailed Framework Document for the governance of clinical research, through the now established, UL/UL Hospitals Clinical Research Unit (CRU).

The governance of this unit is through its Board of Management which has equal representation from both UL and UL Hospitals Group The board members are currently the HRI Director, the CAO UL Hospital Group, the HRI Clinical Operations Manager, a HSE appointed representative and HSE and UL co-opted personnel.

The day to day operational activities of the CR(S)U are managed by the HRI Clinical Operations Manager. The below organogram depicts the current CR(S)U structure:



2.2 Quality and risk mitigation structures

The CR(S)U QMS is directed by the Clinical Operations Manager who reports to the Director of the HRI.

The Quality &Regulatory Clinical Research Associate (Q&R CRA) will be responsible for the development and implementation of the quality structures including Standard Operating Procedures (SOPs) & written instructions and they will also oversee the conduct and update of the CR(S)U QMS.

The Q&R CRA will also be responsible for escalating any quality issues to the Clinical Operations Manager and the CRU Management Board if necessary

Processes such as change control, non-conformance, staff training, management of equipment, validation of computer systems, vendor selection processes are all designed to manage and mitigate risk.

The CR(S)U will undergo internal audits every 2 years or earlier if deemed necessary. Internal audits will be conducted by the Q&R CRA who is also tasked with membership of the Clinical Research Coordination Ireland (CRCI) Quality Working Group. External audit by sponsor companies or regulatory inspections will be facilitated as requested.

2.3 Resources

The CR(S)U and management are committed to appropriately resourcing the quality management system in order to meet regulatory requirements and to maintain and improve the effectiveness of the quality management system and its processes.

2.3.1 Premises

The CR(S)U provides and maintains adequate infrastructure needed to provide service to our users and conform to required regulations including:

- Office space and clinical rooms in the CERC building at University Hospital Limerick
- Process equipment (both hardware and software);
- Support services (e.g IT).

2.3.2 Staff

Staff Designation: The CR(S)U has 2 types of staff designation, largely determined by their employment contract.

Staff designations are:
CR(S)U Core or project staff are UL employees, have an immediate line of reporting to the Clinical Operations Manager for all matters and are fully subject to the CR(S)U QMS.
CRU Core staff are HSE employees, have an immediate line of reporting to the Clinical Operations Manager for their research related activities, have an immediate line of reporting to an appropriate Directorate Assistant Director of Nursing for administrative management and are fully subject to the CR(S)U QMS

All staff employed in the CR(S)U will undergo a process that ensures they have the right qualifications, skills, competencies and disposition to carry out their roles and be ambassadors for the CR(S)U. All staff have clearly defined job descriptions and will receive regular training as appropriate to their role and education. Staff are actively encouraged to undertake continuous professional development courses and to attend conferences and seminars to ensure that their skills are continuously developed and updated.

All CR(S)U staff have a responsibility to report any areas of concern with the QMS to the Clinical Operations Manager.

2.3.3 Work environment

The CR(S)U manages the work environment ensuring that the workspace is suitable for appropriate use.

3. Document control

The QMS has documented procedures (CRU QTY-13 *Document Control*) to control and manage the documentation associated with the operational and administrative procedures within the CR(S)U.

3.1 Documents

The CR(S)U QMS includes the following documents:

- The Statement of the CR(S)U's Quality Policy (CRU QTY POL STAT)
- This quality manual (CRU QTY MAN)
- Documented SOPs to ensure the effective planning, operation and control of the processes of the CR(S)U
- Work instructions that are prepared as necessary and detail how specified work should be carried out to ensure a systematic approach
- Templates and forms to assist with compliance with SOPs and policies

These documents (SOPs, Work Instructions, Templates, Forms) are all controlled i.e. they have a number within the QMS and are all version controlled.

SOPs are held on the CR(S)U shared drive with appropriate editing and traceability controls in place and are accessible to CRSU staff as necessitated by their role.

The Q&R CRA manages the controlled paper copy of the SOPs (Master). These Master copies are kept in a file in a lockable space with limited accessibility in the CR(S)U open plan office.

Local hospital policies are located on hospital systems and are available to HSE CRU staff via login to the local portal. Relevant hospital policies are available in hard copy in the CR(S)U open plan office.

3.2 Change control of documents

A system is in place to ensure that the latest copies of all documents are readily available to ensure effective functioning of the CR(S)U QMS.

There is 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 CRU-QTY-13 *Document Control*.

3.3 Retention of Records

Records are maintained in compliance with the various documents listed in the Reference Section, and to support the effective operation of the QMS.

Obsolete or updated SOPs are kept electronically in an "Archived SOP" folder and a hard copy folder marked "Superseded" is also maintained by the Q&R CRA.

3.4 Periodic review

All documents are subjected to periodic review every two years to ensure that the content remains up-to-date, in line with best practice and compliant with the applicable regulatory requirements. If a change in regulations that governs clinical research occurs this review may happen earlier.

4. Study Management & Approval Process including Greenlight Process

Application to Conduct Research in the CRU (CRU QTY-03) provides detail on the engagement process for Investigators and Sponsors wishing to work with the CR(S)U.

All studies will follow *Greenlight procedure for CR(S)U studies (*CRU QTY-14) and if the Sponsor has their own separate Greenlight process to be documented this will be facilitated in parallel.

5. Non-Conformance & CAPA

5.1 Non-Conformance

A non-conformance is defined as any discrepancy or deviation that demonstrates non-fulfilment to specified requirements of a task or a process. Reporting non-conformance is an essential part of the QMS.

5.2 CAPA Corrective Action and Preventive Action

A Corrective Action Preventive Action (CAPA) is defined as the process of identifying and taking actions that will permanently adjust people, machines, and procedures. The CAPA will be a specific, measurable, actionable, relevant, and time constrained verification plan to ensure that the corrective action had the intended result.

The Corrective Action is implemented to eliminate the causes of non-conformities, so as to prevent recurrence.

The Preventive Action is the Action taken to prevent the occurrence of such non-conformities, generally as a result of a risk analysis.

5.3 Procedure for CAPA and non-conformance

The CR(S)U has a documented procedure (CRU QTY-10 *Handling non-compliance in research*)

Any Non Compliance Reports (NCRs) raised will be reported to the CRU Board of Management meeting on an ongoing basis.

Findings or observations identified during an inspection or audit are responded to and resolved in a timely manner by the PI or delegated member of the CR(S)U staff.

5.4 Complaints

Any complaints or compliments on the service provided by CR(S)U should be reported to the Clinical Operations Manager, by whoever received the complaint/compliment.

The COM will bring complaints if deemed necessary to the CRU Board of Management meeting and appropriate action will be agreed and implemented.

6. Equipment Tagging, Calibration & Servicing

Equipment and consumables are purchased from approved vendors. All equipment is asset tagged, calibrated and maintained according to *Equipment/Resources tagging, servicing and calibration (*SOP-QTY-09).

CR(S)U staff will follow the instruction manual as the primary resource and instruction for use of all equipment and further training of the use of the equipment will be carried out if necessary (this training will be documented)

If necessary, the QMS document system will be amended to include additional documents such as SOPs or work instructions may be written for use with some equipment if the risk and complexity necessitates this. This will be managed with the QMS Change Control process.

6.1 Introduction of Equipment

Where applicable, CR(S)U new equipment is:

- Given a unique identifier for traceability and record keeping - a log of all unique identifiers will be kept by the Q&R CRA;
- Validated - which will included the operational Qualification (OQ) and equipment qualification (EQ)
- Calibrated against traceable international or national standards;
- Maintained
- Protected from damage and deterioration during handling, maintenance and storage;
- Kept clean and fit for use;
- Decommissioned when no longer required.

6.2 Fridges

The Fridges within the Unit will be temperature monitored as per manufacturers instruction. (The range of temperature excursions will be documented as part of a work instruction should they occur). The Fridge is kept in a store room where access is restricted to authorised personnel only.

6.3 Calibration, Maintenance and Identifications

Where appropriate, equipment will be calibrated and regularly maintained to ensure it is fit for use. The schedule for maintenance and calibration will be according to the manufacturer's instructions. This schedule will be the responsibility of the Q&R CRA who will maintain a file containing the calibration and servicing records (this will include the supplier, date received, serial numbers, as well as calibration and maintenance details as per SOP CRU QTY-09) A sticker affixed to the equipment can provide a quick visual confirmation that calibration is valid.

It is the responsibility of each staff member using the equipment to ensure it is within its service/calibration date.

The COM along with the Q&R CRA will perform an annual review of all equipment in the unit and determine it appropriateness and if fit for purpose including decommission equipment.

6.4 Identification & Traceability

All equipment is allocated a unique identifier which is displayed on the equipment. A comprehensive log of all equipment in the Unit is maintained by the Q & R CRA (as per SOP CRU-QTY-09). This includes details of the supplier, date received, serial numbers, as well as calibration and maintenance details.

6.5 Decommissioning equipment

Any equipment that is no longer required or is faulty must be decommissioned, taken out of use and disposed of appropriately. Some equipment while not in active use may be temporarily decommissioned and will be clearly labelled as such and stored separately to distinguish it from equipment in active use.

Such decommissioned equipment must be re-commissioned prior to being returned to active use. (As per SOP CRU QTY 09)

6.6 Computer system validation

All computer systems used in the CR(S)U must be validated either by ITD Enterprise Architecture procedure for non-cloud based systems or by the ITD Cloud Governance protocol.

7. Training

The CR(S)U ensures that all staff working in the Unit are appropriately qualified and have received adequate training to enable them to carry out their duties and the duties that may be delegated to them by the Principal Investigator (PI).

The CR(S)U Training Matrix (see CRU IN-04)) outlines the training and competencies necessary for each role.

7.1 Induction

All CR(S)U staff are appropriately inducted following the procedure in SOP QTY-08, *Research Staff Induction, Responsibilities and Training*. Training needs are assessed by the Clinical Operations Manager or a designee.
Personnel will also be provided with the list of SOPs / Working Instructions outlined in the specific training plans needed for the new employees and to which they must be trained before they can start work on their duties and studies.

7.2 Training File Maintenance

A training file is maintained for each staff member. This includes their CV, job description, training log, and training certificates in line with SOP CRU QTY-08. The file is populated as their induction training progresses and the relevant SOPs they train on before they commence their duties with the CR(S)U. Each staff member is responsible for ensuring that their training file is kept up to date.

Training files are kept by the COM in a secure locked office.

If a staff member leaves their position within the CR(S)U their training file will be kept for a period of 5 years to allow it to be reviewed if any of their studies are being inspected. After this retention period has ended the file will be shredded/destroyed.

7.3 Training Competency

The Clinical Operations Manager is responsible for ensuring that training and resources are available to enable staff to have the necessary competence for their specified role. Staff training in some areas may require a competency assessment to provide evidence of competency.

7.4 Quality Management System Training

The Q&R CRA will provide an introduction and overview to the QMS and training on all relevant SOPs and documentation to all staff within one month of its effective date. For new members of staff, they will receive this within 1 month of their start date.
After undergoing this training staff are required to record the fact that they have "*read and understood*" all required documentation as specified by the Staff Training Matrix (CRU In-04)

7.5 GCP Training

Certified ICH-GCP training is essential for all staff working on clinical trials that fall under the remit of the HPRA: this training must be refreshed every two years. Staff are responsible for ensuring that details of ICH-GCP and other essential training are recorded on their training log and the associated certificates kept in individual training files.

8. Investigational Medicinal Products/Devices

At present there is no pharmacy facilities in the CR(S)U. The process and procedures of the ULHG pharmacies will be followed for any studies where IMP is used.

Receipt and storage of Investigational Medicinal Product and devices will be the responsibility of the Principal Investigator of the study

It will also be the responsibility of the PI or delegated Pharmacist to ensure that all processes and procedures with regards to the Temperature monitoring and mapping and IMP accountability are carried out as per sponsor instructions and operating procedure of the Pharmacy.

Should any deviations to the process outlined be noted by CR(S)U staff this will immediately be reported to the PI or delegated pharmacist and follow up procedures will be monitored and reported if necessary

9. Audit

9.1 Quality control

Quality control is a pivotal part of the CR(S)U Quality System and will ensure:

- protection of human subjects from **research** risk,
- reliability of the data, and
- will also assure internal consistency of the QMS

Quality Control is undertaken by those performing, managing or supervising each process to ensure that the required standards have been met. It is the responsibility of all staff in the CR(S)U and those who are associated to the CR(S)U to adhere to the quality processes outlined in the QMS and ensure these standards are always met.

9.2 Internal audits

- Internal audits are conducted regularly to verify that each CR(S)U quality system is in compliance with the established QMS and regulatory requirements and to verify the effectiveness of each system. The internal audit process is documented in SOP CRU-QTY-11 (*Internal and External Audit*). The Q&R CRA compiles and administers the internal audit programme in the CR(S)U. This internal audit will occur once every 2 years and each area of the QMS will be audited in this time period. This involves implementing, scheduling, communicating, maintaining, performing and monitoring the audit programme
- Audit activities are selected according to the programme & CR(S)U priorities/requirements and are performed by persons not responsible for the area being audited. As part of the role the Q&R CRA will carry out all internal audits, the exception to this will be if they are responsible for a project being audited, in this case the COM will appoint an independent reviewer.
- An internal audit report is created to summarise internal audit findings. This will document observations and findings with comment and recommendations where appropriate. The report is issued to the CRU Management Board
- Continual review of audit findings and management of associated non conformities will be performed to ensure continuous quality improvement

9.3 Third Party Audits & Regulatory Authority Inspections

Systems are maintained to manage regulatory inspections and third party audits and any associated responses and actions, refer to SOP CRU QTY-11 *Internal and External Audit*, and SOP QTY-12 *Preparing for and hosting a Regulatory Inspection*.

References

- ICH GCP Guideline :www.ema.europa.eu/en/documents/scientific-guideline/ich-e-6-r2-guideline-good-clinical-practice-step-5_
- Declaration of Helsinki
- EU Directive 2001/20/EC.
- EU Directive 2003/94/EC.
- ICH E2A
- SI 190 of 2004. European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations, 2004.
- Amended SI 878 of 2004, European Communities (Clinical Trials on Medicinal Products for Human Use) (Amendment) Regulations 2004.
- Amended SI 374 of 2006 European Communities (Clinical Trials on Medicinal Products for Human Use) (Amendment No. 2) Regulations 2006.
- EudraLex volume 4, Annex 13: EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use.
- EU Medical Device Directive (93/42/EEC) labelling requirements – Annex 1