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Author	Dr Ruben Keane
Reviewed by	Maire McCarthy/ Dr Muiris Dowling
Approved by	Prof Joe Eustace
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Signature	
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2.0	25 May 2015	<ul style="list-style-type: none"> • Updated section 1.1 re use of local hospital policies to include response to Acute Anaphylaxis, Cardiac Arrest and how to deliver a subcutaneous injection. • Updated section 3.1 re document to indicate how to access local hospital policies • Updated section 7.3 re training to include existence of training matrix and to include core competencies for nurses. • Updated section 6.3 re-equipment to specify responsibility of staff to check that equipment is in service before they use it.
3.0	01 September 2017	<ul style="list-style-type: none"> • Include explicit reference to Sponsor risk assessment and management activities (as per ICH-GCP R2, section 5.0) • Include reference to SOP-QTY-25 Risk Assessment and Management of Sponsor Clinical Trial Activities at CRF-C

HRB- CRF-C Quality Manual



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Acknowledgements

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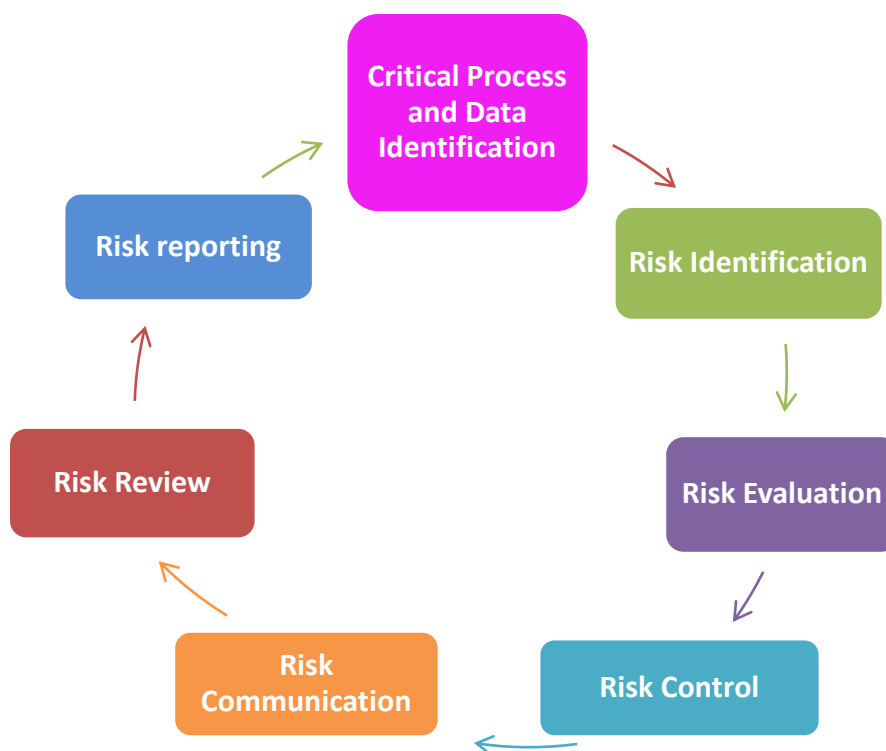
Purpose of this document:

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 HRB-Clinical Research Facility – Cork (CRF-C), which is co funded by the Health Research Board and University College Cork. This manual includes a description some of the essential elements of the quality system.

The CRF-C Quality Management System (QMS) incorporates risk assessment and risk management and mitigation into its key processes.

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.

Figure 1: Risk based approach to Quality management



The Quality Manual demonstrates how the quality management system of the CRF-C 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 Facility, 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 QMS and hence can provide a useful overview of the QMS for new staff, new investigators, auditors, inspectors and external users/ potential users of the CRF-C services.

The mission of the CRF-C 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 CRF-C supports the delivery of research projects to the highest standards of research and clinical governance, ensuring that the rights, safety and wellbeing of trial subjects are paramount and that quality and safety considerations are embedded throughout the Facility and promote a culture of continual assessment and quality improvement. The Clinical Research Facility has documented and maintained a QMS in accordance with the requirements of International Conference Harmonisation Good Clinical Practice (ICH GCP R2, section 5.0) Guidelines and all applicable regulatory requirements.

1.1 Adherence to Hospital Policies and Procedures

As the CRF-C research units are located within the University hospitals (Adult Research Unit – Mercy University Hospital; Paediatric Research Unit – Cork University Hospital) for the following activities the CRF-C staff adhere to the local hospital policies and procedures:

- Hand Hygiene
- Waste Disposal – including Hazardous Waste and Sharps
- Blood and Body Fluid exposure
- Blood Spillage.
- Acute Anaphylaxis
- Cardiac Arrest
- Administration of Subcutaneous Injection.

Some studies / trial may be carried out at other hospitals including South Infirmary Cork.

Similarly, local hospital policies will be followed there for the activities listed above. Local hospital policies can be accessed by those working in the hospitals using their personal log in and password. For temporary staff or students who do not have direct access to these systems, their supervisor will train them in any local hospital policies necessary to their role. This training will be documented in their training log (refer to SOP-QTY-2 Staff training and induction).

1.2 Scope of the Quality Manual

This Quality Manual applies to all staff that fall under the remit of the CRF-C Quality Management System namely CRF Core staff 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 Abbreviations Section

Abbreviation	Definition
CAPA	Corrective Action and Preventative Action
CRF-C	Clinical Research Facility-Cork
CSV	Computer System Validation
CTA	Clinical Trial Authorisation
ICH GCP	International Conference on Harmonisation of Good Clinical Practice
HPRA	Health Products Regulatory Authority
IMP/ N-IMP	Investigational Medicinal Product/non-IMP
SOP	Standard Operating Procedure
WI	Work Instructions
CAC	CRF-C Advisory Committee
UMTO	University Management Team - Operations
QRM	Quality and Regulatory Affairs Manager
CRRO	Clinical Research Reporting Officer
SRN	Study Research Nurse
UCC	University College Cork
HSE	Health Service Executive
VP-RI	Vice President for Research and Innovation
SRG	Scientific Review Group
QMS	Quality Management System
NCR	Non Conformance Report

Abbreviation	Definition
CUH	Cork University Hospital

2 Management Responsibility

2.1 Overview of Management structure of CRF-C

The CRF-C is co-funded by the HRB and by UCC. It is established by UCC's Operations Management Team (UMTO) as a non-academic independent Department within the UCC College of Medicine and Health (COMH), answerable to a dedicated Management Board, and advised by an independent CRF-C Advisory Committee (CAC). The UMTO meets quarterly and membership includes: the Head of COMH, Vice President for Research and Innovation (VP-RI), the Corporate Secretary / assistant Corporate Secretary, the University Bursar, a clinician-researcher and a representative from the Health Service Executive (HSE). The CRF-C provides an annual progress report to the HRB and is assisted in the prioritization of potential projects by a Scientific Review Group (SRG).

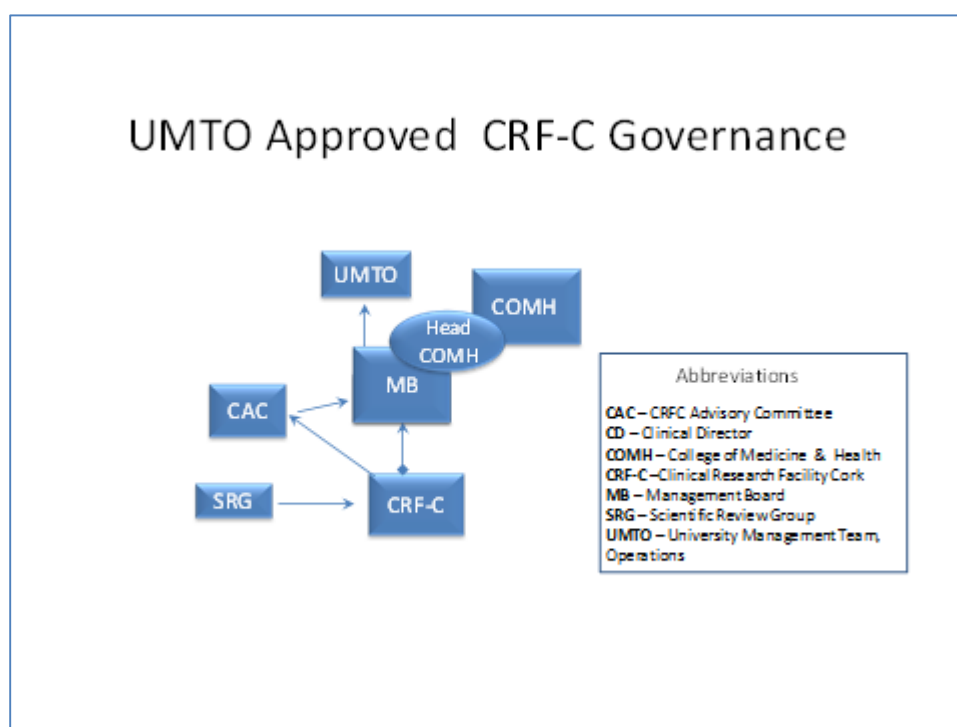


Figure 2: Governance Structure of CRF-C

Further details on the Governance structures may be found in 'HRB CRF-C Paper I- Governance Structures'.

2.2 Quality and Risk Mitigation Structures

The CRF-C Quality structures and Risk Mitigation Plan has also been approved by the UMTO (**CRF-C Paper II: The CRF-C Risk Mitigation Plan**). The CRF-C QMS is headed by a Quality and Regulatory Affairs Manager (QRM) who reports to a dedicated university compliance officer for clinical trials (Clinical Research Reporting Officer, CRRO), who in turn reports to the VP-RI. The QRM reports in parallel, for informational purposes, to the Director of the CRF-C. The VP-RI may avail of the advice as necessary of the UCC Risk Committee on issues of strategic concern to the University.

The QRM is responsible for the development and implementation of the CRF-C quality structures and Standard Operating Procedures (SOPs). This includes writing Sponsor SOPs to help ensure that UCC fulfils its sponsor responsibilities for clinical trials for which UCC is the legal sponsor. The QRM will also carry out Quality reviews and sponsor audits as required. The CRRO will review and sign off all UCC sponsor audits. An independent review of CRF-C quality structures (the Independent Risk Inspection) will be undertaken on an intermittent basis by an independent external consultant by way of quality assurance of the above structures. These independent reviews may involve selected processes / sponsor responsibilities (e.g. Pharmacovigilance) or selected UCC sponsored studies.

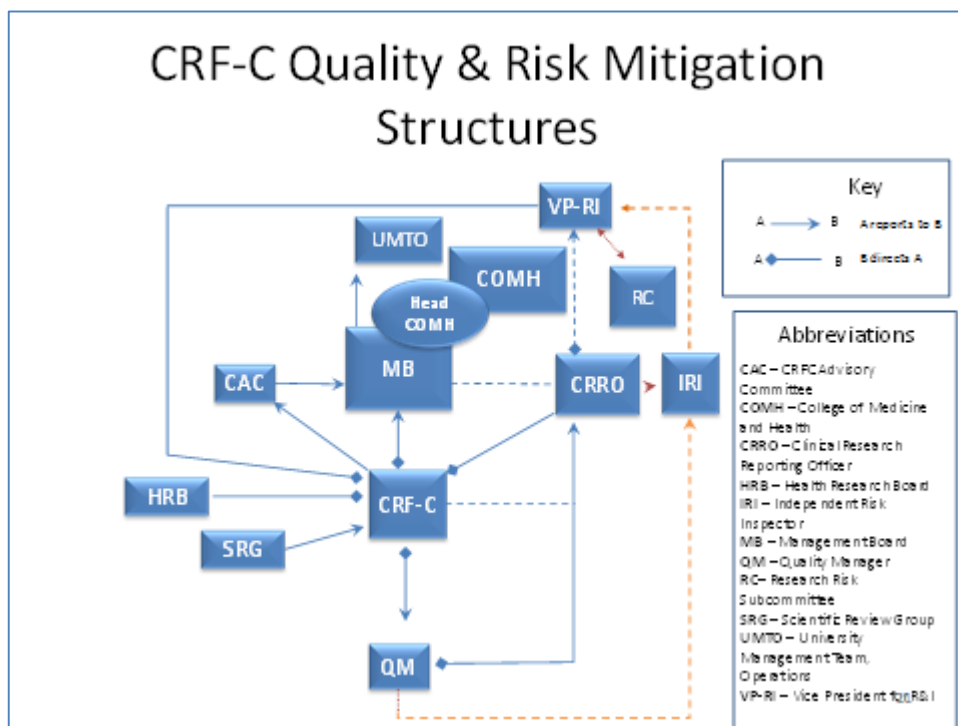


Figure 3: Quality and Risk Mitigation Structure

2.3 Constituent Units:

The CRF-C is divided along functional and geographical lines into several units.

- a. The Adult Research Unit (ARU) is located in the Mercy University Hospital (MUH) and includes the CRF-C administrative office, dedicated research rooms, pharmacy storage facility and laboratory.
- b. The Research Coordination and Management Unit is located in Lancaster Hall and houses the backroom research staff such as data managers, pharmacovigilance, regulatory, quality staff and research coordinators/ project managers.
- c. The Research Support Hub supports HSE clinicians - who would not otherwise have a substantive UCC interaction - in the conduct of individual research projects, these are often Pharma sponsored and conducted under contract between the Hospital, Principal Investigator (PI) and Sponsor. In these circumstances the PI, who is an Honorary Senior Clinical Lecturer in the University, requests the support of the CRF-C in conducting the study (using the processes outline in CRF-C Business development SOPs). If approved, the CRF-C provides these supports (e.g. advice, expertise staff, and equipment) to the PI. The PI remains fully responsible for the subsequent conduct of the trial. The Research Support Hub is a virtual unit in as much as it consists of different offices, in different locations used for research for differing periods of time. The CRF-C does not own or lease these offices which are instead owned by the HSE and remain under the applicable HSE governance and risk management structures.
- d. Affiliated Research Units: On occasion, if the scope of a proposed project is very large and prolonged, (such as a 5 year multicentre FP7 funded academic project) then the project may be established as an Integrated Research Unit within the CRF-C.
- e. External Projects Unit: The CRF-C also supports to a greater or lesser extent various established research groups through the provision of specific staff, equipment or research space; these groups are based outside of the CRF-C (though in many cases within UCC) and are considered collectively as the External Projects Unit, e.g. studies undertaken within the Adult Research Unit by visiting staff from centres such as APC.
- f. The CRF-C also has an education unit, the 'Patient Focused Research Unit' based within the UCC Department of Epidemiology. This unit is responsible for education and primary research in innovative research methods and not in conducting patient focused research.

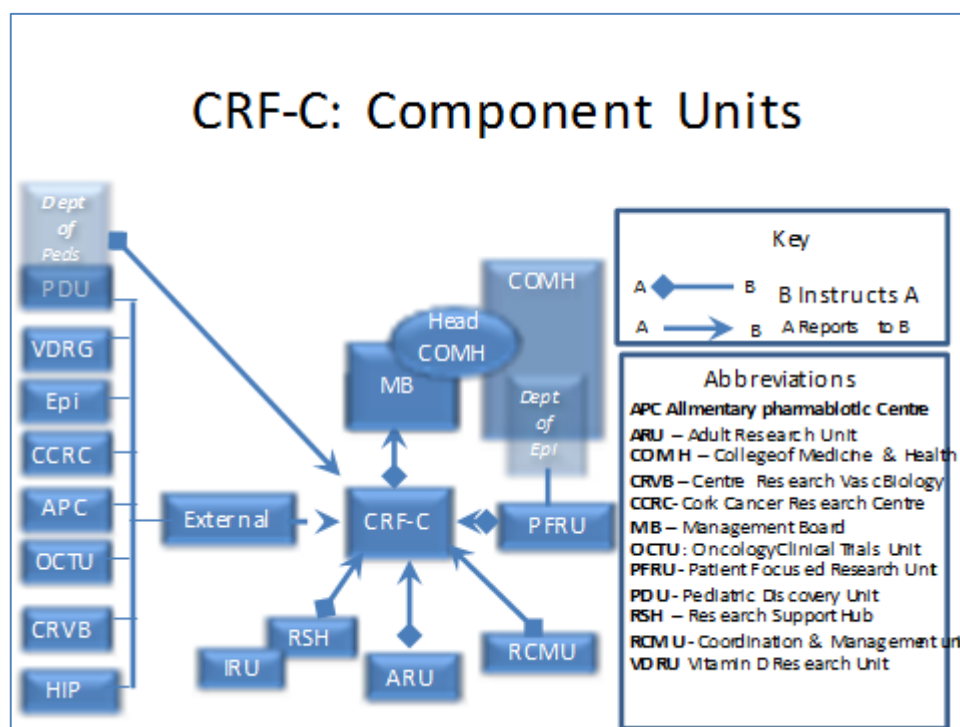


Figure 4: CRF-C Component Units

2.4 Resources

The CRF-C and management are committed to appropriately resource 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.

2.4.1 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 (e.g., domestic, porters etc.).

2.4.2 Staff

Staff Designation: The CRF-C has 4 types of staff designation, largely determined by their contract and the project on which they are working. Designation is dependent on

1. The individuals route of funding (whether via a CRF-C account or otherwise),

2. Their day to day line of reporting (whether within CRF-C or to an external research director), and
3. Whose QMS they fall directly under (the CRF-C QMS or an external centre's QMS).

Staff designations are:

- **CRF-C Core staff** are funded via the CRF-C, have an immediate line of reporting within the CRF-C and are fully subject to CRF-C QMS.
- **CRF-C Affiliated Staff** are funded via CRF-C and work within the CRF-C Integrated Research units, they are fully subject to its QMS but have an immediate line manager who is not a CRF-C core staff member (e.g. the PI of an FP7 funded project)
- **CRF-C Extramural Staff** are funded via the CRF-C, but have a line manager and comply with quality structures of an outside research group/centre. The extramural line manager is responsible for their training and professional development. This category includes some Research nurses who are embedded in the Oncology Clinical Trials Unit at CUH.
- **CRF-C Visiting staff** are not directly employed by or directly answerable to the CRF-C nor are they directly subject to the CRF-C QMS. However, CRF-C has requirements for any visiting staff including (at minimum) undergoing an orientation to the premises and emergency procedures and reading the CRF-C Quality Manual. If visiting users wish to use pharmacy storage area and or laboratory they are also required to comply with additional CRF-C procedures relating to these areas.

Staff are assigned to a portfolio, in accordance with their line of reporting, their qualifications, training and experience and also into one of 4 work streams. Staff will be assigned to only a single portfolio although they may work within 2 or more work streams.

The CRF employs staff who have been rigorously selected to ensure that they have appropriate qualifications, skills and competencies to carry out their roles adequately. All staff have clearly defined job descriptions, are assigned a supervisor and undergo an initial induction training (refer to SOP-QTY-2 on Staff Induction and Training).

Staff are actively encouraged to undertake professional development courses and attend conferences and seminars to ensure that their skills are continuously developed and updated.

All CRF-C staff have a responsibility to report any areas of concern they have relating to the quality system to their line manager, the Clinical Director and/or the Quality and Regulatory Affairs Manager.

2.4.3 Work environment

The CRF-C manages the work environment ensuring that the workspace is suitable for appropriate use. The centre manager is responsible for health and safety in the work environment and regularly updates the Health and Safety Risk Register.

2.4.4 Functional Organisation of the CRF-C

Portfolios: The work of the CRF-C is divided into several portfolios, based around common specific functions. Portfolios are overseen by a portfolio lead who is an expert in that area. The portfolios (and their leads) are Administration (Centre Manager), Business Development (Centre Manager), Facilities (Centre Manager) Clinical Trial Conduct (Clinical Trial Nurse Manager), Data Management (Data Network Manager), Biostatistics (Senior Lecturer in Biostatistics), Quality (QRM), Pharmacovigilance (QRM), Regulatory affairs (QRM), Research Education (Senior Lecturer in Education) and Methodology Research. The portfolio leads are responsible for the resourcing, staff development and strategic development of portfolio activities.

Work Streams: For day to day direction and the scheduling of workloads the CRF-C staff are grouped into 4 work streams, Commercial, Academic, Patient Focused Research Unit, and Quality. The work stream lead will be the immediate line manager for the staff within their work stream. Staff within individual portfolios may work across different work streams.

An organisational chart providing generic details is provided below (Figure 5.0) to demonstrate reporting lines in the CRF. The organisational chart is maintained by the Centre Manager and updated when required.

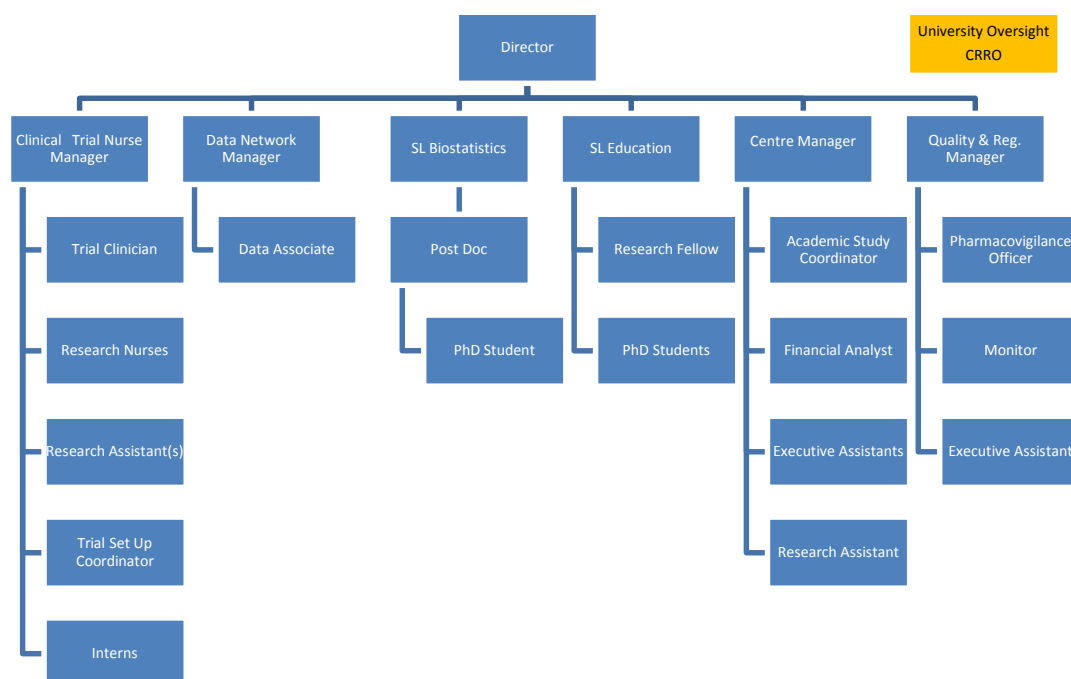


Figure 5: CRF-C Staff Organogram

Note: Members of integrated Research Teams report to their individual PI, Quality Staff report to UCC CRRO

3 Document Control

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:

- CRF-C Quality Policy Statement
- Quality manual.
- Documented standard operating procedures (SOPs) to ensure the effective planning, operation and control of the processes of the CRF. SOPs are in place in the areas of Quality, Administration, Business Development, Clinical Operations, Statistics, Data Management and Pharmacovigilance.
- Work instructions are prepared as necessary and detail how specified work should be carried out to ensure a systematic approach. (e.g. CRF-C-WI-01 Use of minus 80 Freezer)

SOPs are held on the CRF-C shared drive in pdf format) and are accessible to all core and affiliated staff.

The QRM keeps a hard copy of the SOPs in a folder in her office. A master log of SOPs, including version number and date, is kept electronically by the QRM. The master log is located on the CRF-C shared drive and can be accessed by all core and affiliated staff.

Local hospital policies are located on hospital systems and are available to the research staff working in the hospital via a personal log in and password.

For research assistants, students (who do not have direct access to the hospital system) they can request access to policies and procedures relevant to their roles via their supervisor who will train them on these policies and document this in their training record.

For visiting staff in MUH (who do not have direct access to hospital system) they can request access to relevant policies via the Executive assistant or Centre manager.

To facilitate easy access, the executive assistant will keep a folder in her office with a hard copy of MUH policies/ procedures for the following activities:

- Hand Hygiene
- Waste Disposal – including Hazardous Waste and Sharps
- Blood and Body Fluid exposure
- Blood Spillage.
- Acute Anaphylaxis
- Cardiac Arrest
- Administration of Subcutaneous Injection.

This folder will be checked and updated with new hard copy versions of policies (if relevant) every 6 months.

3.2 Change to documents - Control

A system is in place to ensure that the latest copies of all documents are readily available to ensure effective functioning of the CRF-C QMS. SOPs are kept on the CRF-C shared drive where all core staff can access them. A documented process is used to ensure that changes to SOPs are appropriately controlled, documented and approved by designated functions and that updated SOPs are introduced in a controlled and coordinated manner (refer to SOP-QTY-01 Preparation, review and approval of CRF-C SOPs, and SOP-QTY-13 Document Control and Archiving).

3.3 Retention of Records

Records are maintained in order to provide evidence of conformity to the requirements listed in the references section, and of the effective operation of the quality management system. Obsolete or updated SOPs are kept electronically in an 'Archived SOP' folder and a hard copy, marked Superseded, is kept by the QRM.

3.4 Periodic Review

All documents are subjected to periodic review to ensure that the content remains up-to-date, in line with best practice and compliant with the applicable regulatory requirements. The documents in the QMS were initially reviewed after six months (as it was a new system and following first competent authority GCP systems inspection) and thereafter will be reviewed every 2 years.

4 Study Management and Approval Process

4.1 Non UCC sponsored studies

Business development SOPS specify how external users can apply to use the CRF_C resources, staff and facilities. External sponsors normally have their own green light procedures which are carried out by the monitor/ Clinical Research Associate.

New studies are not subject to change control SOP.

4.2 UCC sponsored studies: A Sponsor green light procedure is in place (SOP-QTY-16) for both IMP and for essential documents. The QRM or designee carries out a review of IMP and Investigator site file/ Trial master file to ensure that all required approvals and training are in place prior to study start up. The CRRO reviews and approves the green light. Recruitment cannot begin until the CRRO has given the green light. This is part of the sponsors risk management process.

5 Non Conformance and 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 risk based QMS. The CRF-C takes action to eliminate the cause of non-conformities in order to prevent recurrence. Line Managers are responsible for the quality of the work carried out within their team and for escalating any quality issues to the quality representative and the Clinical Director if applicable.

5.2 Procedure for Non-Conformance

The CRF has a documented procedure (SOP-QTY-9 Non-conformance) which defines the requirements for:

- reporting non-conformances and raising a non-conformance report (NCR);
- determining the root causes of non-conformance;
- determining and completing corrective actions;
- determining and implementing preventative actions;
- reviewing the effectiveness of the corrective and preventative actions (CAPA) taken;
- Reviewing non-conformances regularly to address unfavourable trends.

NCRs will be reviewed at the monthly quality meeting. This meeting will be attended by the Clinical Director, QRM, Monitor, Centre Manager, Clinical Trial Nurse Manager and CRRO. Other functional areas may also be represented if appropriate. Non-conformances are risk assessed (refer to SOP-QTY-25) and risk mitigating actions agreed as part of the CAPA.

6 Equipment Logging, Calibration and Servicing.

Equipment and consumables are purchased from approved vendors (refer to SOP-QTY-11 Selection and management of Third Party Vendors and Suppliers). Selection of suitable vendors is a risk management process. According to the level of risk posed by the equipment being purchased, a suitable pre selection assessment will be done. This may be a phone questionnaire, a desk audit or on site audit of the vendor.

Once a piece of equipment is received at CRF-C it is asset tagged with a unique number (e.g. CRFC- 001), logged in an excel spreadsheet and due date of calibration and service noted (Refer to SOP-QTY-14 Equipment logging, servicing and calibration). Training in the use of equipment is carried out and documented on the training log (SOP QTY-2 Staff induction and training).

CRF-C staff will use the instruction manual as the primary resource and instruction for use of all equipment. Depending on the risk and the complexity of the equipment, additional documents such as work instructions may be written (e.g. WI-01 Use of minus 80 Freezer).

6.1 Equipment Introduction

Where applicable, CRF-C equipment is:

- given a unique identifier for traceability and record keeping;
- validated;
- 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.

Introduction of a new piece of equipment is subject to change control (SOP-QTY-6 Change Control). At the monthly quality meeting the change control committee will discuss the change and agree on appropriate actions including training on use of new equipment, servicing and maintenance. The change control committee consists of the attendees at the monthly Quality meeting namely: clinical director, QRM, Monitor, CM, CTNM and CRRO.

6.2 Fridges and Freezers

Fridges and freezers within the facility are temperature monitored according to SOP-QTY-22 Temperature monitoring at CRF-C. Fridges and freezers are kept in rooms where access is restricted to authorised personnel only.

6.3 Calibration and Preventative Maintenance

Where appropriate, equipment is calibrated and regularly maintained to ensure it is fit for use. Ordinarily, the schedule for maintenance and calibration is according to the manufacturer's instructions. A file containing the calibration and servicing records is kept as evidence of maintenance and calibration. A sticker affixed to the equipment indicates the date that service was carried out and when next service is due. This information is also recorded in the excel equipment log.

It is the responsibility of each staff member to ensure that the equipment is within its service date, before using it.

6.4 Computer System Validation

All computerised systems used to support the conduct of clinical trials are validated by the data manager or designee according to SOP-DM-2 Framework SOP-Computer System Validation for Clinical Trials... CRF-C can only be responsible for their own systems and not those of the Health Service Executive (HSE) e.g. in the

case of electronic patient records.

6.5 Identification and Traceability

All equipment is allocated a unique CRF-C identifier and which is displayed on the equipment. A comprehensive log of all equipment in the facility is maintained by the executive assistant, on the CRF-C shared drive. This includes details of the supplier, date received, serial numbers, as well as calibration and maintenance details.

6.6 Decommissioning of 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 equipment in active use. Such equipment must be re-commissioned prior to being returned to active use. Decommissioning of equipment is not subject to change control, the QRM and Centre Manager will decide on any necessary actions regarding disposal of the equipment.

7 Training

The CRF-C ensures that all staff working in the CRF-C 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. The CRF-C training matrix indicates what training and competencies are necessary for each role.

Having competent, adequately trained staff is part of the risk management processes of CRF-C.

7.1 Induction

All CRF-C staff are appropriately inducted following the procedure in SOP-QTY-2-Staff Induction and Training. Training needs are assessed by new staff and the line manager when a new staff member arrives and thereafter at least annually. New staff are provided with the list of SOPs / WIs 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-QTY-02 Staff induction and training... Each staff member is responsible for ensuring that their training file is kept up to date. As CRF-C staff are located in several locations, for practical reasons the training file is split over several locations including CUH and

MUH.

7.3 Training Competency

Each line 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 may require a competency assessment to provide evidence of competency.

7.4 Quality Management System Training

The QRM will provide an introduction to the QMS and training on all relevant quality SOPs to new core and affiliated staff within 1 month of their start date.

Staff are then required to read and record the fact that they have read and understand this quality manual and any relevant Quality SOPs, as specified in the training matrix.

7.5 GCP Training

Certified ICH-GCP training is essential for all staff working on trials that fall under the remit of the HPRA. CRF-C recommends that this training 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 Agents

8.1 IMP Receipt and storage

Investigators are responsible for receipt, storage and record keeping for the IMPs for their studies. The CRF-C provides a pharmacy storage facility which may be used by investigators for storage of Investigational Medicinal Product (IMP) and for Non IMPs (e.g. food supplements, OTC medications). The QRM assumes oversight of the pharmacy facility and its use is governed by SOP-QTY-17 Use of the CRF-C Pharmacy Storage Facility.

The investigator or delegated pharmacist is 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.

IMP for some pharmaceutical studies taking place in CUH may be stored in the research office or in the fridges or freezers in CUH. The designated study research nurse (SRN) will assume responsibility for IMP for his/her own study.

8.2 Temperature Mapping

Temperature mapping is completed as appropriate by the investigator/pharmacist/SRN to demonstrate that there is uniformity in temperature throughout the areas where IMP and ancillary supplies are stored.

8.3 Temperature Monitoring

All IMP storage areas within CRFC are monitored by wireless temperature monitoring systems, ICESPY in MUH and RTLS in CUH (refer to SOP-QTY-22 Temperature monitoring at CRF-C). All IMPs have instructions for storage with specified temperature ranges. It is the responsibility of the Investigator/pharmacist/SRN to ensure that IMPs are stored in secure, temperature monitored locations to ensure that the temperature range specified is not breached. The QRM will carry out monthly checks on the storage conditions in the CRF-C pharmacy facility and the CUH facilities

8.4 Temperature Excursions: A Temperature Excursion (in CRF-C) is defined as 10 minutes or more outside the specified temperature range. In the event of a temperature excursion, SOP-QTY-22 Temperature monitoring at CRF-C is followed. IMP is quarantined by QRM or designee and the sponsor companies are informed of the temperature deviation.

8.5 Accountability

Accountability of all IMP (and NIMP) is the responsibility of the Investigator/pharmacist or SRN as described above.

Accountability should be maintained at all times, ensuring that adequate reconstruction of IMP and NIMP movement is documented

8.6 Handling of Non-Conforming IMP

Any non-conforming IMP is quarantined, as per SOP-QTY-17 use of the CRF-C pharmacy facility, ensuring that no product is used until the disposition of the product has been decided upon by the sponsor. See also SOP-QTY-22 Temperature monitoring at CRF-C. The Sponsor and research team is notified of the non-conformance and the non-conformance is logged and followed up by using SOP-9 Non Conformance.

9 Audit

9.1 Quality Control

Quality control is a pivotal part of the CRF-C Quality System; Quality Control is undertaken by those performing, managing or supervising each process to ensure that

the required standards have been met, thus everyone at CRF-C has a role in Quality Control.

There are quality control steps in all required processes in the CRF-C to check and ensure that processes meet the predefined requirements.

9.2 Internal Audits

- 9.2.1** Internal audits are conducted regularly to verify that each CRF-C quality system is in compliance with the established CRF-C and regulatory requirements and to verify the effectiveness of each system. This is a pivotal part of the risk assessment and management processes of the QMS. The internal audit process is documented in SOP-QTY-7 Internal and External Audit.
- 9.2.2** The QRM compiles and administers the internal audit programme in the CRF-C. This includes implementing, scheduling, communicating, maintaining and monitoring the routine audit programme. The audit program is discussed and agreed with the CD and CRRO at the monthly Quality meetings. CD or CRRO may request that the QRM carry out audit if they have concerns re a particular study or process.
- 9.2.3** Audit activities are selected according to the audit programme and CRF-C priorities and requirements. Audits are performed by persons who are not responsible for the area being audited. QRM may request QRMs from other CRF/Cs in the region to audit a study or a process, or an external auditor may be contracted to carry out such audits.
- 9.2.4** An internal audit report is created to summarise internal audit findings (refer to SOP- QTY-7). The audit report documents the observations and findings of the components audited, with a comment and recommendations where appropriate. The report is issued to the personnel responsible for the area audited for review and action and for escalation to senior management as required.
- 9.2.5** A summary of audit findings is presented by QRM at the monthly Quality meeting. This regular review of audit findings and the management of associated corrective and preventive actions are performed to ensure continual quality improvement.
- 9.2.6** Audit findings (at discretion of the QRM/ CD/CRRO) may be escalated to become a NCR and then managed according to SOP-QTY-9 Non Conformance.

9.3 Third Party Audits and Regulatory Authority Inspections

Systems are maintained to manage regulatory inspections and third party audits and any associated responses and actions, refer to SOP-QTY-7 Internal and External Audit, and SOP-QTY-12 Preparing for and hosting a Regulatory Inspection. Findings or observations identified during an inspection or audit are responded to and resolved in a timely manner.

10 Researcher, Participant, Sponsor and Staff Feedback

10.1 Complaints/ Compliments- Customer Satisfaction

- 10.1.1** 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-C.
- 10.1.2** Any complaints or compliments on the service provided by CRF-C are reported to the Centre Manager and Clinical Director, by whoever received the complaint/compliment. Complaints and compliments will be discussed at the bi weekly Operations meeting and appropriate actions agreed, documented and implemented.
- 10.1.3** The Centre Manager keeps a log of complaints and compliments.
- 10.1.4** The centre manager seeks customer feedback by sending out customer satisfaction surveys at regular intervals.
- 10.1.5** Positive comments may be reported back to staff to encourage and motivate and constructive feedback is used to improve our users' experiences.

11.0 Risk assessment and management of Clinical Trials Activities

11.1 SOP on Risk Management: *SOP-QTY-25 Risk assessment and management of sponsor clinical trial activities* outlines how and when risk is assessed and managed within the CRF-C. ICH-GCP R2 (section 5.0) indicates that sponsors should identify processes and data that are critical to ensure human subject protection and reliability of trial results. Sources of risk include staff, equipment, processes, products, changes. Reputational and business risks will also be considered, as well as risk of not meeting regulatory or contractual obligations.

11.2 Key issues to consider in relation to risk management include:

- What are the risks associated with the HRB-CRF-Cs organization's context and objectives - and why does each risk occur? (Risk)
- What would be the likely negative consequences of process, product, service or system nonconformities? (Consequence)
- How likely is it that the organization will deliver nonconforming products/ services in relation to the risks we have identified? (Probability)

We also need to consider the effectiveness of existing controls and what additional actions we may need to put in place to further mitigate the risk.

A formal risk assessment and mitigation process is described in SOP-QTY-25 Risk assessment and management of sponsor clinical trial activities. This is carried out at critical points for example when a new UCC sponsored study is being set up, when new equipment is purchased (Risk assessment included as part of the change control process- SOP-QTY- 6), when non-conformance is identified (Risk assessment included in non-Conformance process SOP-QTY-9). Mitigating actions for controlling risks of staff changes are included in SOP-AD-18 Staff changes at CRF-C. Actions for controlling risks due to new studies and new users of CRF-C are included in Business development SOPS.

SOP-QTY- 25– Risk Assessment and Management of Sponsor Clinical Trial Activities

- Defines roles, responsibilities and authorities for managing risk, and carrying out risk assessments,
- Defines conditions for carrying out formal or informal risk assessments
- Outlines what records need to be made and retained in relation to risk assessment and management.

Figure 6: the risk assessment matrix used at HRB-CRF-C is shown below.

	Severity for Negative Event (S)			
Negative Event Probability of Occurrence (P)	3 - Critical	2 - Moderate	1 - Minor	0 - Not significant
3 - High	Critical Risk	Critical Risk	Unacceptable Risk	Acceptable Risk
2 - Medium	Critical Risk	Unacceptable Risk	Acceptable Risk	Acceptable Risk
1 - Low	Unacceptable Risk	Acceptable Risk	Acceptable Risk	Acceptable Risk

11.3 Risk Management Plan (RMP): A risk management plan (RMP) is written for all critical and unacceptable risks. The risk management plan will outline the actions which will be taken to manage and mitigate the risk and QRM will communicate these actions to the relevant people. QRM will review the outstanding actions once a month (at monthly Q and S meeting) and update the RMP as necessary. The RMP will be formally reviewed annually (or more frequently if specified) by the author and reviewer(s). Date that RMP is to be reviewed will be noted on the RMP. Study specific risk management plans will be filed in the Trial Master file for that study. Important deviations from remedial action taken will be reported in the final study report (as per ICH-GCP R2)

11.4 Review of Risk Control measures: The QRM and CRRO will review the risk control measures annually to ascertain if the QM activities are effective and relevant.

References:

- ICH GCP Guideline (R2)
- Declaration of Helsinki
- EU Directive 2001/20/EC.
- EU Directive 2003/94/EC.
- EU Directive 2005/28/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.