University College Cork

Patient Focused Research Quality System.

Version 1.0

Contents

Executive Summary

- All Patient Focused Research in UCC falls under the UCC Quality System *(PFR sponsor's office, quality reporting structures, research appropriate SOPs).*
- For all Clinical Trials, the default (unless otherwise approved by the Clinical Research Reporting Officer - CRRO) is that these are conducted through the CRF-C.
- Any clinical trial approved by the CRRO for conduct through one of UCC's other research centres will report Quality through the CRF-C.
- This document formally established the role and function of the UCC Sponsor's Office within UCCs research administration.
- A Patient Focussed Quality Working Group is already in place in UCC to share best practice, and this document formally establishes this working group.

1. Purpose The document describes the structures and functions of the UCC Patient Focused Research Quality System (PFR Quality System).

2. Scope This policy applies to all UCC staff and/or where the proposed research is being conducted in or is being supported by a UCC research unit. It applies to Clinical trials and Patient Focused Research and as such to any project that requires CREC approval (or in the case of Regulated trials approval by an appropriately recognized ethics committee). See appendix 4 for a definition of a clinical trial and patient focused research.

3. Research Authorization**:** The ability of UCC investigators to undertake research involving patients or healthy subjects is not an automatic entitlement. It requires that several prerequisites are met in order to safeguard the rights, safety and wellbeing of participants before the research can be conducted. These requirements are distinct from requirements for Ethics Committee approval or any hospital approval process –as required- and are analogous but separate to the University's governance and oversight requirements in areas such as financial probity, intellectual property, research integrity and legal contract review. To be in a position to conduct Patient Focused Research, it is required that:
    - The research team can demonstrate the appropriate experience and expertise in the type of research being conducted, both individually and, as necessary, on a collective basis.
    - The proposed research setting is appropriate to safeguard the health and wellbeing of both participants and researchers and that it meets the relevant standard(s) of clinical care
    - The research team is able on a real time and ongoing basis to identify and mitigate any potential risks associated with the study to the fullest extent possible and to assure the accuracy and validity of the study data. Appropriate quality measures are an essential component of research integrity. The extent and complexity of these quality processes is dependent on the nature and risk profile of the study.

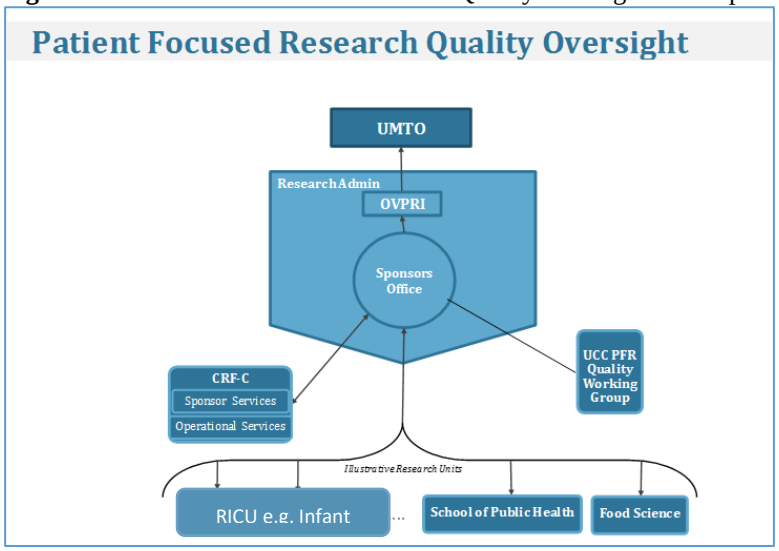
    To assist researchers in meeting these requirements and to protect the rights, safety and wellbeing of research participants and, where relevant, to assure UCC's compliance with its legal requirements as research sponsor, it has developed a comprehensive Patient Focused Research Quality System. In view of the risks inherent in conducting research that involves conducting interventional experiments on human subjects (i.e. clinical trials) and the conditions attached by the underwriters to the University's Clinical Trial Indemnity Policy that cover such research,

the *University has decided on a default position that all Clinical Trials will be conducted through the HRB Clinical Research Facility- Cork (unless otherwise approved by the CRRO.)*

4. UCC Patient Focused Research Quality System Overview**.** The PFR Quality System refers to the aggregate institutional Quality structures and processes, including all of its constituent components. UCC has a single PFR Quality System. It comprises:
    - *PFR Sponsor*s Office. The UCC PFR Quality System is overseen by the UCC Sponsors Office based within the Office of the Vice President of Research and Innovation.
    - *PFR SOPs* The quality system includes an array of Standard Operating Procedures specifying how various core research activities should be undertaken. The number of relevant SOPs will vary depending on the nature of the study being undertaken. Some are relevant to all research, some are limited to Clinical Trials and others to Regulated studies. Clinical Trial related SOPs are maintained by the CRF-C.
    - RICUs within UCC (other than CRF-C) may also have SOPs which cover Clinical trial activities. Such Sops must be at least equivalent to CRF-C Clinical Trial SOPs.
    - RICUs may also have additional specialised SOPs e.g. SOPs covering populations.
    - *Quality* Reporting *Structures.* All research units and investigators must have a clearly defined structure for communicating, and escalating as necessary, routine quality reports and any quality issues to the University. It is expected that investigators would achieve this by working with the centre or Department/School in which they are based.
    - *UCC PFR Quality Working Group* consisting of the Quality Officers from UCC research units which meets regularly in order to help guide and advise on the development and dissemination of best PFR quality practises.

5. UCC Sponsor's Office is based in Research Administration in the Office of Vice President of Research and Innovation and oversees the running of the UCC PFR Quality System, see Figure 1. It reports directly to the VP-RI. It currently is staffed by:
    - Clinical Research Reporting Office (CRRO), who serves as the university Compliance Office for PFR
    - Senior Quality Manager who reports to the CRRO.
    - Executive Assistant.

Figure 1: UCC Patient Focused Research Quality Oversight and Reporting.



The advantage of establishing a formal PFR Sponsor's Office, as distinct to simply having the staff based within Research Administration generally, is that it will:

- Facilitate long term planning and the succession planning of staff within the Sponsors office.
- Help to highlight to funders some of the additional resources required to oversee PFR, over and above those needed for other forms of biomedical research generally.
- Allow for cross cover during planned absences of staff.
- Increase the awareness and visibility of the work undertaken by the Sponsor's Office.
- Provide clarity to Investigators regarding where to seek regulatory and related advice on PFR and ensure that such advice is provided by appropriate staff and is in keeping with UCC approved policies.

The Sponsor's Office has several principal functions:

- Risk assessment of new proposals or projects in accordance with the approved UCC policy, including assessment as to whether the proposed unit has sufficient resources and quality processes to undertake the proposed research.
- Carrying out a sponsor greenlight process for regulated clinical trials and clinical investigations, and for medium/ high risk, non-regulated interventional studies sponsored by UCC.
- Providing the capacity to undertake (on behalf of Research Administration) a quality review or sponsor audit on an individual project or a 'systems audit' of a Research Unit's PFR quality processes.
- Providing a system for tracking and reviewing major Non-conformances (including major protocol deviations or breaches of ICH GCP, Data Protection, research integrity or other relevant regulations or policies).
- Escalating major non-conformances (NC) and their associated Corrective and Preventative Actions (CAPA)to the VP-RI.
- Reviewing reports arising from regulatory inspections, sponsor audits and monitoring and quality reviews of UCC studies undertaken by external agencies.
- Providing guidance and advice to Research Units regarding the expected generic standards for the local quality processes, and advice as to their development.
- Providing central quality processes governing the specific activities of the Sponsor's Office.
- Facilitating the further development of a UCC PFR Quality Working Group (see below).

The Sponsor's Office does not itself directly undertake any Patient Focused Research and therefore its SOPs will be concise and related to the above processes.

6. PFR Standard Operating Procedures

Some SOPs are relevant to all research (e.g. obtaining consent), some are limited to Clinical Trials and some are only relevant to Regulated Clinical Trials (e.g. preparing for a regulatory Inspection). Some SOPs for non-regulated trials (basic essential SOPs) have been developed by the UCC PF QWG and are available on the UCC Research Support Services (RSS) website. SOPS relating to regulated trials have been developed and are maintained by Quality and Regulatory Affairs Director (QRD) at CRF-C in consultation with Sponsor CRRO. These are reviewed every two years. They are available to research groups in UCC on request. RICUs within UCC (other than CRF-C) may also have SOPs which cover Clinical trial activities. Such Sops must be at least equivalent to CRF-C Clinical Trial SOPs. RICUs may also have additional specialised SOPs e.g. SOPs covering populations. A unit will often benefit from individualizing an

SOP to its own specific requirements, this can be facilitated by the assistance of the UCC Patient Focused Research Quality Working Group and the Sponsors Office. However, any modification of the SOP cannot result in a reduction in the frequency or level of reporting below that set out in the standard SOP. The Sponsors Office will each year request quality reviews of selected studies, which will include in part a review of the units' SOPs and related quality processes.

7. Individual Research Unit Quality Management Systems and Reporting Structures.

The University currently has a range of research units that undertake Patient Focused Research of varying degrees of complexity. Each of these units should have the necessary policies and structures in place in order to:

- Mitigate the risk to all parties (especially study subjects / patients) arising as a result of PFR.
- Ensure that all necessary approvals, including Green Light (if appropriate), are in place before project commencement.
- Establishing that research is conducted to necessary standards in accordance with the approved protocol, current guidelines and relevant legislation and regulations.
- Ensure the integrity of the data produced by the study.
- Identify, report and respond to any protocol deviations or other non-conformances.
- Take steps necessary to limit untoward consequences of any protocol deviation, non-conformance or other quality concern, and to develop and execute a Corrective and Preventative Action plan.

The standard route of reporting for observational studies is via the investigators Research Unit or university Department/School.

The HRB CRF-C has specific detailed Quality Reporting Structures that comply with the legal requirements for regulated studies. Many of these processes been reviewed by the Irish Competent Authority (Health Products Regulatory Authority- HPRA) and have been specified by the University's underwriters as a requirement for coverage under the university's Clinical Trial Indemnity Policy. The CRF-C has extensive SOPs, dedicated QMS software, a monthly Quality and Safety Meeting attended by the CRRO and specific reporting procedures to the senior university leadership.

A research unit's Quality Management System has several components:

- A process for identifying key specific risks that require specific assessment or monitoring.
- Appropriate safeguards/controls to mitigate the identified risks, e.g. identify the activities that require specific SOPs /or forms.
- A set of appropriately detailed SOPs for key activities conducted by the unit.
- A regular meeting of designated senior staff responsible for overseeing changes within the unit that may impact on quality and to examine any non-conformances (including protocol deviations, SOP deviations, breaches of data protection etc.) and other quality related issues.
- A process for reporting Non-Conformances to the UCC Sponsor's Office and for developing a Corrective Action and Preventative Action plan.

Each research unit should have a designated person (Quality Officer/Quality Manager) responsible for coordinating local quality activities and assisting the Investigator(s). However, it is important to note that the investigators remain ultimately responsible for the conduct of the study. Depending on the number and type of PFR being carried out this local quality function may be part of someone's role, or a dedicated quality person may need to be in place.

The designated Quality person will be a member of the UCC PFR Quality Working Group and will attend their meetings on a regular basis. This person will in conjunction with the Quality Working Group will:

- Undertake horizon scanning of relevant national and international developments which might impact on the unit's research, such as new legislation.
- Disseminate updates on quality related issues to Unit staff and ensuring existing processes remain current.
- Carry out monitoring/ quality reviews of PFR within the unit.
- Facilitate the conduct of sponsor's audits and/or quality reviews within the unit.

The above policies and structures should be appropriate to the size of the unit and the nature of the research being undertaken. They should be fit for purpose but not place an unnecessary burden on the research, especially the conduct of low risk observational research. In most cases the essential SOPs for simple observational studies can be downloaded directly from the RSS webpage along with the Research Reporting Structures Template which can be rapidly completed. In some cases, where the Research Units research includes particular risks and specific measures to mitigate these risks, then the basic SOPs may benefit from being individualized or in having additional SOPs put in place.

8. UCC PFR Quality Working Group

This group meets regularly and includes quality representatives working within UCCs various Research Units in the broad area of PFR and a representative from the PFR Sponsor's office. The group provides a cohort of specialists with a strong interest in and focus on quality issues.

The UCC PFR Quality Working Group will refine its terms of reference, which will include:

- Foster an appropriate quality-focused PFR environment in UCC
- Support individual unit's Quality Officers as they develop and maintain their local quality processes.
- Develop an appropriate introductory document as to the basic requirements of a Unit's Quality Processes.
- Develop teaching materials/ presentations that could be delivered on an annual or as need be basis to relevant research staff within the university.
- Draw up templates and generic SOPs which could be customised by each Research Unit. SOPs and templates developed by the group to date are available on https://www.ucc.ie/en/research/support/policies/patient-focused-research/
- Support horizon scanning and dissemination of new information to the individual quality representatives.

9. Quality Approval Process.

A Patient Focused Research Questionnaire (PFQ) is completed for all PFR in UCC and is reviewed by the Clinical Research Reporting Officer in the UCC Sponsor's Office. This review involves categorisation of the type of study (appendix 1) and a risk assessment. The default position is that all clinical trials will be conducted through the HRB CRF-C. The appropriateness of the quality processes in place at the study centre will be considered by the CRRO during study review and will be assessed by a regular audit cycle undertaken by the Sponsor's Office. At the discretion of the Sponsors Office observational studies that are assessed to be high risk (such as some with invasive testing) may be required to involve the HRB CRF-C to some extent as agreed with the Principal Investigator (PI) and the CRF-C.

In the case of Externally Sponsored or UCC Sponsored Clinical trials where the HRB CRF-C does not have the necessary subspecialty research staff to conduct specific functions within the trial but an alternative specialist centre does have such staff, then specific trial functions may be carried out at the specialist study centre, if the CRRO is satisfied that the specific centre has the necessary expertise and appropriate resources in place. In all such cases the trial will continue to report quality metrics and reports through the CRF-C.

Where researchers undertaking a Clinical Trial request that they need to directly undertake some trial functions themselves, rather than using the HRB CRF-C, they will discuss this with the UCC Sponsors office. This need will most usually arise where specialist staff are required which the CRF-C does not have. Potential responses by the Sponsors Office to such a request would include:

- Decline the request and Instruct site to conduct the trial via the CRF-C.
- Approve the use of specialist unit staff for specific purposes, while continuing to report Quality Issues to the CRF-C
- Approve the use of specialist unit staff for specific purposes with the additional assistance/supervision by CRF-C staff, as agreed with the PI and the HRB CRF-C, and with the reporting of Quality Issues to the CRF-C
- **Thus, as is required by UCC Clinical Trial Indemnity Policy, all Clinical Trials will provide risk-based quality reporting via the CRF-C**.

10. Justification for conducting /reporting clinical trials through the HRB CRF-C

- More cost effective than outsourcing to a commercial provider for technical services such as monitoring.
- As the HRB CRF-C is a 'Designated Entity' under States Claims Agency Clinical Indemnity Scheme research that falls under the CRF-C quality reporting structures is covered for medical malpractice even where the PI is a full time UCC employee rather than a HSE employee.
- Ensures consistency of output and uniformity of processes in conduct of high risk studies across UCC
- Allows development of critical mass of quality staff whose primary focus is on quality issues in high risk trials
- Provides a consistency in training regarding high risk trials which improve the quality of research being undertaken at UCC.
- Provides a sufficient volume of work so as to maintain familiarity with rare events such as reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs) to the regulatory authorities and undergoing a HPRA inspection
- Enables UCC to develop positive relationships with the HPRA via the dedicated Sponsor Quality Regulatory personnel.
- Provides a single source of informed advice/ guidance regarding regulatory requirements for high risk trials
- Provides Investigators with assurance that a trial is being conducted to appropriate standards
- Provides PI and study teams with the necessary support when undergoing regulatory Inspection of studies or Sponsor audits.
- Helps develop and protect the reputation of UCC as a sponsor of high risk Academic Clinical Trials.
- Facilitates training, cross cover and horizon scanning

Note that the CRRO may deem a unit competent to carry out trial using their own QMS, under the supervision /oversight of CRF-C Quality staff.

Appendix 1: UCC patient focused research classification table

1 Investigational Medicinal Product	
1A	This is a regulated clinical trial where an academic institution assumes the role of legal Sponsor.
1B	This is a regulated clinical trial where the academic institution has a role but where a third party assumes the role of Sponsor (for example pharma company)
2. Medical Device for example from a bandage to a cardiac stent - key issue is the risk classification of the device trial, is it assessed as Class I, II, III (with III being the device investigation with the highest risk).	
2A	This is a regulated clinical investigation where an academic institution assumes the role of Sponsor.
2B	This is regulated clinical investigation where an academic institution has a role but where a third party assumes the role of Sponsor (for example device company).
3. Non (Competent Authority) regulated clinical trials such as trials of nutritional products, exercise programs, care pathways.	
3A	This is a non- regulated clinical trial where an academic institution assumes the role of academic Sponsor.
3B	This is non- regulated clinical trial where an academic institution has a role but where a third party assumes the role of academic Sponsor.
4. Non-interventional/observational studies which can be further sub-divided into I, II and III, where observational studies involve: I - no invasive testing II - low risk tests, such as blood or swabs (includes observational testing of medical devices) III - invasive clinical procedure such as lumbar puncture and tissue biopsy (e.g. additional stomach or bladder biopsies for research purposes taken during clinically indicated procedure)	
4A	This is an observational study where an academic institution assumes the role of academic Sponsor.
4B	This is an observational study where an academic institution has a role but where a third party assumes the role of academic Sponsor.

Appendix 2: UCC default quality expectations by research type (as determined by Sponsor's Office)

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	Observational			Interventional, non HPRA-regulated							Interventional, HPRA-regulated	
				Non-IMP (food, herbal products homeopathic product, radiotherapy, surgery research studies etc.)			Device				IMP	Device
							CE marked product		Non-CE marked product			
	Non-invasive testing (data collection only)	Low risk tests, such as blood, swab, etc.	Invasive clinical procedure such as lumbar puncture, tissue biopsy, CT Scans etc.	Trials of nutritional products, exercise programs, care pathways etc.	Trials of interventions that may have physiological or clinical effects.	Trial of invasive or potentially harmful non-IMP intervention.	invasive / potentially harmful Intervention	Non-invasive intervention	invasive / potentially harmful Intervention	Non-invasive intervention		
Sponsorship Risk level	Low	Low	Medium	Low	Medium	High	High	Medium	High	Medium	High/ regulated	High/ regulated
Requirements												
Explicit consent/CDC waiver	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Approval by Risk Committee	No	No	No	No	No	Yes (if requested by CRRO)	Yes (if requested by CRRO)	Yes (if requested by CRRO)	Yes (if requested by CRRO)	No	Yes (if requested by CRRO)	Yes (if requested by CRRO)
Sponsorship Risk assessment	No	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Risk-benefit analysis (procedures must be within PI's competencies and must be indemnified by medical malpractice insurance /indemnity).	No	No	Yes (e.g. undergoing biopsy for clinical reasons, additional biopsies taken for research)	No	Yes - to ensure that the risk / benefit ratio is positive.	Yes – to ensure that the risk / benefit ratio is positive	Yes – to ensure that the risk / benefit ratio is positive	Yes – to ensure that the risk benefit ratio is positive	Yes – to ensure that the risk benefit ratio is positive	Yes – to ensure that the risk benefit ratio is positive	Yes – to ensure that the risk / benefit ratio is positive	Yes – to ensure that the risk benefit ratio is positive
ICH-GCP risk assessment	No	No	No	No	No	No	No	No	No	No	Yes	Yes
Risk management plan	No	No	No	No	No	No	Yes	No	Yes	No	Yes	Yes
Pharmacovigilance Plan	No	No	No	No	No	No	No	No	No	No	Yes	Yes
Contract with clinical site (CTA)	No*	No*	No*	No*	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Green light	No	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Monitoring	No	No	No	No	Yes – risk based	Yes – risk based	Yes – risk-based	Yes – risk based	Yes – risk based	Yes – risk based	Yes – risk- based	Yes – risk based

*generally clinical trial agreements are not required for observational or low risk interventional studies unless there are special circumstances such as third-party involvement etc.

Appendix 3: Abbreviations used in this document

CRF-C	Clinical Research Facility Cork
CRRO	Clinical Research Reporting Officer
CREC	Clinical Research Ethics Committee of the Cork teaching hospitals
CAPA	Corrective and Preventative Action(s)
GCP	Good Clinical Practice
HPRA	Health Products Regulatory Authority
HRB	Health Research Board
ICH	International Council on Harmonisation
PFQ	Patient Focused Research Questionnaire
PI	Principal Investigator
PFR	Patient Focused Research
RICU	Research Institute, Centre or Unit
RSS	Research Support Services
SOP(s)	Standard Operating Procedure(s)
UCC	University College Cork
UMTO	University Management Team Operations
VP-RI	Vice President of Research and Innovation.

Appendix 4: Definitions used in this document

Clinical Trial:

Throughout this document the term 'Clinical Trial' refers to interventional studies which may come under the regulation of the HPRA (IMP and Medical devices) or which may involve other interventions e.g. exercise, food, clinical therapies etc

Patient Focused Research:

Throughout this document the term 'Patient Focused Research' refers to all health-related research involving patients or healthy volunteers/ participants.

Patient focused research includes observational studies where patient data are collected and / or where there are biological samples or tests / investigations which are not part of normal clinical care.

Patient focused research does not include clinical audits, quality improvement projects or service evaluations which are carried out by a hospital or other clinical facility under that healthcare facility's governance arrangements and which are led by healthcare facility staff.

Appendix 5: Flow sheet of quality oversight of patient focused research