NIHR Oxford Clinical Research Facility Operational Policy

The NIHR Oxford CRF aims to provide a world class multi-speciality clinical research facility and clinical research service for translational research at the University of Oxford and Oxford University Hospitals NHS Foundation Trust.

PURPOSE

This document aims to provide an overview of the NIHR Oxford Clinical Research Facility's Operational Policies.

Further details about each section can be found in the relevant SOPs. This manual is based on the UKCRF Network QA Workstream Quality Manual Guideline (V2). The guidance template details the minimum requirements for a CRF quality system. Hence the CRF Operational Policy has been developed using a tool which is recognised by the Chief Scientist Office, UKCRF Network and NHS NIHR for this purpose.

Note for readers

Relevant policies and procedures have been signposted, rather than reproduced in this manual. A full list of Standard Operating Procedures (SOPs) and Work Instructions (WI) are available within the QMS. Refer to the current, approved detailed instructions when performing specific duties and tasks.

ACRF Study Visit SOP and CRF Building and Facilities Guide (Location Specific) for Study Teams is available which details daily activities and procedures within the CRF.

Note for SOP editors and line managers

This document should not require frequent updating. However, it is a key document to signpost the main quality measures which all staff and stakeholders need to be aware. When drafting a new or amended procedures please consider if the Operational Policy may need to be amended.

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1 INTRODUCTION

The NIHR Oxford CRF supports the delivery of experimental research projects to the highest standards of research and clinical governance. The infrastructure and processes ensure that quality and safety considerations are embedded throughout the facility and promote a culture of continual quality improvement. The facility has a documented and maintained quality management system in accordance with the principles of GCP and all applicable regulatory requirements. The CRF also aims to work to the best practice principles outlined by the NIHR UKCRF Network workstream and current MHRA Guidance for CRF accreditation. It takes a risk adaptive approach to assuring participant safety.

2 SCOPE OF THE NIHR OXFORD CRF

The NIHR Oxford CRF is multi-user, multi-speciality facility for early phase and experimental clinical research involving both patients and healthy volunteers. The CRF is an adult facility. Whether a study is suitable for the CRF will be based on study specific risk assessments. The risk assessments will consider the participant group, intervention type and how these can be managed in the facility.

The NIHR Oxford CRF includes:

- Experimental Medicine Clinical Research Facility (EMCRF) on the Churchill Hospital Site
    - 5 overnight rooms, with negative pressure ventilation
    - Endoscopy room
    - Treatment room
    - 2 multi-occupied bays (4 spaces in each)
    - 4 Consulting rooms
    - Sample processing laboratory with Microbial Safety Cabinet
- Nuffield Orthopaedic Centre (NOC) CRF on the NOC Hospital Site
    - Multi-occupied bay (4 spaces)
    - Ultrasound room
    - Dexa scanner
    - Consulting room
    - Simple sample processing facilities#

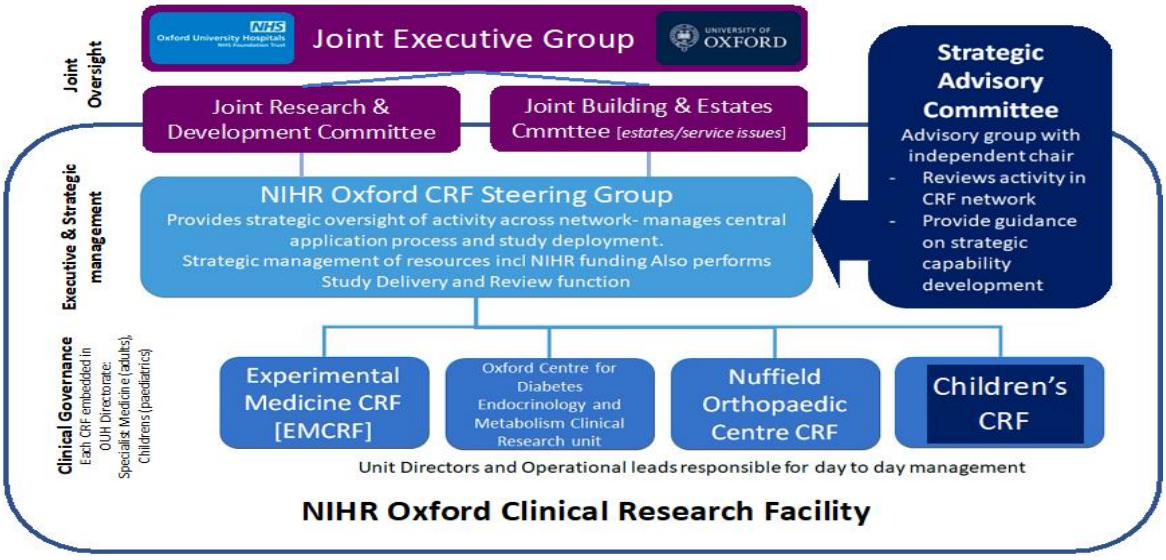
3 DEFINITIONS

Abbreviation	Definition
BRC	Biomedical Research Centre
CRF	Clinical Research Facility
HRA	Health Research Authority
ICH GCP	International Conference on Harmonisation Good Clinical Practice (E6 R2)
JEG	Joint Executive Group
JRO	Joint Research Office
MHRA	Medicines and Healthcare Products Regulatory Agency, UK
NOC	Nuffield Orthopaedic Centre
OUH	Oxford University Hospitals NHS Foundation Trust
Oxford EMCRF	Oxford Experimental Medicine Clinical Research Facility
QM	Quality Manual
QMS	Quality Management System
SDRC	Study Deliverability and Review Committee
SAC	Strategic Advisory Committee
SOP	Standard Operating Procedure
WI	Work Instructions

4 GOVERNANCE AND OVERSIGHT

The Oxford NIHR CRF is a formal collaboration between the University of Oxford and the Oxford University Hospitals NHS Foundation Trust. A Collaboration Agreement exists detailing the legal components of the relationship and the division of responsibilities relevant to the relationship.

As a result of the collaboration, the CRF has levels of management and responsibility through both institutions. These levels oversee the strategic objectives as well as the deliverability and conduct of the research. An organisational chart providing generic details is provided below to demonstrate the governance structure in the CRF.



* The organisational chart is approved by the Joint Executive Group (JEG) who oversee the collaborations of the University of Oxford and Oxford University Hospitals NHS Foundation Trust.

4.1 Nuffield Department of Orthopaedics, Rheumatology & Musculoskeletal Sciences (NDORMS)

The Nuffield Department of Orthopaedics, Rheumatology & Musculoskeletal Sciences (NDORMS) is the host department in the Medical Sciences Division at the University of Oxford for the CRF. The facility sits within the Business Management systems of the department. NDORMS supports the facility by providing: a portal and system for financial transactions; patient and public involvement and engagement support; facilities management support; biological safety guidance and governance oversight representatives.

4.2 Specialist Medicine Directorate

The CRF is embedded within the Specialist Medicine Directorate for clinical governance purposes. This provides the organisation framework to ensure the CRF remains aligned with OUH clinical governance policies and procedures. The CRF is represented at Directorate Executive Management and the Directorate Clinical Governance meetings.

4.3 CRF Staffing

The CRF employs a team of core staff who have been selected to ensure that they have the right qualifications, skills and competencies to carry out their roles. All core staff have clearly defined job descriptions.

All staff working with the CRF are required to have either a substantive or honorary contract with OUH. In keeping with all substantive and honorary OUH staff, CRF staff will complete and maintain OUH Statutory and Mandatory training and, for clinical staff, an annual OUH appraisal will also be required.

5 Management Responsibility and organisational structure

5.1 NIHR Oxford CRF Network Management Committee (NMC)

The NIHR Oxford CRF Steering Group provides executive and strategic management of the NIHR facilities. The Steering Group will provide the Scientific and Deliverability Review (SDRC) function by reviewing new business applications, conducting a proportionate risk assessment, and establish if studies can be effectively implemented in the facilities of the network. The Committee will also consider which facilities within the network are suitable for conduct of the proposed study. The committee is made up of representatives from: key stakeholders; the Joint Research Office (both University and Trust representatives); and Patient representatives. Details of the committee's role are provided in OR-SOP-005_NMC Charter.

5.2 NIHR Oxford CRF Operations Group

The CRF Operations Group is primarily responsible for the implementation of the strategy for the facility and maintenance of the quality system and of day-to-day oversight of the operational policies within the CRF. Members include (but are not limited to) the Operational Lead; Quality Assurance Coordinator; Administrator; Senior Research Nurse. Examples of the work of this committee include:

- Devise the implementation strategy for initiatives agreed at the SAC
- Review User Guidelines and SOPs
- Liaise with and report to the OUH Clinical Governance team regarding clinical activity in the facility
- Develop relevant SOPs
- Implement relevant SLA's for external services required
- Plan and respond to internal and external audits
- Review and respond to Customer Feedback and Complaints
- Provide oversight of Deviation Reports and CAPA projects relevant to the facility
- Identify and implement recommendations for improvement

5.3 NIHR Oxford CRF Director

The CRF Clinical Director shall act as the primary contact person for the OUH in relation to issues arising in connection with the CRF, unless another postholder has been nominated in relation to a specific issue.

5.4 The Clinical Operational Lead

The CRF Clinical Operational Lead is responsible for the activities of CRF. The post will be substantively employed by the OU, have honorary clinical research status in the OUH and will ensure relevant policies and procedures from both institutions are considered in the operational policy of the facility. They shall be the first point of contact for both the OU and OUH issues arising in connection with the CRF.

6 Quality Management System

The Operational Team are committed to resource the quality management system and operational policies to meet regulatory requirements and to maintain and improve the effectiveness of the quality management system and its processes. Policies from both the OUH NHS Foundation Trust and the University of Oxford have informed the operational processes of the facility.

6.1 Study Management models

Oxford EMCRF can provide a range of study site services by agreement with the trial PI and Sponsor. These will be decided via delegation and trial agreements. It offers three basic delegation models:

1. **Full:** All study site operations managed by CRF on behalf of the PI, includes site administration, management of participant visits and follow-up, liaison with monitor/ sponsors and provision of clinical cover.
2. **Partial:** A bespoke agreement by which study site responsibilities are shared between the PI study team and CRF.
3. **Minimal**: the PI study team arranges to use CRF to perform participant visit procedures and access specialist cover and resources.

Oxford CRF QMS and procedures will apply to any activity delegated or performed within it. These will include assurance that arrangements are feasible.

6.2 Internal Audits

The CRF will plan and conduct a regular programme of internal audit as per **OR-SOP-016 Internal audit.** The aim is to verify the QMS effectiveness in delivering the required operational standards and help achieve continuous quality improvement.

The internal audit programme will include all aspects of the CRF operations. Hence everyone is required to cooperate and participate in audit activities. The internal audit will address the CRF priorities and requirements.

6.3 Clinical Audits

The facility will participate in clinical audits as per OUH policy and procedures.

6.3.1 Third Party Audits

NIHR Oxford CRF may be required to accommodate audits conducted by third parties. These may be regulatory authorities or study specific audits. Reports will be sent to the CRF Management Committee and feedback filtered accordingly. Findings in these audits may inform policy and procedure reviews.

6.3.2 Training

The CRF ensures that all staff working in the CRF, including core staff and study team members, 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.

6.4 NIHR Oxford CRF Induction

Induction is mandatory for everyone coming to work in the facility and will include:

- Registration onto the induction programme
- Attend the induction training/orientation session
- Provision and validation of qualifications and other relevant training documents
- Read and sign assigned CRF SOPs and policies
- Completion of mandatory role-based training plus any identified individual training or refresher needs
- Complete induction check list
- Agree on-going training/mentoring plan

7 Patient & Public Involvement and Engagement (PPIE)

Involvement, engagement and outreach work will be conducted in collaboration with the research groups' own activities as well as CRF specific ones. The aim of engagement is to improve involvement through the research process in the facility. See the NIHR Oxford CRF PPIE Strategy for further details https://www.ndorms.ox.ac.uk/oxford-emcrf/patient-and-public-involvement-and-engagement-ppie-1.

8 Risk Management and Study Approval Process

PIs and study teams wishing to run their study in a CRF apply to do so. Study applications are risk assessed; reviewed by the SDRC and costed up accordingly. All studies will still process through standard OUH NHS Trust Research & Development Trust Management Approval process.

8.1 Risk Assessment & Study Review

The Risk Assessment and Study Review process is detailed in the Risk Assessment SOP OR-SOP-004. The review process identifies any mitigation measure considered important to conducting the study within theCRF. The risk assessment will seek to distinguish between the risk associated with:

- The study intervention
- The study design and procedures
- Other feasibility and business considerations

The study will be reviewed by the Study Deliverability Review Committee (part of the Steering Committee). They will assess:

- Scientific merit and fit with current strategic objectives
- Operational considerations and deliverability – including participant safety
- Alignment with the clinical profile of participants and clinical procedures which EMCRF have capabilities to support

Allocation of space will be determined by the risk assessment and the clinical profile of the study population:

- Studies that require minimal input/support from CRF staff and are considered low risk will generally be allocated to utilise the CRF NOC space
- Studies that are more intensive and/or are considered moderate/high risk and/or require support from CRF staff will be supported on the CRF Churchill site
- See Appendix 1 and 2 – CRF Clinical Procedures and Profiles for details

Issues to be resolved before the study is given the Green Light for the study will be communicated to the study team and PI. Satisfactory resolution of these issues is required and will be documented before the study is activated in the facility.

9 Study Conduct

9.1 Responsibilities

The PIs and their study teams remain responsible for the study conduct and activities in theCRF.

9.1.1 Principle Investigators:

- Patient safety, the overall conduct of the study and for members of their research team
- Ensuring members of their research team have appropriate contracts with the host institution (research, honorary, substantive or letter of access)
- Ensuring their research team members have appropriate training
- Providing appropriate medical cover for their participants
- Provide CRF with protocol amendment details for review

The CRF team will inform PIs and their study teams about any changes to the facility resources and procedures.

9.1.2 Study teams

Principal Investigators will provide the CRF with the contact details of all study staff who need to be granted access to the facility. Their induction needs to be completed as part of the study set-up procedure. The CRF must be notified of changes to study team personnel without delay to maintain continuity.

Study team members will undergo an induction and relevant CRF training in order to conduct research activity in the CRF.

9.2 Medical Cover

The CRF will not provide medical cover for studies. This must be organised and agreed by the individual study teams, per study. The required level of cover and any special arrangements are assessed during the study onboarding process and agreed prior to green light. The name and contact details of study specific medical cover will be provided by the study team during the study set-up process.

9.3 Medical Emergency arrangements

The CRF may also develop guidance document for management of medical emergencies (e.g. cytokine release syndrome) as needs dictate.

The EMCRF has an Emergency Transfer SOP specific to the EMCRF location and is used for studies that do not have protocol defined arrangements.

Clinical Emergencies in the NOC CRF space are managed according to the internal transfer arrangements in the NOC/OUH Guidance.

9.4 Other Emergencies

The unit business continuity plan defines the actions to be taken in the event of complete or partial failure of key services (e.g. electrical, water).

9.5 Incident Reporting

The CRF has an Incident Reporting SOP which details lines of responsibility in both the University and the OUH Trust; how different incidents will be reported and how they are managed. Clinical incidents, and incident involving OUH staff are reported via the OUH Ulysses system. Incidents related to the physical facility, laboratory incidents and incidents involving University staff are reported via the University's ISIS system.

9.6 Study Specific Safety Reporting

PIs and study teams are responsible for ensuring that all Adverse Events (AEs), Serious Adverse Events (SAEs) and Suspected Unexpected Serious Adverse Reactions (SUSARs) that occur within the CRF are recorded and reported in compliance with the study protocol, Sponsor requirements and regulatory requirements.

9.7 Progress Reports

Study progress will be reviewed regularly by the NIHR Oxford CRF Network Management Committee. The information in these reports will inform the deliverability and capacity for in-coming studies and also inform CRF stakeholder reports. Reports submitted to the Joint Research Office will be shared with CRF.

9.8 Trial closure and archiving

The Declaration of the End of Trial form (CTIMPs) or the HRA declaration of the End of Study form (non-CTIMPs) must be submitted to oxcrf@ndorms.ox.ac.uk once the study is completed. The study team retain responsibility for archiving of their study documents. There are no archiving capabilities within the facility.

9.9 Withdrawal of support

The NIHR Oxford CRF reserves the right to suspend work on any project conducted in the facility should staff become concerned about participant or staff safety or research governance e.g. deliberate protocol violation or deviation of Oxford EMCRF processes and SOPs.

10 Finance

Both the University and OUHT have finance processes which need adhering to. Arrangements for charging studies; how funding flows between the two institutions and operational costs are detailed in the CRF Finance SOP.

11 Premises

The NIHR Oxford CRF provides and maintains adequate infrastructure needed to provide services to our users and conform to required regulations and local policies including:

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

Facilities Management services for the capital building and equipment are provided through NDORMS and the University of Oxford Estates Services. Soft facility services are provided from both external service providers and the OUH NHS Trust. All facilities services are undertaken according to an agreed schedule and appropriately adhere to OUH NHS Trust or University standards.

12 Publications policy

Investigators must acknowledge the NIHR Oxford in publications and inform the CRF of all publications that relate to work facilitated by the the CRF, either physically or intellectually. The following statement must be included in all appropriate publications:

This study is funded/supported by the National Institute for Health and Care Research (NIHR) Clinical Research Facility (CRF). Conduct of the study was supported by the NIHR Oxford Clinical Research Facility. The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

13 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, v3.3
- MHRAs guidelines: 'Guidance on the maintenance of regulatory compliance in laboratories that perform the analysis or evaluation of clinical trial samples'
- The clinical and research governance provisions of the Oxford University Hospital NHS Trust R&D Office and applicable Trust policies.
- The clinical and research governance provisions of Oxford University Research Governance, Ethics and Assurance (RGEA)

14 APPENDIX 1 – EMCRF CLINICAL PROCEDURES

Clinical Procedure	Description
Routine clinical procedures	
Weight and height	
Blood pressure	Taken using automated or manual machines
ECG	Specific equipment with battery back up
Venepuncture	Collection of blood from a vein
Cannulation	Insertion of small plastic cannula into vein
Lung function	Measurement of lung function using dedicated equipment
Drug administration:	All will follow OUH procedure
Injections- intramuscular, intradermal, subcutaneous	Delivered by hypodermic needle
Infusion – intravenous	Delivered through a cannula
Oral	
Suppository	
Intranasal	By instillation or spray
Intrathecal*	Specialist procedure
Intra-articular	Specialist procedure
Specialist procedures	
Fine Needle aspiration (lymph nodes)	With or without ultrasound guidance
Local anaesthetic	
General anaesthetics will not be administered on EMCRF. Some procedures may involve light sedation	
Arterial line	Small cannula placed into artery- usually in arm. Sometimes use local anaesthetic
Lumbar puncture	Needle in back to collect fluid from around spinal cord. Local anaesthetic
Skin biopsy	Punch biopsy of skin. Local anaesthetic
Synovial biopsy	Needle biopsy of joint lining. Local anaesthetic. Ultrasound guidance
Joint injection	Needle injection into joint.
Lip biopsy	Small biopsy of lip under local anaesthetic
Laser Doppler assessment of skin blood flow	Non invasive assessment using a CE marked device
Dexa scan ^	
C-Arm xrays ^	
Specialist procedures*	
NB these procedures will be low throughput 1-2 procedures per morning or afternoon	
Flexible sigmoidoscopy	Telescope examination of lower bowel. Does not usually require sedation
Upper GI endoscopy	Telescope examination of stomach. Usually does not require sedation
Colonoscopy	Telescope examination of full lower bowel. Sedation usually used
Bronchoscopy	Telescope examination of lungs. May include sedation
Bone Marrow Biopsies	Local anaesthetic. May include sedation
*EMCRF Churchill Site only ^EMCRF NOC Site only	

15 APPENDIX 2 - CLINICAL PROFILES

		NOC	CHURCHILL
AGE	Adults	Yes	Yes
	Adolescents (12-18)	Yes if non invasive day case consistent with outpatient profile of NOC	No
	Children (<12)	Yes if non invasive day case consistent with outpatient profile of NOC	No
GENDER	Males and Females	Small unit with low numbers of participants. Privacy maintained though use of separate spaces and curtains	If overnight stay is required male and female participants will be accommodated in separate areas
	Transgender participants	Should a participant apply and be eligible for the study appropriate accommodation for the visit(s) will be identified. Trans people will be accommodated according to their presentation: the way they dress, and the name and pronouns they currently use.	Should a participant apply and be eligible for the study appropriate accommodation for the visit(s) will be identified. Trans people will be accommodated according to their presentation: the way they dress, and the name and pronouns they currently use.
IMMUNO-SUPPRESSION	Participant on biological drugs for inflammatory conditions	Yes	Yes
	Participant living with HIV	Yes	Yes
	Participant with AIDS defining illness	No	No
	Participant with complement disorder	Yes	Yes
	Neutropaenic participants	No	No
	Transplant participants on stable medication	Yes	Yes
COGNITIVE ISSUES	Participants with previous history of mental illness or currently well controlled	Participant to protocol exclusions and risk assessment of study procedures	Participant to protocol exclusions and risk assessment of study procedures
	Acute Psychosis	No	No
	Participants with current known suicidal ideation	No	No
	Mild cognitive impairment	Participant to protocol exclusions and risk assessment of study procedures	Participant to protocol exclusions and risk assessment of study procedures
	Severe cognitive impairment including behavioural issues	No	No
BODY MASS INDEX	<40 and ambulatory	Yes	Yes
	>40 and or reduced mobility	Participant to specific risk assessment and availability of suitable equipment	Participant to specific risk assessment and availability of suitable equipment
OTHER	Dialysis	Haemodialysis is not conducted at CRF. Participants on haemodialysis may participate on non dialysis days. Participants on self administered peritoneal dialysis may participate. All participant to protocol requirements	Haemodialysis is not conducted at CRF. Participants on haemodialysis may participate on non dialysis days. Participants on self administered peritoneal dialysis may participate. All participant to protocol requirements

		NOC	CHURCHILL
	Chronic oxygen therapy	Participants to use their own equipment. Participant to safety risk assessment.	Participants to use their own equipment. Participant to safety risk assessment.
	Obstructive sleep apnoea	CRF is day unit. Yes participant to protocol requirements	If study requires overnight stay requires a specific risk assessment and care plan
	Overnight stay	No	Yes participant to safe staffing levels
INFECTION CHALLENGE STUDIES	Respiratory pathogens	No	Yes – participant to risk assessment and use of negative pressure rooms
	Other pathogens	Participant to specific risk assessment and NOC site restrictions no isolation facilities available	Participant to risk assessment