IRNM

CLINICAL RESEARCH NURSE AND MIDWIVE ORIENTATION PACK

An introduction to the role of the clinical research nurse and midwife, and to the regulations and guidelines governing clinical research in Ireland

Version 4: August 2022

IRNM
Irish Research Nurses & Midwives

About IRNM

The role of the IRNM is to act as a resource for research nurses and midwives, allied healthcare professionals and patients through:

- Providing regularly updates for research nurses/midwives, allied healthcare professionals and patients on the changing guidelines and laws relating to the conduct of clinical research.
- Serve as a vehicle for advertising research vacancies.
- Organise annual conferences with a variety of speakers at the forefront of research and provide research nurses/midwives the opportunity to present and share their work with their peers.

The IRNM network delivers:

- Events* (study days and annual conferences) for Clinical Research Nurses/ Midwives. Educational events are accredited by the Nursing & Midwifery Board of Ireland (NMBI)
- On-line presentations, accredited by the NMBI, for Clinical Research Nurse/ Midwives*
- At least six newsletters* a year with updates on guidelines and laws related to clinical research; research training and events; employment opportunities as well as updates on the work being done to enable greater, more secure, recognition of the Clinical Research Nursing/ Midwifery workforce
- Orientation and Competency packs for all Clinical Research Nurses/ Midwives
- Collaboration with international colleagues, examples include the International Association for Clinical Research Nurses (IACRN) and National Institute for Health and Care Research (NIHR)

- For more information about resources and IRNM membership, visit our website (www.irnm.ie)
- Updates are shared on the IRNM's Twitter account (@Irish_RNM)
- If you would like to get in touch with IRNM, please email hello@irnm.ie

*Events are included in the membership of IRNM members; On-line presentations and newsletters are accessible to IRNM members only.

Foreword

Irish Research Nurses & Midwives (IRNM) is a voluntary network advancing the professio development of clinical research nurses and midwives (CRNMs) in Ireland. This orientation pack is a national resource to support the induction and orientation of CRNMs to this area of specialised practice. It will guide you through some of the complexities of this multifaceted role and point you in the direction of further information and resources. We hope that this document will also prove a useful tool for mentors in orientating novice CRNMs into their new role. Aspects of this document are equally applicable to the induction and orientation of other members of the clinical research team.

IRNM hope you find this document beneficial and wish you well in your career in clinical research. For more information about IRNM please visit our website: https://irnm.ie/. Membership of IRNM provides access to addition training and development opportunities.

Acknowledgements

We wish to acknowledge and thank the Health Research Board (HRB) whose support has made publication of this resource, and many other IRNM activities, possible.

We also wish to acknowledge the Dublin Centre for Clinical Research (DCCR) and the UK Clinical Research Facility (UKCRF) Network who kindly allowed us to adapt sections from their orientation, competency and induction framework documents for inclusion in the original draft of this resource. The publication has been updated and extended in response to changes in the governance and regulation of clinical research, and the developing research infrastructure in Ireland. Contributors to previous versions of the Orientation Pack are listed in Appendix 4.

Clinical Research Nurse and Midwife Orientation Pack, Version 4

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Using This Orientation Pack

This resource may be used during a period of orientation to a new role or workplace setting. If possible, it should be utilised as part of an orientation process supported by a mentor or line manager. Section 1.3 provides recommended timelines for completion of various elements of an orientation process. This can be adapted according to local circumstances, and according to the inductee's prior experience. The authors recommend that a signed and dated checklist is used to record achievement and completion of these processes. This can be a locally developed tool or adapted from the sample checklist/signature sheets provided (Appendix 1).

New Staff Member/Inductee

- Discuss orientation/induction needs with mentor/line manager, taking into considerations prior experiences and responsibilities associated with new role
- In conjunction with mentor/line manager identify objectives to be achieved and timelines for completion
- Identify and avail of opportunities and resources available to achieve agreed objectives
- Sign and date completed objectives in a timely manner
- Identify barriers to completion of objectives or areas of non-completion of expected targets

Mentors/Line Managers

- Assess orientation and induction needs of new staff member
- In conjunction with new staff member/inductee identify objectives to be achieved and timelines for completion
- Provide opportunities and resources for inductee to achieve agreed objectives
- Sign and date completed objectives in a timely manner
- Identify barriers to completion of objectives or areas of non-completion of expected targets

All

Should issues of concern arise about failure to meet objectives identify these in a timely manner and address them in line with human resources (HR) and local management policies.

1. ORIENTATION PROCESS

1.1 INTRODUCTION

The training and educational needs of clinical research nurses and midwives (CRNMs) and study coordinators are complex due to the level of specialist knowledge necessary to fulfil the role at a professional level. Responsibilities include the care of patients and their families as well as the planning, coordination and administration aspects of the clinical research itself. This necessitates the development of a wide range of skills, knowledge, training, education and experience.

1.2 OBJECTIVES OF THE ORIENTATION PROGRAMME

The aim of this programme is to standardise the orientation of CRNMs in Ireland. It will orientate you to the clinical research environment and the role and responsibilities of the CRNM. Learning about clinical research, the people involved, systems and procedures is likely to be an incremental process during the coming months and much learning will occur informally in the workplace. This pack will provide a structure for self-directed and/or supported orientation, and an introduction to clinical research processes and governance. It will provide you with information about the relevant legislation and regulations underpinning clinical research in Ireland and the role and responsibilities of a CRNM.

Protected time should be allocated during the induction period to allow you to work through this folder. Ideally, your manager or mentor should agree objectives with you and agree on a timeframe to achieve your targets. It is recommended that you complete a structured orientation process to ensure you have received an introduction to all aspects of clinical research applicable to your role (see Sample Checklist, Appendix 1). The opportunities available to you will depend on your workplace. Training methods for orientation and continuing professional development may include:

- In-service induction & training programmes, conferences and seminars
- Shadowing experienced staff members to observe practice
- Reviewing relevant literature and web resources

1.3 ORIENTATION PROCESS

This section contains suggested induction processes and timelines that can be adapted to individual needs.

Areas of Induction	Target Timelines
Local Orientation ➢ Tour of facility and familiarisation with layout including building opening times, authorised access and emergency exits, toilets and hand-washing facilities, tea/coffee facilities ➢ Shared resources (e.g. fax, photocopier as applicable) ➢ Allocation of workspace, computer, phone etc. ➢ Hours/time of working day ➢ Fire, emergency & cardiac arrest information	First day on premises
Introductions ➢ Introduction to core staff and associate staff within the facility ➢ Introduction to porters and building administration staff ➢ Introduction to affiliated hospital personnel as required	First opportunity after commencement
Institutional Orientation ➢ Tour of institution and explanation of history, ethos and mission of the institution ➢ Introduction to institutional resources – library, website etc. ➢ Familiarisation with institutional HR policies – annual leave, sick leave, etc	Prior to or as soon as possible after commencement
Organisation of identity badge/swipe card, computer and e-mail access ➢ Passwords ➢ Remote access to server	First week in post
Training in and access to electronic systems for: ➢ Scheduling and reporting time allocated to specific activities ➢ Managing patient appointments and accommodation bookings ➢ Using study specific databases ➢ Using hospital/HSE reporting systems e.g. for lab results	First Month

Meeting with the nurse manager, department manager and/or your designated mentor to: ➢ Identify specific learning needs, and book attendance at training days: for example, ICH GCP, lab safety, venepuncture & cannulation, CPR, First Aid, and other mandatory or optional training sessions ➢ Organise shadowing with other research nurses, specialist nurses, etc. as indicated ➢ Provide information about education and training resources, organisations, networks, and other resources as applicable ➢ Set objectives and targets for current role ➢ Arrange schedule for future personal & professional development (PPD) meetings as per local policy	First 2 weeks
Training in Standard Operating Procedures, Policies and Guidelines. ➢ Seek guidance from your mentor/manager regarding which are specific to your trials or activities. ➢ Sign and date to indicate that each SOP has been read and understood. ➢ Complete associated training as necessary, for example, use of specific equipment	From day 1 to 6 weeks
Introduction to Principal Investigator/Research Team ➢ Introduction to the research team and the research specialty multidisciplinary team for allocated studies ➢ Read protocols and specific trial information including Patient information Sheets and Consent, and if applicable, Assent forms ➢ Meet study managers/monitors, if applicable, and complete study specific training (provided by monitor or study team) before starting any study activity ➢ Orientation to inpatient wards, outpatient departments etc. associated with allocated studies	First 2 weeks
Understanding of importance of performing delegated study activities only ➢ You must have received training in ICH GCP E6(R2), the study protocol training and trial specific activities before performing any delegated duties for a clinical trial ➢ You must have signed the delegation log, and have responsibilities countersigned by PI, before performing delegated duties in a clinical trial	First month

1.4 INTRODUCTION TO THE RESEARCH NURSE/MIFWIFE ROLE

'Clinical research nursing is nursing practice with a specialty focus on the care of research participants. In addition to providing and coordinating clinical care, clinical research nurses have a central role in assuring participant safety, ongoing maintenance of informed consent, integrity of protocol implementation, accuracy of data collection, data recording and follow up' ***http://clinicalcenter.nih.gov/nursing/crn/crn_2010.html***

1.4.1 Areas of Responsibility

IRNM (http://irnm.ie) identifies three key areas of responsibility associated with the CRNM role: clinical, managerial and educational.

Clinical: The CRNM acts as the primary advocate for the patient, both prior to and throughout their participation in a research study. They also educate the patient and family about their disease process, study related procedures and alternative options should they choose not to take part in the proposed study. The CRNM is also involved in the informed consent, and where applicable assent, process. He/she/they schedules procedures and performs initial patient interviews, nursing/midwifery assessments and clinical duties such as venepuncture, drug administration and adverse event management.

Managerial: The most significant and extensive aspect of the role of the CRNM is the management and co-ordination of individual research studies. Whilst always working within his/her/their scope of practice and delegated responsibilities, the CRNM *may* be responsible for:

- preparation of study protocols
- the preparation, submission and maintenance of ethics and regulatory documents
- developing study related documents
- screening and recruitment of patients
- data collection, data entry, adverse event reporting
- preparation of biological samples for shipment to reference laboratories
- managing the study budget, from set up to archiving
- establishment of Standard Operating Procedures

Educational**:** Education is a vital role of the research nurse or midwife. Patients are educated about studies and procedures. It may also be necessary to inform clinical colleagues about studies taking

place in their departments. There is also a responsibility for CRNMs to continue their own education about the research process and study specific procedures, and to engage in opportunities for continuing professional development (CPD).

A study of the CRNM workforce in Ireland, completed on behalf of IRNM (Schilling & Hyland 2019) reported the tasks most commonly completed by CRNMs (Table 1).

Table 1: Responsibilities and Roles of CRNMs in Ireland (Schilling & Hyland 2019)

Responsibility	%	Responsibility	%
Participant recruitment	85.5	Study set-up	69.5
Informed consent process	78.0	*Staff orientation/training	65.2
Adverse event management	78.0	*Project management	48.2
Study visits	77.3	*Ethics application	47.5
Site file management	77.3	IMP management	44.0
Case report form completion	73.8	*Study development	39.0
Sample processing	70.9	*Research site management	34.0

*** I**ndicates activities associated with higher level or management functions

1.4.2 The Clinical Research Nurse/Midwife Role

Numerous reports on the status of clinical research in the Irish setting allude to the role of the CRNM, and its value in forwarding the research agenda, but there is still little formal recognition or definition of the role. A report compiled by Dr Sarah Condell (2008) for the Health Research Board (HRB) and National Council for the Professional Development of Nursing and Midwifery (NCNM) was published in 2008. It identified a number of challenges associated with the role:

- Variety of titles, with different grades and pay scales and large variance in contracts, conditions and entry criteria
- Lack of visibility – role of CRNM largely unknown
- Wide range of roles and responsibilities; Role is diverse depending on setting, type & stage of study, composition of research team
- No standardisation of professional development and lack of opportunity for role progression

However, the report also identified that CRNMs enjoy the role:

- Tasks within the role cluster around the centre of the research continuum
- Role utilises nurse/midwife clinical practice skills
- Role itself is good source of job satisfaction

- Potential to build nursing & midwifery research in parallel with medical-led research

Irish research staff engage collaboratively with the UK Clinical Research Facilities (UKCRF) Network, including representation by Irish CRNMs on working groups and committees. The Whitehouse Report (2017) recommends a cross-border group to establish collaborative approaches to sharing working practices and conducting research to benefit all across the UK and Ireland, believing that this would assist in international understanding and promotion of work conducted by both CRNMs and nurse/midwife researchers. In the UK, the National Institute for Health Research (NIHR) (2017) published a Clinical Research Nursing Strategy that recognised Clinical Research Nurses/Midwives place as 'visible leaders' and set goals for 2017-2020. This is the first focused strategy of its kind. It acknowledges the CRNM workforce for their knowledge, skills and unique leadership position in forging evidence-based change, promoting areas where more work is required.

In a major breakthrough for CRNMs internationally, the American Nurses Association (ANA) has recognised clinical research as a specialist area of nursing practice and published Clinical Research Nursing: Scope and Standards of Practice in 2016. This document states that 'clinical research nursing practice requires a unique body of knowledge consisting of specialised training in nursing care, research regulations, scientific process, and data collection, analysis and interpretation'. It defines five domains of CRNM practice:

- Human Subject Protection
- Care coordination & Continuity
- Contributing to the Science
- Clinical Practice
- Study management

In Ireland, the 'Count Me In' study, completed in 2019 (Schilling & Hyland 2019) was the most comprehensive examination of the national CRNM workforce to date. The study confirmed that there is still considerable variation on the terms and conditions of employment of CRNMs, with limited job security or recognition of the role. The lack of a systematic approach to the employment and professional development of CRNMs also persists. However, the strategic development of a national clinical research infrastructure, the increased recognition and support of IRNM by the Health Research Board (HRB), and efforts to integrate clinical research in general into HSE services, has led to optimism about the future development of the CRNM role.

In 2021 IRNM collaborated with NIHR 70@70 Senior Research Nurse Leader Claire Whitehouse to complete a scoping 'census' of research nurses and midwives across the UK and Republic of Ireland.

The census aimed to understand the true size of the clinical research nursing and midwifery workforce through self-reporting of those within this community. In the Republic of Ireland, 157 CRNMs participated in the census, and preliminary data is available here: https://www.nihr.ac.uk/health-and-care-professionals/career-development/nurse-and-midwifery-census-data.htm

1.4.3. CRNM Responsibilities

The CRNM is responsible for the day-to-day running of research studies, including identification and recruitment of patients according to agreed protocols, assisting in, or undertaking, the informed consent process and management of study related procedures and data.

CRNMs must have the ability to work independently, to prioritise his/her own workload, to communicate effectively with all members of the research team and be able to meet tight deadlines.

All clinical research activity must be compliant with the ethically approved study protocol and conducted in line with current legislation and guidelines. Table 2 provides a summary of responsibilities associated with the role and associated attributes and skills.

Key CRNM Responsibilities	**Key CRNM Attributes**	**Associated skills**
➢ Patient identification and recruitment ➢ Patient consent & assent ➢ Organisation and completion of study visits ➢ Completion and maintenance of study documents ➢ Maintenance of Study Files ➢ Liaison with PI/research team/clinical staff ➢ Participating in Auditing and Inspection Activities. ➢ Assisting with Safety Reporting according to study requirements and specified timelines ➢ Liaison with CRA/Sponsor/ Institutions	➢ Clinical experience ➢ Knowledge of research theory and the research process ➢ Professional approach to care ➢ Attention to detail - organisation/ managerial ➢ Time management! ➢ Ability to work autonomously ➢ Good communication skills and interpersonal relationships	➢ Patient assessment ➢ Venepuncture and cannulation ➢ Ability to learn new skills or techniques as needed ➢ Safe Laboratory practice ➢ Biological sample collection, processing and storage management. ➢ Data entry ➢ Teaching skills ➢ Organisation and time management ➢ Effective communication

Table 2: Roles of the CRNM, and associated attributes and skills.

Advanced areas of responsibility associated with the CRNM role *may* include:

- Protocol development
- Trial design
- Preparing and submitting Ethics and/or Regulatory submissions
- Budget assessment and negotiation
- Budget management and invoicing
- Feasibility assessment
- Project management
- Grant applications and management of funds
- Reporting studies and dissemination of results
- Clinical Expertise in product design review and risk assessment.
- Nurse/Midwife-led research

1.5 THE CLINICAL RESEARCH SITE

Clinical research studies should be conducted in an environment that is suitable for this purpose and ensures a positive experience for research participants. Increasingly, clinical research is located in dedicated clinical research facilities (CRFs) or centres (CRCs), often operated by an academic institution but physically located on a hospital campus. Research for specific disease areas (e.g. oncology) may be located in specialist departments of hospitals or in dedicated Clinical Trial Units (CTUs). CRNMs may work exclusively for a principal investigator (PI) without a supporting research infrastructure, or team.

1.6 CLINICAL RESEARCH TEAM MEMBERS

Depending on the location and the resources available, members of a Clinical Research team may include:

- Director/Head of Department
- Nurse/ Midwife manager
- Administrator
- Quality and Regulatory Affairs Manager
- Research nurses/ midwives
- Research assistants
- Investigators
- Data managers
- Laboratory technicians
- Clinical informatics manager

- Statistician

Some of these roles are discussed further in Section 3.3 of this document. The research site may also have an institutional governance structure, such as a sponsorship office or Research and Development (R&D) department.

1.7 TRAINING RECORDS

All CRNMs should develop and maintain their own training records, which serve to demonstrate evidence of experience and training during an audit or inspection. Typically, this would include an up-to-date Curriculum Vitae (CV), training certificates, and materials, agendas from meetings or conferences attended, certification of professional registration or qualification, publications, and any other evidence of experience, qualification and continuing professional development. Local SOPs may be available to outline this process further.

1.7.1 Training in Good Clinical Practice (GCP) and Research Governance

It is mandatory that all research staff involved in clinical trials of investigational products (CTIMPs) complete training in good clinical practice (GCP), including ICH GCP E6 (R2), relevant EU and Irish legislation. GCP training is equally applicable to other areas of research. While there is a separate guidance document for medical device research (ISO 14155/2020) recent updates to legislation and guidelines seek to harmonise practice across all areas of research.

Opportunities to complete GCP training should be identified during the orientation process, and completion of an appropriate course prioritised. All clinical research staff should complete GCP training, regardless of whether their research involves a medicinal product, with refresher training and updates at a minimum of every two years (or more frequently if either required by the study protocol or if there are updates to ICH CGP that require research staff to update).

1.7.2 Skills and competencies

As with all areas of nursing/midwifery practice, CRNMs must work within their scope of professional practice. This requires that they do not accept delegation for tasks that fall outside their present skills and competence. The orientation period, and ongoing personal development processes in the organisation, aims to identify areas of practice to be developed and opportunities to improve and maintain skills and competencies.

CRNMs do not always have access to professional nursing/midwifery support and oversight from their affiliated healthcare institutions. IRNM advocates for the creation of service level agreements and memorandums of understanding between institutions to enable this support.

1.7.3 Research Support/Training

Depending on their work location CRNMs can face challenges accessing the required training for their role. The orientation process should direct the new staff member to available training options. In academic settings these might be provided by Health and Safety Department – such as laboratory safety training, or first aid – or by the research office or library services. Staff development modules may be available as face-to-face events or through the virtual learning environment (VLE) of the organisation (or through HSE land). There may be mandatory training modules, such as Data Protection, that all are required to complete, but the new recruit may also have access to other modules or courses that are available for self-enrolment by staff members.

Within the national clinical research infrastructure, other training and networking opportunities may be available, and IRNM plays its part in providing educational resources to CRNMs. To ensure maintenance of professional competency CRNMs may also need to liaise with hospital nurse educators to avail of additional training from the nursing/midwifery and clinical perspective. CRF/Cs tend to sit at the interface between academic and clinical services. As far as possible agreements should be in place to allow CRNMs not employed through HSE services to hold honorary contracts with the health service provider, and to avail of online and in person training relevant to their roles. It is also recommended that CRNMs who are based in, or carrying out research activities in, a hospital, are orientated to hospital requirements in areas such as infection control and other practices relevant to their roles.

2. REGULATIONS AND LEGISLATION GOVERNING CLINICAL RESEARCH

2.1 BACKGROUND TO CLINICAL RESEARCH GUIDELINES AND LEGISLATION

Research involving human participants is necessary in order to advance knowledge in the field of biomedical science. However, there are many examples throughout history of human research subjects being treated unethically, and of atrocities in relation to human research having occurred throughout the world. Therefore, regulations, guidelines and ethical codes of conduct are required to ensure that the rights and welfare of research participants are protected and that similar events are not repeated. This section provides an overview of important guidelines and legislation with regard to clinical research, from an Irish and European perspective in particular.

2.2 THE NUREMBERG CODE

The Nuremberg Code is a set of research ethics principles for human experimentation published in 1947 following the Nuremberg Trials. During the Nuremberg War Crimes Trials, in a subset of trials that became known as the 'Doctors Trials', German physicians were charged with crimes against humanity for performing medical experiments on living human subjects, without their consent. Experiments included torture, forced sterilisation, simulated hypothermia and hypoxia, tissue transplantation and induced infection. Attempts to justify some of the atrocities as research led the judges to seek clarification from experts in the field as to what was reasonable human experimentation. The points drawn up were subsequently published as the Nuremberg code. The

Nuremberg Code was the first international document that advocated voluntary participation and informed consent of research participants. It lays the foundation for later guidelines for ethical research.

2.3 DECLARATION OF HELSINKI

The Declaration of Helsinki (Appendix 2) is the World Medical Association's (WMA) best-known policy statement. The first version was adopted in 1964 and the document has been amended many times since, most recently at the WMA General Assembly in October 2013 (See full document in Appendix 2). The current version is the only official one; previous versions should not be used or cited except for historical purposes. The Declaration of Helsinki is not legally binding in its own right - its power lies in the extent to which its underlying principals are incorporated into guidelines and law internationally. It is a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects.

2.4 ICH GOOD CLINICAL PRACTICE (GCP) GUIDELINES

The International Conference on Harmonisation, (ICH), now called the International Council for Harmonisation, was formed in 1990, bringing together regulatory authorities and pharmaceutical representatives from the USA, Europe and Japan. Its purpose was to establish an agreed minimum standard for the development and manufacture of drugs, including the conduct of clinical trials, so that date from different jurisdictions could be mutually recognised and shared. This was primarily to avoid replication of studies, thereby speeding up the drug development process.

ICH has formulated numerous guidelines in four different categories – Safety, Quality, Efficacy and Multidisciplinary. The guideline of most relevance to clinical research staff is E6: Guideline for Good Clinical Practice (GCP). ICH GCP is a phrase that all research staff must be familiar with and is the definitive code of good research practice. It is not only a guideline – adherence to ICH GCP guidance is enshrined in legislation, including in the Clinical Trial Regulation (EU 536/2014) that came into effect on 31st January 2022.

Good clinical practice' means a set of detailed ethical and scientific quality requirements for designing, conducting, performing, monitoring, auditing, recording, analysing and reporting clinical trials ensuring that the rights, safety and well-being of subjects are protected, and that the data generated in the clinical trial are reliable and robust' EU 536/2014 (Clinical Trial Regulation).

First published in 1996, the ICH GCP guideline was revised in 2016 (E6 (R2)), and came into effect in June 2017. While the ICH guidance focuses exclusively on drug trials, it was based on other guidelines for research conduct, the World Health Organisation stresses that the principles of GCP

apply to all types of research, not just drug trials, and there is deliberate harmonisation with principles for other types of research. Extensive renovation of the ICH GCP guidelines is currently underway, and the expanded third version of the guideline will be published in 2024.

ICH GCP guidelines (E6, (R2) 2016) provide details for responsibilities for all involved in research activity. It includes specific sections listing responsibilities of ethics committees, investigators and sponsors. There are also sections detailing the format of clinical trial protocols, investigator brochures and essential documents required for clinical trials. ICH GCP guidelines are a key focus of regulatory inspections of drug trials, and it is expected that anyone involved in trials of an Investigational Medicinal Product (IMP), has not only had training in GCP, but undertakes refresher training every two years**.**

2.5 THE PRINCIPLES OF GOOD CLINICAL PRACTICE

1. Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and applicable regulatory requirement(s).
2. Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.
3. The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.
4. The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.
5. Clinical trials should be scientifically sound, and described in a clear, detailed protocol.
6. A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee approval.
7. The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when app. a qualified dentist.
8. Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).
9. Freely given informed consent should be obtained from every subject prior to clinical trial participation.
10. All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification. This principle applies to all records referenced in this guideline, irrespective of the type of media used.

11. The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).
12. Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.
13. Systems with procedures that assure the quality of every aspect of the trial should be implemented. Aspects of the trial that are essential to ensure human subject protection and reliability of trial results should be the focus of such systems.

2.6 CLINICAL TRIALS REGULATIONS

2.6.1 EU Clinical Trial Regulations 2014

On 16 April 2014 the EU published a new Regulation on Clinical Trials on Medicinal Products for Human Use: EU No 536/2014 (the "Clinical Trials Regulation" or CTR), thereby repealing Directive 2001/20/EC. However, the proposed changes depended on the development of a complex IT system for managing all aspects of clinical trials oversight, and that resulted in lengthy delays in implementing the regulation. Following a period of testing the Clinical Trial Information System (CTIS) is now fully functional and the regulation came into effect on 31st January 2022.

In the context of CTR, the term clinical trial applies to interventional clinical trials of medicinal products (CTIMPs) only. It does not apply to device trials – which has separate legislation – or to other interventional trials.

The aim of the CTR is to create an environment that is favourable for conducting clinical trials, with the highest standards of patient safety, for all EU Member States. Intrinsic to this is the simplification of current rules, for example:

- A streamlined application procedure via a single-entry point (The Clinical Trial Information System – CTIS) for all clinical trials conducted in Europe. Registration via the portal will be a prerequisite for the assessment of any application;
- A single authorisation procedure for all clinical trials, allowing a faster and thorough assessment of an application by all Member States concerned, and ensuring one single assessment outcome and authorisation per Member State;
    - This has led to the formation of National Research Ethics Committees (NREC) for clinical trials and a coordinated national clinical trial assessment process.
- The extension of the tacit agreement principle to the whole authorisation process which will give sponsors and researchers, in particular small to medium enterprises (SMEs) and academics, more legal certainty;

- Strengthened transparency for clinical trials data.

CTIS will have a public section so that patients can find out about ongoing studies, and sponsors are required to provide a laypersons summary of results. Inspection reports will also be publicly available, with some redaction of confidential or commercially sensitive information.

For trials already underway in January 2022 there will be a period of overlap between the CTR and previous legislation, but by 31st January 2025 all ongoing clinical trials must have transitioned to CTIS.

EU Regulations are binding legislative acts that are applicable across all Member States, and have primacy over national laws. However, most regulations allow some flexibility, and give discretion to Member States as to how they transpose certain elements. With the CTR, Member States can decide how to organise the involvement of ethics committees. In

Ireland, the CTR led to the enactment of two new Statutory Instruments (SIs):

S.I. No. 99/2022 - European Union (Clinical Trials on Medicinal Products for Human Use) (Principle) Regulations 2022: https://www.irishstatutebook.ie/eli/2022/si/99/made/en/print

S.I. No. 41/2022 - European Union (Clinical Trials on Medicinal Products for Human Use) (National Research Ethics Committees) Regulations 2022:

https://www.irishstatutebook.ie/eli/2022/si/41/made/en/print

2.7 MEDICAL DEVICE RESEARCH

The term 'medical device' covers all products, except medicines, used in healthcare for the diagnosis, prevention, monitoring or treatment of illness or disability. The Health Products Regulatory Authority (HPRA) is responsible for the regulation of medical devices on the Irish market. The range of products classified as medical devices is diverse. There are three types of medical devices outlined in the legislation. These are:

- General medical devices
- Active implantable medical devices
- In-vitro diagnostic medical device

2.7.1 EU Medical Devices Regulations 2017

Regulation 2017/745 on Medical Devices (MDR) and Regulation 2017/746 on In-Vitro Diagnostic Devices (IVDR) were formally published in the Official Journal of the European Union on 5th May 2017. The Regulations allowed for a staggered transitional period. The MDR entered into effect in May 2021, and the IVDR too in May 2022. The regulations increase the regulatory oversight of device manufacturers and of notified bodies responsible for certificated of

medical devices. This may lead to an increased requirement for clinical investigations in higher risk devices, and will also introduce regulatory inspection if device studies.

Statutory Instrument (S.I.) 261/2021 provides for a national interpretation of aspects of the MDR – see https://www.irishstatutebook.ie/eli/2021/si/261/made/en/pdf

2.7.2 Clinical Investigation of Medical Devices for Human Subjects - Good Clinical Practice

ICH GCP does not formally apply to device trials – this area of research is guided by an International Standards document - ISO 14155. ISO 14155:2020 addresses good clinical practice for the design, conduct, recording and reporting of clinical investigations (device trials) carried out in human subjects to assess the safety or performance of medical devices for regulatory purposes. It specifies general requirements intended to protect the rights, safety and well-being of human subjects, ensure the scientific conduct of the clinical investigation and the credibility of the results, define the responsibilities of the sponsor and principal investigator, and assist sponsors, investigators, ethics committees, regulatory authorities and other bodies involved in the conformity assessment of medical devices.

The current version of ISO 14155, published in 2020, expanded considerably on previous versions. There was a deliberate effort to harmonise with other existing guidelines to ensure consistency across all types of health research.

2.8 RESEARCH ETHICS COMMITTEES

A Research Ethics Committee (REC) reviews application to undertake medical research. Its remit is to protect the safety and welfare of research participants, and primarily to weigh the risks and benefits for research participants, of individual research projects

Legislation for the membership of REC that approve regulated studies is very specific and sets out how many members the committee should have, and what proportion of these must be lay members. The Clinical Trial Regulations (EU 536/2014) and Medical Device Regulations (EU 745/2017) have led to the development of a national framework for ethics committees in Ireland. As of 26th May 2021, all new ethics application for IMP Trials must be submitted to the National Research Ethics Committee for Clinical Trials – NREC-CT. The remit of NREC-CT includes interventional and low-interventional clinical trials of investigational medicinal products (CTIMPs). Two NREC-CTs run in parallel – NREC-CT A and NREC-CT B – with each committee meeting monthly.

Trials that continue to fall under the previous clinical trial legislation - SI 190/2004 -will transition to the NREC system through the submission of a substantial amendment. However, due to capacity issues other trials will stay under approving REC for now. More information about NREC-CT

is available at: https://www.nrecoffice.ie/wp-content/uploads/NREC-Operational-Framework-v1.1-Final.pdf

The Office of National Research Ethics Committees will work in coordination with the HPRA to review clinical trials submitted through CTIS under the CTR.

A similar mechanism now exists for ethical approval of clinical investigations (CIs) of medical devices. As of 26th May 2021, all new CIs are submitted to National Research Ethics Committee for Medical Devices – NREC-MD. The remit of the National Research Ethics Committee for Clinical Investigations of Medical Devices (NREC-MD) is to review the submission of ethics applications related to Clinical Investigations of Medical Devices as defined in MDR: "any systematic investigation involving one or more human subjects, undertaken to assess the safety or performance of a device." This includes:

- Non-CE marked medical devices being used in a clinical investigation for one or more of the purposes outlined in Article 62 of the Medical Devices Regulation (EU) 2017/745
- CE-marked medical devices being used in a clinical investigation outside the scope of its intended purpose
- CE-marked devices being further assessed in a clinical investigation (PMCF) within the scope of its intended purpose, which involves submitting participants to additional procedures deemed invasive and/or burdensome
- Clinical investigations of medical devices which do not fall under Article 62 of Medical Devices Regulation (EU) 2017/745

More information about NREC-MD is available at: https://www.nrecoffice.ie/committees/nrec-md/

2.8.1 Ethics Approval of 'Other' Research

NRECs, as described above, provide a single opinion for IMP or medical device trials in Ireland, regardless of the number of research sites involved. For all other research it is necessary to obtain separate ethical approval for each research site involved. These RECs may be in hospitals, at HSE group level or in academic institutions. A large percentage of research taking place in a teaching hospital would fall into the category of research other than clinical trials.

While there are no specific regulations for these studies, research governance is still applicable. All research must comply with Data Protection Regulations (2018), the Health Research Regulation (2018), Freedom of Information Legislation, HSE National Consent Policy (2019), and common law on consent for medical treatment and research. In due course the National Research Ethics Framework may extend to include other types of research. Research staff are required to be alert to changes and

updates to these and other relevant policies. Most RECs have websites that provide advice, guidelines, submission templates and checklists for the applicant.

2.9 HEALTH PRODUCTS REGULATORY AUTHORITY (HPRA)

The HPRA is the national competent authority in Ireland. It was established in 1995 (as the Irish Medicines Board (IMB)), replacing the National Drugs Advisory Board). The fundamental role of the HPRA is to protect and enhance public and animal health through the regulation of medicines, medical devices and healthcare products. The HPRA is responsible for the assessment of clinical trials with medicinal products conducted in Ireland. The types of trials assessed range from first-in-man studies for new compounds to studies with products that already have marketing authorisations. Before any trial can commence it must have received authorisation from the HPRA. The HPRA reviews the scientific aspects of the application and reaches a conclusion on the likely balance of any benefits versus risk of the product before arriving at a decision. The HPRA has the authority to inspect sponsors, investigators and sites involved with clinical trials of new medications or medical devices to assess patient protection and compliance with good clinical practice. For further information about the role of the HPRA visit: http://www.hpra.ie/homepage/medicines/regulatory-information

2.10 DATA PROTECTION AND HEALTH RESEARCH REGULATIONS

The Data Protection Commission (DPC) is the independent authority in Ireland responsible for upholding each individual's fundamental right to have their personal data protected.

2.10.1 Data Protection Act and Health Research Regulation 2018

The EU General Data Protection Regulation (GDPR) came into force on 25 May 2018. This is an overarching European law and is applicable to all member states of the EU, but with some provision for national interpretation. Within Ireland, both the Data Protection Act of 2018 and Data Protection Act 2018 (Section 36(2)) (Health Research) Regulations 2018 gives effect to aspects of GDPR that are specific to Ireland. The Data Protection Act 2018 (Section 36(2)) (Health Research) Regulations 2018, which is more commonly known as the Health Research Regulations (HRR) outlines the mandatory measures for the processing of personal data for the purposes of health research.

The Health Research Regulations 2018:

1. outline the mandatory suitable and specific measures for the processing of personal data for the purposes of health research (Regulation 3(1))
2. provide a definition of health research for the purposes of the regulation (Regulation 3(2))
3. provide for the possibility of applying for a consent declaration for new research (Regulation 5)

4. provide for transitional arrangements in respect of the granting of consent declarations for health research that is already underway (Regulation 6)
5. provide for the establishment and operation of a committee of persons to make decisions on applications for consent declarations, including an appeals process (Regulation 7-13 and Schedule)
6. include a number of miscellaneous provisions (Regulations 14-16)
7. The Health Research Regulations 2018 can be viewed in full here.

Certain aspects of the HRR created barriers to the day-to-day conduct of clinical research and ongoing dialogue led to amendments that addressed some of the key concerns. These were published in S.I. No. 18/2021 - Data Protection Act 2018 (Section 36(2)) (Health Research) (Amendment) Regulations 2021: https://www.irishstatutebook.ie/eli/2021/si/18/made/en/print

It is recommended that all staff working in clinical research become familiar with the legal requirements for collected and processing data for research purchases. It is also important to note that the Data Protection Act is specific to Ireland and has introduced layered consent for research studies.

The nature of research implies that there is a large amount of paper and electronic data held about the research subject. Research staff have a responsibility to their research subjects and their employer regarding data protection.

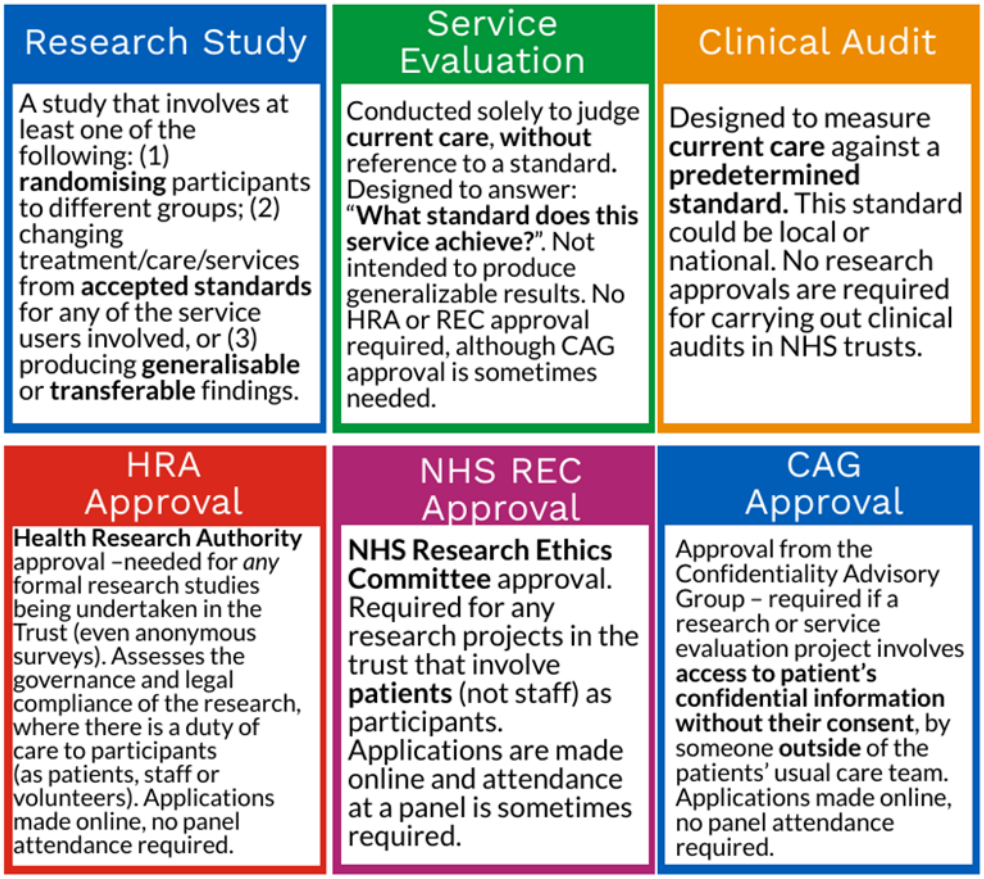
- Data should be stored in a secure location
- Data must be locked away if unattended
- No one should access subject data unless authorised to do so by research personnel and/or data protection officer (DPO).
- Research subject confidentiality should be maintained by the use of study specific codes as unique identifiers on research material.
- Electronic data must be password protected.
- Personal data that could potentially identify research subjects should be kept in a secure place, separate from research files.
- For more information visit https://www.dataprotection.ie

2.11 ARE YOU ENGAGED IN CLINICAL RESEARCH?

It is not always clear whether activities carried out to collect health information are clinical research or a form of legitimate service evaluation. It is vital to correctly class these activities, to avoid the risk of breaching data protection regulations, or possibly carrying out research without obtaining informed consent.

The National Office of Clinical Audit (NOCA) have provided a GDPR Assessment Table - to assist in determining if you are conducting Clinical Audit, Service Evaluation, Research, Healthcare Record Review or collecting data for a Clinical Register and how the purpose relates to GDPR, Data Protection Act 2018 (including the Research Regulations 2018)
http://s3-eu-west-1.amazonaws.com/noca-uploads/general/GDPR_Assessment_Table_-_Clinical_Audit.pdf

In the UK, all research carried out in the NHS requires Health Research Authority (HRA) approval. @HRA_Latest have produced an online decision tool to help you decide if your project is classed as research & what other approvals it might need. View here: http://hra-decisiontools.org.uk/research/



3. CLINICAL RESEARCH

3.1 OVERVIEW OF THE CLINICAL RESEARCH PROCESS

In general, clinical studies are designed to add to medical knowledge related to the treatment, diagnosis, and prevention of diseases or conditions. The Health Research Regulations (2018) provide us with an official Irish definition of health research:

- Research with the goal of understanding normal and abnormal functioning, at the molecular, cellular, organ system and whole-body levels
- Research that is specifically concerned with innovative strategies, devices, products or services for the diagnosis, treatment or prevention of human disease or injury
- Research with the goal of improving the diagnosis including rehabilitation and palliation, of human disease and injury and of improving the health and quality of life of individuals
- Research with the goal of improving the efficiency and effectiveness of health professionals and the health care system
- Research with the goal of improving the health of the population as a whole or any part of the population through a better understanding of the ways in which social, cultural, environmental, occupational and economic factors determine health status.

3.2 Health Research Regulations 2018

At its heart clinical research is about generating knowledge to support healthcare and clinical practice:

- Finding out why people get ill and identifying ways to prevent or slow down illness.
- Ensuring that patient receive the best treatment possible for their condition.
- Where there are a lot of treatment options, or maybe disagreement about which treatment is best, clinical research can be used to support clinical decision making, both at the level of the individual patient and sometimes at unit or national level.

3.3 CLINICAL TRIALS

In a clinical trial, participants receive specific interventions according to the research plan or protocol created by the investigators. These interventions may be medical products, such as drugs or devices; procedures; or changes to participants' behaviour, such as diet. Clinical trials may compare a new medical approach to a standard one that is already available, to a placebo that contains no active ingredients, or to no intervention. Clinical trials are usually designed to assess the safety and efficacy of an experimental therapy, to assess whether the new intervention is better than standard therapy, or to compare the efficacy of two standard or marketed interventions. Post marketing surveillance/observational studies are another aspect of clinical research and provide ongoing safety information about a licenced product. Pharmaceutical or manufacturing companies, academic institutions or individual investigators may sponsor clinical trials. Income from commercial clinical trials is used to support research staff posts and fund additional research or resources.

3.3.1 Stages of a Clinical Trial

Regardless of the type of study or the source of funding, most clinical trials follow a similar pathway from beginning to end. The main steps are briefly outlined below:

- **Protocol development**: a protocol, and all ancillary documents and processes, is developed by the investigator or sponsor.
- **Feasibility assessment:** Sponsors must select the most appropriate research sites at which to conduct their studies, and investigators will carefully review the requirements of the protocol before deciding whether to take part.
- **Ethics approval:** All research protocols and associated documents must be submitted to and approved by a REC before subject recruitment can begin. They may refuse approval, grant conditional approval subject to changes, or grant full approval. REC websites provide details of processes for approval and ongoing communication.
- **Regulatory approval:** The HPRA must approve all IMP trials before subject recruitment can begin. Certain clinical investigations of medical devices are also subject to HPRA review.
- **Clinical Trial Indemnity**: Required for externally sponsored IMP trials. The standard HSE Form of Indemnity is used – see: https://stateclaims.ie/uploads/publications/Clinical-Trial-Indemnity-Form-180821.pdf Depending on the level of risk investigator-initiated trials may be sufficiently covered by the clinical indemnity scheme or may require indemnity.
- **Contractual Agreement:** Contracts need to be agreed and signed between the institution and the sponsor before a trial commences. This is often referred to as a Clinical Trial Agreement (CTA).

Hospitals have processes in place to review risk and legal, data protection and financial aspects of the trial before the CTA is signed.

- **Site Initiation Visit (SIV):** The SIV is a meeting between the sponsor representative (usually a clinical research associate/monitor) and the site staff to ensures that all resources are in place, site staff are appropriately trained and delegated, and the site is ready to start enrolling subjects in the clinical trial. This includes protocol training, access to portal platforms, electronic case report forms and source documents.
- **Recruitment:** Once all steps above have been completed, patient recruitment may start. All research protocols stipulate strict inclusion and exclusion criteria, which all research personnel should be familiar with prior to approaching patients. Informed consent is the most important aspect of any research trial. A subject should not undergo any research related procedure until written informed consent has been obtained, in accordance with the procedures approved for the study.
- **Visits as per protocol:** The type of study will dictate the visit schedule. Every procedure that a patient receives as part of a research trial must be documented accurately and clearly. Any non-compliance with the protocol must be documented and explained, and actions taken to prevent future non-compliance. It is important that the research subjects have contact details for the study team should they have any concerns or need to report adverse events between visits.
- **Monitoring visits:** Monitoring is performed during a clinical trial to ensure adherence to the trial protocol and compliance with GCP and applicable regulations. The sponsor will develop a monitoring plan based on a risk assessment when planning the study. Monitoring will be on site, centralised or a combination of both.
- **Study Close-out**: When a trial ends a close out visit takes place to confirm that all documentation is complete and data queries are resolved. Study files are destroyed or archived in accordance with the approved process and applicable legislation. Data analysed and reported. Clinical trials and investigations are reported in accordance with timelines and procedures set out in applicable regulations.

3.4 ROLES AND RESPONSIBILITIES

Please note: Some of the main responsibilities of research team members are outlined below, however this is by no means an exhaustive list. Not every research trial will have all these staff members available, and the CRNM may fulfil these roles.

3.4.1 Study Sponsor (IMP Trial)

A Sponsor is *'An individual, company, institution, or organization which takes responsibility for the initiation, management and/or financing of a clinical trial' (ICH 2016)*

The study sponsor is responsible for:

- Providing the investigational products, as well as appropriate information to support the safe use of these products.
- Ensuring that the trial is conducted in accordance with sound scientific principles and good clinical practice.
- Selection of investigator sites.
- Provision of the clinical trial protocol and investigators brochure.
- Establishing the distribution of trial related responsibilities.
- Providing procedures and management of the clinical trial, record keeping, monitoring and quality assurance.
- Ensuring compliance with the protocol and with applicable legal, ethical and regulatory requirements.
- Provision of compensation and indemnity for trial related injury according to local laws and regulations.

3.4.2 Principal Investigator (PI)

An investigator is 'A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.' (ICH 2016). The PI must ensure that the study is carried out in accordance with the protocol and to ensure that he/she/they has the patient availability to conduct the study within the period defined in the study protocol. The PI also holds additional responsibilities:

- To ensure that the study is conducted in full conformance with the principles of the Declaration of Helsinki
- To ensure that the study is performed in accordance with the international Good Clinical Practice standards and according to all local laws and regulations concerning clinical studies.
- Submission of the protocol, patient information sheets and consent forms to local ethics committee for approval.
- To ensure that all staff involved in the study have a full understanding of the protocol and its requirements.

- Obtaining and recording patient consent and where applicable patient assent.
- To withdraw a patient from the clinical trial for any reason that is in the best interests of the subject.
- To ensure subjects anonymity is maintained.
- To ensure the completeness and accuracy of case report forms.
- To agree to allow the monitor/auditor/inspector to have access to any or all of the study materials needed for source data verification and proper review of the study progress.
- To report all adverse events in the case report form.
- To publish the clinical study results as soon as possible following study completion. In a multi-centre study, the principal investigator must ensure that the data from one centre is not published before the publication of the whole study without his/her/their consent.
- To retain all essential documents until after two years after the approval of the marketing application or longer if required by the regulatory requirements.
- To comply with the study sponsor and regulatory authority requirements regarding the auditing of the study.

3.4.3 Sub Investigator

The Sub-Investigator is responsible for medical care of patients participating in research studies, working under the supervision of the principal investigator. Certain PI responsibilities may be delegated to the sub-investigator, but there must be evidence that the PI has oversight of the conduct of the study and is satisfied that all duties and functions are carried out to a satisfactory standard.

3.4.4 Clinical Research Manager (titles may vary)

The responsibilities of the clinical research manager are:

- Management of the research network team.
- To ensure that there are sufficient resources in terms of time, staff and facilities to conduct the trial.
- To ensure that all protocols are reviewed, by all relevant departments in order to facilitate the conduct of the study.
- To ensure that ethical approval has been granted prior to any patient entering the trial.
- To monitor workload levels and delegate duties and responsibilities accordingly.
- To ensure that appropriate training and education has been provided in order to conduct the clinical trials.

- To act as liaison between study sponsors, investigator, the clinical trials research team and any other departments involved in the conduct of the trial.
- Where necessary, to maintain the flow of information regarding the progress of clinical trial activity within the research team and relevant groups
- Education of all staff of all grades in relation to clinical trials.
- Production of annual reports and monthly reports for trial meetings.

3.4.5 Clinical Research Nurse/Midwife (CRNM)

Taking account of the previous discussion about the complexity and variation of the CRNM role, within the research team CRNMs are typically responsible for:

- Co-ordinating the clinical trial in terms of patient recruitment, organising screening procedures, randomisation and management of procedures necessary during subsequent patient visits.
- Confirmation of patient eligibility according to the inclusion/exclusion criteria stated in the protocol in collaboration with the clinicians.
- Assessing patients per protocol and reporting findings to investigators as necessary.
- Attending the initiation meeting and undertaking appropriate training prior to trial commencement.
- Accountability of investigation agents/treatments
- Handling, processing, labelling, storage and shipping of biological samples.
- Ensuring that source documentation is a true reflection of decisions and actions taken for each individual patient.
- Completion of case report forms
- Education of patients about the study – medication compliance, completing quality of life or patient reported outcome (PRO) data, and other study specific requirements.
- Timely reporting of serious adverse events.
- Liaison with study sponsor regarding the conduct of the trial.
- Dissemination of trial related information to relevant staff and departments
- Staff education and training.
- Submitting local ethics approval/research and development applications.

3.4.6 Data Manager

Data managers work closely with investigators, CRNMs and study coordinators to ensure accurate and appropriate data collection. They can be responsible for:

- Designing, developing, and modifying databases to meet study requirements
- Assisting with development of paper and electronic case record forms
- Writing data management guidelines, policies and SOPs and monitoring their implementation and adherence
- Providing support in identifying and defining site data requirements
- Training and supporting other members of the research team in any aspect of data management, when required.
- Ensure all data protection legislation is adhered to within all study activities
- Ensure IT systems and electronic databases in use comply with GCP guidelines and applicable legislation
- Carry out or supervise data entry and validation
- Prepare data for analysis and reporting

3.4.7 Research Assistant

A research assistant may be employed for study specific or task specific duties at a research site. Duties may include:

- Providing an efficient secretarial/administrative support service to the research project(s) and Principal Investigator or his/her/their nominee.
- Supporting the research activities of the Principal Investigator or his/her/their nominee.
- Liaising with related departments and project leaders within the research area to help co-ordinate their research activities.
- Liaising with the Principal Investigator and colleagues on matters relating to the research project.
- Data entry or validation (paper or electronic)
- Sample processing, shipping etc.
- Carrying out laboratory procedures
- Laboratory and equipment care and maintenance

3.4.8 Research Pharmacist

As the number and variety of trials continues to increase it is vital that there is good communication between the sponsor company, the research team and the trials pharmacist. This will

ensure that issues are raised and resolved at an early stage, allowing the trial to run smoothly and effectively. Early input from pharmacy in the planning of a clinical trial enables early recognition of potential pharmaceutical issues; pharmacy should be given a copy of the protocol at the earliest opportunity.

- The design of prescription so the correct trial supplies are ensured.
- How blinding of trial medication is to be achieved and maintained.
- The requirements for documentation and record keeping.
- Labelling requirements.
- Drug receipt, delivery, re-ordering and stock checks.
- The mechanism for continuation of supplies, if appropriate, once the trial period has finished.
- Storage conditions of the trial medication.
- Size of packaging, which has implications for storage space.
- For parenteral administration of medicinal products there may be a requirement for aseptic preparation.

3.5 STANDARD OPERATING PROCEDURES (SOPs)

Standard operating procedures are defined in the ICH GCP guidelines as ***'detailed written instructions to achieve uniformity of the performance of a specific function".***

The purpose of SOPs are to ensure that any procedure performed as part of a research trial/study is done to a consistently high standard, thus enhancing the quality of the data produced. SOPs are of particular importance when a trial is being run over several sites and involves a number of research personnel. SOPs are relevant to all aspects of a research study. That is general study organisation, pre-study procedures, actual study procedures and end of study procedures. Before commencing a trial specific procedure, the appropriate SOP should be read and understood. If applicable, training in the procedure outlined should be completed before performing the procedure.

The format of SOPs will normally include:

- Title and number of SOP
- Purpose
- Who is responsible for the SOP
- Who the SOP applies to
- Other related procedures
- Description of the procedure/process
- When and how the procedure should be performed

- Date of approval and/or implementation of version in use
- Name of author and approval signature(s)

3.6 CASE REPORT FORMS

A Case Report Form (CRF) is a record of all the data and other information on each subject, required by the research protocol. ICH GCP guidelines include strict guidance relating to CRF completion as they are the official documentation of the trial. CRFs, along with the source documentation, will be closely examined during monitoring visits and in the event of a regulatory audit, therefore accurate and thorough completion is essential. Data contained within the CRF should match exactly that information recorded in the subject's source documents. The CRF should collect necessary information about:

- The subject
- Administration of the study drug/intervention
- Study specific procedures
- Outcome of any assessments
- Details of any adverse/serious adverse events

Following the study initiation visit only those personnel authorised on the delegation log by the principal investigator should complete CRFs. These may include co-investigators, research nurses, radiographers and data managers. CRFs should be completed during, or as soon as possible after the associated study visit/patient assessment, to ensure the information is up-to-date and accurate.

The following guidelines should be taken into account when completing paper CRFs:

- Black ball point pen must always be used to complete the CRF.
- If the CRF is on carbon or no carbon required (NCR) duplication paper, ensure that an appropriate separator is inserted.
- Never leave blank spaces. If a section cannot be completed document as appropriate: e.g. not known, not done etc.
- Never enter a research subject's full name on a CRF.
- CRFs must be signed off by the principal investigator at the end of the trial or as appropriate throughout the trial, to indicate that they believe the information to be complete and correct.
- All entries must be legible.
- Corrections must be made in a GCP compliant manner that maintains an audit trail:
- Cross out incorrect entry with a single line, so that the original entry is still legible.
- Enter the correct data
- Initial and date correction

Electronic CRFs (e-CRF) are now commonly used in clinical trials. Electronic systems must meet the same essential elements of data quality that are expected of paper records. It is important to never share usernames or passwords for e-CRFs, and to confirm the audit trail capabilities of an electronic data capture system which should record data processing activities, including viewing and exporting.

3.7 ADVERSE EVENTS

Adverse event reporting is an important aspect of clinical trial coordination and management. The definitions provided below are specific to IMP trials – different terminology applies for medical device research but the general principles are similar. It is important to know the specific requirements of each study in which you are involved.

An adverse event (AE) is defined as any unfavourable and unintended sign including any abnormal laboratory finding, symptom or disease associated with the use of an investigational medicinal product (IMP), regardless of whether or not it is considered to be caused by the IMP.

3.7.1 Expected Adverse Event

Those adverse events that have been identified in nature, severity, or frequency in the current investigator brochure, investigational protocol and current patient information leaflet/informed consent form (PIL/ICF).

3.7.2 Unexpected Adverse Event

Any adverse event whose nature, severity or frequency of which is not consistent with the current investigator brochure; or with the risk information described in the PIL/ICF. Unexpected refers to an experience that has not been previously observed. This includes events that are more serious than expected or occur more frequently than expected.

3.7.3 Grading of Adverse Events

All adverse events should be categorised according to severity, seriousness and expectedness. Protocols may have a unique approach to grading AEs and the Principal Investigator/site staff should consult the protocol for specific grading scales. PI must assign seriousness and causality.

3.7.4 Medical Events of Special Interest

On occasion a protocol will require reporting of an event – such as an altered laboratory value – that would not normally be considered an adverse event but is of particular interest in the context of the study. This may be due to the results of preclinical studies.

CRNMs working on a trial must be fully knowledgeable of trial specific adverse events, their grading and necessary actions and reporting specifics as detailed in each trial protocol. Only a physician (the investigator or sub-investigator) can assign relatedness and make decisions about whether the patient should continue to receive the IMP.

3.8 INFORMED CONSENT AND ASSENT

Freely given informed consent, and, when applicable, assent, is the cornerstone of ethical research. Each prospective participant and/or their legally acceptable representative must:

- Understand the nature of the proposed research
- Be informed of purpose, risks, and benefits and alternative therapies
- Make a **voluntary decision** about study participation

The informed consent +/- assent process must be completed before any protocol specific activities are performed. If protocol specific activities are done the same day as informed consent +/- assent is obtained, there must be clear documentation of the chronological order in the patient's medical record. The process is described in the study protocol and in the ethics application, and compliance with the ethically approved process is essential. The person obtaining consent +/- assent should have sufficient knowledge about the research and be capable of answering questions from prospective participants (HSE 2019).

For regulated trials of medicinal products, a registered doctor or dentist is responsible for taking consent. CRNMs will play a part in the consent +/- assent process, and all related activities must be documented. Until recently, this was interpreted as meaning that only physicians could obtain consent for IMP trials. However, the EU Clinical Trial Regulations (2014) states that the consent form should be signed by the person conducting the interview with the subject or their representative, in accordance with national law. Subsequent Irish legislation (S.I. 99/2022) makes provision for a suitably qualified and experienced nurse or midwife to take consent in IMP trials, when delegated to do so. It is vital that CRNMs accept this delegation only if they are satisfied that they are fully informed about the study, the disease area, and the informed consent process.

In other types of research, CRNMs may be responsible for obtaining consent +/- assent, and should only accept delegation to do so if they are certain they have the requisite knowledge and skills to assume this responsibility.

The HSE National Consent Policy, updated in 2022, provides guidance on consent in clinical practice and contains a detailed section on consent and assent in research https://www.hse.ie/eng/about/who/qid/other-quality-improvement-programmes/consent/hse-national-consent-policy.pdf.

Paediatric research can present additional challenges when obtaining informed consent. For IMP trials the regulations recommend that, in addition to the informed consent given by a guardian, a minor who is capable of forming an opinion and assessing the information given to him/her/they, shall also assent in order to participate in a clinical trial. Similar principles apply for other types of research.

The European Network of Paediatric Research at the European Medicines Agency (Enpr-EMA) produces documents on informed consent and assent for all stakeholders (such as patients, sponsors and investigators) involved in paediatric clinical trials in Europe across all age groups (birth to less than 18 years of age). According to the HSE National Consent Policy (2022) 'it is sufficient for one parent/legal guardian to provide consent for a child's participation in research unless the REC has found that the risks involved in participation require the consent of both parent(s)/legal guardian(s)'. It is recommended that when undertaking regulated neonatal and paediatric studies, researchers confirm that both the REC and the HPRA are satisfied with the proposed consenting process. If the signature of only one parent/legal guardian is required, it may also be necessary to provide documentation to show that other representatives were aware of the planned research and did not object – e.g. through phone contact.

The rights of parents to guardianship are set down in Section 6 of the Guardianship of Infants Act 1964 and Children and Family Relations Act 2015. It is important to note that a mother who is under the age of 16 years may consent her child to participate in research but the mother (under 16 years of age) can't consent herself to participate in a clinical trial. Depending on the duration of the research study the assent of the child may need to be obtained more than once to match their level of development and understanding of the study they are participating in.

4 GENERAL INFORMATION

4.1 CONFIDENTIALITY

All research personnel must ensure that only authorised persons enter the workplace, to prevent unauthorised access to confidential patient information.

- All computer equipment must be located away from public access. If this is not possible then equipment must always be supervised or screen-locked when unattended.
- Printed materials must be retrieved from printers or fax machines as quickly as possible in order to prevent unauthorised observation.
- Desks must be cleared of information sources (patient data, contact information etc.) when the office is unattended.
- Computers/laptops must be switched off at the end of the day before leaving the office.
- Computers must not be left logged in when staff are away from their desk
- All old information must be disposed of securely. Paper based items must be shredded.

4.1.1. Personal Computer/Laptop Security

- All accounts & database systems must have secure password access only.
- Passwords must be kept secret at all times; use of a co- worker's password is forbidden, and passwords should never be recorded where they may be visible to a casual observer.
- Up to-date anti-virus software must be installed on an ongoing basis.
- Personal firewalling must be installed if the internet is to be accessed from outside the hospital network or from home. The firewall will protect the computer/laptop by preventing unauthorised access.
- Free software programs must not be downloaded from the internet as they may contain viruses etc. which could cause damage to the computer and/or the data on it.
- Laptops must be kept in a secure location when not in use.
- All laptops must be encrypted in order to prevent unauthorised access to data should the equipment be lost or stolen.

You are expected to be aware of, and adhere to, your organisations IT policies and procedures

4.2 GLOSSARY OF COMMON TERMS

Adverse Drug Reaction: An adverse reaction or side effect is an unwanted or unintentional reaction that a person may have after taking a medicine.

Adverse Reaction (in IMP trial): Any untoward and unintended response in a subject to an investigational medicinal product which is related to any dose administered to that subject;

Chief Investigator: (a) in the case of a clinical trial conducted at a single trial site, the investigator for that site, or (b) in the case of a clinical trial conducted at more than one trial site, the authorised health care professional, whether or not he or she or they is an investigator at any particular site, who takes primary responsibility for the conduct of the trial;

Clinical Investigation: An investigation to study the safety and/or performance of a medical device.

Clinical Study (Under CTR): Any investigation in relation to humans intended:

a) To discover or verify the clinical, pharmacological or other pharmacodynamic effects of one or more medicinal products
b) To identify any adverse reactions to one or more medicinal products or
c) To study the absorption, distribution, metabolism and excretion of one or more medicinal products, with the objective of ascertaining the safety and/or efficacy of those medicinal products

Clinical Trial: A clinical study which fulfils any of the following conditions:

a) The assignment of the subject to a particular therapeutic strategy is decided in advance and does not fall within normal clinical practice of the Member State concerned
b) The decision to prescribe the investigational medicinal products is taken together with the decision to include the subject in the clinical study or
c) Diagnostic or monitoring procedures in addition to normal clinical practice are applied to the subjects.

Clinical trial protocol: A document that describes the objectives, design, methodology, statistical considerations and organisation of a clinical trial and includes any successive versions of the protocol and protocol amendments.

Competent Authority: A body which has the authority to act on behalf of the government to ensure that legislation is implemented and followed. The HPRA is the Competent Authority for human and veterinary medicines, medical devices, cosmetic products, blood and blood components, tissues and cells.

Confidentiality Agreement: A legal agreement to protect confidential information being revealed during discussions or negotiations with another party; applicable where either or both parties are individuals or an organisation. The agreement also contains the following clauses;

- Protection against the copying or retention of confidential information.

- Protection against disclosure to third parties of information not already in the public domain.
- Remedy for any breach of the agreement.

Department of Health (DoH): The aim of the DoH is to improve the health and wellbeing of people in Ireland. Their website contains information, publications and links to other health related information sources. See: www.health.gov.ie

EudraCT: A database of information on the content, commencement and termination of all clinical trials in the European Union (from 1 May 2004 onwards). It was established in accordance with Directive 2001/20/EC and is managed by the European Medicines Agency.

EudraVigilance: The system for managing and analysing information on suspected adverse reactions to medicines which have been authorised or being studied in clinical trials in the European Economic Area (EEA). The European Medicines Agency (EMA) operates the system on behalf of the European Union (EU) medicines regulatory network.

https://www.ema.europa.eu/en/human-regulatory/research-development/pharmacovigilance/eudravigilance

Good Clinical Practice: A set of internationally recognised ethical and scientific quality requirements for clinical trials involving humans

Health care professional means:

(a) a registered medical practitioner,

(b) a registered dentist,

(c) a registered nurse,

(d) a registered pharmacist,

(e) a person registered in the Register of Optometrists established under the Opticians Acts 1956 and 2003, or

(f) any other person holding another such professional qualification that would entitle him or her to provide health care;

Investigational medicinal product: A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including a medicinal product that is already the subject of a marketing authorisation, but—

(a) is used, formulated or packaged in a way different from the form that is the subject of the authorisation,

(b) is used for an indication that is not included in the summary of product characteristics under the authorisation for the product, or

(c) is used to gain further information about the form of the product that is the subject of the authorisation;

Investigator's Brochure: Means a document containing a summary of the clinical and non-clinical data on the investigational medicinal product (or device) which are relevant to the study of the product in human subjects;

Investigator-sponsor: Means, in relation to a clinical trial, a chief investigator who is also acting as the sponsor for that clinical trial (i.e. Investigator initiated study).

Multi-centre clinical trial: A clinical trial conducted according to a single protocol but at more than one site, and therefore by more than one investigator, in which the trial sites may be located in a single Member State, in a number of Member States or in a Member State or Member States and a third country or third countries

Serious adverse event or serious adverse reaction: In IMP trials means any adverse event or adverse reaction that at any dose -

(a) results in death,

(b) is life-threatening,

(c) requires hospitalisation or prolongation of existing hospitalisation,

(d) results in persistent or significant disability or incapacity, or

(e) consists of a congenital anomaly or birth defect;

Pharmacovigilance: Watchfulness in guarding against danger from drugs or providing for safety of drugs. It may also be a dedicated department whose role is to monitor toxicity and safety of drugs both in the development phase and post marketing.

Sponsor: means, in relation to a clinical trial, the person who takes on responsibility for the initiation and management (or for arranging the initiation and management) of, and the financing (or arranging the financing) for that clinical trial;

Subject: in relation to an IMP trial, means an individual, whether a patient or not, who participates in a clinical trial—

(a) as a recipient of an investigational medicinal product or of some other treatment or product, or

(b) without receiving any treatment or product, as a control;

Trial site*:* A hospital, nursing home, health centre, surgery or other establishment or facility at or from which a clinical trial, or any part of such a trial, is conducted;

Additional definitions may be found at http://www.ncpe.ie/for-patients/glossary-of-terms/ and at https://getitglossary.org/listing/c

5 REFERENCES & RESOURCES

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Government of Ireland: S.I. No. 41/2022 - European Union (Clinical Trials on Medicinal Products for Human Use) (National Research Ethics Committees) Regulations 2022: https://www.irishstatutebook.ie/eli/2022/si/41/made/en/print

Government of Ireland: S.I. No. 99/2022 - European Union (Clinical Trials on Medicinal Products for Human Use) (Principle) Regulations 2022: https://www.irishstatutebook.ie/eli/2022/si/99/made/en/print

Health Services Executive (2022) National Consent Policy https://www.hse.ie/eng/about/who/qid/other-quality-improvement-programmes/consent/hse-national-consent-policy.pdf

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Whitehouse, C. (2018) Review of Research Nursing and Midwifery Across the UK and Ireland: Structures, Strategies and Sharing (The Whitehouse Report). The Florence Nightingale Foundation, London. Available at: https://florence-nightingale-foundation.org.uk/wp-content/uploads/2018/06/FNF-Whitehouse-report-CWhitehouse-final-revisions-6June2018.pdf

APPENDIX 1: SAMPLE ORIENTATION CHECKLIST

Name: _____ Preceptor/Mentor: _____ Work Location: _____

Role Title: _____ Date commenced post: _____

SECTION 1 - INTRODUCTION TO SITE PERSONNEL				
Area of Induction	**Date**	**Comment if applicable**	**Sig: Mentee**	**Sig: Mentor**
Outline of role				
Introduction to CRF/C staff members				
Introduction to CRF/C management team				
Introduction to key hospital staff, as applicable				
SECTION 2 - CONDITIONS OF EMPLOYMENT				
Contract of employment, working hours, period of notice				
Method of recording attendance (as applicable)				
Systems for requesting/recording annual leave				
Sickness Policy & how to report sickness				

Processes for assessment of probationary period – as applicable				
Processes for annual personal & professional development (PPD) planning				
SECTION 3 - STANDARD OPERATING PROCEDURES (SOPs) AND WORK INSTRUCTIONS (WIs)				
Area of Induction	**Date**	**Comment if applicable**	**Sig: Mentee**	**Sig: Mentor**
How to access Quality manual, SOPs and WIs				
Policy for reviewing and understanding SOPs				
Policy for recording SOP and WI training				
Process for updating and distributing amended SOPs				
SECTION 4 – INTRODUCTION TO CRF/C and HOSPITAL FACILITIES				
Tour of CRF/C and relevant departments				
Access & security procedures				
Changing room/lockers and toilet facilities				
Fire exits & System for raising alarms				

Access to drug keys and storage areas				
Telephone operation systems				
Notice boards – including virtual/online				
Identity badge / Swipe card				
IT set up and passwords (Email, shared drives, Hospital Information System as applicable)				
Occupational Health access and resources				
Tour of the hospital as applicable (Introduction to key OPD, pharmacy, radiology, stores staff)				
Staff restaurants/café facilities				
Parking on site processes				
SECTION 5 - ADMINISTRATIVE PROCESSES				
Area of Induction	**Date**	**Comment if applicable**	**Sig: Mentee**	**Sig: Mentor**
Data protection / Patient confidentiality				
Hospital admissions procedures				
Making Hospital outpatients appointments				
Process of organising screening investigations & retrieving results				

Process for obtaining and tracking medical records				
Training in hospital IT systems as applicable				
Training in Study Manager system				
Processes for reserving space & equipment in CRF/C				
SECTION 6 - HEALTH & SAFETY				
Health and Safety resources on RCSI website				
Fire safety training				
Infection control and hand hygiene training				
Manual handling training				
Personal security				
Awareness of overnight study policy (if applicable)				
Awareness of lone worker policy (if applicable)				
Awareness of risk assessment processes				
Safe handling of biological samples				
Safe handling of dry ice				
Sharps and spills policy				
Vaccination access and processes				

SECTION 7 – CLINICAL SKILLS and COMPETENCIES Skills and Competencies required are determined by the roles and responsibilities of the mentee's role. Not all will be applicable at time of induction but can be completed at a later stage, and additional skills may be added to the list as necessary. It may be necessary to complete a training course and then to observe and/or perform a task under supervision in order to demonstrate competency.				
Area of Induction	**Date**	**Comment if applicable**	**Sig: Mentee**	**Sig: Mentor**
Cardiopulmonary Resuscitation (CPR) training				
Basic Life Support (BLS) Training				
Phlebotomy				
IV cannulation				
Processing biological samples				
Centrifuging blood samples				
Packing biological samples for shipping				
Using Dry Ice safely				
ECG recording				
Patient assessment – routine (list in comment section as applicable)				
Patient assessment – study specific (list in comment section as applicable)				

SECTION 8 - STUDY COORDINATION				
Area of Induction	**Date**	**Comment if applicable**	**Sig: Mentee**	**Sig: Mentor**
Documentation in Clinical Research (CRF, Source Documents, Databases)				
Study set-up in CRF/C				
Study Protocol review				
Study approval processes in hospital site/s				
Investigator Site Files (ISF) management				
Informed Consent Process (Examples of PIL/ICF's)				
Informed Assent Process (Examples of PIL/ Assent Forms)				
Observation of Study Coordination role (site initiation, patient visits, study monitoring)				
Study archiving processes				
Safety Reporting processes				

SECTION 9 - RESEARCH GOVERNANCE				
Area of Induction	**Date**	**Comment if applicable**	**Sig: Mentee**	**Sig: Mentor**
ICH Good Clinical Practice training and certification				
Role of national and local Research Ethics Committees				
REC approval processes				
Role of Health Products Regulatory Authority				
HPRA review and authorisation processes				
Clinical trial monitoring				
HPRA Inspections				
Hospital and or institution research approval processes (Risk and Legal, Finance, Data Protection, Indemnity, Clinical Trial Agreements)				
HSE Indemnity Form				
Role of RCSI Sponsor Office				

SECTION 10 - EMPLOYEE COMMUNICATION AND SUPPORT				
Area of Induction	**Date**	**Comment if applicable**	**Sig: Mentee**	**Sig: Mentor**
Staff and management meetings				
Research team meetings				
Social and sports clubs etc.				
Staff communication channels (e.g. bulletins, website)				
SECTION 11 – MISCELLANEOUS				
Area of Induction	**Date**	**Comment if applicable**	**Sig: Mentee**	**Sig: Mentor**
Irish Research Nurses & Midwives Network (IRNM)				
UK Clinical Research Facilities Network (UKCRF)				

It is the responsibility of each nurse/ midwife to ensure that they seek further training if they feel they need it.

Acknowledged by _____ on date _____

APPENDIX 2: WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

ETHICAL PRINCIPLES FOR MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the: 29th WMA General Assembly, Tokyo, Japan, October 1975 35th WMA General Assembly, Venice, Italy, October 1983 41st WMA General Assembly, Hong Kong, September 1989 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996 52nd WMA General Assembly, Edinburgh, Scotland, October 2000 53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added) 55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added) 59th WMA General Assembly, Seoul, Republic of Korea, October 2008 64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data. The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.
2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”
4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.
5. Medical progress is based on research that ultimately must include studies involving human subjects.
6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.
8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.
9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.
10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.
11. Medical research should be conducted in a manner that minimises possible harm to the environment.
12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.
13. Groups that are under-represented in medical research should be provided appropriate access to participation in research.
14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.
17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition

under investigation. Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed. When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm. All vulnerable groups and individuals should receive specifically considered protection.
20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as

applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she or they freely agree.
26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.
29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.
30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.
31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.
32. For medical research using identifiable human material or data, such as research on material or data contained in biobank or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.
36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

APPENDIX 3: COMMON ABBREVIATIONS USED IN CLINICAL RESEARCH

Abbreviation	Definition
ABPI	Association of the British Pharmaceutical Industry
ADR	Adverse Drug Reaction
AE	Adverse Event
ATIMP	Advanced Therapy Investigational Medicinal Product
CA	Competent Authority(s)
CIP	Clinical Investigation Plan (term for protocol in medical device studies)
CIOMS	Council for International Organizations of Medical Sciences
CIS	Clinical Indemnity Scheme
CONSORT	Consolidated Standards of Reporting Trials
CRA	Clinical Research Associate (aka Monitor)
CRC	Clinical Research Centre
CRDI	Clinical Research Development Ireland
CRF	1. Clinical Research Facility 2. Case Report Form
CRNM	Clinical Research Nurse/Midwife
CRO	Contract Research Organization
CSET	Centres for Science, Engineering & Technology
CSFP	Clinician Scientist Fellowship Programme
CSTAR	Centre for Support and Training Analysis Research
CTA	Clinical Trial Agreement
CTCAE	Common Terminology Criteria for Adverse Events
CTIF	Clinical Trial Indemnity Form
CTI	Cancer Trials Ireland
CTIMP	Clinical Trial of Investigational Medicinal Product
CTR	Clinical Trial Regulations
CV	Curriculum Vitae
DAMC	Dublin Academic Medical Centre
DCCR	Dublin Centre for Clinical Research
DM	Data Management
DPO	Data Protection Officer
DSMB	Data Safety Monitoring Board

DSMC	Data and Safety Monitoring Committee
DOHC	Department of Health and Children
EC	Ethics Committee (or REC – Research Ethics Committee)
e-CRF	Electronic Case Report Form
EEA	European Economic Area
EI	Enterprise Ireland
EMEA	European Agency for the Evaluation of Medicinal Products
EPA	Environmental Protection Agency
ERIC	European Research Infrastructure Consortium
EU	European Union
EUPATI	European patients Academy on Therapeutic Intervention
FDA	Food and Drug Administration (USA Competent Authority)
FSAI	Food Safety Authority of Ireland
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GLP	Good Laboratory Practice
GMO	Genetically Modified Organism
GMP	Good Manufacturing Practice
GMS	General Medical Services
HEA	Higher Education Authority
HIQA	Health Information and Quality Authority
HPRA	Health Products Regulatory Authority
HRA	Health Research Authority (UK)
HRB	Health Research Board
HRG	Health Research Group
HSE	Health Service Executive
HRCI	Health Research Charities Ireland (formally Medical Research Charities Group)
HRR	Health Research Regulations
IACRN	International Association of Clinical Research Nurses
IB	Investigators Brochure
ICF	Informed Consent Form
ICH	International Council on Harmonisation

IMDA	Irish Medical Devices Association
IMI	Innovative Medicines Initiative
IMP	Investigational Medicinal Product
IP	Intellectual Property
IPHA	Irish Pharmaceutical Healthcare Association
IPPOSI	Irish Platform for Patient Organisations, Science and Industry
IRB	Institutional Review Board (USA term - aka Ethics Committee)
IRNM	Irish Research Nurses & Midwives
ISF	Investigator Site File
IT	Information Technology
ITT	Intention to Treat
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
MDR	Medical Device Regulations
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medical and Healthcare Products Regulatory Authority (UK)
MED	Minimal Effective Dose
MTD	Maximum Tolerated Dose
NCTO	National Clinical Trials Office (formally Clinical Research Coordination Ireland)
NHS	National Health Service (UK)
NREC	National Research Ethics Committees
NSAI	National Standards Authority of Ireland
OECD	Organisation for Economic Cooperation and Development
ORECNI	Office for Research Ethics Committees Northern Ireland
PD	Pharmacodynamics
PHA	Public Health Agency (Northern Ireland)
PI	Principal Investigator
PIL	Patient/Participant Information Leaflet
PIAG	Patient Information Advisory Group
PK	Pharmacokinetics
PMCF	Post Marketing Clinical Follow-up (for medical devices)
PMS	Post Marketing Surveillance

PPD	Personal & Professional Development
PPI	Public & Patient Involvement
PRTLI	Programme for Research in Third Level Institutions
QA	Quality Assurance
QC	Quality Control
QMS	Quality Management System
RCT	Randomised Controlled Trial
R&D	Research and Development
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SCA	State Claims Agency
SDV	Source Data Verification
SFI	Science Foundation Ireland
SI	Statutory Instrument
SIV	Site Initiation Visit
SME	Small to Medium Enterprise
SMF	Study Master File
SOP	Standard Operating Procedure
SpR/SR	Specialist Registrar/ Senior Registrar
SSA	Site Specific Assessment (form)
SUSAR	Suspected Unexpected Serious Adverse Reaction
UKCRF	United Kingdom Clinical Research Facilities (Network)
WHO	World Health Organisation
WMA	World Medical Association

APPENDIX 4: IRNM CRNM ORIENTATION PACK – VERSION HISTORY

Version	Date	Authors/Reviewers:
Clinical Research Nurse Orientation Pack Version 1 Based on the DCCR Research Nurse Orientation Pack originally developed for use in DCCR affiliated CRF/Cs	September 2013	Ms Deirdre Hyland, RCSI CRC, Smurfit Building, Beaumont Hospital, Dublin 9 Ms Mary Clarke Moloney, Vascular Research Unit, University Hospital Limerick Ms Mary McGrath, UCD CRC, St. Vincent's University Hospital, Dublin Ms Veronica McInerney, HRB Clinical Research Facility, NUI Galway Ms Catherine Delaney, HRB/Wellcome Trust CRF, St. James Hospital, Dublin 8 Ms Claire Foley, RCSI CRC, Smurfit Building, Beaumont Hospital, D9 Ms Elaine Walsh, HRB CRF, NUI Galway
Clinical Research Nurse Orientation Pack Version 2 Revised in response to our survey of the use of the pack, and to reflect changing legislation and guidelines	June 2015	Ms Deirdre Hyland, RCSI Clinical Research Centre, Smurfit Building, Beaumont Hospital, Dublin 9 Ms Hazel Ann Smith, Research Midwife/PhD Student, University College Cork. Dr Mary Clarke Moloney, Clinical Research Support Unit, University of Limerick Ms Jean Foley, HRB Clinical Research Facility, University College Cork Dr Veronica McInerney, HRB Clinical Research Facility, National University of Ireland Galway
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