IRISH RESEARCH NURSES NETWORK (IRNN) CLINICAL RESEARCH NURSE AND MIDWIFE ORIENTATION PACK

Version 3, November 2019

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

IRISH RESEARCH NURSES NETWORK

CLINICAL RESEARCH NURSE AND MIDWIFE ORIENTATION PACK

VERSION 3: NOVEMBER 2019

http://irnn.ie/

NAME: _____

JOB TITLE: _____

MENTOR/LINE MANAGER: _____

COMMENCEMENT DATE: _____

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Irish Research Nurses National Orientation Programme

Foreword

The Irish Research Nurses Network (IRNN) is a voluntary group that supports networking and professional development of clinical research nurses and midwives (CRN/Ms) in Ireland. This orientation pack was developed as a national resource to support the induction and orientation of CRN/Ms 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. It is hoped that this document will also prove a useful tool for mentors in orientating novice CRN/Ms into their new role. Aspects of this document are equally applicable to other members of the clinical research team and may be used for their orientation also.

The IRNN Committee hope you find this document beneficial and wish you well in your career in clinical research. For more information about the Irish Research Nurses Network see: https://irnn.ie/

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Clinical Research Nurse Orientation Pack Version 1	November 2013	Based on the DCCR Research Nurse Orientation Pack originally developed for use in DCCR affiliated CRF/Cs
Clinical Research Nurse Orientation Pack Version 2	April 2015	Revised in response to our survey of the use of the pack, and to reflect changing legislation and guidelines
Clinical Research Nurse and Midwife Orientation Pack Version 3	November 2019	Revised and updated to reflect changes in practice guidelines and regulations. Incorporation of aspects of Competency Assessment pack (June 2015)

USING THIS ORIENTATION PACK

This pack has been designed for use during a period of orientation to a new role or a new workplace setting. Ideally 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. It is recommended that a signed and dated checklist be 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 i).

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
- Should issues of concern arise about failure to meet objectives identify these in a timely manner and address them in line with local management and Human Resources policies

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
- 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.

SECTION 1

Orientation Process

1.1 INTRODUCTION

Congratulations on your new position in Clinical Research. The training and educational needs of clinical research nurses/midwives (CRN/Ms) 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 and of CRN/Ms in Ireland. It will orientate you to the clinical research environment and the role and responsibilities of the CRN/M. 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 CRN/M.

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 i).

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
- Shadowing experienced staff members to observe practice
- Introduction to appropriate departments/personnel etc.
- Reviewing relevant literature and web resources
- Attendance at relevant local and national research meetings and seminars

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) • 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	1st week in post
Training in and access to electronic systems for: • Scheduling and reporting time allocated to specific activities • Managing patient bookings • Using study specific databases	First Month

• Using hospital/HSE reporting systems e.g. for lab results	
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 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	First month

1.4 INTRODUCTION TO THE RESEARCH NURSE 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

The Irish Research Nurses Network (IRNN) identifies three key areas of responsibility associated with the CRN/M role: clinical, managerial and educational (http://irnn.ie).

Clinical: The CRN/M 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 choices. The CRN/M is also involved in the informed consent, and where applicable assent, process. He/she 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 CRN/M is the management and co-ordination of individual research studies. Whilst always working within his/her scope of practice and delegated responsibilities, the CRN/M *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. Patients are educated about studies and procedures and on occasion the research nurse educates the clinical team about the studies. There is also a responsibility for CRN/Ms to continue their own education through literature review, meeting and workshop attendance relevant to their clinical area or research specialty.

A recent study of the CRN/M workforce in Ireland, completed on behalf of IRNN (Schilling & Hyland 2019) reported the tasks most commonly completed by CRNMs (Table 1).

Table 1: Responsibilities and Roles of CRN/Ms in Ireland (Schilling & Hyland 2019)

Responsibility	%	Responsibility	%
Participant recruitment	85.5	Study set-up	69.5
Informed consent process	78	*Staff orientation/training	65.2
Adverse event management	78	*Project management	48.2
Study visits	77.3	*Ethics application	47.5
Site file management	77.3	IMP management	44
Case report form completion	73.8	*Study development	39
Sample processing	70.9	*Research site management	34

***** indicates activities associated with higher level or management functions

1.4.2 THE RESEARCH NURSE ROLE WITHIN THE CLINICAL RESEARCH TEAM

Numerous reports on the status of clinical research in the Irish setting allude to the role of the CRN/M, 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 and National Council for the Professional Development of Nursing and Midwifery 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 CRN 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 nurses 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

During the past decade Irish research staff have developed collaborative relationships with UK clinical research networks, including representation by Irish CRN/Ms on working groups and committees. The Whitehouse Report (2017) recommends a cross-broader 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 CRN/Ms and nurse/midwife researchers.

In the UK, the National Institute for Health Research (NIHR) (2017) published a Clinical Research Nursing Strategy which recognises Clinical Research Nurses/Midwives place as 'visible leaders' and sets goals for 2017-2020. This is the first focused strategy of its kind which acknowledges the CRN/M workforce for their knowledge, skills and unique leadership position in forging evidence-based change, promoting areas where more work is required. However, the Whitehouse Report (2017) concluded that contracts are still a challenge.

In a major breakthrough for CRN/Ms in the USA 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 CRN/M practice:

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

The 'Count Me In' study, completed in 2019 (Schilling & Hyland 2019) was the most comprehensive examination of the CRN/M workforce in Ireland to date. It confirmed that there is still considerable variation on the terms and conditions of employment of CRN/Ms, with limited job security or recognition of the role, and lack of a systematic approach to the employment and professional development of CRN/Ms. However, the development of a national clinical research infrastructure has had positive benefits, and the increased recognition of the role by the HRB, and efforts to integrate clinical research in general into HSE services, has led to optimism about the future development of the CRN/M role.

The CRN/M is responsible for the day to day running of research studies, including identification and recruitment patients according to agreed protocols, assisting in the informed consent process and management of study related procedures and data. CRN/Ms 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.

Table 2: Roles of the CRN/M, and associated attributes and skills.

Key CRN/M Responsibilities	Key CRN/M Attributes	Associated skills
• Patient identification and recruitment • Patient consent – varies depending on study type • Organisation and completion of study visits • Completion and maintenance of study documents • Maintenance of Investigator Site 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

Advanced areas of responsibility associated with the CRN/M 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 its purpose and ensures a positive experience for research participants. The area for clinical research activity / review will be designated by your institution. Increasingly, clinical research is located in dedicated clinical research facilities or units, usually under the auspices of an academic institution, but physically located on a hospital campus. Research for specific disease areas (e.g. oncology) may be located within the specialist department. CRN/Ms not located in such a unit may face challenges securing dedicated space for clinical trial activity, and this should be factored into the planning stage of proposed trials.

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 CRN/Ms should develop and maintain their own training records, which can be used to show evidence of experience and training during an audit or inspection. Typically, this would include an up-to-date Curriculum Vitae (CV), training certificates, with hand-outs from training if applicable, 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 have training in good clinical practice (GCP), including ICH GCP E6 (R2), EU Directives and Regulations and Irish legislation. This includes legislation relevant to the area of clinical practice, such as Data Protection Act 2018 and Children and Family Relationships Act 2015. Training opportunities should be identified during the orientation process. 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.

1.7.2 Skills and competencies

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

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

1.7.3 Research Support/Training

CRN/Ms can face challenges accessing the required training for their role, particularly when they are based in an academic institution, without a formal academic or clinical status. Within academic institutions relevant training opportunities are generally advertised on web portals and sent via email to the staff mailing list. Depending on the level of local support available participation in these events may largely be self-directed. Within the clinical research infrastructure training opportunities may be available nationally, and IRNN plays its part in providing educational resources to CRN/Ms.

To ensure maintenance of professional competency CRN/Ms 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 CRN/Ms not employed through HSE services to hold honorary contracts with the health service provider.

1.8 POST-GRADUATE TRAINING OPPORTUNITIES

There is currently no bespoke specialist postgraduate training programme for CRN/Ms. A Postgraduate Certificate in Nursing (Clinical Research) was available in RCSI from 2009 – 2016 but is not running at time of publication. A number of universities – University College Dublin, (UCD) University College Cork (UCC) and NUI Galway run Masters in Clinical Research programmes. CRN/Ms who complete a postgraduate certificate or diploma programme are well placed to progress to MSc by Research, due to their existing involvement in clinical research, and their inherent understanding of the research process.

SECTION 2

Regulations & Legislation Governing Clinical Research

2.1 BACKGROUND TO CLINICAL RESEARCH PRACTICE 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 to ensure 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 published in 1947, is a set of research ethics principles for human experimentation drawn up as a result of the Nuremberg Trials held at the end of the Second World War (WW2). It is a seminal document in the history of the ethics of medical research and the first of its kind to ensure the rights of subjects. Specifically, the principals were set in response to the inhumane human experimentation, carried out in concentration camps during WW2, by Nazi doctors such as Dr Josef Mengele. The Nuremberg code includes such principles as informed consent and absence of coercion; properly formulated scientific experimentation; and beneficence towards experiment participants.

2.3 DECLARATION OF HELSINKI

The Declaration of Helsinki 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 ii). The current version is the only official one; all previous versions have been archived and should not be used or cited except for historical purposes. The Declaration of Helsinki is not legally binding but its power lies in the extent to which its underlying principals have been 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 INTERNATIONAL COUNCIL ON HARMONISATION

Originally known as the International Conference on Harmonisation, ICH 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, in order that data from different jurisdictions could be mutually recognised and shared. This was primarily to avoid replication of studies, thereby speeding up the drug development process.

The 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, Revision 2: Guideline for Good Clinical Practice (GCP). ICH GCP is a phrase that all research staff must be familiar with and is the code of good research practice that must be adhered to. It is not only a guideline – adherence to GCP is enshrined in legislation: ***"Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and are consistent with Good Clinical Practice and the applicable regulatory requirements"*** SI 190/2004.

First published in 1996, the ICH GCP guideline was revised in 2016, and came into effect in June 2017. While it is primarily aimed at those involved in drug trials, it was based on other guidelines for research conduct and the World Health Organisation stresses that the principles of GCP apply to all types of research, not just drug trials. At time of writing there is an extensive renovation of ICH GCP guidelines underway.

The ICH GCP guidelines (E6, (R2) 2016) are very comprehensive and list 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.

When first published the GCP guideline had no legal status. However, in 2001 the European Union (EU) issued a clinical trial directive (2001/20/EC) which required the ICH GCP guidelines to be adopted into national legislation in member states, ensuring that all parties practising research now must adhere to the guidelines. 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 EUROPEAN CLINICAL TRIALS DIRECTIVE

The EU Clinical Trials Directive of 2001 (2001/20/EC), and subsequent amendments, sought to harmonise and streamline clinical trial conduct and IMP manufacture in EU member states. It relates to all trials involving medicinal products for human use, and encompasses all personnel involved with clinical trial activities. Member states were required to implement the directive by May 2004. In Ireland the EU directive was transposed into law under Statutory Instrument 190 (S.I 190/2004) European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations, 2004.
S.I. 190/2004 has been amended to include S.I. 878 of 2004 and S.I. 374 of 2006, reflecting amendments to the EU directive. These regulations replaced the Control of Clinical Trials Acts, 1987. SI 190 provided the Irish legal interpretation of elements of the EU Directive. It also provided for the establishment of recognised ethics committees for provision of a single national ethics opinion for trials that fall under the legislation and for regulatory inspection of clinical trials by the Health Products Regulatory Authority.

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.

The CTR entered into force on 16 June 2014 but to-date the Clinical Trials Regulation has not been applied and has not replaced EU Clinical Trials Directive of 2001 (2001/20/EC). 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 (an EU portal and

database) 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;
- 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.

One of the main effects of the CTR is to be the creation of a central web portal to streamline clinical trial applications and reporting. Articles 80 and 81 of the Regulation assign the European Medicines Agency (EMA) the task of developing the EU Portal and Database. The EU Portal will be a single-entry point for submission of data and information relating to clinical trials required by the Regulation. It will have a public section so that patients can find out about ongoing studies and also a layman's summary of results. The EU Database will contain all data and information submitted via the EU Portal.

These systems are expected to be the backbone of the new regime for clinical trials in Europe. The EMA together with the EU countries and the Commission are currently working in order to set up the portal and database. EMA's Management Board endorsed a timeframe for the delivery of the Portal and Database in December 2015. However, due to technical difficulties with the development of the IT systems, and delays caused by the need for EMA to relocate as a consequence of Brexit, the portal's go-live date had to be postponed. It is now expected that the EU Clinical Trial Regulation will come into application during 2020 instead of October 2018, as previously scheduled. For further information please consult the EMA website.

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 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

Medical devices are divided into classes dependent on risk, which can be low, medium and high risk. Although we are in a transition period at present the principle legislation covering medical devices are:

- Directive 90/385/EEC concerning Active Implantable Medical Devices (AIMDD)
- Directive 93/42/EEC concerning General Medical Devices (MDD)
- Directive 98/79/EC concerning *In-vitro* Diagnostic Medical Devices (IVDs)

The above Directives (and subsequent amendments) were transposed into national law, as follows:

- S.I. No. 253 of 1994, European Communities (Active Implantable Medical Devices) Regulations, 1994 that became mandatory on 1st January 1995.
- S.I. No. 252 of 1994, European Communities (Medical Devices) Regulations, 1994 that became mandatory on 14th June 1998.
- S.I. No. 304 of 2001, European Communities (*In-vitro* Diagnostic Medical Devices) Regulations, 2001 that became mandatory on the 7th December 2003.

Clinical investigations (i.e. device trials) are usually required to gather clinical data that is sufficient to demonstrate conformity of a non-CE marked medical device.

2.7.1 EU Medical Devices Regulations 2017

Regulation 2017/745 on Medical Devices and Regulation 2017/746 on In-Vitro Diagnostic Devices were formally published in the Official Journal of the *European Union* on 5th May 2017. The Regulations in in the process of a staggered transitional period, with full application of the MDR expected after 3 years and full application of the IVDR after 5 years. The MDR and IVDR represent a significant

development and strengthening of the existing regulatory system for medical devices in Europe and will replace the original Directives which have been in place for over 25 years. The legislation now being in the form of a Regulation, rather than a Directive, means that the EU law is directly applicable at national level without requiring transposition through specific national legislation. This should allow for greater legal certainty and prevent variation in the approach taken or in the rules relating to medical devices that are applied across EU Member States. It is expected that the MDR will lead to an increased requirement for clinical investigations in higher risk devices.

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

ICH GCP does not apply to device trials – this area of research is guided by an International Standards document - ISO 14155. ISO 14155:2011 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.

2.8 MEDICAL RESEARCH ETHICS COMMITTEES

A Medical Research Ethics Committee (REC) reviews applications 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. A REC must at all times be ICH/GCP compliant. At time of any research studies involving patients or healthy volunteers are required to apply for ethical approval at each research site, with the exception of clinical trials of investigational medicinal products (CTIMPs). Clinical Trials regulations (SI 190/2004) provides for a single ethical opinion from a recognised ethics committee for IMP trials.

There are currently 12 RECs in Ireland that have been recognised by the Department of Health to review applications for CTIMPs for the whole of Ireland. The REC in Children's Health Ireland at Crumlin is the only paediatric REC, to be recognised by the Department of

Health, in Ireland. The remaining 11 RECs are based in adult (medical) hospitals. In addition, the drug trial must have a European Clinical Trial (EudraCT) number https://eudract.ema.europa.eu/ and have received regulatory approval.

Legislation for the membership of a recognised ethics committee is very specific and sets out how many members the committee should have, and what proportion of these must be lay members. S.I 190 (2004) sets out how many members must be at a meeting in order to have a quorum. It also sets out specific timelines within which a REC must make a decision in relation to a clinical trial and in relation to amendments to a clinical trial. Clinical trials of IMPs, which are primarily funded by pharmaceutical companies, require an indemnity agreement, and a clinical trial agreement, which are both legal contracts, drawn up between the sponsor and the hospital/principal investigator. Adequate insurance must be in place in case of an injury occurring to a trial participant.

2.8.1 Approval of 'Other' Research

A REC reviews many other types of research other than IMP trials. For example, it reviews clinical investigations of medical devices, e.g. stents and pacemakers. There are statutory instruments in place also in relation to medical devices, which the committee must comply with. Unlike drug trials however the device legislation does not allow a REC to give a central favourable opinion for Ireland. Some medicine device trials also require HPRA approval.

Academic or non-interventional research taking place in a hospital are generally reviewed by the local REC. A large percentage of research taking place in a teaching hospital would fall into the category of research other than clinical trials, and there is no specific legislation governing the REC's role in this area. It is expected that this will change with the implementation of the National Research Ethics Framework. REC must also comply with additional legislation, including Data Protection Legislation, the Health Research Regulation, Freedom of Information Legislation, HSE National Consent Policy (2019), and common law on consent for medical treatment and research. In addition, there are relevant publications from the Irish Council for Bioethics to consider and many professional organisations have guidelines in place e.g. the Nursing & Midwifery Board of Ireland (NMBI) and The Irish Medical Council.

In July 2019 the Government of Ireland published the General Scheme of the National Research Ethics Committees Bill confirming plans to develop a streamlined, regulated and fit-for-purpose model for the ethical review of health research projects. The Bill will modernise the current system, will support more consistent and more efficient decisions for research studies and will mean better results for patients.
Speaking at the launch of the National Research Ethics Committees Bill, Minister for Health Simon Harris said: “The government is committed to supporting health research development in Ireland as it means better care and outcomes for patients, recruitment and retention of a high-calibre and innovative health workforce, better returns on healthcare expenditure and achievement of broader government goals in terms of employment and economic gain. This Bill is essential to achieving those goals."

The reform of the current ethics committee structure will see the establishment of a number of National Research Ethics Committees, starting with one in the area of clinical trials of medicinal products, and these single-opinion national committees will be supported by dedicated and professional staff in a National Office for Research Ethics Committees (to be hosted by the Health Research Board). At time of writing there was little clarity about how this will impact on local RECs and what resources will be available for these services. Due to lack of a harmonised approach currently you are advised to refer to information provided by your local ethics committee about submitting an application. Most RECs have websites that provide advice, guidelines, submission templates and checklists for the applicant. If submitting to a REC for a paediatric drug trial it is recommended that you seek the advice and approval from the REC based in Children’s Health Ireland at Crumlin.

2.9 HEALTH PRODUCTS REGULATORY AUTHORITY (PREVIOUSLY IRISH MEDICINES BOARD)

The HPRA is the regulatory or 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 which 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 CTIMPs to assess patient protection and compliance with GCP. For further information about the role of the HPRA visit: http://www.hpra.ie/homepage/medicines/regulatory-information

2.10 DATA PROTECTION

The Data Protection Commission (DPC) is the Irish independent authority 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 latter act, 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 (Regulation 3(1)). HRR has had a mixed response and its implementation in certain areas of research is still under consideration. The main implication for the CRN/M is the necessity to be aware of and compliant with data privacy requirements at all times.

The HRB provides educational and informational guidance on GDPR and the Health Research Regulation for researchers in the healthcare system: https://www.hrb.ie/funding/gdpr-guidance-for-researchers/. 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. In situations where data are being transferred to countries outside the EU or EEA special

safeguards must be in place to ensure that the protection offered by GDPR is maintained. The European Commission has developed Standard Contractual Clauses for data transfers from data controllers in the EU to data controllers or processors outside the EU or EEA.

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 room
- 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.
- Research subject confidentiality should be maintained by the use of initials and/or research numbers 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 UPCOMING CHANGES IN RESEARCH GOVERNANCE IN IRELAND

Long awaited changes in the governance of clinical research will be implemented in the coming years, as outlined above. The cumulative effect of these changes is it will soon be possible for researchers to apply to one ethics committee only, when conducting any research study at any state-funded site in the Republic of Ireland. We may see an increase in medical device research as the regulations take effect, and researchers will be obliged to comply with the requirements of the HRR to avoid the risk of a data breech. There is as yet no indication of a national system for inspection of research that does not come under the remit of the HPRA, however, academic institutions are increasingly putting resources in place to ensure oversight of all research carried out their establishments.

SECTION 3
Clinical Research

3.1 OVERVIEW OF CLINICAL TRIAL PROCESS

In general, clinical studies are designed to add to medical knowledge related to the treatment, diagnosis, and prevention of diseases or conditions. Some common reasons for conducting clinical studies include:

- Finding ways to prevent the initial development or recurrence of a disease or condition.
- Examining methods for identifying a condition or the risk factors for that condition
- Evaluating one or more interventions aimed at identifying or diagnosing a particular disease or condition
- Exploring and measuring ways to improve the comfort and quality of life through supportive care for people with a chronic illness.

At its heart clinical research is about generating knowledge to support healthcare and clinical practice. It's about finding out why people get ill and identifying ways to prevent or slow down illness. It's about 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.

CRN/Ms may be involved in many types of clinical research, including:

- Patient-oriented research, involving a particular person or group of people or uses materials from humans.
  - Studies of the mechanisms of human disease
  - Studies of treatments or interventions for disease
  - Studies to develop new technology related to disease
  - Clinical trials
- Epidemiological and behavioural studies, looking at incidence/distribution of disease, factors affecting health, and how people make health-related decisions.
- Outcomes and health services research, intended to identify the most effective and efficient interventions, treatments, and services.

3.2 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, or 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 after a product has been licenced. Pharmaceutical companies, academic institutions or individual investigators may sponsor clinical trials. Income from clinical trials is used to support research staff posts and fund additional research or resources.

3.2.1 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 outlined – very broadly – 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: There is not currently a standard approach to the procedures followed by REC nationally. However, most institutional RECs have a website that provides the necessary information about their service. All research protocols and associated documents must be submitted to and approved by the ethics committee before subject recruitment can begin. They may refuse approval, grant conditional approval subject to changes, or grant full approval. Ethics committees should be notified in writing when a study ends and of any serious adverse events that happen during the course of the study.
- Regulatory approval: The HPRA must approve all IMP trials before subject recruitment can begin. Certain clinical investigations of medical devices must also be submitted for HPRA review.
- Clinical Trial Indemnity: is required only for trials involving drugs supplied by pharmaceutical companies. The standard HSE Form of Indemnity should be used.

- 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) the purpose of which states how the trial will be conducted.
- Site Initiation Visit (SIV): The SIV is usually carried out by a Clinical Research Associate (CRA) who ensures that all appropriate research staff 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 of the 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. Written consent needs to be obtained for everything, including potential storage of and access to data/material. A subject should not undergo any research related procedure until written informed consent has been obtained.
- Visits as per protocol: the type of study will dictate the visits. Every procedure that a patient receives as part of a research trial must be documented accurately and clearly. Any reasons for non-compliance with the protocol must be documented. It is important that the research subjects have a name and number for the study team to contact between visits should they have any concerns.
- Monitoring visits (quality assurance by sponsor) will be performed during the clinical trial to ensure adherence to the trial protocol and compliance with GCP and the regulations
- Study Close-out: All documentation is complete and data queries are resolved. Patients revert back to standard care.
- Data are analysed and reported. The Investigator or sponsor will decide when the trial documents can be archived. For trials that are subject to inspection by the HPRA files must be readily accessible if needed for regulatory inspection.

3.3 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 CRN/M may fulfil these roles.

3.3.1 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 investigators.
- Provision of clinical trial protocol and ensuring protocol compliance.
- Establishing the distribution of trial related responsibilities.
- Providing procedures and staff management of the clinical trial, record keeping, monitoring and quality assurance.
- Ensuring compliance with applicable legal, ethical and regulatory requirements.
- Provision of compensation and indemnity for trial related injury according to local laws and regulations.

3.3.2 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)

It is the responsibility of the PI to conduct the study according to the protocol and to ensure that he/she 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 principle investigator must ensure that the data from one centre is not published before the publication of the whole study without his/her consent.
- To retain all essential documents until after 2 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.

3.3.3 Sub Investigator

The Sub-Investigator is responsible for medical care of patients participating in research studies, working under the supervision of the principle 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.

3.3.4 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.

3.3.5 Clinical Research Nurse/Midwife (CRN/M)

Taking account of the previous discussion about the complexity and variation of the CRN/M role, within the research team CRN/Ms 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.

3.3.6 Data Manager

Data managers work closely with investigators, CRN/Ms 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

3.3.7 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 nominee.
- Supporting the research activities of the Principal Investigator or his/her 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

3.3.8 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.

3.4 STANDARD OPERATING PROCEDURES (SOP'S)

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
- Other related procedures
- Personnel involved with procedure
- 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)

3.5 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. CRF's, along with the source documentation, will be closely examined during the 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 data, which has been recorded in the subject's source notes. The CRF should collect necessary information about:

- The subject
- Administration of the study drug
- Study specific procedure
- 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 CRF's. These may include co-investigators, research nurses, radiographers and data managers. CRF's 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 CRF's:

- Black ball point pen must always be used to complete the CRF.
- If the CRF is on carbon duplication paper, ensure that an appropriate separator is inserted.
- Never leave blank spaces. If a section cannot be completed write: as appropriate, not known, not done etc.
- Never enter a research subject's full name on a CRF.
- CRF's 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 as follows:
- 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-CRF's, and to confirm the audit trail capabilities of an electronic data capture system which should record all operations of the data including viewing and exporting.

3.6 ADVERSE EVENTS

Adverse event reporting is an important aspect of clinical trial coordination and management. The definitions provided below are specific to IMP trials – there is different terminology for medical device research but the general principles are quite 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.

3.6.1 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).

3.6.2 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.

3.6.3 Grading of Adverse Events

All adverse events should be categorised according to severity. Each protocol may have a unique approach to grading AEs and the Principal Investigator/site staff should consult the protocol for specific grading scales. Multi-centre studies generally include such a table, sometimes called a toxicity table within the protocol.

3.6.4 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.

CRN/Ms 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.

3.7 INFORMED CONSENT AND ASSENT

Freely given informed consent is the cornerstone of ethical research. Each prospective participant and/or the legal representative must:

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

Informed consent must be obtained prior to any protocol specific testing being conducted. If protocol specific testing is done the same day as informed consent is obtained, there must be clear documentation of the chronological order in the patients' medical record.

Details of how informed consent is to be obtained, by whom and details of the research project the participant must be provided with to adequately provide an "informed" decision to participate is clearly detailed in the ICH GCP booklet. The person obtaining consent should have sufficient knowledge about the research and be capable of answering questions from prospective participants (HSE 2019).

The Health Service Executive (HSE) National Consent Policy (2019) states that a person over 16 can consent for clinical trials on his/her own behalf, and that, for all other research, the person must be 18 years or over. Parent(s)/ legal guardian(s) who are under 16 years of age can consent for their child to participate in a research study, including a clinical trial, as they are signing the form as parent/ legal guardian and not as a minor. Children who by definition of the HSE's National Consent Policy are minors require the consent of their parent(s)/ legal guardian(s) to participate in research studies. In Ireland, only one parental/ legal guardian signature is required but the HPRA prefers if both signatures can be obtained. It is therefore recommended that if you are unable to get both parents'/ legal guardians' signatures that you document the reasons in the child's medical chart.

The HSE policy advocates that, while children should never be exploited, or inappropriately enrolled in research, they should be allowed to participate in research that might benefit them. The information leaflets and assent forms must match the developmental age of the child. The age at when assent is sought is outlined in the study protocol and must be followed (unless the PI can clearly document otherwise). As children

grow older their ability to understand research develops and you may need to seek their re-assent to remain in the study. Again, this should all be included in the study's protocol.

All research personnel must be familiar with ICH GCP guidelines and legislation for obtaining valid informed consent.

SECTION 4
General Information

4.1 INFORMATION TECHNOLOGY

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 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.

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 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 Trial: Any investigation in human subjects, other than a non-interventional trial, intended:

(a) To discover or verify the clinical, pharmacological or other pharmacodynamic effects of one or more investigational medicinal products, or

(b) To identify any adverse reactions to one or more such investigational medicinal products, or

(c) To study absorption, distribution, metabolism and excretion of one or more such investigational medicinal products, or

(d) To discover, verify, identify or study any combination of the matters referred to at subparagraphs (a), (b), and (c), with the object of ascertaining the safety or efficacy of such products, or both.

(Note: The Clinical Trial Regulation, when implemented, will include new definitions in this category).

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.

(Note: Called Clinical Investigation Plan in medical device trials)

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;

Non-interventional trial: In the case of IMP trials means a study of one or more medicinal products which have a marketing authorisation, where the following conditions are met -

(a) the products are prescribed in the usual manner in accordance with the terms of that authorisation,

(b) the assignment of any patient involved in the study to a particular therapeutic strategy is not decided in advance by a clinical trial protocol but falls within current practice,

(c) the decision to prescribe a particular medicinal product is clearly separated from the decision to include the patient in the study,

(d) no diagnostic or monitoring procedures are applied to the patients included in the study, other than those which are ordinarily applied in the course of the particular therapeutic strategy in question, and

(e) epidemiological methods are to be used for the analysis of the data arising from the study.

(Note: The Clinical Trial Regulation will bring additional definitions in this area).

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: n 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

4.3 COMMON ABBREVIATIONS USED IN CLINICAL RESEARCH

Abbreviation	Definition
ABPI	Association of the British Pharmaceutical Industry
ADR	Adverse Drug Reaction
AE	Adverse Event
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
CRCI	Clinical Research Coordination Ireland
CRDI	Clinical Research Development Ireland
CRF	1. Clinical Research Facility 2. Case Report Form
CRN/M	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
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)
IRNN	Irish Research Nurses Network
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
MED	Minimal Effective Dose
MTD	Maximum Tolerated Dose
NSAI	National Standards Authority of Ireland
OECD	Organisation for Economic Cooperation and Development
PD	Pharmacodynamics
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
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
REC	Recognised Ethics Committee (for single national opinion IMP trials)
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

5.0 REFERENCES

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APPENDIX i. SAMPLE ORIENTATION CHECKLIST

Name: _____ Commencement Date: _____

Preceptor/Mentor: _____

SECTION 1 - INTRODUCTION TO SITE PERSONNEL			
Area of Induction	Date	Signature of Preceptor	Signature of New Employee
1. Outline of role			
2. Introduction to core research staff			
3. Introduction to Medical Research Ethics Committee Administrator			
4. Introduction to core support staff			

SECTION 2 - CONDITIONS OF EMPLOYMENT			
Area of Induction	Date	Signature of Preceptor	Signature of New Employee
1. Contract of employment, working hours, & breaks and period of notice			
2. Electronic & paper timesheet (as applicable)			
3. Holidays & local arrangements for leave			
4. Sickness Policy & how to report sickness			

SECTION 3 - CRC STANDARD OPERATING PROCEDURES			
Area of Induction	Date	Signature of Preceptor	Signature of New Employee
1. Location of SOP's			
2. Policy for reviewing and signing SOPs			
3. Process for updating and distributing amended SOPs			

Notes:

SECTION 4 – INTRODUCTION TO FACILITIES			
Area of Induction	Date	Signature of Preceptor	Signature of New Employee
1. Tour of research facilities			
2. Access & security procedure			
3. Changing room/lockers and toilet facilities			
4. Fire exits & System for raising alarms			
5. Awareness of drug key storage			
6. Telephone operation			
7. Notice boards			
8. Identity badge / Swipe card			
9. IT set up and passwords (Email, Hospital Information System)			
10. Attend Occupational Health for introduction (if applicable)			
11. Tour of the hospital if appropriate (Introduction to key outpatient, pharmacy and radiology staff)			
12. Staff restaurants			
13. Parking arrangements - check permit issued (if appropriate)			
Notes:			

SECTION 5 - ADMINISTRATIVE PROCESSES			
Area of Induction	Date	Signature of Preceptor	Signature of New Employee
1. Data protection / Patient confidentiality			
2. Hospital admissions procedures			

3. Making Hospital outpatients appointments			
4. Process of organising screening investigations & retrieving results			
5. Process for obtaining and tracking medical records			
6.Training in hospital information system			
7. Training in study manager system			
Notes:			

SECTION 6 - HEALTH & SAFETY			
Area of Induction	Date	Signature of Preceptor	Signature of New Employee
1. Attendance at fire training			
2. Attendance at infection control training (Hand Hygiene)			
3. Attendance at manual handling training			
4. Personal security			
5. Awareness of overnight study guidelines (if applicable)			
6. Awareness of lone worker policy (if applicable)			
7. Awareness of risk assessments			
8. Safe handling of biological samples			
9. Safe handling of dry ice			
10. Sharps policy			
11. Spills policy			
12. Vaccination screening			
Notes:			

SECTION 7 – CLINICAL SKILLS Some of the clinical procedures that you may be involved in are listed in the table below; Your mentor will help to identify the skills associated with your role, and other skills should be added as appropriate			
Area of Induction	Date	Signature of Preceptor	Signature of New Employee
1. CPR training			
2. CRC Medical Emergency policy			
4. Laboratory techniques			
5. Dry ice training			
6. Anthropometry			
7. Phlebotomy			
8. ECG recording			
9. Central Laboratory (Lab kits, processing, packaging & shipping)			

SECTION 8 - RESEARCH GOVERNANCE			
Area of Induction	Date	Signature of Preceptor	Signature of New Employee
1. ICH Good Clinical Practice Training and certification			
2. Phases of Clinical trials			
3. Study protocols			
4. Investigator's Brochure			
5. Role and composition of research ethics Committees			
6. REC application and approval process including protocol amendments			
7. Case report form completion (Source documents, data verification)			
8. Legal issues i.e. indemnity			

9. Declaration of Helsinki			
10. Good Laboratory Practice			
11. Introduction to Site Files & Filing			
12. Introduction to Informed Consent Process (Examples of PIL/ICF's)			
13. Study Co-Ordination Training (Initiation visit, pt visit, monitoring visit)			
14. Study archiving			
15. Safety Reporting (Adverse events/Serious adverse events)			
SECTION 9 - EMPLOYEE INVOLVEMENT AND COMMUNICATION			
Area of Induction	Date	Signature of Preceptor	Signature of New Employee
1. Staff meetings			
2. Journal club meeting / research meetings			
3. Social and sports club			
4. Irish Research Nurses Network			

SECTION 10 – Miscellaneous			
Area of Induction	Date	Signature of Preceptor	Signature of New Employee

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 ii: 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 underrepresented 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 freely agrees.

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.

IRISH RESEARCH NURSES NETWORK

Clinical Research Nurse and Midwife Orientation Pack

Version 3

November 2019

http://irnn.ie