



Molecular
Medicine
Ireland



Clinical Research

Irish Situation Analysis

2008

Compiled by:

Margaret Cooney, ICRIN Co-ordinator



This Report was made possible with the support of the Health Research Board and Health Service Executive to Molecular Medicine Ireland in support of ICRIN

Published in March 2009

CONTENTS

FOREWORD	3
EXECUTIVE SUMMARY	5
1 INTRODUCTION	6
1.1 Irish Clinical Research Infrastructure Network	8
1.2 European Clinical Research Infrastructures Network	9
2 ORGANISATIONAL STRUCTURE.....	11
2.1 Institution/Teaching Hospital Overview	11
2.2 Trans-Institutional Partnerships.....	11
2.2.1 Molecular Medicine Ireland	11
2.2.2 Clinical Research Centres.....	12
2.2.3 Hospital Based Research	14
2.2.4 Primary Care Based Research	14
2.2.5 All Ireland Cooperative Oncology Research Group.....	14
2.2.6 European Institute for Clinical Trials in Rare Diseases.....	15
2.2.7 Northern Ireland Clinical Research Network	16
3 FUNDING AND SPONSORSHIP	17
3.1 Funding Bodies.....	17
3.1.1 Health Research Board	17
3.1.2 Science Foundation Ireland	18
3.1.3 Wellcome Trust	18
3.1.4 Higher Education Authority	19
3.1.5 Health Information and Quality Authority	19
3.1.6 Enterprise Ireland	19
3.1.7 Industrial Development Authority.....	20
3.1.8 Patient Organisations.....	20
3.2 Industry.....	21
4 REGULATION, LEGISLATION, GUIDANCE AND INSURANCE	22
4.1 Directives and Statutory Instruments	22
4.2 Clinical Trials on Medicinal Products	25
4.2.1 Clinical Trial Applications	26
4.2.2 Ongoing Review, Substantial Amendments and Urgent Safety Measures.....	28
4.2.3 End of Trial	29
4.3 Medical Device Clinical Investigations.....	30
4.3.1 Clinical Investigation Evaluation Requirements	30
4.3.2 Clinical Studies in Medical Devices.....	31
4.3.3 Medical Device Applications and Review Process	32
4.3.4 Changes or Modifications in Protocol.....	32
4.3.5 End of Clinical Investigation.....	33
4.3.6 Notified Body	33
4.4 Clinical Investigation of Drug-Device Combinations	34
4.5 Other Clinical Studies.....	34
4.6 Insurance	35
4.6.1 Clinical Indemnity Scheme	35
4.6.2 Industry Indemnity and Insurance	37
5 ETHICS	38
5.1 Ethics Committees.....	38
5.1.1 Recognised Ethics Committees for Clinical Trials on Medicinal Products.....	38

5.1.2	Ethics Committees for other Categories of Clinical Study Research	39
6	SAFETY/PHARMACOVIGILANCE/INVESTIGATIONAL PRODUCT	40
6.1	Notification of Adverse Reactions for Medicinal Products.....	40
6.1.1	Periodic Safety Summary Reports.....	41
6.1.2	Annual Safety Reports.....	42
6.1.3	Investigational Product.....	42
6.2	Notification of Adverse Incidents for Medical Devices	43
6.3	Notification of Adverse Events and Reactions for Transplantation and Transfusion Trials .	44
6.4	Notification of Adverse Incidents for other Clinical Studies	45
7	DATA MANAGEMENT AND DATA MONITORING	46
8	QUALITY CONTROL, AUDITS AND EVALUATION.....	48
8.1	Good Clinical Practice Inspections.....	48
9	EDUCATION AND CAREERS.....	50
9.1	Masters of Science in Pharmaceutical Medicine	50
9.1.1	Diploma/MSc in Pharmaceutical Medicine – TCD.....	50
9.1.2	MSc in Pharmaceutical Medicine – Hibernia College.....	51
9.2	Other Available Training.....	51
9.2.1	Health Research Board Training Courses	51
9.2.2	Mater Misericordiae University Hospital – Introduction to Clinical Investigation	51
9.2.3	International Conference on Harmonisation-Good Clinical Practice Training	51
9.2.4	Molecular Medicine Ireland Clinician Scientist Fellowship Programme.....	52
9.3	Careers.....	52
10	CONCLUSIONS	54
11	REFERENCES	55
12	ACRONYMS USED IN REPORT	56
13	CONTRIBUTORS	58
14	ACKNOWLEDGEMENT	58

FOREWORD

On behalf of Molecular Medicine Ireland and the Irish Clinical Research Infrastructure Network (ICRIN), I am delighted to present this report, *Clinical Research, Irish Situation Analysis, 2008*.



ICRIN exists within Molecular Medicine Ireland and was created with funding from the Health Research Board (HRB) and Health Service Executive (HSE) to promote harmonisation of training, processes and practice in all aspects of clinical research in order to support academic and industry sponsors in clinical research in Ireland.

The Irish Government's *Strategy for Science, Technology and Innovation 2006-2013*¹ has recognised the need to “*upgrade existing infrastructure and develop new facilities to support research*”. Significant investment towards the establishment of a world class research infrastructure for Ireland has taken place through the creation of Clinical Research Centres/Clinical Research Facilities (CRCs/CRFs), funding biobanking facilities and high quality clinical researchers. The Government has highlighted how its strategic vision and commitment to develop Ireland as an internationally renowned centre for excellence in research can be achieved through “*continued engagement with the EU institutions and appropriate international organisations in a coordinated and strategic manner with Irish input being promoted in all areas to ensure the optimum return for our research sector*”.

A 2006 report by the Advisory Council for Science, Technology and Innovation entitled *Towards Better Health: Achieving a Step Change in Health Research in Ireland*² recommended that the “*HRB remit be expanded in the areas of infrastructure and training in addition to translational and clinical research and that its budget be increased substantially in order to build critical mass in these areas*”. Subsequent to the publication of this report, the HRB has invested significantly in the development of CRCs/CRFs and provided funding to ICRIN. In addition, this report also noted the need to “*fully exploit the potential for international networking and leveraging funding for health research under the EU's Seventh Framework Programme for Research, 2007-2013*”. ICRIN participates in the European Clinical Research Infrastructures Network (ECRIN) to achieve this aim.

The Higher Education Authority (HEA) and Forfás commissioned report *Research Infrastructure in Ireland – Building for Tomorrow 2007*⁴ states, “*the reviewers felt strongly that in a country the size of Ireland, it is of paramount importance that an organised and coordinated approach is taken to the*

running of each CRF". Reference was made to ICRIN which had just been established at the time of that report's publication.

A strong national clinical research network with well developed national infrastructure linking CRCs/CRFs, as well as participation in a transnational clinical research network will facilitate all of the above benefits by allowing access to:

- Collaborative Studies
- Patient Populations
- Shared Intellectual Property
- FP7 and Innovative Medicines Initiative Funding.

This document aims to provide an overview of the status of all types of clinical research and associated infrastructure in Ireland at the time of writing in November 2008. It will serve as a resource for key stakeholders involved in clinical research and facilitate future publication of an ICRIN Roadmap for Clinical Research to address mapping and implementation of improved, streamlined clinical research infrastructure.



Margaret Cooney

***Coordinator, Irish Clinical Research Infrastructure Network
Molecular Medicine Ireland***

EXECUTIVE SUMMARY

Those seeking to promote Ireland as a centre of excellence in clinical research are challenged by the complexity of the conduct of clinical research and the myriad of associated regulatory, ethical, safety and quality requirements. Expert knowledge of the area of clinical research is in abundance in Ireland. However, the key stakeholders supporting clinical research in a more indirect way require a general understanding of the requirements for conducting research and the infrastructure currently pending or in place to conduct research to a high standard. These stakeholders include academia, industry, patient organisations and enterprise and healthcare agencies. Knowledge of the current status of clinical research in Ireland and the general requirements needed will enable these stakeholders to promote Ireland as a centre of excellence for clinical research conduct on an international platform. This report, *Clinical Research, Irish Situation Analysis, 2008*, provides such information.

This report sets out the organisational structure of the facilities that have the capacity to conduct clinical research and those agencies and organisations that have the ability to support clinical research. This information will serve as a resource for those seeking to determine where clinical research might best be facilitated.

Requirements for clinical research conduct with Investigational Medicinal Products (IMPs) are generally well understood but clinical research involving medical devices and nutritional products or observational studies is less well defined. Details of the regulations, legislation and guidance for all categories of clinical research are provided in this report to provide a reference tool for any personnel involved in initiating clinical research in Ireland and Europe.

The day to day operational aspects of clinical research management are described, including ethics committee approval, safety reporting, data management and quality requirements for all categories of clinical research. A brief summary of educational opportunities and career paths in clinical research is also provided in this report.

1 INTRODUCTION

This report, *Clinical Research, Irish Situation Analysis, 2008*, provides a detailed overview of the status of all types of clinical research and associated infrastructure currently established or emerging in Ireland. The target audience to which this consolidated overview will be relevant includes:

- Clinicians
- Investigators
- Research Nurses
- Health Managers
- Biostatisticians
- Data Managers
- Research Scientists
- ECRIN European Correspondents
- Research Ethics Committees Members
- Clinical Research Associates
- Medical Directors/Advisors
- Regulatory Personnel
- Patient Organisations
- Funders
- Regulators
- Staff of Development Agencies
- Relevant Government Ministries.

Topics discussed in this document pertain to:

- Organisational Structure: Centres, National Networks, Institutional Partnerships
- Funding and Sponsorship
- Regulation, Legislation, Guidance, Insurance
- Ethics
- Safety, Pharmacovigilance, Investigational Product
- Data Management and Data Monitoring
- Quality Control, Audits and Evaluation

- Education and Careers.

Recent substantial investment indicates a long-term commitment by government to the development of research infrastructure in Ireland. The Programme for Research in Third Level Institutions (PRTLTI) has provided significant funding, permitting sustained expansion of Research and Development (R&D) capabilities in third level institutions. The Wellcome Trust and Health Research Board (HRB) are jointly funding a major clinical research centre in Dublin, to be known as the Dublin Centre for Clinical Research (DCCR). The DCCR encompasses a new Clinical Research Centre (CRC) to be constructed at St. James's Hospital and the deployment of a clinical research network that will link the new centre with the Beaumont Hospital/Royal College of Surgeons in Ireland CRC and University College Dublin's CRCs at the Mater Misericordiae and St Vincent's University Hospitals. The HRB and the Health Service Executive (HSE) will jointly fund the establishment of CRCs in Cork and Galway. Approximately €54 million will be invested over the next five years in the development of appropriate networking, staffing, shared processes, standards and information technology systems, leading to a substantial increase in clinical research capacity and highly trained personnel.

Although Ireland is a small country, it has the potential to be recognised as a world-class provider of quality clinical research whether in the provision of specialised areas of expertise or as part of a region in multi-national trials. Although there is a legal framework in place for some forms of clinical trials, many types of clinical research are not covered by the available legislation. Clinical research continues to be hampered for a variety of reasons such as:

- Lack of consistency in ethics committee adherence to guidance for clinical trials on medicinal products
- Need for multiple local ethics committee opinions rather than a single central opinion for any research falling outside current clinical trials on medicinal product legislation
- Sequential ethics and competent authority review of medical device clinical investigations.

Irish Clinical Research Infrastructure Network (ICRIN) exists within Molecular Medicine Ireland (MMI) and was created with funding from the HRB and HSE to promote harmonisation of training, processes and practice in all aspects of clinical research in order to support academic and industry sponsors in clinical research in Ireland. In this document, ICRIN provides a detailed situation analysis on the status of clinical research in this country. Conclusions will be drawn on areas of prioritisation to be presented in the forthcoming *Roadmap for Clinical Research* which will recommend an improved, streamlined clinical research infrastructure.

This Situation Analysis draws upon a number of reports and publications that have been issued to date. These include:

- Department of Enterprise, Trade and Employment. *Strategy for Science, Technology and Innovation 2006-2013*. DETE. 2006¹
- Advisory Council for Science, Technology and Innovation. *Towards Better Health: Achieving a Step Change in Health Research in Ireland*. Forfás. November 2006²
- Cross Sectoral Clinical Trials Taskforce. *Enhanced Clinical Trials Infrastructure Required to Benefit Public Health*. Irish Medical Devices Association and Irish Business and Employers Confederation. October 2006³
- Forfás, Higher Education Authority. *Research Infrastructure in Ireland – Building for Tomorrow*. Forfás. 2007⁴

1.1 Irish Clinical Research Infrastructure Network

The objectives of ICRIN are:

- To engage with the established and emerging CRCs, medical schools and constituent teaching hospitals in the process of developing a national clinical research infrastructure to perform cutting edge clinical research in a safe and regulated environment. This will enable patients to benefit from the latest interventions carried out under international standards of ethics, applicable legislation and Good Clinical Practice (GCP)
- To lead on the development of a framework for the harmonisation of different operating norms for clinical research into a common system, as the Irish partner in the European Clinical Research Infrastructures Network (ECRIN)
- To ensure that education and training programmes are put in place for clinical and nursing staff that allow standards to be updated and constantly improved
- To facilitate Irish academic and non-academic clinical investigators to participate in multi-centred/multi-national public/private funded clinical studies
- To drive harmonisation of procedures in Ireland with respect to Research Governance, Informed Consent, Ethical Review, Data Monitoring and Safety Reporting in line with ongoing work in Europe
- To drive a standardised approach to biobanking at all sites.

To achieve its objectives ICRIN is preparing a document entitled *Roadmap for Clinical Research* to recommend clinical research infrastructure and processes. This Roadmap will provide:

- An in-depth description of bottlenecks hampering clinical research in Ireland, taking into account changes to national regulations
- Proposals and recommendations directed to national stakeholders and regulators which aim to reduce such bottlenecks and fragmentation in clinical research in Ireland.

ICRIN, when fully established, will enable the coordination of the complex activities involved in clinical research across the country.

1.2 European Clinical Research Infrastructures Network

Fragmentation of health and legislative systems in the European Union (EU) hampers the competitiveness of clinical research. European clinical research needs an efficient, integrated, and professionalised infrastructure, based on competence centres able to provide efficient support through a consistent set of services for clinical trials such as patient recruitment and investigation, data management, Good Manufacturing Practice (GMP) of biotherapy products, quality assurance, monitoring, ethics, regulatory affairs and adverse event reporting. This integrated, EU-wide infrastructure will facilitate the conduct of academic-led multinational trials in Europe, taking advantage of the EU population and competencies, unlocking latent expertise, and combining and connecting patients currently scattered across the EU member states.

ECRIN is one of the research infrastructures recommended by the European Strategy Forum for Research Infrastructure (ESFRI) and its preparatory phase is being funded under the EU's 7th Framework Programme.

ECRIN is designed to develop an infrastructure permitting harmonisation of support, training, and practice of clinical research in Europe. One of its major objectives entails stimulating and facilitating the creation of Centres and National Networks for their subsequent connection to the European network. Connecting these national networks within a broad European network will create a critical mass at European level for clinical research. The current consortium of clinical research infrastructure participants in the ECRIN network are Austria, Denmark, Finland, France, Germany, Hungary, Ireland, Italy, Spain, Sweden, Switzerland, and the United Kingdom. The European Organisation for Research and Treatment of Cancer (EORTC), the European Forum for Good Clinical Practice and the Telematikplattform participant as associated partners. ECRIN membership is open to national infrastructure networks within other member states and it is encouraging the

establishment of new national networks. This unique and integrated clinical research infrastructure, when fully functioning, will provide support for any type of clinical research in any medical field.

ICRIN, with the support of the HRB, became an Irish partner of ECRIN on 12th October 2006.

2 ORGANISATIONAL STRUCTURE

2.1 Institution/Teaching Hospital Overview

There are six medical schools in the Republic of Ireland, each of which is linked to academic teaching hospitals. Three medical schools are located in Dublin (Trinity College Dublin [TCD], University College Dublin [UCD] and Royal College of Surgeons in Ireland [RCSI]), one in Cork (University College Cork [UCC]), and one in Galway (National University of Ireland, Galway [NUIG]). Recent grant funding has been awarded to the University of Limerick (UL) which has now established a graduate medical school programme. Their first intake of students occurred in 2007. With the exception of RCSI, which is a private, not-for-profit medical school, all the other institutions are public universities.

Each medical school is associated with one or two academic teaching hospitals. The main academic hospitals include: St James's (TCD); Adelaide & Meath Incorporating the National Children's Hospital (TCD); St. Vincent's University Hospital (UCD); Mater Misericordiae University Hospital (UCD); Beaumont Hospital (RCSI); Cork University Hospital (UCC); University College Hospital, Galway (NUIG); Midwestern Regional Hospital, Limerick (UL). Our Lady's Hospital for Sick Children, Crumlin, is linked to the medical schools in TCD, UCD and RCSI. The National Maternity Hospital, Dublin is affiliated with UCD and RCSI; the Rotunda Hospital, Dublin is affiliated with TCD; and the Coombe Women and Infants University Hospital, Dublin has medical students from RCSI, TCD and UCD who attend the hospital as part of their undergraduate programme. There are 45 other acute hospitals in Ireland.

2.2 Trans-Institutional Partnerships

2.2.1 Molecular Medicine Ireland

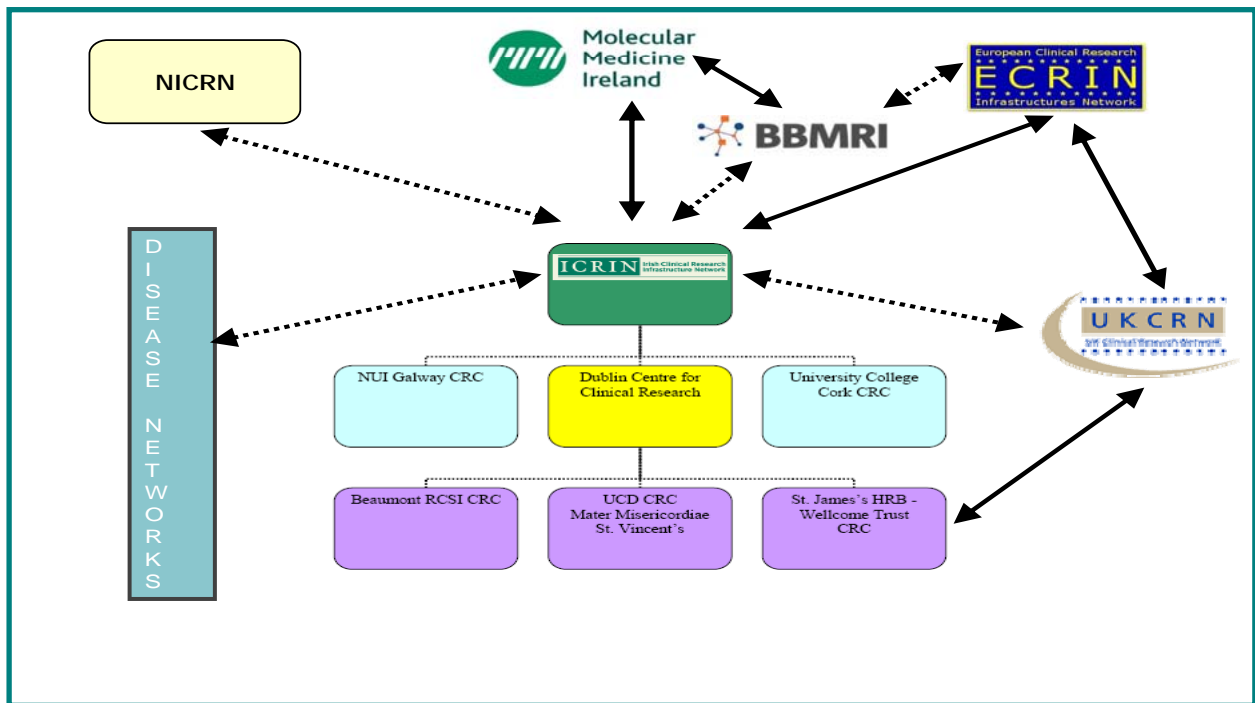
Molecular Medicine Ireland (MMI) is a not-for-profit company formed to align the research and postgraduate activities of five of Ireland's premier biomedical research institutions and affiliated teaching hospitals. MMI was formed in April 2008 by NUIG, UCC, UCD, TCD and RCSI. UCD, TCD and RCSI had previously formed the Dublin Molecular Medicine Centre (DMMC) which was subsumed by the formation of MMI. The DMMC was established in 2002 through the Higher Education Authority's (HEA) PRTL as part of the National Development Plan (NDP). It coordinated the Programme for Human Genomics (PHG) – a €45m initiative. The DMMC represented a highly

focused research partnership in life sciences between UCD, TCD and RCSI, with the associated network of affiliated hospitals providing the setting for accelerated translational bioscience. MMI is integrating and synergising expertise in research and postgraduate training to position Ireland as a state-of-the-art, internationally competitive and sustainable centre of excellence in molecular medicine. ICRIN is contained under the umbrella of MMI.

2.2.2 Clinical Research Centres

Clinical Research Centres (CRCs), also referred to as Clinical Research Facilities (CRFs), are academic led facilities dedicated to academic and industry clinical research. Currently, there are three functioning CRCs based in Dublin at academic teaching hospitals: UCD CRC (Mater Misericordiae University Hospital and St Vincent’s University Hospital) and RCSI CRC (Beaumont Hospital). These CRCs are networked via the Wellcome Trust – HRB Dublin Centre for Clinical Research (DCCR) and supported by ICRIN under MMI. The structure of the network is illustrated in Table 1.

Table 1 MMI/ICRIN/DCCR Relationships



Key: BBMRI - Biobanking and Biomolecular Resources Research Infrastructure

Each CRC is equipped with clinical laboratories as well as outpatient consultation and procedure rooms. A wide variety of services are offered:

- Study design
- Competent Authority and Ethics Committee approval
- Design of databases for studies
- Data collection and analysis
- Provision of resources for patient phenotyping/sample collection
- Sample storage and labelling, processing and analysis
- Laboratory research programme development and support
- Provision of laboratory bench space and equipment access
- Patient beds.

The CRCs are managed by their parent academic institutions, although they are physically located in the campus of the teaching hospitals. In most cases, the CRCs operate rent-free on the hospital premises.

In 2006, the Beaumont RCSI CRC had the following clinical research activity:

Number of industry sponsored trials	34
Number of academic trials (medical device or drug related)	3
Number of academic trials falling outside EU Clinical Trial Directive and Medical Device legislation (e.g. epidemiology, non-interventional)	10

In 2006, the UCD CRC had the following clinical research activity:

Number of industry sponsored trials	12
Number of academic trials (medical device or drug related)	8
Number of academic trials falling outside EU Clinical Trial Directive and Medical Device legislation (e.g. epidemiology, non-interventional)	20

In 2006, the DMMC coordinated a successful application to the Wellcome Trust and the HRB to establish the DCCR (previously referred to in Chapter 1 and Section 2.2.2 of this chapter). The DCCR is responsible for the construction of a new CRC at St James’s Hospital which is scheduled

for completion in 2010. When completed, it will network with Beaumont RCSI/CRC and UCD/CRC as part of the DCCR. The network will drive a common approach to data management and data analyses systems, Standard Operating Procedures (SOPs), research nurse recruitment and staff training in the participating CRCs. A total of €3 million has been committed to the DCCR by the Wellcome Trust and the HRB between 2008 and 2013.

The HRB and the HSE will jointly fund the establishment of CRCs in Cork and Galway with expected completion dates by 2010. Approximately €31 million will be invested over the next five years (2008-2013) in buildings and staffing of the new centres. CRC research will begin prior to completion of the buildings, with activities linked under the ICRIN structure.

2.2.3 Hospital Based Research

Clinical research in each of the hospitals is not limited to activity within the CRCs. The majority of hospital based research is conducted by Principal Investigators with recruitment often based on clinic patients attending the hospital for a specific condition. Research is conducted with the assistance of staff including registrars, specialist registrars, data managers and research nurses. This research is frequently funded or supported by industry or disease dedicated patient organisations. Main areas studied are cardiology, endocrinology and oncology.

2.2.4 Primary Care Based Research

The primary care arena conducts a significant amount of clinical studies, particularly in the area of non-interventional trials such as epidemiology and observational studies. Currently this research is almost exclusively commercial, however the Irish College of General Practitioners (ICGP) is beginning to embark on academic trials.

2.2.5 All Ireland Cooperative Oncology Research Group

The All Ireland Co-operative Oncology Research Group (ICORG) is the main cancer clinical research organisation and is the only publicly funded, disease specific, clinical research network in Ireland. It is a collaboration of three parties – the Irish Clinical Oncology Research Group in Dublin, the Clinical Research Support Centre (CRSC) in Belfast, and oncology professionals throughout Northern Ireland and the Republic of Ireland. The aims of the Group are to promote, design, conduct and facilitate clinical cancer research on the island of Ireland. ICORG plays a large role in the

training of research nurses and data managers in the cancer Clinical Trial Units (CTUs) located in 11 hospitals.

There are eleven cancer CTUs under the umbrella of ICORG. These are located in the Mater Misericordiae University Hospital, St. James's Hospital, Beaumont Hospital, St Vincent's University Hospital, The Adelaide and Meath, Incorporating the National Children's Hospital and St Luke's Hospital; all of which are located in Dublin. The remaining CTUs are located in Sligo Regional Hospital, University College Hospital, Galway, Cork University Hospital, Limerick Regional Hospital and Waterford Regional Hospital. All of these CTUs are funded by a HRB grant, coordinated by ICORG.

ICORG is a not-for-profit entity funded mainly by the HRB, the Health and Social Care Research and Development Office (HSCR&D Office) of Northern Ireland and the Irish Cancer Society. The mission of the group is to enable Irish patients to gain early access to new cancer treatments. ICORG has international links with leading cancer research groups such as EORTC, the National Surgical Adjuvant Breast and Bowel Project (NSABP) and Breast Cancer International Research Group (BCIRG). In addition, they link with industry to facilitate clinical research in Ireland allowing Irish patients access to the most promising new cancer treatments. Since their inception, ICORG has opened 71 research protocols and more than 2,600 Irish cancer patients have had access to research treatments. The work of ICORG facilitates academic and industry research and includes:

- Sponsorship role for investigator initiated studies
- Clinical indemnity liaison with the States Claims Agency for investigator initiated studies
- Protocol design, feasibility and review
- Competent authority and Ethics Committee process management including authorisations, continuing reviews and pharmacovigilance
- Standard Operational Procedure (SOP) development
- Research staff training
- Monitoring and data collection.

2.2.6 European Institute for Clinical Trials in Rare Diseases

The European Institute for Clinical Trials in Rare Diseases is based in the clinical trials unit in University College Hospital, Cork. Through clinical research, its role is to make Orphan Medicines available to patients suffering from rare diseases. The Institute conducts clinical trials to ensure medicines are safe and effective, provides clinical development services on a not-for-profit basis, and

trains inexperienced investigators in GCP and Good Laboratory Practice adherence. It helps sponsors to define study endpoints, identify clinical experts in different countries, provide ethical guidance on study protocols, promote recruitment of studies, and maintain study participant interest and involvement in clinical trials.

2.2.7 Northern Ireland Clinical Research Network

The Northern Ireland Clinical Research Network (NICRN) has been established to support the clinical research community in Northern Ireland. Its aims are:

- To promote research within Northern Ireland
- To develop close partnerships and productive working relationships with key individuals and groups across the Network and the wider research community
- To ensure that targets, including accrual of patients into trials, are achieved and maintained.

Through information sharing and various all-island liaisons, there is a clear opportunity for ICRIN and NICRN to work synergistically to facilitate all-island clinical research.

3 FUNDING AND SPONSORSHIP

Clinical research in Ireland is not usually supported by a dedicated, core hospital budget. The hospital generally provides space, but equipment, maintenance and staff salaries for research staff other than the salary of the principal investigator are mostly covered by the academic institution, research grants, income from clinical trials and sponsorship from industry.

3.1 Funding Bodies

3.1.1 Health Research Board

The Health Research Board (HRB) is the national funding body responsible for the development of health research and a number of health information systems. The HRB works closely with other health agencies, other research funding bodies, the economic development agencies and partners in Northern Ireland, Europe and the United States to develop Ireland's potential in health research. The HRB's sponsoring department is the Department of Health and Children (DoHC) from which it receives the bulk of its funding. The HRB funds a broad spectrum of healthcare research by competitive peer review. The majority of funding calls are open but a number are targeted at building capacity in health research to address particular health problems. In conjunction with the Wellcome Trust and the HSE, the HRB has invested significantly in the development of clinical research infrastructure. In association with the HSCR&D Office of Northern Ireland, the HRB has awarded a grant to MMI to undertake the preparatory phase of establishing GeneLibrary Ireland, a control biobank of 10,000 DNA and blood samples from volunteers on the island of Ireland along with key phenotypic information which will serve as a control population to study the genetic determinants of common diseases which significantly impact patients in Ireland and Northern Ireland. These diseases include cardiovascular disease, cancer, diabetes, arthritis, respiratory disease and cognitive disorders, along with key areas which are over represented in the population such as Coeliac disease, Multiple Sclerosis, Cystic Fibrosis and Haemachromatosis.

The HRB does not directly fund clinical trials but serves to facilitate trial conduct by providing funding for clinical research and clinical research facilities to academic institutions such as the DCCR, to cooperative groups such as ICORG, or occasionally directly to hospitals. Depending on the grant scheme, HRB funding supports both recurrent and capital expenditures. The operating budget of the HRB in 2007 was approximately €39 million.

3.1.2 Science Foundation Ireland

Science Foundation Ireland (SFI) is the largest national research funding agency. It is a key organisation in the implementation of the *National Development Plan (NDP) 2007-2013*⁵ and the *Strategy for Science, Technology and Innovation (SSTI) 2006-2013*¹. A sum of €8.2 billion has been allocated for scientific research under the NDP and SSTI of which SFI has responsibility to invest €1.4 billion in academic researchers and research teams in the fields underpinning biotechnology, information and communications technology.

SFI's primary focus is on basic and applied research, other than clinical research, although a number of SFI grants supports translational and biomedical projects through a variety of initiatives, including awards to individuals, academic-industry partnered centres, and research visitor awards. Significantly, SFI has awarded funding for Centres in Science, Engineering and Technology (CSET) to the Alimentary Pharmabiotic Centre at UCC, specialising in gastrointestinal health and the Regenerative Medicine Institute (REMEDI) at NUIG, specialising in gene therapy and stem cell research. CSET grants are five-year grants worth up to €5 million per annum to support partnerships across academia and industry. Another funded CSET is the Biomedical Diagnostics Institute (BDI) in Dublin City University. BDI's research programmes focus on the development of next generation biomedical diagnostic devices.

SFI also funds Strategic Research Clusters (SRCs). The aim of SRCs is to link scientists and engineers in partnerships across academia and industry to address crucial research questions, foster the development of new and existing Irish based technology companies, and grow partnerships that could make an important contribution to Ireland and its economy. Awards are for up to five years and worth up to €1.5 million per annum. SFI grants are administered through academic institutions only, and support recurrent costs. In exceptional cases, funds have formerly been provided for capital costs.

3.1.3 Wellcome Trust

Principal Investigators from Ireland are eligible to apply for many of the programmes from the Wellcome Trust, including awards to fund CRCs, clinical research PhD training schemes and project grants. As previously referred to in this report, the Wellcome Trust together with the HRB are providing funding of approximately €23 million to establish the DCCR⁶. The DCCR will support clinical research staff, data management infrastructure and a new CRC which will be situated on the St James's Hospital campus, as part of a network to support clinical research across the city. The

Wellcome Trust is a privately endowed charity, independent of government or industry. In 2006-2007, its total charitable expenditure was £519.8 million.

3.1.4 Higher Education Authority

The Higher Education Authority's (HEA) PRTLTI provides integrated financial support for institutional strategies, programmes and infrastructure to build research capacity. To date, €605 million has been allocated to third level institutions under this competitive programme⁷. PRTLTI has funded three dedicated CRCs in Dublin through the PHG grant, which is shared by RCSI, TCD and UCD. The PHG funded the former DMMC Directorate, prior to its transformation to MMI. Launched in 1998, PRTLTI funding comprises both public and private matching funds; the latter includes generous donations from Atlantic Philanthropies. This funding supports both recurrent and capital costs.

3.1.5 Health Information and Quality Authority

The Health Information and Quality Authority (HIQA) was established in 2007 by the DoHC to drive continuous improvement in Ireland's health and social care services and to develop a high quality health information infrastructure. HIQA undertakes and commissions research to support its work in quality assurance, accreditation, health technology assessment and health information.

3.1.6 Enterprise Ireland

Enterprise Ireland is the government agency responsible for the development and promotion of the Ireland's indigenous business sector. The overall goal of the agency is to accelerate the development of world-class Irish companies to achieve strong positions in global markets, resulting in increased national and regional prosperity. One of their objectives is to increase the level and quality of R&D within organizations by facilitating collaborative links between third level colleges and enterprise both nationally and internationally. They also achieve this by providing funding for the commercialization of research projects and advising on technology acquisition.

In May 2007, Enterprise Ireland commissioned the CIRCA Group to recommend infrastructural and other initiatives that would support and stimulate activity within the Irish healthcare industry. Areas identified for development included clinical trial facilities, biobanks, stem cell production facilities, biomarker identification and validation. On the basis of the CIRCA report, Enterprise Ireland has agreed to support the creation of an information and mentoring service for small and start-up

companies. This service, provided by a Clinical Trial Liaison Officer and funded for two years under the umbrella of MMI and ICRIN, will provide on-going information on the clinical trial process through seminars, website, literature and individual guidance.

3.1.7 Industrial Development Authority

The Industrial Development Agency (IDA Ireland) is the Irish Government agency with responsibility for securing new investment from overseas in manufacturing and internationally traded services sectors. It also encourages existing investors to expand and develop their businesses in Ireland. IDA Ireland has a good track record in terms of attracting foreign investment of significant value, requiring high skill levels and a sophisticated business environment in which to operate. Key areas of focus are Pharmaceuticals, Biopharmaceuticals and the Medical Technologies sectors. Investment in R&D has been substantial. In 2006, 54 R&D investment projects were supported by IDA Ireland involving a total investment of almost €470m. The corresponding values were €140m and €260m in 2004 and 2005 respectively⁸.

3.1.8 Patient Organisations

There are a number of patient organisations that support clinical research projects, including Cancer Research Ireland, Fighting Blindness, Irish Heart Foundation, Irish Platform for Patients' Organisations, Science and Industry (IPPOSI) and the Cystic Fibrosis Society of Ireland. The Children's Medical and Research Foundation at Our Lady's Hospital for Sick Children in Dublin raises money to support their Children's Research Centre. The Medical Research Charities Group (MRCG) is an umbrella organisation comprising a number of patient organisations with research agendas. In 2005, the HRB in partnership with the MRCG, launched a fellowship scheme called the Research Fellowships for Rare Diseases designed to build capacity in research into rare diseases in Ireland by enabling researchers or those working in related common disorders to develop research careers at an advanced level in rare diseases. In 2006, the Minister for Health and Children made €1 million available for research to MRCG associated organisations, matching €1 million raised by these charities. The scheme was managed by the HRB and over 30 research studies were funded.

Funding from patient organisations to support research projects, while not as large as from the major funding agencies, is in the region of several million euro per annum. Awards are usually drawn down by the Principal Investigator directly from the patient organisation.

3.2 Industry

Industrial support for clinical research is usually in the form of company-sponsored clinical trials. In addition, some companies provide financial donations to assist with human capital in support of clinical research such as funding research nurses and registrars. Support can be provided for the enablement of Investigator Initiated Studies including the donation of investigational product or financial assistance to employ contract research organisations to conduct studies in accordance with International Conference on Harmonisation-Good Clinical Practice (ICH-GCP).

Recently, several strategic partnerships in translational research have been forged between academia, pharmaceutical and medical device companies with substantial investment provided by industry. Examples include:

- Cardiovascular disease – UCD and Servier
- Neuroscience – UCD and Wyeth
- Gastrointestinal inflammation – UCC/Alimentary Pharmabiotic Centre and GlaxoSmithKline
- Gene therapy, stem cell therapy and tissue engineering – NUIG/REMEDI and Medtronic, Smith & Nephew.

4 REGULATION, LEGISLATION, GUIDANCE AND INSURANCE

In Ireland, legislation governs clinical research involving medicinal products and research involving medical devices. The European Commission has clarified that stem cell use in clinical trials is also governed by the legislation covering clinical trials on medicinal products. Various Statutory Instruments (SIs) may be relevant in certain biomedical research such as the use of tissues, cells and blood products. A number of EU and Competent Authority (CA) guidances are complied with, as well as standards such as International Organisation for Standardisation (ISO) and ICH-GCP.

4.1 Directives and Statutory Instruments

In Ireland, clinical trials on medicinal products are governed by:

- European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations, 2004, SI No 190 of 2004
- European Communities (Clinical Trials on Medicinal Products for Human Use) (Amendment) Regulations, 2004, SI No 878 of 2004
- European Communities (Clinical Trials on Medicinal Products for Human Use) (Amendment 2), SI No 374 of 2006.

Together these regulations are cited as European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations, 2004 to 2006. The Regulations transposed into Irish law the provisions of Council Directive 2001/20/EC and Council Directive 2005/28/EC.

The regulations supersede the Control of Clinical Trials Acts 1987-1990 for clinical trials using medicinal products. However because of the Act's definition of the conduct of a clinical trial in Article 6 (as amended), the Act still applies to clinical trials involving non-medicinal substances in some instances¹⁵.

Medical technology trials and clinical investigations of medical devices are governed under Directive 90/385/EEC concerning Active Implantable Medical Devices, Directive 93/42/EEC concerning General Medical Devices, and Directive 98/79/EC concerning *In Vitro* Diagnostic Medical Devices (IVD). The Medical Devices Directives (MDDs) have been transposed into national law, as:

- SI No 253 of 1994, European Communities (Active Implantable Medical Devices) Regulations, 1994
- SI No 252 of 1994, European Communities (Medical Devices) Regulations, 1994

- SI No 304 of 2001, European Communities (IVD) Regulations, 2001.

Medical technology trials are also covered by the International Standard EN ISO 14155 and reference should be made to EN540 Clinical Investigation of Medical Devices for Human Subjects.

A revision to the MDD 93/42/EC has been undertaken by the EU Commission and Member States that must be transposed into Irish law within 15 months of publication and applied within 30 months of publication. Effective from March 2010, Directive 2007/47/EC of the European Parliament and of the Council of 5 September 2007 is amending the following Directives:

- Council Directive 90/385/EEC on the approximation of the laws of the Member States relating to active implantable medical devices
- Council Directive 93/42/EEC concerning medical devices
- Directive 98/8/EC concerning the placing of biocidal products on the market.

There are also regulations pertaining to the use of tissue and cells which could apply to other types of research including experimental transplantation. These regulations are not explicitly applicable to clinical trials. Council Directive 2004/23/EC lays down standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells. An associated Commission Directive, 2006/17/EC, sets out technical requirements for the activities of donation, procurement and testing of human tissues and cells and came into force on 1 November 2006. Both of these Directives were transposed into Irish law via the European Communities (Quality and Safety of Human Tissues and Cells) Regulations 2006, (SI No158 of 2006). The Irish Medicines Board (IMB) is designated as the competent authority for the implementation of this legislation.

Another associated Commission Directive, 2006/86/EC, sets out the traceability requirements, notification of serious adverse reactions (SARs) and events and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells. This was published in October 2006 and transposed into Irish law as European Communities (Human Tissues and Cells Traceability Requirements, Notification of Serious Adverse Reactions and Events and Certain Technical Requirements) Regulations 2007, SI No 598 of 2007.

Legislation also applies to the use of human blood and blood components. The European Communities (Human Blood and Blood Components Traceability Requirements and Notification of

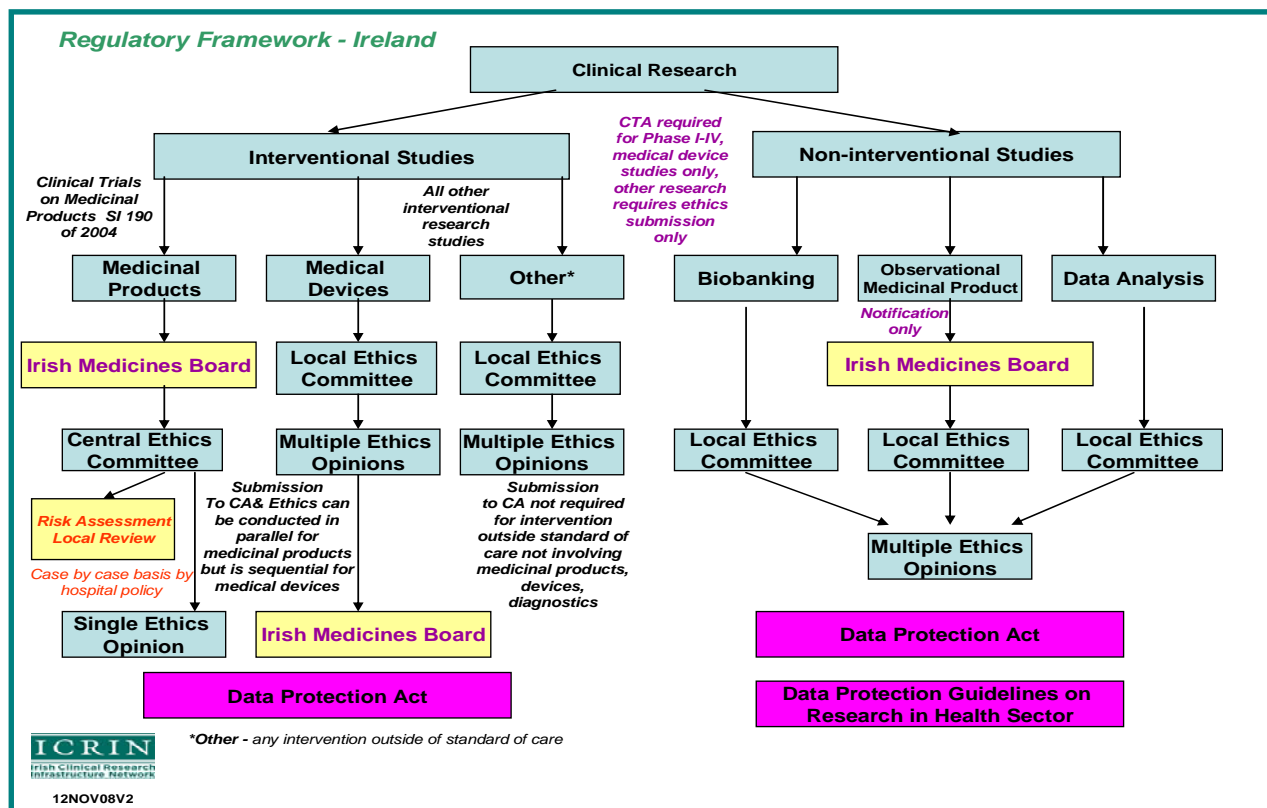
Serious Adverse Reactions and Events), SI No 360 of 2005 and SI No 547 of 2006, transposed into national law, the provisions of Directives 2002/98/EC and 2005/61/EC as regards traceability requirements and notification of SARs and events to human blood and blood components. Any such reactions or events relating to blood and blood components must be reported to the IMB.

The Data Protection Act, 1988 and the Data Protection (Amendment) Act, 2003 transposed into Irish law, Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the Protection of Individuals with regard to the Processing of Personal Data and on the Free Movement of Such Data. Taken collectively with the Freedom of Information Act, 1997-2003 and the Health (Provision of Information) Act, 1997, there are implications for the collection, processing, movement and retention of personal data pertaining to participants in medical research.

Anonymisation of patient records and/or freely given and informed patient consent to access records for the purposes of research are the foundation stones of how the Data Protection Office wishes to see medical research undertaken from a privacy perspective⁹. Information must be provided to patients by means of very clear and understandable information leaflets and informed consent forms explaining the uses and potential uses of their personal data. Data that have been anonymised can be used for research and for biobanking. Identifiable data may not be used without consent for research or building patient registries or biobanks. The Data Protection Commissioner has called for legislation to permit the establishment of patient/disease registries. Guidelines have been issued by the Data Protection Commissioner on research in the health sector which has clarified use of anonymised and pseudo-anonymised data¹⁰.

The current regulatory framework in Ireland is outlined in Table 2 on the following page.

Table 2 Current Regulatory Framework for Clinical Research - Ireland



4.2 Clinical Trials on Medicinal Products

The IMB has prepared a *Guide to Clinical Trial Applications*¹¹. In this guide, the definition of a clinical trial in the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations, 2004, SI No 190 of 2004 and Amendment 2, Regulations, 2006, SI No 374 of 2006, is as follows:

“.....studies on clinical, pharmacological, pharmacodynamic or pharmacokinetic effects or studies to identify adverse reactions to investigational medicinal products (IMPs), i.e., all Phase I to Phase IV studies.

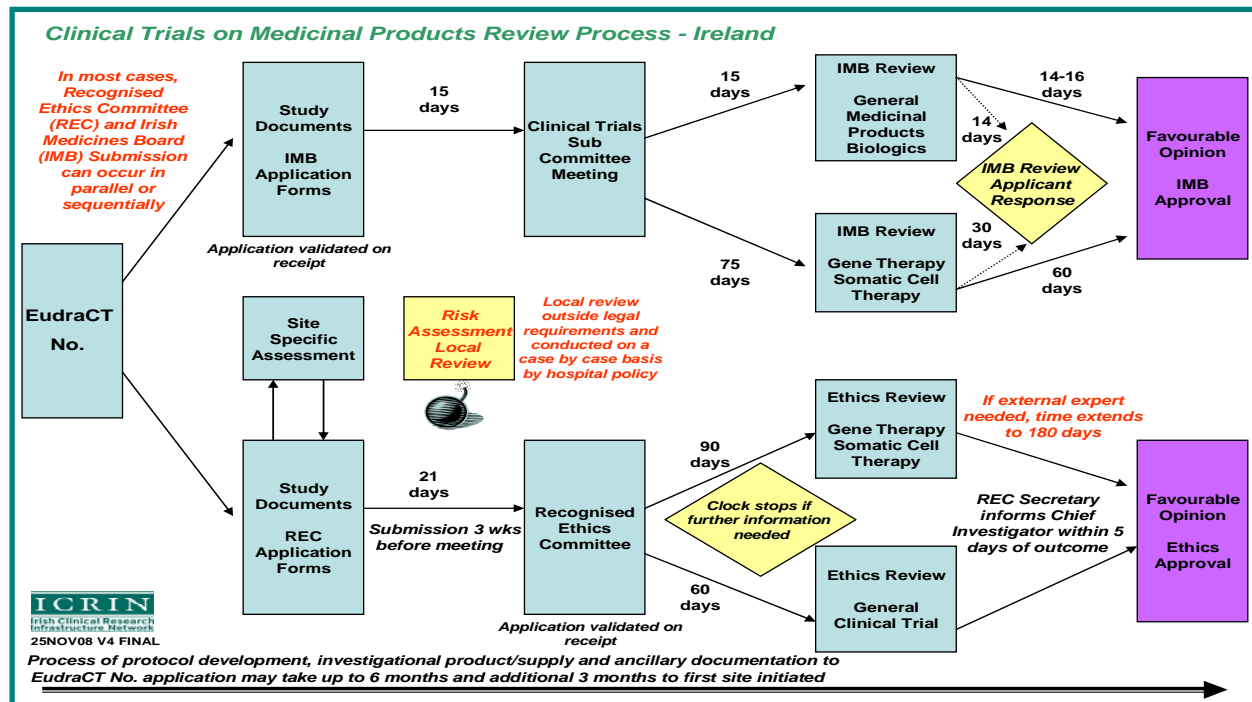
Investigational medicinal products include placebo products and both authorised and unauthorised medicines with any type of active substance, including herbal and homeopathic products. It is also possible that a trial using a food supplement may be considered as a clinical trial within the definition outlined in SI 190 of 2004. Authorised products may be used in accordance with the terms of the Product Authorisation (PA) or used in a different way,

e.g., at a higher dose, for a new indication or when packaged in a different container” (Pages 3-4).

4.2.1 Clinical Trial Applications

When preparing to undertake clinical studies from Phase I to Phase IV, Clinical Trial Applications (CTAs) must be submitted to the IMB by the sponsor of the trial. In the event that the sponsor is not established in the EU, his/her legal representative, or an applicant authorised by the sponsor to make the application must submit. Before an application can be submitted to the Board, a EudraCT number must be obtained from the website of the European Agency for the Evaluation of Medicinal Products (EMA). EudraCT is a database of all clinical trials commencing in the Community from 1 May 2004 onwards. It has been established in accordance with Directive 2001/20/EC. CTAs should be supplied in the format described in the IMB’s form for Additional National Requirements for Clinical Trial Authorisation. The Clinical Trials on Medicinal Products Review Process is detailed in Table 3.

Table 3 Clinical Trials on Medicinal Products Review Process – Ireland

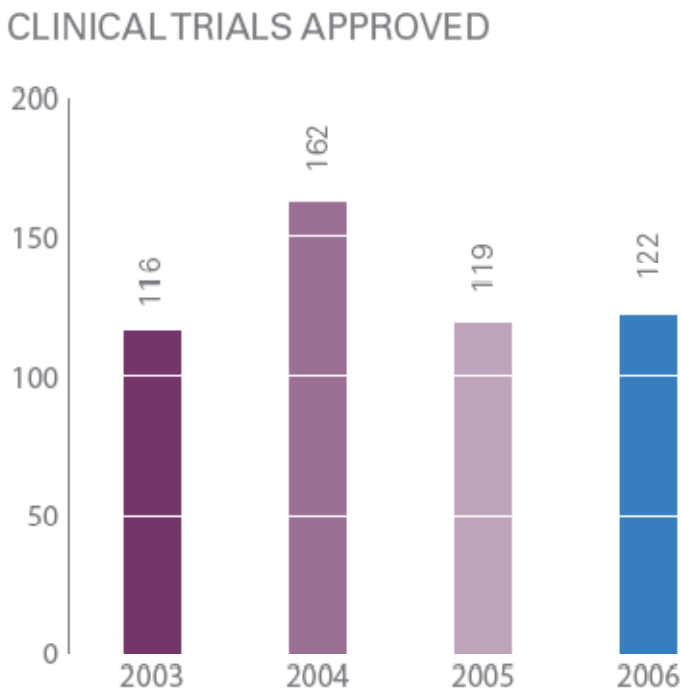


A Clinical Trials Sub-Committee meets to review all applications. This committee is a sub-committee of the Advisory Committee for Human Medicines. The clinical trials sub-committee meets once a month and applications are submitted two weeks before the meeting. After the meeting and after any queries are resolved, applications are approved by the Management Committee of the IMB which meets weekly.

The assessment of a CTA and the assessment of any subsequent application for Product Authorisation (PA) for the same medicinal product are two separate assessments. The approval of a clinical trial does not determine the acceptability or otherwise of the PA application.

During 2006, 122 applications to conduct clinical trials were approved by the IMB. This represents a similar figure to that of 2005 as depicted in Table 4 from the IMB 2006 Annual Report¹².

Table 4 Clinical Trial Applications IMB Approved – IMB Annual Report 2006



In 2006, there was an output of 409 clinical trial amendment applications, which represents a minor increase from the 2005 figure of 368. At the time of writing this report, the data for 2007 were not available.

4.2.2 Ongoing Review, Substantial Amendments and Urgent Safety Measures

Substantial amendments to the application or any accompanying documentation must be notified to the IMB using the EU Notification of Amendment Form. Examples of substantial amendments are given in the EU guidance document on application to competent authorities¹³.

Non-substantial amendments do not have to be notified to the IMB, however, they must be recorded and available on request or on inspection at the trial site and/or the sponsor's premises, as appropriate.

One amendment notification may cover more than one protocol or may cover a number of amendments. Where the amendment relates to a number of protocols, the protocol numbers and Clinical Trial (CT) numbers must be clearly indicated in the amendment form. Application forms which cover a number of different changes must clearly indicate each individual change.

Amendments should be sent in parallel to ethics committees, which also are subject to the same timelines as the IMB. Additional trial sites or a change in a trial site may be notified using the amendment form or by letter.

Once validated, the application is assessed and, within 35 days of receipt of a valid application, written notice is sent to the applicant setting out either acceptance of the request for authorisation, with conditions if necessary, or grounds for non-acceptance of the request. If grounds for non-acceptance are sent, the applicant must respond with an amended request (ie, a response to grounds for non-acceptance) 14 days before the amendment is due to be made. Following assessment of the response and within 14 days of receipt of the response, written notice is sent to the applicant setting out either acceptance of the request for authorisation, with conditions if necessary, or grounds for non-acceptance of the request.

The IMB may require amendments to be made to the conduct of the trial to ensure compliance with GCP or to ensure the safety or scientific validity of the trial. Where an amendment is required, the Board serves notice on the sponsor that a specified amendment is required in 14 days, and will give the reason for the proposal. The sponsor may make written representations to the IMB within the 14 days, which will be taken into account in the final decision by the Board.

If the sponsor and investigators consider that urgent safety measures need to be taken to protect the health or safety of trial subjects, the sponsor must notify the Board no later than three days after the date the measures were taken. The notification should specify the measures taken and the reasons.

If the trial is temporarily stopped, the sponsor should notify the IMB within 15 days using the Declaration of End of Trial Form. If the trial completes as planned, the ethics committee and IMB must be notified within 90 days and a full clinical trial report sent to both the ethics committee and the IMB within one year of completion.

4.2.3 End of Trial

The end of a trial, whether it ends earlier than planned or according to the protocol, must be notified to the IMB using the *EU Declaration of End of Trial Form*. The form must be submitted when the trial has ended in Ireland, when the trial has ended in all countries in which the same trial was taking place, and if the trial does not take place at all. The form should be received within 90 days of the end of the clinical trial or within 15 days if it has ended earlier than planned.

Within one year of the date of completion or cancellation of the trial, a report should be submitted to the IMB. The report should include the following:

- Numbers of subjects recruited overall and per Irish clinical trial site
- Numbers completed overall and per Irish clinical trial site
- Numbers withdrawn and the reason for withdrawal per Irish clinical trial site
- Summary of the safety data since the last annual safety report, including the following:
 - an updated report on the subject's safety in the trial, with a line listing of all Serious Adverse Drug Reactions (SARs) including all Suspected Unexpected Serious Adverse Reactions (SUSARs)
 - an aggregate summary tabulation of SARs that occurred in the trial
 - reports from the drug safety monitoring committees, if available
 - notification of any changes in expectedness of suspected Adverse Drug Reactions (ADRs)
 - updated assessment of non-clinical and clinical safety issues since last submission.

4.3 Medical Device Clinical Investigations

Medical Devices are governed by:

- SI No 253 of 1994, European Communities (Active Implantable Medical Devices) Regulations, 1994
- SI No 252 of 1994, European Communities (Medical Devices) Regulations, 1994
- SI No 304 of 2001, European Communities (*In-vitro* Diagnostic Medical Devices) Regulations, 2001.

The IMB have issued Guidance Notes for Manufacturers on Clinical Investigations carried out in Ireland¹⁴.

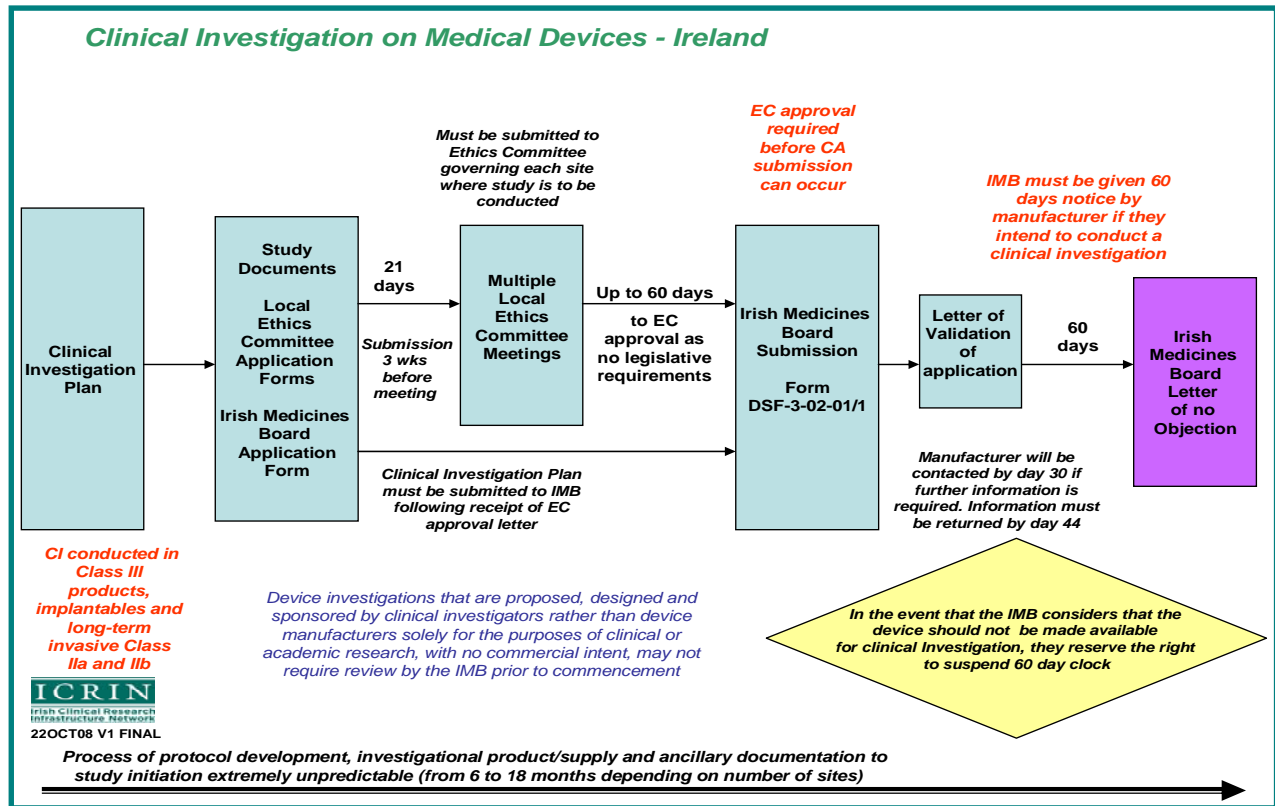
4.3.1 Clinical Investigation Evaluation Requirements

European Conformity (CE) marking is a mandatory European marking for all medical devices to indicate conformity with the essential health and safety requirements set out in European Directives. In order to obtain a CE mark for a medical device, the manufacturer must demonstrate that it legally conforms to the requirements of the pertinent EU Directive. In order to demonstrate this compliance, clinical data may be required. Clinical Investigation will be required in the following circumstances:

- Where a new device is to be introduced into clinical practice where components, features and/or methods of action are previously unknown
- Where an existing device is modified and the modification might significantly affect the clinical performance and/or safety of the device
- If a device contains materials previously untested in humans coming into contact with the human body
- Where existing materials are applied to a new location in the human body, compatibility and biological safety will be considered
- Where a device incorporates existing materials but the device will be used for a significantly longer period of time
- Where a device is proposed for a new purpose or function.

The number of devices to be used in a clinical investigation must be sufficient to demonstrate performance satisfactorily and to reveal significant risks to patients' health and safety. At the same time, the number should not be so great as to place at risk more patients than are necessary. The Clinical Investigation on Medical Devices Review Process is detailed in Table 5.

Table 5 Clinical Investigation on Medical Devices Review Process – Ireland



As detailed in Section 4.1, a revision to the Medical Devices Directive 93/42/EC has been undertaken by the EU Commission and Member States. The Directive will come into effect in March 2010. Significant amendments have been made to Annex 10 of the Directive in the area of Clinical Evaluation and the requirements detailed above will be amended in 2010. The amended legislation can be accessed at:

<http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2007:247:0021:0055:EN:PDF>

During 2006, the IMB received six clinical investigation applications of general medical devices and one clinical investigation of an active implantable device¹².

4.3.2 Clinical Studies in Medical Devices

In certain cases, a clinical study in medical devices may be initiated which does not require IMB notification. These are classed as studies exempt from clinical evaluation or investigation. The instances where this applies are as follows¹⁴:

- If a healthcare professional carries out clinical research within the professional and ethical use, the clinical study does not need to be reported provided the study is not for commercial use and serves for research purposes only
- If a device is manufactured in-house by a clinician for hospital use with no intention to commercialise the device, then it is classified as a study and is exempt
- If additional studies are carried out on a CE marked product for marketing or regulatory reasons they are classified as studies and are exempt.

4.3.3 Medical Device Applications and Review Process

The IMB must be given 60 days notice by the manufacturer of a device that they intend to make available for clinical investigation. The clinical investigation may proceed if within the 60-day period, the IMB does not issue a written refusal. The application for assessment of the proposed clinical investigation must be made on form, *DSF-3-02-01/1 Clinical Investigation Application Form*. The form must be accompanied by the appropriate fee and supporting documentation including an investigation plan detailing the purpose, scientific, technical or medical grounds, the informed consent form, product description and a copy of the local ethics committee opinion.

The IMB will validate the application on receipt and notify the manufacturer of its acceptability. The letter of validation will detail the date of the 60-day notice period commencement. A detailed expert review of the application will be completed by day 30 and the manufacturer will be contacted if there is further information required. In this event, the manufacturer has until day 44 to return the information. The IMB review of the data will be performed by day 49 and a final report prepared. Following an expert meeting convened by day 55, the IMB will notify the applicant by day 60, provided all grounds relating to health and safety are addressed. However, in the event that the IMB considers that the device should not be made available for clinical investigation based on queries relating to the health and safety of patients, users or others of the device, they reserve the right to suspend the 60-day clock until a satisfactory response has been received by the manufacturer. If a satisfactory response is not provided within the timeframe, the application may be rejected.

4.3.4 Changes or Modifications in Protocol

A letter of agreement must be obtained from the IMB for all changes in protocol whether relating to the device, the clinical investigation plan, investigators or their institutions. No change can be implemented until this agreement has been received in writing. In the event that the modification is

considered by the IMB to increase the risk to either the patient or the user, they reserve the right to request a new clinical investigation modification.

4.3.5 End of Clinical Investigation

The manufacturer or their Authorised Representative must prepare a written report on completion of the clinical investigation. This final report must be available upon request should the IMB require a copy.

4.3.6 Notified Body

As noted previously, CE marking on a product is a manufacturer's declaration that the product complies with the essential requirements of the relevant European health, safety and environmental protection legislation.

The MDDs set out essential requirements to ensure that a medical device will not compromise the health and safety of the patient, user or any other person, and that any risks associated with the device are compatible with patient health and protection. Medical Devices that conform to these requirements are entitled to apply the CE Marking, which then allows the product to be freely placed on the market within the EU in compliance with the EU MDDs.

The IMB, as the competent authority in Ireland, monitors and has approved the National Standards Authority of Ireland (NSAI) as a Notified Body to carry out the conformity assessment tasks for the following medical directives:

- MDD (93/42/EEC) – Annex II, Annex V and Annex VI
- Active Implantable MDD (90/385/EEC) – Annex II and V
- IVD MDD (98/79/EC) – Annex II – List A virology products and List B products – Self test products.

NSAI works closely with the relevant Competent Authorities in Ireland and in other countries, and has specific expertise in providing CE Mark certification for Drug-Device Combination products. For high risk medical devices, the Notified Body needs to review the clinical investigation data along with other relevant provisions of the Directive prior to the manufacturer affixing a CE mark. Where NSAI, as a Notified Body is involved, the Notified Body number (0050) appears with the CE Marking.

While NSAI is the Irish Notified Body, there are a number of other Notified Bodies in Europe who can be used by Irish manufacturers to carry out the relevant conformity assessment procedure for the Medical Directives. The list of Notified Bodies designated to carry out conformity assessment can be located on the European Commission website at the following address: <http://ec.europa.eu/enterprise/newapproach/nando/index.cfm?fuseaction=notifiedbody.main>.

4.4 Clinical Investigation of Drug-Device Combinations

In the clinical investigation of drug-device combinations it is necessary to determine the appropriate legislation governing the study. When a medical device incorporates a medicinal substance (as defined in Directive 2001/83/EC) which is liable to act upon the body with action ancillary to the device, the safety, quality and usefulness of the substance must be verified by analogy with the relevant medicinal products legislation as required by Annex I section 7.4 of the Medical Devices Directive (93/42/EEC). To obtain CE marking for a product of this type the manufacturer must provide evidence for assessment by a notified body that the device conforms with the 'essential requirements' of Directive 93/42/EEC. The notified body must undertake a conformity assessment appropriate to the type of device and as defined, for example in Annex II section 4.3 of the Medical Devices Directive (93/42/EEC), must consult a competent authority for medicinal products in a member state before making a decision on its conformity assessment.

4.5 Other Clinical Studies

Non-interventional studies and disease registries fall outside the EU Clinical Trials Directive and SI No 190 of 2004. Interventional registries and non-interventional studies involving review of a medicinal product or substance should be notified to the IMB. The establishment or the existence of a non-interventional disease registry does not require IMB notification as there is no medicinal product or device involved. The Regulatory Framework for clinical studies is illustrated in Table 2, Section 4.1.

Studies looking at medicinal products where the product is being used within the license and no procedures are performed outside of the routine patient care, are considered as non-interventional. The decision to enroll the patient is separate to the decision to prescribe the product to the patient and is made after the patient is prescribed the medication (observational study). These types of studies are often considered post-authorisation safety studies (PASS) in addition to Phase IV clinical trials, and

can be conducted either at the decision of the sponsor or by request of the competent authority. The Vol 9A Pharmacovigilance document states in Section 7.4:

“Studies performed at Marketing Authorisation Holder’s initiative

When the study has commenced, the Marketing Authorisation Holder should inform the relevant Competent Authorities of all Member States where the study is being conducted, as well as the Agency and (Co) Rapporteur for centrally authorised products and the Reference Member State for products authorised through the mutual recognition or authorisation procedures. Any major amendment to the protocol should be reported to the relevant Authorities accompanied by a justification for it. Refinements of exposure and/or case definitions will normally not require notification.”

The aforementioned document also contains information on pharmacoepidemiology requirements.

There is no IMB authorisation required for non-interventional and interventional disease registries where there is no medicinal product involved. Interventional studies looking at a medicinal product where the product is being used within the license but additional procedures are performed (eg, additional blood test) are treated as Phase IV trials and require IMB authorisation.

Studies on usual care, quality studies and clinical audits are usually treated as non-interventional studies. However, depending on whether the data collected in these trials are truly anonymised and not pseudo-anonymised, it may be possible to collect data such as prescription monitoring and retrospective studies where consent cannot be obtained. This must be collected in line with the Data Protection Acts of 1988 and 2003, with consideration of the possible application of the Control of Clinical Trials Acts 1987-1990. As mentioned in Section 4.1, because of the Act’s definition of the conduct of a clinical trial in Article 6 (as amended), the Act may apply to some clinical trials involving non-medicinal substances.

4.6 Insurance

4.6.1 Clinical Indemnity Scheme

Indemnity is the provision of a written assurance or contract confirming that liabilities will be provided for and is routinely agreed between the sponsor and the trial centre (eg hospital). The

Clinical Indemnity Scheme (CIS) was established in 2002 in order to rationalise pre-existing medical indemnity arrangements by transferring to the State, via the HSE, hospitals and other health agencies, responsibility for managing clinical negligence claims and associated risks. Under the scheme, which is managed by the State Claims Agency, the State assumes full responsibility for the indemnification and management of clinical negligence claims, including those which are birth-related.

Cover extends to the following in the context of clinical care;

- All HSE facilities, public hospitals and other agencies providing clinical services
- Non-consultant hospital doctors, nurses and other clinical staff employed by health agencies whether permanent, locum or temporary
- Consultant hospital doctors are covered with effect from 1 February 2004 in respect of alleged clinical negligence incidents on or after that date
- Clinical support staff in pathology and radiology services
- The clinical activities of public health doctors, nurses and other community-based clinical staff
- Dentists providing public practice.
- Certain other ancillary healthcare providers.

The CIS will cover claims from patients whose treatment was part of a clinical trial or other approved research project subject to certain criteria:

- The trial has received approval from the relevant Ethics Committee
- The trial is designed by an enterprise, or any of its employees, covered by the scheme.

Where a trial is sponsored by external organisations such as pharmaceutical companies, the CIS cover extends to treatment only and does not cover product liability or claims arising from trial design or protocol.

An ethics committee established by an agency covered by the CIS will also be covered by that Scheme. This cover extends to individual committee members whether or not they are employees of the agency concerned. The same situation prevails if an ethics committee is established by a number of agencies covered by the CIS, acting conjointly.

4.6.2 Industry Indemnity and Insurance

Industry sponsored clinical trials require the sponsoring company to provide indemnity to the investigator and their institutions. To facilitate the effective initiation of trials and the removal of administrative barriers, a single HSE Clinical Trial Indemnity Form (HSE CTIF) has been agreed between the State Claims Agency and the Irish Pharmaceutical Healthcare Association for the conduct of industry led pharmaceutical trials in Ireland. This form is applicable to the conduct of any pharmaceutical industry sponsored clinical trial in any HSE funded hospital in Ireland. In addition, the sponsor will need to provide a certificate of insurance evidencing the commercial sponsor's insurance arrangements for the trial being conducted.

5 ETHICS

Ethics Committee review of clinical trials on medicinal products in Ireland is also governed by the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations, 2004 to 2006. As stated previously, these regulations supersede the Control of Clinical Trials Acts 1987-1990 for clinical trials using medicinal products. However, because of the Act's definition of the conduct of a clinical trial in Article 6 (as amended), the Act applies to clinical trials involving non-medicinal substances and thus, ethics committee review of those trials is not governed by the clinical trials on medicinal product regulations¹⁵. It is worth noting that different ethics committees work to different SOPs and processes. Review can extend to both ethical and scientific methodological review of clinical studies.

5.1 Ethics Committees

5.1.1 Recognised Ethics Committees for Clinical Trials on Medicinal Products

There are currently 13 Recognised Ethics Committees in Ireland for the purpose of central review of clinical trials on medicinal products, as designated by the DoHC¹⁶. These 13 committees are located throughout the country and are hospital associated, with the exception of the ICGP Research Ethics Committee. Sponsors may submit proposals for clinical trial projects to any of the Recognised Ethics Committees for approval. All Recognised Ethics Committees are required to follow the EU Guidelines for GCP: ref CPMP/ICH/135/95 and any subsequent amendments. The Irish Council for Bioethics published guidelines on Operational Procedures for Research Ethics Committees in 2004¹⁷. In addition, the DoHC has issued Ethics Committee Guidance on the Application for Recognised Ethics Committee Opinion and the Ethical Review on Clinical Trials on Medicinal Products for Human Use¹⁸. The aim of this guidance is to assist investigators and Recognised Ethics Committees in their work by establishing SOPs for the making of applications for an ethics committee opinion and the ethical review of clinical trials involving medicinal products for human use.

The definition of a clinical trial in the Regulations covers studies on clinical, pharmacological, pharmacodynamic or pharmacokinetic effects or studies to identify adverse reactions to IMPs, ie all Phase I to Phase IV studies. A clinical trial on a medicinal product may only be started or conducted in Ireland if:

- The Ethics Committee has issued a favourable opinion
- The IMB has granted authorisation

- The sponsor or legal representative of the sponsor is established within the EU.

Application to an Ethics Committee is made by the chief investigator for the trial in the case of multi-centre trials. Under SI No 190 of 2004, the Chief Investigator is an authorised health care professional who takes primary responsibility for the conduct of the trial. It is not required that the chief investigator be an investigator at a particular site. The process for ethics committee submission and approval of clinical trials on medicinal products is outlined in Section 4.2.1, Table 3.

5.1.2 Ethics Committees for other Categories of Clinical Study Research

The 13 Recognised Ethics Committees in Ireland for the purpose of central review of clinical trials pertain only to those trials governed under SI No 190 of 2004. All other categories of research (eg medical device, surgical, non-interventional) on human participants must be submitted for review and approval to the local ethics committee governing each site of the research. Guidance from the IMB is available for ethics committees reviewing medical device applications²⁰. The process for ethics committee submission and approval of medical devices is outlined in Section 4.3.1, Table 5.

For all other categories of research, in the absence of legislation and national guidance, each ethics committee implements different requirements and SOPs for review and approval. Composition of committees, submission fees and timelines differ nationally, making it a key obstacle to the streamlined and efficient conduct of clinical research on a national scale. Review by a research ethics committee may not be required for:

- (a) Research utilising existing publicly available documents or data
- (b) Observational studies in public places in which the identity of the participants remains anonymous
- (c) Case study of one patient with the proviso that written informed consent has been obtained
- (d) Quality assurance studies
- (e) Audits.

Draft guidelines intended to replace the 1991 Council for International Organisations of Medical Sciences guidelines on International Ethical Review of Epidemiological Studies are available and may be referred to in the conduct of studies where there is an absence of national legislation or guidance.

6 SAFETY/PHARMACOVIGILANCE/INVESTIGATIONAL PRODUCT

The IMB is the competent authority in Ireland overseeing safety reporting pertaining to clinical trials on medicinal products and medical devices. In addition, it is the competent authority for the implementation of EU and national legislation relating to blood and blood components, tissues and cells. All other clinical research, including surgery and radiology, is not governed by a competent authority and as such, no national policy or practices exist.

6.1 Notification of Adverse Reactions for Medicinal Products

For those clinical trials on medicinal products governed by the European 2001/20/EC Directive, SUSARs may be notified to the IMB by investigators or sponsor pharmaceutical companies on a company form, CIOMS I form or other report forms, specific to individual pharmaceutical companies. Whichever form is used, it is important that it contains the basic information/data elements described in Annex 3 of the European Commission's detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use¹⁹.

All suspected adverse reactions related to an IMP (the tested IMPs and comparators) which occur in the concerned trial, and that are both unexpected and serious (SUSARs) are subject to expedited reporting. Cases which meet the requirement for expedited reporting are to be submitted to the IMB no later than 15 days from the first/last contact date. Cases which meet the requirement for expedited reporting and are life threatening, or involve a death, are to be submitted to the IMB no later than seven days from first contact date, with follow up to be submitted within eight days of last contact date. The timelines start as soon as the sponsor has first knowledge of the minimum criteria required for expedited reporting.

Other safety issues deserving expedited reporting are as follows:

- Single case reports of expected SARs with an unexpected outcome (eg a fatal outcome)
- An increase in the rate of occurrence of an SAR, which is judged to be clinically important
- Post-study SUSARs that occur after the patient has completed a clinical trial and are reported by the investigator to the sponsor
- A new event relating to the conduct of the trial or the development of the IMP likely to affect the safety of the subjects, such as:

- a serious adverse event which could be associated with the trial procedures and which could lead to modification of the trial
- a significant hazard to the subject population such as lack of efficacy of an IMP used for the treatment of a life threatening disease
- a major safety finding from a newly completed animal study (such as carcinogenicity).

A Sponsor must ensure that data on SUSARs occurring in the concerned clinical trial at any site in Ireland and which are fatal or life-threatening, are reported in writing to the Ethics Committee as soon as possible and no later than seven days after first becoming aware of them. Within eight days of filing this initial report, the Sponsor must, where necessary, send any additional information to the Ethics Committee. In the case of SUSARs occurring in the concerned clinical trial at any site in Ireland and which are not fatal or life-threatening, the Sponsor must report them, in writing, to the Ethics Committee as soon as possible and no later than 15 days after first becoming aware of them. Expedited safety reports, and any further information relating to them, should be acknowledged in writing and filed by the secretary of the Ethics Committee. Ethics Committees do not have access to the Eudravigilance database nor do they have sufficient resources or expertise to analyse the safety data contained therein. EudraVigilance is a data processing network and management system for reporting and evaluating suspected adverse reactions during the development and following the marketing authorisation of medicinal products in the European Economic Area. Therefore, the responsibility of Ethics Committees in this context is inevitably limited. They are, however, responsible for ensuring that the consent of research participants remains valid and based on accurate and up to date information on the risks and benefits associated with the clinical trial.

6.1.1 Periodic Safety Summary Reports

As well as expedited reports, the Sponsor should provide the Ethics Committee with six-monthly reports on the concerned clinical trial. The six-monthly reports will consist of line listings of SUSARs occurring in the concerned clinical trial worldwide. Six-monthly reports must be reviewed by at least the Chair of the Ethics Committee and, where necessary, an expert adviser, eg, a clinical pharmacologist, a pharmacist or a specialist in the concerned disease. Reports should be reviewed in order to assess the continued safety of the concerned clinical trial and assess the accuracy of the benefit-to-risk ratio analysis contained in the protocol.

6.1.2 Annual Safety Reports

In addition to the expedited reporting requirements of individual SUSARs, sponsors will need to submit an annual safety report to the competent authorities and Ethics Committees throughout the course of the concerned clinical trial. The annual safety report should be submitted within 60 days of the data lock point. The data lock point is the date of first authorisation of the concerned clinical trial within a member state.

In the event the sponsor is conducting several clinical trials with the same IMP, only one annual safety report should be compiled including all the safety information from all the clinical trials.

For short-term trials, the annual safety report should be notified to the competent authorities and ethics committees in each of the countries conducting the clinical trial, within 90 days of the end of the trial together with the end of study notification.

The annual safety report should have three parts:

- A report on the subjects' safety in the concerned clinical trial
- A line listing of all suspected SARs including all SUSARs that occurred within the trial
- An aggregate summary tabulation of suspected SARs that occurred in the clinical trial.

6.1.3 Investigational Product

Investigational medicinal products (IMPs) include placebo products and both authorised and unauthorised medicines with any type of active substance, including herbal and homeopathic products. Authorised products may be used in accordance with the terms of the PA or used in a different way, eg, at a higher dose, for a new indication or when packaged in a different container. IMPs include not only the test product but also comparators, blinded comparators, blinded test products and placebos. If any product used in the study is a genetically-modified organism (GMO), a separate application for a licence must be made to the Environmental Protection Agency.

The procedures for authorisation of clinical trials depend on the type of IMP in the study. There are three categories of trials:

- General medicinal products
- Medicinal products which are unauthorised and referred to in Part A of Annex A to Regulation 2309/93 (ie products of biotechnological origin), products containing a biological active or component or manufactured using a biological component

- Medicinal products for gene therapy, somatic cell therapy including xenogenic cell therapy or products containing genetically-modified organisms, known also as ‘advance therapy’ products.

Written authorisation is required for the advanced therapy category of products and may be required for the biological, biotechnological and special characteristics category. No written authorisation is required for trials using general medicinal products (the majority of applications to the IMB) but a written notice, with conditions, will be sent to the applicant accepting the application.

Where written authorisation is to be granted for a biological or biotechnological product, the regulations require that the IMB will send a notice to the applicant within seven days of the receipt of the valid application, informing them that written authorisation is required.

For applications for trials involving products for gene therapy, somatic cell therapy or containing a GMO, the IMB will consult its Clinical Trials Sub-committee before issuing the written authorisation. Applications involving products for xenogenic cell therapy are not subject to any timelines, as provided for in Article 17(9) of the regulations.

6.2 Notification of Adverse Incidents for Medical Devices

Incidents resulting from a clinical investigation may require notification to the IMB depending on their nature. According to the IMB’s *Guide for Ethics Committees on Clinical Investigation of Medical Devices*²⁰, criteria relating to the reporting of adverse events which occur during the course of a clinical investigation should be established. These may be specifically agreed at a local level between the Ethics Committee and the investigation sponsor and may include reporting of events which occur at the local centre and also summary reporting of adverse events occurring in other international centres.

Serious adverse events and device effects should be reported by the investigator to the device manufacturer/investigation sponsor. The principles relating to what constitutes a reportable event and the timeframes involved are aligned with those of the medical devices vigilance system (reference MEDDEV 2.12-1 Rev5²¹) and the international standard (ISO14155 Part 1). Adverse Incident definitions are detailed in Article 10 of MDD 93/42/EC and can be accessed at:

<http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31993L0042:EN:HTML>.

An adverse event is deemed reportable under the medical devices legislation when either an event which led to death, serious deterioration in health, necessitated further medical/surgical intervention etc, occurred, or there was the potential for such an event to occur were it not for the timely and preventative intervention of a healthcare professional, or if such an event was avoided by good fortune. Timeframes for reporting of adverse events for the medical devices vigilance system are as follows:

- Serious public health threat: immediately (without delay that could not be justified) but not later than 2 days of the manufacturer becoming aware of the threat
- Death or unanticipated serious deterioration in health: immediately but not later than 10 days
- Others: immediately but not later than 30 days.

Consideration should be given to what represents anticipated versus unanticipated events, which may be difficult to determine for very novel/investigational devices. The IMB recommends that a similar timeframe to the time requirements for reporting adverse events for the medical devices vigilance system should be used for adverse events from Clinical Investigations. The IMB also recommends that investigators report serious adverse events/device effects or concerns about the device to the IMB Medical Devices Department directly. Summary reporting of incidents/adverse events from other investigational centres may also be requested.

The IMB's *Guidance Note 5 for Manufacturers on Clinical Investigations Carried Out in Ireland*¹⁴ also notes that any serious incident involving a device under clinical investigation within the scope of the Medical Devices Directive should be reported to the IMB as required by the Medical Devices Regulations SI No 252 of 1994. Specific adverse event reporting requirements may be required and summary safety reporting is also required.

6.3 Notification of Adverse Events and Reactions for Transplantation and Transfusion Trials

No statutory obligation is currently in place to report events relating to clinical studies involving transplantation. SI No 158 of 2006 The European Communities (Quality and Safety of Human Tissue and Cells) regulates tissue banks, a hospital unit or body where activities of donation, procurement, testing, processing, preservation, storage or distribution of human cells and tissues intended for human application are undertaken. In the context of this regulation, the IMB requires notification of the following SARs and serious adverse events of the following definition:

Serious adverse reactions: An unintended response, including a communicable disease, in the donor or in the recipient associated with the procurement or human application of tissues and cells that is fatal, life-threatening, disabling, incapacitating or which results in, or prolongs, hospitalisation or morbidity.

Serious adverse event: Any untoward occurrence associated with the procurement, testing, processing, storage or distribution of tissue and cells that might lead to the transmission of a communicable disease, to death or life-threatening, disabling or incapacitating conditions for patients or which might result in, or prolong, hospitalisation or morbidity.

Although there is no statutory obligation to report events relating to transfusion trials, SI No 360 of 2005 and SI No 547 of 2006 The European Communities (Human Blood and Blood Components Traceability Requirements and Notification of Serious Adverse Reactions and Events) transposed Directives 2002/98/EC and 2005/61/EC into national law, regarding traceability requirements and notification of SARs and events involving human blood and blood components. Any such reactions or events relating to blood and blood components require reporting to the IMB.

6.4 Notification of Adverse Incidents for other Clinical Studies

Regarding adverse event reporting for other clinical studies outside the scope of the legislation for medicinal products, medical devices and human tissue/transplantation, there is no statutory obligation to report events to the competent authority but it is considered best practice for the investigator to report serious adverse events to the relevant ethics committee. There is no notifiable body for radiation and radiotherapy trials.

7 DATA MANAGEMENT AND DATA MONITORING

There is an increasing amount of electronic source data being utilised in clinical trials. In addition, electronic Case Report Forms are also being used more frequently. These computerised systems must meet the same fundamental elements of data quality that are expected of paper records. In the USA, the Food and Drug Administration (FDA) has regulated the use of electronic data by implementing Part 11 of Title 21 of the Code of Federal Regulations; Electronic Records; Electronic Signatures (21 CFR Part 11). In Europe, the EMEA GCP Inspectors Working Group has issued a draft paper on *Expectations for Electronic Source Documents Used in Clinical Trials*. The Working Group has chosen to centre this draft paper around 12 user requirements defined in a publication by the Clinical Data Interchange Standards Consortium (CDISC) and electronic Source Data Interchange (e-SDI) Group entitled *CDISC Standards and Electronic Source Data Within Clinical Trials 20 November 2006*. The twelve user requirements refer to source data, irrespective of the media or technology used to hold the data, and describe a group of high-level principles, which if they are adhered to, provide a good basis for the acceptability of source data. These principles provide a good reference for sponsors or investigators establishing such systems, and for monitors and auditors or regulatory inspectors reviewing them. The requirements have their basis in Directive 2001/20/EC and Directive 2005/28/EC, in the Recommendation on the content of the trial master file and archiving (July 2006), and in the Note for Guidance on GCP (CPMP/ICH/135/95).

The UCD CRC is facilitating the development of a data management system for clinical research conducted across a number of sites and the DCCR is appointing a Clinical Informatics Manager who will be responsible for overseeing the design and implementation of a city wide informatics network to support the research activities of the Centre. Implementation of this system will face a number of challenges arising from the unique nature of each clinical study, each of which will require different kinds of data to be integrated and connections made to different systems within the participating hospitals and academic centres.

As yet, compatible systems do not exist nationally. Company sponsored studies use SOPs and study software provided by the company. The data are not retained by the centre or unit, and go to the company either in hard copy or in electronic format. Currently, there are no databases at other centres in Ireland. The data are usually sent off-site to companies, or to third level institutions for academic studies, but not to other hospitals. In-house IT systems are maintained by either the hospital or the academic institution's IT department.

The European Institute for Clinical Trials in Rare Diseases at UCC collaborates with the Robertson Centre in Glasgow, where the Institute's data is sent for storage and analysis. The unit registers with the European Register of Clinical Trials and the National Institutes of Health registry in the USA (Ref: <http://www.clinicaltrials.gov/>).

The International Federation of Pharmaceutical Manufacturers and Associations hosts a clinical trials registry portal that permits access to multiple clinical trials registries worldwide. This pertains only to clinical trials on medicinal products. There is currently no international registry that contains clinical study information for all clinical research other than medicinal products.

In Ireland, there is no single clinical trial registry that has been adopted as the standard registry for the uploading of clinical trials and data being conducted on a national level. ICRIN could perhaps play a role in recommending systems for study registration and ensuring interface with international central study registers that provide free public access.

8 QUALITY CONTROL, AUDITS AND EVALUATION

Most clinical trials in Ireland are company sponsored, and therefore the guidelines for study conduct are provided in the company manual specific to the study under investigation. For in-house academic studies, there are more general SOPs for procedures such as blood collection, or the collection of biological samples. As yet, there is no requirement for nationally-devised SOPs, although exchange of SOPs between sites does occur. ICRIN is tasked with the development of these SOPs nationally.

Audits of clinical research SOPs and methodologies are carried out by the IMB and by sponsors. In addition, for European and US studies, audits can be conducted by other regulatory authorities including the FDA.

8.1 Good Clinical Practice Inspections

Good clinical practice (GCP) is a set of international ethical and scientific quality standards that must be observed in designing, conducting, recording and reporting clinical trials that involve the participation of human subjects. Compliance with GCP provides assurance that the rights, safety and well being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the results of the clinical trials are accurate and credible. Regulations governing clinical trials on medicinal products require that all clinical trials covered by the provisions of the Regulations, including bioavailability and bioequivalence studies, shall be designed, conducted and reported in accordance with the principles of GCP.

In addition to the principles of GCP, clinical trial sponsors should take into account other applicable European Community guidelines relating to the quality, safety and efficacy of medicinal products for human use and updates as adopted by the Committee for Proprietary Medicinal Products (CPMP), for example, the Note for Guidance on GCP (CPMP/ICH/139/95) and the Note for Guidance on Good Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (CPMP/ICH/377/95). Annex 13 to the GMP Guide on Manufacture of IMPs should also be considered.

In accordance with Article 15(1) of Directive 2001/20/EC, any site involved in a clinical trial, particularly, the investigator sites, the manufacturing sites of the IMP, any laboratory used for clinical trial analyses and the sponsor's premises, may be subject to inspection. Contract research

organisations/contractors acting under arrangements with a sponsor to perform some or all of the functions of the sponsor of a clinical trial may also be subject to GCP inspection.

Inspections may be conducted on a routine basis, or may arise as a result of a specific trigger. Inspections may be conducted on ongoing or completed studies. Trials sponsors should be aware that if data from a clinical trial conducted outside the EU are to be relied upon for the purpose of an application for Irish product authorisation, the trial must have been conducted in accordance with the principles of GCP. In such cases, these sites may be subject to a GCP inspection by the IMB.

GCP inspections may be announced or unannounced. However, the former is generally the case. In general, inspectees will be given approximately one month's notice of a forthcoming inspection.

The following information may be requested from the inspectee prior to the inspection:

- Patient status per trial site (number randomised, drop-out rate, and number of SAEs reported per site)
- Copies of company SOPs (eg monitoring procedure, informed consent procedure, SAE reporting procedure, drug supply management procedure)
- Trial specific documents such as Source Data Verification guidelines, product handling instructions, laboratory manual and randomisation code breaking procedure.

An inspection plan, outlining the units to be inspected, the time and duration for each major inspection activity and the schedule of meetings to be held with the investigator and/or sponsor personnel, will be provided to the inspectee prior to the inspection.

The conduct of a GCP inspection can vary depending on the scope and objectives of the inspection. After an inspection, a report is issued to the inspectee. Responses to the report should be provided within 30 working days of the date of issue. Once all findings and observations of the inspection have been addressed satisfactorily, the inspectee will be advised that the inspection is closed.

During 2006, the IMB carried out 17 GCP inspections in Ireland of pharmaceutical companies (sponsors) and clinical research sites, including commercial and non-commercial research investigators.

9 EDUCATION AND CAREERS

Education programmes and courses relevant to clinical research are becoming more available in Ireland. A small number of courses have been developed by both universities and commercial colleges in an effort to bridge the gap in knowledge of clinical research. There is a need for standardisation and accredited/recognised education and training programmes for staff involved in clinical research conduct in Ireland to equip them for a career in clinical research. The Irish Pharmaceutical Healthcare Association recently wrote to ICRIN and noted that *“No single internationally recognised Good Clinical Practice training course is continually available for staff involved in clinical research in Ireland”* and proposed that such training could be effectively coordinated or developed by ICRIN. In time, with education and accreditation, career pathways should become more evident and structured for both industry and academic researchers.

Personnel involved in clinical research conduct, such as research nurses, data managers and biostatisticians are often employed either by the hospital or the CRC on short term contracts, without an organised career structure. The temporary nature of employment, in addition to the lack of available clinical research focused education and training, can hamper recruitment and retention of these valuable members of staff.

In addition, clinicians interested in conducting research are similarly hampered by the lack of training and availability of qualified staff to assist them. This can slow down or obstruct clinical study conduct. In time, with education and accreditation, career pathways should become more evident and structured for both industry and academic researchers.

9.1 Masters of Science in Pharmaceutical Medicine

9.1.1 Diploma/MSc in Pharmaceutical Medicine – TCD

In 2006, TCD introduced Diploma and Masters of Science (MSc) programmes in Pharmaceutical Medicine. The courses are administered by the Department of Pharmacology and Therapeutics, in association with the Centre for Advanced Clinical Therapeutics, St James’s Hospital, Dublin. They were developed to provide medical and science graduates with specialist knowledge and skills in the areas of clinical pharmacology and pharmaceutical medicine. Components include principles of:

- Pharmacology and biostatistics
- New drug development and the regulatory environment

- Pharmacoeconomics and rational use of drugs
- Pharmacovigilance and drug information.

The courses involve completion of taught modules and written assignments, and for the MSc, the additional undertaking of a research project. The modules consist of formal teaching sessions and personal assignments and are run over five terms on a part-time basis (approximately two modules per term). Some of the modules are undertaken by distance learning. Prospective students for this course generally hold a primary degree in either medicine or another relevant health or science subject. Candidates should have a minimum of two years' practical experience in their area of qualification/pharmaceutical industry.

9.1.2 MSc in Pharmaceutical Medicine – Hibernia College

Hibernia College, an Irish online college, offers an MSc in Pharmaceutical Medicine. This MSc was developed in conjunction with Pfizer and is accredited by the Higher Education and Training Awards Council. The course syllabus consists of ten modules covering topics such as drug discovery, clinical pharmacology, data management and statistics. This degree is aimed at both medical and non-medical professionals working in the pharmaceutical industry.

9.2 Other Available Training

9.2.1 Health Research Board Training Courses

The HRB offers a number of short training courses in the areas of grant writing, scientific writing and systematic reviews by the Cochrane Collaboration. These courses are open to all research staff.

9.2.2 Mater Misericordiae University Hospital – Introduction to Clinical Investigation

The Mater Misericordiae University Hospital offers an introductory course in clinical investigation covering study design, control and basic analysis. The course is open to all clinical research staff, and is primarily attended by clinicians.

9.2.3 International Conference on Harmonisation-Good Clinical Practice Training

Research staff including investigators and research nurses can attend registered ICH-GCP courses and update courses offered in Ireland and the United Kingdom. This training is provided via contract research organisations such as Scope Clinical Research Ltd or the Institute of Clinical Research based in the UK. On-line courses are also available but these are not specifically designed for the

Irish research environment, and as such do not prepare the Irish researchers for Irish issues eg ethics applications, IMB additional national requirements, IMB GCP inspections.

Currently there is no nationally recognised body to provide GCP training. Various groups including IPPOSI and MRCG have all recognised that ICRIN is the national vehicle by which a course of this nature can be developed and implemented. The DCCR has also been tasked to implement this type of training programme. Considering the links between the DCCR and ICRIN via MMI and ICRIN's national remit, ICRIN will develop and implement a national GCP training program on behalf of the DCCR/CRC members and the CRCs in Cork and Galway. This course will be open to academic and non-academic personnel with an interest in clinical research.

9.2.4 Molecular Medicine Ireland Clinician Scientist Fellowship Programme

In September 2007, the HEA awarded funding under PRTL I Cycle 4 for a Clinician Scientist Fellowship Programme in translational medical research to be coordinated by MMI. The objective of the Clinician Scientist Fellowship Programme is to train the next generation of clinician scientists (academic medical leaders) with the unique and specialised knowledge essential to fulfill Ireland's research needs in translational medicine. This training programme transcends institutional boundaries to give Fellows unparalleled access to the top biomedical researchers in the country and to state-of-the-art basic and clinical research facilities. The aim is to educate biomedical investigators who, motivated by the intellectual challenge of understanding disease at the molecular level, will lead the quest for new therapeutic strategies. The programme is to provide a systematic way to train this essential group of clinician researchers through a structured PhD programme for medical graduates of three years in length. ICRIN provides a module to the programme entitled 'Translating your research into the clinical setting'. The workshop includes an introduction to clinical research, the drug development pathway, the clinical trial process and responsibilities of the Sponsor, Monitor and Investigator.

This research programme will equip clinicians with the knowledge to stimulate translation of basic discoveries to innovative therapies for patients.

9.3 Careers

The IPPOSI report entitled *Clinical Research Infrastructure in Ireland, Remaining Barriers, Potential Solutions* notes the need to "create formal career structures for health professionals

interested in research, especially (but not only) for research nurses”. The report of the Advisory Council for Science Technology and Innovation, *Towards Better Health: Achieving a Step Change in Health Research in Ireland*, notes in Section 3.4, the need to “*devise a range of incentives, including attractive career structures to attract both clinical and non-clinical staff to pursue research careers”*.

Research personnel, such as research nurses, data managers and biostatisticians are employed either by the hospital or the CRC on short-term contracts, without an organised career structure. Until this career structure is implemented, there is a need to recommend a possible career development path linked to intermediate and advanced training and education opportunities for staff involved in clinical research conduct in Ireland.

The DCCR has established a representative group of research nurses, with appropriate input from the three Dublin Schools of Nursing, to develop:

- A research nurse profile so that the role of research nurses can be communicated to the nursing profession and other stakeholders
- A list of research nurses across the country, acknowledging that it will be difficult to compile a complete or up to date list
- A consensus on the scope of nursing practice issues and concerns with respect to particular practices of nursing research (eg obtaining consent, nurse prescribing)
- A consensus on any representations that may need to be made to the Irish Nurses Organisation, An Bord Altranaís and other professional bodies.

Professional concerns will be addressed in due course (short term contracts, nursing grade, etc) following the articulation of the role and competencies of research nurses.

ICRIN will be involved in these meetings with a view to extending the group nationally.

As mentioned, above, other disciplines involved in clinical research conduct including data managers, project managers, biostatisticians and academic monitors also require the tools necessary to allow for a possible career development path linked to intermediate and advanced training and education opportunities.

The significant investment by the HSE, HRB and Wellcome Trust in clinical research infrastructure will serve to improve the employment environment for research staff in the future, however, research staff outside of this network must also be included.

10 CONCLUSIONS

In summary, it is clear that Ireland is active in all fields of clinical research, despite the lack of infrastructure, regulations, guidance and harmonised SOPs. In review of this report, there is a clear need to develop such guidance and SOPs nationally in order to maximise the impact of innovative research initiatives in place and in development. The establishment of ICRIN, under the auspices of Molecular Medicine Ireland, will enable the development of a national infrastructure for clinical research, maximising the return on the investment by the HRB, Wellcome Trust and HSE of over €54 million in CRCs and programmes in hospitals in Dublin, Cork and Galway over the next five years. ICRIN, as the national coordination network and as the Irish participant in ECRIN, can leverage the harmonisation of the CRCs across the country making Ireland a very attractive option for conducting clinical research, as well as enabling investigator and patient access to cutting edge national and transnational clinical studies.

11 REFERENCES

- 1 Department of Enterprise, Trade and Employment. *Strategy for Science, Technology and Innovation 2006-2013*. DETE 2006.
Also available at <http://www.entemp.ie/publications/science/2006/sciencestrategy.pdf>
- 2 Advisory Council for Science, Technology and Innovation. *Towards Better Health: Achieving a Step Change in Health Research in Ireland*. Forfás. Nov 2006
- 3 Cross Sectoral Clinical Trials Taskforce. *Enhanced Clinical Trials Infrastructure Required to Benefit Public Health*. Irish Medical Devices Association, Irish Business and Employers Confederation. October 2006
- 4 Forfás, Higher Education Authority. *Research Infrastructure in Ireland – Building for Tomorrow 2007*. Forfás. 2006
- 5 <http://www.ndp.ie/documents/ndp2007-2013/NDP-2007-2013-English.pdf>
- 6 <http://www.wellcome.ac.uk/Achievements-and-Impact/Initiatives/UK-biomedical-science/Clinical-Research-Facilities/WTD028387.htm>
- 7 <http://www.hea.ie/index.cfm/page/sub/id/448>
- 8 <http://www.idaireland.com/home/index.aspx?id=65>
- 9 http://www.dataprotection.ie/documents/guidance/Health_research.pdf
- 10 Sheikh, Asim A, *The Data Protection (Amendment) Act, 2003: The Data Protection Directive and its implications for medical research in Ireland*. Eur J Health Law 2005 Dec;12(4):357-72
- 11 http://www.imb.ie/images/uploaded/documents/9294939_GuideCTApp1.pdf
- 12 <http://www.imb.ie/images/uploaded/documents/IMB%20Annual%20Report%20final.pdf>
- 13 <http://eudract.emea.europa.eu/docs/Detailed%20guidance%20CTA.pdf>
- 14 http://www.imb.ie/images/uploaded/documents/GN05-1_CisCarriedOutinIreland.pdf
- 15 <http://acts.oireachtas.ie/zza17y1990.1.html#zza17y1990s2>
- 16 http://www.dohc.ie/issues/clinical_trials_2004/ethics_committees.html
- 17 <http://www.bioethics.ie/pdfs/guide.pdf>
- 18 http://www.dohc.ie/issues/clinical_trials_2004/rec_guidance_2007.pdf
- 19 http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-10/21_susar_rev2_2006_04_11.pdf
- 20 http://www.imb.ie/images/uploaded/documents/AUT-G0044_Guide_for_ethics_committees_on_clinical_investigation_of_medical_devices_v1.pdf
- 21 http://ec.europa.eu/enterprise/medical_devices/meddev/2_12_1-rev_5-2007-fin2.pdf

12 ACRONYMS USED IN REPORT

Abbreviation	Description
ADR	Adverse Drug Reaction
BBMRI	Biobanking and Biomolecular Resources Research Infrastructure
BDI	Biomedical Diagnostics Institute
CDISC	Clinical Data Interchange Standards Consortium
CE	European Conformity
CIS	Clinical Indemnity Scheme
CPMP	Committee for Proprietary Medicinal Products
CRC	Clinical Research Centre
CRF	Clinical Research Facility
CRSC	Clinical Research Support Centre
CSET	Centres for Science, Engineering & Technology
CTA	Clinical Trial Application
CTIF	Clinical Trial Indemnity Form
CTU	Clinical Trial Unit
DCCR	Dublin Centre for Clinical Research
DMMC	Dublin Molecular Medicine Centre
DoHC	Department of Health and Children
ECRIN	European Clinical Research Infrastructures Network
EEC	European Economic Community
EMA	European Agency for the Evaluation of Medicinal Products
EORTC	European Organisation for Research and Treatment of Cancer
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMO	Genetically Modified Organism
GMP	Good Manufacturing Practice
HEA	Higher Education Authority
HRB	Health Research Board
HSCR&D Office	Health and Social Care Research and Development Office
HSE	Health Service Executive

Abbreviation	Description
ICGP	Irish College of General Practitioners
ICH	International Conference on Harmonisation
ICORG	All Ireland Cooperative Oncology Research Group
ICRIN	Irish Clinical Research Infrastructure Network
IDA	Industrial Development Agency
IMB	Irish Medicines Board
IMP	Investigational Medicinal Product
IPPOSI	Irish Platform for Patients' Organisations, Science and Industry
ISO	International Organisation for Standardization
IVD	<i>In Vitro</i> Diagnostic Medical Device
MMD	Medical Devices Directive
MMI	Molecular Medicine Ireland
MRCG	Medical Research Charities Group
MSc	Master of Science
NDP	National Development Plan
NICRN	Northern Ireland Clinical Research Network
NSAI	National Standards Authority of Ireland
NUIG	National University of Ireland, Galway
PA	Product Authorisation
PHG	Programme for Human Genomics
PRTLII	Programme for Research in Third Level Institutions
RCSI	Royal College of Surgeons in Ireland
R&D	Research and Development
REMEDI	Regenerative Medicine Institute
SAR	Serious Adverse Reaction
SFI	Science Foundation Ireland
SI	Statutory Instrument
SOP	Standard Operating Procedure
SRC	Strategic Research Cluster
SSTI	Strategy for Science, Technology and Innovation
SUSAR	Suspected Unexpected Serious Adverse Reaction
TCD	Trinity College Dublin
UCC	University College Cork

Abbreviation	Description
UCD	University College Dublin
UL	University of Limerick

13 CONTRIBUTORS

Dr Caroline Ang, Former Programmes Manager, Dublin Molecular Medicine Centre

Dr Ruth Barrington, Molecular Medicine Ireland

Ms Jackie Breidan, UCD Clinical Research Centre (Mater Misericordiae University Hospital)

Prof Brendan Buckley, University College Cork

Ms Ailbhe Cullen, Beaumont Royal College of Surgeons Clinical Research Centre

Prof Jacques Demotes-Mainard, INSERM, ECRIN

Dr Seámas Donnelly, UCD Clinical Research Centre (St. Vincent's University Hospital)

Dr Peter Doran, UCD Clinical Research Centre (Mater/St. Vincent's University Hospitals)

Ms Siobhan Gaynor, ICRIN/Molecular Medicine Ireland

Dr Jan Guerin, Molecular Medicine Ireland

Mr Paul Harkin, UCD School of Medicine and Medical Science

Dr John Kennedy, St. James's Hospital, Dublin

Prof Dermot Kenny, Beaumont Royal College of Surgeons Clinical Research Centre

Prof Tim O'Brien, National University of Ireland, Galway

Dr Siobhán O'Sullivan, Irish Council of Bioethics

14 ACKNOWLEDGEMENT

Special acknowledgment should be extended to Dr Caroline Ang, former Programmes Manager, Dublin Molecular Medicine Centre. Dr Ang was instrumental in the development of this report.