



Molecular
Medicine
Ireland



Clinical Research Roadmap

2010



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FOREWORD

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The mission of Molecular Medicine Ireland is to mobilise the strengths of our five partner institutions and their associated hospitals to build a sustainable national system to coordinate, support and promote translational and clinical research. In 2006 our partners, NUI Galway, the Royal College of Surgeons in Ireland, Trinity College Dublin, University College Cork and University College Dublin, created the Irish Clinical Research Infrastructure Network (ICRIN) to help us achieve our mission in clinical research. We were pleased that the Health Research Board and the Health Service Executive recognised the importance of this initiative and funded the preparatory phase of ICRIN. The *Clinical Research Roadmap* is an important output of ICRIN and a significant step in defining the next steps in creating a sustainable national system to support clinical research.

Why do we need clinical research? First of all we need it for patients and the general public. Patients and the general public are the primary beneficiaries of clinical research – they benefit from new understandings of disease, new vaccines, new diagnostics, new therapies and medical devices. In that sense, today's health research is tomorrow's healthcare. Second, clinical research is helping to build Ireland's reputation for high quality research and science. It is adding to the reputation of our universities, medical schools and academic hospitals for scientific excellence and contributing to the teaching and learning environment. Third, we need clinical research because it facilitates the transfer of knowledge from the laboratory to the clinic and, when a benefit to patients is shown, to the commercial arena. In this way, clinical research adds economic value and contributes to the creation of the knowledge economy.

There are great opportunities for clinical research in Ireland – we have patients and volunteers willing to participate in studies to prevent and treat disease more effectively and we have highly trained physicians, surgeons and nurses committed to advancing knowledge and improving outcomes for patients. However, academic investigators find it difficult to overcome deficits in governance, sponsorship and support to conduct multi-centre studies on the scale required to demonstrate an effect or to lead European wide studies. Ireland's reputation with international pharma in the delivery of clinical studies is not as good as it should be. There is too much fragmentation, too much dependence on individual contacts, performance is not predictable, the cost of conducting studies is high, compliance is not as good as it should be and restrictions on the recruitment of research nurses have undermined confidence in the capacity to undertake

studies. In addition, our indigenous industry finds it difficult to access clinical resources to develop their products on to the market.

On a positive note, there is a strong commitment by the Irish Government to provide an infrastructure for clinical research linking our medical schools and academic hospitals. In October 2009, the Government in the *Renewed Programme for Government*¹ made a commitment to increasing Research and Development in the health sector and to making Ireland a leading country for timing, access and relevance of clinical trials. Subsequent to this commitment, Mary Harney TD, Minister for Health and Children, launched the *Health Research Action Plan*. The *Action Plan* is a programme of actions that are essential to creating a health research system that supports outstanding researchers, working in world-class facilities and conducting leading-edge research focused on the needs of patients and the public. The Government's *Action Plan* is reinforced by the *Strategic Business Plan* of the Health Research Board which has identified the development of excellent clinical research within a coherent health research system as one of four goals in the period to 2014. This commitment is underpinned by significant financial support for clinical research centres and expertise, in partnership with the Wellcome Trust.

MMI welcomes the commitment of Government to building capacity for clinical research in Ireland and offers the *Clinical Research Roadmap* as an important contribution from the academic sector as to how, in practice, these national objectives can be achieved. What we now need to do is to build quickly on these opportunities and investments and create a sustainable national system to support clinical research, as outlined in this *Roadmap*.

The *Roadmap* reflects a convergence of thinking among a broad cross section of those involved in clinical research about how we can create, in Ireland, a supportive, national system. The draft *Roadmap* was circulated in June 2009 to key stakeholders with responsibility for delivering aspects of clinical research capability in Ireland and the final version reflects their input and advice. I would like to thank all those who contributed to the preparation of the *Roadmap* – those that participated in working groups and those who responded on behalf of the stakeholders. Their names are listed in Appendices I and II. I would like to acknowledge in particular the contribution of Margaret Cooney, ICRIN Coordinator 2007-8, Marie Mellody, ICRIN Coordinator 2009-to date, Siobhan Gaynor, ICRIN Associate/ECRIN Correspondent and Ruth Barrington and Virginia Walls of Molecular Medicine Ireland, to the compilation of the *Roadmap*. I believe that MMI and ICRIN have demonstrated their value in creating this consensus document. We hope to work closely with Government and its agencies in delivering on a shared mission of building capability for clinical research in Ireland.

EXECUTIVE SUMMARY

In the *Strategy for Science, Technology and Innovation 2006-2013*, the Government declared its ambition that:

“Ireland by 2013 will be internationally renowned for the excellence of its research, and will be to the forefront in generating and using new knowledge for economic and social progress, within an innovation driven culture².”

The *Renewed Programme for Government* makes a commitment to increasing research and development in the health sector and to making Ireland a leading country for timing, access and relevance of clinical trials³. The *Health Research Action Plan* and the *Strategic Business Plan, 2010-14* of the Health Research Board provide a national policy and funding framework for the development of clinical research. Extensive investment is underway to build an infrastructure for clinical research in Ireland. Over €54m is committed by the Health Research Board and the Wellcome Trust for the development of clinical facilities and expertise over the next five years. While progress is being made, deficits and roadblocks remain to be addressed if Ireland is to have an effective system of clinical research. This *Roadmap* has been prepared to recommend how these deficits and roadblocks can be overcome so that Ireland can arrive at the desired destination for clinical research – a coordinated, networked clinical research system that supports the health service in its mission to prevent illness and cure disease, supports academia to pursue excellence in teaching and research and supports innovation and the creation of a knowledge based economy and society. The recommendations of the *Roadmap* are primarily addressed to the Minister for Health and Children, the Department of Health and Children and the Health Research Group, the Health Service Executive, the Health Research Board, the Irish Medicines Board, the Irish Clinical Research Infrastructure Network (ICRIN) and academic hospitals, third level institutions, patient organisations and the health care industry.

The Executive Summary highlights the priority recommendations that would facilitate a step change in Ireland’s capacity to undertake high quality clinical research and realise this country’s potential for involvement in the development phase of new medicines and medical devices by the multi-national and indigenous healthcare industry. An urgent priority is to reform the structure and operation of ethical review of clinical research.

- The Minister for Health and Children should establish six to eight national research ethics committees to provide a multi-site single opinion review for all categories of clinical research involving the recruitment of participants through the health service.

- The Minister for Health and Children should establish a Central Office for Research Ethics Committees, with the necessary legal underpinning for the oversight and support of ethics committees in Ireland.
- The Irish Medicines Board should issue formal guidance to the research community and ethics committees to encourage parallel review of studies involving medical devices to promote a consistent approach.

All clinical research conducted in Ireland should be carried out within appropriate governance structures and with the assurance of compliance to the highest international standards. The ability to demonstrate that Irish researchers have the appropriate structures and skills in place to enable sponsorship and oversight of research activities is crucial to being able to lead on Irish research ideas that require the participation of multiple sites and multiple countries. This means we must develop more robust arrangements for research governance in our hospitals and universities and between those institutions.

- Each hospital should develop a research strategy in close association with its affiliated university to reflect its commitment to research as a core mission of the hospital and assign responsibility for implementation of the strategy to a senior member of staff.
- Molecular Medicine Ireland and ICRIN could play a useful role in building consensus on the detailed requirements for an effective approach to research governance and sponsorship, with the outputs to become part of the Health Research Group considerations in the implementation of the *Health Research Action Plan*.
- The Health Research Group should agree and encourage the adoption of metrics of research support in hospitals that could be tracked over time and the contribution of hospitals to government policies on innovation measured.

Much progress is being made in developing elements of a research infrastructure in Ireland. However, we are still in a catch-up situation as a country in terms of the deficits and in connecting the individual elements into a research system. These deficits must be addressed and the connections between the elements made in order to have a fully functioning, competitive and best-in-class research environment which will support our researchers:

- In bringing their research ideas from the bench to the bedside of our patients
- In becoming a partner of choice for multi-national companies in the development of their research portfolios
- In providing indigenous companies access to the clinical expertise and resources

- necessary to develop their products;
- all in the context of improving the health of the population and of patients.

The Irish clinical research system should develop as a component of the emerging European biobanking and clinical research infrastructures which are being developed as part of the European Research Area.

- The Health Research Board and Health Service Executive should support ICRIN for a period of three to five years as a coordinating hub for clinical research in all those diseases that need such a service. They should review the options for a governance structure that would engage the support of the key stakeholders but which would enable ICRIN to operate at 'arm's length' from any one stakeholder.
- The Department of Health and Children and the Health Research Board should support Ireland's continued membership of the European Union's research infrastructures for biobanking - Biobanking and Biomolecular Resources Research Infrastructure - and for clinical research -European Clinical Research Infrastructure Network.
- The Health Research Board and the Medical Research Charities Group should jointly support disease or special interest groups to form and to construct the registries and bio-collections to agreed standards that are needed to advance the treatment of many diseases.
- The Health Research Group should agree a strategy for the funding and development of standardised biobanking as a key pillar to support clinical and translational research in Ireland.
- The Health Research Group should assign responsibility for commissioning a national informatics platform to support translational and clinical research.
- The Department of Health and Children and the Health Service Executive should incentivise the widespread adoption of electronic patient records on the model of the epilepsy patient record developed in Beaumont Hospital.
- The Minister for Health and Children should provide a legislative framework for the registration and regulation of biobanks in the proposed Human Tissue Bill.
- The Health Research Board and Health Service Executive should support the development of a national data management facility/capability to analyse and report on multi-centre trials with the appropriate national software for analysis and reporting.
- The Minister for Health and Children should provide for the registration and regulation of patient registries in the proposed Health Information Bill, including registries without individual consent, where the proposed registry will produce a demonstrable benefit to

health. The Bill should also provide a framework to permit the linking of patient data where such linkage will lead to improved care or better outcomes for patients.

- The Minister for Health and Children should provide for the introduction of a unique patient identifier in the Health Information Bill.

A highly educated and motivated core of health professionals is essential to the success of creating a clinical research system in Ireland. The lack of protected time, targeted training programmes and career structures is holding back the potential contribution of health professionals to clinical research.

- The Health Service Executive should agree with the medical schools a competitive and structured training track in academic medicine, equivalent to that recommended in the Walport Report, to ensure a sufficient number of clinician scientists to lead clinical research in the future.
- The Health Research Board, possibly in partnership with the Wellcome Trust, should offer senior fellowships on a competitive basis for medical graduates who have completed a PhD in clinical and translational research, to enable them to develop as independent investigators.
- The Health Service Executive and Higher Education Authority should fund the appointment of additional medical academics as recommended in the Fotrell Report of 2006⁴.
- The Health Service Executive should recommend a role profile for research nurses, entry level qualifications and experience and opportunities for further training.
- Hospitals should ensure that all nurses involved in research report to a nurse manager, who in turn, is integrated within the senior nursing structures of the university and hospital. The nurse manager of the CRC should in turn, have a good working relationship with senior nursing management in the hospital.
- The Health Service Executive should ensure that health employers meet their responsibilities to fill funded research posts in all disciplines.

INTRODUCTION

Ireland has the potential to be a leading country for quality clinical research including clinical trials, to be a partner of choice in multi-national clinical trials and to generate innovative products to improve health and reduce disability. The Irish Government is committed to providing the infrastructure for clinical research in Ireland, as evidenced by large-scale investment in recent years in facilities and expertise, the policy commitments in the *Renewed Programme for Government*, the *Health Research Action Plan (HRAP)* and the prioritisation of clinical research for funding in the *Strategic Business Plan 2010-14* of the Health Research Board (HRB).

The Programme for Research in Third Level Institutions (PRTL) has provided significant funding for clinical and translational research, permitting sustained expansion of research and development capabilities in third level institutions. The Wellcome Trust and HRB are jointly funding a major clinical research initiative in Dublin, known as the Dublin Centre for Clinical Research (DCCR). The HRB is also funding clinical research centres (CRCs⁵) in Galway and is committed to funding a CRC in Cork. Approximately €54 million will be invested over the next five years in the development of facilities, networks, staffing, shared processes, standards and information technology systems, leading to a substantial increase in clinical research capacity and highly trained personnel.

The Irish Clinical Research Infrastructure Network (ICRIN) was created in 2006 by University College Dublin (UCD), Trinity College Dublin (TCD), University College Cork (UCC), National University of Ireland, Galway (NUIG) and the Royal College of Surgeons in Ireland (RCSI) and operates as a business unit of Molecular Medicine Ireland (MMI). Its preparatory phase is funded by the HRB and the Health Service Executive (HSE) and its goal is to promote harmonisation of training, processes and practice in all aspects of clinical research in Ireland in order to support academic and industry sponsors of research. As a result of the recent investment in clinical research described above and the acknowledged obstacles to conducting clinical research in Ireland, ICRIN was tasked by the HRB and the HSE to convene the key players in clinical research in Ireland in a series of workshops to develop a comprehensive set of recommendations in the form of a *Roadmap* for the development of clinical research infrastructure in Ireland. ICRIN also drew on other initiatives with which it was associated in preparing the *Roadmap*, such as the conference on clinical research organised by the Irish Platform for Patients' Organisations, Science and Industry (IPPOSI) in June 2008 and November 2009⁶, experience gained as the Irish partner of the European Clinical Research Infrastructure Network (ECRIN)⁷, the report on the design phase of GeneLibrary Ireland⁸, the first year's experience of deploying the DCCR and

the seminar organised jointly with the State Claims Agency in April 2009 on indemnity for clinical research.

At the invitation of ICRIN, working groups met in the second half of 2008 to consider the following issues:

- Ethics and interaction with ethics committees
- Regulation/governance and interaction with competent authorities
- Safety reporting and investigational product management
- Data management
- Study monitoring
- Quality assurance
- Education and training.

A list of those who participated in the working groups is attached in Appendix I. A stakeholder meeting of those who participated in the workshops or who contributed in other ways to the preparation of the *Roadmap* was held on 3 December 2008 at which the preliminary recommendations of the *Roadmap* were presented and discussed. The *Roadmap* recommendations reflect the consensus of those who participated in the workshops and those who participated in other initiatives taken or sponsored by ICRIN and MMI. They are addressed to the Minister for Health and Children, the Department of Health and Children and the Health Research Group (HRG), the HRB, the HSE and the academic hospitals, third level institutions, research funding bodies, regulators, patient organisations, the health care industry and the European Commission.

In June 2009, a copy of the draft *Roadmap* was sent to each of the bodies to which its recommendations were addressed, with an invitation to comment on the contents. A list of the bodies that received a copy of the draft *Roadmap* is included in Appendix II. Valuable written comments were received from a number of bodies and some face to face meetings took place. The final draft of the *Roadmap* reflects the input of these comments and meetings.

The *Roadmap* sets out the steps that need to be taken if Ireland is to arrive at its planned destination, that is, a well functioning clinical research system that supports the health service in its mission to prevent illness and cure disease, an academic system which pursues excellence in teaching and research and which, through innovation, contributes to the creation of a knowledge-based society, a 'smart' economy and an industrial infrastructure comprising both indigenous and external players.

What is an Infrastructure for Clinical Research?

A clinical research infrastructure comprises the buildings, people and supporting structures and processes that enable a functioning clinical research system. The infrastructure must provide a core foundation of supporting logistics to facilitate the integration of the various partners in the research process – government, scientists and academics, clinicians and hospital research teams (nurses, pharmacists, and laboratory staff) and industry⁹.

ECRIN, of which ICRIN is the Irish partner, describes this infrastructure as comprising three core elements:

1. CRCs that are the local infrastructures providing support and services to clinical studies by way of support to:
 - Clinical investigation such as dedicated beds, equipment, or specialised staff (study nurses, etc)
 - Trial or study management (clinical trial or research units): trial design and operational methodology, randomisation, data management, analysis and reporting
 - Sponsors: interaction with ethics committees and competent authorities, adverse event reporting, quality assurance and monitoring.
2. National clinical research networks that are the harmonised country networks of CRCs, clinical trials units and/or disease-oriented networks, reaching the critical mass and representing the standard in its country, with the ability to provide support to any category of clinical research, in any disease area.
3. National clinical research hub which is the co-ordinating centre for the national network, acting as the national contact point of ECRIN and part of the legal framework which will enable full participation in ECRIN-supported studies at European level.

The Irish clinical research infrastructure needs to be appropriate to national research requirements but must also be consistent and competitive with the research infrastructures in other countries in order to ensure Irish investigators can lead European and international studies and that Ireland is a preferred country in which multinational companies wish to perform their research programmes.

An effective research infrastructure should be organised so that it improves all processes related to the design, approval, start-up, enrolment and completion of clinical trials and other research programmes with a measurable impact on productivity and research outcomes for industry and academic driven research programmes.

Ireland's size can offer a competitive advantage in that it is easier to establish the initial core infrastructure via the integration of the key academic sites through the networking of their CRCs, which then work jointly on clinical trials with hospital and community-based health care providers. The hospitals and other care providers complete the system by providing access to large groups of well-characterised patients. MMI currently provides the forum for this phase of infrastructural development as its partners are the five academic institutions, who with their affiliated hospitals and the established and emerging CRCs, have the strongest commitment to clinical and translational research in Ireland.

ICRIN and MMI are engaged in developing the clinical research infrastructure through networking the CRCs participating in the DCCR, and linking the DCCR with the emerging CRCs in Galway and Cork and the research teams within their affiliated hospitals. The objective is to develop decentralised coordinating centres or networks of research expertise, which are connected to the national clinical research hub, currently ICRIN.

Ireland has unique strengths in clinical and translational research in, for example, oncology, neuropsychiatric and degenerative diseases, immune related diseases and infectious disease and the research infrastructure is being developed around these strengths. This will ensure that it is focused and develops further the unique elements which Ireland already brings to the biopharmaceutical, medical device, diagnostic, neutraceutical and other healthcare research communities.

The *Roadmap* is intended to complement the prioritised programme of actions set out in the Government's *HRAP*¹⁰. Among the deliverables envisaged for the *HRAP* are:

- A significantly enhanced infrastructure for health research, including fully functional and networked clinical research facilities in the main academic hospitals
- Enhanced partnerships between the health system, academia and industry to achieve the objectives of the 'smart economy', including more clinical trials networks delivering clinical research outcomes of the highest quality in priority areas
- Increased numbers of clinicians and other health professionals engaged in excellent research and innovation
- Strategic clusters of academics, healthcare professionals and industry in experimental and translational medicine.

The particular *HRAP* actions that the *Roadmap* is intended to support are:

- Leading a national health research system

- Developing research capacity in the health services
- Building academic and enterprise links with the health research sector, and
- Reforming health research governance structures.

The *HRB Strategic Business Plan 2010-2014* published in association with the *HRAP*, commits the HRB to driving the development of excellent clinical research within a coherent health research system. In particular, it commits to supporting the development and coordination of CRCs, strengthening clinical research at a national level by way of data management, study design, support and training and establishing clinical research/trial networks. The *Roadmap* offers recommendations on how best to achieve these strategic objectives.

CHAPTER 1: COMPLETING THE INFRASTRUCTURE FOR CLINICAL RESEARCH

Overview

The Government's *Strategy for Science, Technology and Innovation 2006-2013* recognised the need to 'upgrade existing infrastructure and develop new facilities to support research'¹¹. Under the *Strategy*, major investment is taking place to provide an infrastructure for clinical research. Approximately €54 million from public and philanthropic sources will be invested over the next five years to provide facilities, networks, trained staff, shared processes, standards and information technology systems which will greatly increase national capacity to undertake clinical research. This chapter describes some of the most significant investments in clinical research infrastructure and then identifies the key deficits still to be addressed.

Key Investments in Clinical Research Infrastructure

The HRB, the Health and Social Care Research and Development Office (HSC R&D Office) in Northern Ireland and the Irish Cancer Society have supported the development of the Irish Clinical Oncology Research Group (ICORG) to support clinicians, scientists and hospitals on an all-island basis in the conduct of high quality studies to improve the treatment of cancer. ICORG has demonstrated the value of an all-island coordinating organisation for clinical research in cancer. The HRB and the Irish Cancer Society have supported the Prostate Cancer Research Consortium which is a network of clinicians and scientists across Dublin mandated to develop a biobank of patient tissue and samples for research on prostate cancer and a sophisticated clinical informatics system to maximise the value of the information collected.

The HRB, HSE and Higher Education Authority (HEA) have invested in building clinical research expertise through support for clinician scientists as joint appointments to academic institutions and hospitals and fellowships to train, in Ireland, the next generation of clinical investigators. The Minister for Health and Children and the State Claims Agency have provided a supportive regime for the indemnity of those involved in clinical research in public hospitals and associated CRCs, and the current medical consultant contract includes provision for clinicians to dedicate more time to clinical research, with the agreement of their clinical director.

The Centre for Advanced Medical Imaging (CAMI) at St. James's Hospital Dublin has been funded through a HRB research infrastructure call as a national resource for clinical and translational research. The grant was awarded in response to a proposal by clinical and scientific

investigators at St. James's Hospital and TCD to develop a clinical human imaging research centre with an initial focus on MRI. Following a tender process, a Philips 3T Achieva MRI was chosen as the first CAMI imaging modality. A new building required to house CAMI on the hospital campus and the facility opened in 2008 with an initial focus on research in the cardiovascular, neurology and oncology areas. It is located beside the planned HRB/Wellcome Trust CRC, described below.

One of the most important investments is the creation of the DCCR. Under this initiative, the Wellcome Trust is funding TCD to build a new CRC on the campus of St James's Hospital and the HRB is funding the development of a clinical research network in Dublin, linking the UCD CRC at St Vincent's University Hospital and the Mater Misericordiae University Hospital, the RCSI CRC at Beaumont Hospital and TCD's planned CRC in St James's Hospital to create the DCCR. MMI is playing a key role in coordinating and networking the development of the DCCR. The HRB is also funding new CRCs at Cork University Hospital and University College Hospital Galway.

The HRB and HSE have funded MMI to establish the preparatory phase of ICRIN to engage with the CRCs, medical schools and constituent teaching hospitals to develop the 'soft' infrastructure for clinical research in Ireland, that is, to harmonise standards, to address deficits in education and training, to facilitate multi-site studies across a range of diseases and, through consensus, recommend solutions to common problems.

The Centre for Support and Training in Analysis and Research (CSTAR), based in UCD, is an additional infrastructure element funded by the HRB to strengthen research quality by providing advice, consultancy, training and education in research methodologies, study design, project management, analysis, reporting, appropriate dissemination to inform practice and other support services. CSTAR began offering research support services in 2009.

The HRB is funding an innovative research project in Beaumont Hospital to develop an electronic record for patients with epilepsy, that is improving the delivery and quality of care to over 3,000 patients attending the national centre for the treatment of this disorder and which has a strong research focus¹². The challenges of creating the e-record have been overcome and by January 2010 the records of over 1000 patients had migrated to the new system, with significant improvements noted in the effectiveness and quality of care provided to patients. The electronic records are also providing a valuable resource for investigators engaged in epilepsy research and they are facilitating a much quicker identification of patients suitable for participation in studies of new therapies and of genetic factors associated with the disorder. The epilepsy e-record provides a model for adoption throughout the health service for improved clinical care and as a resource for clinical research.

MMI and ICRIN, with the support of the HRB and CSTAR, are piloting a programme of actions to assess the current state of 'research readiness' in a subset of developed and emerging CRCs and university-affiliated hospital research teams. The goal of this research readiness pilot programme is to identify, at a more granular level, the national and local processes that need to be prioritised for completion to serve as the core of a supporting framework for researchers. The aim is to harmonise the research practices of the CRCs and their affiliated hospital research teams in the first phase of the development of the infrastructure to support clinical and translational research.

The primary research support systems being assessed during the research readiness programme are:

- Research governance, sponsorship and links with clinical and hospital governance
- Quality management (standard operating procedures, training)
- Trial management and oversight - project management, medical and safety management
- Regulatory affairs and ethics
- Administration support – finance and legal
- Trial logistics – pharmacy, laboratory, biobanking
- Trial design and statistical methodology
- IT solutions and data management.

The output of this pilot will inform the national central clinical research hub requirements and identify the most effective interactions with the supporting expertise in the CRCs for MMI, the HRG and HRB in 2010.

ICRIN is also piloting a selection of research processes and procedures (listed below) which have been adapted from the policy documents developed as a member of ECRIN. These will be validated during the research readiness programme with the CRCs and affiliated hospital research teams with a view to assembling a starting kit of template standard operating procedures (SOPs), guidance documents and tools to be made available as a central resource for all research sites in Ireland.

- Trial design
- Trial risk assessment
- Protocol development
- Data validation and handling
- Safety monitoring and pharmacovigilance
- Regulatory and ethical approval

- Investigational medicinal product (IMP) management
- Informed consent management with model consent form and patient information leaflet
- General supply management
- Service provider evaluation and contracting
- Management of audits and inspections
- Quality management
- Site selection and training
- Site management and monitoring
- Trial management
- Trial closure
- Trial document management and archiving
- Trial reporting and communication
- Trial team training
- Clinical trial for investigational medicinal product (CTIMP) device and diagnostics process maps (Ireland, EU)
- Agreements and contracts
 - Delegation of responsibilities
 - Master service agreements and work orders
 - Collaborate agreement templates
- Trial costing guidance and templates
- Protocol, report, trial management forms and templates
- Sponsorship considerations and implications
- Disease network and clinical interest group guidance, terms of reference, tools and templates.

At the end of the research readiness pilot phase, a proposal for a national accreditation system for clinical research in Ireland will be developed for evaluation by the HRG and HRB in consultation with the other stakeholders. This proposal will be aligned to similar initiatives by ECRIN and its members.

In support of the development of a Central Office for Research Ethics Committees, the DCCR and ICRIN are also engaged in the piloting of a single form for use by ethics committees in the evaluation of research protocols for studies other than those of medicinal products. The goal of the single form pilot project is to streamline and harmonise the ethical approval process for non-IMPs. Guidance documents and training modules are being developed as part of this initiative which may be of value to the Central Office when it is formed.

Deficits in Clinical Research Infrastructure

While major progress has and is being made in building the infrastructure for clinical research, there are still significant deficits that require investment. Key deficits that need to be addressed are support for disease and special interest groups and patient registries, an infrastructure for biobanking, a national clinical informatics platform and an effective means of coordinating clinical research activity nationally. The next section of this chapter considers what is required to support disease groups, patient registries, a biobanking infrastructure and the coordination of clinical research activity.

Disease Groups and Patient Registries with linked Biocollections

The most important participants in clinical research are patients and physicians. Both need to be encouraged and supported to participate in research. It is encouraging that groups of specialists in different disease areas are forming to pursue common research interests, including those associated with the DCCR. These include groups of specialists in diabetes, respiratory disease, neuropsychiatry, neurology and prostate cancer. These groups seek to link pre-clinical, translational and clinical research activities in an effort to expedite the development of novel therapies for the prevention and treatment of the disease of the patients they treat. It is critical to the success of these disease groups, and to the success of Ireland's efforts in clinical research, that specialists in different hospitals and academic institutions can share information and create registries of patients with a particular disease. A patient registry, on the model of the Cystic Fibrosis Registry, is a record of the medical history and relevant genetic characteristics of patients and is an invaluable means of understanding the nature of a disease and its impact on the lives of patients. As more is known about the genetic variations associated with diseases and the different responses of patients with different gene variations to therapies, the value of patient registries in identifying those patients who may benefit from new therapies and who should be invited to participate in clinical studies, will grow. Patient registries are all the more valuable if they are complemented by collections of biomaterial relevant to the disease. While a number of patient registries have been developed, few are of the necessary scale or comprehensiveness, or, have associated biocollections to be valuable for clinical research. The absence of a unique patient identifier (UPI), that would allow discreet episodes of treatment of individual patients to be linked, makes the creation of patient registries all the more difficult.

A priority for further investment should be to encourage the formation of disease or special interest groups and to support them to develop patient registries and biocollections. The creation of patient registries and biocollections must have the active involvement of healthy volunteers, patients and patient organisations. There is an opportunity for the HRB and the Medical Research

Charities Group (MRCG), representing over 30 patient charities involved in research, to work together to encourage disease or special interest groups to form and to construct the registries and biocollections that are needed to advance treatment of many diseases. Disease groups that have the support of their associated patient groups could be funded to construct the registries and biocollections, using the resources of the network of the CRCs being developed, the clinical informatics platform and the biobanking infrastructure discussed below.

Recommendations

The HRB and the MRCG should jointly support disease or special interest groups to form and to construct the registries and biocollections to agreed standards that are needed to advance the treatment of many diseases

Biobanking and Clinical Research

A biobank is a collection of blood and/or tissue donated by healthy volunteers and/or patients with linked clinical and medical information which is made available for medical research. Biobanks of large standardised collections of biological specimens with linked clinical, environmental and lifestyle information are increasingly recognised as major assets in disease research. As medical research moves from the study of simple monogenetic disorders to the investigation of complex diseases, biobanks play a significant role helping to dissect the interplay of genetic and other factors that contribute to complex polygenic diseases. Typically, researchers will study patient groups with the same disease or trait of interest and compare the data generated with samples from a group of healthy people to discover more about the genes involved in disease. Biomedically-relevant, quality-assessed biological materials and data are essential if clinical, academic and commercially-driven research is to diagnose, treat and prevent common and rare human diseases.

The importance of '*a national approach to biobanking*' and in particular that '*all Irish research centres and hospitals adopt standardised biobanking practices as a matter of priority*' has been highlighted in a recent report published by Forfás on the health related life sciences¹³.

The National Cancer Strategy also recognised the importance of biobanks to the advancement of cancer research. The Minister for Health and Children tasked an expert group to advise on the establishment of a National Cancer Biobank for Ireland as part of the Cancer Control Programme. The report was published in 2009 and is awaiting implementation¹⁴.

MMI has recognised the importance of standardised biobanking for clinical and translational research in Ireland. To this end MMI, in association with Queen's University Belfast and the University of Ulster, prepared the design phase of GeneLibrary Ireland in response to a funding call from the HRB and the HSC R&D Office of Northern Ireland. GeneLibrary Ireland, as proposed, is an all-island control bio-resource, to be developed jointly in the two jurisdictions of Ireland and Northern Ireland. GeneLibrary Ireland would provide an all-island reference library of 10,000 standardised biological specimens donated by healthy volunteers with linked health and lifestyle information. It would offer a shared control group for a wide range of clinical and translational studies by health and biomedical scientists and provide a unique resource to answer many questions about the interplay between genes and the environment in predisposition to disease. The design phase, which outlined the scientific case for such a resource and recommended how it could be assembled and how ethical and governance issues could be handled, was completed in February 2009¹⁵. Due to financial constraints, the HRB and the HSC R&D Office were not in a position to fund the collection phase of GeneLibrary Ireland.

As a contribution to a more strategic approach to biobanking and to support the clinical research infrastructure in Ireland, MMI has prepared guidelines to standardise the collection, processing and storage of biological materials to ensure a level of consistency and harmonisation across the different clinical and research centres in Ireland. These guidelines stemmed from the work of the design phase of GeneLibrary Ireland. The use of standardised protocols for sample collection, processing and storage will help to provide the proper safeguards and assurances required for sample quality, consistency and integrity among bio-collections at different clinical and research sites. This harmonisation will allow for the universal interchange of biological materials across sites and the amalgamation of samples for research studies. Once published, MMI believes that the adoption of these guidelines, for all newly funded bio-collections, will be a first step towards harmonising biological collections across different research fields and CRCs. It would be an important move towards a more strategic approach to biobanking if all those who support or are engaged in research that involves biobanking, including research funding agencies, hospitals and CRCs, clinical networks and disease groups, adopted the guidelines as the basis for all newly funded collections of biological material.

Biological collections assembled with public funding should form part of a national or all-island collection, with access guaranteed to all researchers, subject to the quality of the scientific question to be answered and adherence to the highest ethical safeguards. By moving in this direction, Ireland could develop a most valuable resource for clinical and translational research. The creation of a biobanking infrastructure that would provide access to large standardised biological materials with linked phenotypic data, would give researchers in Ireland a resource that

will drive advances in pharmacogenetics, disease screening tools, biomarker discovery and validation and would ensure Ireland's competitiveness in the era of personalised medicine. The *HRAP* identifies the need to develop priority biobank requirements and charges the HRG with this task.

Biobanking – Ireland and Europe

The member states of the EU are committed to an ambitious project to provide state-of-the-art infrastructures at European level to enable academic and industry investigators conduct research of a nature or on a scale that has not been possible up to now. In relation to biobanking, the EU is supporting the development of the Biobanking and Biomolecular Resources Research Infrastructure (BBMRI) to establish a European network of bioresources for research. In its preparatory phase, BBMRI is preparing an inventory of bioresources, mapping these resources and associated technologies, defining standards and rules of access and facilitating exchange of bio-materials and associated data. Ireland is one of the member states participating in BBMRI and MMI is the Irish scientific partner. Ireland, through the involvement of IPPOSI, is also chairing and supporting the BBMRI Stakeholder Forum, which provides a mechanism for consultation with the many interests in biobanking in Europe, including patient groups, clinicians, funding organisations, associated project partners, industry and researchers. The expertise available through BBMRI was of invaluable assistance to MMI in preparing the design phase of GeneLibrary Ireland and has helped MMI chart a more strategic approach to biobanking in Ireland. MMI has made a major contribution by preparing the *Guidelines for Standardised Biobanking* which are being adopted by BBMRI as the recommended standards for Europe. The preparatory phase of BBMRI concludes in February 2011.

In 2009, the Council of Ministers agreed a new governance arrangement for EU research infrastructures known as the European Research Infrastructure Consortium (ERIC) to support the infrastructures into their mature phase. Continued membership of BBMRI will require a formal decision at national level to join the ERIC, with a financial contribution probably linked to the GDP of each participating member state. In return, Ireland will continue to be at the heart of creating a biobanking infrastructure for Europe, investment in biobanking in Ireland will benefit from being part of an European strategic initiative, principal investigators (PIs) in Ireland will have access to an unprecedented range of bio-resources in Europe and this country will stand to benefit from the additional resources that the EU Framework Programmes are expected to direct in support of networked biobanking infrastructures.

Recommendations

- The HRB, Science Foundation Ireland (SFI) and the research charities should adopt the MMI guidelines on standardised biobanking and require investigators collecting biological samples to do so in accordance with the guidelines. They should also require the investigator responsible for any collection they fund to facilitate access to the samples by other investigators, subject to the scientific ethical merits of the proposed research.
- The HRG should agree a strategy for the funding and development of standardised biobanking as a key pillar to support clinical and translational research in Ireland
- The Department of Health and Children and the HRB should support Ireland's continued membership of the EU's research infrastructure for biobanking – BBMRI.

Informatics and Clinical Research

The networking of the existing CRCs in Dublin (RCSI/Beaumont, UCD/Mater Misericordiae and St. Vincent's University Hospitals) with the planned TCD CRC at St James's Hospital in the HRB/Wellcome Trust funded DCCR, and the opportunity to network the Dublin facilities with the planned NUIG/University College Hospital Galway and UCC/Cork University Hospital CRCs, underlines the need to develop a national approach to informatics and data management for clinical research. Such an approach will facilitate the joint collection, management and collation of information for translational and clinical research between centres in national and international studies.

Some progress has been made in recent years in developing common informatics and data management approaches to facilitate multi-site translational and clinical research. The UCD CRC has developed a clinical research informatics and data management system for certain kinds of studies that has national application. The Prostate Cancer Research Consortium has developed an informatics system for biobanking biological samples from patients with prostate cancer across participating hospitals in Dublin that facilitates translational research and that can be extended nationally. The DCCR has appointed a Clinical Informatics Manager who is responsible for overseeing the design and implementation of a citywide informatics network to support a broad range of translational and clinical research activities that will also have national applications. The further development of Dublin-wide and national systems will face a number of challenges arising from the unique nature of each clinical study and the slow progress towards developing a common informatics and data management platform for the health service.

A key recommendation of the HEA and Forfás report entitled *Research Infrastructure in Ireland – Building for Tomorrow 2007*⁷ was the establishment of “a common information technology

platform capable of providing comparable data sets across all facilities (which will also enable multi-centre trials)". An advanced informatics platform capable of networking patient data sources from hospitals and community based care providers, with the established and emerging CRCs on the sites of the major academic hospitals in Dublin, Cork and Galway, is needed to support clinical and translational research at a national level in Ireland. A shared informatics platform will facilitate the undertaking of all research programmes at a national level that are not possible or extremely difficult at present. A common informatics platform, taking advantage of the development of web technology and availing of increased broadband connectivity, is needed to support a wide range of clinical and translational research activities. The research activities include identification of target patient populations from clinical records and the storage of large volumes of phenotypic and genetic data linked to patients participating in studies. Funding has been made available in the CRC awards for clinical informatics managers and data managers which will advance the data management agenda. What is required is an initiative to develop a nationally integrated biomedical and clinical research informatics platform, ideally linked with the adoption by the health service of an electronic patient record and a UPI.

Biomedical research today increasingly involves cross-institutional collaborations necessitating standardised approaches, policies, procedures, and practices, for example, SOPs and good clinical practice (GCP), for the collection, storage, management and analysis of biomedical information. The Prostate Cancer Research Consortium is an excellent example of one such consortium which has developed standardised approaches, policies, procedures and practices in informatics for biobanking and prostate cancer research among the participating hospitals in Dublin. The overhead involved in establishing the appropriate standards and governance framework is significant and typically has to be repeated for each collaborative study. A shared informatics platform would avoid the need for a new solution for each study or biobank and would include systems to handle multi-institutional ethics approval, participant consent, participant information, biospecimen sample information and tracking, sharing of data internationally and biomedical information management. It would also ensure the privacy, confidentiality and security of participant data. These systems must be sufficiently generic to map the workflows and best practices of the medical practitioners, clinicians and researchers. The use of international standards would ensure interoperability and it would enable and facilitate Irish involvement in EU and other international initiatives, for example, BBMRI which is networking biobanks across Europe. In particular, systems that allow for the sharing and collation of biomedical information with international consortia will be vital for Irish participation in international studies. A shared platform will facilitate a flexible approach which can be adapted for both centralised and distributed biomedical resources.

In an effort to address this deficit, MMI and the Dublin Institute of Technology have proposed the development of a common modular platform which can be customised to meet the needs of collaborative translational and clinical studies. This platform would be developed over five years in a modular, incremental-phased approach, taking into account legislative changes such as the proposed introduction of a UPI and progress within the health system with the adoption of electronic patient records and the electronic transmission of information. When developed, the platform would be made available, licence-free, to the Irish translational and clinical research community as a shared service. On-going development and maintenance of the national platform could be provided through the studies availing of the services. The platform development will incorporate an international dimension supporting interoperability with a range of other clinical resources such as those being developed for pan-European studies by ECRIN or for biobanking in Europe by the BBMRI. It could also provide a standardised approach to describing these resources which will enable researchers to search multiple repositories concurrently at a national level.

Recommendations

- The HRG should assign responsibility for commissioning a national informatics platform to support translational and clinical research.
- The Department of Health and Children and the HSE should incentivise the widespread adoption of electronic patient records, on the model of the epilepsy patient record developed in Beaumont Hospital.

Coordination of Clinical Research at National Level

MMI is committed to the development of a clinical research infrastructure in Ireland. ICRIN was created in 2006 by a memorandum of understanding between the MMI partner institutions and was funded for a preparatory phase by the HRB and the HSE to engage with the constituent teaching hospitals, universities and their CRCs, to develop a national clinical research infrastructure. ICRIN's objectives are to link the CRCs across the country under shared SOPs; devise nationally recognised GCP training programmes; foster clinical development activity; and, drive a more standardised approach to biobanking. On its establishment, ICRIN was recognised by the HRB, HSE and SFI as the national, trans-disease coordinating network, for clinical research other than in cancer, and from 2006, became the Irish scientific partner in the ECRIN. Since July 2007, ICRIN has published the *Situation Analysis of Clinical Research in Ireland*; devised and delivered GCP training for academic, health and industry staff involved in clinical research; secured the support of Enterprise Ireland to provide a liaison service for start-up

companies and small to medium sized enterprises (SMEs) which need access to clinical resources; clarified issues in relation to indemnity for clinical studies; contributed strategic advice and authored SOPs for ECRIN; initiated a Research Readiness programme; prepared this *Clinical Research Roadmap*; and, by bringing the key players involved in clinical research together, developed thinking around the role of trans-disease coordination of clinical research in Ireland. MMI and ICRIN's contribution to developing a standardised approach to biobanking has been described above.

It is clear from the preparatory phase of ICRIN that there is a role for a central national, trans-disease coordinating organisation to link the research expertise of the CRCs, academic teaching hospitals and disease networks, patient registries and bio-collections together, and to provide the support services that will facilitate the conduct of clinical research and clinical trials on a national, European and international level. ICRIN can act as a central resource for tools and training in research ethics, data protection, GCP, standard protocols for biobanking, good laboratory practice (GLP), good manufacturing practice (GMP), medical device legislation and observational trial considerations. ICRIN can also provide a portal for start-up companies and SMEs that need access to clinical resources to bring their products to market. For a relatively small investment, ICRIN can offer a nationally and internationally recognised coordinating hub to facilitate the conduct of multi-centre clinical research and clinical trials across a wide range of diseases. It can, for example, work toward a solution to the challenge of the sponsorship of multi-site investigator-led trials; a category of trials which PIs in Ireland have difficulty in leading at present. While the focus of ICRIN's support would be primarily on investigator-led trials, the establishment of a central national research hub would also facilitate the development of a support system which is more industry facing. This industry interface should be developed in parallel with the active engagement of Enterprise Ireland for indigenous SMEs and start-up companies as well as the Industrial Development Authority (IDA) for external industry stakeholders.

The responsibilities of a national clinical research hub should evolve to providing oversight and continued harmonisation and standardisation of research practices in Ireland, as well as the management of an up-to-date web based communication platform. The hub should also ensure external promotion of the Irish research capacity and be the point of contact for the various stakeholders.

The national hub should become the source of expertise and training in the research environment and ensure fit-for-purpose process, training and support of the existing and emerging CRCs and other groups performing research in Ireland. This should include the provision of advisory and consulting services on the navigation of the research processes in Ireland for external parties who

wish to engage effectively with the Irish research system as well as up-to-date knowledge, via ECRIN participation, of the European and other international research requirements for Irish researchers who wish to perform activities internationally.

As the resources invested in clinical research grow, so does the need to link the different facilities and actors to ensure coherence nationally and to maximise the return on taxpayers' investment. The HEA and Forfás report entitled *Research Infrastructure in Ireland – Building for Tomorrow 2007* 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 (clinical research facility)”. Reference was made to the potential of ICRIN to assist with this task.

The MMI partners identified the need for a national, trans-disease coordinating mechanism and took the lead by establishing ICRIN and supporting it during the preparatory phase. As ICRIN matures and its value as a national coordinating mechanism for clinical research is more widely understood, the governance of ICRIN could be examined to engage a wider group of stakeholders in clinical research. What is important is that the governance of ICRIN has the support of key stakeholders including patient representatives, leaders of disease groups, the medical schools, the HRB, academic hospitals, directors of CRCs, the HSE and the enterprise development agencies. It is also important that it has a mandate to act in the best interest of all stakeholders in clinical research in Ireland.

The alternative to ICRIN is that each disease group would develop the support services it needs to undertake multi-site studies and that a separate structure emerges to coordinate the CRCs. This is an expensive alternative which would be hard to justify in a country the size of Ireland. It would be preferable if the HRB and HSE were to commit to supporting ICRIN for a period of three to five years as a coordinating hub for clinical research in all those diseases that need such a service. During that period, ICRIN should agree clear, tangible benefits with each stakeholder to link ICRIN's goals to theirs, thereby developing the infrastructure for clinical research in Ireland.

The experience from ECRIN member countries would suggest that the coordination of a national clinical research infrastructure should be met primarily from public funding.

Recommendations

- The HRB and HSE should support ICRIN for a period of three to five years as a coordinating hub for clinical research in all those diseases that need such a service. They should review the options for a governance structure that would engage the support of the

key stakeholders but which would enable ICRIN to operate at 'arm's length' from any one stakeholder.

Coordination of Clinical Research at European Level

As mentioned above, the member states of the EU are committed to an ambitious project to provide state-of-the-art infrastructures at European level to enable academic and industry investigators conduct research of a nature or on a scale that has not been possible up to now. In relation to clinical research, the ambition is to overcome the current difficulties of conducting such research across a number of member states and to realise fully the potential of Europe's excellent health systems and expertise in clinical research to drive the next generation of medical discoveries. ECRIN was established for this purpose and is being funded under EU Seventh Framework Programme 7.(FP7) Ireland joined ECRIN in 2006, with ICRIN as the Irish scientific partner. Thirteen EU member or associated states are participating in ECRIN. Much work has been done towards overcoming the fragmentation of the national systems and providing a means of conducting academic studies at European level. The European infrastructure is being created by networking the national coordinating hubs for clinical research, such as ICRIN. The first ECRIN supported studies will be conducted in 2010. The preparatory phase of ECRIN concludes in February 2011. Participation in the preparatory phase of ECRIN has been an invaluable learning experience for ICRIN and has ensured that thinking and practice in clinical research coordination in Europe and Ireland are aligned.

As mentioned above, the Council of Ministers agreed in 2009 a new governance arrangement for EU research infrastructures known as the European Research Infrastructure Consortium (ERIC) to support the infrastructures into their mature phase. Ireland's continued membership of ECRIN will require a formal decision at government level to join the ERIC. In return, Ireland will be central to the creation of a clinical research infrastructure for Europe, PIs in Ireland will be supported to design and undertake European wide studies and this country will stand to benefit from the additional resources that the EU Framework Programmes are expected to direct in support of such infrastructures.

Recommendations

- The Department of Health and the HRB should support the continued participation of ICRIN as a full member of ECRIN.

CHAPTER 2: RESEARCH GOVERNANCE AND SPONSORSHIP

Overview

The conduct of clinical research is a highly complex process. It begins with a commitment to improve the lives of patients and the public and requires scientifically robust questions, methods and observance of the highest ethical standards. Furthermore, it involves highly trained research staff and the active participation of patients and volunteers, and it relies on the active support of the hospital and health system to achieve its outcomes. The Report of the Advisory Council for Science, Technology and Innovation entitled *Towards Better Health – Achieving a Step Change in Health Research*¹⁶ recognised the complexity of health and clinical research when it recommended that the Department of Health and Children develop a national strategy for health research that has the support and commitment of Government, the educational system, research bodies, hospitals, medical and health professions and other stakeholders. It noted that international best practice in health research was to integrate the resources of academia, hospitals and other agencies to research the questions of most relevance to patients and the health services and to support innovation. The Council recommended the establishment of clear and transparent governance structures between hospitals and universities underpinned by clear and explicit legal agreements which identify and regulate areas such as joint appointments, career structures, budgetary arrangements and mechanisms to manage and exploit intellectual property (IP) arising from research. It proposed that the clinical directorate structures in hospitals should have clear relationships with the academic structures within the universities and that hospitals that implement such structures should be rewarded by an increased budget allocation. The Council also recommended that, over the longer term, consideration should be given to developing a single governance model for teaching hospitals and their associated universities – a model which may be appropriate for a small number of major academic medical centres in the country. This chapter of the *Roadmap* builds on the recommendations of the Council and considers what is needed by way of active support for clinical research by hospital authorities and their affiliated universities, and how the potential contribution of hospital based clinical research to innovation could be harnessed.

The quality of research governance and the capacity for sponsorship of clinical research are the two key areas which are assessed in research proposals to EU and other funding bodies.

Strategic Commitment to Research

There is a variety of governance arrangements among hospitals in Ireland. Some academic hospitals are under the management of the HSE, some are corporate bodies and others are managed by charitable bodies. Some academic hospitals are affiliated to one academic institution while others are affiliated to two or more. What all academic hospitals have in common is a strong commitment to the clinical care of patients, an overwhelming reliance on public funding for their activities and poorly defined relationships with their affiliated academic institutions. Recently, efforts have been made to define more clearly the relationship between academic hospitals and academic institutions. The creation of the Dublin Academic Medical Centre (DAMC) by the Mater Misericordiae University Hospital, St Vincent's University Hospital and University College Dublin to provide a governance structure for the shared interests of the hospitals and the university in clinical care, education, research and innovation is evidence of a new approach to defining the hospital/academic relationship in an Irish context. Because of the variety of hospital governance arrangements, however, it is unlikely that one model of governance will work for all hospitals and academic institutions. A more in-depth analysis is needed to identify the core elements which will be relevant to all institutions so that a harmonised approach to research governance can be implemented nationally with flexible local requirements.

Whatever the governance model, it is vital that every hospital with an affiliation to a university or medical school should have an explicit commitment to support and promote high quality research as best practice in the delivery of treatment and care of patients. This commitment should be underpinned by a strategy for research that outlines the hospital's vision for research and how it proposes to achieve it. The research strategy should be developed in close co-operation with the affiliated university and with those responsible for the schools of medicine, nursing, allied health professions and health sciences. The research strategy should complement and support the hospital's other missions of patient care and the education of health professionals. The strategy should identify the strengths and weaknesses of the hospital and the university in disease and patient focused research, and how it is proposed to build on the strengths and address the weaknesses. The research strategy should reflect the wider commitments of the hospital and the university to building regional and national capacity in clinical research, such as participation in the DCCR, ICORG and ICRIN, as well as involvement in European and international networks. The research strategy should address how the hospital will facilitate innovation arising from the research conducted in it.

As part of the preparation of a research strategy, each hospital authority and its affiliated university need to clarify the governance arrangements for CRCs and other research activities

conducted in the hospital. There are different models of governance for the CRCs that can work in an Irish context such as a hospital facility with a strong university involvement or a university facility with a strong hospital involvement. The key objective is to ensure that the CRC functions as an integral part of the hospital to facilitate the active involvement of clinicians, the recruitment of hospital patients, coverage by the clinical indemnity scheme, staff recruitment and management, harmonised standards for the collection, processing and storage of biological collections and the coordination of all clinical research activities in the hospital.

When a research programme falls under the auspices of the EU Clinical Trial Directives, additional responsibilities apply in undertaking the role of legal sponsor. Article 2 of the 2001 Directive defines a 'Sponsor' as an *"individual, company, institution or organisation that takes responsibility for the initiation, management and/or financing of a clinical trial"*. The sponsor is responsible for ensuring that the trial is conducted in accordance with GCP and adheres to the national statutory instruments pertaining to the conduct of these types of trials. Trials and research activities which fall outside this more regulated framework must also have oversight bodies to ensure adherence to good research practices, data protection legislation, the Declaration of Helsinki and other national regulations and rules. Many investigator-led studies are hampered in this country by the unwillingness or unpreparedness of hospitals to take on the responsibilities of sponsorship and active oversight of the full research portfolio being conducted. Governance structures, which include ethical review committees, should include an expertise in understanding the implications of trials where a sponsor is required in order to facilitate these studies and also to ensure appropriate and consistent oversight of all research activities conducted.

A strong commitment to research at a strategic level should translate into practical steps that facilitate research in the day-to-day workings of the hospital with the ultimate goal of the integration of research into standard of care. In each hospital there should be a senior figure who is responsible for implementing the research strategy.

The interface between hospital and research governance will be part of the research readiness assessment being conducted by MMI and ICRIN and the CRCs, with the support of the HRB. The DAMC, comprising UCD and the affiliated Mater Misericordiae and St. Vincent's University Hospitals, has made significant advances in the development of policies and structures for research governance and sponsorship. There is an opportunity to build on the progress already made in the DAMC and to extend the experience to a wider audience. MMI and ICRIN could play a useful role in building consensus on the detailed requirements for an effective approach to

research governance and sponsorship, with the outputs to become part of the HRG considerations in the implementation of the *HRAP*.

Commitment to Scientific Review

Each hospital should ensure that any research study conducted by or with its staff or involving patients of the hospital, is of the highest scientific standards. Under its research strategy, each hospital should commit to the scientific review of all research conducted in the hospital by independent experts. In many cases, the research study will have been reviewed independently through the scientific review processes of the HRB, the EU's Framework Programmes, the Wellcome Trust or other funding bodies and there is no need in such cases for further scientific review. In relation to studies sponsored by industry, a hospital should satisfy itself that the hypothesis and methods of the proposed research study are scientifically sound and have been reviewed by independent experts. There should be close engagement of the hospital and its affiliated academic institution to ensure good science. There is no need for each hospital to have its own independent experts when such an opinion on a proposed study has been provided to another hospital or review group, for example an external peer review, in particular for a multi-centre study.

In recent years universities stimulated by the HRB, Wellcome Trust and other bodies, have adopted procedures for ensuring good scientific practice in the conduct of research and for handling problems that arise when these standards are not observed. Each hospital should adopt the policy of good scientific practice in its affiliated academic institution.

Each hospital should actively track the research outputs and impacts (publications, PhD students, patents, new diagnostics, therapies, devices, use of bio-collections and numbers of staff undertaking post-graduate qualifications in clinical research) of the research conducted by or with the staff of the hospital. The changes to standard of care based on research findings should also be measured to understand and communicate the benefits of research to the wider community.

Commitment to Ethical Standards

Hospitals in Ireland have a strong commitment to ensuring high ethical standards in clinical research. This commitment is reflected in the number of research ethics committees and the association of most of these committees with hospitals. While legislation provides for a single ethical opinion for studies involving medicinal products that hospitals can accept or reject, no such provision is made for other clinical studies, including medical device studies. In Chapter 3 of the *Roadmap*, proposals are put forward to streamline the number of research ethics committees

and the processes used in order to facilitate research in all categories of clinical studies taking place on multiple sites. Whatever process is put in place for ethical review of research, hospital authorities remain responsible for ensuring that research conducted by or with its staff has a solid ethical basis

Hospital authorities should also adopt best international practice on other ethical issues that arise in relation to the conduct of research, such as, when it is not ethical for an employee of the hospital to seek or accept funding for research, or, the limits of any relationship that an investigator may have with a commercial sponsor of research in the hospital.

Site Specific Approval for Multi-Centre Investigational Medicinal Product Trials

Once ethical approval has been given for an IMP in multi-centre trials, a hospital has to decide whether or not to participate in a clinical study in a process known as 'site specific approval' (SSA). Different governance arrangements can affect the length of time it takes for a hospital to commit to participating in a particular study, posing particular challenges for multi-centre studies. Each hospital management has to satisfy itself that it is appropriate to participate in a study approved by a recognised ethics committee (REC), that the investigator and the research team will not be overstretched and that there are no issues in terms of compliance with regulations, indemnity, hospital procedures or recruitment. In the interest of facilitating research, it is important to streamline as far as possible the SSA that is required before a study with ethical approval from a REC can commence in a particular hospital. The remit for SSA should be clearly defined with agreed parameters and conducted in parallel with the single opinion process. A strict timeline, such as 35 days, should be set for the completion of the SSA process in all hospitals. This timeline for SSA should be adhered to by the hospital's chief executive officer and board of directors as part of its commitment to good research governance.

Research and HR Policy

The current contract for medical consultants provides that clinicians may, with the agreement of their clinical director, dedicate some of their contracted time to research. This provision is a major advance on the previous contract but it is still too early to assess its impact on dedicated time for research among medical specialists. The impact is likely to be influenced by the overall level of consultant manpower in the hospital and by the commitment of the clinical directors to research as a core function of the hospital. The Department of Health and Children should monitor the impact, if any, that the new contract has made to building the clinical research capacity in hospitals.

In the absence of a commitment to research at a corporate level in hospitals, it has been common practice for clinical investigators in hospitals to recruit nurses and other health professionals to assist them in conducting research studies. Such staff, who are recruited with funding from research grants and from industry, are typically employed on short-term contracts sometimes independently of the hospital's procedures for recruiting staff. Because of the short-term nature of the contracts, there has been a high turnover of such staff with the consequent loss of expertise and awareness of the contribution that such staff make to the conduct of clinical research. The ad hoc nature of these employment arrangements is one of the reasons for the low profile of research among the nursing profession¹⁷. Since the introduction of legislation protecting staff on short term contracts, some hospitals have found that they are obliged to offer permanent contracts to research staff who were previously employed on fixed term contracts. This legislation and the development of the CRCs provides an opportunity for hospitals to develop a new HR policy towards research staff which, on the one hand, supports research careers, defines reporting relationship and commits to on-going training, and on the other, sets out the procedures for the recruitment of such staff by the hospital. In those hospitals with a CRC, the opportunity now arises to group research staff as a core resource for all clinical investigators in the hospital. Such a development will enable good reporting relationships, broaden expertise and facilitate career paths for research nurses, as well as increase the capacity of the hospital to undertake high quality clinical research.

The HSE should include provision for research staff when determining employment ceilings for hospitals and should ring-fence these posts for research within the overall hospital staff complement.

All hospital staff are bound to observe the highest standards of confidentiality in relation to patient information and to adhere to the requirements of data protection legislation. Hospitals need to ensure that their policies and procedures encompass all research related activities of research staff.

Each hospital is obliged to promote a healthy and safe environment for its patients, staff and visitors. In relation to research, there is an added dimension to health and safety standards that needs to be addressed. Each hospital with laboratory based research activities, needs to promote GLP. The small number of people likely to be involved in gene therapy or stem cell research need to adhere to GMP. Furthermore, all hospitals that involve patients or healthy volunteers need to comply with GCP and other applicable legislation. Compliance is assured by the adoption of defined standards and continuing training of all those involved in research in the hospital. ICRIN could become a central resource for tools and training in these areas of research competence

and with the active involvement of hospitals, assist them in enhancing the research skills of their staff in line with regulatory requirements. ICRIN is in the process of validating tools and training in these areas of research competence with the CRCs to assist them in enhancing the research skills of their staff and affiliated research teams in the hospitals.

Research and Finance Policy

Research in hospitals is often funded from different sources and has not until recently been accounted for centrally by management. Hospital management tends not to know at corporate level how much research funding comes into the hospital, has little information on the cost of research conducted and does not have policies on costs and overheads. As part of its strategic commitment to research, each hospital should develop a finance policy to support research that includes a research account for all income from research, calculation of research costs and a policy on charging overheads. This financial policy should apply to all research conducted in the hospital and not only to research conducted through the CRC. The hospital should ensure that the financial processes supporting research are as transparent as possible. The Department of Health and Children and the HSE could encourage an explicit accounting of research funding by hospitals through service agreements, accounting standards and financial reporting.

Hospitals have to ensure that the research activities undertaken by its employees or using its facilities or involving patients of the hospital are appropriately indemnified. The inclusion of the word 'research' in the scope of the clinical indemnity scheme (CIS) managed by the State Claims Agency in 2007 has been helpful in making explicit that research activities of hospital investigators and associated staff are covered by the scheme. The provision for inclusion by the Minister for Health and Children of named CRCs as enterprises that are covered by the scheme is also helpful. The CIS covers negligence arising from protocol development and the clinical care of the patient participating in the research study. The CIS does not cover product liability, which is usually provided by the sponsor, and public liability which is provided by the hospital. The recent adoption by the pharmaceutical industry of a common agreement to cover product liability in industry-sponsored clinical studies has helped to streamline and simplify hospital sign-off on participation in clinical studies.

It is the responsibility of hospital management to ensure that each study is appropriately indemnified before it commences. The examination of indemnity issues usually takes place after a study has received ethical approval and is part of the process by which a hospital agrees to support a study. It is vital for the conduct of research in hospitals that there should be no unnecessary delay in the examination of indemnity issues. Each hospital should have the

competence to approve studies that do not give rise to any unusual risks while seeking advice from the State Claims Agency on particularly complex or high risk studies¹⁸.

ICRIN is in the process of developing costing models and risk-based trial operating models arising from its involvement in ECRIN. These models are being developed in collaboration with the CRCs and other research teams and should in turn lead to greater harmonisation of the costs of conducting clinical research across the country. Harmonisation of costs would assist those planning studies and trials by reducing the time required for negotiations at each site.

Insurance Requirements and National Patient Compensation Guidelines

All clinical research needs to be indemnified or insured. In relation to research involving medicinal products, Statutory Instrument (SI) No 190 of 2004 specifies that:

“‘insurance or indemnity’ includes a contract of insurance, a contract of indemnity, a guarantee, a surety, a warrant and a bond and which in any case shall be available to cover the liability of the sponsor and the investigator to provide for compensation in the event of any injury, loss or damage to, or the death, of any subject arising out of the arrangement for, or conduct of, the clinical trial and which the sponsor, or investigator, shall become liable to pay to such subject, or in respect of such subject, by way of damages or costs.”

The CIS operated by the State Claims Agency, provides explicit indemnity for the research activities of medical staff, and implicitly for other staff of hospitals that are listed as enterprises under the legislation¹⁹. Under the CIS, research studies must have the approval of the research ethics committee of the relevant hospital and, where required, of the Irish Medicines Board (IMB).

Scope of CIS Cover

The CIS covers claims from patients, in respect of personal injuries arising from participation in a clinical trial or other approved research project. In trials sponsored by external organisations, such as pharmaceutical companies, cover extends to injury only and does not cover product liability or claims arising from trial design or protocol. Indemnification against such claims remains the responsibility of the sponsor of the trial or research project. The appropriate indemnity must be secured from another source.

Where the clinical trial is designed by a hospital covered by the CIS, or by any of its employees (including investigator-led trials where the investigator is an employee), cover will extend to claims

arising from trial design or protocol. In all trials (whether sponsored or hospital/investigator led), it is a condition precedent to CIS cover that the ethics committee of the relevant hospital or state authority, together with the IMB, has approved the trial.

To be covered by the CIS, a hospital or state authority must be listed as an enterprise by the Minister for Health and Children for the purposes of the Scheme²⁰. The CRCs at the Mater Misericordiae University Hospital and St Vincent's University Hospital have been listed as enterprises for the purposes of the CIS and other CRCs can apply to be listed. All employees of the enterprise engaged in research are covered by the CIS, provided the research has ethical approval and if a clinical trial, has IMB approval in addition. The cover provided by CIS is underwritten for an unlimited amount.

CIS cover includes healthy volunteers in hospital-based research studies provided the studies meet the other criteria for cover. With a few exceptions, CIS cover does not extend to research conducted in private hospitals.

Under current arrangements, general practitioners involved in clinical research, including research initiated in a clinical research centre or hospital, are not covered by the CIS. As clinical research increasingly includes patients in the community as well as the hospital, consideration needs to be given to including general practitioners involved in studies under the CIS, where those studies meet the other criteria specified by the CIS.

Standard Indemnity Template for Clinical Trials

The State Claims Agency, in conjunction with the Irish Pharmaceutical Association, has drawn up a standard indemnity template, to be used by all hospitals and state authorities covered by the CIS, in relation to product liability arising from clinical trials²¹. This template has facilitated speedier approval by hospitals of participation in research studies, particularly multi-site studies.

The following summarises what indemnity or insurance is needed for clinical research depending on whether it is industry- or investigator-led:

Industry-led clinical trials/research

- Product liability and protocol liability are covered by the sponsor (for example, pharmaceutical company)
- CIS covers medical negligence in public hospitals
- Hospital covers public liability

Investigator-led clinical trials/research

- CIS covers clinical medical negligence in public hospitals
- CIS covers protocol liability
- Investigator must arrange for product liability
- Hospital covers public liability

In the case of the ICORG, CIS cover is extended exceptionally to cover investigators and hospital enterprises arising from trial design or protocol in relation to ICORG conducted trials and research. Effectively, the hospitals and the investigators will be treated, for purposes of the application of CIS cover, as if the trial was designed by the hospital of the investigator and where cover in those circumstances extends to claims arising from trial design or protocol.

Indemnity for Product Liability for Investigator-led Trials

The inclusion of the research activities of employees of listed enterprises in the indemnity provisions of the CIS has addressed most of the indemnity/insurance issues associated with clinical research. New CRCs can be listed by the Minister as enterprises for the purposes of the scheme. The standard template for indemnity for public liability has streamlined hospital approval for participation in research studies. An outstanding issue is indemnity for product liability for investigator-led studies, the one aspect of investigator led studies not covered by the CIS. ICORG acts as sponsor for some investigator-led clinical trials in cancer and is insured separately against injury to patients due to product liability. ICRIN could provide a similar service for investigators in other disease areas.

A university employee, for example a nurse, who is not employed in a listed CRC or who is not working under the supervision of a hospital employee covered by the CIS, is not covered by the CIS for clinical negligence arising from his or her participation in a research study. In Northern Ireland, research nurses conducting research in hospitals who are not covered by indemnity, are provided with honorary contracts by the trust body in whose jurisdiction they are collating patient data. For frequent access of research nurses or data managers to hospital data, the Northern Ireland model of a 'Research Passport' could be implemented where the university employee is given access to the data by the HSE or hospital authority.

Patient Compensation Guidelines

Industry sponsors of clinical studies in Ireland use the Association of the British Pharmaceutical Industry (ABPI) compensation guidelines for patients and healthy volunteers participating in clinical research²². Currently, there are no national guidelines in place in Ireland for compensation

for participants in clinical research, and in their absence, the ABPI guidelines are often referenced in clinical study documents such as informed consent forms and clinical trial indemnity forms. National guidelines should be established for compensation for participants in clinical research and this would be best developed by the Irish Pharmaceutical Healthcare Association (IPHA) in collaboration with the Irish Medical Devices Association (IMDA).

Research and IT Systems

High quality information on patients and biological samples is a core resource for translational and clinical research. Patients should be made aware of the hospital's commitment to research as a core mission of the hospital before, or, at the time of admission. They should be advised that they may be invited to participate in studies to advance knowledge of disease or improve outcomes for patients or, subject to strict rules of confidentiality, that their health information may be used for the same purpose. As with education, patients should be able to opt out of participation if they so decide. Each hospital should, subject to appropriate safeguards, facilitate access by researchers to information in the hospital and to the World Wide Web by way of the most up to date IT systems. Each academic hospital should commit to working with other such hospitals to develop a national informatics platform for clinical research, as recommended later in the *Roadmap*. Information on all research activities in the hospital should be collected and made available on a database that is open to all interested parties. As clinical research increases in hospitals, the information requirements of regulatory bodies such as the IMB, the European Agency for the Evaluation of Medicinal Products (EMA) and the US Food and Drug Administration (FDA) will grow. It is important that hospitals have the information systems to support the requirements of the regulatory bodies and that, as far as possible, there is a single point of contact in each hospital for the provision of information to such bodies.

Research and Innovation

Innovation, "*the process of turning research ideas into products, services and new ways of doing things that can build Ireland's knowledge economy and society*", has been identified by the Irish Government as a major challenge of this decade²³. In March 2009, Trinity College Dublin and UCD announced an 'Innovation Alliance' in which they committed their institutions to pursue innovation as one of the core missions of both universities. Other universities are also addressing the challenge of translating new ideas developed through research into new products and services. Hospitals are natural partners of universities in facilitating the translation of ideas into products and services that benefit patients. Hospitals are nurseries of innovation because all the ingredients for innovation are present: the commitment of hospital staff to improve outcomes for

patients by developing new diagnostics and therapies; the highly skilled clinicians who understand what is important to improve clinical outcomes for patients and who can influence the questions asked by researchers; the critical mass of patients willing to participate in studies to test new approaches; the links to academic researchers who are at the cutting edge of their scientific discipline; and, the presence of health professionals in training bringing the insights and energies of a new generation to the challenges of overcoming disease and disability. What is needed is a systematic approach to capturing the potential for innovation of these constituent parts. Each hospital, through its research strategy, should commit to partnering with its affiliated hospital in advancing innovation in the health sector, both for products and services, and new ways of organising and delivering care and treatment.

In relation to potential products and services hospitals need, as a first step, to have a policy to protect IP to make it worthwhile to bring an idea to market. Irish universities have developed policies to protect IP arising from the research conducted by their staff and each hospital should adopt the policy of its affiliated university. An IP policy does not compromise a PI's commitment to the publication of research findings but it aims to protect any IP arising from the research before publication of such findings. The technology transfer offices of the universities have also developed expertise in licensing and supporting start-up companies and it would make sense for each hospital to link closely with the technology transfer office of its affiliated university in extending such expertise to hospital based activities. Enterprise Ireland could encourage this linkage by supporting posts in the technology transfer offices dedicated to fostering innovation in the affiliated hospitals, thereby building on the existing expertise in technology transfer in the universities and colleges.

Each hospital should commit to facilitating clinical studies that have the potential to contribute to innovation, of both new products and services, and of new ways of organising and delivering care. Each hospital should review all its research processes from the point of view of how best to support the national goal of innovation. For example, unnecessary delays in the process of ethical approval or sign-off on indemnity cover, poor clinical information systems and difficulties in accessing a critical mass of patients in a reasonable time frame, and the absence of a central coordinating point for accessing clinical resources, are among the main reasons why it is not attractive for start-up or established companies to undertake studies on new products in Irish hospitals and why it is so difficult to undertake studies that would change the way care is organised and delivered. The HRG could play a useful role in agreeing metrics relating to research support in hospitals and in encouraging their adoption nationally. Such metrics could be used to measure change over time and to compare performance between hospitals. They would

also help to highlight the close link between hospital performance and support for government policies on innovation.

Recommendations

- Each hospital should develop a research strategy in close association with its affiliated university to reflect its commitment to research as a core mission of the hospital and assign responsibility for implementation of the strategy to a senior member of staff.
- MMI and ICRIN could play a useful role in building consensus on the detailed requirements for an effective approach to research governance and sponsorship, with the outputs to become part of the HRG considerations in the implementation of the *HRAP*.
- Where independent scientific review has not already been performed by funders or other peer groups, each hospital should make arrangement for the independent scientific review of research conducted in the hospital and ensure that the highest ethical standards are observed in all aspects of the conduct of research.
- The Department of Health and Children and the HSE should encourage each hospital to account separately and in a standardised manner for all research funded in the hospital. Each hospital should identify the costs of research and develop a policies on trial costing and research overheads.
- IPHA in collaboration with the IMDA should develop national guidelines for compensation for participants in clinical research.
- Enterprise Ireland should encourage the linkage between clinical research and innovation by supporting posts in the technology transfer offices of third level institutions dedicated to fostering innovation in the affiliated hospitals.
- The HRG should agree and encourage the adoption of metrics of research support in hospitals that could be tracked over time and the contribution of hospitals to government policies on innovation measured.

CHAPTER 3: IMPROVING THE SYSTEM OF ETHICAL APPROVAL

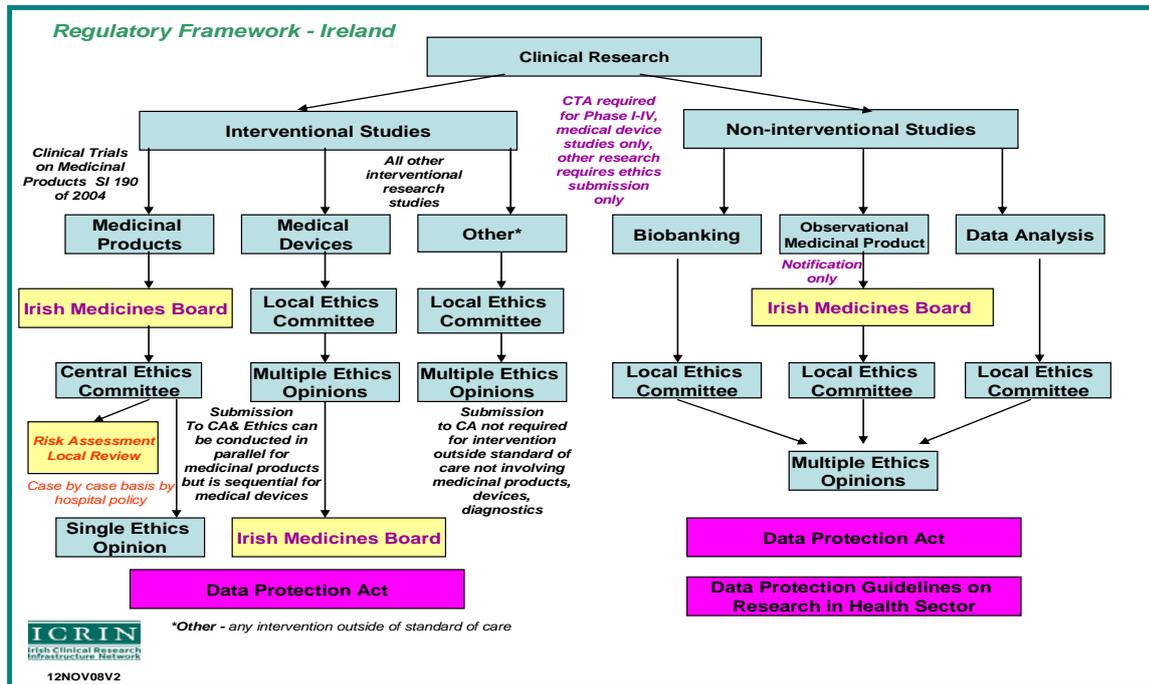
Overview

The ethical review of research involving human subjects is an important way of protecting people from harmful or poorly designed studies and of ensuring that participants are properly informed of the nature of the research to which they are consenting. The ethical review of clinical trials on medicinal products in Ireland is governed by the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations, 2004-2006²⁴. These regulations supersede the Control of Clinical Trials Acts 1987-1990 for clinical trials using medicinal products. Under this legislation, the Minister for Health and Children is the supervisory body for the ethical approval of studies falling under the scope of this legislation. The Minister has recognised 13 research ethics committees as competent to give a 'single opinion' for the ethical approval of a clinical trial on medicinal products. This means that an investigator who wishes to undertake a study of a medicinal product in a number of hospitals has to submit a proposal to only one of the RECs and that approval, if granted, is accepted by the other RECs. All other categories of clinical research (involving medical devices, surgical interventions, nutraceuticals or observational studies) on human participants must be submitted for review and approval to the ethics committee responsible for reviewing clinical research in each hospital in which the research is to be conducted. It is estimated that there are over 40 research ethics committees in addition to the 13 RECs for the purposes of providing a single opinion of a clinical trial on medicinal products²⁵. In the absence of legislation and national guidance, each ethics committee implements different requirements and operating procedures for review and approval, creating a major obstacle to multi-site or national research studies. The submission fees and timelines of committees also differ, adding to the complexity and cost of undertaking national scale studies.

The current organisation of ethics committees is the major roadblock to the effective conduct of clinical research in Ireland. Delays in the ethics committee application and approval process significantly hamper all categories of research thereby having an adverse influence on patients access to cutting edge therapies and diagnostics, on the ability of academia to undertake patient and disease focused research, and on the reputation of Ireland as a country in which industry-led research can be undertaken in a predictable fashion.

Diagram 2 overleaf illustrates the complexity of the regulatory and ethics framework for clinical research in Ireland.

Diagram 2 – Regulatory and Ethics Framework for Clinical Research in Ireland



Source: Clinical Research – Irish Situation Analysis, ICRIN/MMI, 2009

Recognised Ethics Committees

The 13 Irish RECs for the purpose of central review of clinical trials on IMPs are located throughout the country and are hospital-associated, with the exception of the Irish General Practitioner Ethics Committee and the three HSE area committees. A list of these recognised RECs is attached at Appendix IV. Sponsors may submit proposals for clinical trial projects to any one of the RECs for approval. All RECs are required to follow the *EU Guidelines for Good Clinical Practice*²⁶ and any subsequent amendments. In addition, the Department of Health and Children has issued *Ethics Committee Guidance on the Application for Recognised Ethics Committee Opinion and the Ethical Review of Clinical Trials on Medicinal Products for Human Use*²⁷. The aim of this guidance booklet is to assist investigators and RECs in their work by establishing SOPs relating to the submission of applications for an ethics committee opinion and the ethical review of clinical trials involving medicinal products for human use. The IMB has also provided ethics committee guidance in their publication, *Guide for Ethics Committees on Clinical Investigation of Medical Devices*, which is available on the IMB website to assist researchers.

A clinical trial may only be started or conducted in Ireland if:

- A recognised REC has issued a favourable opinion

- The IMB has granted an authorisation
- The sponsor or legal representative of the sponsor is established within the EU.

Applications to ethics committees are made by the chief investigator of the trial in the case of multi-centre trials. The chief investigator is an authorised healthcare professional who takes primary responsibility for the conduct of the trial. The chief investigator is not required to be an investigator at a particular site but may serve as the national coordinator for the study.

Ethics committee approval of clinical studies other than of medicinal products is not governed by the above legislation and thus requires approval by the ethics committee at each site of actual conduct, adding to the complexity, time and cost of research.

Towards a more Streamlined System of Ethical Review

A number of influential reports have recommended improved arrangements for reviewing the ethical aspects of research involving human subjects. The Advisory Council for Science, Technology and Innovation has recommended the streamlining and consolidation of clinical study review procedures to a reduced number of ethics committees with professional, paid members²⁸. The Cross Sectoral Clinical Trials Taskforce²⁹ recommended the establishment of a single ethics committee specialising in medical devices. The Irish Council for Bioethics published guidance in 2004 on operational procedures for RECs³⁰. A Report by the HSE has also drawn attention to the need to reduce the complexity of arrangements for ethical approval and to streamline procedures³¹.

Key questions that need to be addressed include:

- What is the optimum number of RECs required in Ireland to conduct effective ethical review of all types of clinical studies, taking into account the requirements of multi-centre single opinion review currently governed by the EU Clinical Trials Directive?
- How can processes be streamlined and all types of clinical studies be allocated to an appropriate ethics committee for review?
- How best to establish harmonised guidelines, equip members of ethics committee for their role, introduce standard operating procedures and working instructions and also application forms for new and ongoing review?
- How to involve more patient representation in the one-third cohort of laypersons required for the composition of RECs?

MMI welcomes the commitment in *The Smart Economy* that the proposed Health Information Bill will provide a legal structure for ethical approval for health research studies other than those covered by the Clinical Trials on Medicinal Products for Human Use Regulations 2004³². MMI also notes the action in the *HRAP* to streamline and consolidate ethical approval procedures through the Health information Bill in 2010³³.

Number and Role of Research Ethics Committees

A solution is required which will, on the one hand, ensure the highest standards of ethical review of research involving human subjects and on the other, will facilitate researchers to undertake studies in a number of sites, or nationally, in a timely and cost effective manner. In many respects, a model for what is required already exists in the requirements for the ethical approval of studies involving medicinal products. The number of research ethics committees nationally should be reduced to between six and eight, all of which should be recognised. These new RECs should be created to review all research involving health service patients, clients and healthy volunteers recruited for studies through the health service. Each REC would be competent to give a single opinion on the ethical aspects of the proposed study. With a favourable opinion, an investigator could commence the study through the health service, subject to SSA from participating centres. There should be oversight of the RECs by a national office, which would operate an on-line application and allocation process. The new RECs should not be affiliated to universities, hospitals or professional bodies but should have a national mandate. There should be an open and transparent system for the recruitment of members to RECs with the objective of involving a broad cross-section of professional and lay representation. These changes would need to be implemented in consultation with relevant stakeholders, such as current research ethics committees, hospitals (including private), universities and patient associations. The open recruitment process for membership of the newly established RECs would allow those involved in the current research ethics committees to apply for a role in the new structure.

Central Office for Ethics Committees

The Minister for Health and Children, who is already the supervisory body for research ethics committees providing single opinions for studies involving medicinal products under EU legislation, should establish a Central Office to oversee the proposed six to eight RECs with the necessary legal underpinning. A single ethical opinion from an appropriate REC should be required for any research proposal involving:

- a. Patients and clients of HSE funded services. This includes all potential research participants recruited by virtue of the patient's or client's past or present treatment by, or

use of, HSE funded services. It includes HSE funded patients and clients treated under contracts with private sector institutions

- b. Individuals identified as potential research participants because of their status as relatives or carers of patients and clients of HSE funded services, as defined above
- c. Access to data, organs or other bodily material of past and present patients of HSE funded services
- d. Foetal material and in-vitro fertilization (IVF) involving patients of HSE funded services
- e. Recently deceased individuals in HSE funded premises
- f. The use of, or potential access to, HSE funded premises or facilities
- g. HSE funded staff – recruited as research participants by virtue of their professional role.

The Central Office should be overseen by the Department of Health and Children to avoid potential conflicts of interest with research performing and funding bodies in the health service. The Central Office should provide an inclusive service, considering all research proposals for review, even if they fall outside the criteria above. The researcher should be seen as a customer of this service. The Central Office would have an important role in liaising with other research ethics committees (for example, in universities) in the transition period required for the development and operation of the Central Office

The Central Office would perform the following functions:

- Offer a secretariat service for researchers and research ethics committees by developing an on-line application process for researchers and allocating studies for review to the committee with sufficient resources and/or relevant expertise to review the proposal
- Organise training of members of ethics committees and researchers in the relevant regulations or guidelines, research methodology and other ethical issues
- Provide accreditation of ethics committees
- Agree parameters and a timeline for SSAs.

Membership of Recognised Ethics Committees

The membership of RECs should include people with appropriate qualifications and skills to assess the complexities of different types of studies, such as, biotechnology trials, advanced therapies, diagnostic studies, medical device and drug combinations trials, Phase 1 studies, the greater complexity in proof of concept and proof of principle trials and adaptive clinical trial models. Membership of the national RECs should be voluntary, with expenses paid where deemed necessary. The process for recruiting members must be open and transparent. One third of all membership should comprise lay people, with a strong representation of patients. The

definition of lay membership should be clarified by the proposed Central Office. The Central Office should ensure that training programmes are in place for members of RECs. ICRIN is developing a training programme and guidance documents to support the development and piloting of a single ethics committee application form which has been led by the DCCR partners and which can be subsumed into the Central Office when established.

Electronic Application Form

The Central Office should develop a common electronic application form for all categories of research. Ideally, this would be a self-deleting form which allows the user to move through it quickly. This form should be similar to that used by other ECRIN members and should be as similar as possible to the form which must be completed for the IMB, so that duplication of information is avoided.

Parallel Review by Ethics Committee and IMB of Medical Device Studies

The Cross Sectoral Clinical Trials Taskforce recommended provision for the parallel review of clinical investigations of medical devices by ethics committees and the IMB, on the model already in place for investigations of medicinal products³⁴.

The current requirement to obtain ethics committee approval from each site where the clinical investigation of the medical device is being conducted prior to submission to the IMB is an unnecessary obstacle to the conduct of clinical research on medical devices in Ireland. An REC should provide a single opinion for all categories of clinical research involving human subjects, including medical devices conducted in multiple centres, and there should be parallel review by the ethics committee and IMB of clinical investigations. MMI has been informed that the current legal framework does not prevent parallel review. It would be helpful if the Minister for Health and Children would issue formal guidance to the IMB and the ethics committees to encourage parallel review and promote a consistent approach.

Recommendations

- The Minister for Health and Children should establish six to eight national RECs to provide a multi-site single opinion review for all categories of clinical research involving the recruitment of participants through the health service.
- The Minister for Health and Children should establish a Central Office for Research Ethics Committees with the necessary legal underpinning, for the oversight and support of ethics committees in Ireland.

- The IMB should issue guidance to the research community and the ethics committees to encourage the parallel review of studies involving medical devices and promote a consistent approach.
- The Central Office should introduce an open and transparent process for the recruitment of members of the national RECs. Members should be paid expenses where necessary.
- The Central Office should develop an electronic application and allocation process for all categories of research proposals.

Consent and Standards in Research Conduct involving certain Patient Populations

There is a need to set criteria or minimum requirements for informed consent (oral and written) for all types of clinical research involving enrolment of healthy volunteers and patients. In addition, both within the context of clinical studies and outside, there is a need to consider informed consent standards for biomarker studies, non-interventional studies where biological samples are taken, biobanking and unspecified future use of human tissue, samples and data. It is understood that the forthcoming Human Tissue Bill will propose a legislative framework that will deal with some of these issues.

Definitions of Vulnerable Populations

There are multiple definitions of vulnerable groups contained in various regulations, policies and guidance documents yet there is no consensus on the involvement of vulnerable populations in research protocols. There are specific difficulties with the involvement of certain populations in research such as those with an intellectual disability or who are deemed to be incompetent adults. This is due to the fact that under Irish law, no adult can consent on behalf of another adult. The Law Reform Commission has published a report on vulnerable populations that touches on issues of consent³⁵. It is recommended that the proposed Central Office for Research Ethics Committees should have the responsibility of developing definitions of these patient populations and also of standards for their involvement in research, where appropriate. The Central Office should work with the groups in question including the service providers for people with intellectual disabilities to define criteria in accordance with best international practice. ICRIN could play a role in providing training to researchers and members of ethics committees on informed consent and in providing templates to foster best practice.

Informed Consent Process/Administration

Legislation does not require that a consultant physician personally administer the process of securing the informed consent of participants to study involving medicinal products. It is

acceptable to delegate the administration of the informed consent process to an appropriately trained member of the research team including the research nurse.

The ABPI guidelines are referenced in a number of essential documents for Irish clinical trials including the informed consent form and the HSE Clinical Trial Indemnity Form. While the guidelines are robust and appropriate, it would be better if there were guidelines developed that are specific to this jurisdiction. IPHA and the IMDA should adopt equivalent guidelines for this jurisdiction.

Recommendations

- The Central Office overseeing national ethics committees should define vulnerable populations for the purposes of research and set standards for involvement in research, including for informed consent, taking into account the current constraints whereby the legal system does not permit one adult to consent on behalf of another.
- The Central Office should consider issues of informed consent for future unspecified use of data and bio-resources in the context of the ongoing national initiatives such as the implementation of the National Cancer Biobanking report.
- IPHA and the IMDA should review the ABPI guidelines for compensation involving medicinal product and adopt equivalent guidelines for this jurisdiction.

CHAPTER 4: BEST PRACTICE IN REPORTING CLINICAL RESEARCH AND USE OF PATIENT INFORMATION AND SAMPLES

Overview

The best clinical research is characterised by the highest ethical standards in the publication of results, in the way in which information about patients and volunteers is collected and used and in the collection and storage of human biological material. These standards are set in some cases by agreed guidelines and in others by legal frameworks. This chapter examines best practice in relation to the registration and reporting of the results of clinical research in assembling and using patient information and biological collections, and recommends how some of the issues arising should be handled in this country.

Registration and Reporting of Results

The registration of all trials and relevant research results for public access is becoming the international standard in order to ensure that scientific information is shared and can be built upon by other researchers. The Consolidated Standards of Reporting Trials or CONSORT is intended to improve the reporting of a randomised controlled trial (RCT), enabling readers to understand a trial's design, conduct, analysis and interpretation and to assess the validity of its results. The main product of CONSORT is the CONSORT Statement, which is an evidence-based, minimum set of recommendations for reporting RCTs³⁶. The CONSORT Group is an international group of trialists, methodologists and medical journal editors who work together to improve the reporting of different types of health research and to improve the quality of research used in decision-making in healthcare. The Consort Statement emphasizes that better reporting can only be achieved through complete transparency from authors.

Considered an evolving document, the CONSORT Statement is subject to periodic changes as new evidence emerges. The CONSORT *Explanation and Elaboration Document*³⁷ explains and illustrates the principles underlying the CONSORT Statement. It is recommended that it is used in conjunction with the CONSORT Statement. In addition, 'Extensions' of the CONSORT Statement have been developed to give additional guidance for RCTs with specific designs, data and interventions. The CONSORT Statement is endorsed by prominent general medical journals, many specialty medical journals and leading editorial organizations.

Journals linked to the International Committee of Medical Journal Editors (ICMJE) require, as a condition of consideration for publication in their journals, registration in a public trials registry. In

order to comply with the ICMJE requirement, clinical trials must be registered prospectively on a clinical trials registry. The ICMJE³⁸ has adopted the World Health Organisation (WHO) definition of a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Health-related interventions include any intervention used to modify a biomedical or health-related outcome (for example, drugs, surgical procedures, devices, behavioural treatments, dietary interventions and process-of-care changes). Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. Purely observational studies (those in which the assignment of the medical intervention is not at the discretion of the investigator) will not require registration.

The CONSORT principles and definitions should be considered for adoption by research funders and agencies. It would be important that in each CRC, clinical studies are assessed for compliance with these definitions and those studies fitting the criteria registered appropriately. There are many registries available. The WHO has an International Clinical Trials Registry Platform³⁹, the mission of which is to ensure that a complete view of research is accessible to all those involved in healthcare decision-making. This will improve research transparency and will ultimately strengthen the validity and value of the scientific evidence base.

It is not necessary to specify which registry should be used as each has different areas of specialty. The ICMJE accepts all those registries that are listed with the WHO. Those studies requiring registration should be listed on one of the WHO approved registries as these comply with ICMJE requirements. There may be a role for ICRIN to play in providing a national portal for all types of research to the WHO website.

Research and the Data Protection Acts

The Health Information Strategy (2004) promised “*proper information governance arrangements on a system-wide basis throughout the Irish health system*” through “*a set of rules to ensure full and proper use of information while fully protecting the privacy of the individual*”. The Strategy also identified health research as an area that needs facilitating and commented that, “*it is essential that there is a robust legislative basis to support appropriate research activities, together with inbuilt safeguards to protect privacy and confidentiality*⁴⁰”.

Ireland has a highly developed legal framework for the protection of personal information concerning individuals. This regime needs to be balanced by an equally effective legal framework for the sharing and use of individual health information for the common good. There is no inherent

conflict between the aims of data protection legislation and the use of health information for the common good – data protection legislation already provides for the exclusion of health information under certain conditions. While the *Data Protection Guidelines on Research in the Health Sector (2007)*⁴¹ issued by the Data Protection Commissioner permit the use of identifiable data without consent for research purposes within an institution (such as a hospital) under the remit of a data controller, they do not permit use by third parties such as staff of a university or the aggregation of data from a number of data controllers into a single database. The Data Protection Commissioner, in the same Guidelines, recognises the limitations of the Data Protection Acts in providing a public good exemption for health research and recommends that where full coverage of a population is required, specific legislation be introduced for such databases with inbuilt safeguards.

MMI, in a submission to the Minister for Health and Children on the *Discussion Paper on the proposed Health Information Bill*⁴², welcomed the initiative that would place the processing of health information on a secure footing and introduce clarity and consistency in the legal framework within which this processing occurs. Such legislation is urgently needed to address the many obstacles to the use of information to improve the quality of care for patients, to protect the health of the population and to build capacity for health research that will benefit patients and facilitate economic and social development.

As well as providing “a sound base for the use of information throughout the health system so as to provide best patient safety and advice”⁴³, the policy objectives for the Bill should facilitate the use of information for audit, surveillance, evaluation and research to improve the quality and effectiveness of health care and services and the overall health of the population. The ‘health system’ should be defined to include institutions involved in teaching health professionals and in conducting health research.

A Legal Framework for Patient and Disease Registries

The *Data Protection Guidelines on Health Research* advise that obtaining the consent of the person to the intended use of his or her data is the most straightforward way in which access to patient identifiable information for research or clinical audit purposes can take place in accordance with the requirements of the Acts. The *Guidelines* note that the key issue is respect for the patient’s reasonable expectation that their health information will be kept confidential and not used or disclosed without their consent other than to those directly involved in patient care and any directly related activity.

The *Discussion Paper on the Proposed Health Information Bill* refers to the need for a legal framework for patient and disease registries. Such registries (for example for cancer and cystic fibrosis) are vital for monitoring outcomes and quality of care in the relevant patient populations and are a major resource for research into new and more effective diagnosis and treatment. Such registries cannot be developed on the basis of anonymised information, as it is necessary to follow patients over time to link episodes of care and to avoid double counting. While individual consent to participate in the registry is desirable, it is often not feasible to establish a registry that does not have full coverage of the population affected. Instead the emphasis in the regulation of such registries must be to protect the privacy of each person included in the registry by high levels of security, a strong ethos of confidentiality and penalties for any breach of trust by those involved in managing the registry. The confidentiality of the patient's information has to be protected and their health information should only be accessed and used under strict safeguards. The assurance of confidentiality could be maintained by ensuring that personnel accessing confidential health information are required by their contract of employment to adhere to the highest standards of confidentiality in accessing and using patient data. Despite the availability of the *Data Protection Guidelines*, there is a general lack of understanding among researchers of the relevant requirements of data protection legislation. National training by the Office of the Data Protection Commissioner on this topic would be of enormous benefit.

Another feature of creating a patient or a disease registry for such conditions as cystic fibrosis and multiple sclerosis is the need to aggregate data from many hospitals. The creation of such registries is often feasible only if undertaken by a third party. Under data protection guidelines, a data controller in a hospital is precluded from providing identifiable patient information to a third party (other than to the National Cancer Registry).

At present, the National Cancer Registry is the only disease registry to have a statutory basis. New legislation should provide for the establishment and maintenance of a registry without individual consent (on the model of the National Cancer Registry), where the promoters can demonstrate that:

- It will contribute to patient or population health through facilitating the planning and delivery of services, surveillance, audit and/or research
- It has appropriate governance structures and standards to protect the privacy of the individuals included and the confidentiality of their information
- It requires complete or almost complete coverage for the purposes of accuracy, and
- It is not possible to achieve this level of coverage on the basis of individual consent.

The legislation should provide a mechanism for approval of such registries, possibly by the Minister for Health and Children or the Health Information and Quality Authority (HIQA), and custodianship by an institution. The legislation should provide for a list of all approved registries to be maintained and for the categories of information held in each registry to be made public. The legislation should protect those involved in transferring information to the registry, or those managing the registry within the terms of reference of those registries, from any civil action or action under data protection legislation.

Legislation should permit information from two separate registries or biobanks (such as that collected by the National Cancer Registry and the Prostate Cancer Research Consortium) to be collated for research on cancer or to understand more about outcomes of treatment for patients. The linkage of information from two information sources such as the National Cancer Registry and the Prostate Cancer Research Consortium needs to balance risk to patient confidentiality versus the benefit to be gained to improve care or outcomes for patients.

In the UK, the Patient Information Advisory Group (PIAG) is enabled by legislation to make binding decisions with respect to the use of health data. The legislative mandate of the PIAG allows a broader view of the benefits of linking information than is permitted under data protection legislation. The PIAG examines each proposal to link patient data to ensure that it is an acceptable use of the data and that people's rights are protected. The proposed Health Information Bill offers an opportunity to provide a similar legislative framework in this jurisdiction to permit the linking of patient data where such linkage will lead to improved care or better outcomes for patients.

Research and a Unique Patient Identifier

The accuracy of patient and disease registries depends on being able to link data from different sources to individual patients. A UPI is essential to identify and collate data accurately and to avoid error arising from duplication of information. The proposed Health Information Bill provides an opportunity for the Minister for Health and Children to provide a legislative framework for a UPI.

A Legal Framework for Biobanking

A number of European countries including Estonia, Norway, Sweden, Latvia, France, the UK and Spain have enacted legislation to regulate the collection, storage and use of human tissue. The Human Tissue Act 2004 regulates biobanking practices in England, Wales and Northern Ireland and no person can store or use human material as defined under the Act without a license from

the Human Tissue Authority⁴⁴. There is no comparable legislation governing the collection, storage and use of human tissue in Ireland. To address this matter in 2009, the Department of Health and Children published the discussion document on a draft Human Tissue Bill⁴⁵ which will provide the much needed legal framework to support the use of human tissue for research purposes. It is important that the proposed legislation is harmonised as far as possible with similar legislation in other European countries to facilitate research collaborations involving human tissue across the EU. As proposed, the Human Tissue Bill will recognise informed consent of the donor as the core principle for research involving human tissue. Donors could give general consent to include future, unspecified uses, in recognition of the significant pace at which research develops and would avoid donors having to be re-contacted for each study involving their biological material.

While individual informed consent is standard practice in establishing and developing current biobanks, there are a number of situations that need clarification in law. Some biobanks were established before consent became standard practice or before data protection legislation was passed. Rather than discard valuable biological material that could improve patient care and improve healthcare, the use of such collections for audit and research should be given the protection of law. Under the proposed Human Tissue Act 2009, custodians of biobanks will be institutions rather than individuals. The proper regulation of the biobank is critical to ensure appropriate use over time. The proposed Human Tissue Bill provides for the registration and regulation of biobanks and, when implemented, will address some of the current governance deficits. It would be helpful for clinical research if the proposed legislation permitted individual information from a registered biobank to be linked with data from an approved patient registry where there is a strong scientific case for linking the data and where there is approval by a REC.

Recommendations

- Research funders should promote the CONSORT guidelines for all relevant research trials and studies in Ireland. They should also recommend how information on studies which are registered on a WHO listed site is made available, so that all those involved in health care decision-making have access to information on all clinical studies taking place in Ireland.
- The Minister for Health and Children should provide for the registration and regulation of patient registries in the proposed Health Information Bill, including registries without individual consent, where the proposed registry will produce a demonstrable benefit to health. The Bill should also provide a framework to permit the linking of patient data where such linkage will lead to improved care or better outcomes for patients.
- The Minister for Health and Children should provide for the introduction of a unique patient identifier in the Health Information Bill.

- The Office of the Data Protection Commissioner should support the provision of training for data managers and researchers on relevant data protection legislation and guidelines. Anyone accessing personal health information should be required to undergo such training.
- Health service and associated academic employers should ensure that the employment contracts of personnel accessing personal health information require adherence to the highest standards of confidentiality in the access and use of patient information.
- The Minister for Health and Children should provide a legislative framework for the registration and regulation of biobanks in the proposed Human Tissue Bill.

CHAPTER 5: SAFETY REPORTING AND INVESTIGATIONAL PRODUCT MANAGEMENT

Overview

Safety reporting for medical devices is governed by three medical device directives. Drug accountability and safety reporting requirements are governed by the *European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations, 2004-2006*⁴⁶. These regulations supersede the *Control of Clinical Trials Acts 1987-1990*. The competent authority in Ireland overseeing safety reporting pertaining to clinical trials on medicinal products and medical devices is the IMB. In addition, it is the competent authority for the *EU Tissue and Blood Directives*⁴⁷. All other categories of research, such as surgical, non-interventional and radiotherapy trials on human participants, are not governed by a competent authority and as such no national policy or practice exists.

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 product authorisation or used in a different way, for example 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. IMP is an area where many non-commercial studies fail inspections by competent authorities due to weaknesses of IMP management, certification, and stability and in the requirement for a qualified person to take legal responsibility for IMP release and recall measures.

Definition of Investigational Product for Clinical Studies

SI No 190 currently defines IMP as:

“ ‘investigational medicinal product’ means a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including a medicinal product that is already the subject of a marketing authorisation, but –:

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

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

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

Whilst this predominately applies to pharmaceutical products, clarity is required in relation to situations where there are combinations of pharmaceutical, complementary, herbal and nutritional medicines.

In addition to the *European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations, 2004-2006*, the requirements have to take into consideration the following pieces of legislation and guidance documents. The varying definitions of IMP in use in Europe can cause additional confusion where trials are conducted in multiple countries.

Medical Device Definitions

The term 'medical device' covers all products, except medicines, used in healthcare for the diagnosis, prevention, monitoring or treatment of illness or disability. A medical device refers to any instrument, apparatus, appliance, software, material or other article whether used alone or in combination, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of:

- diagnosis, prevention, monitoring, treatment or alleviation of disease
- diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap
- investigation, replacement or modification of the anatomy or of a physiological process
- control of conception.⁴⁸

Clarity and guidance would be useful where a medical device is being used together with a drug in a clinical trial, as it is not always clear whether the trial falls under medical device or IMP legislation.

National guidance on Investigational Product Management

The *International Conference on Harmonisation Good Clinical Practice (ICH-GCP) Guidelines*⁴⁹ requires full drug accountability for the IMP from manufacturer to destruction or return. Responsibility for investigational product accountability rests with the investigator or institution. For investigator-led trials this can lead to a significant resource and knowledge requirement due to requirements which include:

- Records of the product's delivery to the trial site, the inventory at the site, the use by each subject and the return to the sponsor or alternative disposition of unused product (where applicable)

- Storage specifications (temperature monitoring, limited secured access)

For functional foods, the relevant legislation is Regulation (EC) 1924/2006 of the European Parliament and of the Council of 20 December 2006 on nutrition and health claims made on foods⁵⁰.

In relation to herbal and alternative medicines, the IMB has been nominated as the competent authority for the implementation of European legislation on the registration of traditional herbal medicinal products. The legislation came into force in July 2007⁵¹. Under this legislation, the applicant is required to present a bibliographic review of safety data, together with an expert report. Regulatory authorities, where justified, may ask for more data in order to assess the safety of the product.

In addition, in accordance with Article 17 (1) and (2) of SI No 540 of 2007, each applicant is required to have a pharmacovigilance system in place to monitor the safety of traditional herbal medicinal products once they have been placed on the market. There is no requirement for formal clinical trials to be carried out.

In the case of homeopathic medicinal products, a product registration may be granted where satisfactory evidence of safety and quality has been established and it must be sufficiently diluted to guarantee safety⁵². Therefore, there is no requirement to conduct clinical trials for homeopathic medicines that fall within the scope of the guidelines.

It would be appropriate that a national guidance document on the monitoring of side effects for all of the above categories be developed. This needs to be done in consultation with the relevant national bodies with a remit in this area, such as the IMB, the Food Safety Authority of Ireland (FSAI) and the National Standards Authority of Ireland (NSAI). A national co-ordinating group such as ICRIN or another independent group, would have a role to play in the drafting of this guidance document in association with the relevant national bodies.

Pharmacovigilance in Academic Clinical Studies

For academic studies in hospital and in primary care, there is a clear need for procedures to be developed for pharmacovigilance management and regulatory reporting. For academic trials, the current rules require trained personnel access to Eudravigilance. Eudravigilance is the pan-European data-processing network and database management system for the exchange, processing and evaluation of adverse drug reactions that may result following the use of one or several medicinal products. It is designed for the electronic transmission of Individual Case Safety

Reports (ICSRs) related to medicinal products authorised in the EU, and Iceland, Liechtenstein and Norway. The objective of Eudravigilance is to support pharmacovigilance activities and responsibilities which are shared between marketing authorisation holders and competent authorities in the EEA, such as, the IMB. It also aims to improve pharmacovigilance on a European scale, providing more consistent and detailed data and faster access to the relevant information to the competent authorities⁵³. In addition, significant resource is required for legislative compliance in serious adverse event and suspected unexpected serious adverse reaction reporting to competent authorities, ethics committees and investigators.

The stringent requirements for pharmacovigilance reporting mechanisms contained in the regulations for IMPs are difficult to achieve in the context of academic clinical trials. In addition, there is a need to ensure greater education of the medical professionals and ethics committees generally in the area of pharmacovigilance. The Minister for Health and Children, as the supervisory body for RECs, should ensure that training in pharmacovigilance is available for members of research ethics committees. ICRIN could play a role in providing training and guidance documents for researchers and members of research ethics committees on pharmacovigilance.

Recommendations

- ICRIN should provide training and guidance documents on pharmacovigilance for members of research ethics committees and to health professionals engaged in research.

Harmonisation of Definitions of Adverse Event and Safety Reporting Requirements for Non-Drug/Non-Device Clinical Studies

At present, adverse event definitions and reporting requirements apply only to drug and medical device trials. Other trials, for example surgical and radiotherapy trials do not require reporting to any regulatory authority. The level of adverse event reporting requirements in these studies is dictated by the relevant ethics committee(s). This does not allow for central capturing of adverse events on a national level. In the UK, the Central Office for Research Ethics Committees has developed a national procedure for adverse event reporting of adverse events in all clinical studies⁵⁴. The recommended Central Office for Research Ethics Committees in this country should provide similar guidance in this country.

Recommendations

- The proposed Central Office for Research Ethics Committees should develop national guidance for the reporting of adverse incidents in those clinical studies outside the scope of regulations.

CHAPTER 6: DATA MANAGEMENT IN CLINICAL RESEARCH

Overview

There are differing levels of requirements for data management depending on the type of research that is being conducted, ranging from excel spreadsheets to GCP compliant data management systems for clinical trials. The objective of a clinical research data management system should be to produce credible and reliable data in compliance with GCP. Developing such a system is a key objective in creating a coordinated, high quality infrastructure for clinical research in Ireland. Relevant guidance on what is required includes the ECRIN report on GCP compliant data management⁵⁵ and the Clinical Data Interchange Standards Consortium (CDISC)⁵⁶ standards on electronic source documents. A national data management capability for translational and clinical research would maximise the return on investment in physical infrastructure and highly trained personnel in CRCs.

Data Management Plan

Many aspects of data management should be included in the process of developing a clinical research protocol. Data management principles and techniques should be part of the study design, and not added on after the study has started. The following key elements of data management should be considered in the context of each clinical research project:

- Study design
- Epidemiological advice
- Statistical input
- Source data extraction
- Data validation
- Database and case report form design
- Data analysis

Study Design

Study designs need to be in line with current good research practice guidelines and conform to international guidelines for good study design such as the CONSORT statement⁵⁷ and the *ICH Guidelines on Statistical Principles*⁵⁸. Good study design at the start of the protocol development procedure is vital to the success of the study. It is not ethical to enrol a patient in clinical research study if the design is inappropriate or unlikely to produce a significant result.

This study design phase should include detailed discussions and consultations with a qualified biostatistician to ensure that the study proposed will allow a statistically significant outcome to be reached. Issues such as randomisation and blinding also need to be considered at this stage. Those public bodies funding research should require a data management plan to ensure that research money spent is good value for the taxpayer.

Quality Assurance/Quality Control

All steps of the process from design, database production, data collection, data validation, analysis and reporting must have quality control processes associated with each step.

Monitoring as an appropriate quality control tool, in particular, source data verification must be considered for all studies. Consideration should be given to one CRC checking another's data as an approved quality control procedure.

Analysis and Reporting

A biostatistician should be involved in the process of analysis and reporting on the results of the study and a data analysis plan must be included in the protocol

Procedures need to be developed about appropriate integration of data from different systems, for example, integrating hospital laboratory data with CRC data. In addition, it should be possible to integrate data from different hospitals and to interrogate databases.

A national data management facility needs to be developed that could analyse and report on multi-centre trials with appropriate national software for analysis and reporting, rather than replicating this activity at all centres.

A data report must be ICMJE compliant and the results of all clinical trial reports should be available in the public domain, for example, in public clinical trial registries.

Personnel Requirements

A high level of expertise is required to set up good data management processes in clinical research. The Advisory Council for Science Technology and Innovation has advised that core competencies required to achieve good data management practices are those of epidemiologists, biostatistician, research nurses and IT experts skilled in clinical research⁵⁹. A national clinical research infrastructure element should provide the necessary expertise for high quality data design and management to support clinical research investigators.

Data Management Processes

A number of data management processes should be standardised to facilitate quality assurance and multi-site studies in Ireland. Data management processes in the following area are being validated by ICRIN, the DCCR and a number of other CRCs and research teams participating in the research readiness evaluation:

- System (evaluation, configuration, change control, security)
- Database development (including CRC design, validation, programming and standards)
- Data protection
- Data security (data entry, back-up, blinding, disaster recovery, archiving)
- Training (job specs, minimum qualifications, education)
- Quality management systems

Recommendations

- Every clinical investigator should develop a data management plan as part of the protocol development process before the clinical research study starts.
- The HRB and HSE should support the development of a national data management facility to analyse and report on multi-centre trials with appropriate national software for analysis and reporting.
- ICRIN should facilitate adoption of SOPs for data management by all CRCs.

CHAPTER 7: CLINICAL STUDY MONITORING

Overview

Monitoring is a key quality step for all clinical research. The purpose of monitoring is to assure the safety and well-being of patients and the integrity of data from clinical research studies and trials. All clinical research studies and trials should include an appropriate monitoring component in accordance with the principles of ICH-GCP and relevant legal or regulatory requirements.

Monitoring of clinical trials under the EU Directive and SI No 190 of 2004 is an onerous task and has significant resource implications for the sponsor, particularly if the sponsor is an academic. This chapter is concerned with how effectively to manage and streamline the process of monitoring. In addition, the monitoring requirements for medical device studies and other studies that fall outside the legislation such as surgical and radiotherapy studies are also considered.

Current Data Monitoring Tools and Strategies

All trials on medicinal products under SI No 190 of 2004 are currently required to be monitored using ICH-GCP criteria. Medical device studies are usually monitored to this standard. The extent and frequency of monitoring is described as follows, per ICH GCP:

“The sponsor should ensure that the trials are adequately monitored. The sponsor should determine the appropriate extent and nature of monitoring. The determination of the extent and nature of monitoring should be based on considerations such as the objective, purpose, design, complexity, blinding, size, and endpoints of the trial. In general there is a need for on-site monitoring, before, during, and after the trial; however in exceptional circumstances the sponsor may determine that central monitoring in conjunction with procedures such as investigators training and meetings, and extensive written guidance can assure appropriate conduct of the trial in accordance with GCP. Statistically controlled sampling may be an acceptable method for selecting the data to be verified”⁶⁰.

Each sponsoring company currently has its own procedures in this regard and the level and frequency of on-site monitoring can vary considerably as a result. Equally, the regulatory bodies have not produced a detailed guidance in relation to a monitoring plan for clinical trials but at the same time it has been reported that inadequate trial oversight and monitoring is frequently cited as a finding of GCP inspections.

Therefore, there is a need to identify a position on study monitoring which would form a common convention for industry sponsors, investigator-led studies and regulatory and research ethics committees.

There are a number of monitoring tools available to assist in the process of monitoring. When developing a monitoring plan, a combination of these tools would be considered appropriate depending on the nature of the study.

Remote monitoring can include:

- Trend analysis
- Data Safety Monitoring Committee oversight of data (including interim analysis)
- Requirement on-site to fax to data centre anonymised copies of key data, for example, signed but anonymised informed consents.

On-site monitoring can include:

- Traditional on-site monitoring visits by monitors to include source data verification of key data
- One colleague quality checking another's work, on a pre-planned basis
- One CRC research nurse (or other research personnel) monitoring another clinical research centres data

The purpose of monitoring is to protect the patient in research and ensure the integrity of the data collected in the course of the study. This applies to any type of research where non-compliance should be assessed. Monitoring is a quality step and should be part of good research practice. Some form of quality control or assessment should be conducted to ensure rigour and robustness of data. Monitoring strategies are currently driven by the nature of the institution or organisation and not the study type. Funding for monitoring is often a key factor in the implementation of a quality check within the conduct of the study.

Research funding agencies, such as the HRB and charities supporting research, should provide for quality check and monitoring resources within grant applications for translational and clinical studies. As the study design is assessed by scientific peer review, so too should the grant allow for resources to assess the integrity of the study data. Currently, peer review only focuses on the scientific and medical validity of the study design. Follow-up reports indicating appropriate management of the study should be considered necessary.

While the term 'sponsor' has a legal origin in the European Clinical Trial Directives 2001 and SI No 190 of 2004, the concept is a useful one to apply to all types of clinical research. The term 'sponsor' refers to the person or organisation with overall responsibility for the management, financing and overall coordination of resources (including delegation or contracting) in a clinical research study. There is no legislation that defines a sponsor for trials conducted which are not covered by SI No 190 of 2004 but the IMB Act⁶¹ and the Non-Fatal Offences Against the Person Act 1997 may apply. Not all research requires the same level of regulation as commercially-driven research and it is important to implement the correct level of trial oversight and monitoring to assure the safety and well-being of participants and data integrity.

The implications of sponsorship usually distinguish between industry and academia. The same level of monitoring is required for both industry and academia under SI No 190 of 2004 to ensure patient safety and well-being, integrity of data and overall compliance with relevant legislation and guidelines. All clinical research, however, requires a level of monitoring appropriate to the type of research being undertaken and not the organisation that is conducting the research. It is critical that the need to monitor all clinical research studies to an appropriate level is recognised by non-commercial or academic investigators.

Where industry provides grant aid for a study, there is necessity for a clear delineation of responsibilities to ensure there is no ambiguity in relation to sponsorship and oversight of the research activity.

Recommendations

- Research funding bodies, such as the HRB and charities supporting research, should ensure provision for review of quality management oversight in grant applications for clinical research projects.
- Each clinical investigator should ensure that all clinical research studies have a level of monitoring appropriate to the type of research being undertaken.

Criteria for Assessment of Risk in Clinical Study Monitoring

A risk-based approach to the monitoring of all clinical studies is reasonable and should apply across the spectrum of clinical research to be undertaken. Requirements for monitoring are dictated for those studies conducted under SI No 190 of 2004 and medical device legislation. Other than these studies, the requirements for monitoring are unclear. For academic research, it is suggested that a formalised approach should be developed to assure the quality of the data.

The best approach for most studies is a combination of remote and on-site monitoring. The development of a suite of tools to assess the degree of monitoring required is suggested to decide *a priori* the appropriate approach to monitoring on a study-specific basis.

Commercial and academic research organisations are developing monitoring strategies based on the level of risk involved in the research activity as an appropriate and cost-effective solution to the level of monitoring for non-commercial sponsors. These groups have used various different risk assessment tools to establish criteria for low, medium and high risk studies⁶².

A risk-based approach to the monitoring of clinical trials on medicinal products and clinical investigations on medical devices would be greatly facilitated by the provision of anonymous GCP inspection findings by the IMB. Awareness of those items considered of paramount importance found on inspection by the competent authority would greatly enhance the conduct of clinical studies and assist sponsors in designing quality and monitoring plans.

If the defined risk is considered during the design of the clinical study, an algorithm-based approach could be developed. The defined risk could be assessed by literature review and observations. A precedent exists in the area of Devices and Engineering which employs Failures, Modes and Effects Analysis which seeks to define possibilities and scenarios ahead of time. The following are some elements that should be considered in the development of guidance documents:

- Sponsor-related risks
- Nature of construction of sponsorship - academia, industry, partnerships
- Significant regulatory burden
- Non-compliance to legislation
- Potential for litigation by patient or investigator
- Ambiguous inclusion or exclusion criteria
- Potential for poor quality data or fraud
- Vulnerable study participants
- Subject-related risks
- Worsening of the disease or illness
- Adverse events causing other symptoms or sequelae
- Potential for ineligible patients to be enrolled
- Improperly conducted or documented informed consent
- Potential for poor quality data
- Complex inclusion or exclusion criteria or clinical treatment complexity

- Confidentiality
- Dignity
- Future use of data, for example, personal genetic data
- Investigator-related risks
- Non-compliance with legislation
- Lack of availability of high quality data
- Ambiguous inclusion or exclusion criteria
- Significant legal or regulatory burden
- Lack of availability of high quality data
- Potential for ethical dilemmas

Recommendations

- ICRIN should validate a risk assessment tool in the research readiness pilot programme with research teams and should promote a risk-based approach to the monitoring of clinical studies, based on the output of this exercise.

Harmonisation of Processes for Monitoring Clinical Studies

Under current legislation monitoring of clinical studies is required in relation to the trials of drugs and certain categories of medical devices. The level, degree and type of monitoring requirements vary enormously. In addition, studies outside these categories do not have any legal requirement for monitoring. Is it possible to harmonise procedures for the monitoring of all types of clinical studies?

As outlined above, it is desirable to establish the level and type of monitoring required on a study-by-study basis. A monitoring plan should be developed in line with the study protocol before the study commences. As part of the study review process the scientific peer review could include the monitoring plan and provide comments as appropriate. In this way harmonisation of approaches to monitoring would evolve over time.

In addition, SOPs should be developed by ICRIN on behalf of the CRCs for risk assessment techniques and monitoring requirements for clinical studies.

In the short-term, simple steps could be taken to improve communication for monitoring and other purposes. For example, many research nurses do not have email addresses assigned to them within their institution and, in the era of electronic communication, this is a major handicap to the effective conduct of clinical studies.

There are also different understandings of the terminology used in clinical research, such as 'source data' and 'PI'. ICRIN could play a useful role by developing a glossary of terms used in clinical research that could be used by those involved in conducting research and assessing level of monitoring requirements for studies.

Recommendations

- Each clinical investigator should develop a monitoring plan in conjunction with the protocol for a study, detailing risk assessment and level of monitoring to be considered during the study.
- ICRIN should develop and validate a procedure for risk assessment and monitoring of clinical studies.
- ICRIN should develop a glossary of terms for clinical research.
- The IMB should make GCP inspection findings publicly accessible in an anonymous format.
- Hospitals should ensure that all research staff have email addresses and access to the web.

CHAPTER 8: EDUCATION, TRAINING AND CAREER PATHS

Overview

Education programmes and courses that have components 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. These courses are further detailed below.

There is a need for standardised and accredited or recognised education and training programmes for staff involved in clinical research conduct in Ireland to equip them for a career in clinical research. In 2008, IPHA 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, tend to be employed on short-term contracts without an obvious career structure. Combined with the lack of clinical research-focused education and training, the absence of opportunities to make a career in clinical research hampers the recruitment and retention of these valuable members of staff.

Clinicians interested in conducting research are discouraged by difficulty in securing protected time for research and by the lack of trained and qualified staff available to assist them conduct clinical studies. The difficulty in recruiting and retaining research staff, together with heavy clinical responsibilities, are a major roadblock in building national capacity in clinical research.

Programmes for Training Clinical Research Personnel

The disincentive to move between practice and research in the current healthcare system does not easily accommodate clinician scientists who wish to train and carry out clinical research. This is due to lack of protected time for research, lack of structured training programmes (for example, study design, methodologies) and insufficient numbers of clinical research staff to meet the increasing demand. As previously mentioned, a small number of courses have been developed by both universities and commercial colleges in an effort to bridge the gap in the knowledge of clinical research. There is a clear need to identify the gaps in education and training required to allow clinicians to conduct clinical studies, facilitating their ability to conduct clinical research by

providing the necessary tools to design and conduct a clinical study. Knowledge of requirements should include the ability to formulate a clearly defined hypothesis as well as the accompanying study considerations such as randomisation, comparator, blinding, drug labelling, patient recruitment, inclusion and exclusion criteria, sample size, duration, statistical procedures, parameter selection and safety and efficacy assessments.

The following programmes are currently available for training clinical research personnel.

Molecular Medicine Ireland Clinician Scientist Fellowship Programme:

In September 2007, the HEA awarded funding under the Programme for Research in Third Level Institutions (Cycle 4) for a Clinician Scientist Fellowship Programme (CSFP) in translational medical research to be coordinated by MMI. The objective of the CSFP is to train the next generation of clinician scientists with the unique and specialised knowledge essential to fulfil 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 will lead the quest for new therapeutic strategies. The CSFP provides a systematic means to train this essential group through a structured PhD programme for medical graduates of three years in duration. The fellows come together to participate in the structured element of the programme, which taps into the research and teaching strengths of the five MMI partner institutions and for an annual scientific meeting.

MMI issued the first call in November 2007, attracting 75 expressions of interest and 21 candidates in its five partner institutions have been awarded MMI Clinician Scientist Fellowships. This first group of fellows began the structured training part of their programme in July 2008. MMI proposes to mainstream the structured training programme of the fellowship so that all medical graduates undertaking PhDs in the partner institutions in future will benefit from structured training.

HRB/HSE Academic Fellowship Programme:

In working towards implementing one of the key recommendations of the *Buttimer Report*⁶³ on postgraduate medical education and training, the HSE together with the HRB, the Forum of Irish Postgraduate Medical Training Bodies and the university academic medical departments, have established an innovative fellowship programme entitled the National SpR/SR (Specialist Registrar/Senior Registrar) Academic Fellowship Programme (NSAFP) that will provide a coherent and integrated training and career path for a small number of clinical academics.

Following successful completion of this fellowship programme, the trainee will be awarded a Certificate of Satisfactory Completion of Training in his or her specialty and a PhD in his or her area of research expertise. As well as ensuring that candidates do not have to postpone or step out of their clinical training in order to complete a PhD, successful fellows will also be able to prepare an *ad persona* integrated training plan to cover the clinical and research training components rather than working to a prescribed plan.

The NSAFP is targeted at medical trainees at the early stages of, or about to commence, higher specialist training who wish ultimately to specialise in research or follow a career in academic medicine. Eligible applicants must either be currently on a SpR/SR training programme or applying for entry at the immediate subsequent uptake. Only candidates that are successful in securing a place on a specialist training programme can be considered for the NSAFP. The fellowships will be funded jointly by the HSE and HRB and up to four fellowships have been offered in the first call. Funding will be provided for salary and salary-related costs (based on the trainee's appropriate point on the scale), for research running costs, a travel grant to facilitate research experience abroad and a training and development allowance. Successful fellows began their integrated training programme in July 2009.

HRB Research Training Programme Fellowships for Healthcare Professionals

HRB research training fellowships provide three years full-time funding to health and social care professionals who wish to undertake training in clinical research in a recognised research institution on the island of Ireland, leading to a PhD (or in exceptional cases and where suitably justified a Master's degree by research). The fellowship scheme is aimed at individuals of outstanding potential working within the HSE or within a voluntary/not-for-profit organisation in Ireland involved in health and social care provision. While it is primarily targeted at those engaged in clinical practice, applicants from higher education institutes may apply where they can demonstrate appropriate practice-based experience and where the focus of their application is relevant to the objectives of the programme. Health care professionals working in private practice but providing services to clients under the General Medical Services (GMS) scheme will also be considered.

Diploma/MSc/PhD in Molecular Medicine – Trinity College Dublin

Molecular medicine is playing an increasingly important role in the practice of medicine and research in the biological, medical and pharmaceutical or life science arenas, with major implications for society and the economy. Personnel trained and knowledgeable about key developments in molecular medicine will be required in the clinical, research and industrial

arenas. The Post-graduate Diploma in Molecular Medicine offered by TCD furnishes candidates with an advanced, state-of-the-art knowledge of current developments in molecular medicine. It is ideal for individuals who have limited available time.

Students who successfully complete the Post-graduate Diploma programme may transfer to the Master's programme subject to availability. The MSc in Molecular Medicine offers a comprehensive and up-to-date overview of the area provided by experts in their fields. It provides participants with the knowledge to evaluate the literature and perform independent research. The programme covers everything from basic science to highly specialised topics, practical work and a research project. The course is offered by the Faculty of Health Sciences and the Institute of Molecular Medicine, Trinity College Dublin and is held at the Trinity Centre for Health Sciences campus at St. James's Hospital, Dublin.

The PhD in Molecular Medicine is a prestigious integrated four-year doctoral programme which is supported by the HRB and aimed at producing doctoral scientists trained to the highest international standards. The programme consists of a first year incorporating lecture modules and laboratory rotations with subsequent years focusing on a research programme leading to the award of a PhD degree.

MSc in Pharmaceutical Medicine

In 2006, TCD introduced diploma and 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 at St James's Hospital, Dublin. They were developed to provide medical and science graduates with specialist knowledge and skills in the area 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.

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

Certificate in Nursing (Clinical Research) – Royal College of Surgeons in Ireland

The Certificate in Nursing (Clinical Research) programme is offered by the Faculty of Nursing and Midwifery of RCSI in association with the RCSI CRC at Beaumont Hospital and the UCD CRC at the Mater Misericordiae University Hospital and St Vincent's University Hospital . The programme is unique in the context of Ireland and indeed the EU. It consists of three modules designed to provide students with specialist knowledge, attitudes and competencies related to clinical research nursing. A clinical attachment to a research site or centre has been incorporated into the programme to assess student competence in areas of clinical research under the guidance of a named mentor who may be a PI, experienced researcher or research nurse.

The programme provides a combination of theoretical and practical knowledge and experience. Opportunities are also provided to generate an understanding of research methodologies, clinical trial practice and management. With the emphasis on the practical aspects of conducting clinical trials, this programme provides the healthcare sector with clinical research nurses who are trained and highly competent in this challenging and developing area. The first programme commenced in September 2009.

Other Training

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. 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, though to date, it has been primarily attended by clinicians. The TCD Centre for Advanced Clinical Therapeutics in St. James's Hospital provides short courses on modules within the MSc in Pharmaceutical Medicine covering pharmacoeconomics, critical appraisal and biostatistics. There are also a number of Postgraduate Diploma/MSc courses in Clinical Research available in the UK that can be attended by research staff conducting clinical research in Ireland.

MMI (previously the Dublin Molecular Medicine Centre) Courses & Workshops have, since 2003, offered widely available lecture-based and hands-on practical training focused on the development of translational biomedical research skill sets, with broad support from teaching staff and attendees across MMI partner institutions and beyond. Courses have covered research in particular disease areas (for example, *Cancer Biology to Cancer Medicine*), technologies (microarrays, proteomics, imaging, SNP (Single Nucleotide Polymorphism) analysis), drug discovery and development (for example, *Drug Design & Delivery; MMIA/Myeth Molecules to*

Medicines) and important allied professional skills (for example, *Reading, Writing and Coping with the Biomedical Literature*).

Minimum Requirements for GCP Training

GCP is an international ethical and scientific quality standard for designing, conducting, recording and reporting clinical trials that involve the participation of human subjects. Compliance with this standard provides public 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 Helsinki⁶⁴, and that the clinical trial data are credible. The principles of these guidelines may also be applied to other clinical investigations that may have an impact on the safety and well-being of human subjects.

The clinical trial regulations require that clinical trials on medicinal product are conducted in accordance with GCP. There is therefore an urgent need for all those with an interest in clinical research, both academic and non-academic, to have access to a recognised GCP Training Course to ensure compliance with the legislation and the protection of patients.

Research staff including investigators and research nurses can attend registered ICH-GCP courses and update courses offered in Ireland and the UK. 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 Irish researchers for Irish issues, for example, ethics applications, IMB additional national requirements and IMB GCP inspections.

Currently, there is no nationally recognised body to provide GCP training. Various groups including IPPOSI, and the MRCG, have all recognised that ICRIN is the national vehicle by which a course of this nature can be developed and delivered. The DCCR has also been tasked to implement this type of training programme and in response to this request, ICRIN has developed and implemented on a pilot basis, a national GCP training programme for the DCCR and the CRCs in Cork and Galway. This course is open to academic and non-academic personnel with an interest in clinical research. The programme was offered on four occasions in 2009. Courses were well attended and evaluated highly. Feedback has identified the need for advanced and bespoke courses to support the needs of the research community

The frequency of attendance at the course and re-certification in GCP should be driven by changes in legislation at a national and EU level as well as by the amount and complexity of clinical research activity in which people are involved. Retraining every three years is probably a

good benchmark, unless changes to legislation occur more frequently. GCP training should be available to all staff including pharmacists, basic researchers and anyone with a role in clinical research activity.

Recommendations

- The HRB should engage with ICRIN to provide an appropriate nationally recognised GCP suite of training for all staff involved in clinical research conduct.

Education and Training in Clinical Research for Other Health Professionals

There are deficits in core specialist education modules in clinical research for other health care professionals. These professionals include pharmacists, health economists, clinical pharmacologists and health science graduates. Some of these deficits could be met by Masters programmes in clinical research. A complementary series of lectures, organised through MMI, by world leaders in the field of clinical research might also be made available. These series of lectures would be open to a wider audience.

Recommendations

- The HRB and HSE should commit to increasing the number of clinician scientist training fellowships and to offering fellowships each year.
- MMI partner institutions should develop multidisciplinary training programme in translational and clinical research at diploma and master's degree levels.
- MMI should organise a lecture series with world leaders in clinical research available to all professionals interested in clinical research.

Career Paths in Clinical Research

The IPPOSI conference report entitled *“Clinical Research Infrastructure in Ireland, Remaining Barriers, Potential Solutions”*, identified the insufficient number of clinical research staff as a roadblock to the development of clinical research in Ireland. It noted the need to *“create formal career structures for health professionals interested in research, especially (but not only) for research nurses”*.⁶⁵ In its report entitled *Towards Better Health: Achieving a Step Change in Health Research in Ireland*, the Advisory Council on Science, Technology and Innovation noted that *“the shortage of researchers in hospitals is due, partly to the lack of research policies and strategies, and, in the case of consultants partly to issues relating to consultant contracts.”* It referred to the need to *“devise a range of incentives, including attractive career structures to attract both clinical and non-clinical staff to pursue research careers”*⁶⁶.

Career Track for Clinician Scientists

While the joint HSE/HRB Academic Fellowship Programme described above is a welcome development, the number of medical graduates supported under the programme is too few to provide sufficient numbers of clinician scientists in the future. The MMI coordinated CSFP is supporting a much larger cohort of medical graduates in training for careers in medical research but the funding made available for the programme under PRTL Cycle 4 is sufficient to support only one cohort. What is needed is a permanent and enhanced training track in academic medicine that will attract a sufficient number of medical graduates to ensure a continuous 'pipeline' of clinician scientists in the future. Such a training track has been put in place in the UK with the implementation of the Walport Report⁶⁷. Medical graduates with an interest in research can pursue their interest during part of their foundation or intern training. During the first two years of specialist training, they can compete for positions in strong host environments (university and National Health Service (NHS)) that enable them to spend 25 per cent of their time in research training. Subsequently, they can compete for positions in higher specialist training that enable them to undertake a PhD and complete their specialist clinical training. These positions are funded by the NHS as part of the budget for medical training. In Northern Ireland, there is funding available to support up to 30 medical graduates who chose this career training track. The academic career track involves close cooperation between the NHS, the Dean of Medical Training and the School of Medicine at Queen's University Belfast.

The HSE, as the body responsible for the organisation and funding of postgraduate medical education in this country, should agree with the medical schools a competitive and structured training track in academic medicine, equivalent to that recommended in the Walport Report, to ensure a sufficient number of clinician scientists to lead clinical research in the future.

The lack of senior fellowships for registrars and specialist registrars who have completed their PhD but who are not yet at the stage of independent investigators is a deficit in academic career structures. Given the existing investment by the HRB, HSE and HEA in providing medical graduates with the opportunity to undertake PhDs as a step towards a career as a clinician scientist, it would be unfortunate if those graduates did not have the opportunity to compete for senior fellowships when their research training is complete. The Wellcome Trust offers such fellowships in the UK and Ireland but few Irish-based applicants apply. The HRB should consider funding a small number of fellowships each year, perhaps in partnership with the Wellcome Trust, with the objective of developing the fellows as independent investigators capable of securing research awards in their own right and leading a research team. The fellowships should be at

least four years duration of which the initial two years could be spent at a world leading academic medical centre.

One of the most positive steps in recent years towards providing a career track has been the HRB Clinician Scientist Fellowships. The effect of these awards has been to release outstanding clinician scientists from most of their service commitments for a period of five years to enable them to pursue disease and patient focused research. Applicants for the awards must have a strong, internationally competitive track record in research and those who are medically qualified must hold a contract as a medical consultant in a public hospital. All candidates must be sponsored by an academic institution and have the support of their employing hospital.

To date, seven clinician scientist awards have been made by the HRB, with a total value of over €12m. These HRB Clinician Scientists are unique in the community of health researchers, providing the link between clinical practice, the discovery of disease mechanisms and new diagnostic and therapeutic interventions. A drawback of the scheme is that it has been limited to applicants who already hold contracts as medical consultants and is not open to applicants abroad who might be interested in such posts. There is also the question of support for the posts after the HRB five year commitment has expired. The HRB, in its *Strategic Business Plan 2010-2014* makes a welcome commitment to increasing the number of clinician scientists.

The Fotrell Report, noting the relatively small number of academic appointments in Irish medical schools, recommended a significant increase in the number of such appointments to support the teaching and research mission of the schools⁶⁸. A total of 24 academic posts have been approved arising from the Fotrell Report. The HSE, HEA and the HRB should work closely together to ensure the appointment of sufficient clinician scientists to support the education and research mission of the medical schools and to ensure sufficient leadership of clinical research in academic hospitals.

Career track for Research Nurses

At present, most research personnel, such as research nurses, data managers and biostatisticians are employed by either the hospital, the university or by investigators on short-term contracts, without an organised career structure⁶⁹. A first step in formalising a career path is to define qualifications for posts and the roles and responsibilities of such staff. In relation to nursing, the Irish Research Nurses Network has been formed with the support of three Dublin Schools of Nursing. The formation of the Network was encouraged by the DCCR with ICRIN facilitating the group to ensure roll-out on a national level. The group is in the process of developing:

- 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 have a complete or up to date list
- A consensus statement on the scope of nursing practice issues and concerns with respect to particular practices of nursing research (for example, obtaining consent, nurse prescribing)
- A consensus statement on any representations that may need to be made to An Bord Altranaís

The profile of a research nurse, detailing the minimum requirements and duties for research nurses employed in CRCs, is attached in Appendix III. Ideally, a nurse would have three years clinical experience before becoming a research nurse, have successfully completed degree level or equivalent nursing education, or have completed the RCSI Certificate in Nursing (Clinical Research).

The National Council for the Professional Development of Nursing and Midwifery has identified the career pathways for nurses in clinical research as being either in management or as investigators. It is the view of the Council that the professionalisation of research nursing is not through the clinical career pathway as currently structured, and for which the Council has responsibility.

An important step towards the professionalisation of research nursing would be an agreed employment grading structure, taking into account competence, level of experience and professional grade. If clinical research is to attract sufficient numbers of nurses, comparable opportunities for secure, pensionable employment to those enjoyed by nurses in other specialist areas of nursing should be provided. Ideally, nurses should be able to move between research and clinical practice without any loss of pension or other entitlements. The HSE should agree an employment grading structure for research nurses based on the profile for research nurses, with minimum entry qualifications and facilitate opportunities for further training.

The professional reporting structure for nurses involved in research in hospitals needs to be considered, and in particular, the absence of any such structure for many nurses employed on contract by PIs to assist with research studies. All registered nurses, including those involved in research, are covered by the scope of nursing practice and are answerable to An Bord Altranaís for their professional practice. Research nurses, as all other nurses, need to work in an environment that supports and develops their professional competence. This environment can

best be achieved through a structure in which nurses involved in research report to a nurse manager, who in turn is integrated with the senior nursing structures of the university and hospital. Ideally the professional development needs of research nurses should be addressed as part of the hospital's commitment to continuing nurse education.

The CRCs in a number of the major academic hospitals provide an opportunity to standardise the reporting arrangements for all nurses in the hospital currently employed to undertake research and to create a more supportive professional nursing environment. All nurses employed to undertake research in a hospital with a CRC should report to the nurse manager of the CRC, who in turn should have a good working relationship with senior nurse management in the hospital. In those hospitals without a CRC, research nurses should report to a designated nurse manager who would be responsible for ensuring the professional competence and development of those nurses. Such a structure will provide an appropriate professional environment for nurses involved in research.

There are two possible routes for career development of research nurses, either as investigators of nursing research or in research management. For those nurses with an interest in conducting clinical research, the entry level qualification might be a Diploma in Clinical Research with the option to progress to a Master's in Clinical or Translational Medicine. Support for nurses to undertake PhDs in Clinical Research is available from the HRB.

Nurses interested in professional development in management might undertake qualifications such as Masters degrees in Management or Healthcare Management or in Business Administration with modules specifically focused on medical research, pharmaceutical and medical device industry.

Career Paths for other Staff involved in Clinical Research

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. Draft documents recommending the minimum requirements and duties for biostatisticians and data managers employed in CRCs are detailed in Appendices III and IV.

The significant investment by the HSE, HRB and Wellcome Trust into CRCs should serve to improve the employment environment for research staff in the future by providing a core resource of staff to support all clinical investigators in the hospital.

Employment Controls and Research Staff

One of the most significant factors in damaging this country's reputation in clinical research in recent years has been the difficulty in filling research posts in hospitals, even when funding is available to fill the posts. Although there is agreement in principle at national level that such posts do not come within the scope of health service employment controls and may be filled, local factors may make it difficult to fill these posts in practice. The HSE should ensure that health employers meet their responsibilities to fill funded research posts in all disciplines.

Recommendations

- The HSE should agree with the medical schools a competitive and structured training track in academic medicine, equivalent to that recommended in the Walport Report, to ensure a sufficient number of clinician scientists to lead clinical research in the future.
- The HRB, possibly in partnership with the Wellcome Trust, should offer senior fellowships on a competitive basis for medical graduates who have completed a PhD in Clinical and Translational Research, to enable them to develop as independent investigators.
- The HSE and the HEA should fund the appointment of additional medical academics as recommended in the Fotrell Report.
- The HSE should recommend a role profile for research nurses, entry level qualifications and experience and also opportunities for further training.
- Hospitals should ensure that all nurses involved in research report to a nurse manager, who in turn is integrated with the senior nursing structures of the university and hospital. The nurse manager of the CRC should in turn, have a good working relationship with senior nurse management in the hospital.
- The HSE should ensure that health employers meet their responsibilities to fill funded research posts in all disciplines.

CHAPTER 9: QUALITY ASSURANCE

Overview

Harmonisation or compatibility in quality management systems is a prerequisite for the conduct of national multi-site studies. In addition, shared SOP principles will spread best practice and improve the quality of the conduct of studies (national and transnational) performed within the CRCs operating within the ICRIN network. This will ensure that duplication of efforts is avoided for the centres conducting studies.

The different aspects of clinical trials on medicinal products are covered by SOPs that control and standardise the planning and performance of the study. Quality management (QM) is based on quality assurance (QA) and on quality control (QC). ICH-GCP defines QA as: *“All those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded) and reported in compliance with GCP and applicable regulatory requirements”*, and QC as *“The operational techniques and activities undertaken within the system to verify that the requirements for quality of the trial-related activities have been fulfilled⁷⁰”*. This means that QM is defined by two processes, one planning and performing the trial, and another process controlling the first process and its outcome.

SOPs are also required for the conduct of other clinical research including clinical investigation on medical devices, non-interventional, surgical and radiotherapy studies.

Audit Strategies for Clinical Research Centres

There is a need to establish a comprehensive quality management system (QMS) for the CRCs to include the audit of SOPs, methodologies and facilities in line with regulatory requirements. Issues that need to be considered include quality governance systems and an organisational structure such as inspectors and audit committees.

Duty of care to the patient requires robustness of quality management. Good research practice requires harmonised quality standards when conducting multi-centre clinical research. ICORG has established a common quality system across 12 hospitals with a centralized QMS located within the ICORG administrative centre. This model could perhaps be used for wider application. The common ground already established includes the Declaration of Helsinki, ICH-GCP and other European and US guidance for clinical research. From these consensus documents, ICRIN could prepare a template of principles and standards which could be adapted locally at the CRC.

In order to ensure the robustness of the standards across the research community, there is a need for a QM oversight function to review adherence to processes and procedures. This should be located within the central clinical research hub such as ICRIN and/or CSTAR and supplemented at a local level via an assigned principal with responsibility for QM at each CRC.

ICRIN, in collaboration with CSTAR and with the support of the HRB, is currently piloting a research readiness programme with a view to establishing a national accreditation system for research competence in some existing and emerging CRCs and affiliated hospital research teams.

Recommendations

- ICRIN, in collaboration with CSTAR, should develop high level principles of quality management standards according to categories of study type, with local adaption by each CRC.
- ICRIN should review adherence to quality processes and procedures supplemental to the IMB inspection process
- The HRG should adopt a national accreditation system, in line with developments in ECRIN member countries, to assist in the harmonisation of research practices and use of best practice across new and existing CRCs and hospital research teams.
- Each CRC should establish a quality process with a designated quality resource responsible for managing quality.

Standard Operating Procedures Requirements

ICRIN should provide a list of template SOPs and associated documents to the CRCs based on general high level principles such as Declaration of Helsinki and ICH-GCP. The local designee should adapt the template SOP to incorporate local processes and procedures to ensure that local practices are documented.

It is critical at a local level to identify which SOPs are applicable to specific research personnel. As part of the research personnel job description it is recommended that an SOP matrix be generated highlighting the necessary SOPs. Training on these locally adapted SOPs should be provided by the local quality designee. Training for any core processes common among CRCs should be provided by the central designated auditor or inspector. Each CRC should have access to a web-based document management system to manage quality documents appropriately.

Recommendations

- ICRIN should develop template SOPs and associated documents to be adapted at local level by the assigned local quality designee.
- Each CRC should have access to a web-based document management system to manage quality documents appropriately.
- ICRIN should establish a core quality process training programme and accreditation system for new and emerging CRCs and affiliated hospital researchers.

CHAPTER 10: CONCLUSIONS AND NEXT STEPS

This *Roadmap* has gathered together the experience and analysis of many involved in clinical research and its recommendations reflect their commitment to improving the environment of clinical research in Ireland. Its contents have also been informed by Irish engagement with the European research infrastructures, ECRIN and BBMRI, and by collaborations with PIs and research groups in FP7 and the Innovative Medicines Initiative funding calls. The *Roadmap* is presented as a contribution to the implementation of the *Health Research Action Plan* and in support of the *HRB Strategic Business Plan 2010 - 2014*.

There is much clinical research expertise in Ireland. The challenge now is to address the remaining deficits and connect the existing elements to create a coherent and effective research system that has the active involvement of all key stakeholders.

There is a window of opportunity to make Ireland a destination of choice for clinical research, provided there is commitment by all bodies with responsibility to complete the construction of a clinical research system, by taking the steps outlined in the recommendations of the *Roadmap*. MMI and ICRIN are committed to progressing those aspects of the clinical research environment that are within our competence to deliver and hope that the collaboration of all the other stakeholders in clinical research will be forthcoming.

The implementation of the recommendations of the *Roadmap* will enable the research community to capture the benefits of clinical research to enhance the health and wealth of Ireland and the Irish people. Completing the clinical research system will result in improvements in health and the effectiveness of the health service. Furthermore, it will enhance Ireland's reputation in academic and commercial research and it will create new jobs by the translation of innovations from bench to bedside.

APPENDIX I: ROADMAP WORKING GROUP MEMBERS

Ethics and Interaction with Ethics Committees

Name	Job Title	Organisation	Role
Dr Siobhan O'Sullivan	Scientific Director	Irish Council for Bioethics	Chair
Siobhan Gaynor	ICRIN Senior Associate	Molecular Medicine Ireland	Rapporteur
Dr Ruth Barrington	CEO	Molecular Medicine Ireland	Expert Member
Margaret Cooney	ICRIN Coordinator	Molecular Medicine Ireland	Expert Member
Linda Foley	Director	Cystic Fibrosis Register	Expert Member
Patrick Little	CEO	Migraine Association of Ireland	Expert Member
Dr Teresa Maguire	Head of Research Management Unit	Health Research Board	Expert Member
Dr Siobhan McGrath	Manager	Office for Research Ethics Committees (OREC) Northern Ireland	Expert Member
Veronica McInerney	Oncology Clinical Trials Manager	University College Hospital Galway	Expert Member
Dr Eve O'Toole	Research Manager	Health Intelligence Unit HSE	Expert Member
Prof David Smith	Professor of Health Care Ethics and Law	RCSI	Expert Member
Gillian Vale	Secretary	Beaumont Hospital Ethics Committee	Expert Member

Regulation, Governance and Interaction with Competent Authorities

Name	Job Title	Organisation	Role
Professor George Shorten	Consultant Anaesthetist	University College Cork	Chair
Margaret Cooney	ICRIN Coordinator	Molecular Medicine Ireland	Rapporteur
Dr. Karen Bailie	Director	Clinical Research Support Centre Northern Ireland	Expert Member
Dr Ruth Barrington	CEO	Molecular Medicine Ireland	Expert Member
Dr. Anthony Chan	Director Clinical Operations	Pfizer	Expert Member
Dr. Rebecca Cramp	Scientific and Regulatory Manager	IPHA	Expert Member
Eibhlin Mulroe	CEO	Irish Platform for Patient Organisations Science and Industry	Expert Member
Dr. Paul Roben	Director of Lifesciences and Commercialisation	Enterprise Ireland	Expert Member
Kieran Ryan	Surgical Research Manager	RCSI	Expert Member

Safety Reporting and Investigational Product Management

Name	Job Title	Organisation	Role
Dr Tracy Cunningham	Medical Director	GlaxoSmithKline Pharmaceuticals Ireland	Chair
Ailbhe Cullen	Director of Nursing	RCSI Clinical Research Centre	Rapporteur
Siobhan Gaynor	ICRIN Senior Associate	Molecular Medicine Ireland	Rapporteur
Dr. Ruth Barrington	CEO	Molecular Medicine Ireland	Expert Member
Orla Cantwell	Independent Consultant	Datawise Ltd;	Expert Member
Margaret Cooney	ICRIN Co-ordinator	Molecular Medicine Ireland	Expert Member
Dr Ronan Donelan	European Director Regulatory affairs	Quintiles Ltd	Expert Member
Deirdre Hyland	Senior Research Nurse	RCSI Clinical Research Centre	Expert Member
Fionnuala King	Chief (II) Pharmacist	HOPE Directorate, St James Hospital	Expert Member
Dr Ailis Quinlan	Head of the Clinical Indemnity Scheme	States Claims Agency	Expert Member
Dr Mary Teeling	Director	Centre for Advanced Therapeutics, Trinity College Dublin	Expert Member
Prof Helen Whelton	Director	Oral Health Services Research Centre, UCC	Expert Member

Data Management

Name	Job Title	Organisation	Role
Dr Peter Doran	Scientific Director	UCD Clinical Research Centre	Chair
Siobhan Gaynor	ICRIN Senior Associate	Molecular Medicine Ireland	Rapporteur
Dr Geoff Bradley. Executive Director	Trinity Centre for High Performance Computing	TCD	Expert Member
Dr Mary Codd	Senior Lecturer in Epidemiology/Biostatistics	UCD School of Public Health	Expert Member
Rachel Flynn	Health Information Manager	HIQA	Expert Member
Martin Molloy	Head of IT services	University College Hospital Galway	Expert Member
Dave Toomey	Database Designer	Beaumont Clinical Research Centre	Expert Member
Jeremy Towns	Programme Manager	Dublin Centre for Clinical Research	Expert Member
Valerie Trimble	Research Nurse	St James' Hospital	Expert Member
Prof Douglas Veale	Chair of Translational Medicine	UCD	Expert Member

Study Monitoring

Name	Job Title	Organisation	Role
Kieran Ryan	Surgical Research Manger	RCSI	Chair
Siobhan Gaynor.	ICRIN Senior Associate	Molecular Medicine Ireland	Rapporteur
Margaret Cooney	ICRIN Co-ordinator	Molecular Medicine Ireland	Expert Member
Mary De Voe	Research Nurse	University College Cork	Expert Member
Fionnuala Gibbons	Oncology Scientific Adviser	Sanofi-aventis, Ireland	Expert Member
Dr Fiona Manning	Programme Manager	Perinatal Ireland, Rotunda Hospital	Expert Member

Education and Training

Name	Job Title	Organisation	Role
Dr Seamas Donnelly	Consultant, Respiratory and General Medicine/ Medical Director	UCD Clinical Research Centre/ St. Vincent's University Hospital	Chair
Margaret Cooney	ICRIN Coordinator	Molecular Medicine Ireland	Rapporteur
Dr Ruth Barrington	CEO	Molecular Medicine Ireland	Expert Member
Sarah Condell	Nursing Research Adviser	Health Research Board/National Council for the Professional Development of Nursing and Midwifery	Expert Member
Prof. Seamus Cowman	Head of School of Nursing and Midwifery	RCSI	Expert Member
Dr Mary Teeling	Director Centre for Advanced Therapeutics	St. James's Hospital, TCD	Expert Member
Dr. Mark Watson	Programme Manager Education and Training	Molecular Medicine Ireland	Expert Member

Quality Assurance

Name	Job Title	Organisation	Role
Dr Ian Callanan	Clinical Audit Facilitator	St. Vincent's University Hospital /Health Information and Quality Authority (HIQA)	Chair
Margaret Cooney	ICRIN Coordinator	Molecular Medicine Ireland	Rapporteur
Orla Cantwell	Consultant	Datawise Consultants Ltd	Expert Member
Celine Creighton	Consultant	Celine Creighton Consulting	Expert Member
Dr. Catherine Gill	Project Officer	Health Research Board	Expert Member
Siobhan Gaynor	ICRIN Senior Associate	Molecular Medicine Ireland	Expert Member
Dr Jan Guerin	Programme Manager Research	Molecular Medicine Ireland	Expert Member
Mary McGrath	Senior Clinical Research Coordinator	UCD Clinical Research Centre	Expert Member
Donal O'Sullivan	Vice President Quality Assurance	Medtronic	Expert Member

APPENDIX II: BODIES INVITED TO COMMENT ON THE DRAFT ROADMAP

NAME	JOB TITLE	ORGANISATION
Ms Mary Harney	Minister for Health and Children	Department of Health and Children
Mr Michael Scanlan	Secretary General	Department of Health and Children
Mr Enda Connolly	Chief Executive	Health Research Board
Professor Brendan Drumm	Chief Executive	Health Service Executive
Mr John Mc Cormack	Chair	Medical Research Charities Group
Dr Michael Neely	Operational Director	NI Health and Social Care, Research and Development Office
Professor Dermot Kelleher	Head of School & VP of Medical Affairs	Trinity College Dublin
Professor Cathal Kelly	Dean of Medicine and Health Sciences	Royal College of Surgeons in Ireland
Professor David Kerins	Head of School of Medicine	University College Cork
Professor Bill Powderly	Head of School of Medicine	University College Dublin
Professor Gerry Loftus	Dean of Medicine, Nursing and Health Sciences	National University of Ireland, Galway
Ms Anne Nolan	Chief Executive	Irish Pharmaceutical Health Association
Dr Gerald Farrell	Chair	Irish Pharmaceutical Health Association
Dr Brian Moulton	Chief Executive	ICORG
Ms Sharon Higgins	Director	Irish Medical Devices Association
Dr Helen Ryan	Chair	Irish Medical Devices Association
Mr Liam Duffy	Chief Executive	Beaumont Hospital
Mr Tony McNamara	Chief Executive	Cork University Hospital

Mr Pat Madden	Chief Executive	Mercy University Hospital
Mr Brian Conlan	Chief Executive	Mater Misericordiae University Hospital
Mr Ian Carter	Chief Executive	St James's Hospital
Mr Nicholas Jermyn	Chief Executive	St Vincent's University Hospital
Ms Bridget Howley	General Manager	Galway University Hospital
Mr Billy Hawkes	Data Protection Commissioner	Office of the Data Protection Commissioner
Ms Yvonne O' Shea	Chief Executive	National Council for the Professional Development of Nursing & Midwifery
Ms Tracey Cooper	Chief Executive	Health Information & Quality Authority
Mr Tom Boland	Chief Executive	Higher Education Authority
Mr Pat O' Mahony	Chief Executive	Irish Medicines Board
Dr Siobhan Roche	Scientific Programme Manager	Science Foundation Ireland

APPENDIX III: ENTRY LEVEL REQUIREMENTS FOR CLINICAL RESEARCH CENTRE RESEARCH NURSES, BIostatisticians AND DATA MANAGERS

1. RESEARCH NURSES

Prepared by: Ailbhe Cullen, RCSI and Siobhan Gaynor, ICRIN

Selection Criteria:

Requirements:

- Must be registered with an appropriate division of An Bord Altranais
- Have a minimum of 3 years post registration experience
- Successfully completed degree level or equivalent nursing education OR have completed the RCSI level 9 module for clinical research nurses (OR equivalent).
- Have proven clinical skills
- Have excellent oral and written communication skills
- Have good organizational and 'problem solving' skills
- Have the interpersonal skills required to integrate as part of a diverse research team.
- Have good IT skills including Microsoft Office

Desirable:

- Experience in the field of clinical trials and/or other academic studies.
- Experience in translational "bench to bedside" research
- Proven leadership and management skills

Research responsibilities will include

- To work to the CRC standard operating procedures for clinical trials and academic research.
- To play an active role in driving ongoing clinical research projects.
- To actively participate in the implementation of clinical investigations and trials
- To assist in ensuring the overall smooth running of the CRC as per best practice.
- To arrange study specific research meetings if necessary, including staff notification, completion and writing of minutes where applicable.
- To ensure patient confidentiality and dignity is assured and maintained at all times during a clinical trial/research project.
- To take responsibility for maintenance and upkeep of CRC clinical research documentation, including: site files, case record forms, monitoring arrangements, data correction and data collection.
- To complete (with the help of the sponsor company if necessary) all ethical and regulatory procedures (submissions, query resolution etc.) for the clinical trial studies you are assigned.
- To review proposed research protocols and provide input to site study feasibility reports (e.g. annual site patient numbers, equipment / test availability etc.)
- To attend investigator meetings as appropriate relative to studies assigned to you.

- To ensure prompt management of all study related correspondence.
- To prepare your studies for Internal / Sponsor / Irish Medicine Board audits as required.
- To ensure that patients are fully informed of all details pertaining to the clinical trial/research project prior to their recruitment.
- To screen patients in order to identify suitable study candidates.
- To ensure that all studies undertaken by the CRC from the time of appointment are completed to the highest standards in accordance with ICH-GCP, IMB/EU Directive requirements.
- To carry out other duties as appropriate to the post as may be assigned from time to time by the CRC Director and/or the CRC Clinical Research Coordinator.

Clinical Practice responsibilities will include

- Provide nursing or midwifery knowledge, expertise and care to patients participating in a clinical trial.
- Ensure patients have an understanding of their disease and the proposed research and standard treatment options.
- Work with a Multidisciplinary Team in evaluating and treating clinical problems, as they arise in the research settings.
- Be competent in phlebotomy procedures or be willing to train.
- Adhere to nursing policies and procedures within the CRC and the Hospital.
- Ensure continuity of patient care by liaising with outside health care professionals, and those who are involved in clinical work.
- Use agreed protocols to deal with referrals and enquiries from other hospitals
- Promote a safe clinical environment for patients, visitors and staff to the CRC with due regard to Health and Safety and Risk Management issues.
- Professional development
- Maintain professional registration.
- Undertake further education as appropriate to keep updated with changes within the field of Clinical Research.

Attend and participate in:

- In service and staff education
- Staff Conferences
- Appropriate outside conferences and/or other professional development activities

Identify nursing/midwifery research opportunities

Take responsibility for own professional development and updating, including maintaining a record of activities.

Quality Assurance:

- Help maintain the system for recording clinical activity.
- Demonstrate commitment to evidence based practice.
- Maintain clinical and administrative records and reporting arrangements.
- Provide a high quality service, efficient and effective, respecting the needs of each patient.
- Continually monitor the service ensuring it reflects current needs and implement change where required.

All other duties, responsibilities and requirements to be at the discretion of the local CRC management.

2. BIOSTATISTICIANS

Adapted by Margaret Cooney, ICRIN from Biostatistician Job Description – Duke University, North Carolina, USA

Job Description:

Manages trial/project responsibilities independently. Handles multiple competing projects and deadlines, and coordinates all the statistical needs of each clinical trial/project. Performs intermediate and advanced statistical analysis and programming for multi-center phase I- IV clinical trials and/or clinical research projects.

Selection Criteria:

Required

- A minimum of a Doctoral degree in biostatistics or related field and no relevant experience, or a Master's degree in biostatistics or related field and 2 years relevant experience, or a Bachelor's degree in biostatistics or related field and 4 years relevant experience.

Desirable

- Contribution to analysis of clinical trials and/or clinical research projects, and/or participation in preparation of academic manuscripts or other written summaries of analysis results.
- Thorough experience with SAS, and solid command of the English language.
- Desirable experience includes prior role as a lead statistician on clinical trials and/or clinical research projects that have delivered the agreed-upon end products on time, and prior guidance of lower level or less experienced staff.

Responsibilities will include

- With minimal or no guidance, prepares statistical analysis plans and performs and interprets basic and complex analyses. Uses statistical and medical understanding to propose and perform additional analyses appropriately and independently. Learns new statistical methods and applies new skills to future projects.
- Documents analyses, creates summaries, and presents results in written and verbal form to requestors. Writes statistical text for study reports and clinical publications. Prepares methods sections and analysis plans for incorporation in abstracts, manuscripts, grants.
- Discusses analytic issues related to other findings within a clinical trial/project. Understands how clinical trial/project results fit in the context of results from similar clinical

- Writes own SAS and/or S-plus code, finds errors, corrects, and validates output and results. Performs complex programming efficiently, uses complicated SAS procedures and options. Programs analysis datasets using SAS and/or reviews those programmed by others to ensure quality products; combines multiple disparate raw databases and derives analysis variables accurately. Considers alternative programming approaches to improve quality and/or efficiency.
- Collaborates effectively with statistical programmers that support clinical trial/projects. Identifies potential data problems from analytic queries and takes appropriate initiative to guide the process of resolution. Demonstrates thorough understanding of clinical trial/project data collection processes and data sets and shares knowledge with collaborators, fellow statisticians, and programmers. Helps less experienced programmers and/or statisticians with programming skills.
- Participates in all statistical aspects of a trial/project with minimal guidance. Collaborates with project leader, principal investigator, other clinical investigators, and external government or industry representatives to affect significant decisions regarding the trial/project, and to jointly achieve objectives and timelines. Represents the functional group in project team meetings and contributes constructively to project discussions.
- Contributes to the thought process of endpoint selection and study design. Calculates samples sizes, power calculations, and interim stopping guidelines, with guidance. Provides review and approval of data collection tools, data correction criteria and procedures, identification of critical data fields, and endpoint collection documents. Understands study data and the intricacies of the process through which it is being collected.
- Collaborates closely with investigators, sponsors, and other trial leadership to ensure that trial/project results and conclusions are presented accurately and without bias. Leads the statistical team responsible for designing and validating analysis data sets, programs, and statistical output products (tables, listings, figures).
- Adheres to SOPs of the functional department as they apply to documentation and validation of clinical research statistics. Understands and remains abreast of guidelines from the ICH, EMEA, FDA or other regulatory agency as they apply to statistics and programming. Demonstrates solid understanding of the clinical drug and/or device development process.

3. DATA MANAGERS

Adapted by Margaret Cooney, ICRIN from Data Manager Job Description – University of Oxford, Nuffield School of Clinical Medicine

Job Description:

The Data Manager will be responsible for data entry and managing the consistency, integrity, security and backup of the clinical research centre databases for clinical research studies, working closely with the CRC research staff.

Selection Criteria:

Required:

- A sound computer literacy and good practical knowledge of databases and use of spreadsheets, alongside a working knowledge and compliance with the local, national and international research regulations relating to data storage and security.
- Significant experience of working with different types of computer software.
- Excellent problem solving skills.
- Meticulous attention to detail.

Desirable

- Experience of working as a data programmer/manager in a research environment
- Previous experience of working in a clinical or research environment.
- Some understanding of statistical packages (e.g. SPSS).
- Some understanding of bibliography packages (e.g. Endnote).

Responsibilities will include

- To design and manage systems to ensure the strict confidentiality of patient records in line with local and statutory requirements.
- To carry out checks on forms sent for missing, inconsistent and incorrect data prior to being entered onto the study database.
- To enter trial data meticulously, accurately and consistently in a timely fashion.
- To maintain the consistency and integrity of the study database, including carrying out quality checks at regular intervals, enabling audit trails to be carried out easily and effectively and regularly backing up the data.
- To write a study specific standard operation procedure for data entry and database management with sufficient clarity and simplicity that this can be picked up by another trial team member, so that the progress of this trial is not held up by unpredicted absences.
- To ensure that all legal and ethical security and privacy requirements are adhered to.
- To understand the nature of the study data and the aims and outcomes of the research sufficiently to manage the database sensibly.
- To design and generate clear, intelligible and appropriate reports in a timely fashion.
- To assist the study biostatistician in extracting and collating data for analysis.
- To maintain a good working relationship, including regular and effective communication, with the Clinical Research Centre staff.
- To assist in the preparation and presentation of reports of the study data for study-specific meetings as well as research forums, conferences and publications.

**APPENDIX IV: DEPARTMENT OF HEALTH AND CHILDREN
RECOGNISED ETHICS COMMITTEES**

Name of Ethics Committee	Address for correspondence	Date of recognition	Area for which committee may act	Description or class of clinical trials for which committee may act
SJH/AMNCH Research Ethics Committee	Secretary, SJH/AMNCH Research Ethics Committee AMNCH, Tallaght ,Dublin 24 – (01) 4142860	13 July 2004	The whole State	Clinical trials of all descriptions and classes.
St Vincent's Healthcare Group Ethics and Medical Research Committee	Administrator, St Vincent's Healthcare Group Ethics and Medical Research Committee, Education and Research Centre, Elm Park, Dublin 4. – (01) 2774117	13 September 2004	The whole State	Clinical trials of all descriptions and classes.
Clinical Research Ethics Committee of the Cork Teaching Hospitals	Secretariat, Clinical Research Ethics Committee of The Cork Teaching Hospitals, 1 st Floor, Lancaster Hall, 6 Little Hanover Street, Cork – (021) 4901901	27 September 2004	The whole State	Clinical trials of all descriptions and classes.
HSE North East Area Research Ethics Committee	Secretary, HSE North East Area Research Ethics Committee, Dublin Rd, Kells, Co. Meath – (046) 9280521/564	26 January 2005	The whole State	Clinical trials of all descriptions and classes.
Research Ethics Committee, Mater Misericordiae University Hospital	Administrator, Research Ethics Committee, Mater Misericordiae University Hospital, Eccles Street,	22 February 2005	The whole State	Clinical trials of all descriptions and classes.

and Mater Private Hospital	Dublin 7 – (01) 8032971			
Beaumont Hospital Ethics Committee	Gillian Vale, Administrator, Ethics Committee, Beaumont Hospital, Beaumont Road, Dublin 9 – (01) 8092680	9 March 2005	The whole State	Clinical trials of all descriptions and classes.
Galway Regional Hospitals Research Ethics Committee	Secretary Research Ethics Committee, Unit 4, Merlin Park Hospital, Galway. - (091) 775022	21 April 2005	The whole State	Clinical trials of all descriptions and classes.
Research Ethics Committee, Our Lady's Children's Hospital, Crumlin.	Secretary Research Ethics Committee, Our Lady's Children's Hospital Crumlin, Dublin 12. – (01) 4096243/6307	17 May 2005	The whole State	Clinical trials of all descriptions and classes.
Irish College of General Practitioners Research Ethics Committee	Administrator, ICGP Research Committee, 4/5 Lincoln Place, Dublin 2 – (01) 6763705	17 May 2005	The whole State	Clinical trials of all descriptions and classes.
Ethics Research Committee, National Maternity Hospital	Ms Denise O'Brien, Secretary, Ethics Research Committee, Masters / CEO Office, National Maternity Hospital, Holles Street, Dublin 2 – (01) 6373100	20 July 2005	The whole State	Clinical trials of all descriptions and classes.
HSE South-Eastern Area Research Ethics Committee	Secretary, Research Ethics Committee Office, Old School Of Nursing, Waterford Regional Hospital, Dunmore Road, Waterford – (051) 842391	30 August 2005	The whole State	Clinical trials of all descriptions and classes.

Research Ethics Committee Sligo General Hospital	Administrator, Research Ethics Committee, Sligo General Hospital, The Mall, Sligo – (071) 9171111 ext: 4204	20 September 2005	The whole State	The Committee shall act in relation to clinical trials of all descriptions and classes other than those to which Regulation 13 (4) refers(i.e. gene therapy, somatic cell therapy etc.).
Ethics Research Committee HSE Mid-Western Area	Secretary, Ethics Committee, Mid-Western Regional Hospital, Dooradoyle, Limerick – (061) 482482	22 March 2006	The whole State	Clinical trials of all descriptions and classes.

APPENDIX V: ABBREVIATIONS

Abbreviation	Description
ABPI	Association of the British Pharmaceutical Industry
BBMRI	Biobanking and Biomolecular Resources Research Infrastructure
CAMI	Centre for Advanced Medical Imaging
CDISC	Clinical Data Interchange Standards Consortium
CIS	Clinical Indemnity Scheme
CONSORT	Consolidated Standards of Reporting Trials
CRF	Clinical Research Facility
CRC	Clinical Research Centre
CSFP	Clinician Scientist Fellowship Programme
CSTAR	Centre for Support and Training in Analysis and Research
CTIMP	Clinical Trial for Investigational Medicinal Product
DAMC	Dublin Academic Medical Centre
DCCR	Dublin Centre for Clinical Research
ECRIN	European Clinical Research Infrastructures Network
EMA	European Agency for the Evaluation of Medicinal Products
ERIC	European Research Infrastructure Consortium
FDA	Food and Drug Administration
FP7	Seventh Framework Programme
FSAI	Food Safety Authority of Ireland
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GMS	General Medical Services
HEA	Higher Education Authority
HETAC	Higher Education and Training Awards Council
HIQA	Health Information and Quality Authority
HRAP	Health Research Action Plan
HRB	Health Research Board
HRG	Health Research Group
HSC R&D Office	Health and Social Care Research and Development Office
HSE	Health Service Executive

ICORG	All-Irish Cooperative Oncology Research Group
ICH	International Conference on Harmonisation
ICH-GCP	International Conference on Harmonisation Good Clinical Practice
ICMJE	International Committee of Medical Journal Editors
ICRIN	Irish Clinical Research Infrastructure Network
ICSR	Individual Case Safety Report
IDA	Industrial Development Authority
IMB	Irish Medicines Board
IMDA	Irish Medical Devices Association
IMP	Investigational Medicinal Product
IP	Intellectual Property
IPHA	Irish Pharmaceutical Healthcare Association
IPPOSI	Irish Platform for Patient Organisations, Science and Industry
IVF	In-vitro Fertilization
MMI	Molecular Medicine Ireland
MRCG	Medical Research Charities Group
NHS	National Health Service
NSAI	National Standards Authority of Ireland
NSAFP	National SpR/SR Academic Fellowship Programme
NUIG	National University of Ireland, Galway
PI	Principal Investigator
PIAG	Patient Information Advisory Group
PRTL	Programme for Research for Third Level Institutions
QA	Quality Assurance
QC	Quality Control
QM	Quality Management
QMS	Quality Management System
RCSI	Royal College of Surgeons in Ireland
RCT	Randomised Controlled Trial
REC	Recognised Ethics Committee
SFI	Science Foundation Ireland
SI	Statutory Instrument
SME	Small to Medium Sized Enterprises
SNP	Single Nucleotide Polymorphism

SOP	Standard Operating Procedure
SpR/SR	Specialist Registrar/Senior Registrar
SSA	Site Specific Approval
TCD	Trinity College Dublin
UCC	University College Cork
UCD	University College Dublin
UPI	Unique Patient Identifier
WHO	World Health Organisation

REFERENCES

- ¹ Department of the Taoiseach, *Renewed Programme for Government*, October 2009.
- ² Department of Enterprise, Trade and Employment, *Strategy for Science Technology and Innovation 2006-2013*, 2006.
- ³ See 1 above.
- ⁴ Department of Health and Children, *Medical Education in Ireland – A New Direction* (Fotrell Report) 2006.
- ⁵ The term *Clinical Research Centre (CRC)* also refers to and is used in place of *Clinical Research Facility* throughout this document.
- ⁶ IPPOSI, *Clinical Research Infrastructure in Ireland – Remaining Barriers, Potential Solutions*, Conference Proceedings, June 2008.
<http://www.ipposi.ie/images/news/ipposi%20report%20dublin%20castle%20low%20res.pdf>
IPPOSI, *Flash Report from National Strategic forum for Clinical Research*, November 2009
<http://www.ipposi.ie>.
- ⁷ ICRIN joined the European Clinical Research Infrastructure in October 2006. For more information on ECRIN see www.ecrin.org.
- ⁸ Molecular Medicine Ireland in association with Queen's University Belfast and the University of Ulster, *GeneLibrary Ireland – an All-Island Biomedical Research Infrastructure, Design Phase*, February 2009,
http://www.molecularmedicineireland.ie/uploads/files/GeneLibraryIrelandReport_Final.pdf.
- ⁹ The components of strong systems of clinical research have been set out in the UK's Academy of Medical Science Report, *Strengthening Clinical Research – A Report from the Academy of Medical Sciences (2003)* and in the European Science Foundation *Investigator-Driven Clinical Trials- An ESF Forward Look*, 2009.
- ¹⁰ Department of Health and Children, *Health Research Action Plan*, November 2009.
- ¹¹ See 2 above
- ¹² Health Research Board, *A Picture of Health, 2007*, pg 46 www.hrb.ie.
- ¹³ Forfás, *Health Life Sciences in Ireland – An Enterprise Outlook*, 2009.
- ¹⁴ Department of Health and Children, *Report of the Expert Group on Cancer Biobanking*, 2009.
- ¹⁵ See 8 above.

¹⁶ Advisory Council on Science, Technology and Innovation, *Towards Better Health - Achieving a Step Change in Health Research*, Forfás, 2006
http://www.forfas.ie/media/forfas061123_towards_better_health_full_report.pdf.

¹⁷ Sarah Condell, *Report on the Role of the Nurse or Midwife in Medical-led Clinical Research*, in, National Council for Nursing and Midwifery, 2008.

¹⁸ The State Claims Agency has contracted Aon Insurances to provide advice on CIS coverage of research studies.

¹⁹ Under the National Treasury Management Agency (Delegation of Functions) Order, 2003 as amended in 2007, “*Professional Medical Services*” means

a) “*Services provided by registered medical practitioners or registered dentists of a diagnostic or palliative nature, or consisting of the provision of treatment, or the conduct of research in respect of any illness, disease, injury or other medical condition.*”

b) *Services provided by other health professionals in the performance of their duties, including pharmacists, nurses, midwives, paramedics, ambulance personnel, laboratory technicians,*

Services connected with the provision of health or medical care provided by persons acting under the direction of a person to whom paragraph (a) or (b) applies.”

²⁰ Schedule 1, Part 1 of the National Treasury Management Agency (Delegation of Functions) Order 2003 (SI No 63 of 2003).

²¹ See State Claims Agency- www.stateclaimsagency.ie – go to Clinical Indemnity Scheme.

²² Association of the British Pharmaceutical Industry, *Clinical Trial Compensation Guidelines*, <http://www.abpi.org.uk/Details.asp?ProductID=156>.

²³ Department of the Taoiseach, *Building Ireland’s Smart Economy*, December 2008, Executive Summary.

²⁴ 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 and European Communities (Clinical Trials on Medicinal Products for Human Use) (Amendment 2) SI No 374 of 2006 (Cited as European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations, 2004 to 2006)

²⁵ Health Service Executive. *Review of Research Ethics Committees and Processes in Republic of Ireland, 2008*
http://www.hse.ie/eng/services/Publications/corporate/etr/Review_of_Research_Ethics.pdf

²⁶ EU ref CPMP/ICH/135/95 <http://www.ich.org/LOB/media/MEDIA482.pdf>

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- ²⁷ See http://www.dohc.ie/other_health_issues/clinical_trials/rec_guidance_2007.pdf
- ²⁸ See 16 above.
- ²⁹ 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 .
- ³⁰ Irish Council for Bioethics, *Operational Procedures for Research Ethics Committees, 2004*.
- ³¹ See 25 above.
- ³² Department of the Taoiseach, *Building Ireland's Smart Economy- a Framework for sustainable Economic Renewal, December 2008*
- ³³ Department of Health and Children, *Health Research Action Plan*, November 2009
- ³⁴ See 29 above
- ³⁵ Law Reform Commission. *Vulnerable Adults and the Law*. 2006
- ³⁶ Consort Guidelines - see <http://www.consort-statement.org/consort-statement/overview0/>.
- ³⁷ Consort 2010 Explanation and Elaboration Document - see <http://www.consort-statement.org/consort-statement/overview0/>.
- ³⁸ See http://www.icmje.org/publishing_10register.html.
- ³⁹ WHO Clinical Trials Registry, see www.who.int/ictrp/.
- ⁴⁰ Department of Health and Children, *Health Information – A National Strategy*, 2004, p74.
- ⁴¹ Office of the Commissioner for Data Protection, *Data Protection Guidelines on Research in the Health Sector*, November 2007
see http://www.dataprotection.ie/documents/guidance/Health_research.pdf.
- ⁴² Department of Health and Children, *Discussion Paper on the Proposed Health Information Bill*, June 2008. A synopsis of the comments made on the Discussion Paper are available at <http://www.dohc.ie/issues/hib/synopsis.pdf?direct=1>
- ⁴³ See 42 above, pps 11-12.
- ⁴⁴ Human Tissue Authority, see <http://www.hta.gov.uk/legislationpoliciesandcodesofpractice/legislation/humantissueact.cfm>.
- ⁴⁵ Department of Health and Children *Discussion Document on Human Tissue Bill*, 2009

⁴⁶ See 24 above.

⁴⁷ EU Tissue and Blood directives <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:102:0048:0058:en:PDF> and <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2003:033:0030:0040:EN:PDF>.

⁴⁸ European Union, Directive 98/79/EC, Article 1.2, Official Journal L 331.

⁴⁹ See 26 above.

⁵⁰ See <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2006:404:0009:0025:EN:PDF>.

⁵¹ Statutory Instrument No 540 of 2007. See <http://www.attorneygeneral.ie/esi/2007/B25461.pdf>.

⁵² Irish Medicines Board, *Guide to the Registration of Homeopathic Medicinal Products*, 2008

⁵³ See www.eudravigilance.emea.europa.eu.

⁵⁴ National Health Service, *Adverse Reporting Advice for Clinical Researchers*, available at <http://www.northoftyne.nhs.uk/publications/research/research-files/aerAcademics.pdf>.

⁵⁵ ECRIN report on GCP compliant data management, see http://www.ecrin.org/fileadmin/user_upload/public_documents/About_ecrin/downloads/ECRIN_Report_D10_Vers1_final_150908.pdf

⁵⁶ See <http://www.cdisc.org/standards>.

⁵⁷ See 36 above

⁵⁸ See <http://www.ema.europa.eu/pdfs/human/ich/036396en.pdf>.

⁵⁹ See 16 above

⁶⁰ See www.ich.org/LOB/media/MEDIA482.pdf, Article 5.18.3

⁶¹ Irish Medicines Board (Miscellaneous Provisions) Act 2006

⁶² For example, UKCRN Risk assessment criteria, http://www.ct-toolkit.ac.uk/db/documents/Trial_RA.pdf, UKCRN guidelines on monitoring of non-commercial clinical trials, http://www.ct-toolkit.ac.uk/db/documents/Trial_MP.pdf UKCRN guidelines on a monitoring checklist, http://www.ct-toolkit.ac.uk/db/documents/Trial_M_CL.pdf

⁶³ Report of the Postgraduate Medical Education and Training Group (Buttimer Group), *Preparing Ireland's Doctors to meet the Health Needs of the 21st Century*, Department of Health and Children, 2006.

⁶⁴ Declaration of Helsinki, 2000 <http://www.wma.net/epolicy/pdf/17c.pdf>

⁶⁵ See 6 above, Executive Summary.

⁶⁶ See 16 above, Section 3.4.

⁶⁷ Report of the Academic Careers Sub-committee of Modernising Medical Careers and the UK Clinical Research collaboration, *Medically – and dentally – qualified academic staff. Recommendations for training the researchers and educators of the future*, March 2005.

⁶⁸ Department of Health and Children, *Medical Education in Ireland – A New Direction* (Fotrell Report) 2006.

⁶⁹ See 16 above.

⁷⁰ European Medicines Agency, ICH Topic E6 (R) *Guidance for Good Clinical Practice*, p9 July 2002.