THE SPONSORSHIP AND GOVERNANCE OF IRISH RESEARCH ACTIVITIES

A CALL TO ACTION

REPORT OF THE SEMINAR ON RESEARCH GOVERNANCE AND SPONSORSHIP – 16 SEPTEMBER 2010
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FOREWORD

The Irish Clinical Research Infrastructure Network (ICRIN) was created in 2006 by UCD, TCD, UCC, NUIG and 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 so that investigator led multi-centre research can be performed to the highest standards and Ireland is positioned as a more attractive location for multi-national industry to perform research.

Earlier this year, MMI and ICRIN published the Clinical Research Roadmap which identified the absence of a well developed system of research governance as one of the major obstacles to the development of clinical research in our hospitals and universities and the broader research community.

The key Roadmap recommendations around Sponsorship and Governance systems are:

- “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.”

- “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 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.”
• “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 Health Research Group (HRG) considerations in the implementation of the Action Plan for Health Research.”

As part of its commitment to moving these recommendations forward, ICRIN hosted a seminar on Research Governance and Sponsorship on 16th September 2010 in the UCD Clinical Research Centre at the Catherine McCauley Centre in Dublin. This document is a report of the proceedings of this seminar and of the recommendations proposed.

One of the key messages from speakers was that if research is to be seen as a core component of health service delivery, it has to be driven from the top down. For research to be valued in the hospital setting there has to be a research metric against which hospitals are measured and a funding stream to support research.

Professor Larry Egan
ICRIN Clinical Director, Professor of Clinical Pharmacology and Head of the Department of Pharmacology and Therapeutics at NUI Galway, Consultant in Clinical Pharmacology and Gastroenterology at University Hospital, Galway
SUMMARY MESSAGES AND NEXT STEPS

- Sponsorship of multicentre and multi-national clinical research is a complex task and needs to be considered carefully in the context of hospital and university research governance arrangements.

- Research governance and oversight mechanisms are needed in each academic hospital to:
  - Capture the clinical research that is being carried out;
  - Assess the research for its relevance to the institutional and national health and research objectives as well as to the innovation and economic agenda.

- The model of the Academic Medical Centre (AMC), a structure comprising a university and its associated academic hospital/s, fulfills research governance and sponsorship requirements as well as progressing the research agenda. The triple mandate of the AMC is the promotion of an integrated approach to:
  - Service delivery
  - Research
  - Education

- Ireland should be strategic in its approach to the conduct of clinical research and universities and hospitals, and together with the relevant government departments and funding agencies, should work together to ensure that research is conducted in the areas in which Ireland has a particular expertise and which is of most benefit to patients.

- Support systems for researchers are needed to provide the information and services that will allow them to carry out their research in compliance with best research practice as well as relevant legislation and guidelines.

- Some services required by the research community to undertake clinical trials, such as sponsorship, trial management, quality assurance, data management, statistics, and pharmacovigilance, could be provided by a combination of emerging and existing CRC’s and/or a single, national centre.

- The hospitals, universities and AMCs need to offer more flexible employment and resourcing contracts (fixed term) to increase the critical mass of researchers in the hospitals who have the time to engage in research and education to complement their clinical service roles.

- The EU Framework Programme (FP7) calls provide an opportunity for Irish researchers to include the development of sponsorship and governance as work-
packages. The research offices, national contact points and others need to signpost this opportunity to applicants so that there is a strategic approach taken to support this initiative in all FP7 applications from Ireland.

- The FP7 calls also provide a learning framework for considering the issues that need to be taken into account as Irish institutions develop capacity for sponsorship and governance of research. The learning from successful FP7 applicants should be compiled at national level and built into a national system for governance and research sponsorship.

- A strategic national initiative is needed to engage the patient community and patient groups actively in raising awareness in Ireland on the benefits of research. A policy on patient education and research dissemination should be adopted by CRCs and research teams in consultation with patient organizations.

Next Steps

ICRIN proposes to take the following steps to promote research governance and sponsorship of clinical research, all of which align with the Department of Health and Children’s Action Plan for Health Research (2009-2013) and the Health Research Board Strategic Business Plan (2010-2014).

1. ICRIN will continue to promote the benefits of and coordinate the development of support systems via the CRCs and research institutes for investigator-initiated clinical trials to effect a modern, evidence-based healthcare environment which enhances Ireland’s innovation and economic agenda.

2. ICRIN will work with interested national stakeholders to develop a consensus on the detailed requirements for a national approach to research governance and sponsorship, looking to models of sponsorship and governance currently used in other countries to facilitate the sponsorship of academic investigator-driven research.

3. ICRIN will work with Enterprise Ireland, HRB and relevant national contact points to highlight to FP7 clinical trials applicants the importance of building work packages into the applications to address the issues of sponsorship and governance.

4. ICRIN will coordinate the preparation of a business case for a national research support centre or consortium, building on the MMI partners’ research resources and involving other nationally funded clinical research resources which will propose how issues associated with sponsorship and governance of clinical research should be handled.
5. ICRIN will work with stakeholders to define the workload and costs associated with sponsoring an investigator-initiated clinical trial from a national perspective.

6. ICRIN will forward the proceedings of the seminar to the Health Research Group chaired by Jim Breslin of the Department of Health and Children which is examining the issue of research governance.
SEMINAR PROCEEDINGS

Welcome and Introduction

Siobhan Gaynor, ICRIN Senior Associate opened the seminar by asking the question: Why is it so difficult for academic investigators in Ireland to act as sponsors for research studies?

Siobhan said that the purpose of the seminar was to explore why an effective and coherent framework for research governance and sponsorship is the answer to the question she posed, and is the necessary foundation to guarantee that Irish research activities will be performed to best national and international research practice. The seminar would examine how a national framework assures funders and agencies that principal investigators (PIs) performing research are doing so in an environment that provides the appropriate level of research oversight and ensures research compliance and adherence to legislative and regulatory requirements.

Speakers had been invited to sketch the current landscape of research governance and sponsorship nationally and internationally. The goal was to identify what needs to be done to optimise and facilitate PIs to perform research in a supportive environment for all types of research involving human participants, such as, medicinal products, surgical and radiotherapy research, biomarker and diagnostic research, medical devices, stem cell and other advanced therapies, neutraceuticals and health outcomes.

The outputs of the seminar would focus on issues and propose solutions to enable:

- Single centre research
- Multi-centre research in Ireland only
- Multi-centre and multi-national research – where an Irish institution is acting as research lead/sponsor or as a participant in an externally sponsored project

The seminar would look at the current developments in addressing the needs of research governance and sponsorship, using case studies that demonstrate the progress to date and the challenges remaining.
The target audience of the seminar were PIs, clinical scientists, hospital and university based clinical researchers and research directors and managers; GPs and community based researchers; hospital CEOs and managers; ethics committee representatives; sponsors of research in medicinal products, medical devices and diagnostics; patient organisations, and; agencies that interface with the variety of research activities being conducted by the Irish research community, research funders and economic development agencies.

Siobhan indicated that the goal of the seminar was to answer key questions with respect to facilitating and conducting clinical trials by academic PIs in Ireland. These questions are:

- Why is an effective and coherent system for research governance and sponsorship necessary?
- How to establish appropriate oversight and governance mechanisms to ensure that PIs can conduct clinical research studies in Ireland and internationally?
- What processes do we need to enhance so that Irish research activities will be performed to best national and international practice?
- How do we make sure that the research system is "fit for purpose" for Ireland?
- How will this framework assure funders and agencies nationally and internationally that PIs performing research are doing so in an environment which meets:
  - Appropriate level of research oversight?
  - Appropriate assurance of research compliance?
  - Adherence to legislative and regulatory requirements?
- How do we ensure the system creates a supportive environment for academic PIs conducting all types of research involving human participants, including:
  - Medicinal products?
  - Medical devices?
  - Biomarker and diagnostic research?
  - Surgical and radiotherapy research?
  - Stem cell and other advanced therapies?
  - Neutraceuticals?
- How to ensure that the system which is developed is oriented towards supporting the researchers who, at the end of the day, will have to implement the governance and sponsorship requirements?

Siobhan referred to the difficulties that may arise in complying with regulations and which must be kept in mind when devising a framework to enable clinical trials. There is a need for
a transparent and flexible framework that is easily navigable by the research community and that facilitates innovation as well as meeting regulatory requirements.

It is a complex task to meet the requirements for sponsorship of clinical research, both nationally and internationally. It is important to create systems and infrastructures to make sure the solutions do not end up being worse than the problem. A framework needs to be developed to meet current needs but also to take into consideration future medical interventions and directions in healthcare provision.

A good system should raise the confidence of our research community, so that they can lead research nationally and internationally. The metrics of the system should aim to facilitate an increase in research that will have a high impact on science and medical practice, so that PIs will become thought leaders in their areas of expertise and so that our patients have access to and can benefit from medical innovations and best practice.
SESSION I: THE CHALLENGE OF SPONSORING SINGLE CENTRE RESEARCH

Chair: Mr Jim Breslin, Assistant Secretary, Department of Health and Children and Chair, Health Research Group

The Challenge of Research Governance and Sponsorship in Ireland
Professor Bill Powderly, Chief Academic Officer, Dublin Academic Medical Centre and Head of School, UCD School of Medicine and Medical Science.

Professor Powderly set the scene in terms of how to establish a framework for research governance and sponsorship in the hospital/university setting.

Now five years old, the Dublin Academic Medical Centre (DAMC) is a tight alliance between UCD Medical School, the Mater and St Vincent’s University Hospitals. Established as a limited company, the DAMC has developed a framework for dealing with issues around governance and sponsorship of research.

The mission of the DAMC, as for any Academic Medical Centre (AMC) in the world, is:

- The recognition that excellence in patient care, particularly in terms of bringing the best patient care to the people is done by purposefully linking treatment and care with teaching and research.

The three taken together produce a patient care system that we believe, and worldwide experience tells us, is better than the sum of their parts.

The DAMC had at the outset modern clinical research facilities on both campuses. The Genome Resource Unit facilities at the Mater Misericordiae and St Vincent’s University Hospitals were established under Cycle 3 of the Programme for Research in Third Level Institutions. To ensure maximum impact of these infrastructures, UCD merged these facilities under a single operational and governance framework to create the UCD Clinical Research Centre. Since opening in 2006, the UCD CRC has completed over 16,000 research patient visits, has an investigative faculty of over 60 PIs and has enabled this faculty to leverage over €11 million in research funding. Ongoing research at the CRC spans all aspects of the clinical and translational research continuum, including clinical trials.
CRC Governance
In terms of operational leadership, a CRC executive has been formed. This executive reports to the DAMC’s Chief Academic Officer (CAO) and is composed of the:

- CRC Scientific Director
- CRC Clinical Directors
- DAMC Director of Translational Research
- Director of Strategy.

The CRC executive is charged with overseeing the day to day operations of the CRC.

In addition, a CRC advisory committee has been established. This advisory committee is populated by:

- Nominees of the DAMC Medical Executive
- A nominee of the UCD School of Medicine and Medical Science
- A nominee of the UCD Conway Institute
- A nominee of the UCD VP for Research
- Members of the CRC Executive

The Chair of this committee is a senior investigator.

The role of the CRC advisory committee is to review and evaluate applications for CRC resources and to oversee and implement CRC policies. In addition, the CRC advisory committee plays a significant role in overseeing the implementation of research strategy developed by the DAMC Research Strategy Group.

The DAMC Research Strategy Group is responsible for developing the overall research strategy for the DAMC and reports to the DAMC board. This group comprises senior investigators and representatives from major UCD research institutes and centres, and is chaired by the DAMC’s CAO.

The governance structure created provides the coherent strategic and operational leadership to enable the CRC to continually respond to the needs of the investigative community.
**Sponsorship**

The DAMC recognises that investigator-initiated clinical trials are a key, strategic research activity:

- They make a contribution to the care of patients as they provide access to novel treatments in particular
- Investigator-initiated clinical trials are critical in treatment studies where combinations of therapies from different suppliers are investigated
- The hospitals that are part of the DAMC are national centres to which patients are referred for treatment of rare diseases. Clinical trials are an important part of the development of centres of excellence in these diseases
- In addition, the DAMC recognises that investigator-initiated clinical trials are an essential part of the enquiry-based focus of academic medical centres (AMCs).

The DAMC aim was to create a structure which can collaborate with like-minded institutions across Europe, thus opening up opportunities for the best young doctors and researchers to move to other sites for postdoctoral education and experience and to attract the best international doctors and researchers to the DAMC.

The EU Clinical Trials Directive presented significant challenges to the DAMC, as investigator-initiated clinical trials still had to be supported in the context of an onerous framework of responsibilities.

In conducting clinical trials it is necessary to work within a legal and regulated framework. Each clinical trial requires a sponsor. A sponsor can be an individual, a company or an institution that takes responsibility for all of the aspects of the clinical trial. The legal obligations on the sponsor of a clinical trial are onerous and can include criminal liability. The regulatory framework requires adherence to good clinical practice (GCP) to ensure that the study is done to recognised and regulated standards and that patients are not exposed to undue harm.

Whilst recognising the significant challenges of sponsorship, DAMC also commits to providing this role for investigators, to ensure that the research vision of DAMC could be realised.
To address this issue, Professor Powderly asked the CRC to look at the challenges and develop a framework whereby UCD could sponsor investigator-initiated clinical trials.

In relation to being the Sponsor, there are many issues to work through including:

- What are the definitive responsibilities for the DAMC as an institute?
- What is the current in-house expertise?
- What processes are needed to help the business of sponsoring?

Many investigators are unaware that they have wide ranging responsibilities in leading clinical trials. There needs to be education of the investigator community so that in the modern world clinical trials are not something that can be done as a hobby.

The CRC examined these issues in detail and created a framework whereby UCD could act as sponsor, and accept the responsibilities of the sponsor for DAMC investigator-initiated clinical trials. (See Peter Doran’s presentation below for more detail on this process and framework.)

“If Ireland is to be a credible player in the international arena we have to have this capability (of sponsorship) and be able to do it.”

Bill Powderly

It is important to remember that clinical trials are but one component of the translational research agenda and the development of a translational research infrastructure. Biobanking is also an important element and requires systems to support the active collection of data to recognised and regulated standards and ethically for future use in research. The research landscape also includes high quality observational studies and a framework is needed to perform these activities to the highest possible standard.

Translational medicine is performed by people who work in hospitals but who have an academic mindset and whose culture is one of enquiry. If Ireland is to be truly competitive internationally, the fundamental difference between a hospital delivering a service only and an AMC where enquiry, research and education adds value to service delivery has to be understood.
“Clinical research and translational research is not just about clinical trials; it is about creating an environment where investigation and asking the questions is encouraged, if the facilities to ask them are there.”

Bill Powderly

The DAMC (through UCD) is now capable of being a sponsor in investigator-initiated studies. It can also act as a legal representative in Europe for multi-national trials. In fact, a number of studies led by DAMC investigators are now ongoing, with all sponsorship arrangements in place. This is a major advantage for DAMC investigators, as we have created a framework which allows their investigator-initiated studies to advance because they can act as sponsor. The role of the CRC in facilitating this activity cannot be overstressed.

The DAMC will continue to develop innovative solutions in response to the needs of their investigators. As an AMC, it is committed to providing the best care possible to patients, care that is enhanced by the supporting culture of enquiry and investigation that we are creating and supporting.
Sponsorship Considerations and Implications

Dr Elaine Breslin, Clinical Assessment Manager, Irish Medicines Board.

Dr Elaine Breslin from the IMB presented the views of the competent authority and addressed the regulations required for sponsorship of clinical trials.

The IMB is the competent authority for clinical trials, which means it is responsible for the authorisation of all trials and ensuring compliance with good clinical practice.

The relevant legislation is:

- The Control of Clinical Trials Act 1987 and 1990
- The EU Clinical Trials Directive, which was implemented nationally by SI 190 of 2004 – referred to as ‘the regulations’ – and which supersedes the Control of Clinical Trials Acts 1987 and 1990

Clinical trials are also covered by the International Conference on Harmonisation Guideline for Good Clinical Practice (ICH E6).

The trials that are outside the scope of the regulations include:

- Non-interventional clinical trials where a medicinal product is used within the terms of the authorisations used as in usual clinical practice
- Clinical trials involving only non-drug interventions (e.g., food supplements or other non-medicinal interventions such as surgery) are not covered not by SI90.

The decision as to whether a research proposal is a clinical trial usually comes down to randomisation and the involvement of additional diagnostic or monitoring interventions that would be used in normal clinical treatment of a patient. In accordance with the regulations, there is no requirement to submit non-interventional studies for authorisation. If there is doubt, investigators should consult directly with the IMB for advice.

A non-commercial clinical trial is one conducted by the investigator/sponsor without the participation of the pharmaceutical industry and in circumstances where the investigator or sponsor has no commercial or financial interest in the outcome. Such a trial is not part of the development of a marketing authorisation for a profit-making organisation such as a pharmaceutical company.
The trial can start when the IMB gives authorisation, a responsible ethics committee opinion has been obtained and the sponsor or the legal representative is established in the EU. In terms of compliance with good clinical practice (GCP), there is an onus to have sponsorship and to ensure that all third party agreements are all in place before the trial starts.

The most common major findings relating to GCP from the experience of IMB site inspections are deficiencies in protocol compliance, informed consent, pharmacovigilance and the management of the investigational medicinal product (IMP). The reasons for poor compliance with GCP are usually due to:

- Lack of adequate resources at the site
- Poor quality of monitoring
- Poor understanding of the legislation or guidance by either the sponsor or investigator and their team, and
- Inadequate knowledge of the protocol.

Every clinical trial must have a sponsor, which can be an individual, a company, an institution, or organisation. A sponsor is a person who is responsible for the initiation and management of the trial. The sponsor does not necessarily have to be the person that finances the trial.

Before initiation of the trial, the sponsor should define, establish and allocate all trial-related duties and functions. A sponsor can delegate the trial-related functions but is ultimately responsible for all aspects of the trial. In multinational trials, there can be co-sponsors or joint sponsors. If sponsorship of the trial is split, then the responsibility must be clearly defined and transparent.

Quality assurance and control needs to be performed with systems in place to ensure that the trial is conducted in an appropriate manner and fit for purpose to the individual trial. As part of the quality control, there must be robust data systems. This does not mean there has to be sophisticated quality management systems in place for every trial. More sophisticated management will be required for multi-centre trials or when running trials with large multidisciplinary teams.

Thorough written agreements of trial duties and responsibilities need to be put in place between the sponsor and investigator/institutions to ensure conduct of the trial in accordance
with GCP and regulatory requirements. The sponsor should receive written acceptance of the protocol by the trial investigator(s) prior to its commencement.

The investigator should comply with procedures for reporting data, permit monitoring, auditing and inspection by the sponsor and the IMB of that data and retain the trial documents for the required period of time.

A written protocol is mandatory - it is not a guideline. It may be appropriate to include recommendations for the steps in a protocol that are not mandatory, particularly for a multi-centre trial conducted internationally where there may be differences in practice between countries participating. This is particularly important when it comes to publishing the data.

All the endpoints of the trial – primary and secondary endpoints - need to be addressed in the data management plan and the statistical analysis plan. It may be appropriate to include a plan for interim analysis in the statistical plan if results are to be presented at a meeting prior to the completion of the trial. The sponsor has the responsibility for data processing and for establishing a data monitoring committee, particularly, if the trial has morbidity and mortality endpoints.

Pharmacovigilance is imperative and the sponsor must keep all records of adverse events reported by the investigators and must ensure prompt recording and reporting. It must ensure that all other investigators in a multi-centre trial are informed of suspected unexpected serious adverse reactions (SUSAR’S) and that these are reported in accordance with mandated timelines. The sponsor is also responsible for supplying an annual list of serious adverse events (SAEs) and a safety report to the IMB.
Key Note Speech: Facilitating Investigator-Led Research - The Imperial Experience

Professor Stephen Smith, Principal of the Faculty of Medicine and Chief Executive of the Imperial College Healthcare NHS Trust

Professor Stephen Smith shared his experience of the Imperial College healthcare system and how a research governance system was established within it.

Imperial College Healthcare NHS Trust was created on 1 October 2007 by merging Hammersmith Hospitals NHS Trust and St Mary’s NHS Trust. The new trust and Imperial College formed a partnership to become the first AMC in the UK which is constituted by UK law to support clinical academic research. There are 10,000 staff and 880 consultants. The local population is two million but of the one million referrals to the hospital area, 50% are not from the catchment area.

As an academic medical centre, it was necessary to be internationally competitive so a vision, mission and strategic objectives were created. To be a world player, it was decided that there was a requirement to do clinical trials and basic research.

Patients suffer if local investigators are not part of multicentre/multinational trials. There is plenty of data that show that if a nation is not at the forefront of clinical trial activity then the nation’s application and uptake of new drugs lags by about three years. This is based on the premise that every new drug that comes onto the market should theoretically be better than the one that came before. Thus, it is the patients who suffer at the end of the day if not given the opportunity to participate in clinical trials.

“We can no longer do medicine where we have people who do medical service provision and others who research. You cannot really call yourself a doctor in the modern world if you are not at the same time an educator and/or a researcher.”

Stephen Smith

The function of the CEO/Head of a Medical School is also evolving. Professor Smith emphasised that everybody who works in the organisation has to have a triple mission – service delivery, education and research. As a result in the Imperial model, every new consultant appointed has included sessions that cover service and either education or research. No single consultant is allowed to practice based on service delivery alone.
To run an AMC it is important to be professional in research and to embed in the organisation the concept of an institution-wide research culture.

There is a single research strategy and one research office. There are agreements in place that share the legal responsibility to varying degrees, depending on who is the sponsor. There is an academically-led clinical trials unit bringing the NHS and the university together. The primary goal is to support clinical trials developed by academics. There is a centre for translational medicine and nine clinical trials facilities.

All of the structures are embedded into one single organisational strategy that involves leadership at all sorts of levels, so that the Director of Research at the Academic Health Sciences Centre is also the Director of the NHS and for the university activities. The Director of Education is a single person. There are nominated places on the board of the Trust for university individuals. The interplay is an absolutely crucial issue which sends a clear message all the way down through the organisation that research is not a luxury. The legality of these structures is also crucial, as when the going gets tough all the structures need to be in place.

Fifteen percent of the total cost of a clinical trial is allocated to administration. There is a centralised approach and access to contracting, finance, grant development and management and research governance is available to every single person undertaking clinical trials.

“If a clinician wants to do a Clinical Trial (CT) they have to go to the CT office. This is where all of the regulatory aspects are handled such as financing, contracting, pre-and post-study management. We have continuous oversight and that requires very robust compliance systems to protect the patient. It has been put in place to protect the patient and to ensure they are not harmed.”

Stephen Smith

There is an integrated model of oversight, employing 80 people, with parallel processes so there is not one for the hospital and another for the university. There is a defined process to guide researchers through the maze of trial development.

The joint research office does all the submissions for regulatory and research ethics approval. The difference between the investigator and the sponsor is clearly made. There is
a stringent and transparent process of determining the cost of a clinical trial through which the cost-benefit can be calculated. Using this streamlined process, the time taken from study proposal to initiation has been reduced from one year to a fast track of eight weeks.

The joint research office has to understand that the PIs are customers. The research office is providing a service and should not be excessively bureaucratic. Investigators may report back if there is a problem. All the mechanisms work smoothly and are transparent.

“Every single patient who comes to the institution is asked if they want to become part of a clinical trial, if they fit the necessary trial requirements. Patients recruited to clinical trials have higher patient satisfaction than those who are not.”
Stephen Smith

Investigator-led research is of particular importance for patient care and the health of the nation. This has a high resonance in the political environment. It is also about generating wealth for the nation which also resonates highly in the current political environment.
Investigator-led research is critical for an AMC. There is a requirement to support our investigators in programmes of clinical research. In the summer of 2009, the responsibility was passed to the CRC to enable studies in the DAMC. The process of bringing a study from the design concept stage through to completion has required putting a number of different steps in place. It was essential to ensure that the development and implementation, rollout and completion of these projects comply with legislation. There are a huge number of relationships involved and it is a complex job to develop and manage studies. There are issues involving funders and contracts and in working with corporate and legal people. There are more challenges in terms of contracts with sites, agreements with investigators and summarising the operational issues to the investigator community.

Single investigators face a significant amount of work to implement their study. The CRC is the first port of call for a DAMC investigator when they want to perform a clinical research study that falls under the Clinical Trials Directive. The role of the CRC is then to manage all of the other relationships and to make sure that all responsibilities and all requirements are met. This is where the staff of the CRC spends a large portion of its time.

“We have not removed the responsibilities from the investigator - we have just channelled the process so a single point of contact is used.”

Peter Doran

The CRC will then guide the investigator through the process. This has now been done for a lot of studies - from single centre studies funded by public agencies through to complicated trials involving multinational agencies where the CRC may be a co-sponsor.

The CRC executive works with and guides DAMC investigators through this process. The process is very complex and there is no way round it. There are a lot of things that need to
be done to take a trial through to completion. This is not a hierarchical process and in many cases the different conversations are in parallel. A major element of the discussion is based around the feasibility of the study that the CRC facilitates. Before we get to the patient or think about an IMB submission, the question is asked: Is the study feasible in the local context?

After funding is secured, the investigator will write the protocol. It is important for the investigator to realise that this is a real document - it is not a couple of pages of guidelines. The CRC staff work closely with investigators to make sure that the protocol is formatted the right way and contains all of the necessary information. The Clinical Director of the CRC plays a significant role at this point in terms of protocol development and making sure that the protocol that has been put together by the investigator will actually address the research question. For the CRC, the study should have high scientific standards as well as regulatory compliance. The study is then reviewed by the CRC executive to see if it fits with the CRC strategy, if there are resources available to complete the study and if there is a budget.

“When an investigator is constructing a budget for a study we have to educate them that it is not just the cost of research or the cost of the drug. There is a whole range of costs that are also involved in order to fulfill the role of sponsor appropriately.”

Peter Doran

Regulatory issues will be finalised in parallel. The CRC supports the investigator through the European clinical trials database (EudraCT) process, IMB submission and submission to the ethics committee. The CRC is deeply involved in facilitating this process and signoff comes from the sponsor and not the investigator. The CRC advisory board reviews the study and the science behind it and confirms the strategic fit with the DAMC.

There are often issues relating to SOPs and defining all of the reporting responsibilities and requirements. The contract with the funder is usually straightforward but the study site agreements with the investigator and any third parties tend to be more complex. If the CRC is delegating sponsor responsibilities, there is a need to make sure that the agreement assigning these responsibilities is appropriate. When the study has been initiated, there are a number of issues that require attention regarding monitoring, reporting and the close-out of the study.

Investigator-initiated research is critical to continue the evolution of treatments for disease. The DAMC CAO recognises that we must support investigators when they want to do these studies. The delegation of these responsibilities to the CRC, whilst creating significant
increased workload, has meant that DAMC investigators are in a position to undertake these studies, to the benefit of both the DAMC and patients.

“We need to develop the conversation nationally around resourcing of interventional clinical trials and very importantly in our context when working across the university into hospitals.”

Peter Doran
Assessing EU FP7 Health Proposals and Leading EU Studies

*Dr Geraldine Boylan, Senior Lecturer, College of Medicine and Health, University College Cork*

Dr Geraldine Boylan, Neurophysiologist and successful FP7 applicant, provided practical insight into how she is involved in two research paediatric consortiums (Co-ordinator of one) and the challenges of sponsoring a multinational trial in the European setting.

Dr Boylan is Director of the Neonatal Brain Research Group in UCC and coordinates the EU FP7-funded NEMO project in Ireland. The NEMO project addresses the FP7 Health call 'Adapting off-patent medicines to the specific needs of paediatric populations' by investigating the safety and efficacy of bumetanide for the treatment of seizures in babies. Bumetanide is included in the European Medicines Agency's (EMA) revised priority list for studies into off-patent paediatric medicinal products.

A multicentre study at the European level was necessary in order to recruit enough patients for an effective study. An important requirement for the EU Framework Programme, is that the applicant must clarify why the study cannot be done at a national or a local level.

Dr Gene Dempsey from the Neonatal Brain Research Group in Cork is co-ordinating the second FP7 funded project in Cork: The HIP trial. This study is also funded under the same FP7 Health call. It is a multicentre, multinational, randomised trial of two different approaches to the management of hypotension in the extremely low gestational age newborn (ELGAN) infant.

Both the NEMO and the HIP study are important initiatives because the EU has realised that commercial companies do not fund these kinds of studies and aren’t interested in funding paediatric clinical trials as there is no return on investment. This FP7 call is very well funded and there is €30-40million available every year for successful applicants.

It is relatively straightforward to do a good scientific proposal on a good cause. This however is not sufficient as the management of a trial at EU level involves the management and oversight of partners in many different countries.

The reviewers look at the science, methodology and the technical quality of the proposal and they evaluate the objectives to see whether or not the proposal goes beyond the current
They then look at the operational implementation and how the group of people in the multiple centres will be organised. The proposal needs to include a project governing board, a scientific advisory board, data safety monitoring boards and advisory boards.

Co-ordination and good project management are key to success. Having a project management company involved shows that the applicants have thought about how the project will be managed. The overall impact of the project is the last evaluation criteria. The impact of the proposal on a European level needs to be elucidated, as the EU needs to know that they are getting value for money and that the project will have high impacts at a European level. It is important to show them that there are mechanisms to keep them up to date at all stages of progress with the proposed research.

There are some other characteristics of the application that the EU pays particular attention to:

- They look at the participants (project partners) of the study to ascertain whether this is the best consortium to conduct the study. Hence good partners are required.
- Has each individual centre got the resources to do the project?

The involvement of stakeholders such as patients, families and, in the case of the NEMO study, parents and patient groups is advisable. It is also important to outline:

- How are you going to educate and train your colleagues, parents, patient groups, etc.
- How will your proposal improve research in the area?
- How will it promote research networks in Ireland/Europe? There is currently no paediatric research network in Ireland. The EU Commission would like to have one. By funding more paediatric research in Ireland, the Commission hopes that it will help to set up an Irish Paediatric Network.
- How are you going to disseminate your message? They want more detail than just publishing in the journals. What journals will you target? What conferences do you propose to present at? How are you going to get the results out? Will you set up a website or, for example, will you send out a newsletter to all stakeholders in the project every month updating them on how the research is going?

Having a sponsor is essential for all studies involving a clinical trial, and for paediatric trials that means a sponsor with the experience and expertise of the requirements and
responsibilities of sponsorship. In the NEMO study, the sponsor is a pharmaceutical manufacturing company with experience of sponsoring clinical trials in the paediatric area. Great Ormond’s St Hospital is a co-sponsor offering additional expertise.
A Hospital CEO’s View of Sponsorship of Clinical Studies

Ian Carter, CEOs of St James’s Hospital

From the hospital perspective, the questions with respect to research activities that need to be answered include:

- What is impact of the research and how is the research optimised?
- What is the focus of the hospital’s endeavours?
- What is the relationship with the paymaster – the HSE?
- Is the working environment stable and how complex is it?

There are about 200 consultants in St James’s Hospital. Of that number, only 20 have a contract that includes some dedicated and protected time to do research and education. Despite this, there is still the expectation that full time service providers will somehow teach and do research at the same time as having a busy clinical schedule.

Within St James’s Hospital there are some able and capable people undertaking basic research. Most hospitals in Ireland don’t have that capacity. Many hospitals are driven by income generation.

In Ireland in recent decades there has been an organic development of hospitals. Consequently, there is duplication of services at multiple sites. There is also a lack of appropriate clinical mass to support research effectively. This makes it more essential to collaborate in research but there is a challenge to do so with 20-30 different institutions. Hospitals need to have a better balance between competing and collaborating in the sector.

However, there is fairly strong recognition at the corporate level that we need to engage more strongly with research. This is going to be more important in the future. Currently, there is no specific allocation in St James’s Hospital budget for research and education.

A recent expert advisory group on financing pointed out that there is a requirement to first look at how mainstream funding mechanisms can be used to support the development of research. According to the service plan in the HSE, some work has been done in terms of the implementation of clinical academic posts. However, it is not embedded as there are no metrics for research and health outcomes and most of the so-called key success factors are process oriented.
“In terms of the agreement I have with the HSE, there is no formal benefit coming to the hospital if I support research.”
Ian Carter

The full recognition of the time needed to undertake research hasn’t been fully understood by and demonstrated to the HSE yet. If someone has a great research idea, there is a need for time and space to carry it out. A replacement for that researcher will be needed for up to two years and this is difficult to manage from a practical recruitment perspective bearing in mind the current headcount freezes, and in an organisation that is predominantly driven by clinical service. Currently, funding in relation to research is mainly indirect. In research there can be multiple funders with a fixed duration and timeframes of funding. The hospitals in Ireland are used to a block grant, which is roughly the same each year, and will therefore have a learning curve working in the research environment where they have to accommodate to a fixed duration the hiring of staff to perform research.

The stability of the hospital work environment in the future is uncertain. There is a strong movement and orientation to community service delivery, which means that the engagement process is now becoming more complex with potentially more partners and more people to talk to.

In future, the money may follow the patient into community service provision. This is the biggest challenge for anyone working in the health sector, particularly on the hospital-side. This shift will have great implications and will result in further complexity and it could start to destroy the integrity of the hospitals if we don’t move service units in a balanced way.

“The AMC set up between St James’s Hospital and Trinity has three core related functions – services, education and training, and research. The aim was to have clear and objective outcomes relating to these three functions.”
Ian Carter

It was important to look at things geographically and strategically to see how to coalesce appropriately. In some areas there was a divergence in expertise which had to be considered. In Trinity College one of the hot research areas is neurology/neurosciences. However, the hospital currently isn’t a specialist in this area so how are the strengths best aligned?
Challenges and issues also arise around a singular mode of engagement as the university talks to the Department of Education and the hospital to the Department of Health.

The development of an AMC is a clear fit. From a hospital perspective, there is the potential generation of innovative patient treatments and education and training. It helps attract the best staff. The AMC model provides a mechanism for a single investment effort that avoids conflict and provides a unified planning agenda. This type of association (AMC) is a way to start to get a critical mass between both the university and its two hospitals so that we can compete more effectively.

Some of the key issues that need to be dealt with:

- Governance issues
- Hospitals and university having an agreed research agenda
- Development of trust between organisations. A transparent agenda which needs to be approached in a spirit of cooperation and engagement
- There has to be strategic management plan with money behind it. Lip service won’t work.

There are significant change implications in a service-driven organisation where expectations of clinicians and scientists from their current day job have to change. There may be issues around critical mass if there is more than one hospital in a particular expertise sector and this has implications in terms of service and territory.

AMCs will develop with specific research portfolios and must be prepared to integrate with community based research. This will present another set of different challenges and hurdles.

“We are moving towards a model of health system which is geographically based. Academic medical centre research with links to research in the community has to be part of the agenda.”

Ian Carter
The ICORG Experience – Sponsoring National and Multi-national Cancer Studies

Professor Paul Browne, Chair ICORG, Consultant Haematologist, St James’s Hospital

Professor Paul Browne outlined the experience of ICORG in sponsoring national and European clinical trials and trials emanating from American institutions in Europe.

ICORG has the capacity to act as a sponsor of multi-centre, multi-national clinical trials for several years and is a not-for profit limited company.

ICORG now needs to enhance its governance structure with an external advisory board to provide critical analysis. In the ICORG setting, that effectively means constituting a new structure with a governance board that includes independent external people, for example, experts in law and finance, people from outside the country, people from industry, as well as internal ICORG people. Without these changes, ICORG will be in an unsafe position in the future as a corporate entity in terms of functioning as a sponsor.

The resources required for pharmacovigilance of multi-centre and multi-national drug trials is usually significantly underestimated in investigator-led trials. This is especially the case when you get beyond the stage of design and early feasibility testing to the 3-5 year post-initiation phase, in which 1000 to 5000 patients are accrued per annum. This follow-up phase represents a significant cost. To comply with regulations, for example, the pharmacovigilance and data monitoring aspects usually continue. We have also found that scientifically there are important outcomes issues that we didn’t anticipate.

In the cancer arena, this has big implications. Industry does not have the same challenges as a company usually focuses on a single agent in a highly controlled environment. Many investigator-led cancer trials are looking at assessing chemotherapeutic agents from two to three companies, often involving off-license usage. When you are doing these types of trials there can be problems if there is a side-effect that is not mentioned on the product characteristics but is well known in medical practice. Being aware of the implications in terms of trial design, safety reporting mechanisms and regulatory responsibilities are the sponsor’s responsibility and require the appropriate knowledge, systems and resources to manage those responsibilities effectively.
There may be a need in Ireland, to create a stand-alone-corporate entity which can take on the sponsorship requirements in a multi-centre or multi-country setting and that that works with the well established three to four AMCs, the HSE and other private institutions.

This entity could perform quality oversight, statistics and data monitoring as well as safety and pharmacovigilance for investigator-led and academic research.
An Insurance Industry Issue Perspective

*Christopher Bryce, Senior Vice President, Marsh Ltd.*

Insurance has a key role in getting a clinical trial approved. There is a trend towards multinational trials and this raises issues about insurance provision in different jurisdictions.

“In most parts of the world insurance is taken as evidence that you have the ability to compensate someone who submits to a trial if they suffer body injury as a result of something going wrong with that trial.”

Christopher Bryce

There are some contractual issues in the way that insurance is arranged in many countries. In addition, costs and litigation issues are variable. In the emerging economies of the world, insurance and regulatory issues may not be that well developed.

A pan-European insurance initiative is not likely and there is likely to be an increasing divergence of insurance requirements particularly as the emerging world starts to catch up in terms of the high costs of healthcare and the fact that nobody wants to pay for a trial that goes wrong, especially if it is a commercial trial.

The issue that causes insurance companies difficulties with clinical trials is the fact that they are poorly represented when issuing documentation, particularly documentation which has to be in local languages. It may have to be issued by companies domiciled at the location of the country hosting the trial.

There is a requirement to insure for certain limits depending on the number of patients in the clinical trial. Also, it varies from country to country but there is often a requirement to insure for a certain period after the clinical trial has closed.

In Europe, there have not been many claims but when they do occur, they tend to be high profile. The fact that there are few claims makes it a very profitable business for insurers.

There are a number of issues that insurers find difficult in relation to clinical trials:
• Representation and issuing local documentation. One of the challenges of doing a trial in a remote place is finding an insurer. Global representation of insurance companies in this area is not well developed.

• Aggregation of insurance limits per drug. Taking the ICORG investigator-led trial using multiple drugs from different companies in multiple countries - if there is a limit of €5m for a trial of drug A, then you move to drug B and then drug C. With different requirements in different countries, it is necessary to factor in this aspect as well in case things go wrong.

• The EU Clinical Trials Directive has led to a fragmented interpretation by member states of how compensation and indemnification requirements for clinical trials should be applied.
QUESTIONS AND ANSWERS

How are Intellectual Property (IP) and conflict of interest issues handled?

Stephen Smith: We have a legally binding agreement between the university and the hospitals. In open competition, Imperial Innovations, a public company, won the bidding for handling the IP for the Trust. We use Imperial Innovations to do the negotiations. There are a set of rules as to how much the investigator gets and how much the university gets, up to certain amounts.

Bill Powderly: The issue around IP in Ireland is fairly tightly regulated. In terms of UCD, Nova UCD manages IP on behalf of the University. We have an agreement between the two hospitals and the university that IP is managed by Nova UCD. This is because Nova UCD has the infrastructure to manage IP and cover all of the issues of potential beneficiaries whether they are hospital consultants employed by the hospital sponsoring the research or done by the university. The reality is that in the Irish context, return on IP is an issue for the future because much activity is in an early stage in translational research and it is unlikely there will be any immediate benefits. It is possible to negotiate IP within the Irish legislative framework and guidelines in a fairly simple fashion. We have an agreement to do so through the university management structure and the hospitals are comfortable with that.

Elaine Breslin: A key point in relation to the sponsor’s responsibilities is that there is no difference between a commercial and non-commercial trial in terms of the GCP requirements. IP does not come into the legal definition within the legislation. However, it does come into the Eurovigilance guidelines, so it is part of the guidelines that the non-commercial investigator should own the data. The European Medicines Agency (EMA) foresee a situation where a clinical non-commercial investigator would be involved in future product authorisations.

Bill Powderly: Regardless of the “commercial” or “non-commercial” distinction, in fact there is always a conflict of interest. Investigators always do a study for a reason. The reason may their own prestige or it may be because funding is available or there are rewards within the institution if they publish. The most important thing about conflict of interest is transparency. Where there is an overt conflict of interest, this should be communicated to the patient in a clear statement in the consent process. There are sometimes institutional conflicts because the institution might be getting a large research grant, while the investigator may not. With
respect to consultants receiving consultancy fees from pharmaceutical or device manufacturers, it is really about transparency and having a culture that understands there are conflicts in everything we do. It is important we recognize that we should communicate conflict of interest about the research we are involved in appropriately.

**Stephen Smith:** We asked the senior consultants for advice on this IP issue. They said en masse that you should not publish if you are taking a consultancy fee. We took it to the Council of the University and introduced it as a bill of the university. So now if an investigator takes a consultancy fee, they are no longer allowed to be part of clinical trials and are not allowed to publish. It was their choice and I could never have forced it upon them.

*Investigators tend to have multiple employers. How do you deal with this when they don’t follow the structures or stick to the rules?*

**Bill Powderly:** We looked at multiple models in terms of our AMC. The Imperial model is the direction that we would like to take. There are important differences in the aspects of management.

**Stephen Smith:** We have two sets of contracts. The Government through the NHS is taking all of the litigation risk. Each individual has their own insurance because the hospital might sue. We have some people that are hospital employees and some are university employees. We decided against a joint (A plus B) contract for exactly these reasons. All are employed by either the NHS or the university.

**Nicky Jermyn, CEO, St Vincent’s Hospital** There are important differences in the UK structure in terms of how clinicians are employed compared to the Irish structure. One of the things that we have identified and have discussed with the Department of Health and the HSE is that the AMC should be the single employer and that people wouldn’t have a university contract for x amount of their time and a hospital contract for y amount of their time. Managing the individual employee and creating the right kind of expectations along with reward systems where you can reward the appropriate behaviours is crucial. This can only be done in the context of a single employer. Irish consultants have for many years had a tradition of much more independence than their UK counterparts, so this will bring its own problems if and when we adopt this system.
How do we ensure that our Irish Consultants are involved in research and/or education?

Stephen Smith: The UK model is that every NHS consultant has 10 units (each one worth half a day). Every consultant must ascribe some time to education (mandatory). The most a consultant is expected to do is 7.25 units in direct patient care. Most of the Imperial College AMC consultants want to do some sort of research and education, that is why they work for us.

Is there a difference between how an academic research trial is perceived by the Irish public compared with an industry-led one?

Bill Powderly: I don’t think the general public knows the difference. We have not been good in this country at explaining the importance of research and the development of research and personalizing it for the individual. They are much better at patient engagement in the UK. You can see advertising campaigns that highlight the importance of research in cancer/heart disease in particular and other areas.

Where good patient organisations have supported research, there is a better patient understanding and therefore the patients are more receptive to research. In AMCs, we need to be serious about patient engagement and we need to work on public awareness and perception. It is critical at multiple levels.

It is very important to develop the public consensus about supporting research for ‘my disease’ but also for research in general and the value research has to society. The US gay community in the advent of the HIV epidemic became involved in decision-making around the type of trials to be run. They now have the same agenda as the investigators and they speak the same language. They became friends, advocates and colleagues. The important lesson is to engage the community. In Ireland, people are very suspicious about people in authority but we have to engage if we want to be successful.
Patients who are admitted to the Imperial AMC are routinely asked do you want to participate in educational activities. How far are we away from asking do you want to participate in clinical trials?

Bill Powderly: We are not that far away. It involves two phases. First ask people – would you be willing for the information that is generated in the hospital to be used for research purposes? Second, would you be interested in volunteering for a study? In the US there are posters about studies and trials all over the public spaces in the hospitals. It is about creating awareness that we are an institution that does research and that participates in trials and the patient then sees it as part of the culture. Patients have a much higher culture of risk than the regulators. They are much more likely to get involved in activities that we perceive as risky for them. They don’t want us to make the decisions on their behalf for them, particularly in terms of authorizations of medicinal products.

In setting your research strategy in your institutions how much is it a top down strategy? Do you use recruitment/infrastructure to promote particular areas of strength? To what extent is it bottom up?

Bill Powderly: In the Irish context it has to be top down with consultation but the decision has to come from the top. Ireland is small and one of the drawbacks in terms of biomedical research is that we want to be a player in everything. We have to accept as a country and then as institutions within that country that we cannot be a major player in everything. We have to decide what we are really good at and where we can make a difference. It doesn’t mean if a really bright person comes along they can’t bubble and shine. But in setting a strategic direction for the institution in an Irish context we need to look at our strengths and capabilities and what can be accomplished. We have to collaborate as patient numbers are too small.

Stephen Smith: The big strategy investments have to be more focused. We focus on cardiovascular disease, infectious disease, diabetes and respiratory disease. Having set the strategy you make the appointments aligned to the strategy.
Where do we go now with sponsorship?

**Bill Powderly:** The HSE is the key stakeholder in this debate. The Imperial model is a model for success as it is doing its own R&D and the NHS is investing £1.5 billion back into R&D. If we were to do the equivalent in Ireland it would require a €150m investment for clinical research in a time of economic constraints. If the country is to have a future then we need to compete. Conducting clinical trials is an opportunity and the lack of vision and foresight is disturbing.

What is the solution to sponsorship? How should PIs be supported?

**Geraldine Boylan:** There is a tremendous enthusiasm for doing clinical trials. The EU is very keen to promote Ireland and want us to apply for funding and see us do clinical trials. They will fund investigator-led trials. If there was a work package for sponsorship/monitoring submitted with applications then it would be funded to quite a high level for each application. There are millions of Euros being devoted to that activity within each project. If we had a national, centralized approach to sponsorship/monitoring then we could create an entity that would provide this service for all investigators.

It is frustrating for the isolated PI trying to work out what to do about sponsorship. We need to start discussions about it because we don’t want to be seen to not address this issue. We have the people and the talent to do these kinds of trials so now we just need the governance arrangements.

**Paul Browne:** ICORG has provided a clear model but it cannot be replicated for every disease process. There is a substantial cost but it must be met for the sake of patient safety and the monitoring of clinical trials. It has to be a shared responsibility and could become a national resource.

MMI is owned by five universities working with their affiliated teaching hospitals. It represents the majority of places where clinical research will take place in Ireland. It is incumbent on us to create a research network. It could be a spin-off company that can compete in the SME domain or another mechanism. The complexity and the cost should not be underestimated.
### APPENDIX I  AGENDA AND SPEAKERS

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Mr Jim Breslin, Assistant Secretary, Dept of Health and Children and Chair, Health Research Group

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Professor Stephen K. Smith, Chief Executive of Imperial College Healthcare NHS Trust

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Dr Geraldine Boylan, Senior Lecturer, College of Medicine and Health, UCC

Professor Paul Browne, Chair ICORG

Mr Ian Carter, CEO, St James’s Hospital

Mr Christopher Bryce, Senior Vice President, Marsh Limited.

Professor Larry Egan, ICRIN Director, Chair of Clinical Pharmacology and Head of the Department of Pharmacology and Therapeutics, NUI Galway

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Virginia Walls, Molecular Medicine Ireland

Jonathan Coyle, FAS Work Placement Trainee at MMI

Conor Caffrey, Medical Writer

Staff of the UCD Clinical Research Centre at the Mater Misericordiae University Hospital
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This list represents the list of attendees who registered on the day of the seminar. It may not represent a complete list of all attendees.