

Insights into Rare Disease Research

Seminar Proceedings

Dublin

26 March 2012

Seminar Programme

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9:30 – 1:30, 26 March 2012

Davenport Hotel, Dublin

This seminar brought together national and international speakers and Irish researchers. **Keynote presentations** on the elements involved in successful research in the area of rare disease were followed by a **panel discussion** on the barriers, solutions and opportunities in rare disease research.

The meeting provided an opportunity to input to planning for the future of rare disease research in Ireland and inform deliberations in the area of research for Ireland's first **National Plan for Rare Diseases**.

9:00 – 9:30	Registration
9:30 – 9:40	<i>Opening Remarks</i> Dr Helen McAvoy, Institute of Public Health in Ireland; Steering Group on a Rare Disease Plan for Ireland
9:40 – 10:10	Prof Orla Hardiman, Trinity College Dublin
10:10 – 10:40	Dr José Maria Millan, Deputy Director of CIBERER, Valencia, Spain
10:40 – 11:10	Prof Brendan Buckley, University College Cork
11:10 – 11:30	Coffee break
11:30 – 12:00	Céline Hubert, Operational Director, Rare Diseases Foundation, France
12.00 – 12.30	Panel discussion

Dr Helen McAvoy, Senior Policy Officer, Institute of Public Health in Ireland – opening remarks

Dr Helen McAvoy opened the event by welcoming speakers and delegates to this timely seminar in the context of Ireland's development of a national rare diseases plan. She also referred to the recent presentations on rare diseases to the Seanad and Joint Oireachtas Committee on Health and Children that had occurred in February as part of Rare Disease Day.

Quoting the European definition of a rare disease as 'a disease with a prevalence of less than 5 people per 10,000 European population', she emphasised that rare diseases as a group represent a significant population health challenge. At least half are children, and rare diseases are often associated with significant mortality and morbidity.

Dr McAvoy emphasised that many strands are needed to improve the lives of those with rare diseases. As rare diseases are diverse in nature, solidarity across many fields is critical to the development of research and good practice, with patients at the centre.

Dr McAvoy outlined that the Institute of Public Health in Ireland was asked by the Department of Health to support the development of a national rare disease plan for Ireland. The Department of Health has convened a steering group in this regard. The steering group for the national rare diseases plan has 4 subgroups; information and research, centres of excellence, patient empowerment, orphan drugs and technologies. Dr McAvoy briefed the delegates on the progress being made by the information and research subgroup, of which she is chair, in the areas of definitions, coding, epidemiology, and basic, clinical, translational, health services and population health research. The benefits of improved information and research on rare disease in Ireland were outlined in terms of delivering better outcomes for patients, evidence-based commissioning and management of service delivery and better coordinated and supported researchers.

The aim of the seminar is to bring people together to inform the work of the research and information subgroup and inform any strategic recommendations made by the subgroup to the overall rare disease plan. Dr McAvoy expressed her wish to identify ways to work more effectively to identify and to learn about opportunities and challenges for rare disease research in Ireland from those who are currently engaging in research. Funding, facilities, networks, international collaboration, infrastructure, leadership, training and expertise were mentioned as priority issues.

A general consultation on the overall plan is planned for later this year.

Professor Orla Hardiman

Professor Hardiman gave a presentation on her experience in research on motor neurone disease (MND) and Amyotrophic Lateral Sclerosis (ALS) in Ireland over the past decade. MND fulfils the criteria of a 'rare disease' with a prevalence of 6 per 200,000. Although rare, MND is benefiting from developments in the pharmaceutical industry's interest in developing orphan drugs. The challenge with MND as with other rare diseases is the difficulty in developing meaningful expertise with small numbers of patients in Ireland and the issues related to quality of care and delayed diagnosis.

The following observations and recommendations in respect of research in rare diseases in the clinical setting in Ireland were identified:

- Investment in quality patient registers is critical. Registers may need to start with small numbers but can accumulate sufficient cases in the long-term to inform epidemiological analyses. A long-term view is needed to develop critical mass datasets suitable for applied epidemiology, good clinical monitoring and the determination of relevant clinical hypotheses and survival analyses. Cohort analyses are required to allow for time and period effect modelling.
- A MND register commenced in Ireland in 1993, ascertainment was completed in 1995 and epidemiological data analysis has been undertaken on two waves (1995-1997, 2005-2007). There are more than 1400 patients on the register and work is ongoing to produce a HEAT map as well as work with Health Atlas to map disease frequency with population density. Work in this field would greatly benefit from engagement with good biostatisticians.
- Encouragement should be given for people to be engaged in the development and analysis of registry data and allow career progression to ensure they remain in Ireland.
- Registers should be HSE funded as they are tools to inform evidence-based quality care, improve patient outcomes and create efficiencies
- Ireland is well placed for population-based registers due to the small well-defined base population. However, Ireland does not have a good track record in data collection. When we do, as is the case for the cancer registry, this has led to considerable advances in health services.
- When considering legislation on health data, there is a need to balance public good with personal autonomy.
- Appropriately operated and analysed clinical registers can demonstrate the real differences in patient outcomes associated with specialised multidisciplinary care. Beaumont Hospital in Dublin is a multi-disciplinary clinic which has demonstrated a better outcome for MND patients through their on-site access to clinical specialists (e.g. palliative care, nutrition). The data suggests better outcomes for MND patients in the Republic of Ireland

than in Northern Ireland which has no specialised service and this may play a role.

- Registers can also be used to better understand genotypes, phenotypes and other factors associated with shorter life expectancy. The prognosis for MND is poor – 70% of people die within 1000 days, while 30% live much longer. Better understanding can assist clinicians to give a more realistic prognosis to the patient.
- Ireland is a small country, and looking at a rare disease occurring infrequently in a population means we need to look beyond borders. There is scope for more all-island working, as well as tapping into genetic signature work in Scotland which has a similar genetic history to Ireland.
- International partnering is beneficial/essential - Ireland is involved in EURALS which facilitates research access to 25 million people, and this project has led to EUROMOTOR which focuses on risk analysis and population based epidemiology for neuromuscular disorders. Data protection is essential to maintain a register and this is currently done for the MND register via informed consent forms. For data sharing internationally, there is a separate process but overall Professor Hardiman considered that data protection legislation can create significant obstacles to research that can deliver outcomes for the common good.
- International collaboration is critical to the development of well-characterised populations for clinical trials.
- MND has both genetic and environmental causes, and the complexity of these origins need further exploration. Around ten percent of MND is genetic – estimated by looking at family histories. MND is probably more heterogeneous than now known, but it is possible that advances like those seen in breast cancer, where treatment is based on the genetic type of breast cancer, will be identified through research in years to come. A breakthrough by an Irish-trained researcher was published in *Lancet Neurology* (September, 2012) where a gene abnormality for MND was identified. This may prove to be of considerable use for clinical trials and orphan drugs.

Further information available at www.mnd.ie

José Millán

Barriers and Challenges in Rare Disease Research

Centre for Biomedical Network in Rare Disease (CIBERER)

Jose Millan gave an overview of the development of the CIBERER network in Spain.

The origins of the rare diseases network was a research programme set up to examine outcomes associated with rare diseases. This grew from an initial research programme related to toxic oil syndrome¹. Research began in 1996, evolving to rare disease research in 2001.

Three main research hubs were established by the Spanish government - CNIO (National Centre for Oncology Research), CNIC (National Centre for Cardiovascular Research), CIBERS (Centre for Biomedical Network) – and it was from this hub that CIBERER was established in 2006. In 2009 a national rare disease strategy was developed.

Challenges identified by CIBERER:

- A lack of epidemiological data on rare disease in Spain as a consequence of the limitations of recording using the ICD system of classification.
- Diversity in data held by different registries and yet an urgency to ascertain the medical/economic burden of rare diseases to obtain a budget.
- Budget for biomedical research in Spain is low generally compared to other EU countries (0.9% of GDP) and the budget for rare diseases is even lower compared to common diseases.
- Lack of incentives and interest by pharma/biotech sector in rare disease research as the investment can outweigh the economic benefits from sales.
- Spanish laboratories undertaking research in the pharma/biotech area for rare disease are small and are principally academic spin-offs which try and collaborate with the pharmaceutical industry.
- Rare diseases are not a priority topic in medical education.
- No formal speciality in clinical genetics in Spain. Therefore, it is difficult to have a rare disease career in this context. There is currently draft legislation in parliament to advance specialism in clinical genetics in Spain.

CIBERER is an integrated hub of research groups. The researchers in the network have become increasingly more connected as the network evolved. An exponential increase in collaborations and publications was observed in the periods 2000-2002, and 2006-2008. Between 2007 and 2011 this increased again with other groups in Spain and more international partnering. CIBERER collaborates with social groups

¹ Toxic oil syndrome resulted from the consumption of rapeseed oil denatured with 2% aniline in the 1980s and is estimated to have affected over 20,000 people in Spain.

and patient associations but CIBERER formally only includes research groups. There are over 700 people working for CIBERER paid for by their own host institution and 159 paid by CIBERER and around half of these are PhDs. They are trained in Spain, and tend to remain in Spain.

CIBERER units are organised into 7 research programmes (for example, genetic medicine, mitochondrial medicine, inherited metabolic medicine), with 60 research groups and 29 associated institutions spread over Spain, but principally in Madrid and Barcelona as the major urban hubs. CIBERER has a biobank of rare disease tissue samples and is an Orphanet partner. Opportunities for public and private partnership are realised as part of CIBERER.

Prof. Brendan Buckley

Clinical trials in rare diseases

Professor Buckley presented on his experience with the initiation, operation and monitoring of clinical trials and the issues related to getting orphan drugs to market.

Clinical trials are defined as prospective studies of an intervention designed to measure the effect of a treatment in a study group compared to a control group. An important principle is that the clinical development of orphan medicines must be safe, effective and of the same quality as commonly available drugs.

For a clinical trial leading to the development of an orphan drug for market, the following steps must be taken prior to starting the trial:

- Validation of a good, relevant non-human *in vivo* model
- Obtain proof of principle
- Work towards GMP production of the medicinal product
- Apply for orphan drug status and avail of the incentives
- Raise the money to cover the trial costs
- Interest industry partners.

The following are the recommended steps for undertaking a clinical trial:

- Design a workable protocol
- Focus on the hypothesis, avoid unnecessary ‘interesting’ questions
- Obtain protocol assistance and scientific advice from EMA
- Obtain adequate funding
- Recruit the right investigators
- Obtain prompt regulatory and ethical approval
- Access sufficient subjects who are the ‘right’ subjects
- Conduct the study to the highest good clinical practice
- Monitor (quality assure) the study efficiently
- Collect, process and report the data
- Communicate the data and use it.

Trials may be deemed unnecessary on compassionate grounds, when no control group is possible, or due to robust bibliographic evidence and data from registries.

- 10% of orphan drugs licensed in Europe had no clinical trial.
- 15% of orphan drugs licensed in Europe had clinical trials of less than 100 people.
- Half of orphan drugs licensed in Europe had 200 people or less in their clinical trials.

Observations and challenges associated with clinical trials for orphan drugs include

- The most difficult element of clinical trials in the field of rare diseases is recruiting patients - registers help, but constructing a robust sampling frame with few people who may have a diversity of phenotypes and who may not have longevity and/or physical ability to attend the trial can make the process difficult. For example, rare cancers, such as non-operable pancreatic cancer, are measured in Europe by incidence rather than prevalence in order to capture cases with a short life expectancy. Recruitment to clinical trials is difficult in such a timeframe.
- A successful clinical trial for orphan drugs relies on the selection of a treatment with a big effect on outcome. Success is also reliant on optimising the design and by early involvement of patient organisations. Small numbers of patients may be adequate if the treatment effect is large, for example, Leonard Thompson, a Canadian citizen with Type 1 diabetes was the only person in the sample for the pivotal clinical trial of insulin. More modern examples would include the small sample size for Carbaglu for Hyperammonaemia associated with NAGS, or the orphan drug Zenas to treat Eaton-Lambert Myasthaenic Syndrome which had 38 people in its clinical trial.
- There has been a steady increase in drugs designated with orphan status, and therefore benefiting from the benefits associated with such designations, although there has been no significant increase in orphan drugs on the market. Forty percent of orphan drugs are for antineoplastic and immunomodulating agents – in other words not genetic rare diseases. Up to May 2011 there were 60 unique orphan designated products, 51% of these for diseases affecting less than 1 in 10,000 patients. Orphan drugs have the best chance of being brought into the market if there are other similar orphan drugs already available – and the market is heavily weighted towards oncology drugs.
- Many people in the field can perceive regulators as gate-keeping barriers to orphan drug status, however this perception must change. The regulator's job is to protect public health by assuring availability of medicines that are safe, effective and of adequate quality. Regulators want drugs to be developed and often can assist with obtaining investment.
- The process of developing and operating a clinical trial requires a rigorous approach to all aspects of study design. One of the greatest causes of failures in trials (aside from drug failure) is investigator failure. Many investigators, do not have sufficient time to dedicate to the trial and may also feel pressure to stretch the boundaries of inclusion on compassionate grounds.

The barriers to developing orphan drugs in Ireland are:

- Lack of expertise in translation from bench to patient
- Access to funding of the required scale
- The academic promotional system; this system is dictated by quantity of publications and this encourages a stream of non-linear research questions, in addition, intellectual property patents means that findings cannot be published for at least 18 months.
- Access to potential trial participants.
- Underestimating the role of patient organisations is a bad mistake. Patient organisations can play a key role as gate-keepers by encouraging patient involvement in good trials, and discouraging involvement in bad trials. Patient organisations also have a wider role to play. The potential exists to lobby, encourage pan-European Centres of Excellence, support patients to travel abroad for trials, to provide ethical guidance and formulate the research questions. In addition, patient organisations can ensure that if a trial fails that the findings are still published.
- In Ireland, orphan drug research should involve integration between higher education, patient organisations, government, capital investment, state-funding agencies, EU agencies, EI and IDA. However, in Ireland the tendency is towards manufacture rather than development. Big Pharma is increasingly outsourcing clinical trials and the focus into the future is into improvements within diseases rather than major breakthroughs in new fields.
- There is a major bottle neck at manufacture stage due to the high costs involved.

Celine Hubert

Rare Diseases Foundation

www.fondation-maladiesrare.org (launched 29th February 2012)

Celine Hubert presented on the Fondation Maladies Rare recently launched in France.

The Foundation is non-profit and funded through patient groups (e.g. AFM; Patients organisation for neuromuscular diseases and Alliance Maladies Rare; an umbrella group of patient organisations) with some support from the French government. The government are particularly interested in the promoting research, networking in rare diseases field and economic costs evaluation, for example, return on investment on the price of orphan drugs. The Foundation has a board of directors (advisors) including people who are not physicians, as well as a scientific committee of 10-12 French experts in rare diseases who will meet three to four times a year, with a larger scientific committee of 25-30 French and International experts in rare diseases meeting biannually.

In France there are 3 million people with at least one of 7000 rare diseases, 200 patient organisations and 1260 diagnostic tests available. There have been two national rare disease plans launched (2005-2008, 2011-2014)

The first plan approved 134 centres of excellence all over France, and though these worked well on their own, more connections were needed. The second national plan had 47 measures and 3 overarching intentions:

- To reinforce quality of care (multidisciplinary, not just medical care)
- To develop research on rare diseases
- To improve European and international partnerships.

The six main fields of action under developing research on rare diseases were to:

- Improve access to resources (expertise, people, knowledge)
- National rare disease database and cohorts
- Clinical trials
- Research on social and human sciences (social impact of rare diseases on the individual, family and society)
- European and international cooperation
- Public health indicators and epidemiology.

The mission was to improve knowledge of rare diseases through structural harmonisation, coordination and improved financing of research. A rare disease foundation was established, a rare disease national database and the RADICO project are in progress (RARE Disease Cohorts). A clinical trials support unit (ORPHANDEV) supplies expertise and assists partnering. Although one building in Paris houses the Foundation and associated agencies, there is a recognition that it cannot be all capital-based so all regions are staffed with the intent of organising networks and promoting research on rare diseases.

Some Points from Panel Discussion

- Consideration should be given to seeing if the French and Spanish models supporting rare disease research and centres of excellence could be scaled down to fit the Irish population size, suggesting that in Ireland just one centre of excellence might be necessary. Spain is connected to shared platforms in Europe, and France is currently negotiating prices for access to shared platforms.
- There are significant cultural challenges to consider in the development of a single national rare disease registry. There are problems around existing infrastructures and systems, professional jealousies and territorial habits, how to fund, how to obtain (and protect) consent, and there is no central ethics committee. A broad national plan is required, with buy in from the HSE legislation on consent and ethics together with appropriate resources.
- Funding for individual rare disease databases is impractical, and the option of accessing cluster grants as an umbrella was raised, perhaps rowing in behind the experience in cancer.

- Obtaining funding can be complex and labour-intensive administratively and not feasible for clinicians and those with full-time posts, however it was noted that measures are underway to streamline procedures to make it more accessible. The French model is desirable whereby the Foundation will take on this role of developing funding expertise for use by others. For Ireland it was suggested that we need to be able to ‘walk before we can run’, and that infrastructure such as databases/registries will be essential to underpin growth in research capacity.
- There is a necessity to engage with international research and undertake longitudinal studies. Ireland will never have a critical mass, particularly for ultra-rare diseases which may be best served through international registries/networks. Ireland should be more outward looking. Engagement in international networks can be led by patient organisations or by clinicians – people with a shared interest coming together.
- The Irish Academy of Medical Sciences acts as an advocacy service around research and may be a group that people would like to tap into. There was a call for a head of research in the HSE to drive and integrate research in Ireland, the HRB does not have jurisdiction over the HSE which would be essential for this role. The UK model was put forward; Sally Davis (current CMO) had a similar role and without extra funding reconfigured money already in the system to drive research. This research lead role is fundamental to research in Ireland.
- Patient groups commissioning research may benefit from behaving like biotechnology companies in being strategic i.e identifying the direction in which research is going and what is most likely to yield patient benefit. A good scientific advisory group should assist this process. It may be advisable to avoid general calls for research as this may lead to non-specific proposals where research questions are massaged to be relevant. Ireland has no problem with taking research money from international sources, and likewise we should not be shy about commissioning research into rare diseases outside Ireland where more expertise may be found due to critical mass.
- Orphan drugs that have been available for a long time can be cheap, but when their status is formalised and marketing authorisation is achieved the cost can go up. The Department of Health need to address this. Health economics expertise is lacking and it was questioned whether there is specific health economic expertise within the Department of Health.
- A parent-volunteer of a rare disease organisation expressed frustration with health professionals’ attitudes and refusal to listen to people who know most about the disease – the child/parent/individual sitting in front of them. It is hoped this will change particularly in light of the introduction of rare disease module into medical education which recognises the layperson’s expertise. There are issues that need to be researched and addressed at the patient/carer – doctor interface as well as at system level. For very many rare diseases there is no orphan drug available or on the horizon so research should not just focus on orphan drugs but consider wider management and quality of life issues.
- It is challenging for GPs to be proficient in the identification of 7000 rare diseases on top of more common diseases. Expertise is required, in particular in clinical genetics and patient groups were asked to lobby for training in this field. Orphanet is an excellent information resource on rare diseases and one with which Ireland needs to become more actively engaged.

- In keeping with the lack of clinical expertise there is also a lack of clinician scientists. It is necessary for new doctors to become engaged in research to build up tomorrow's cadre of researchers.
- Other problems related to the Irish system include: A) Remuneration of physicians in Ireland can be out of synch with the rest of Europe and veate difficulties with international collaborations B) We need to change how we monitor and evaluate our healthcare system; the current metrics of 'number of patients seen' is too crude and gives no sense of quality (move from outputs to outcomes). C) We need to alter the focus of the academic field on number of publications and allow advancement based on other criteria. However, this needs to be balanced with how the rest of the world (particularly Europe and potential FP7 partners) evaluates researchers; if an Irish researcher has lots of publications, they are more likely to be sought out for international collaborations.
- New and innovative ways of raising funding (e.g. In France, SNCF tickets give the purchaser the option of paying one cent more for a charity) are needed at this time. Aside from raising funds, campaigns can serve the purpose of raising awareness.
- The plans for research into social outcomes of rare diseases by the Rare Disease Foundation in France are at an early stage but a structure has been created to support a programme that will do large calls for projects on the impact of rare diseases on patients, families and society. This should facilitate a move from disease to health and society orientation. The term 'citizen' needs to be re-engaged within Ireland, and political philosophy needs be brought into these deliberations.

Conclusion/ Key Findings:

Better information, better research – a priority

The national rare disease plan for Ireland should prioritise the development of research and information as well as developments in clinical care.

Four critical action areas to enhancing rare disease research in Ireland:

(1) Data infrastructure and legal frameworks

Development of rare disease registries and epidemiological analyses is needed in Ireland. This type of basic knowledge on disease burden, needs and patterns of care and life expectancy can reinforce the need for research in the basic, clinical and translational research fields. Registry data can inform service development and provides important evidence to support the ongoing development of effective services, however this activity is scarce. The Department of Health and Health Service Executive should be engaged in the development of health information infrastructure and the associated legal frameworks (data protection and ethical considerations) linked with the Health Information Bill, which in addition to underpinning service development will be essential supports for rare disease research.

(2) Collaborative models of research

Success in clinical trials and bringing new treatments to the market relies on the collaboration of numerous parties including clinicians, patient organisations, industry and the government as well as organisations supporting private enterprise such as Enterprise Ireland/IDA. International collaboration is also critical to getting the most out of registry data to facilitate participation in clinical trials, and to ensure Irish involvement in International rare disease research networks. For many conditions, particularly ultra-rare, international collaboration will be the only pathway to meaningful research. There is also a need to support a rare disease research network in Ireland to maximise the benefits of exchange of information, knowledge and resources across the different research fields and between different sectors such as patient organisations, clinicians, funders and industry.

(3) Developing research leaders in Ireland

There is a range of research skills needed in terms of clinicians, health economists, biostatisticians, epidemiologists and geneticists. There is currently a significant issue with the loss of expertise abroad as career pathways (clinical or research) in Ireland related to rare disease are ill-defined. It is necessary to prioritise the career pathways and development of health service personnel in services critical to rare disease such as clinical genetics is vital. Without the clinical/health services expertise in the first instance it will not be possible to develop research leaders amongst this group.

(4) Strategic approach to the spectrum of research required

There is currently a wide range of research undertaken on rare disease in Ireland but this has developed in a largely ad hoc manner, lacking a strategic framework. While the importance of clinical trials on orphan drugs and technologies is acknowledged, it is also clear that research must focus on those diseases for which orphan drugs are not yet possible. Research allied to the lived experience of the rare disease patient, the interactions with health services, education, employment and society is needed in

order to create better outcomes from long-term management of treatable and non-treatable rare diseases.

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