State of the Art of Rare Disease - Activities in EU Member States and Other European Countries

Ireland Report

Definition of a Rare Disease

The Irish National Plan currently espouses their definition of a rare disease.

National Plan/Strategy for Rare Diseases

The National Plan for Ireland was published with the assent of the Irish Government. It was then formally launched by the Irish Minister for Health. In addition, the recent Programme for Government, 'A Programme for Partnership Government', provides at Page 57 that 'We will implement the National Rare Diseases Plan'.

The opening of a National Rare Disease Office in June 2015 has been funded on an ongoing basis by the National Health Service Executive. The national office is facilitating the coordination and timely access to Centres of Expertise nationally and internationally, and providing up-to-date information regarding new treatments and management options, including clinical trials.

One of the principal recommendations in the Plan was the establishment of a National Clinical Programme for Rare Diseases. This programme is responsible for, among others: Mapping, developing and implementing care pathways for rare diseases; facilitating timely access to centres of expertise – nationally and internationally; developing treatment guidelines for many rare disorders; and developing care pathways with European Reference Centres for those ultra-rare disorders where there may not be sufficient expertise in Ireland. In line with this recommendation, a National Clinical Programme for Rare Diseases was established last year. This clinical programme is the channel for advancing and implementing other recommendations in the plan, such as those on National Centres of Expertise for rare diseases.

A Rare Disease National Office was launched in June 2015. Annual ongoing funding of €200k is being provided and one-off funding for minor capital costs have been provided. The National Health Service Executive is also funding a National Clinical Programme for Rare Diseases that was established last year.
In 2014, the Minister for Health announced €850,000 for investment into charity-led research priorities, which particularly benefits rare disease research. Five charities were to provide matching funding bringing the total investment to €1.9 million. They were to share €850,000 in State funding to take part in international research into rare medical conditions.
In 2016, the next cohort of projects was funded by the State with €1.686M, matched by charity funding of €1.224M. The total funding of €2.91M is shared between 14 charities.

The next round of this joint funding initiative will open in 2017. Finally, the existing National Health Service budget is applied to the care and treatment of all illnesses and conditions, including those that come under the definition of rare disease.

Rare Disease Coding in Health Information Systems

The possibility of adding orpha codes to existing health information systems in Ireland, such as the hospital in-patient system, is being investigated. Under the eHealth strategy (2013) and allied Knowledge and information plan (2015), a National Data Dictionary and Data Model is being developed. This data dictionary and data model will be the single 'point of truth' – describing data types and linking with formalised terminologies for existing and future health service information systems.
A placeholder for Orpha Codes was created within the proof-of-concept (POC - phase 1) of the National Data Dictionary and Data Model. The link to the POC is here: http://hive-worx.com/demo/hwmdt/hw_objects.php?modelkey=5&key=6&title=Healthcare.

Following review and trialling of the POC by stakeholders, the National Health Service Executive is now going to market for a full blown solution and hope to make an award by end of November 2016. Following correspondence between the head of Orphanet and the HSE, the latest dataset containing the most up-to-date

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Orpha Codes was provided for inclusion in the material being provided to potential providers as part of the tendering process. The plan is to load up to 80 data sets to the Dictionary over 3 years (2017-2020).

These would include national systems datasets, business datasets and Health Care Classification Data Sets (Orpha Codes, Snomed CT, ICD codes). The HSE have also been working closely with HiveWorx on further evolving the POC, which involved a number of stakeholders from NIMIS, PAS and HIPE systems.

The HSE, with support from the DOH, are have recently purchased a national SNOMED CT licence. The Enterprise Architecture programme within the Office of the Chief Information Officer is the contact point for use of the national licence.

Expert Advisory Group

An Oversight Group to monitor the implementation of the National Rare Disease Plan was established in 2015. The group is largely comprised of members from the original steering group that led the drafting of the national plan. There have been a number of meetings of the group with a full agenda for each meeting, for which a progress report on the implementation of each recommendation in the national plan featured prominently. This progress report reports on the state of implementation of each of the individual 48 recommendations that were made in the National Rare Disease Plan for Ireland. An Interim Report on the implementation of the plan is also nearly finalised. The members of the Oversight Group are as follows:

- Dr. John Devlin (Chair) - Department of Health
- Prof Eileen Treacy - Health Service Executive
- Dr. Anne Cody - Health Research Board
- Mr. Tony Heffernan - Patient Representative (Bee for Battens)
- Mr. John McCormack - Medical Research Charities Group
- Ms. Avril Daly - Genetics Rare Disorders Organisation (GRDO)
- Dr Geralind O'Dea - The Health Products Regulatory Authority
- Mr. Derek Mitchell - Irish Platform for Patients' Organisations
- Dr. Helen McAvoy - Institute of Public Health in Ireland
- Ms. Helen Byrne - Health Service Executive
- Mr. Philip Watt - Cystic Fibrosis Ireland
- Mr. Liam McCormack - Department of Health
- Ms. Caitriona Connolly - Department of Health

Achievements of the National Rare Disease Plan

The National Clinical Programme for Rare Diseases and the Department of Health encouraged designated centres of expertise to participate in European Reference Networks (ERNs) for Rare Diseases in line with the national plan. With the encouragement of the HSE National Clinical Programme and the Department of Health, five centres of expertise were designated in June this year during the first round of calls from the European Commission for participation in European Reference Networks; four of these designated centres applied for membership of ERNs.

The establishment of a National Rare Disease Office (NRDO) featured prominently in the recommendations of the Rare Disease plan. The national office has now been established by the HSE. Its work is currently led by the NCPRD Clinical Lead, Prof Eileen Treacy, supported by an Information Scientist, part-time Administrative Officer, part-time Genetic Counsellor and by a Consultant Geneticist.

It is, among other functions, providing up-to-date information regarding new treatment and management options, including clinical trials. In addition, the post of Information Scientist for the office is being funded jointly by the HSE and the EU Commission with a number of recommendations in mind. These refer to rare disease registries and the utility of data currently captured in health information systems.

The NRDO has already performed a preliminary situation analysis of the existing rare disease registries and is in the process of assigning these known registries on our national Orphanet site, which is the international rare

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disease reference and information portal funded by the EU. The national plan for rare diseases recommended that the Health Identifiers Bill and the Health & Patient Safety Bill be published. The former was published in 2013 and enacted in 2014. It is now being implemented by the HSE. A revised and much expanded General Scheme of a Health Information and Patient Safety Bill was approved by the government last November and published on the Department's website.

Two recommendations referred to training in rare diseases for healthcare professionals. The Department of Health has contacted formally the various healthcare representative and professional bodies about implementing these recommendations.
Finally, rare diseases have already been tabled on the agenda for North-South meetings. Therefore, future work to deepen cooperation between both jurisdictions on rare diseases is anticipated.

Organisation of Rare Disease Health and Social Care

Centres of Expertise

Ireland operates under a formal National Policy for designating Centres of Expertise, and the designation process is fully implemented. The process for designation of CoEs developed by the National Health Service Executive includes a self-assessment by specialised services/centres/specialist networks based on a number of EUCERD criteria. These include:

• Capacity to provide management of rare diseases

• Evidence of expertise including relevant publications and international recognition

• Availability of multi-disciplinary care including health and social care services

• Capacity to produce and adhere to good practice guidelines for diagnosis and care

• Evidence of the development, measurement and improvement initiatives in quality of care, including patient satisfaction and quality control

• Evidence of teaching and training activities

• Evidence of involvement in research and clinical trials if appropriate

• Capacity to provide expert advice remotely/e-Health solutions

• Development of transition pathways as patients from paediatric to adults' services

• Out-reach/shared care services

• Links and collaborations with patient organisations

• Arrangements for cross border care and referrals

There are five centres of Expertise complying with both National Policy and EUCERD criteria in Ireland.

European Reference Networks (ERNs)

A formal process is in place for endorsing Health Care Providers to participate as coordinators of an ERN. Four of the designated Centres of Expertise have applied to participate in ERNs, in response to the EU Commission call for interest in June 2016.
A process to designate affiliated centres for the purpose of participating in ERNs has also been drafted. At present in Ireland 1 HCP participates as a full member of 3 ERNs.

Members	European Reference Networks (ERNs)
Our Lady's Children Hospital Crumlin	ERN EuroBloodNet ERN Skin VASCERN

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Rare Disease Registration

Currently, neither national nor regional Rare Disease registries exist in Ireland, but disease specific registries are available.

National health information systems

- Hospital In-Patient Enquiry (HIPE) (compiled by Economic and Social Research Institute)
- National Perinatal Reporting System (NPRS) (compiled by Economic and Social Research Institute)
- National Psychiatric In-Patient Reporting System (NPIRS) (compiled by Health Research Board)
- Vital Statistics – death and birth (compiled by the Central Statistics Office)
- National Newborn Screening Programme (run by HSE)
- HSE Health Protection Surveillance Centre
- National Physical and Sensory Disability Database (compiled by Health Research Board)
- National Intellectual Disability Database (compiled by Health Research Board)

Population–based registries

- EUROCAT (Dublin, Galway, South, South East)
- National Cancer Registry
- National Paediatric Mortality Register

Specific rare disease registries

- Cystic fibrosis registry
- Myelodysplastic syndromes registry
- Bernard-Soulier syndrome registry
- Amylotrophic lateral sclerosis and motor neurone disease registry
- Hurler Syndrome registry
- Severe Chronic Neutropenia registry
- National Alpha 1 Patient Registry
- Haemophilia register (National Centre for Hereditary Coagulation Disorders)
- Irish Childhood Diabetes register
- Motor Neurone Disease register

Other registries

- Stroke registry
- Cerebral Palsy registries (West, South)
- Scoliosis database
- Register of patients with PAH (pulmonary hypertension)
- Renal registry
- National Registry of Deliberate Self-Harm
- National Register of Patients with Primary Immunodeficiency
- National Hepatitis C database
- National Cleft database
- Heart and Lung Transplant registry
- Cardiovascular disease registry

Healthcare provider databases

- Records held by clinical specialists operating a particular service for rare diseases
- Records held by support/advocacy groups for rare disease patients
- Laboratory records – pathology, genetic testing, microbiology, etc.

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Genetic Testing

The National Centre for Medical Genetics (NCMG) at Our Lady's Children's Hospital, Crumlin, provides diagnosis and genetic counselling for all genetic rare diseases referred to it. It was opened in 1994 with the objective of providing a clinical and laboratory genetic service for those affected by, or at risk of, a genetic disorder and is the only centre in Ireland providing such a service. The NCMG is organised into three divisions: Clinical Genetics, Cytogenetics and Molecular Genetics.

NCMG processes approximately 13,000 cytogenetic and molecular genetic tests each year and tests for 19 specific gene defects. The cytogenetic and molecular genetic laboratories are externally accredited by CPA UK, a development facilitated by, inter alia, an extension to the NCMG opened in 2007. All tests done at NCMG meet international standards.
Initially, the NCMG had 18 staff and provided a limited service for the Greater Dublin area and the East coast area. Over time, the NCMG has obtained further resources and has been able to extend its coverage to additional areas within the Republic of Ireland. It has always aimed to provide an equitable clinical service nationwide and runs outreach genetic clinics in Cork, Galway and Limerick.

When a genetic test is not available from a laboratory in Ireland but is clinically indicated, DNA samples are sent to specialised laboratories abroad (with 740 'send out' tests listed in the NCMG database). For tests done abroad, the quality of genetic testing meets international standards if sent via the NCMG who ensure that any outsourcing is done in accredited laboratories, with an appropriate audit trail.

Neonatal Screening

Ireland commenced a National Newborn Screening Programme for phenylketonuria (PKU) in 1966. The success of this programme was followed by the introduction of screening for other prevalent treatable conditions preventing mental retardation: homocystinuria in 1971, Maple Syrup Urine Disease and galactosaemia in 1972, and congenital hypothyroidism in 1979 (see Appendix 3). Newborn screening for cystic fibrosis commenced on 1st July 2011. The clinical outcomes of the current National Newborn Screening Programme in Ireland are continually audited and are exemplary as evidenced by international peer review.

The programme is monitored by its Clinical Director, who reports to the programme Governance Group.

Newborn screening is now carried out for a total of 6 conditions meeting Rare Disease definition.

Guidelines and Training Activities

Clinical Practice Guidelines (CPGs)

Ireland has not produced any Clinical Practice Guidelines (CPGs) for Rare Diseases on a national level, nor are there policies for developing, adopting or implementing CPGs.

Training and Education

The National Rare Disease Plan recommended that appropriate modules relating to rare disease feature within all undergraduate and postgraduate programmes of both medical professional and carer disciplines and that in addition to developing competency requirements and training programmes for medical professionals and carers engaged with rare conditions, practical experience and exposure to patients with rare conditions is advantageous.
Letters to the various colleges responsible for training in this area have been issued. The bodies concerned are the Irish College of General Practitioners (ICGP), Royal College of Surgeons in Ireland and Royal College of Physicians in Ireland (RCPI). The letter from the Dept. of Health request the bodies/colleges to consider this recommendation in the context of the organisation of training for health professionals.

The RCSI reported that its medical school creates awareness for the student of the several thousand different diseases leading to ill-health. It referred to students being equipped with all the competencies to recognise and establish a diagnosis for rare disease processes – though it advised that due to the rare nature of these conditions, clinical exposure can be low.

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The RCPI reported to the Department that it facilitates training on rare diseases via a number of specialty study days for doctors on its Higher Specialist Training Programmes. It added that while it is difficult to comprehensively cover all rare diseases in its curriculum, the College ensures that doctors on its training programmes know how to assess the relevant information and resources available for the area. Meanwhile, the RCPI replied that it has included a session on rare diseases in its 2016 Masterclass Series. The session, entitled Clinical Update: Rare Diseases is to take place in the summer (2016) with the aim of exploring the role different specialties play in the management of topical healthcare issues.

Information Resources for Rare Diseases

Orphanet Activities

The national Health Service Executive (HSE), in partnership with the EC 3rd Joint Action on Rare Diseases (2015-2018) is now funding the work of Orphanet Ireland. The HSE has delegated the work of the Orphanet Ireland team to the new National Rare Diseases Office, located at the Mater Hospital, pending the opening of the New Children's Hospital.
This institution is a partner of RD-Action, and annual funding is provided by the National Health Service Executive to support the work of the National Rare Diseases Office which has been delegated the work of the Orphanet Ireland team.

Since 2014, the major activities of the NRDO have been:

- A Business Plan was prepared by the Clinical Programme 2014 -2015 to develop this function which was subsequently supported by the HSE. The HSE is a co-applicant on the (June 2016 – May 2019) 3rd EC Rare Diseases Joint Action (beneficiary 16). The Joint Action provides 3 years part (joint) funding for one Orphanet Information Scientist to be housed within the National Rare Disease Office (NRDO). Prof. E Treacy is the country coordinator for this function and national Orphanet Validator.
- Manchester ceased supporting the Irish arm of their Orphanet operation in September 2014. The Irish Orphanet function was officially launched on June 2015 at the National Rare Diseases Office (MMUH) with Ms. Deborah Lambert as Senior Information Scientist/Project Manager.
- Irish Orphanet data is in the process of being verified and expanded, according to Orphanet quality standards and quality assessment review, under the guidance of the Orphanet Ireland Country Coordinator (Prof E Treacy) and the Orphanet International coordination team in Paris
- The NRDO has performed a preliminary situation analysis of the existing RD registries this year and is in the process of assigning these known registries on our national orphanet site.
- The Irish Health Research Board made 13 awards for rare disease projects in 2014/15. This includes 7 awards jointly with the MRCG partners and 6 awards through HRB only schemes (HRA and HPF). Irish data on Orphanet will benefit from an update in terms of the full scope of rare disease research underway nationally.
- The Irish process for the designation of Centres of Expertise for the purposes of applying to join/collaborate with ERNs has/will also involve Orphanet.

National Helplines

A publically-funded national helpline is available to patients and professionals alike in Ireland, through the National Rare Diseases Office. It provides current and reliable information about genetic and rare diseases to patients, families and health professionals. It was established in June 2015 by the national Health Services Executive (HSE). It is staffed by Information Scientists who have significant experience working with individuals and families affected by rare disorders.

Official Information Centres

The functions of the NRDO include:

- Centralisation of up-to-date Irish rare disease information through Orphanet Ireland (www.orpha.net)

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- The establishment of a rare disease information help line to provide patients, families and health care providers with information and support relating to rare diseases (anticipated to be ready late 2015)
- A website with information and links to relevant rare disease services and organisations around Ireland and Europe Development of national rare disease care pathways and in time, the development of rare disease registries.

The National Rare Diseases Office was launched by the then Irish Minister for Health on June 4th 2015. The NRDO provides information for patients, families and health professionals as outlined above. Information on Irish rare disease resources including:

- Centres of Expertise, Patient Organizations, Clinical Trials, Research Projects, Registries and Biobanks and Diagnostic Laboratories is available on Orphanet (www.orpha.net)
- An information phone line and rare diseases email contact was opened in September 2015 and an 1800 number in February 2016.
- The NRDO website launched in December 2015, is hosted on the HSE website. It contains information for patients and their families as well as for health care professionals. It has a dedicated page describing the Irish process for ERN enrolment
- The National Rare Diseases Information Line is currently developing services under the best practice guidelines of the European Rare Diseases Helpline Forum
- The National Rare Diseases Information Line serves as a reference for the Irish Cross-Border Directive and Treatment Abroad Scheme teams
- The National Rare Diseases Office also provides education and awareness of rare disease through dissemination activities.

Rare Disease Research Activities

Existence of rare disease research programmes/projects

Specific projects for RD are funded from the general research budget. In 2014, the Minister for Health announced €850,000 for investment into charity-led research priorities, which particularly benefits rare disease research. Five charities were to provide matching funding bringing the total investment to €1.9 million. They were to share €850,000 in State funding to take part in international research into rare medical conditions. In 2016, the next cohort of projects was funded by the State with €1.686M, matched by charity funding of €1.224M. The total funding of €2.91M is shared between 14 charities. The next round of this joint funding initiative will open in 2017.

Participation in E-rare and International Research Initiatives

The HRB has put forward proposals in respect of Ireland's membership to ECRIN and BBMRI, which are currently being considered by the Department.

National Alliance of Patient Organisations and Patient Representation

The Genetic and Rare Disorders Organisation (GRDO) is a nongovernmental organisation acting as a national alliance for voluntary groups representing the views and concerns of people affected by or at risk of developing genetic or other rare disorders. The mission of the Genetic and Rare Disorders Organisation is to provide a strong voice for voluntary groups representing people with or at risk of developing genetic or other rare disorders in order to achieve better support and services.

The Genetic and Rare Disorders Organisation acts as a watchdog in relation to legislation concerning disability to ensure that the rights of people with genetic or other rare conditions are protected.

GRDO was incorporated in 1988 and its first achievement was to successfully lobby for a dedicated national centre for medical genetics which was established at Our Lady's Hospital Crumlin in 1994.

An Oversight Implementation Group of relevant stakeholders, including patients' groups, was established to oversee and monitor implementation of the Ireland's National Plan for Rare Diseases. This group was established

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by the Department of Health in 2015 and it has met on a number of occasions. Thus the level of representation and consultation of rare disease patients is at national level.

Integration of Rare Diseases to Social Policies and Services

Ireland has submitted no information regarding social policies, services or integration of people with rare diseases.

Orphan Medicinal Products

The National Rare Disease Plan for Ireland recommended that the national Health Service Executive (HSE) develop a Working Group to bring forward appropriate decision criteria for the reimbursement of orphan medicines and technologies. The approach should include an assessment system similar to that for cancer therapies established under the National Cancer Control Programme and link with the CAVOMP at European level.
The HSE Acute Hospitals Division is developing the terms of reference, required membership and reporting relationship for this committee which will parallel the National Cancer Control Programme Technology Review Committee. This Committee will also be supported by the NCPRD Clinical Advisory Group. The terms of reference for the proposed Rare Diseases Technology Review Group are at final draft stage. A chairperson has been provisionally identified subject to provision of expert pharmacologic support to advise the candidate.

The rare disease drugs to be considered by the Rare Diseases Technology Review Group have not been determined yet.

Rare Disease Day

An Irish conference organised by key stakeholder groups and charities representing the patients was held in 2016. The involved organisations were MRCG (Medical Research Charities Group), GRDO (Genetic and Rare Disorders Organisation and IPPOSI (Irish Platform for Patient Organisations, Science and Industry).

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