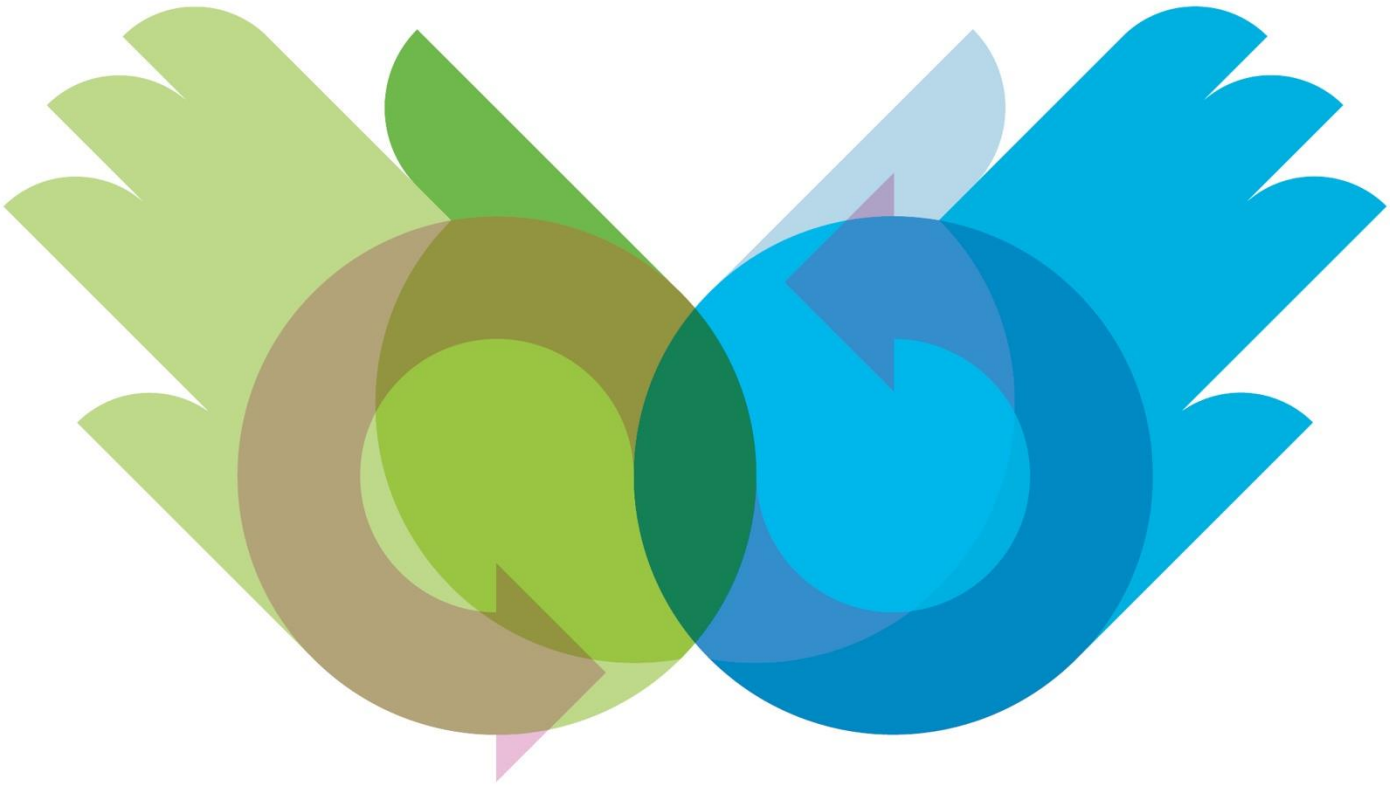
MODEL OF CARE FOR RARE DISEASES



The National Clinical Programme for Rare Diseases

ROYAL COLLEGE OF PHYSICIANS OF IRELAND

Feidhmeannacht na Seirbhíse Sláinte
Health Service Executive

Clinical Design & Innovation
Person-centred, co-ordinated care

Building a Better Health Service | Seirbhís Sláinte Níos Fearr á Forbairt

CONTENTS

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EXECUTIVE SUMMARY

This document was developed by the National Clinical Programme for Rare Diseases. It follows many recommendations of the 2014-2018 Department of Health first National Plan for Rare Diseases. It outlines the current vision for delivery of integrated care for Irish individuals affected with rare diseases both in the national and European contexts. It should be noted that due to very rapid and evolving advances in the diagnosis and care provided for individuals with rare diseases, including advances in reimbursement models for Orphan Medicinal Products, it is considered that this model of care will require continuous updating and review (at least on a five-yearly basis).

A rare disease is defined in Europe as a disease having a prevalence of fewer than five cases for every ten thousand persons. There are currently up to 8,000 described rare diseases. Collectively, these diseases affect around 6% of the population (accounting for at least 300,000 individuals in Ireland). Because of inadequate coding systems for rare diseases, not only nationally but also internationally, the total dimension and extent of the disease burden for these conditions is not currently quantified. It is estimated that approximately 70% of rare diseases have a genetically identified origin (Orphanet 2019).

Many rare diseases have a serious incapacitating and chronic nature often associated with multiple afflictions including physical, sensory and intellectual disabilities. Due to the rarity of these conditions and often lack of national expertise, the diagnosis of these conditions is often delayed for many years. This is associated with significant hardship for patients and families, unnecessary appointments, referrals and tests, loss of income and career prospects and causes delayed opportunities for intervention. In addition, the lack of access of several European Medicines Agency licensed innovative therapies for Irish rare disease patients is an additional challenge.

The European Council 2009 Recommendations on Action in the field of rare diseases (2009/C 151/02) made several suggestions to improve the coordinated care for individuals with rare diseases across Europe. A number of these recommendations have been incorporated into Ireland's first National Plan for Rare Diseases (2014-2018).

Rare diseases pose health challenges for Ireland accentuated by national budgetary constraints since 2009. The care provided to this cohort of patients is often highly specialised and should be considered and commissioned as such. Rare diseases collectively are not rare, and, for a significant number of these conditions, Ireland has a particularly high prevalence. Although specific groups of rare diseases may be included in well-established commissioning models, (e.g. rare epilepsy in the context of the neurology/epilepsy clinical programmes) cohorts of ultra-rare groups of conditions frequently have

poor visibility with very poor national coding and identification systems and are under-resourced and under-funded nationally.

A population-based study in Western Australia (Walker et al, 2017) by record linking, showed that while 2.0% of the population was registered as having a rare disease, this group accounted for 4.6% of people discharged from hospital and had a greater than average length of stay, for a total of 10.5% of overall hospital discharge costs.

As noted in an Irish retrospective study, rare diseases affected at least 3.5% of children who were born in Ireland in the year 2000. However, 64% of all deaths from the National Paediatric Mortality Register data for the years 2006-2016 were accounted for by rare diseases (Gunne at al 2019).

The National Rare Diseases Office has assisted with provision of an accelerated diagnostic pathway for a significant number of rare disease patients and families to date with expected clear cost-savings to the health system. However, it will take time to clearly illustrate the cost-efficiencies of improved integrated care to this cohort of patients within the context of national centres of expertise and the use of IT healthcare through European Reference Networks (ERNs), given the current challenges with coding and registration for these conditions.

The National Clinical Programme for Rare Diseases was established in December 2013 as a joint initiative between the Health Service Executive (HSE) and the Royal College of Physicians of Ireland (RCPI).

The programme's main objectives are to;

1. Improve access to care. Patients with rare diseases and their families should have access to quality information and support so as to enable accurate and timely diagnosis and access to appropriate specialist care.
2. Improve quality. Clinical expertise for rare diseases should be provided through a network of National Centres of Excellence/Healthcare providers or at designated centres abroad.
3. Improve value. Timely access to appropriate diagnosis and care should result in decreased mortality, morbidity and disability and be cost-effective.

This current model of care aims to improve the multidisciplinary care pathway for all Irish patients, families and carers of those with rare diseases with the emphasis on access to safe, high quality care and related clinical research and education tools accessed through national centres of expertise or in collaboration with neighbouring centres of expertise delivered as close to the patient's home as possible. This will be implemented in collaboration with national and international rare disease specialists, hospital and community care providers and psychosocial care providers with the use of approved clinical practice guidelines. This is aligned with the European Commission (EC) Board of

Member States 2019 position paper on developing care pathways nationally for individuals affected with rare diseases.

Central to this model of care is ensuring that patients and families can access reliable information about rare diseases at the point of care, which is frequently in primary care. The model of care also sets out a vision that in the future that doctors, students, all medical and paramedical staff, medical social workers, teachers and pharmacists can access this information. Access to training is essential so that if healthcare providers may not have the due competences to make the specific diagnosis, that they can access general knowledge about rare diseases to enable referral of patients to specialised or expert centres nationally, or for very rare diseases when there is no identified national expert, through the local health provider to European Centres of Expertise within the emerging European Reference Networks (ERNs). This model of care will utilise the National Rare Diseases Office as the central information/coordination 'hub' for Ireland.

As demonstrated by Ireland's national cancer strategy, an early diagnosis for rare diseases and the efficient monitoring of complex situations is most efficient when performed in highly specialised centres that understand and incorporate multidisciplinary care and actively cooperate with patient associations for care and clinical research. Expediting earlier and appropriate access for patients through nationally designated centres of expertise will be paramount for the delivery of improved care.

Integration into national healthcare systems and sustainability of our national rare disease centres of expertise will require the implementation of the appropriate national clinical governance structures and a defined funding model. It will be very important to develop and ensure that these centres have the necessary resources and sustainability structures to provide care nationally for our respective cohorts of patients, and to collaborate with colleagues in ERNs in order to guarantee that Irish patients receive the appropriate high-quality equitable care as close to home as possible. Our national rare disease centres of expertise should align with current European standards and requirements for joining or collaborating with ERNs.

Central to this pathway, the availability of approved clinical practice guidelines, clinical decision support tools and national care pathways, will be the development of appropriate IT and telemedicine solutions as aids to the coordination of national and cross border care. ERNs will facilitate mobility of expertise, virtually or physically, and develop and share information, knowledge and best practice for the diagnosis and multi-disciplinary treatment of rare diseases and access to clinical research and trials within and outside the specific networks.

Access to the appropriate medical genetic diagnostic and genetic counselling services with new technologies, which continue to unravel the diagnosis and better understand the etiology of many rare diseases, will be a central prerequisite to this model of care.

CHAPTER 1 BACKGROUND, HEALTH POLICY & NATIONAL OVERVIEW

1. BACKGROUND

PREVALENCE

We do not have an accurate estimate of the true rare diseases burden in the Irish Republic. The number of individuals in Europe suffering from a rare disease is estimated at over 30 million. If the estimate of 6-8% of the population having a rare disease throughout their lifetimes is accurate, then approximately 300,000 people are currently living with a rare disease in the Irish Republic.

DIAGNOSIS

Accurate and timely diagnosis and access to treatment for individuals with rare diseases is severely hampered by their lack of recognition and visibility in healthcare systems, leading to poor coordination and communication, with limited and fragmented clinical and research resources. Furthermore, the lack of national specific clinical expertise for the condition often leads to inefficient use of limited resources. For most of the last century, many people afflicted by rare diseases had little or no prospects of effective treatments. That situation is now dramatically changing, with major advances in genetic technology and genomic medicine providing a personalised medicine approach with emerging therapies for many conditions previously considered to be untreatable. Implementation of many of the recommendations of the EC 2009 Council Recommendation on action in the field of rare diseases (2009/C 151/02) is facilitating and supporting these actions in many EC Member States (Rodwell and Ayme, 2015).

In challenging times of significantly reduced healthcare spend, marginalized and vulnerable people suffer most unless significant protective mechanisms are put in place. According to Fineberg and Hunter (2013), a successful health system attains the highest level of health possible with superior care that is effective, safe, timely, patient-centred, equitable and efficient, with treatment applied without discrimination and disparities to all individuals and families. Sources of inefficiency well documented for Irish rare disease patients are fragmented and uncoordinated care and lack of continuity of care (HSE 2012 'Have your say' Public Consultation).

A rare disease impact report published by Takeda (formerly Shire) illustrated that it takes on average 5.6 years to obtain a diagnosis for a rare disease in the UK, and 7.6 years in the USA. Patients in the USA saw an average of 7.3 physicians before a diagnosis was made, most of whom were required to provide their healthcare providers with information on their rare disease.

This ‘diagnostic odyssey’ has been recorded around the globe, e.g. in Australia (Elliott and Zurynski, 2015) Italy, (Garrino et al, 2015) and the UK. In the UK, 25% of undiagnosed respondents reported seeing more than 10 doctors in their search for a diagnosis (Rare Disease UK, 2015), with a lack of diagnosis being a major barrier to accessing care.

An Irish 2012 Genetic and Rare Disorders Organisation Survey indicated that 31% of respondents received an incorrect diagnosis and many saw several consultants before the correct diagnosis was made. In 2011 the Europlan 1 public consultation event on Rare Diseases was held at Farmleigh, Dublin. This was followed by the HSE ‘Have Your Say’ on-line public consultation in 2012 (Department of Health National Rare Diseases Plan for Ireland 2014-2018).

Key points from the consultation process regarding challenges experienced by patients with rare diseases included the following: delayed diagnoses, difficulties for General Practitioners in accessing quality information, lack of appropriate diagnostic services and lack of a system for review of the diagnostic journey. Lack of awareness of rare diseases was a cross-cutting issue, evident at all levels of the healthcare system as well as in relation to access to public and private services and entitlements both within the clinical setting and beyond. Better access to specialist care and improvements in accurate and timely diagnosis were considered the areas which could bring most benefit to rare disease patients in Ireland.

In summary, in Ireland, as in other countries, the issues identified with health prevention for rare diseases include

- Lack of awareness and lack of clear referral pathways which result in delays and difficulties in reaching the diagnosis.
- Significant delays in accessing genetic counselling and appropriate genetic testing.
- Insufficient pre- and post-graduate training in rare diseases.
- Lack of coding and registries for rare diseases.
- The lack of specialised and coordinated medical care and often limited access to sufficient psychosocial care, which may be particularly accentuated in a small country with capacity issues.

ECONOMIC BURDEN

The true costs of rare diseases are unknown. They are considered to represent a significant economic burden (Angelis et al, 2015). The hidden costs to patients and their families include the time required to attend appointments, transport costs, costs of over the counter medications, appliances, the loss of earnings of patients and their carers and the loss of contributions to society. Economic evaluations of this burden of care are limited, particularly in the Irish setting (Connolly et al, 2015, Galvin et al, 2016).

EURORDIS published the first European-wide survey regarding the social impact of rare diseases:

'Juggling care and daily life', carried out by, Rare Barometer Voices', May 2017, http://download.eurordis.org.s3.amazonaws.com/rbv/2017_05_09_Social%20survey%20leaflet%20final.pdf. This survey involved 802 diseases and 42 countries, and it illustrated the realities that rare diseases have a serious impact on everyday life. They pose a significant time and care burden for patients and carers, they impact the mental health of patients and their carers and have a very significant impact on work-life balance for the patient and their carers thereby hampering professional activity and causing an associated economic burden. For example, 70% of patients and carers in the survey had to reduce or stop their professional activity due to the disease.

The BURQOL-RD European Research network has evaluated the social/economic costs and health related quality of life of patients with rare diseases across eight European countries (Linertová, 2012). In addition to the direct health costs of rare diseases, many rare diseases are associated with other significant costs that include non-healthcare transportation, social care services, and caregiver's time. In addition, productivity costs have to be measured (the days of sick leave and early retirement for the affected individuals), as well as their carers (for example, for Epidermolysis Bullosa (Angelis et al, 2016), for severe haemophilia CHESS study, (O'Hara et al, 2017) and for motor neuron disease the UK Demos Study (Vibert, 2017)).

In a recent Irish survey about Prader-Willi Syndrome (PWS), (a rare chromosomal abnormality associated with severe developmental delay, behavioural problems and hyperphagia) the hidden costs to patients and their families were quantified to include the time required to attend appointments, the loss of earnings and the loss of contributions to society (Gallagher et al, 2016). Primary carers of people with PWS reported a negative impact on family relationships and on unaffected siblings' mental health. Most respondents or their partners had either given up work or reduced their working hours in order to care for the person with PWS.

Access to respite care for these families in Ireland and access to financial supports was noted to be problematic. Despite the chronicity and high medical need associated with PWS, a significant proportion of individuals had no access to a medical card (50% of 5-12-year olds, 50% of 13-17-year olds and 12% of adults living at home). Caring for an individual with PWS is associated with numerous costs (home modifications, equipment, medication, and travel to appointments). At least 10% of respondents to the survey reported an extreme negative financial impact of the disease. In addition, over 40% of respondents reported having to give up work to care for the individual with PWS.

The benefits of implementing an advanced model of care to include psychosocial care for individuals affected with rare diseases with adequate implementation of primary and secondary prevention would lead to a decrease in mortality and morbidity figures, improved quality of life for those affected, and reduced impact of the disease on patients, relatives, caregivers and society in general. Accurate documentation and registration (epidemiological studies) with an updated coding system (the use of Orphacodes), to assess the true burden of rare diseases and their activity in Ireland will be required to inform the appropriate service planning and required quality improvements.

NATIONAL RARE DISEASE PLAN FOR IRELAND 2014-2018

Ireland published its first national plan for 2014-2018 in July 2014. This plan contains 44recommendations in response to the EC recommendation on action in the field of rare diseases (2009/C 151/02) and includes proposals for;

- Adequate codification of rare diseases and their inventory.
- Identification of the needs and priorities for research on rare diseases.
- Identification of appropriate centres of expertise for rare diseases and support for their creation.
- Fostering the participation of centres of expertise in ERNs based on a multidisciplinary approach to care.
- Development of healthcare pathways.
- Provision of adequate education and training for healthcare professionals in rare diseases.
- Promotion of the development of population screening.
- Taking measures to improve the access to orphan drugs for rare disease patients.
- Assisting with the empowerment of patient organisations.

The vision of the plan is that: 'people with rare diseases receive timely access to the best possible evidence-based, patient-centred and family-centred screening (as appropriate), diagnosis, treatment and care through all stages of their lives, and the needs and experiences of people with rare diseases are recognised, understood and addressed within all aspects of the Irish health system including policy, services and research/information systems'. A recommendation emerging from the national plan was the development of a clinical programme for rare diseases, linked to a central information office.

THE NATIONAL CLINICAL PROGRAMME FOR RARE DISEASES

The National Clinical Programme for Rare Diseases was established in December 2013. The programme strives to ensure that the needs of people with a rare disease are recognised, understood and addressed in a coordinated and patient-centred way.

The programme's main objectives are to;

1. Improve access to care. Patients with rare diseases and their families should have access to quality information and support to enable accurate and timely diagnosis and access to appropriate specialist care.
2. Improve quality. Clinical expertise for rare diseases should be provided through a network of National Centres of Excellence/Healthcare providers or at designated centres abroad.
3. Improve value. Timely access to appropriate diagnosis and care should result in decreased mortality, morbidity and disability and be cost-effective.

Key points from the Irish 2012 public consultation in regard to information sources included difficulties in accessing appropriate information. The consultation showed that respondents felt the following information would be helpful;

- an evidence-based and trustworthy online source of information about the condition
- guidance on how to access appropriate specialist services in Ireland or abroad, and,
- navigating the Irish healthcare system: a summary of the main treatments available, and/or if no treatments are available, information on clinical trials, benefits and entitlements relevant to the condition and points of contact for others with similar conditions or experiences.

THE NATIONAL RARE DISEASES OFFICE

The National Rare Diseases Office (NRDO) was established in June 2015 with the aims to provide information for patients, families and health professionals including information on Irish rare disease resources. This information is available online on the Orphanet site www.orpha.net. An information line and rare diseases email contact was made available in September 2015. The National Rare Diseases Office website www.rarediseases.ie was launched in December 2015. The website contains information for patients and their families and healthcare professionals and also contains online educational modules.

National Rare Diseases Office hosts Orphanet Ireland – the national contribution to Orphanet. Orphanet is the largest international rare disease resource portal. Its aim is to increase the information availability on rare diseases by presenting a comprehensive catalogue of relevant resources (expert management centres, patient organisations, clinical trials, research projects, registries and biobanks, and diagnostic laboratories) and thereby improve the diagnosis, care and treatment of rare diseases. Orphanet is intended to serve the following communities; healthcare professionals, patients, patient organisations, researchers, biotech and pharmaceutical companies, public health, research institutions and public authorities. Orphanet Ireland is co-funded by the HSE and EC funds.

The Orphanet products include;

- An inventory of diseases classified according to existing published expert classifications. Each disease is indexed with ICD10, OMIM, MeSH, SNOMED CT, UMLS, MeDRA and includes the relevant prevalence class, age of onset class, mode of inheritance and associated genes.
- A hierarchical classification system, and encyclopaedia of diseases.
- A search facility by clinical signs.
- An inventory of orphan drugs from orphan designation to market authorisation.
- A directory of expert resources in the partner countries, providing information on specialised expert centres, medical laboratories and diagnostic tests performed, research projects, clinical trials, registries and networks.

CHAPTER 2. DATA EPIDEMIOLOGY, REGISTRIES & EHEALTH

1. INTRODUCTION

This core focus of this model of care is the development and support for patient centred multidisciplinary care pathways for individuals affected in Ireland with rare diseases.

Developing care, taking action and planning for rare disease healthcare, however, means knowing which rare diseases are prevalent in Ireland, and how these conditions impact those affected. Appropriate commissioning and service planning requires accurate coding and registration of rare diseases. Without implementation of these measures funding for this patient cohort will fall behind more common conditions such as cancer and ischaemic heart disease.

Establishing a public health approach to rare diseases includes counting and measuring them. This could then lead to actions to reduce the impact of these diseases on patients and society, with improvements in health, quality of life and life expectancy, rare disease management, and enhanced participation of patients in their communities and society (Valdez et al, 2016).

The 2009 EU Council Recommendation on Action in the Field of Rare Diseases (2009/C151/02) recommended that European Member States should consider supporting at all appropriate levels, including the community level, for epidemiological purposes, registries and databases This was more specifically addressed in the 2013 EU Committee of Experts on Rare Diseases 'Core Statement on Rare Disease Patient Registration and Data Collection' (EUCERD, 2013). The call for registries to be a global priority in the rare disease field is a recurrent theme, noted by the international rare disease patient community in the 'EURORDIS-CORD-NORD Joint Declaration of the 10 Key Principles of Rare Disease Patient Registries' and required to collect 'real world data' urgently needed to enhance national member state reimbursement decisions and to advance the access of patients for innovative medicines and orphan medicinal products (EURORDIS January 2018 position paper). The European Biopharmaceutical Association also stated the importance of rare disease registries for research and post-marketing surveillance in their 2012 Joint EBE - EuropaBio Task Force on Rare Diseases and Orphan Medicines position paper on Rare Disease and Orphan Drug Registries and Databases (EBE/EuropaBio, 2012).

The European Medicines Agency (EMA) recently audited 392 products that received a positive opinion for medicinal products for human use for the period 2005-2013 and 31 related registries. This audit highlighted the need for concepts around patient registries and supported the use of disease-specific registries rather than product related registries for outcome evaluations and benefit-risk monitoring

of medicinal products (Bouvy et al, 2017, Jonker et al, 2017).

The European Commission Joint Research Centre has established a European Platform on Rare Diseases Registration (ERDRI), which provides common services and tools for rare disease registries in the European Union https://eu-rd-platform.jrc.ec.europa.eu/. Since 2018, a common minimum dataset for rare disease registration in Europe is available with the recommendation for implementation in member states.

The Department of Health published its initial commitment on rare disease registration in the National Rare Diseases Plan for Ireland 2014-2018. Nine of the 48 recommendations of the plan directly concern the development of an all-encompassing process of rare disease registration. These recommendations are listed in Appendix 1.

2. BACKGROUND

EPIDEMIOLOGY AND NATIONAL SURVEILLANCE

The precise number of individuals affected in Ireland with a rare disease is unknown. The scientific literature has documented the incidence of several individual rare diseases in Ireland over the past 20 years (National Plan for Rare Diseases 2014-2018), but these give only a point prevalence and do not offer an estimate of the financial or societal burden of these conditions.

Rare diseases, approximately 70% of which have a genetic basis, often show a variation in frequency from population to population. This can be due to genetic variation, both by founder effect and genetic drift, e.g. the rarity of haemoglobinopathies and increased frequency of cystic fibrosis and phenylketonuria in Ireland compared to other European countries. Societal issues also play a role, as exemplified by the relative stability in the frequency over time of Down syndrome and neural tube defects in Ireland compared to the sharp decline in other European countries due to the use of prenatal ultrasound, prenatal diagnosis and termination of pregnancy. In Ireland there is an increased burden of genetic rare diseases, in particular for autosomal recessive diseases, with larger family structures, as noted from the analysis of new-born screening programme data and a small number of rare disease registries. In addition, the Irish Travelling population (although accounting for less than 1.5% of the total population) have a very high incidence of genetic rare diseases (Lynch et al, 2018). Furthermore, Irish national policies on termination of pregnancy to date have resulted in limited prenatal detection, thereby impacting on the prevalence of rare congenital anomalies (EUROCAT 2016).

Current, reliable data on the incidence of rare diseases in Ireland are only available for conditions covered in the current new-born screening programme www.newbornscreening.ie; phenylketonuria, homocystinuria, maple syrup urine disease, classical galactosaemia, congenital hypothyroidism, cystic fibrosis, medium chain acyl dehydrogenase deficiency, glutaric aciduria Type 1, and for rare cancers via the National Cancer Registry. There are 16 rare diseases/groups for which there are active registries (Orphanet). These registries do not have a common core data set, and differ in their goals, which may include population surveillance (e.g. registries of congenital anomalies), case and mutation identification (e.g. sudden cardiac death in the young), disease evolution and monitoring (e.g. Hunter Outcome Survey) and clinical trial participation (e.g. CF registry). Most established registries are primary collectors of data, where the data are held within the clinical team taking care of the patients. The three congenital anomaly registries and the CF registry are secondary collectors of data, where

clinical data are collated by a separate research team from the clinical centres. Several of these registries feed into larger European studies of rare diseases, and as such have common data collection and consent strategies implemented across countries. Some of the registries are wholly or partially funded and structured by pharmaceutical companies as post-marketing surveillance tools for orphan drugs. Irish patients with rare diseases have been key drivers in the establishment of registries in the clinical centres. However, while some patient support organisations are developing data collections of their own, the difficulties in access to research ethics boards (for approval of consent forms) and the costs associated with cyber security remain a challenge for patient organizations that do not have an academic or clinical institutional partner.

TYPES OF REGISTRIES

Registries can be classified into three types;

1. Surveillance registry with non-identifiable data (100% capture of cases).
2. Disease outcome registry, with collection of longitudinal data generated by disease-specific interest.
3. Contact registry for enrolment of patients in clinical trials and research.

The establishment of a registry must depend on the goals of registry, including;

- to describe the natural history of disease, through pooling cases of rare diseases
- to determine clinical and/or cost-effectiveness
- to assess safety or harm and outcomes of new medicinal products
- to measure quality of care
- to serve public health surveillance and disease control
- to connect affected patients, families and clinicians
- to support research on various (genetic, molecular, physiological) bases of rare diseases.

Data protection is a core element of registry formulation, and either consent (‘opt-in’ registries) or legislative exemption from consent (‘opt-out’ registries) is necessary.

3. THE CASE FOR ESTABLISHMENT OF A NATIONAL RARE DISEASE REGISTRY

The recommendations of the 2014-2018 National Plan for Rare Diseases for rare disease data coding and the establishment of rare diseases registration (see appendices) for surveillance and HSE reporting have yet to be put into place. Although the national health identifier was signed into commencement in May 2017, its use has only been adopted in a number of pilot projects, including the eHealth Ireland epilepsy project and the Maternity and New-born Clinical Management System (MN-CMS).

EXISTING CHALLENGES AND OPPORTUNITIES

The lack of basic epidemiology for rare diseases in Ireland contributes to a lack of recognition and hinders the development of appropriate services and policy. Basic prevalence estimates for a rare disease are required to inform;

- Focused service delivery targeted at the specific needs of rare disease patients.
- Pharmacoeconomic evaluations of orphan drugs.
- Appropriate health and social service commissioning.
- Facilitation of clinical trials in Ireland and trial readiness of patient groups.
- Workforce planning.

Information about healthcare system use through rare disease registration could yield important data on;

- Survival, life expectancy and natural history.
- The burden of each disease to the medical system through use of emergency, tertiary, primary and allied health services.
- The burden of disease to patients and their carers through measurement of frequency of hospitalisation, length of stay and frequency of appointments.
- Benchmarking Irish health service performance relative to international standards.
- Assist financial modelling of the cost analysis of the care pathway for rare diseases and efficiencies introduced.

There is currently no central mechanism in place to collate relevant data from rare disease registries and other sources, or to link data sources in the absence of an electronic health record (EHR)and wide-spread use of the new national health identifier. There is no national reporting mechanism for the spectrum of conditions, age profile, mortality/morbidity trends for rare diseases or for the general population, recent demographic changes with population admixtures and new immigration, or the number of Irish Traveller births.

CASE STUDY

A recent Irish study undertaken to establish the prevalence of adult neuromuscular diseases (Lefter et al, 2014) illustrates the difficulties in data collection with the current structure of the Irish health service. The authors ascertained cases from review of records from neuromuscular clinics, hospital neurology databases, hospital discharges via HIPE neuropathology records and via patient communications with the collaboration of two patient organisations. While there was significant overlap in data between these sources, each source also provided unique data about some patients. A review of records by the authors found a significant rate of diagnostic miscoding. The authors cite major obstacles as non-searchable patient databases in two hospitals, miscoding within the HIPE system, and missing dates of birth in clinic and discharge letters. This illustrates the difficulties of capturing data from patients with chronic and rare diseases who are not current hospital attendees or are not followed by a dedicated rare disease centre with an accurate registration system. Morrissey et al, (2013) reported similar challenges in coding/registration of rare inherited metabolic diseases.

The resource implications of rare diseases in Ireland are poorly understood but are likely to be substantial. Rare diseases, whether they are treatable or not, are frequently multisystem, requiring chronic ongoing care with several specialists. As a group, the patients are commonly associated with significant mortality, morbidity and disability, with implications for health services as well as for families and for society. A unique population-based study in Western Australia (Walker et al, 2017) demonstrated by health record linkage that, while 2.0% of the population was registered in the health system as having a rare disease, this group accounted for 4.6% of people discharged from hospital and had a greater than average length of stay, for a total of 10.5% of overall hospital discharge costs.

A recent Irish retrospective study (Gunne et al, 2019) noted that at least 3.5% of children born in Ireland in the year 2000 developed a rare disease by age 15. However, 64% of all deaths from the National Paediatric Mortality Register data for the years 2006-2016 were collectively attributable to rare diseases.

Knowledge of the number of rare disease patients will allow for more accurate pharmacoeconomic studies and may enable the HSE to more accurately negotiate bulk pricing schemes for orphan drugs with pharmaceutical industries. The International Rare Diseases Research Consortium (IRDiRC) has also described the need for registries with a key focus on patient reported outcomes, natural history studies and clinical trials in patient registries, the inclusion of biobanks in registries, patient involvement in registry governance, (Morel and Cano, 2017; Annemans et al, 2017; Parker et al, 2014).

COMMON CODING SYSTEM: IMPLEMENTATION OF 'ORPHACODES'

A core element of establishing a registry will be the appropriate coding and capture of rare diseases within our health information systems. It is estimated that the current World Health Organisation ICD-10 directory captures only about 8-10% (500) of all current identified rare diseases (Bearryman, 2015). So far, 5,400 rare diseases from the Orphanet rare diseases database are present in the foundation layer of ICD-11 (Aymé et al, 2015) but this does not allow for full capture of all rare diseases. The 'Orphacodes' coding system is a hierarchical rare disease classification system that allows different granularity of coding depending on level of diagnosis. Unlike ICD-10 and 11, it is also poly-hierarchical, allowing multi-systemic diseases to be represented in different physiological classifications. For example, an identical Orphacode for 22q11 deletion syndrome appears under 'rare genetic disease'; 'rare cardiac disease'; 'rare intellectual disability'; 'rare clefting' etc. As Orphacodes arises from the Orphanet disease classification system, it allows accurate classification of all rare diseases. Following Europe's 2014 Commission Expert Group on Rare Diseases (CEGRD) publication of 'Recommendation on Ways to Improve Codification for Rare Diseases in Health Information Systems', (CEGRD, 2014), the EC funded Joint Action in Rare Diseases undertook a survey of the state of implementation of Orphacodes in EU Member States (RD-ACTION, 2017a). Of the total of 21 country respondents, 15 had already implemented Orphacodes in their national coding systems and 70% of respondents had further plans to develop this implementation. The EC funded RD-CODE grant (2019-2022) is centralising information about Orphacodes, testing the developed tools for the coding of rare diseases in European Member States, and implementing Orphacodes in four additional member states.

THE BENEFITS OF A NATIONAL RARE DISEASE REGISTRY IN IRELAND

Ideally, over time, a comprehensive rare disease patient registry could;

- monitor the national prevalence and incidence of rare diseases
  instruct the appropriate development of services nationally (or use specialist services abroad)
- establish the natural history of the disease (the disease characteristics, management and outcomes with or without treatment)
- monitor safety after the introduction of new or experimental treatments
- provide an inventory of patients who can be approached for clinical research and participation in multi-centre trials, thereby enhancing 'trial readiness' for Irish subjects
- provide data to inform health economic assessments such as cost-of-illness and cost–effectiveness studies.

4. IMPLEMENTATION OF THE REGISTRY

It is clear from the experience of others that considerable planning and investment must occur if a registry is to contain data that are fit for purpose and to ensure its sustainability, in the areas of;

- Data governance issues (Choquet et al, 2015).
- Defining registry objectives (Bellgard and Hunter, 2013).
- Funding for technology and software development (Bellgard and Hunter, 2013).

For this reason, top-down implementation of the required infrastructure support for a national rare disease registry must occur. Considerable interdepartmental and inter-agency cooperation will likely be necessary to implement a national rare disease registry, as there is currently no single agency or HSE service which provides collection of data as well as its analysis for Department of Health purposes. The Irish rare disease registry should also be consistent with the overall European Registration Platform initiative.

5. RECOMMENDATIONS

A number of recommendations are outlined below, which may be considered in the context of the initial recommendations of the 2014-2018 National Rare Diseases Plan (see Appendix 1) and recent and ongoing developments.

1. EXISTING RARE DISEASE REGISTRIES

1.1 Disease-specific registries, both existing and developing, should continue until the eHealth strategy is completely implemented in all fields of healthcare in Ireland. These registries should be future proofed in terms of technology and changing demographics and should be integrated nationally and within the European registries including ERN registries, where possible.

1.2 Appropriate support should be provided for the ongoing involvement of Irish registries in relevant European collaborations, including the EUROCAT registry and in particular the European Reference Network registries. This will require adoption of the core EC data set and the outcome indicators adopted by the reference networks. Designated Irish Centres of Expertise will require infrastructure funding to support these registries as central to their activities.

1.3 Existing disease-specific registries should adopt Orphacode nomenclature and work towards implementation of the common EC data set so as to standardise rare disease registration and align with HIQA draft guidelines, data protection legislation, and international best practice. Consensus data patient centred outcome assessments should be developed in collaboration with patient representatives for disease-specific outcome registries in line with the ERN specifications, which will enhance outcome evaluations of new medicinal products and interventions.

1.4 Existing registries should incorporate the national Individual Health Identifier consistent with Sláintecare recommendations for eventual interoperability for an overall National rare disease registry.

1. EXISTING NATIONAL REPORTING

2.1 Data from existing publicly funded rare diseases registries should be compiled to form a periodic national report on the epidemiology of rare diseases in Ireland. Reporting on rare diseases should be integrated into the existing HSE reporting on health and disability services, for service development to reflect patient needs.

Demographic data collected should include ethnic identifiers to eventually allow stratification of rare diseases among high-risk cultural and ethnic minority groups for the purposes of population equity, appropriate neonatal screening and improvement of diagnoses and outcomes. This report may be limited in its initial scope but will broaden over time.

3. INDIVIDUAL HEALTH IDENTIFIERS

3.1 Full adoption of individual health identifiers in Irish healthcare, under the 2014 Health Identifiers Act.

The Individual Health Identifier is a is a unique non-transferable number that is to be assigned to all individuals using health and social care services in Ireland, and which will last for their lifetime, as detailed in the Health Information Quality Authority (HIQA) Information Governance and Management Standards for the Health Identifiers Operator in Ireland (2015) https://www.hiqa.ie/system/files/IG-and-M-Standards-for-Health-Identifiers-Operator.pdf Use of an individual health identifier to identify individuals in a rare disease registry would allow for pseudo-anonymisation in general registry use, prevent duplication of records due to identical names and dates of birth, but also allow for re-contact through healthcare providers for purposes of research or clinical trials.

Consideration should also be given to having an additional data field in a rare disease registry for a PPRL (privacy-protecting record linkage) code which would allow for anonymous data linking across Europe.

4. THE DEVELOPMENT OF A NATIONAL RARE DISEASE REGISTRY

4.1 That a National Rare Disease Registration service be established within the HSE.

This organisation governing the national rare disease registry will include responsibility for the following;

- ownership
- funding
- staffing
- data protection compliance including data protection impact assessments
- compliance with HIQA management guidelines for national data collections
- analysis and generation of statistics/reports of the data on the registry.

4.2 That a National rare disease registry be developed by the National Rare Disease Registration service. This should be a multi-stakeholder initiative, with collaboration from the Council of the Chief Information Officer and eHealth Ireland (to develop technical capacity allowing primary data collection of patient information for rare diseases from inpatient, outpatient and primary care settings), representation from the HSE and the Department of Health, as well as patient organisation representatives. This registry will facilitate the most complete ascertainment of cases and productive use of data generated for rare diseases

4.3 That a working committee be formed within the HSE to delineate the stakeholders and structure of the national rare disease registry in line with Sláintecare priorities.

4.4 That a National rare disease registry encompasses the 26 counties, but for the purposes of interoperability, be informed in its structure by established national EU registries, including those of England and Northern Ireland. That wherever possible common data elements and design be developed between the Irish National rare disease registry and that of Northern Ireland to promote collaboration between the two jurisdictions to produce all-Ireland rare disease epidemiological information.

The registry strategy should be developed within the context/governance of the national e-Health strategy (Health Service Executive, 2015) and the (Health Service Executive, 2019 Service Plan and

Sláintecare. See Appendix 2 for details regarding the e-Health Strategy). Preliminary work is required in the short term to ensure that the emerging eHealth roll out contains capacity to work with a rare disease registry (for example, using Orphacodes). Prioritisation will be required to align the roll out of the Electronic Health Record with the implementation plan for the Primary Care E-Health strategy and the New Children's Hospital. The development of a rare disease registry would allow for the harnessing of data from multiple sources without the re-collection of secondary data from multiple primary sources, as occurs currently.

5. THE MODEL OF REGISTRY ('OPT-IN' VS 'OPT-OUT')

5.1 Publication of the Health Information and Patient Safety Bill is pending. Ideally, this legislation will allow assembly of data into a rare disease registry as a legislative requirement, paving the way for an 'opt-out' registry to obtain the greatest possible ascertainment of rare diseases nationally. Further legislative changes to allow registration without consent may be necessary to allow accurate registration, but this may evolve in parallel with eHealth Ireland's development.

The eHealth project will require considerable work on the model of consent that will not differ significantly from that required for a rare disease registry. Boundaries of data viewing and sharing by/between different healthcare providers will be needed. For this, appropriate levels of consent will have to be determined and clarified.

6. CLASSIFICATION AND CODING OF RARE DISEASES

6.1 Develop guidelines on coding and recording of rare diseases within relevant Irish health data systems that are consistent at European and global level.

6.2 Orphanet Ireland should continue to register rare disease resources in Ireland to monitor the availability of services (expert clinical centres, research and clinical trials, and patient organisations). Orphanet Ireland should continue to be funded nationally to provide this function.

6.3 Orphacodes, as the most accurate rare disease classification ontology, should be adopted as a static field in the eHealth EHR, according to the current European Commission approved guidelines, aligned with other medical coding systems such as ICD and SNOMED CT. Orphacodes specified in an EHR should be as central as core demographic variables that are visible to every health professional..

6.4 Orphacodes should be assigned to a patient by experts at rare disease expert centres, as they are associated with chronic disease, and are separate from HIPE codes associated with an admission. This will improve data accuracy. Multiple Orphacodes may be assigned to the same patient as some will have more than one diagnosis.

Orphacodes will also allow for the coding of 'syndrome without a name' patients as they will be able to be classified with an Orphacode until a diagnosis is made, when a more granular Orphacode can be used. For example, a person may be classified as having a 'rare neuromuscular disease' until their diagnosis of 'paramyotonia congenita' is made, at which time the specialist will change the Orphacode designation in the EHR. Systems exist for facilitating accurate Orphacoding of rare diseases.

The LORD (linking open data for rare diseases) tool combines Orphanet, Online Mendelian Inheritance in Man, and Human Phenotype Ontogeny data for rare diseases. Orphacodes for each disease are cross-referenced to different classifications (CIM10, OMIM, SNOMED CT, MEDDRA, MESH, UMLS). Training will be required for healthcare professionals who are inputting Orphacodes.

http://lord.bndmr.fr/#homepagehttp://www.lord.bndmi.fr/

7. COMMON DATA ELEMENTS FOR RARE DISEASE REGISTRIES

7.1 Irish rare disease experts and national registration governance bodies should adopt the defined set of common data elements defined at a European level for use in the national rare disease registry, in line with European best practice and the agreed minimum dataset of the JRC Rare Diseases Registration process.

7.2 Existing disease-specific registries must engage in forward-planning in order to move towards adoption of the defined common data element set to promote interoperability.

Having common data elements (CDEs) in registries is key to the utility of the data and the interoperability of registries between regions or countries. A challenge is defining a unified set of data to collect across all rare diseases with the variability that exists between rare diseases – paediatric vs adult, multisystem, etc. However, a set of CDEs has been proposed for European use in rare disease registration, e.g. EPIRARE project (Taruscio et al, 2014), and in France (Choquet et al, 2015). The JRC Rare Diseases registration project has now defined a minimum core data set (EC-JRC, 2017) and a number of ERNs have added additional outcome parameters. Use of open access software with pre-

defined common data elements for rare disease registration, such as the European Commission Rare Disease Registry Framework, should be promoted.

8. DATA REPORTING AND PATIENT COLLABORATION

8.1 The Irish rare disease registry development should work with Rare Disease Ireland, the national umbrella group for patients with rare diseases and other relevant rare disease national organisations, to discuss the publication of rare disease data.

In Ireland, rare diseases may not be identifiable in the HIPE data due to the exclusion of statistically small numbers. To protect the anonymity of individuals with ultra-rare conditions, cases that number less than 5 are not reported. Unfortunately, this means that those diseases with a prevalence of less than 1 in 50,000 cannot be captured in hospital discharge data. The Public Health England congenital anomaly and rare disease registration service has obtained release from this restriction. A similar approach should be developed collaboratively in Ireland with the cooperation of Rare Diseases Ireland and other patient stakeholder groups.

Also, with the collaboration of Rare Disease Ireland, a patient portal for inclusion of patient-reported outcome measures should be eventually incorporated into the registry design, possibly based on the eHealth Ireland model under development.

9. DATA USE, ACCESS AND SHARING

9.1 The national rare disease registry will contain data to fulfil different goals. Under data protection legislation (GDPR), permission to access and use data must be transparent and patient centred. These goals include the collection of data to a) enhance the provision of direct patient care, b) support quality assurance and quality improvement purposes, c) assist with service planning and evaluation and d) support research. Guidelines must be developed for access to registry data.

The following guidance relates to the type of data to be accessed;

- Aggregate data; national reporting of incidence and prevalence of rare diseases to be managed by the HSE/Department of Health/Central Statistics Office for service planning purposes.

- De-identified health data for research (e.g. regarding longitudinal outcomes or medication): studies would need to be approved by HSE ethics committee before release of datasets.
- Patient identified data: (e.g. for contact regarding clinical trials or research): should only be available to National Rare Disease experts and their collaborators after receipt of HSE ethics approval.

CHAPTER 3. CARE PATHWAYS, CLINICAL PRACTICE GUIDELINES & CLINICAL RESEARCH

1. INTRODUCTION; AN INTEGRATED APPROACH TO DEVELOPING CARE PATHWAYS

As outlined in Chapter 1, adequate care coordination is particularly important for those affected by rare conditions, which are often serious, chronic and complex in nature. This is not only relevant to Ireland but also across Europe and other developed countries. Research conducted by Rare Diseases UK in the last 6 years has indicated that poorly coordinated care is a major issue for patients and families affected by rare diseases (Rare Disease, 2015). This study also identified significant variation and inequity in the way that services are organised, with excessive and uncoordinated appointment scheduling, lack of communication between providers and a frequent lack of capacity and resources within services. Although good examples of care coordination do exist, there is no single agreed model implemented across all rare diseases.

The UK 2011 National Coalition on Care coordination defined care coordination as 'a person-centred, assessment-based, interdisciplinary approach to integrating healthcare and social support services in a cost-effective manner, in which an individual's needs and preferences are assessed, a comprehensive care plan is developed, and services are managed and monitored by an evidence-based process'. This typically involves a designated lead care coordinator. Such coordination may be required, for example, when care is required over a long period of time; when the level of care required increases; when multiple services are required; or when a high frequency of emergency unplanned admissions occurs. These types of service needs are often applicable to many rare diseases, which tend to be multi-systemic across services. For rare diseases, coordination across services is often essential including healthcare, social care, primary, secondary, tertiary and quaternary care and voluntary sectors. Poor coordination of care contributes to significant wasteful spending which is proposed to be significant for rare diseases (OECD 2017).

According to the 2019 Sláintecare proposals, as well as the 2012 HSE Rare Diseases 'Have your say' public consultation, rare disease patients and their families clearly wish to have their care coordinated as close to home as possible. According to a recent EU survey (ERN Coordinators Group, 2018), in contrast to other European countries, Irish patients with rare diseases frequently attend hospitals for ongoing surveillance rather than their General Practitioners. A recent audit conducted by our group has indicated that general practitioners in Ireland are not currently empowered with adequate access to knowledge and care plans to frequently manage complex rare disease patients in the community.

Less than 15% of General Practitioners surveyed were aware of Orphanet (the international rare diseases information portal) (Byrne et al, 2019).

Sláintecare proposes to prioritise the integrated care pathways between the acute hospital systems and community care, in particular for patients with chronic diseases. It is proposed that the rollout of EHR (with the community EHR as a priority) will improve the current status.

According to the 2008 World Health Organisation definition, integrated care can be summarized as 'the management and delivery of health services so that clients receive a continuum of preventive and curative services, according to their needs over time and across different levels of the health system'. For healthcare and support to be 'integrated', it must be person centred, coordinated and tailored to the needs and preferences of the individual, their carer and family. It means moving away from episodic care to a more holistic approach to health, care and support needs, which puts the needs and experience of people at the centre of how services are organised and delivered.

The five core strategies from the World Health Organisation framework are to;

1. empower and engage people
2. strengthen governance and accountability
3. re-orientate the model of care
4. coordinate services
5. create and enable the environment.

Quality care should strive to provide timely access to care, thereby reducing harmful delay and providing effective and efficient care that is equitable and person centred. Due to the multi-systemic nature of most rare diseases, patients often need follow up care and support from different categories of health professionals, often different medical specialists as well as social workers and psychologists, which requires a level of coordination not easily found in our healthcare systems. Studies have shown that the quality of life for people with rare diseases compares unfavourably both physically and psychosocially to those with more common chronic diseases. In addition, patients have a more negative experience in terms of medical care and loss of socioeconomic activities as cited in the EC 2016 position paper 'Recommendations to support the incorporation of rare diseases into social services and policies'. Effective, coordinated, integrated care that includes health, social and local services support is essential to overcome the particular challenges of rare diseases.

2. RARE DISEASES CENTRES OF EXPERTISE

The European Commission 2009 recommendations on action in the field of rare diseases recommends that Member States should promote multi-disciplinary teamwork, holistic approaches, continuous person centred and participatory care in both health and social care for individuals affected with rare diseases.

The emerging role of rare disease Centres of Expertise both nationally and across Europe will have a key role in facilitating integrated care provision in line with the EUCERD 2013 recommendations on quality criteria for Centres of Expertise in Rare Diseases.

Rare disease Centres of Expertise in Ireland, if funded appropriately, should bring together or coordinate multidisciplinary competences/skills, including those for patients and families affected by rare diseases such as medical, surgical, nursing, health and social care professionals and the relevant community services within the specialised healthcare sector. Centres of Expertise could play a key role in facilitating integrated healthcare provision by bringing together or coordinating multi-disciplinary teams and developing multidisciplinary care pathways for patients with approaches that can be coordinated between the acute hospital systems and primary care, so that patients and families can receive care as close to home as possible.

In addition to the Irish 2012 HSE rare diseases public consultation, international research into general practice and community care emphasises the unique role of the General Practitioner and the community support teams in terms of continuity and coordination of care (Starfield, 2012; Elliott and Zurynski, 2015).

This current model of care should define the way health and social care services should be delivered for rare disease patients and describe the delivery of best practice and services for this population according to the requirements at the differing stages of the condition including respite care, rehabilitation and palliative care options, when required. This should incorporate all stakeholder involvement, based on the principles of illness prevention, patient empowerment, multi-disciplinary cross-service care planning and delivery.

3. THE ROLE OF THE NATIONAL RARE DISEASES OFFICE

The National Rare Diseases Office is a HSE service and was opened in 2015. The office is located in the Mater Hospital Dublin and is governed by HSE Acute Operations. The office is staffed by qualified healthcare professionals who have experience in working with people affected by rare diseases. The National Rare Diseases Office is the recognised national coordination 'hub' for rare diseases expertise. It provides information about rare diseases and Centres of Expertise and manages the Irish section of Orphanet. It provides information about rare diseases to a broad range of stakeholders including; patients and the family members, advocacy and patient organisations, healthcare professionals and researchers.

The National Rare Diseases Office is responsible for mapping the location and availability of clinical expertise and Centres of Expertise in Ireland. Over 75 centres have been mapped and listed on Orphanet to date. It also provides information about virtual cross-border consultations and Centres of Expertise in neighbouring Member States. Furthermore, the office has developed a series of educational videos for GPs and members of the public, which are available on the National Rare Diseases Office website www.rarediseases.ie.

4. CARE PATHWAYS

Clinical care pathways are used worldwide to improve and structure care processes within the patient-centred care concepts. These should assist in fast-tracking patients through healthcare and social services, increase efficiency of state resources, and reduce waiting times for accessing support and social services. A Cochrane systematic review defines care pathways as a complex intervention that meets four criteria;

1. Has a structured multidisciplinary plan of care.
2. Translates guidelines or evidence into local structures.
3. Details the steps into a course of treatment or care in a plan, pathway, guidelines, algorithm or other 'inventory of actions'.
4. Standardises the care for a specific population, (Lawal et al, 2016).

The National Rare Diseases Office assists with the identification of the appropriate specialist services and support centres (when available nationally or as appropriate), through neighbouring Centres of Expertise in ERNs. Central to this model will be the integration with patients and expert patient

support groups and advisors. Empowered patients are active participants in decision-making regarding their disease, equipped with understanding their disease and knowledge of the full range of choices and resources available to them. The National Clinical Programmes for Rare Diseases incorporates patient representatives and a patient organisation representative in its working group.

Many rare diseases are chronic and debilitating and many directly affect mental health (Muir 2016, Nunn 2017, Swillen et al, 2015). Liaison psychiatry and specified care pathways will have a central role in provision of care for many rare disease patients. To date efforts are in place to develop paediatric based multidisciplinary clinics for patients with chromosomal and single gene disorders that are associated with significant neurodevelopmental abnormalities and mental health issues. The liaison psychiatry group across the Children's Hospital Group and major adult hospitals could also support the patient and family with a new diagnosis (associated anxiety and depression) and assist with compliance and adherence challenges. With the focus on mental health in the Sláintecare report, this is an area identified in the 2014-2018 rare diseases plan which should be developed.

In addition, many rare diseases are life-limiting conditions, i.e. conditions for which there is no reasonable hope of a cure. This includes many of the rare chromosomal anomalies. For some other rare conditions, they become life-limiting over time with limited treatment success.

Access to high quality palliative care services in the appropriate setting is essential for patients with life-limiting conditions and their families. Palliative care improves the quality of life of people facing the problems associated with life-limiting illness and supports their families. The aim of palliative care is to enhance quality of life and wherever possible, to positively influence the course of the illness.

5. EUROPEAN REFERENCE NETWORKS

European Reference Networks are the physical or virtual networking of doctors and researchers with high expertise in the areas of rare or low-prevalence and complex diseases across Europe. The EU Directive on Cross-Border Health Care (Directive 2011/24/EU, Article 12) recommended the development and funding of the ERNs. 24 ERNs were formally launched in March 2017 involving over 900 highly specialised healthcare providers in 26 Member States in Europe.

Further information about ERNs is available online at
www.hse.ie/eng/services/list/5/rarediseases/ernexpertcentres.html

The goal of an ERN is the improvement in the overall quality and management of care of a single rare or complex disease or a group of rare diseases with similar healthcare needs by complementing, supporting and providing added value to the existing services and expertise at the national level. An ERN can bring additional expertise that may currently be missing in Ireland. This networking activity between national Centres of Expertise promotes the sharing and mobility of expertise rather than the patients travelling themselves. Occasionally patients will still need to travel to cross-border Centres of Expertise.

The virtual consultations are facilitated by a confidential IT platform (Clinical Patient Management System, CPMS) and virtual boards of the networks provide consultations for rare and complex conditions. This platform has been approved by the EU Data Protection Supervisor (compliant with GDPR) and is in use currently across member states.

ERNs will be well placed to implement best practice guidelines, clinical trials and research. The EU Directive states that ERNs 'will facilitate mobility of expertise, virtually or physically and develop and share information, knowledge and best practice and foster developments of the diagnosis and multi-disciplinary treatment of rare diseases within and outside the network'. Centres applying for membership of an ERN must have strategies in place to ensure that care is patient-centred; patients' rights and preferences are respected; and they must show a research component to their work.

Patients are the core focus of ERNs and all ERNs have patient representatives (ePAGs) as members.

In this model of care, in line with core recommendations of the National Plan, patients' rights to appropriate assessment and treatment will be realised through a recognised national Centre of Expertise or by linking a patient to an ERNs. Centres of Expertise are defined as national healthcare providers that are validated using Orphanet criteria. A key point in the model of care and development of care pathways is the importance of identifying Centres of Expertise and supporting those centres to join ERNs. As will be noted in the next section, specified clinical guidelines will be developed and ERN guidelines will be incorporated at the designated centres.

Irish Centres of Expertise wishing to join these ERNs should meet the core safety and quality criteria as set out by the EC 2014 Delegated and Implementing Decisions. To date, 'licensing' of healthcare providers in Ireland is not implemented. Currently, centres that wish to enter ERNs as 'full members' require endorsement by the HSE and the Department of Health based on satisfying the criteria of the ERN independent assessment process (completion of template documentation, external review of documentation and site visit by an independent assessment team). Member States with providers with less capacity that do not have representation as a full Member in an ERN can participate through healthcare providers that are 'associated' or 'affiliated' in order to achieve the widest possible

geographical coverage, exchange of knowledge and best practice. It is proposed that affiliated partners will have access to services for treatment and diagnosis and opportunities to collaborate with the development of guidelines, registries and research as deemed appropriate by the ERN co-ordinating team. Ireland is a member of three ERNs since 2017 and plans to join the majority of the ERNs in the 2019 call for new members.

The National Rare Diseases Office as the 'coordination hub' provides information to stakeholders and patients regarding the location of national expert sites (full or affiliated centres) and linked ERNs and will assist with patient access to the CPMS platform. It is envisaged that over time patients with undiagnosed or complicated cases may seek teleconsultation in Ireland through their healthcare provider to the relevant ERN.

The National Rare Diseases Office is currently involved in an ERN project of knowledge generation and sharing; the development of a taxonomy of information tools for rare disease patients and healthcare providers, which will include the development of a repository of approved clinical practice guidelines, clinical decision support tools, patient information leaflets and documents, and diagnostic pathways that will be linked to our national website and information systems and directly accessible to patients, specialist providers and general practitioners.

6. THE SOCIOECONOMIC BURDEN OF RARE DISEASES

As outlined in Chapter 1, many rare diseases are chronic in nature and have a significant burden of disease, not only for the affected individual but also for the extended family. This model of care acknowledges the socioeconomic burden of having a chronic rare disease. The health service should, in time;

- address the accessibility of healthcare services for affected individuals
- support the required social services and psychological support frequently required
- support the rehabilitation needs and the real financial supports required.

The 2018 Innovative Patient-Centred Approach for Social Care Provision to Complex Conditions project (INNOVCare) provides very relevant recommendations in this respect (INNOVCare, 2018), which will inform EU and member state structural reforms in this area. This project (funded by the EU for 2018) was aimed at developing and testing a holistic person-centred care pathway for individuals with rare diseases that links health services to social and support services based on pilot studies in a number of member states. A preliminary recommendation of INNOVCare was the support of case managers to integrate the care pathways.

Access to medical cards and associate benefits for rare disease patients has been highlighted as an area of concern by patient advocates and by many respondents to the 2014 HSE public and patient consultation process on the review of medical card access (Keane, 2014). It was reported by a number of respondents that the current system for allocation of medical cards did not discern the true costs of these chronic illness and that the 'discretionary system for medical card approval could be reviewed'.

The General Medical Service scheme governs access to medical cards with a legislative basis in Section 45 of the 1970 Health Act. Current legislation requires that an individual's income and expenditure (i.e. their overall financial situation) must be considered during the assessment process. This process may not necessarily take into account the severe disabling burden of disease for many rare disease patients and the 'hidden costs' as elaborated in Chapter 1 (for example for Prader-Willi Syndrome), (Gallagher et al, 2017).

A recommendation of the Keane report was that a supportive approach for those with a combination of financial and/or medical hardship could be addressed by extending the discretionary decision-making process beyond financial hardship, to include an assessment of the burden of the condition. In acknowledgment of the difficulties in extending the current 'discretionary decision' to include an assessment of the burden of diseases, it was recommended that a strategic framework be established. As noted in our recent audit of rare diseases in general practice, rare disease patients with medical cards attend their general practitioner twice as often as rare disease patients who do not qualify for a medical card. This suggests that perhaps the lack of universal health coverage for primary care has resulted in a two-tiered health system in Ireland which creates inequalities for those rare disease patients that can pay and enjoy faster access to services and treatment, reducing the overall burden of the disease for these patients (Forster 2018). The access to medical cards is a significant ongoing concern for patients with chronic rare diseases and their families.

7. GENETIC DIAGNOSIS

Since approximately 70% of rare diseases are genetic in origin, the delivery of effective genetic services (diagnosis, screening and early treatment) through a national service, at national specialised Centres of Expertise or through ERNs, will have a vital role to play in rare disease diagnosis and prevention, and will be cost effective. The HSE is currently planning the development of a National Genetic and Genomics Medicine network for all children, adolescents and adults nationally. The immediate need for genetic testing and delivery of multidisciplinary care for rare disease patients with age appropriate

settings was illustrated in the 2012 'Have your say' consultation. 'Better access to specialist care' and 'improvements in accurate and timely diagnoses' was considered the areas that could bring most benefit to rare disease patients in Ireland. Accelerated diagnosis using genetic testing could reduce health-related sufferings as well as the underuse and misuse of healthcare resources. It is acknowledged that early diagnosis through clinically guided genetic testing with new genomic technologies may avoid the need for unnecessary procedures, inappropriate hospital admissions, incorrect diagnosis, shorten substantially the 'diagnostic odyssey' and will be cost-efficient.

For many patients with rare genetic disorders, national specialist services will be appropriate and available. It is proposed that genetic diagnostic (vs. research) testing, including next generation sequencing technologies, should only be performed at nationally accredited laboratories with the appropriate pre-test counselling (Matthijs et al, 2016; the Irish Disability Act, 2005).

Currently, over two-thirds of genetic tests nationally are provided by neighbouring member states. With the expansion of genomic and genetic testing for ultra-rare conditions cross-border genetic testing will continue to play a central role.

The National Clinical Programme for Rare Diseases strongly endorses the EC position paper: 'Recommendations on Cross Border Genetic Testing of Rare Diseases in EU Nov 2015' (CEGRD, 2015) and the need and right for rare disease patients to obtain accurate and timely diagnoses. Access to genetic testing should be ensured, provided locally or on a cross-border basis, as required. A national reimbursement plan (incorporating public and private insurance models) is essential for Centres of Expertise that provide these tests (if accredited to do so). We propose that Ireland should have a transparent policy pertaining to Cross Border Genetic Testing, guidelines, with a transparent documented policy for national reimbursement (for both public and private patients).

Investment in development of national guidelines for send-outs (ensuring samples only get tested if they meet clinical criteria and are only carried out in accredited laboratories) would reduce clinical risk and be cost-effective. The Rare Diseases Clinical Programme is collaborating with the Pathology Clinical Programme to identify the national laboratories that are accredited to perform rare disease diagnostic testing, including genetic tests. The Orphanet platform currently contains information about laboratories that perform genetic testing for rare and non-rare conditions (the latter in its brief to take over the cataloguing function of the former EUROGENTEST genetic laboratory database), as well as information about laboratory accreditation and external quality assessment.

8. POPULATION GENETIC CARRIER SCREENING

A recommendation of the 2014-2019 National Plan for Rare Diseases was that the HSE Governance Committee/Group on Newborn Screening should consider the population benefits of newborn screening. This would include examining whether existing screening programmes need to be expanded or modified. and establishing the requirement for carrier screening. The national plan also recommends that the Department of Health should also provide a policy framework for population-based screening programmes. Carrier screening for certain autosomal recessive disorders aims to facilitate reproductive decision making (Holtkamp KCA et al, 2017). Technological genomic advances now allow for multiple disease carrier screening in at risk populations for certain prevalent conditions (e.g. Hurler syndrome and I cell Disease in the Irish traveller population, Sickle Cell Anaemia in individuals of African ancestry), in addition to population-based expanded carrier screening for certain conditions. The National Clinical Programme for Rare Diseases does not have a policy role in expanding or modifying the national genetic screening protocols. Responsibility for this area lies with the Newborn Screening Committee at the Department of Health. However, it is proposed that over time that nationally designated centres of expertise will play an important role in the expansion of the HSE Newborn Screening Programme.

9. CLINICAL PRACTICE GUIDELINES

Recommendation 20 of the 2014-2018 Rare Diseases plan states that 'The National Clinical Programme for Rare Diseases through a National Office for Rare Diseases should develop the clinical and organisation governance framework that will underpin care pathways and access to treatment for rare disease patients, particularly in the context of the transition from paediatric to adult care'. In the context of transition this area is addressed in Chapter 4.

Rare Diseases are by their nature encountered infrequently by clinicians. Thus, clinical practice guidelines (CPGs) which address complex diagnostic or therapeutic strategies, or where there may be several possible interventions and linked care pathways, will be the cornerstone of ERNs. CPGs are 'statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options' (Institute of Medicine).

A key step in creating evidence-based guidelines is determining critical disease outcome; factors that are important not just to providers and healthcare systems, but also to patients. Thus, engagement with patients is critical.

Although there are well established methodologies for developing guidelines for treatment for common diseases, such as guidance published by the National Clinical Effectiveness Committee, rare diseases present a challenge for the development of CPGs on a national member state basis, often with a lack of sound evidence, available national clinical expertise, availability of clinical trials for small populations or national publications. It is, however, recognised internationally that there are a limited number of CPGs for rare diseases and that the development of CPGs is a priority commissioned action for the established ERNs (Kremp et al, 2012, Pavan et al, 2017).

The National Clinical Effectiveness Committee was established by the Minister for Health in September 2010. One of the responsibilities of the committee is to commission national clinical guidelines and national clinical audit. To date, the committee has not commissioned clinical guidelines on rare diseases.

Currently, Orphanet provides information for over 300 CPGs and 40 country-specific emergency guidelines, as well as a guide for validation of CPGs.

The European Commission Cross Border Care Directive 2011/24/EU requires that ERNs and healthcare providers wishing to join ERNs should have the capacity to develop good practice guidelines. Currently, all the approved ERNs have declared that the development of clinical practice guidelines is a priority.

The objectives of national clinical guidelines exist to explain the optimal diagnostic and therapeutic management, as well as the care pathway, of the given rare disease to the professionals involved in the patient's care. The clinical guideline can serve as a reference for the primary care physician. Its goal is to optimize and streamline the management and follow-up of the rare disease and assist with the development of a specified national clinical care pathway. It may also include recommendations of specific rare or 'orphan' drug use, or the use of a product not foreseen in the initial drug specification. The guideline should ideally take a holistic view of the person – addressing social, psychological and functional aspects of the patient journey. This may need to involve specialists such as medical social workers, psychologists, psychiatrists, counsellors, rehabilitation specialists, speech and language therapists, occupational therapists, and physiotherapists. Examples of guidelines developed within the context of ERNs are the Treat-NMD guidelines for the care of Duchenne Muscular Dystrophy, which provides an all-inclusive standard of care pathway relevant to primary care (Bushby et al, 2010); and the EURO-WABB Consortium who have developed EC funded and approved guidelines for the rare diabetes conditions, Bardet-Biedl, Alstrom Syndrome and Wolfram Syndrome

and the Alstrom specific guideline at Birmingham Children's Hospital http://www.euro-wabb.org/en/guidelines/guidelines.

It is expected that healthcare providers in Ireland will declare which guideline(s) or clinical decision support tools will be used by the specialist group. If the healthcare provider is a member of an ERN, they will agree to adopt the ERN approved guidelines and clinical decision support tools.

Over time, peer-reviewed and published guidelines, clinical decision support tools and ERN approved patient information booklets will be added to the Orphanet Ireland website.

10. EVIDENCE BASED MEDICATION GUIDELINES AND ACCESS TO NEW AND INNOVATIVE MEDICINES FOR RARE DISEASES

Centres of expertise will have the responsibility to develop clinical trials and clinical guidelines for rare medications and novel therapeutics such as Orphan Medical Products (OMPs) in line with the ongoing work in this area through the ERNs.

The clinical leads of national Centres of Expertise in Ireland will engage with the newly established Rare Diseases Medicinal Products/Technology Review Committee.

An OMP as defined by the European Medicines Agency is a medicine intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting no more than 5 in 10,000 people in the European Union at the time of submission of the designation application. Currently, less than 10% of rare diseases have an effective therapy (Global Genes Project). Although at least 97 OMPs, to date, have received marketing approval in Europe, and these numbers are set to increase over the next ten years according to the IRDiRC recommendations (Austin 2018).

However, access to these medications is unequal across European Member States and the cost of developing these products may lead to a significant gap between the results of innovation and the ability of payers to reimburse these products (affected by very high costs for some of these products). Ireland currently has a lower rate of availability of access to OMPs for rare diseases than a number of neighbouring member states (Detiček et al, 2018). Access to certain licensed OMPs for Irish patients with rare diseases are crucial to provide the highest obtainable standard of care for many rare disease patients in a timely fashion when there is no other therapy available.

The 2000 EU Regulation (EC) No 141/2000 on orphan medicinal products in its preamble states that "patients suffering from rare conditions should be entitled to the same quality of treatment as other patients".

The European Working Group for Value Assessment and Funding Processes in Rare Diseases (ORPH-Val) have made a number of recommendations related to value assessments, pricing, reimbursement and funding processes for OMPs. These recommendations include that;

- at national level funders should take into account all official regulatory and health technology assessments of OMPs taken at European level
- the assessment and appraisal of OMPs use to inform national pricing and reimbursement decisions should incorporate rare disease expertise including both healthcare professionals and patients' perspectives (Annemans et al, 2017).

It was recommended that for sustainable OMP funding in the presence of frequent uncertain outcomes (effectiveness and safety), evidence-based funding mechanisms should be developed and that in the future there should be greater cooperation of OMP value assessment processes at European level with consideration of risk-sharing funding models.

Moreover, the advances in treating genetic diseases and new orphan drug approvals over the last 10 years have impacted significantly the area of rare diseases. The international IRDiRC project, which has already surpassed its goal of 200 new treatments by 2020, will now increase demand for diagnosis and treatment of rare diseases with the availability of novel therapies such as enzyme replacement strategies, substrate inhibition therapy, chaperone treatments, gene therapies and stem cell approaches. IRDiRC's ten year plan is to develop 1,000 new therapies for rare diseases and the means to diagnose all rare diseases (Austin, 2018, www.irdirc.org).

In Ireland, for OMPs pricing and reimbursement, applications are accepted initially for review by the HSE Corporate Pharmaceutical Unit. Health technology assessments are commissioned and carried out by the National Centre for Pharmacoeconomics with an evaluation on whether the OMP satisfies the agreed QALY funding limit (currently €45,000 threshold). Many OMPs do not fulfill this threshold. The Rare Diseases Medicinal Products/Technology Review Committee was established in 2018. The terms of reference are to;

1. review proposals received from industry or expert groups in Ireland for funding of new products for rare diseases, or expanded indications for existing products for rare diseases and making recommendations as to the implementation of the relevant recommendations from the National Rare Diseases Plan 2011-2018; and
2. provide contributions to the development of clinical guidelines for relevant Orphan Medicinal Products and support the implementation of guidelines in conjunction with the National Drugs Management Programme Office, where applicable.

The Committee's remit covers licensed indications for medicines for rare diseases. The Committee's remit excludes unlicensed indications in Europe for medicines for rare diseases. The Committee's remit also excludes medicines for rare cancers and infectious diseases as there is an existing process undertaken by the National Cancer Control Programme for the relevant medicines.

The Committee's recommendations for reimbursement of OMPs are not intended to replace any part of the existing medicines appraisal or reimbursement process. The recommendations will be informed by a Health Technology Assessment submission, or similar, by the National Centre for Pharmacoeconomics or other body, Committee discussion, and guidelines developed by the relevant clinical group/clinical lead of Centre of Expertise.

The Committee reports to the National Director of the Acute Operations Division (or a nominee) and will make recommendations regarding the priority for consideration of funding and availability of a new treatments to the HSE Drugs Committee. The recommendations will be based on the degree of unmet clinical need, clinical effectiveness, alternative therapies available, toxicity (where relevant) and the cost effectiveness of the proposed technology. These criteria are based on Schedule 3, Part 3 of the Health (Pricing and Supply of Medical Goods) Act, 2013. Members of the Committee include rare diseases experts, patient representatives, expert pharmacists, a representative from the HSE Primary Care Reimbursement Service and specialist clinicians from various disciplines and representative from HIQA.

11. CLINICAL RESEARCH

The performance of clinical research will be central to the formation of ERNs and participating healthcare providers, to include outcome analysis, registry data analysis and clinical trials. The three main contributors to successful research for rare diseases as documented by a 2008 EURORDIS study are (EURORDIS 2008);

1. Collaboration across multiple sites
2. The presence of shared registries
3. The support of patient organisations.

Irish SME supported research is competitive and well-funded at a European level. Essential clinical research lags behind (Lynch and Borg, 2016). Article 12 of the 2011 cross border directive states the importance of reinforcing research, the development of registries for epidemiological surveillance, and training for healthcare professionals and patients. The field of rare diseases and genomics is rapidly moving, and experts need to be involved in research so as to keep updated in clinical practice

and meet patient needs for access to clinical trials and research. Clinical research is now an essential part of the care for patients with rare diseases (Davies, 2017).

The UK Strategy for Rare Diseases, launched in November 2013, cites 21 (of over 50 total) commitments directly relating to the role of research. The UK, in support, established the NIHR Rare Diseases Translational Research Collaboration (RDTRC) in 2013 with an initial investment of £20 million over four years ring-fenced solely for rare disease research.

The Irish Medical Charities Research Group (MRCG), which actively supports many rare disease clinical researchers in its report 'The Health Research Landscape in Ireland 2014', identified the following barriers to medical research in Ireland;

- Lack of protected research time for clinicians and other healthcare workers.
- Limited support for researchers at mid-stage in their research careers.
- Lack of prioritisation at national level.

The HRB has made a number of awards for rare disease projects in recent years including a number of awards with MRCG partners. The number of clinician investigators involved in actively funded rare disease research in Ireland is very limited at present.

The current European Joint Programme Co-fund for Rare Diseases (2019 -2024) will help to bridge the gap between care and research, enable more streamlined use of resources, and develop translational research between the laboratories and clinical interface. This programme will directly assist with research training in rare diseases and data access. This will be of direct relevance to clinicians and allied health professionals at our national Centres of Expertise.

The National Rare Diseases Plan for Ireland 2014-2018 highlights the need for a "clear policy on data protection and ethical frameworks which are seen as critical for rare disease research." Many types of research were recognised as important, with clinical research and clinical trials particularly emphasized. The development of basic epidemiology of rare diseases in Ireland through rare disease registries was identified as a priority in the national plan. The development of designated Centres of Expertise and sustainable funding mechanisms were the priority actions identified for enhancing rare disease research.

The National Clinical Programme for Rare Diseases organised a workshop on clinical research in rare diseases in February 2018 with several international speakers. The workshop report is available at www.hse.ie/eng/about/who/cspd/ncps/rare-diseases. It was noted at that workshop that around two-thirds of HRB-funded projects in Rare Disease research were for applied biomedical research, while the remaining one-third were for clinical research with very few projects in health services and population health.

It was noted that Ireland's weaknesses in rare disease research include the lack of an overall strategic approach, the lack of patient registries and the lack of protected time for research among rare disease clinicians in the HSE. The potential challenges of GDPR for patient registries and consent were noted, as was the lack of infrastructure/'scaffolding' for rare diseases in Ireland, delays and lack of collaboration of Ethics Committees, the need for Patient involvement, (patients as collaborators), and the need to focus more research on day-to-day quality of life of patients, as well as diagnosing and developing therapies for diseases.

In preparation for this workshop, The National Clinical Programme for Rare Diseases invited the ten hospitals in Ireland with Centres of Expertise (n=47) in rare diseases to participate in a short questionnaire about clinical research in late 2017. Centres of Expertise are defined as national healthcare providers that are validated using Orphanet criteria.

The survey questions included listing the reasons why research in this field is important. A number of common themes emerged emphasising the importance of developing a research culture in Irish hospitals.

Benefits of conducting research, as noted in responses, were;

- It encourages adoption of latest techniques and technologies in patient care.
- It ensures that a centre adheres to international best practice.
- It makes a hospital attractive to highest quality researchers in training, doctors in training and consultants. Enhances ability to recruit and retain excellent staff.
- It allows clinical services to become trial ready for new orphan drugs.
- It promotes confidence in patients in medical teams.
- It increases local expertise in specific conditions.
- It provides training and career development for staff and employment.
- It academically active centres have better patient outcomes.
- It fosters innovation among clinicians at the patient interface.
- It serves as a source of additional income and resources through clinical trial-related cost reimbursement, access to novel therapies and co-funding of specialised personnel and equipment.
- It improves recognition of the hospital as an academic centre.
- It prompts transition from Research to Clinical Service.
- It improves personalised patient care, which is necessary for outcome analysis for rare and highly specialised conditions so as to inform and deliver best practice.

- It is imperative for translational research applicable to new therapies for rare disease patients and to address cost-effective use of high technology drugs.
- Patients want access to research to be available close to home.

Barriers to research in Ireland, as identified in the responses, include;

- Poor tradition of research culture within our hospitals.
- Lack of protected time for clinicians, NCHDs and research nurses specified in basic consultant, trainee and nurse contracts.
- Limited funding streams.
- Lack of infrastructural support in terms of a) access to grant writers and b) project managers to support on-going administrative tasks associated with being a Principal Investigator.
- Short term contracts preclude research where results will inevitably take time (adversely affects natural history studies, clinical trials etc.).
- Lack of designated support staff (research nurses, data managers, administrative support).
- Inadequate structure to support clinical trials.
- Protracted delay of Ethics Committee reviews and absence of a centralised process.

The National Rare Diseases Plan for Ireland 2014-2018 recommended the establishment of a rare disease research network to;

- Enhance the quality and relevance of rare disease research on the island of Ireland in a strategic manner in line with the priorities of this National Rare Disease Plan.
- Support the integration of rare disease research within relevant forthcoming government research policy and legislation.
- Develop a clearly identifiable online presence, which would act to attract international interest and research partnerships.
- Actively pursue potential international research partners.
- Signpost new and established researchers to relevant resources and contacts.
- Ensure research on rare diseases in Ireland adheres to the EURORDIS guiding principles for conducting rare disease research.

12. RECOMMENDATIONS

CENTRES OF EXPERTISE

OVERARCHING RECOMMENDATIONS FOR CENTRES OF EXPERTISE

1. Centres of Expertise will serve as national reference centres and will liaise with all regional partners and affiliated sites to ensure continuity of care and equity of access to emerging clinical trials, clinical care pathways and clinical practice guidelines for rare disease patients.

2. National Centres of Expertise will be identified on Orphanet Ireland.

3. Centres of Expertise should work with community practitioners including general practitioners, public health nurses, psychologists, medical social workers and psychology services to provide support to patients and families with rare diseases. In particular, the expertise of liaison psychiatry should be sought to assist with anxiety and depression with a new disease diagnosis in the patient and family, and to assist with compliance and adherence issues.

4. Centres of Expertise will engage with national palliative care services for rare disease patients with life-limiting conditions at the earliest possible opportunity in line with the National Clinical Programme for Palliative Care Model of Care.

5. Centres of Expertise should strive to evaluate the need for discretionary decision for provision of medical cards for rare disease patients with chronic diseases to include an assessment of the burden of the medical condition.

6. The Centres of Expertise will contribute to the overall teaching activities pertaining to the care pathway. Education and links to access clinical practice guidelines and clinical decision support tools will be provided for specialists and for primary care providers.

CENTRES OF EXPERTISE, TELEMEDICINEAND CROSS BORDER CARE

7. Telemedicine access should be in place in Centres of Expertise that are full members of ERNs.

8. Patients with rare diseases should receive care or access to clinical trials, care pathways and clinical practice guidelines whenever possible through a Centre of Expertise or linked affiliated site, or for very rare conditions via a national provider who will link by eHealth or cross border care to a designated ERN. Where necessary, patients with rare diseases should be supported by

the relevant specialist to access the Treatment Abroad Scheme or Cross Border Care travel options in collaboration with the National Contact Point.

9. Facilitated access should be provided for all rare disease patients to genetics/genomic diagnosis nationally with the appropriate pre- and post-test counselling, or to a reimbursement pathway for Cross Border Care if the testing is approved by national guidelines.

CENTRES OF EXPERTISE AND PATIENT CENTRED CARE

10. Centres of Expertise or associate/affiliated centres will develop an integrated model of care to include holistic, person centred care for their disease specialty area and will plan the centre's business model and sustainability accordingly.

11. Centres of Expertise will work closely with the patient support groups to develop and evaluate their services.

12. Centres of Expertise should develop a template patient summary to include the Orphacode number for the more common rare diseases treated at the centre. This could serve as an ePatient Summary and Extension for Rare Diseases. This patient summary would be available at the point of care to deliver safe patient care at different sites and for cross border travel.

13. For rare diseases that require multiple specialties, efforts should be made to develop 'one-stop clinics' to minimise the burden for patients, their families and carers.

CENTRES OF EXPERTISE AND CLINICAL PRACTICE GUIDELINES

14. Care pathways and clinical practice guidelines for the most common rare diseases (and where appropriate) and clinical decision support tools will be developed/agreed upon at Centres of Expertise with patient involvement and will be visible on the Orphanet Ireland website.
15. Guidelines should be instituted for national testing at accredited national laboratories when they are linked to Centres of Expertise.

16. National regulation of new technologies should include next generation sequencing/genomic panels.

CENTRES OF EXPERTISE AND EVIDENCE BASED MEDICATIONS GUIDELINES.

17. Centres of Expertise in rare diseases should have a central role in the evaluation and audit of clinical guidelines, which should be accepted by the Clinical Director of the healthcare provider or group.

18. In line with the recommendations of National Rare Disease Plan for Ireland 2014-2018, the capacity to prescribe all orphan medicines and technologies for ultra-rare conditions should be limited to specialist teams designated through the Centres of Expertise. Centres of Expertise should also recommend the most appropriate and cost-effective treatment that is available and licensed in Ireland for the specific rare disease and should develop patient consented password protected disease-specific registries to evaluate 'real world outcomes', clinical outcome assessments of new approved orphan medicinal products in collaboration with patient users and, where possible, use patient centred outcome measures and patient related outcomes. The National Clinical Programme Rare Diseases will support the assessment of orphan medicinal products in collaboration with the HSE Rare Diseases Medicinal Products/Technology Review Committee, and over time should assist with implementation of improved clinical outcome measurements with the use of disease-based registries for the indications and patient reported outcomes. Patient representatives will be supported to gain the appropriate training to engage with development of guidelines.

19. In line with reimbursement of orphan medicinal products, the appropriate infrastructure for safe monitoring, prescribing and outcome evaluation of these products should be provided at Centres of Expertise. This should include supports for an outcome registry, pharmacy, nursing and clinical staff as appropriate.

THE NATIONAL RARE DISEASES OFFICE

20. The National Rare Diseases Office will provide information about the location of Centres of Expertise.

21. The National Rare Diseases Office, supported by the National Clinical Programmes for Rare Diseases and HSE Acute Operations, will continue to map out national Centres of Expertise for rare diseases.

CLINICAL RESEARCH

OVERARCHING RECOMMENDATIONS FOR CLINICAL RESEARCH

22. The potential for industry collaboration in research relevant to rare diseases is explored, particularly regarding research relevant to the diagnosis, treatment and management of rare diseases.

23. The capacity of Ireland's (currently) five resourced Clinical Research Centres facilities to engage in rare disease research nationally or in collaboration with international collaborative research is enhanced.

24. A ring-fenced budget stream could be established through agencies such as the Health Research Board and Science Foundation Ireland.

25. Robust proposals are made to the Department of Health to advocate for Irish involvement in current EU funded research projects, e.g. 2019-2024 European Joint Programme in Rare Diseases and initiatives such as BBMRI-ERIC and ECRIN-ERIC.

26. Facilitate greater international collaboration with ERNs, relevant registries, organisations and consortia, including the International Rare Disease Research Consortium.

CLINICAL RESEARCH AND CENTRES OF EXPERTISE

27. The role of the designated Centres of Expertise in Ireland should include research relevant to rare diseases and focus on outcome registries, health service and translational research. National infrastructure funding, and protected time for clinicians and health and social care professionals, should be incorporated into the weekly schedule for designated full and affiliated Centres of Expertise.

28. Clinical research, to include outcome analysis and audit, should play a central role in Centres of Expertise. A top–down approach to support research for Centres of Expertise is recommended. Consultants, senior trainees and all relevant members of the multidisciplinary team at designated Centres of Expertise should have protected time for clinical research activities.

CHAPTER 4. TRANSITION FROM PAEDIATRIC TO ADULT HEALTHCARE PROVIDERS IN RARE DISEASES

1. INTRODUCTION

For rare diseases in Ireland, collaboration across various healthcare settings is key, given the nature of national services and expertise. This requires system-level solutions that address the alignment of providers in multiple settings, with facilitated communication, record sharing, capacity building and related audit and clinical research nationally.

The concept of transition was defined as the "purposeful and planned movement of adolescents and young adults with chronic physical and medical conditions from child-centred to adult oriented healthcare systems" (Blum et al, 1993). The American Academy of Paediatrics (AAP), American Academy of Family Physicians (AAFP) and the American College of Physicians – American Society of Internal Medicine (ACP-ASIM) 2002 Consensus Statement describes transition as the "process to maximise lifelong functioning and potential through the provision of high-quality, developmentally appropriate healthcare services that continue uninterrupted as the individual moves from adolescence to adulthood" (Blum et al, 1993)".

For successful transition to occur, a developmentally appropriate transition plan should be developed in collaboration with the young person and their family. The transition plan should address not only the young person's specific health issues, but their wider physical, developmental, psychosocial, mental health, educational, lifestyle, cultural and financial needs (CAPHC, 2016). Six key areas have been identified as the core issues for discussion throughout the transition process to ensure a comprehensive and holistic encounter for the participating adolescent and their families. These are;

1. self-advocacy
2. independent healthcare behaviour
3. sexual health
4. psychosocial support
5. education and vocational planning
6. health and lifestyle.

Transition should consist of joint planning with youth, parents and caregivers in order to foster independence and active participation in decision making. It also consists of assistance in identifying adult providers and ensuring a smooth transfer to adult centred care with current medical nursing and

therapeutic information. In this context, it is considered that the transition from a paediatric to an adult oriented service should not be a sudden unanticipated transfer but should be an organised process of preparation and adaptation. To this effect, transition has often been cited as the most important event in the care of patients with chronic diseases, and effective transition has been shown to improve long-term outcomes (Harden et al, 2012, Prestidge et al, 2012, Duguépéroux et al, 2008 and the experience of the young person Shaw et al, 2008).

2. SPECIFIC CHALLENGES IN RARE DISEASES TRANSITION

By virtue of their rarity, patients with rare diseases are frequently small in number and therefore lack the "strength in numbers" or "critical mass" associated with other more common conditions, where dedicated multi-disciplinary clinics can be supported. Furthermore, the empowerment and voice of patient advocacy organisations may not exist for many conditions, and those in existence often compete for resources and access to policy makers with those representing more common conditions. As rare diseases are often associated with greater complexity, a wide range of medical problems and the need for access to more than one physician or specialist, even at multiple different sites in different healthcare settings, can ensue, especially as the patient gets older and an increasing number of complications of the conditions arise such as neurocognitive decline, psychiatric disorders \(Schneider, 2014, Whittington et al, 2015), respiratory compromise, reduced mobility, osteoporosis, and metabolic and sleep problems (Gadoth and Oksenberg, 2014,Forbes, 2001). This multiplicity of healthcare needs is particularly challenging in rare diseases where a defined care pathway may be lacking, and continuity of care is key (West et al, 1993). For many conditions, the imminent or eventual need for palliative or end of life care may need to be addressed (see flow sheet 2)

3. KEY POINTS TO SUCCESSFUL TRANSITION

A successful transition plan is a multi-faceted process that engages multiple care providers and accommodates a patient's condition, age and developmental stage. Keys to successful transition include early preparation of the young person for independence and self-advocacy, an education programme for patient and parent that addresses medical, psychosocial and educational/vocational aspects of care that is age and developmentally appropriate, identification of a key worker, the development of a written transition policy agreed by all members of the multidisciplinary team, and targeted adult services. (Viner, 2008)

The plan for each patient created with the young person and their family should be regularly reviewed and updated with liaison personnel in both paediatric and adult teams. The presence of an interested, capable and adequately staffed adult clinical service is required with good communication throughout the process.

Examining the strategies most commonly used in successful programmes confirms the importance of patient education and skills training and of specific young adult clinics, either jointly staffed by paediatric and adult physicians or dedicated young adult clinics within adult services (Crowley et al, 2011). Care of the child with a chronic condition is largely family centred with the parents providing a very active role. At the time of transition, care in the paediatric setting must adapt to accommodate the emerging adult who needs to be treated independently of the family structure.

Good communication with the physician taking on the adult care is key. One strategy is to use a structured discharge letter template so as to improve communication during the transition phase with a recent positive evaluation (Ramanayake, 2013), and which has already been shown to save time and improve communication from primary to secondary care. An alternative, described in a large German metabolic clinic, is to transfer the complete patient file with consent of the patient (Piel, 2016).

Transition should be a process of preparing the young person for the adult service, which should start at a young age of about 11 years (Nagra et al, 2015), or by 14 years at the latest (Colver and Longwell, 2013), rather than one single event. The involvement of a key accountable individual, who is responsible for supporting their move to adult health services, has been strongly advocated so as to support a smooth transition process.

The success of the transition process will also depend on formal systems that ensure accessibility and transfer of information, including a portable and accessible up-to-date medical summary such as a 'health passport' in order to ensure relevant professionals have access to essential information about the young person. Children's services should be the providers until adult services take over. It is paramount, and should be confirmed with the adult provider, that the paediatrician will be responsible for continuity of care until the young person is seen and transferred to the adult setting.

TABLE 1: MODELS OF TRANSITION

Model	Service description	Examples in Ireland[1]
Dedicated follow-up service	Provided within adult setting. No combined paediatric-adult clinic. No direct input or continuity from paediatric services	• T1DM in most centres
Seamless clinic	A clinic, which begins in childhood/adolescence and continues into adulthood, with both paediatricians and adult physicians providing multidisciplinary care in as appropriate. Duration of combined care can vary from individual to individual.	• YARD – OLCHC and SVUH • Cystic fibrosis – SVUH/OLCHC AMNCH • Combined Rare Cardiac Genetic conditions (Adolescent and Adult) - AMNCH • Hereditary Ataxia Clinic (Adolescent and Adult) • Cardiac arrhythmias and rare cardiac congenital disorders- MMUH • Coagulation disorders/ haemoglobinopathy- OLCHC and St James Hospital
Life-long follow-up within paediatric setting	Common default option especially in the past – often used in patients with life-limiting conditions, complex patients e.g. spina bifida due to parents/physicians who may be reluctant for transfer of care.	• Spina bifida • Life-limiting disorders
Generic transition team within a paediatric hospital	Involves one or two dedicated nurse specialists who ensure that all young people have appropriate transition support.	No current examples
Generic transition services for larger geographical areas	May be more appropriate to relatively rare diseases in Ireland to focus on appropriate co-ordination of care between paediatric services to relevant specialist centres.	• Epidermolysis Bullosa • Rare Epilepsy • Rare Endocrine disorders • Rare Gastroenterology • Pituitary disorders and genetic endocrine tumour syndromes- Cork University Hospital

[1] Please note the services listed are examples and this list is not exhaustive.

4. RECOMMENDATIONS: GUIDING PRINCIPLES FOR A SUCCESSFUL TRANSITION

The National Clinical Programme for Rare Diseases recommends the following guiding principles to ensure a smooth, safe and effective transition of young people with a rare disease from paediatric to adult health services;

1. It is recognised that admission of adolescents/adults to acute adult hospitals may frequently be required in order to provide urgent/intermittent appropriate medical care to individuals prior to initiation or completion of transition/transfer. However, it should be recognised that this does not constitute the appropriate transition/transfer pathway, as outlined in this document, to include agreements of acceptance from the appropriate multidisciplinary team and satisfactory medical record transfer. Under these circumstances, continuing care post-acute stabilisation should be provided by the ongoing healthcare provider until the transition/transfer process has been completed and agreed upon.

2. Care should be provided by staff, if at all possible, with expertise in the management of the particular condition. In line with the recent establishment of ERNs for rare disease, adolescents and young adults with rare diseases should receive care if possible, at, or in conjunction with, a nationally recognised rare disease healthcare provider (i.e. a centre of expertise). All cases of rare diseases should be registered with a national centre of expertise, if possible. If there is no national centre of expertise for the condition, the health provider should liaise with a European centre of expertise. Assistance in identifying European expertise can be sought from the National Rare Diseases Office, as Ireland's 'hub' for ERNs. A shared care model between a tertiary centre of expertise and primary care is recommended.

3. Hospitals that provide children/young adults with specialised services for rare diseases should have a policy in place for transition to adult services. This policy should be publicly available and should be developed in collaboration with the patient stakeholders. It is recommended that a service-specific transition booklet is developed.

4. Paediatric providers should identify the appropriate adult centre (or multiple centres) of expertise to accept and plan transition planning and build relationships with adult providers to include educational sessions on adolescent concepts.

5. Once the adult provider is agreed, it should account for the estimated case number to transfer each year and associated costs in the yearly business plan.

6. A dedicated transition coordinator should be appointed as a point of contact for each centre. This person should be an experienced health professional (with experience in the particular therapy area or services available) who will have the responsibility for co-ordinating/facilitating transition of care in liaison with the individual clinical teams within the speciality, region or hospital group, depending on the condition.

7. Ideally, both paediatric and adult providers should share common care pathways and guidelines across sites (to be accessible on the provider website).

8. Paediatric patients, and their families, should be informed of the process of transition well before they start to move their care to adult services. Patients should be given written and verbal information about the process in developmentally-appropriate language format, allowing for those with sensory impairments (e.g. braille or audio). Young adults should be encouraged to participate in evaluating their self-management and setting their own treatment goals, ensuring that the goals are realistic and focused on providing safe, high quality care.

9. The ideal age for patients to transition will depend on the particular condition and co-morbidities. The psychological maturity and chronological age need to also be considered. Transition should ideally occur between ages 16 to 18, but exceptions may be required for highly complex cases and there is no defined age of transfer in the section on transition of care. The time and age of transfer should be agreed with the patient, family and carer, with agreement with the adult provider.

10. Adequate genetic counselling needs to have been provided to the individual and family. The care pathway and medical summary should be available for each patient (and provided to the patient), to include a lay person summary of the condition and the most recent updated emergency care plan in developmentally appropriate language format, allowing for those with sensory impairments (e.g. braille or audio).

11. The appropriate education, regarding reproductive health and menstrual issues, needs to be addressed commencing from age 12 – 13 or earlier, if indicated (See flow sheet 1).
12. Transition clinics ideally should be held in a paediatric, rather than adult, setting (if feasible). If this is not possible, then they should be held in an appropriate environment that takes account of the patient's developmental stage and needs, or in a shared clinic with the named adult provider

before transition. The carer or family should attend at these clinics. There should be a minimum of one transition clinic visit.

13. Doctors, nurses, dieticians, clinical psychologists (if possible/appropriate), a Medical Social Worker (if required) and additional MDT members from both the paediatric and adult teams should attend the transition clinic and ensure the comprehensive transfer of patient information to the adult team. Where possible, an electronic version should be available for the patient to have available when/wherever they present acutely or unexpectedly in order to ensure that key information is presentable to treating physicians.

14. The date of first adult out-patient appointment should be confirmed. The transfer package, including medical/surgical, nursing and health and social care professionals summary and care plans (as above), should be transferred to adult provider at least four weeks in advance of the adult OPD appointment.

15. If the patient has a multisystem condition, agreement should be reached as to what is the main system affected (e.g. neurological, endocrine, and rheumatologic), and the appropriate physician to manage that system should be the co-ordinator of the ongoing care into adulthood.

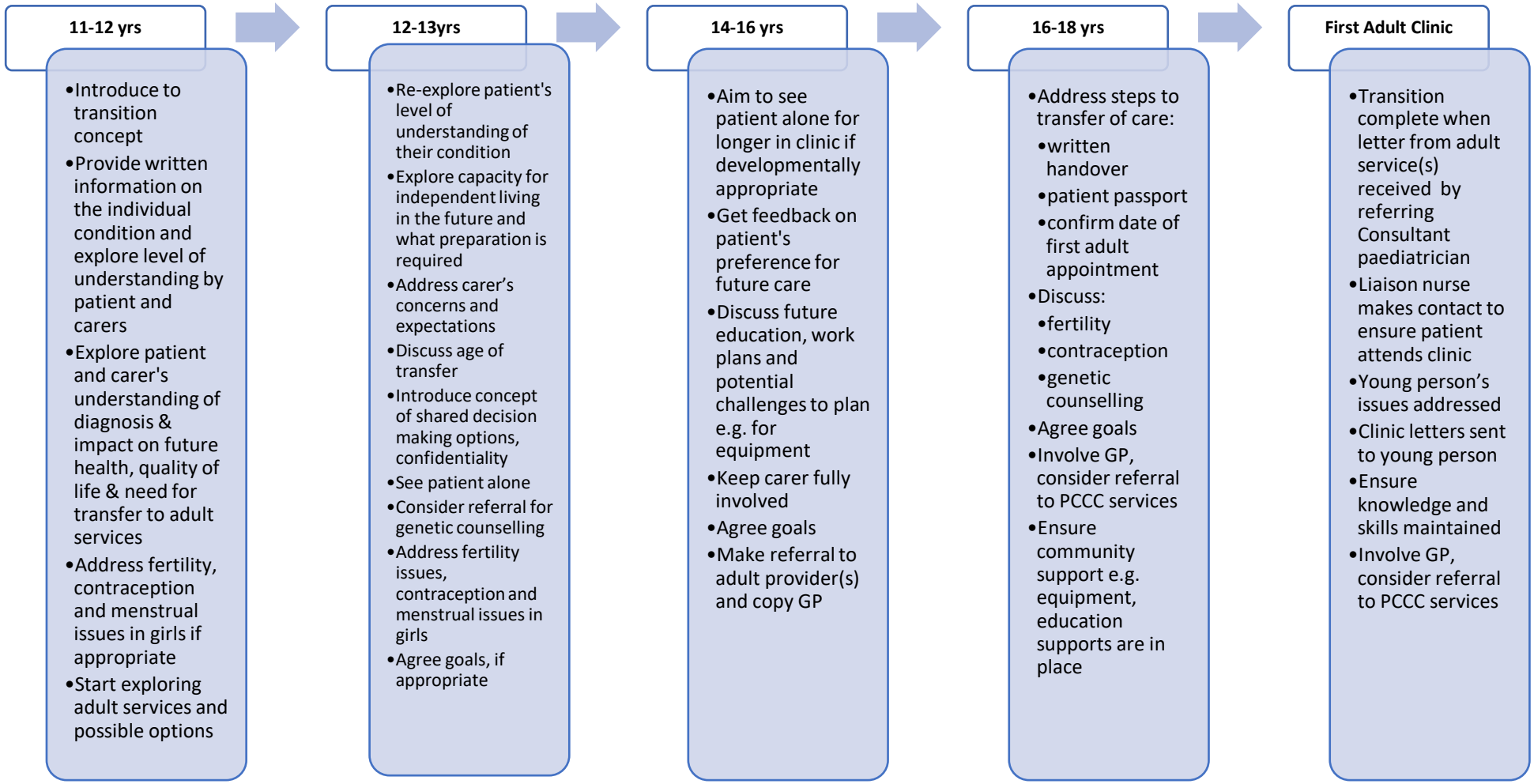
16. A transition flow sheet can be used as a guide to support patients and their families to prepare for transition (see flow sheet 1).

17. Specific developmentally-appropriate discussion and management of contraception/fertility options (including management of puberty/menstrual issues in adolescents with neurodevelopmental disability), depending on the clinical condition, should be offered to all adolescents prior to and during the transition period.

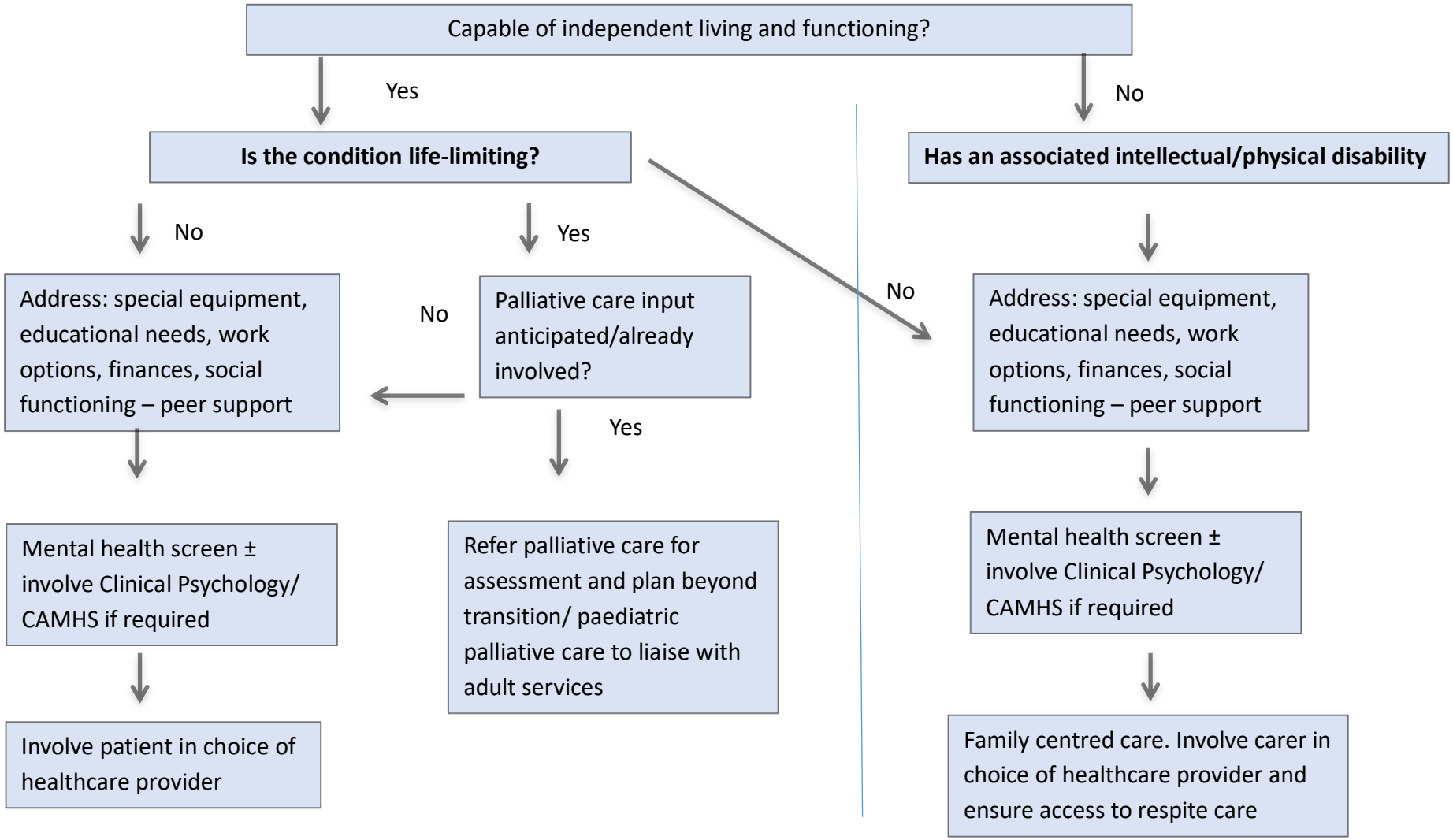
18. Physicians, nurses, health and social care professionals offering outreach services from centres of expertise to affiliated centres as visiting consultants should be supported so that patients can be offered the best possible care and expertise as close to home as possible. This includes resourcing of multi-disciplinary aspects of the visiting consultant service such as clinical nurse specialist and administrative support.

19. Regular audits of the transition process should be carried out, as well as review of patient feedback, ensuring that patients are not lost to follow up and that they are satisfied with the transition experience. Clinic attendance rates should be evaluated on a regular basis.

FLOW SHEET 1: GUIDING PRINCIPLES FOR TRANSITION OF YOUNG PEOPLE WITH A RARE DISEASE ACCORDING TO AGE



FLOW SHEET 2: ISSUES TO CONSIDER IN RARE DISEASE TRANSITION FOR A CHILD WITH COMPLEX NEEDS



APPENDIX 1: RELEVANT RECOMMENDATIONS FROM THE NATIONAL RARE DISEASE PLAN FOR IRELAND 2014-2018

Recommendation 1: Guidelines be developed on coding and recording of rare diseases within relevant Irish health data systems that are consistent at European and global level. The Health and Information Quality Authority (HIQA) will have a role in this, given its functions regarding information standards, including coding standards.

Recommendation 2: The publication of the Health Identifier Bill and the forthcoming Health Information Bill.

Recommendation 3: The Department of Health and the Health Service Executive (HSE) put in place, over 5 years, a coherent system to conduct broad epidemiological surveillance of rare diseases in Ireland. This epidemiological surveillance should include profiling of rare diseases among high-risk cultural and ethnic minority groups for the purposes of appropriate neonatal screening and improving diagnosis and outcomes.

Recommendation 4: A periodic national report on the epidemiology of rare diseases in Ireland be published by the Department of Health, similar to that prepared for the European EUROPLAN report, and that reporting on rare diseases be integrated into the existing HSE reporting on health and disability services.

Recommendation 5: All existing databases to be mobilised. Systems are put in place to enhance the utility of data held in relevant health service-based information systems, including hospital record, laboratory cytogenetic and molecular genetics data.

Recommendation 7: Appropriate support be given for the on-going involvement of Irish registries in relevant European collaborations, including the RARECARE and EUROCAT registries.

Recommendation 8: An All-Ireland Network of Rare Disease Registries, covering the island of Ireland, be developed and that this network work towards enhancing and standardising rare disease registries in line with HIQA draft guidelines, data protection legislation and international best practice. This function should be supported by the new National Office for Rare Diseases.

Recommendation 9: The development of any future information systems provide for a rare disease code in a patient record in order that all people with rare diseases may be easily identified. The development of a rare disease identification card that could be linked to a person's PPSN should also be explored once the provisions of the proposed Information Bill have been enacted and promulgated.

Recommendation 31: The HSE undertake a preliminary economic evaluation of current activity and costs for orphan medicine and technologies for rare disease patients across all hospital settings.

APPENDIX 2: E-HEALTH STRATEGY

An eHealth Strategy for Ireland was launched by the HSE in December 2013, and an allied Knowledge and Information Strategy followed in May 2015 with the purpose of 'integration of all information and knowledge sources involved in the delivery of healthcare via information technology-based systems' (eHealth strategy for Ireland). The eHealth Ireland document: National Electronic Health Record: Vision and Direction describes the EHR as the 'cornerstone' of the eHealth strategy. http://www.ehealthireland.ie/Library/Document-Library/EHR-Vision-and-Direction.pdf The EHR will create a shared patient record that is the primary source for all health and social care professionals by integrating records from public and private, inpatient and outpatient, as well as from primary and specialist care. The eHealth Ireland Knowledge and Information Strategy outlines five key capability areas to support the eHealth reform. Significant overlap with delineators of quality indices for rare disease registration are seen in all 5 of the key capability areas.

http://www.ehealthireland.ie/Knowledge-Information-Plan/Knowledge-and-Information-Plan.pdf

Five Key Capability Area	**Common goals with rare disease registration**
Care delivery enablement	• Patient individual heath identifier • Care provider/facility unique identifier • Security controls supporting data access • Improvement of quality and quantity of data captured electronically
Electronic Health Identifier	• Full electronic capture of clinical events • Data can be analysed to identify areas for review of clinical protocols and outcomes • Health service develops best practice over time due to access to date especially in cases of rare or specialist illnesses/cases
Cross Setting Information Integration	• Foundation to carry out detailed cross-health setting clinical research and identify preventable trends • Enable end to end evaluation of care delivery effectiveness • Combining data sets across care settings allows for a more holistic view
Health Service Insight	• 'A comprehensive data repository allowing consolidation and flexible manipulation of data from disparate data sources – a 'single source of truth'' • Supports healthcare planning for all time horizons • Enables population health and disease surveillance and control and initiation of interventions (e.g. national programmes) to address undesirable trends and effects
National Support Systems	• Ensuring that capacity gaps are identified early, and structural programmes are put in place to address these

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