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Navigating rare neurological diseases: meeting the challenge for policy makers, patients and healthcare professionals

A report by The Economist Intelligence Unit

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Key findings

This report aims to uncover the many facets of the policy challenges facing rare diseases, particularly rare neurological diseases (RNDs). We also explore important opportunities to address these challenges, using data and examples from seven key markets: the US, Canada, the UK, France, Germany, Italy and Spain. This research uncovered several important key findings:

Improving responsive rare disease co-ordination and active management is a critical aspect of addressing RND-related challenges

- The rare disease journey is fragmented, with uneven access to diagnosis and treatment. There is also substantial variation in access to knowledge, expertise and care both within and between countries. Many diseases lack curative therapies, highlighting the need for improved co-ordination to ensure that patients can access the treatments and services that are available.
- National rare disease plans and relevant legislation exist in some form across all study countries. These plans should be live documents that evolve in response to input from all stakeholders, as well as changes in disease understanding and available treatments.
- Best-practice case studies show the potential for collaboration and co-ordination to support patients with rare diseases. These case studies demonstrate the benefits of sharing knowledge and best practice among healthcare professionals, in addition to co-locating and co-ordinating services physically and online to help patients and healthcare professionals alike.

The future of rare disease research, innovation and drug access is bright, but requires an enabling environment

- Orphan drug legislation has been a key driver of industry investment in research and development for rare diseases; such policy frameworks need to be monitored and fine-tuned to ensure that they are used for their intended purpose.
- Reimbursement protocols need continuous adaptation to ensure that new orphan drugs can be financed. Experts project that certain pricing models will become more significant as more therapies come to market, even in countries with developed processes in place.
- National innovation funding must also be sustained, perhaps even increased. RNDs have attracted significant resources to date–45% of projects funded by members of the International Rare Diseases Research Consortium, have been allocated to RNDs. To encourage sustainable, efficient public spending, decision-makers should avoid viewing RNDs as siloed problems and instead take a cross-disease view.
- Improving and linking disease registries will support research in population-limited conditions. The challenge often lies in maintaining registries. Many lay dormant, owing to funding shortfalls or a reliance on project funding that is limited in time or scope. Efforts to increase the impact of registries should be continued, for example continuing efforts to harmonise disease coding would enable the integration of country registries and the pooling of data to support global research.

Introduction

Individually rare, collectively common

Rare diseases are a heterogeneous set of conditions defined by low prevalence, high rates of long-term disability and mortality.[1] The definition of a rare disease varies. In the US it is any condition affecting 6.4 in 10,000 people or fewer (or below 200,000 people nationwide), while the threshold in the EU and Canada is 5 in 10,000.[2-4]

Although each condition affects a small population, the sheer number of rare diseases–estimated at 7,000–means that the overall rare diseases patient population is sizeable.[5] In the EU, around 30m people live with a rare disease, which amounts to more than 5% of the total population.[6] In the UK, around 3.5m people (5%) have a rare disease.[7] The total number of Americans living with a rare disease is between 25m and 30m (8-9% of the population).[5, 8] In Canada, the figure is estimated at 3m (8%).[4, 6, 7]

Rare neurological diseases (RNDs), including neuromuscular and neurodegenerative conditions, constitute a major portion of rare diseases, at over 400 (about 7% of the total).[9] An estimated 500,000 people (approximately 0.01% of the population) in the EU have a RND.[10] In the US, approximately 6% of officially designated rare diseases are primarily neurological (360 out of 6,000), including amyotrophic lateral sclerosis and Huntington's disease (affecting 18,000-30,000 people each), frontotemporal dementia (affecting 48,000), and myasthenia gravis (affecting 64,000).[11] One-third of those in the US with a rare disease experience a neurological component.[8] Table 1 shows the prevalence of three key RNDs which we profile in this report.

Table 1. Prevalence (per 100,000 people) of example rare neurological disorders in Europe, the US and Canada.[12-16]

	EU	Canada	US
Neuromyelitis optica	0.72 to 4.4	0.053 to 0.40	0.053 to 0.40
Huntington's disease	5.25	13.7	7.33
Prader-Willi syndrome	10.7	Not reported	3.33-10

This large affected population is one reason why rare diseases deserve significant attention. The second is the linkage between conditions. For instance, orphan drug legislation and other policies that encourage development for rare disease treatments influence the entire commercial therapeutic development pipeline. Research infrastructures such as registries and innovative uses of alternative data can also benefit researchers across the spectrum, while adapting decision-making models related to assessment and reimbursement can ensure access to therapies beyond any single condition.

But rare diseases pose policy-level challenges for government, public health agencies and the medical research community. These include delayed diagnosis and gaps in service provision as a result of fragmented health services; limited treatment options, due to underinvestment in research and development (R&D); and reimbursement challenges for treatments that exist but do not meet conventional cost-effectiveness thresholds. Addressing rare diseases requires collaboration across the healthcare system to deal with systemic challenges like workforce training and awareness for frontline

healthcare workers so that they can recognise rare diseases and direct patients to effective treatment. Moves must also be made to improve the awareness of patients, so that they can understand their condition and participate in research relevant to them.

Failing to address rare diseases at a policy and systems level will lead to the neglect of some of society's most vulnerable people, leaving them to suffer chronic debilitation, often from childhood, to say nothing of the impact on families and carers. Positively, in the past two decades many countries have taken important steps to tackle all of the problems mentioned above. This report combines national and regional level policy analysis with expert interviews to explore the current policy landscape in the US, Canada and five major European countries (France, Germany, Italy, Spain and the UK).

1. Rare neurological diseases: a diagnostic and treatment odyssey

1.1 Diagnosis

Because of their rarity, RNDs are often either undiagnosed for long periods or misdiagnosed. One European survey of eight conditions, including Duchenne muscular dystrophy and Prader-Willi syndrome, found that 25% of patients had to wait between five and 30 years from early symptoms to a confirmatory diagnosis.[17] In Europe, 60% of people with RNDs are undiagnosed as a result of variations in how these diseases present (i.e. phenotype and genotype heterogeneity). Relevant genes are known for around half of the 7,000 rare diseases (as at 2016), meaning that 3,500 are without a defined molecular pathogenesis.[18] Variations in how diseases present, combined with a lack of understanding of the aetiology of rare diseases, make it challenging for primary care workers such as general practitioners (GPs) to identify these diseases to which they have limited exposure.[19]

Once diagnosis is achieved, patients face moving between different healthcare entities and specialists. Long geographical distances to centres of excellence can mean health inequity for those who lack resources or live in deprived or remote areas (see Figure 1).[20, 21] Experts also identify large variations in access between diseases. "If you have a national service commissioned through NHS England's highly specialised commissioning team … it is highly likely that your care will be well managed and properly co-ordinated, because you'll be fed into a system that is set up for that purpose," says Alastair Kent, a member of the Rare Disease Advisory Group for NHS England. However, people who do not get a diagnosis or have a rare neurological condition that does not have a specialist service will find that the care that they receive "depends on where they live in the country, and how keyed up the local neurologists are to recognising and dealing with the specifics of the condition", says Mr Kent. Antonio Federico, professor of neurology at the University of Siena, makes the same observation of Italy, noting variation between hospitals locally and on a regional level. "Some regions are very interested and improve [their approach to] rare diseases," he says. "For some others, it is not very well organised."

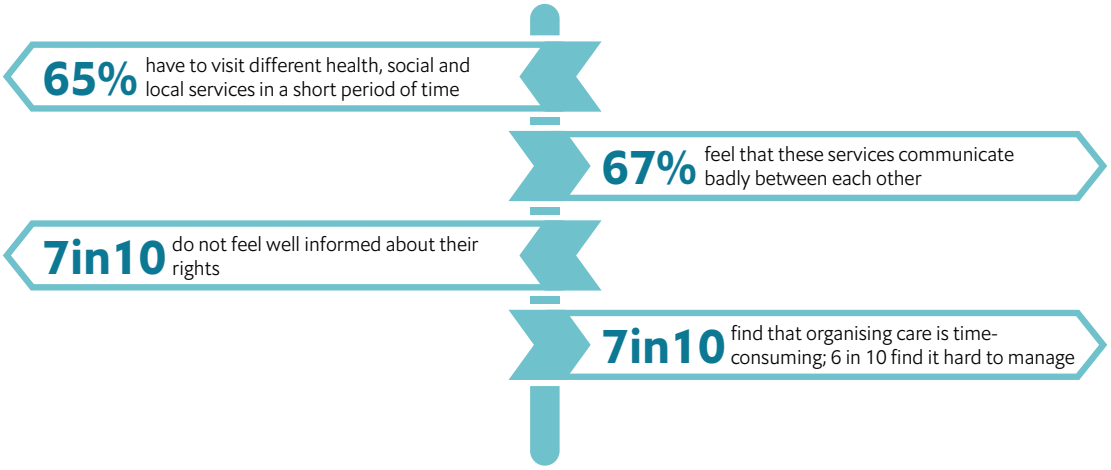
Delays in diagnosis are not just frustrating; they have long-term consequences. For instance, disability in neuromyelitis optica, a disorder that most notably affects the optic nerve and the spinal cord, is cumulative as each attack damages new areas of the central nervous system.[8] Diagnostic delays could also lead to children being born with inherited rare conditions.[20, 22] Juan Carrión, president of the Spanish Federation of Rare Disease (FEDER), affirms that in Spain "half of people living with a rare disease have suffered a delay in diagnosis". Of these, he adds, "20% have had to wait more than a decade, and a similar percentage between four and nine years."

To seek diagnosis and treatment, patients and their families must navigate a fragmented system. Expertise and diagnostic equipment may be in far-flung regions, if available at all. In Canada, for instance, next generation exome or genome sequencing are not readily available for clinical diagnostic purposes, says Bernard Brais of the Rare Neurological Diseases Group at the Montreal Neurological

Institute and Hospital. Canadian provinces also have their own policies and approaches. "That's one of the challenges of Canada: despite the fact that it has a health law and a public system in all provinces, health is a provincial jurisdiction," says Dr Brais.

"In the German healthcare system," says Holm Graessner, co-ordinator for the European Reference Network for rare neurological diseases (ERN-RND), "in general, gene panels are being funded consistently. Yet, exome and genome sequencing are not yet being funded in a standardised manner. However, it is moving in this direction, and there are initiatives in collaboration with healthcare insurers to at least fund exome sequencing for rare neurological diseases."

Figure 1. Evidence of the complex pathways for people with rare diseases and their carers[23]



1.2 Treatment and management

Early treatment affects disease evolution and impact. Patients can have radically different outcomes for some conditions, if treated quickly. For example, early treatment for spinal muscular atrophy can lead to patients having "close to a normal early life development", says Dr Brais. Some drugs, known as orphan drugs, exist for rare diseases. Typically, the type of drugs coming to market are small-molecule drugs or biopharmaceuticals and gene therapies.[24]

Yet many rare diseases have no cures. Only around 5% of rare diseases have treatments that are approved by the US Food and Drug Administration (FDA).[5] As a result, fewer than one in ten patients with rare diseases receive disease-specific treatment.[25] Finding cures is challenging because of the difficulty of conducting clinical trials and inciting commercial investment in the small patient populations of individual diseases. Furthermore, ethical complexities exist around issues such as securing informed consent for children or those with cognitive impairment.[26] RNDs pose an additional challenge related to developing therapies that can cross the blood-brain barrier. One UK expert survey also revealed additional barriers, including the long-term funding of registries and the inconsistency of registry data.[27]

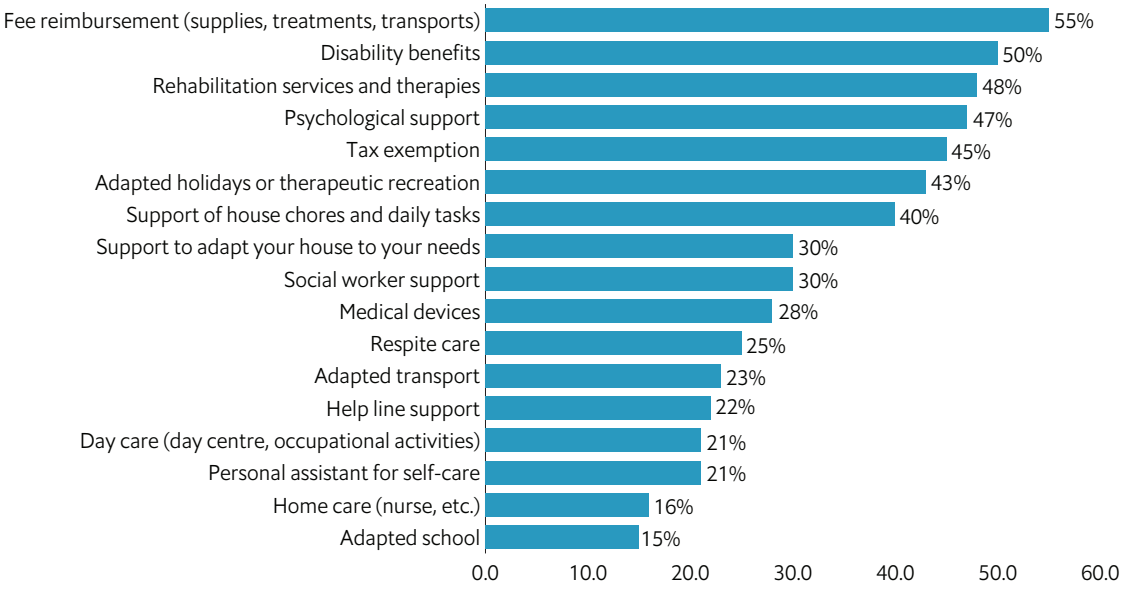
For diseases without a cure, the care pathway covers diverse specialisms that include occupational therapy, physiotherapy, diet and nutrition, and counselling. Dr Federico and Dr Kearney described how non-disease-specific treatment – such as neurorehabilitation and occupational therapy – can provide

transformative care. However, Dr Federico adds that in Italy, "patients with rare diseases have difficulty finding rehabilitation" because of a limited number of people with expertise in rare diseases working in rehabilitation and poor organisation in primary care.

Advocacy groups for large-scale diseases like cancer or heart disease can support patients and press for policy changes. There are many active and committed rare disease advocacy groups, but the small and disparate communities affected by rare diseases mean that it can be difficult for such groups to make themselves heard. In Europe, patient surveys show unmet needs in disease management, from reimbursement for costs incurred to access to medical devices (see Figure 2).[22] These impacts fall heavily on families and carers. One Canadian survey found that 90% of caregivers experienced financial trouble related to their responsibilities.[28] Similarly, Juan Carrión notes that 70% of patients and carers have had to reduce or interrupt their professional activity owing to rare disease. Although relatively prevalent on a collective basis, then, the inherent rarity of individual RNDs creates a host of challenges, covering diagnosis, treatment and management.

Figure 2. Europe-wide survey results on access to social and rehabilitation services[22]

Does your family currently benefit or have access to.. (Subtotal uncovered needs) (n=3067)



2. Policy responses to the challenge of rare diseases

In Europe and North America, legislators, public health agencies, charities and industry have all taken steps to address the challenges outlined in Chapter 1, from formal policies and national plans to public investment in innovation, including data registries. This chapter outlines the main interventions employed by the rare disease community.

2.1. Diagnosis and management–policy solutions

Rare diseases pose significant diagnostic challenges, as outlined in chapter 1. The International Rare Diseases Research Consortium (IRDiRC), which brings together governmental and non-profit funders, set a global goal for 2017-27 of achieving diagnosis within a year if the disorder is known in the medical literature.[29] Currently, the complex maze of healthcare professionals and healthcare settings that people have to navigate to achieve diagnosis is a significant concern. The average time to diagnosis is around 6 years in the UK and 8 years in the US.[30, 31] Patients see an average of 7 physicians prior to correct diagnosis. A review conducted in 2008 identified that GPs' main difficulties in diagnosis were atypical presentations, comorbidity (the presence of other diseases), perceptual features that could easily be missed, and non-specific or rare conditions.[32]

Educating and raising awareness of rare diseases among clinicians is paramount. There is encouraging progress across the countries covered in this report. The prevalence of rare conditions, combined with atypical or confounding presentations, makes it impractical to expect any clinician to be apprised of all potential rare disease diagnoses. The UK Strategy for Rare Diseases focuses on alerting GPs to the possibility of a rare disease or syndrome, to enable an appropriate referral if there is a suspicion of a rare condition, rather than seeking to inform them of the existence of all conditions.[33] The plan includes a commitment to computerised prompts that can help GPs diagnose a rare disease.[33]

Clinical research can aid new diagnostic technologies and greater understanding of the pathophysiology of rare neurological conditions. However, efforts are thwarted by the low numbers that can be recruited to sufficiently powered randomised controlled trials and the ethical challenges of researching orphan drugs. Cross-border collaborations can overcome these challenges by capitalising on technologies, expertise and patient numbers. Dr Mary Kearney, Board Member of Friedreich's Ataxia Research Alliance Ireland & Rare Diseases, points to the role of international registries: "if you have a good registry you can get enough people" and build European Reference Networks (ERNs).

Established in 2017 and funded by a range of EU programmes, including Horizon 2020, ERNs are virtual networks of health providers that aim to facilitate discussion of rare disease presentation. The ERN for rare neurological diseases, is currently working on a range of initiatives, from developing diagnostic support in co-operation with the European Molecular Genetics Quality Network, to the establishment of multidisciplinary care pathways.[34] ERNs are "very good at guideline production for diagnosis, guidelines for treatment that are really important: when to start, when to finish treatment and how long", says Antonio Federico.

One important development has been Orphanet, the European database of rare diseases.[35] Genetic screening for specific mutations is only possible when the clinician has a strong suspicion of the disease, which is challenging, given the range of presentations. More common is that diagnosis will happen following the onset of signs and symptoms. Orphanet facilitates clinical (rather than laboratory) diagnosis following presentation of clusters of signs and symptoms for clinicians. Covering over 6,000 distinct diseases and syndromes, Orphanet offers an important resource for clinicians faced with bewildering clinical scenarios. More than 1,500 laboratories across Europe are registered with Orphanet, providing tests for 2,557 genes and 3,378 diseases.[36] Because of variations between countries, an important area for development is the establishment of cross-border genetic testing to pool expertise and standardise diagnostic tests. With this in mind, Orphanet member countries are required to incorporate strategies for collaborative approaches into their national plans and strategies.

In North America, the National Institutes of Health (NIH) Common Fund initiated the Undiagnosed Diseases Network in 2008 to bring together clinical and research experts to solve medical mysteries using advanced technology.[1] A co-ordinating centre, based at Harvard Medical School, works with clinical sites across 12 locations throughout the country where undiagnosed patients are evaluated, from Los Angeles to Boston.[37] This model has been applied elsewhere, including in Spain, Australia, Austria, Bulgaria, Canada, Hungary, India, Italy, Japan, South Korea and Sweden. The rollout of these programmes has coincided with the expansion of next-generation sequencing technologies that have been adapted to clinical testing.[1]

Because of the difficulties of identifying specific RNDs, one promising avenue for improved diagnosis lies in the opportunity to test many genes with one test, using new-generation sequencing (NGS).[38] Technologies are evolving rapidly, and as such there are no stable criteria or platforms, and many tests are not fully validated. The current focus is on enhancing the "diagnostic yield" (the chance that a genetic variant responsible for a disease can be identified) of these tests. The diagnostic yield will need to be compelling to encourage the introduction of NGS into laboratories and its reimbursement. Despite growing evidence of diagnostic yield and clinical utility of whole exome sequencing (WES) in patients with undiagnosed diseases, there remain significant cost and reimbursement barriers that limit access to such testing. The diagnostic yield and resulting clinical actions of WES for patients who previously faced insurance coverage barriers have not yet been explored.[39]

The onset of RNDs occurs in childhood in 65-75% of cases.[7] As such, childhood screening could be an option for exploration. It would offer the chance of identifying multiple rare diseases earlier and in more people, especially if incorporated into existing screening programmes.[24, 40]

Case study: the NHS neuromyelitis optica service

Neuromyelitis optica (NMO) is an autoimmune condition leading to demyelination (the breakdown of the insulating layer around nerves) and inflammation of the central nervous system, notably, the spinal cord and optic nerves. Although the presentation is similar to that of multiple sclerosis (MS), there are important differences, which make early and accurate diagnosis of NMO essential.[41, 42] The disease causes a stepwise deterioration of motor, sensory, visual, and bowel and bladder function. The disability is also cumulative; each attack damages new areas. Death often arises from respiratory complications.

Prevalence of NMO is around 5 in 100,000 and is slightly more common in people of African or Asian descent and women.[43] Accurate diagnosis can take years, with many people mistakenly diagnosed with MS. The first line of treatment is intravenous steroids to reduce inflammation and relieve symptoms. Blood plasma exchanges or intravenous immunoglobulins are also thought to have a therapeutic role.[44-46] Maintenance treatment uses immunosuppressants, with monoclonal antibodies used as second-line treatments to reduce the frequency of relapses.[47] These treatments do not cure or prevent the diseases.

Many health professionals will never see a patient with NMO, so it is vital that there are resources available to support clinicians who suspect a rare disease but lack the experience to make a diagnosis. One example of such a resource is the UK NHS's NMO Service.[47] With strong links to academic centres at the University of Oxford and Liverpool John Moores University, this online resource provides support for health professionals, patients and carers.

For healthcare professionals the NHS online NMO resource includes guidance on managing relapses, explains the significance of AQP4-IgG antibodies (and signposting to free laboratory antibody testing of samples at the Oxford John Radcliffe Hospital) and information on the use of treatment for relapsing NMO. In April 2017-March 2018, the Diagnosis and Advisory Service for NMO at Oxford John Radcliffe Hospital tested a total of 8025 samples, 7981 of which were from the UK and other NHS-eligible overseas EEA member countries. Of these, 6651 were new patient samples. A total of 91 (1.4%) were positive for AQP4-IgG antibodies.

The NHS NMO resource also serves to inform patients and carers about the condition and associated concerns such as accessing state benefits. Support is required at all stages of the disease trajectory, from pre-diagnosis to the co-ordinated input from a potentially daunting array of professionals and services, including neurologists, general physicians, nurses, sleep and respiratory ventilation services, visual impairment support services, physiotherapists, occupational therapists, pharmacists, social workers, and disability support services. The NHS resource includes a series of leaflets on living with NMO, which include advice around maintaining independence, movement, mobility and travel; alongside extensive information about NMO including symptoms, impact on continence, work and finances, and dietary advice.

The Oxford John Radcliffe Hospital offers fortnightly multidisciplinary clinics for people with suspected NMO, as well as remote advice services for clinicians and patients who are unable to get to the clinic in person. The Walton Centre in Liverpool also offers multidisciplinary clinics and diagnostic support (including AQP4-IgG testing), as well as relapse management, treatment optimisation and symptom control.

Numbers of referrals to the NHS NMO service are steadily increasing year on year, although an analysis of the levels of complexity of calls taken indicates that there are a reduced proportion of level 4 (highly complex) calls. This may be due to patients using newer treatments experiencing fewer relapses, or to the possibility that the needs of patients and carers are being well met by clinics and the provision of other resources.[48] There are also indications that referral to the service is dramatically reducing the time to diagnosis, which in turn has an important impact not only on patient experience but also on prognosis and timely commencement of treatment.

Improving and optimising patient experience of NMO services requires a holistic perspective, tackling many of the same issues affecting all rare diseases. Key areas for improvement include: reducing inaccurate or late diagnosis, streamlining communication between support services across health and social care, voluntary sector and patient-led organisations, investing in ongoing research into biomarkers, and educating frontline healthcare professionals to be alert to the possibility of NMO for people presenting with particular clusters of neurological symptoms.

2.2. Orphan drug legislation and incentives for research and development

Orphan drugs treat a rare disease whose affected community is not large enough to allow pharmaceutical companies to recoup their investments.[49] Orphan drug legislation improves commercial returns via fiscal and administrative supports, from tax credits and marketing exclusivity through to fast-track procedures.[9]

The US set the trend legislatively with the 1983 Orphan Drug Act, which offered incentives for the development of drugs and biologicals for rare diseases. This included expedited review, tax credits, marketing exclusivity and fee reduction.[50] In 2012 another law, the FDA Safety and Innovation Act, created "breakthrough therapy" designation for drugs intended to treat serious or life-threatening diseases.[51] Many other countries and regions have since followed this lead, including Japan, Singapore, South Korea, Australia and the EU.[2]

The EU legislation, passed in 2000, covers all EU member states, including those covered in this study, and includes a number of key incentives (see Table 2).[52] The decision to grant orphan designation is taken by the European Commission, based on the advice of the Committee for Orphan Medicinal Products, which is part of the European Medicines Agency.[53]

Table 2. Key incentives of orphan legislation in the EU and US.[9]

Incentives	In EU	In US
Marketing exclusivity	10 years + 2 if paediatric	7 years
Clinical development costs	-	tax credits (up 50% of clinical development costs)
Orphan designation	free of charge	free of charge
Support from agency during the development process	free of charge protocol assistance	free of charge Office of orphan Products Development assistance
Marketing authorisation application	40% fee reduction; free of charge for small or medium-sized enterprises and for paediatric products	fee reduction
Fee reductions for small and medium enterprises	90% of fee reduction for post authorisation inspections; free of charge pre-authorisation inspections, post-authorisation activities, including annual fees, during the first year after marketing authorisation	-
Public funds	(possible) incentives from European Commission (i.e. research grants)	grants and contract for development of orphan drugs
	(possible) incentives in single Member States, for research, development and market access	

Orphan drug legislation is bringing forth therapeutic advances. Between 2000 and 2015 the FDA approved 84 therapeutics designated as orphan products, accounting for 37% of all approvals (see Figure 3).[54] Orphan drug designations have been granted or approved for 122 rare diseases in the EU and 300 in the US.[9]

There are challenges posed by creating orphan drug legislation. One is whether and how quickly new approved therapies are made available. Reimbursement of orphan medical products by national health systems, based on guidance from health technology assessment agencies, varies in both number and timeline in Europe (see Figure 4). A 2017 study showed that, because orphan drugs often

come with price tags of above €100,000 (US$110,800) per patient, countries were struggling to make the products accessible, with no EMA-approved orphan drug available in every member state.[55]

Figure 3. Orphan drug designation per year, US.[54]

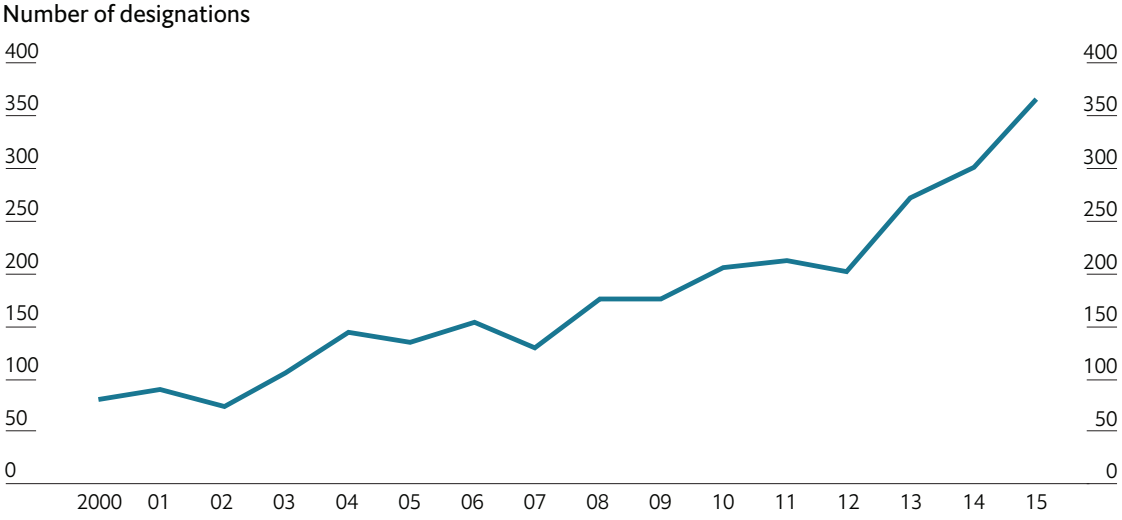
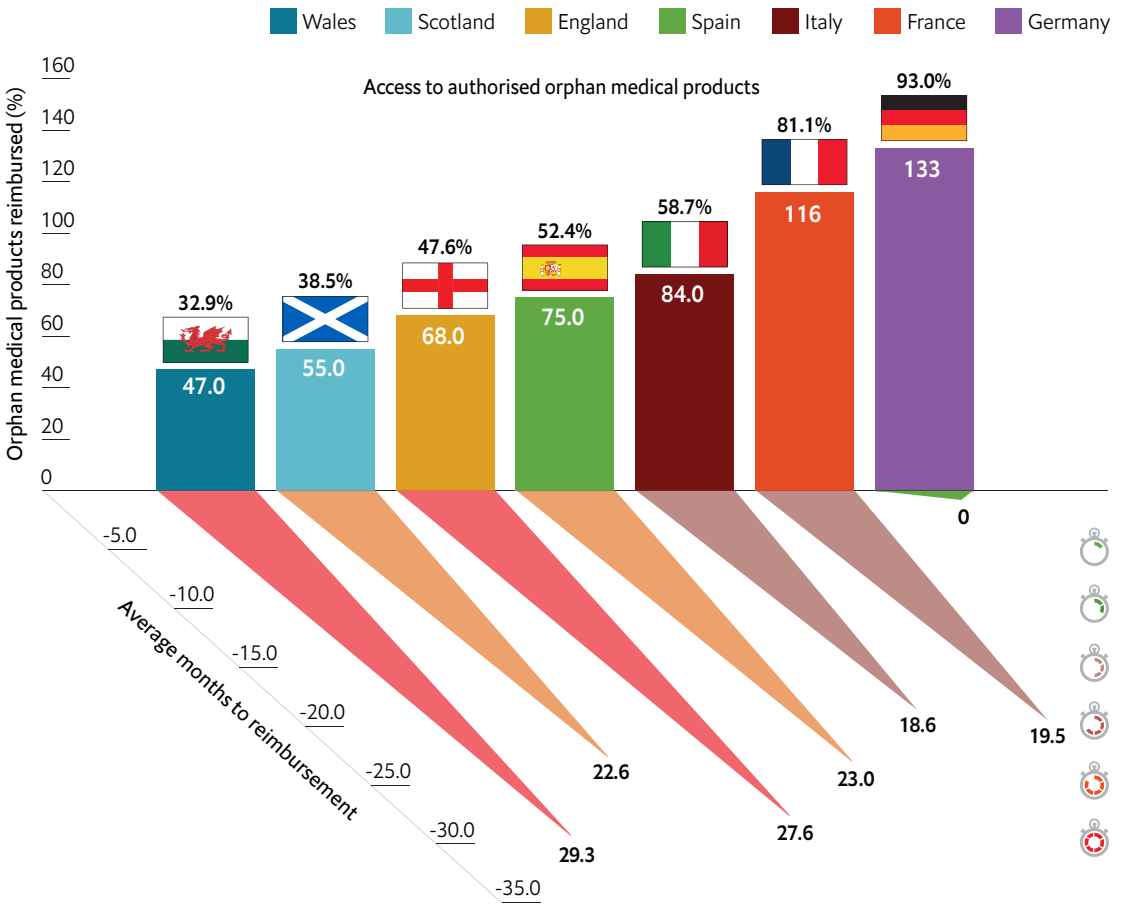
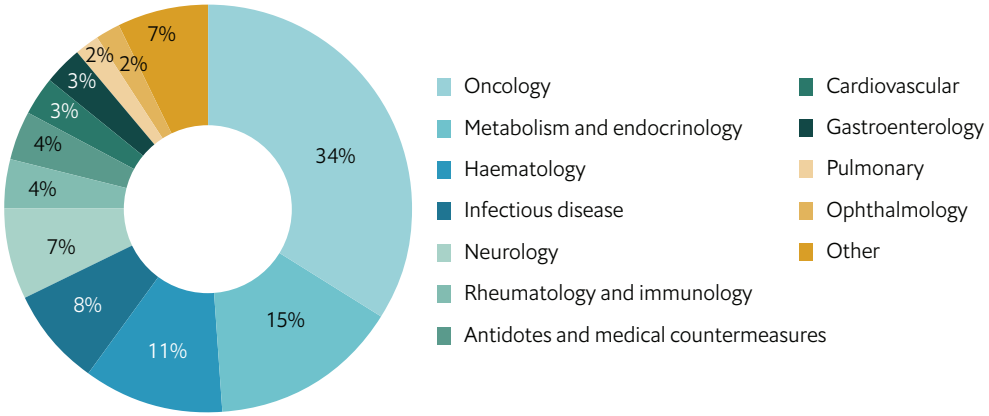


Figure 4. The number of orphan medicinal products approved in the EU and time to approval[56]



Orphan drugs are also emerging for some disease categories more than others, with the vast majority of designated orphan drugs approved by the FDA and EMA focusing on oncology.[57] Neurology accounts for 7% of all FDA orphan drug approvals (see Figure 5) and around a third as many EMA and FDA approvals as oncology.[9, 57] Therefore people with RNDs may not have access to disease-specific treatments.

Figure 5. FDA orphan drug approvals by therapy area.[57]



A further challenge comes with ensuring that no undue commercial advantage is taken. One study noted that between 2009 and 2015, 16% of orphan-designated drugs were for biomarker-derived subsets of more prevalent diseases, indicating that commercial subsidies might be utilised for drug development work that has potentially wider market implications.[58] Another study showed the revenue-generating potential of orphan drugs was in fact greater than that of non-orphan drugs.[59]

Critics generally recognise the value of orphan drug designation, but call for increased submission scrutiny, decreased off-label use benefits and greater price transparency.[60] Orphan drugs frequently come with high price tags, prompting further debate in the context of rising general drug prices and the challenges for reimbursement, which will be explored later in this report.

2.3. National plans for rare diseases

Each rare disease poses unique challenges and requirements, such as the state of its therapeutic R&D pipeline, the mix of healthcare services required to manage the condition (for example, nutritional support, physical therapy and so on) and the disability that it causes. However, there are common challenges across rare diseases that indicate a need for joined-up approaches, for example adapting data protocols for reimbursement decision-making to counter the limitations on clinical trials due to small patient populations.

National rare disease plans allow countries to develop over-arching strategies with cross-cutting benefits and elements at multiple stages of the patient journey, from diagnosis to orphan drug access, registry development and fostering international collaboration.[2, 61]

Table 3. National plans for rare diseases.[52]

Country	National plan	Last Updated
Canada	None at the national level	n/a
France	French National Plan for Rare Diseases	2018
Germany	National Plan of Action for People with Rare Diseases	2013
Italy	National Plan for Rare Diseases (Plano Nazionale Malattie Rare)	2014
Spain	Rare Diseases Strategy of the Spanish Health System	2014
United Kingdom	The UK Strategy for Rare Diseases	2019
United States	None at the national level	n/a

Source: EIU analysis, Dharssi S, et al.

All European countries in this study have national rare disease plans (see Table 3).[62, 63] France is the regional leader, first implementing a plan in 2004, and creating the impetus for action by other European nations.[52] It has also created centres of expertise responsible for co-ordinating diagnosis, care provision and conducting clinical trials.

In 2009 the European Commission called on all members to adopt national rare disease plans.[64, 65] Since 2008 the European Project for Rare Disease National Plans (known as EUROPLAN) has facilitated the creation of national plans and encouraged the sharing of experience.[62, 63] France is again singled out for combining both governmental buy-in and co-ordination of strategy and policy, and France and Germany have both been credited for having well-developed national plans that encompass research, access and co-ordination.[52]

The US does not have a national plan as such, although it boasts a strong legislative front overall, including passing the Rare Disease Act (2002), which established the Office of Rare Diseases at the NIH.[63]

The Canadian Organization for Rare Disorders (CORD) developed a Canadian rare diseases national plan in 2015, in partnership with government representatives, researchers and policy experts.[52, 63, 66-68] However, this document does not represent official government policy so the extent and success of its implementation remains unclear. Canada's provincially devolved healthcare system means that individual provinces, such as Ontario, have developed rare disease plans.[52, 63, 66-68]

"We know that developing a plan and implementing it are two different things, but plans are in place in each [European] country," says Holm Graessner.

Case study: the Scottish National Care Framework for Huntington's Disease

Alongside national plans for rare disease, plans specific to certain disease areas can have an important impact. Scotland's government-funded National Care Framework for Huntington's Disease (HD) is currently the only HD-focused initiative of its kind.[122]

HD can have a broad and devastating impact on the lives and families of those affected. A progressive disorder often described as akin to having motor neurone disease, Parkinson's and Alzheimer's simultaneously, HD affects motor skills and thinking processes, and can cause long-term mental-health issues.[69] Typically progressing over 10-25 years, HD eventually leaves patients unable to walk, talk, eat, drink or care for themselves, requiring 24-hour support for most or all activities.

Death usually occurs owing to complications such as pneumonia and heart failure.[70] There is currently no cure or way to slow the progression of HD. Treatment instead focuses on managing symptoms with medications, therapies and support from specialist services.

Roughly 1 in 5,000 Scots (about 1,100 people) currently have HD, and an estimated 4,000-6,000 are at risk of inheriting it from their parents (each child of a parent with HD has a 50% chance of inheriting the faulty gene that causes the condition). Moreover, the numbers of people affected are increasing: in 2015 the Scottish Huntington's Association (SHA) reported a 55% rise in new referrals over 2012-14, from 709 to 1,103, and highlighted patchy access to specialist care, with only 58% of people affected being properly supported.[71,72,73]

The government responded by providing £112,000 (US$147,500) to co-fund a three-year research fellowship, in addition to awarding the SHA £120,000 to develop a national pathway for people with HD and bring countrywide consistency in standards of HD care.[74] At the beginning of 2017 the National Care Framework was made available online.

The Framework's development was aided by a varied group, including representatives of HD-affected families and carers, psychiatry, psychology, neurology, neuropsychology, genetics, rehabilitation, dentistry, GPs, speech and language therapy, dietetics, physiotherapy, occupational therapy, care homes, palliative care, social work, and academic and research institutions.[71] Designed to evolve over time as evidence and/or health and social care personnel, services and structures change, the Framework is a comprehensive and functional tool to guide care staff and help families affected by HD to receive comprehensive care, regardless of location. Specifically, it offers information on 16 themes, including genetic testing, symptoms guidance, employment-related and financial assistance, end-of-life care, and participation in research.

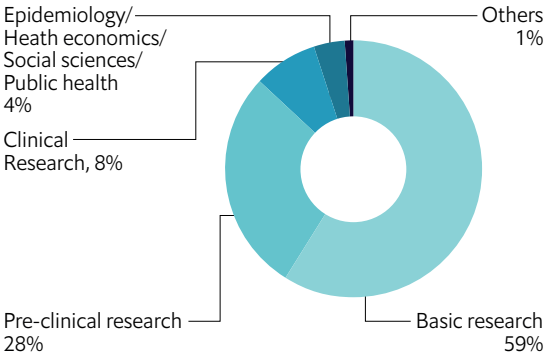
The government has now funded a second phase, aimed at developing localised frameworks for each of Scotland's 11 mainland health board areas. With eight regional frameworks already available online, this second phase of is expected to be completed by early 2020. Although the full impact of the local frameworks will be formally measured by three-yearly staff and service user surveys, the process of developing them has already resulted in increased specialist capacity in the NHS board areas.

The European Huntington's Association's president Astri Arnesen praised how the Scottish National Framework provides "exactly what we need: not just information about HD, but insight on how life with HD can be, and how it can be managed".[75] The Framework has been presented to international conferences in Oslo, Vienna and Houston. Other countries, including Australia, New Zealand, the USA, Norway, Ireland and Wales have also expressed interest in following the model. Given the Framework's success to date, the Scottish government has committed in its National Action Plan on Neurological Conditions to investigate how it could be used for other neurological disorders.

2.4 Public research funding

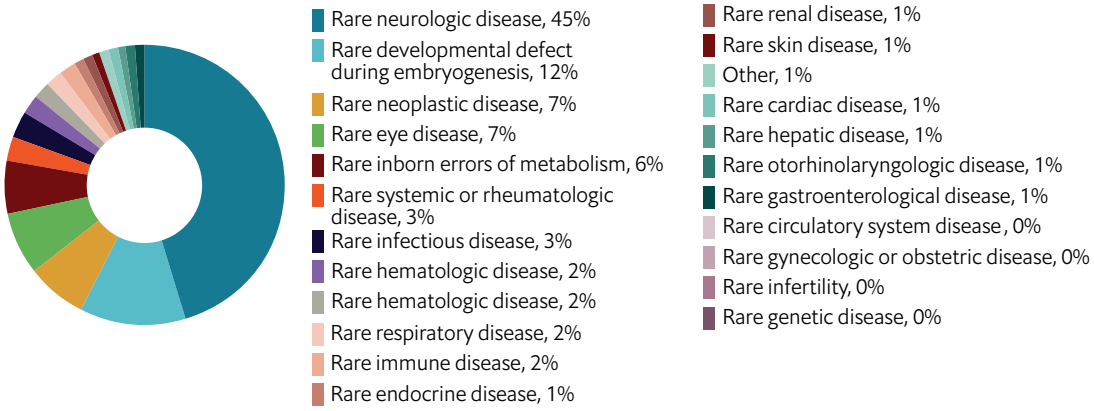
Although orphan legislation has encouraged commercial R&D activities in rare diseases, public funding from governments and national research councils remains critical, as does support from non-profit and charitable groups. Regional funding streams, for example via the EU, are also playing a positive role. Juan Carrión, notes that it is "necessary to establish a financing scheme that favours co-operation and collaboration between the sectors involved, making it necessary for public-sector efforts to be complemented with the appropriate incentives for private-sector resources [such as] industry, patient organisations, foundations [and] academic research centres".

Figure 6. IRDiRC funding by type of research.[76]



From 2010 to 2018, members of the IRDiRC had financed over 3,000 projects, primarily basic and preclinical research (87%). Clinical research, including observational studies and clinical trials, represented 8% of the number of projects, while epidemiology, health economics and social sciences represented 4% (see Figure 6). Basic and preclinical projects covered nearly 1,200 rare diseases (mainly rare neurological and neuromuscular conditions and development disorders) and clinical trials covered 220, mainly rare cancers and rare neurological diseases (see Figure 7).

Figure 7. IRDiRC funding by clinical area.[76]



The EU delivers funding through several channels. Consecutive waves of EU-wide innovation funding in 2002-06 (known as FP6), 2007-13 (known as FP7) and 2014-20 (Horizon 2020) all saw innovation funds directed at rare diseases, primarily via academic institutions (see Figure 8).[77-80] Over €639m (US$709m) was invested in 33 large-scale and 120 small-scale brain research projects from 2002 to 2009, including myasthenia and Mendelian forms of Parkinson's disease.[81]

Figure 8. The types of organisations supported by EU funding programmes.[77]

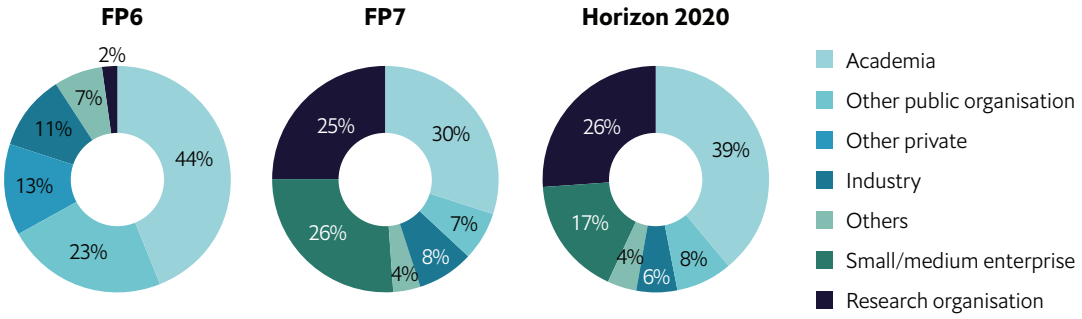
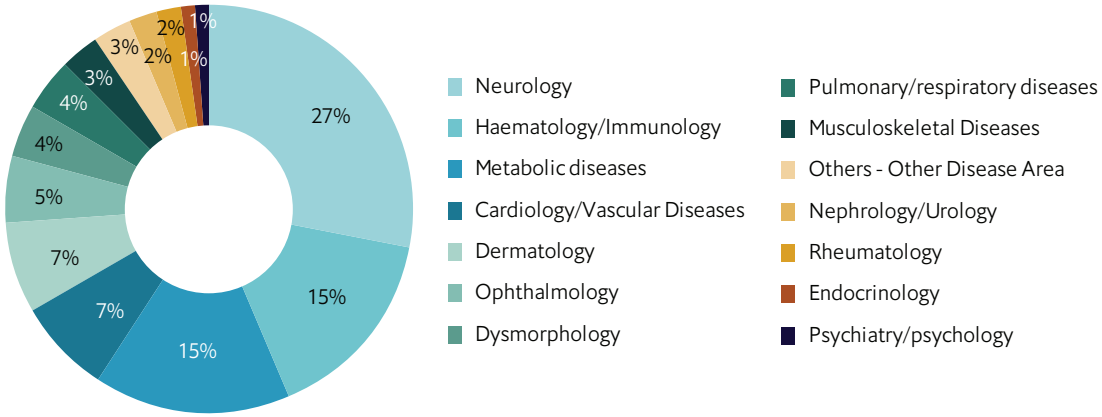


Figure 9. Research projects supported by E-Rare European funding programme by clinical area.[77]



Box 1. Relevant European funding highlights for rare diseases:

- The EU Directorate-General for Health and Food Safety has provided funding for data collection for Orphanet, the European database for rare diseases.[82]
- The European Joint Programme on Rare Diseases, launched in 2019 and convening over 130 institutions from 35 countries, is supported by European Commission funding of €55m (US$61m), which member states will match over five years.[83, 84]
- E-Rare, created in 2006 and funded under the Horizon 2020 programme, has focused on linking funding entities and enabling joint funding opportunities. The largest share of both funded projects (28%) has been for neurology-related diseases (see Figure 9).[77] This includes research exploring disease mechanisms of Huntington's, which may be relevant across a broader range of neurodegenerative diseases, and Project Eden, which aims to establish a European database for NMO and related disorders.[85]
- A €12m European network of excellence for the advancement of clinical gene transfer and therapy.[77]

National funding has been forthcoming in all of this report's study countries. The NIH awarded US$31m in grants in 2019 to rare diseases, including projects tackling two neurological conditions, myasthenia gravis and leukodystrophy. The NIH Common Fund, which focuses on diseases that no single NIH centre can address on its own, provides research funding to tackle undiagnosed conditions, with US$100m earmarked for 2018-22.[86]

The UK Medical Research Council spends approximately 10% of its translational budget on rare disease research. The National Institute for Health Research (NIHR), funded by the Department of Health and Social Care, has made financial contributions, including the recruitment of 13,000 people with rare diseases and their relatives to join the NIHR BioResource databank.

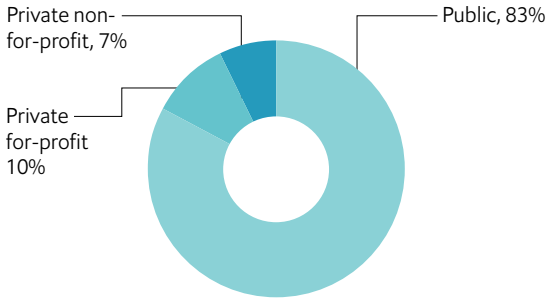
There are flow-through benefits of wider public health innovation investments, such as the UK's Digital Innovation Hubs, a £37.5m (US$49.4m) government investment to create a world-leading data infrastructure that enables safe and secure use of data, including for clinical trials.[87] In 2012 the Wellcome Trust, a UK-based research charity, launched the Pathfinder Awards, which focus on rare and orphan diseases.[27, 87, 88]

2.5 Registries

According to Dr Graessner, registries "are not just useful; they are essential". Patient and drug registries can improve healthcare planning and service delivery, and support innovation by allowing researchers to understand disease progression and outcomes.[27] Registries offer an opportunity for rare diseases that remain poorly understood, are under- and mis-diagnosed, and have small patient populations. Advances in the "-omics" field (such as genomics, metabolomics and pharmacogenomics), along with improvements in electronic health records, real-world data and alternative data–such as data from wearable devices–could add richness to registry data upon which therapeutic advances can be built.[89]

Countries in both North America and Europe have invested significant resources and attention to strengthening registries. Orphanet records a total of 753 rare disease registries in Europe (as at May 2019), with the largest clusters in Germany (149) and France (143), followed by Italy (83) and the UK (74). According to Orphanet, Spain in particular has made great strides, with approximately ten operational registries of rare neurological diseases covering more than 5,000 patients, as well as some population-based records that support policy and planning.

Figure 10. Funding sources for European registries.[90]



In terms of the diseases of focus for this report, Orphanet indicates that 22 registries exist for NMO, spread across Spain, Finland, Germany, France, Belgium and the UK.[90] One Europe-wide database exists for Prader-Willi syndrome, based at the University of Cambridge in the UK. One Huntington's disease registry exits in the UK, and one international registry is based in Germany. European registries are mostly publicly funded (see Figure 10).

A weakness of country-specific registries is that they are independent of each other, which can restrict the research benefits that come with scale. The integration of databases, combined with advances in gene diagnostics, has facilitated the collection of

more detailed information on diseases and symptoms (deep phenotyping) and genotype–phenotype association studies in rare kidney diseases.[91] A further challenge is the large number of dormant registries, says Alastair Kent. In Europe, he adds, many registries "haven't been updated, they haven't been curated because they've either been the initiative of an enthusiastic clinician or an academic, or they've been associated with a particular funding programme. They've just frozen at the point in time at which either the money ran out or the programme changed, or the interested academic moved on to a new job".

There have been several successful initiatives to facilitate and encourage data integration in Europe. An initiative supported by the European Commission that ran in 2012-17 pooled the efforts of RD-Connect, a data analysis platform, with those of NeurOmics and EURenOmics, which convene registry and biobank data. Achievements include identifying over 120 disease genes and next-generation sequencing panels that led to the diagnosis of over 700 patients, along with uncovering novel biomarkers.[91] Another was a genome-phenome analysis platform in Europe which, by 2017, contained exome and genome data for over 3,000 patients with neuromuscular and neurodegenerative diseases, providing various data analysis tools.[91] The European Commission's funding for Horizon 2020, its innovation program, includes the development of a virtual platform for rare disease data, tools and standards, as part of the push towards a European Open Science Cloud, which could further support regional data pooling.[29, 92]

European countries are also moving towards harmonised coding to reduce data fragmentation. A 2014 study argued that a small fraction of rare diseases have codes in international nomenclatures, complicating the tracing of patients with rare diseases in national and international health systems.[93] The Orpha codes system, based on Orphanet data, has been adopted by France, Germany and some Italian regions to complement the International Classification of Diseases (ICD). In addition, France has developed a tool to support the coding process.[93]

Going forward, experts advocate for more global registries that pool together related diseases. "We are discovering that many diseases which are phenotypically dramatically different, [but] at the molecular level have a very similar genetic cause. Registries need to be interoperable so that you can jump across from one disease registry to another, if the paths lead you in that direction," says Mr Kent. Because rare diseases have small individual populations, grouping them together can enable greater levels of statistical analysis. Global registries for neuromuscular diseases now exist in Canada, Australia, New Zealand, the Netherlands and Belgium.[94]

Another challenge is the low number of registries for drugs and therapies, rather than for diseases. In Europe, the EuOrphan project is designed for healthcare professionals and patients and to link administrative and scientific data on designated and marketed drugs from the European Commission and the FDA, although at the time of writing, the resource appeared to be non-functional.[9, 95] In the US, the NIH has funded data development through the Rare Diseases Clinical Research Network (RDCRN), established under the Rare Diseases Act of 2002, which encompasses over 350 sites in the US and 50 in another 22 countries. By October 2019 the RDCRN had encompassed 237 research protocols and included over 56,000 participants in studies that include brain development diseases.[5] The initiative is also encouraging patient participation in research and trials through user-friendly websites on diseases including lysosomal disease.

2.6 Regional and global partnerships

Regional and global partnerships are critical to share best practices, strengthen innovation and maximise the reach of research breakthroughs. Globally, the IRDiRC, established in 2011 by the European Commission, has played a lead role in setting standards and guidelines on issues including diagnostics and data-sharing.[89] It also acts as a co-ordinating body for its members, which include public research agencies, government ministries and patient associations (see Table 4).[89]

Table 4. Selected IRDiRC funding members investing over US$10m over five years.[29]

Country	Funding Member
Germany	Federal Ministry of Education and Research
France	Agence National de la Recherche
Spain	Instituto de Salud Carlos III
UK	National Health Service
US	National Institutes of Health
Canada	Canadian Institutes for Health Research

IRDiRC membership commits participants to implementing its policies, provided that they are consistent with national legislation. IRDiRC sets goals for the rare disease community, such as reaching 200 new therapies and developing the means to diagnose most rare diseases by 2020.[18] It also contributes to the creation of medical "ontologies"–machine-readable, standardised vocabularies for data organisation and sharing. Such ontologies describe the phenotypic features (signs and symptoms) of a disease and disease groups. Standardised vocabulary makes data interoperable and shareable across platforms. Disease-specific international mechanisms can also support harmonisation. One example is the International Panel for NMO Diagnosis, which has fine-tuned diagnostic terminology to create a spectrum-based approach to NMO.[96]

EU harmonisation efforts can also help to support research infrastructure. For example, a series of projects on statistical design methodologies for clinical trials for small population groups have helped to support scientific research.[97]

European regional partnerships have stimulated cross-border collaboration too. ERNs are one example, using virtual communities of practitioners and researchers, to convene and pool expertise and laboratory resources, ultimately creating structured knowledge-sharing and care co-ordination to improve access to specialised care.[98] Twenty-four ERNs were launched in 2017, involving 900 medical teams. They focused on disease areas including Huntington's disease, atypical Parkinsonism syndromes and cerebellar ataxias.[22, 89, 98, 99] Beyond this, Mr Kent points to NHS England's process to create "collaborative networks" for rare diseases not covered by ERNs.

The EU is also investing in patient-centred collaborative platforms, notably European Resource Centres, an online one-stop shop, and INNOVCare (see case study).[100, 101] Some countries also complement the focal areas of ERNs with dedicated support structures.

Case study: INNOVCare[102]

Patient need for co-ordinated care after diagnosis has been well articulated in the literature, particularly linking health services to employment, social and support services. The Innovative Patient-Centred Approach for Social Care Provision to Complex Conditions (INNOVCare) project, funded under the European Programme for Employment and Social Innovation, was a three-year project (running from 2015 to 2018) to develop and test an innovative care pathway for social inclusion of people with rare conditions, and propose up-scaling and "roadmaps". INNOVCare aimed to give a voice to the social and everyday needs of people living with a rare disease and address the need for co-ordination between service providers in EU member states.

Through in-depth assessment of the needs of patients and their families, INNOVCare showed that care pathways can be developed to unite national resource centres for rare diseases, regional case managers and public bodies. These care pathways provided co-ordination through a resource centre for rare diseases, with case managers allocated to patients regionally. Care requirements by people with RNDs were drawn from a range of providers, from health to social care, requiring complex co-ordination and collaboration across 17 different systems and organisations. Achieving consensus on shared goals, language and timescales pointed to the need for higher-level steer, using co-ordinators employed by the respective political bodies responsible for knowledge exchange.

The INNOVCare project developed roadmaps for a set of countries to upscale co-ordination of management. Spain is one of the focal nations. It boasts a relatively high level of policy-maker awareness of rare diseases in comparison with the rest of Europe; the rare disease strategy forms one of Spain's fifteen National Health Strategies and is the only one with a dedicated budget. In some regions, like Murcia, the establishment of a closer network of primary care doctors, social care professionals and other non-medical health care professionals with closer ties to the reference centres is expected to be achieved, as regional plans for the development of these networks already exist. Case management in public hospitals enables connection of patients with reference centres and co-ordination with primary community services such as family physicians.

In Catalonia, case managers were tasked with co-ordinating multidisciplinary team meetings on specific rare diseases. Case managers operated at two levels: expert care entailed secondary (hospital-based) co-ordination of the multi-professional teams, while territorial case managers facilitated the co-ordination between primary health care services, social services, educational centres and support equipment services. Both case managers supported the contact between the patient and patient organisations. Moreover, e-health tools and ICT facilitated the exchange between all professionals involved.

Further steps can be taken to professionalise case management in Spain. One is to define the profile of case managers and agree on the role, function and necessary competences. The development of a training curriculum for case managers was a part of a pilot INNOVCare project and included a range of case studies demonstrating applications of the principles of case management, including the Navigators Project in Denmark and ProRaris in Switzerland. This curriculum stressed that the clear definition of the role should be a priority.

After 18 months participants with rare diseases reported feeling better informed and empowered to perform self-care, with care-giver burden also reduced. INNOVCare showed that well-organised care pathways with case managers to help patients to navigate the health system benefit people with rare diseases, their families and carers.

Cross-border regulation can also support patients seeking care abroad. A 2011 EU directive enables patients with a rare disease the right to EU-wide healthcare services if their country's national healthcare system is not able to provide essential treatment.[2] According to Mary Kearney, recent developments such as medical passports are a good supplement for such directives, and enhance the coordination required for cross-border care.

For Mr Kent, the EU has been instrumental in improving R&D and patient care in rare diseases, highlighting the value of regional and international collaboration "The UK punches well above its weight in terms of research initiatives that support patients with rare diseases. But that has been possible because we have been part of a 28-member state collaborative where the opportunities exist for people to create the critical mass necessary".

Case study: the French network of Reference and Competence centres for Prader-Willi syndrome

Prader-Willi syndrome (PWS) is a complex neurodevelopmental genetic disorder, considered to be the most frequent known genetic cause of obesity. The condition results from the loss of expression of paternally derived genes in the PWS critical region on chromosome 15q11-q13. With a prevalence of 1 in 10,000 to 1 in 30,000 live births, PWS affects both genders equally and occurs in people from all geographic regions.[103]

Affected infants usually display severe hypotonia (decreased muscle tone), failure to thrive and feeding problems. Several nutritional phases occur during the development of older affected children; between three and four years of age, an insatiable hunger (likely due to hypothalamic dysfunction) begins to develop, which in untreated children leads to severe obesity.[104] Other symptoms include behavioural problems, cognitive impairment, dysmorphic features, hypogonadism and short stature.[105] Death at an early age occurs because of complications usually linked to obesity, such as respiratory problems and diabetes. Choking (mainly during bouts of heavy eating) and stomach rupture or necrosis of tissue have also been described.

There is no cure to date. However, the presence of an organised path to care from the very early days onwards, with the co-ordinated efforts of a multidisciplinary team of clinical geneticists, paediatricians, orthopaedists, endocrinologists, speech therapists, psychologists, dieticians, nutritionists and other healthcare professionals can greatly improve the overall health and quality of life for affected individuals and their families.[106] Growth hormone therapy, labelled in 2000 as an orphan drug for PWS, is the standard treatment and is particularly effective when started at a very early age.[107, 108] Thanks to the development of DNA methylation tests, the average age for a confirmed diagnosis of PWS has decreased from eight years in the 1990s to the first weeks of life now.[109-111]

France has reached particularly high standards of care and research thanks to specific action within the National Plans for Rare Diseases, which

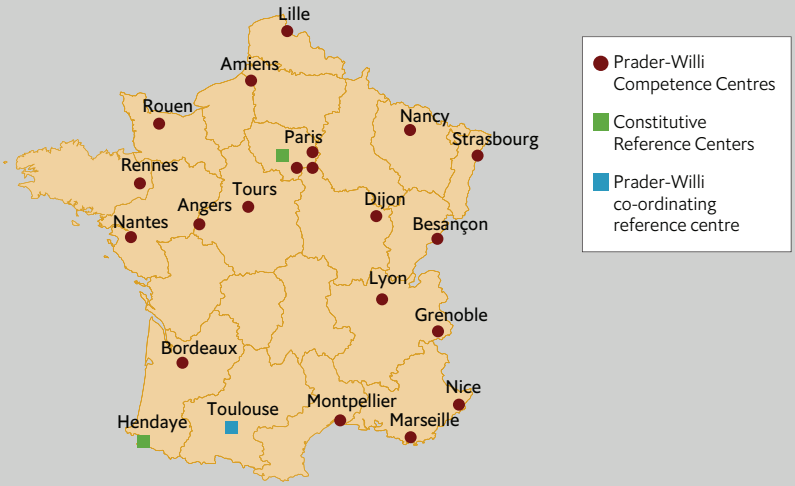
aim to offer structured organisation of healthcare for rare disease patients.[112] From the late 90s, French teams involved in PWS care initiated collaborations to share clinical knowledge and experience. In November 2004, the Ministry of Health approved a reference centre ("centre de référence") for PWS; there are now three sites: Hôpital des Enfants, Toulouse (responsible for co-ordination); La Pitié-Salpêtrière, Paris and Hôpital Marin d'Hendaye. The aim of the reference centres is to optimise access to care for patients of all ages by improving knowledge on the disease and good practices, and by training and organising hospitals throughout the country with expertise in PWS care—the so-called competence centres ("centres de competence"), first introduced in 2008.

The 20 regional competence centres assume responsibility for diagnosis, treatment and follow-up of the patients close to their home. At a higher level, PWS reference and competence centres are part of DéfiScience, a national network created in 2014 as part of the Second National Plan for Rare Disease, which groups centres focused on rare brain developmental defects and intellectual deficiency and connects them with the relevant stakeholders, including diagnostic and research laboratories, imaging facilities, health and social care providers, and professionals and patients' associations. A strong collaboration is also in place between the PWS reference centres and Prader-Willi France, a family association which falls under the umbrella of the International Prader-Willi Syndrome Organisation. Prader-Willi France offers both guidance and practical assistance such as organisation of holidays and short stays for patients and their families.

In addition to offering training and co-ordination, the reference centres conduct research on PWS, which encompasses basic research, clinical trials and epidemiological surveillance. For this purpose, a national database has been built, which includes medical data of children and adolescents with PWS, details about their management, socio-demographic data on their families, psychological data and data regarding the quality of life of the parents.[113]

The database now provides a large amount of information resulting from more than ten years of knowledge gathering and experience at the reference centres, which has provided a unique opportunity for detailed and comprehensive epidemiological studies, the most recent of which

Figure 11. Prader-Willi centres in France[116]



focused on the causes of death among PWS patients.[110] Clinical trials conducted on patients recruited through the reference centres have explored the use of oxytocin to improve feeding and social skills in infants, and the promising effect of topiramate on eating behaviour.[114, 115]

2.7 Non-profits and patient associations

Non-profit and advocacy groups play a major role in awareness, influencing policy and directly funding research. The Guthy-Jackson Charitable Foundation, a non-profit organisation, has raised over US$40m to date for NMO. The US-based CHDI Foundation, focused on Huntington's disease, has an estimated annual budget of US$100m, nearly three times higher than NIH spending on HD research in 2016.[117]

Non-profit, advocacy and support groups provide resources to support patient access to research and expertise, helping them navigate fragmented systems and the diagnosis and care pathway. "There are a lot of support groups for some of these conditions that will help the individuals and their families to find their way in the system, wherever they are in Canada," says Bernard Brais. These groups can help patients access expertise and resources that they may be unaware of or unable to access by themselves without guidance and support. They also support healthcare workers; for example, the Huntington's Disease Society of America contains instruction modules for physiotherapy dealing with early to late-stage HD.

Leveraging their communications and outreach strengths, such groups also work with public health agencies to raise awareness. For instance, the Association of Medical Research Charities is working with the UK's NIHR on the "OK to Ask'" campaign to enhance patient awareness about clinical research in the NHS and give patients more confidence to seek out information from their healthcare providers, something that patients are often reluctant to do. Germany's Care-for-Rare Foundation works with doctors and clinics to help children with rare diseases to gain access to cross-border support.

These groups can also directly influence policy change; a patient movement under the banner of the National Organisation for Rare Disorders is credited for mobilising the US Congress to pass orphan drug legislation in 1983.[52, 118] It continues to provide an interface and advocacy platform on everything from new-born screenings to caps on out-of-pocket costs. In France too, patient groups have directly shaped policy. "Policy improvements for action on rare diseases have been primarily driven by patient associations," says Daniel Scherman, director of the French Foundation for Rare Diseases. The French Ministry of Health's third national rare disease plan was also a response to patient advocacy and a need to follow-up the two first national plans, he says.

2.8 Reimbursement and adapting health technology assessments

While orphan drug legislation quickens the approval process, health technology assessments (HTAs) are needed to make medicines accessible and reimbursable. This is challenging for HTAs because RND therapies do not meet conventional cost-effectiveness thresholds and the usual assessment tools will not apply well.[30, 119] Critical data may not exist, such as that indicating comparable efficacy, effectiveness and associated costs of new interventions. Validated, disease-appropriate quality of life instruments are often absent, and limited data on disease natural history, combined with the progressive and degenerative nature of rare diseases, complicates the modelling and projections used by HTAs.

In response to these challenges, HTAs have adapted their protocols. In Sweden, the cost-effectiveness threshold has been adapted based on disease severity. The Scottish Medicines Consortium accepts a higher-than-usual incremental cost-effectiveness ratio (ICER) for rare diseases if a medicine meets adapted criteria related to substantial quality of life and life expectancy. The UK National Institute for Health and Care Excellence (NICE, covering England and Wales) has broader criteria, including higher ICER threshold ranges, dependent on quality of life gains.[119] In Germany, orphan drugs are appraised through a simplified evaluation process, which assumes clinical benefit based on orphan designation, provided that annual sales are below €50m during the first 12 months.[119] Germany and the UK are credited for achieving the highest reimbursement of orphan drugs in one European study.[120] These countries also act as trend-setters for other, less developed contexts; Romania, for instance, manages the reimbursement of drugs based on processes used in the UK, Germany and France.

There are also disease-specific initiatives to support HTAs. In November 2017 Duchenne UK launched Project HERCULES to support access to new treatments for Duchenne muscular dystrophy, working to develop tools and evidence to support HTA and reimbursement decisions for new treatments for the disorder.[121]

3. Conclusion: Building on policy progress

A collective problem

Rare diseases affect over 60m people in North America and Europe, with a substantial proportion either neurological in nature or with neurological manifestations. Each pose unique challenges, from the size of the therapeutic pipeline to the professional resources and specialisms required for chronic management. But they are also interlinked. Genetic causes can be similar, as can specific disabilities. They face similar structural constraints, such as the need for R&D incentives and adapted reimbursement protocols. In Europe and North America, rare disease policy, in both neurological conditions and generally, is a blend of national-level policy and regional collaboration to share resources, ideas and practices critical to improving outcomes for patients.

Europe and North America have made substantial gains in supporting people with rare diseases over the past four decades. Working together to build on past successes, tackle deficiencies, and design flexible, adaptable and evolving frameworks can support people living with rare diseases. This report, combining policy analysis with expert interviews, shows the progress achieved so far and identifies foundations on which to build in the future.

Key findings

- **Research and development (R&D) spending has increased thanks to legislative and regulatory changes focused on rare diseases, but reimbursement protocols need to adapt to manage pricing and access challenges.** Led by the US, regulators have implemented orphan drug legislation to attract commercial R&D into rare diseases, increasing the pipeline of therapies. Oncology dominates, with nearly 1,200 orphan drug designations approved by the US Food and Drug Administration and the European Medicines Agency, as at 2017. Neurological diseases, combined with psychotic diseases, form the second largest tier, at over 400. Owing to small population sizes, the costs of resulting therapies can be high. Such prices can still be cost-effective in the long term if they are curative or represent a substantial advance on current options. However, high prices pose a challenge for payers (whether social security or private insurers) who are unaccustomed to these high up-front and sometimes one-off price points. Protocols used by health technology assessment agencies in countries such as Scotland, England and Germany are adapting to allow approvals based on differentiated data and thresholds.

- **National rare disease plans and legislation are found across the study's group of countries, providing coherence and strategic direction, but they vary in their effectiveness and implementation.** The European countries covered in this study have all adopted national plans and legislation, led by France in 2004, and aided by support and directives from the European Commission since 2009. National plans support synchronisation and disease epidemiology, raise public awareness, support early diagnosis and screening, and provide mechanisms to promote access. The US does not have a rare disease plan as such but has passed comprehensive legislation covering orphan drugs (1983) and rare diseases (2002). Canada at present only has a non-

governmental national health plan, although its devolved health system means that rare disease plans exist in individual provinces, such as Ontario.

- **Public funding is supporting research, including in relation to neurological diseases; to build momentum, rare neurological diseases (RNDs) should be linked to the growth of wider basic science research into the brain.** Although rare diseases have attracted more commercial R&D, non-commercial funding is also critical, both from public sources, such as governments and national research councils, and charitable groups. The International Rare Diseases Research Consortium (IRDiRC), whose members are funding organisations committing a minimum of US$10m to rare diseases over five years, financed over 3,000 projects between 2010 and 2018, of which 45% were for RNDs. Regional funding streams, such as Europe's Horizon 2020 programme and its predecessors, have channelled significant resources into neurological conditions; they formed the largest share of submissions to E-Rare (24.2%), a European rare disease funding initiative. National research funding is also forthcoming into RNDs. In 2019 the US National Institutes of Health (NIH) awarded US$31m in grants to rare diseases. Understanding rare neurological conditions provides vital insights into how the brain functions (and to what happens when it does not). Therefore, RND research can play into the wider growth in brain disease research in Europe and North America, driven by rising incidence of age-related cognitive decline. Non-profit groups and foundations are also raising sizeable investment in research, at times exceeding national funding streams, such as the CHDI Foundation, a US-based biomedical research institution focused on Huntington's disease, whose estimated US$100m annual budget far exceeds that of the NIH.
- **Registries are key to support research and innovation, but they need to be live, co-ordinated and interoperable.** Patient and drug registries can improve healthcare planning and service delivery. They also support innovation by allowing researchers to understand disease progression and outcomes, as well as finding linkages between conditions. Positively, there are thousands of registries for rare diseases and RNDs, especially in Europe. However, experts warn that many are dormant or outdated, owing to funding shortfalls or over-reliance on individual researcher efforts that may later discontinue. Sustained funding and commitment, technical advances (such as harmonising disease coding to allow interoperability and integration), and the development of global registries that pool together related conditions can all empower the research community.
- **Regional and international collaboration has successfully pooled knowledge and resources, especially in Europe, owing to the policy infrastructure of the EU.** Collaboration across borders is essential to nurture innovation and give patients access to care. Globally, IRDiRC, established by the European Commission and the NIH in 2011, has played a catalytic role, including setting standards and guidelines on issues including diagnostics and data sharing, and co-ordinating its members, including public research agencies, ministries and associations. Regionally, the EU has promoted collaboration and harmonisation efforts, from a national rare disease plan directive in 2009 to the formation of European Reference Networks–virtual communities of practitioners–with the aim of pooling expertise and resources, creating structured knowledge sharing, and promoting co-ordination. Neurological conditions have been prominent: 24 networks focused on disease areas including Huntington's disease and atypical Parkinsonism syndromes were launched in 2017. EU

mobility legislation is also helping patients to attain care in other EU states in cases where it is lacking domestically. Advocacy groups are vital to synchronising services and identifying gaps, supporting patients' access to research and expertise, guiding them through the diagnostic "odyssey", and working with public health agencies to raise awareness.

- **Four "best practice" case studies show the benefits of collaboration and connectivity to support patients with RNDs.** This report includes case studies covering Prader-Willi syndrome in France, Huntington's disease in Scotland, and neuromyelitis optica in the UK's National Health Service (NHS), and a cross-cutting case study of INNOVCare, a European initiative exploring interventions to co-ordinate care. Each case study shows how public sector health actors can support patients and improve healthcare delivery. Prader-Willi syndrome reference centres in France optimise access to care by improving knowledge, sharing best practices and training hospitals. Scotland developed a national care framework specific to Huntington's disease, funded by government and based on input from a wide-ranging group including families and carers, psychologists, dentists, GPs, and speech and language therapists. In the NHS, a one-stop resource for neuromyelitis optica, with links to academic centres, provides resources for health professionals, patients and carers. INNOVCare investigates care co-ordination across rare diseases, partly by conducting patient-focused research to improve understanding of the diagnostic and management journey, and the impact of case management officers.

Appendix 1: List of tables and figures

Appendix 2: References

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Appendix 3: methodology

This project began with a pragmatic literature review to identify emergent themes, which informed the comparative policy analysis,case study selection and interviews.

The literature review identified key recent literature by searching selected databases and grey literature sources for papers related to rare neurological diseases in general and the three diseases of focus.

Table 5: database and grey literature searching summary

Databases and sites searched	Dates searched	Number of hits
MEDLINE	2009-Oct 2019	217
EMBASE	2009-Oct 2019	92
Cochrane Database Syst Rev	2009-Oct 2019	0
Specialty databases Cinahl/HMIC/Scopus/Wos	2009-Oct 2019	26+22+2+6
Grey lit databases Oaister/OpenGrey/BASE/ Google/Google Scholar	2009-Oct 2019	15
Total number of hits		419
Total number after de-duplication		349
Total number after first appraisal		76 top-level papers 70 specific to conditions

The themes identified during the literature review informed interviews with 7 experts (see Appendix 4 for the list of interviewees) who provided insights into policy challenges and opportunities at an international and country level. The findings of the literature review and interviews were supplemented by further ad-hoc research. The final analysis sought to identify and describe policy challenges and health systems responses, including four case studies highlighting best practice.

Appendix 4: acknowledgements

Due to their small prevalence rates and often complex care pathways, rare diseases continue to present policy and health systems challenges globally. Given the related gaps in understanding around best practice to address challenges related to rare diseases, the EIU conducted research to highlight the burden, unmet needs and opportunities related to these diseases.

Key rare disease experts and stakeholders were engaged to illuminate these challenges, and to stimulate discussion on opportunities for addressing rare diseases. Our sincere thanks go to several people for both their time and contributions to this work (in alphabetical order):

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- **Daniel Scherman**, Director, French Foundation for Rare Diseases (France)
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LONDON
20 Cabot Square
London
E14 4QW
United Kingdom
Tel: +44 (0) 20 7576 8181
Email: london@eiu.com

NEW YORK
750 Third Avenue
5th Floor
New York, NY 10017
United States
Tel: + 1 212 698 9717
Email: americas@eiu.com

HONG KONG
1301 Cityplaza Four
12 Taikoo Wan Road
Taikoo Shing
Hong Kong
Tel: + 852 2802 7288
Email: asia@eiu.com