

Delivering for patients with rare diseases: Implementing a strategy

A report from the UK Rare Disease Forum



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Foreword

The publication of the UK Strategy for Rare Diseases in 2013, represented a landmark for patients with rare diseases. The Strategy was a result of close collaboration across all UK Governments and healthcare services which set out key recommendations that, when fully enacted, would transform the experience of patients with rare diseases and their care pathway.

This report is the first from the UK Rare Disease Forum on implementation of the UK Strategy for Rare Diseases (the Strategy). There has been significant progress made in addressing many of the strategy recommendations but there is still a lot more to be done. Given that the Strategy was always planned to take until 2020 to fully implement this is to be expected.

One of the key principles when drafting the Strategy was to ensure that the patient was placed at the centre of service development and decision making. The report shows that the role and importance of patients in the planning and delivery of care continues to grow. There are excellent examples of where the patient voice has been central to the design of new services and has provided key insights into the value and potential benefit of new treatments. The experience of patients is also important for both the appraisal and the commissioning of new therapies. It is essential to ensure that these welcome improvements go from strength to strength and become fully embedded in healthcare culture. There is a need to be vigilant and assure ourselves that, among the increasing challenging discussions that will need to be had in a health and social care world of competing and often conflicting demands, there remains a strong patient voice in the implementation of the Strategy and development of services.

Access to standardised, high-quality data is the bedrock of understanding rare diseases, the development of innovative technologies and healthcare tools and supporting improved service delivery. Since the publication of the UK Strategy, there has been a considerable increase in the availability of high-quality information for rare diseases and this trend is likely to continue. The expansion of social media has opened up significant new opportunities for patients to form networks and support groups. This same technology also allows patients and their families to compare experiences, which can be useful in identifying where service provision can be improved. Healthcare providers too are active in adopting this technology to offer new forms of interaction and remote access to specialist healthcare.

The creation of Genomics England and the building of whole genome sequencing capacity in the NHS holds the most potential to transform the diagnosis of rare disease. The 100,000 Genomes Project is still in its early phases but it is likely to have a significant and lasting impact on transforming molecular diagnostics across the UK. The creation of a unified registry of rare disease patients by Public Health England, with support from the Department of Health, is welcome and will have a significant impact on assessing, planning and research for rare diseases. It is a concern that codification of rare diseases is still an outstanding issue. Clear and consistent coding is essential to effective data sharing and analysis. Despite being widely recognised as an important factor in addressing rare diseases, there still does not seem to be a single body with the ability or leadership to deliver a credible response to this key challenge.

Among pharmaceutical companies, there seems increasing recognition that understanding rare human conditions can provide unique and powerful insights into human biology and can directly influence the delivery of more targeted and effective technologies. The increasing subdivision of relatively common diseases might mean that more conditions fall within the definition of a rare disease. It seems probable that the adoption of strategies used by the rare disease community will be essential to manage the shift towards mainstream healthcare therapies and services being informed by the patient's DNA data, leading to the provision of more personalised treatments.

Rare diseases do not recognise national boundaries and this report emphasises the need for collaboration across the UK. Much of the care for patients with rare diseases is most effectively delivered via a small number of specialised centres and facilitating this will require careful UK-wide coordinated approaches to ensure patients all receive the best available care. Although the UK continues to be a world leader in rare disease research, it does so within a European and global context. This report provides a flavour of the initiatives that are taking place at EU level that will help establish broader networks and partnerships focused on rare diseases.

The next report from the UK Rare Disease Forum is planned for 2018 and a number of specific challenges are likely to emerge in this period. The constraints placed on public expenditure will mean that budget pressures on all health and social care services will continue. The recent announcement of the outcomes from the 2015 Comprehensive Spending Review, while containing positive news such as the renewed commitment to the 100,000 Genomes Project, will shape this debate going forward and the Forum will continue to monitor the impact of the review. A related issue is how to maintain equity of access to services with a move to greater regional devolution in England's healthcare system. The Forum will be interested to see the effect of the changes brought about by more regional decision making, for example initiatives such as those being put in place in

Manchester, and their more general impact on health and social care provision.

There will always be some underlying tension between those commissioning and those receiving health and social care services and support. Delivering many of the recommendations in the UK Strategy has the potential to save money in the long term, for example the time to obtain a diagnosis can take far too long and represents an inefficient use of resources. All too often, the time to obtain a diagnosis still takes far too long and represents an inefficient use of resources. A faster, more accurate and more informed diagnosis is not just better for patients and their families. It also represents a better use of resources by the healthcare system, avoiding patients being referred around the system and supporting families to return to a more settled, economically active, home life.

Finally, I would like to extend my personal thanks to forum members for all their hard work and the UK health Departments and services to their continued commitment to implementing the Strategy.

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Executive summary

- i. The UK Government published the UK Strategy for Rare Diseases in November 2013. This high-level framework set out 51 specific commitments designed to improve the lives of all those affected by rare diseases. The UK is a recognised leader in the research, treatment and care of rare diseases and the Strategy seeks to build on successes to date and drive further improvements to ensure that people with rare diseases receive the highest quality treatment and care.
- ii. The UK Rare Disease Forum has been tasked with monitoring the implementation of the Strategy. This report represents the first opportunity for the Forum to comment on progress since the publication of the UK Strategy and offers the chance to highlight where further action is needed (or where existing action needs to be accelerated). Further reports will be published in 2018 and 2020.
- iii. The UK Strategy for Rare Diseases covers five specific areas:
 - empowering those affected by rare diseases
 - identifying and preventing rare diseases
 - diagnosis and early intervention
 - coordination of care
 - the role of research.
- iv. The four countries of the UK have taken different approaches to addressing the recommendations in the Strategy and these are set out in **section 1**. Scotland, Wales and Northern Ireland have separate implementation plans. Implementation of the Strategy in England is the responsibility of a number of organisations but falls largely to NHS England, which has issued a Statement of Intent to implement the Strategy. NHS England will continue to work on implementation of the Strategy as part of its Five Year Forward View.
- v. **Section 2** outlines the action taken to date to empower patients (and patient groups) to raise awareness of rare diseases, to contribute to service improvement and to take part in research. It acknowledges that patients with rare diseases are important champions of the need to develop specialised services, to improve understanding of rare diseases and thereby develop new treatments. Case studies highlight the value of involving patients at every level. The importance of providing patients with good-quality, comprehensive information to help them make informed choices cannot be overstated. The patient perspective brings valuable insights – for example, in making technical information more accessible to a lay audience.
- vi. In terms of identifying and preventing rare diseases, **section 3** of the report highlights recent advances in population-based screening programmes across the UK. All four countries of the UK have seen significant developments in the provision of genetic testing. This section highlights the benefits of a UK-wide approach. The creation of regional Genomic Medicine Centres (GMCs) as part of the 100,000 Genomes Project will form the core of specialist centres where patient services and research will be increasingly integrated. Northern Ireland and Scotland are also in the process of establishing regional GMCs, thereby providing an essential gateway to participation in the 100,000 Genomes Project.

- vii. Delays in diagnosis represent one of the biggest challenges faced by people with rare diseases. The Policy Innovation Research Unit report, *Diagnostic odyssey for rare diseases*, brings these challenges into sharp focus. **Section 4** of this report sets out a range of actions designed to improve diagnostic pathways and to reduce delays in diagnosis.
- viii. Scientific advances in diagnosis continue at a rapid pace. The 100,000 Genomes Project and the establishment of a network of regional GMCs and the existing network of diagnostic laboratories will accelerate progress in this area. It will lead to earlier and more precise diagnoses, new diagnostics and devices and more tailored treatments.
- ix. The implementation of the UK Strategy for Rare Diseases complements the UK Government's broader Strategy for Life Sciences. This sets out a vision for the UK to be a global leader in life sciences through a series of initiatives aimed at supporting the growth of the UK life sciences industry and to support researchers, clinicians and ultimately patients through improved healthcare outcomes. Many of the associated initiatives, such as the Biomedical Catalyst, actively support research into rare diseases.
- x. Patients with rare diseases often have complex needs and providing effective treatment requires special coordinated efforts involving different parts of the health and care systems. **Section 5** outlines progress to date across the UK to achieve more effective coordination of care.
- xi. In Scotland, services for rare diseases are largely nationally commissioned and each service has a clear definition of function with agreed patient pathways. Plans are being developed to provide comprehensive support to, and clinical management of, patients with rare diseases by building on existing collaboration between Scottish and UK specialist centres. In Northern Ireland, there is a growing evidence of the benefits that clear service specifications and care pathways can provide for patients, carers and health and care professionals. There is an appetite to build on existing good practice such as the mucopolysaccharoses (MPS) clinics run in partnership with clinicians and specialist nurses from Manchester.
- xii. In England, although it is acknowledged that many services for patients with rare diseases are delivered locally, NHS England generally commissions expert centres for rare diseases on a national basis. These services are commissioned according to nationally agreed service specifications, which are refined and developed over time. NHS England is also refining the processes by which it assesses the costs and benefits of treatment for patients with rare diseases and how these are prioritised for investment.
- xiii. The UK Genetic Testing Network (UKGTN) *Guide to Centres with Specialist Expertise for Rare Genetic Disorders* continues to be a valuable resource in terms of mapping specialist genetic services across the UK. The guide is being updated and will be distributed widely across NHS organisations, including specialised services and Clinical Commissioning Groups.
- xiv. The UK is recognised as a world leader in research into rare diseases and **section 6** of the report examines the role played by research in (a) increasing the evidence base and (b) engaging patients and rare diseases stakeholders to improve the quality and effectiveness of the evidence base. The Department of Health continues to make substantial investment in infrastructure for research into rare diseases through the National Institute for Health Research (NIHR).
- xv. One specific NIHR investment is the NIHR Rare Diseases Translational Research Collaboration (RD-TRC) which was launched in parallel with the Rare Diseases Strategy, with an investment of £20 million over four years. This provides world-class research infrastructure in the NHS to support the translation of fundamental

discoveries into translational research (experimental medicine) on rare diseases.

- xvi. There are examples from across the UK of investment in research infrastructure related to rare diseases. These include the Wales Gene Park, and work being undertaken by the National Congenital Anomaly and Rare Disease Registration Service. The UK has also played a major role in rare diseases at the European level, including the European Union Committee of Experts on Rare Diseases (EUCERD) Joint Action (coordinated by Newcastle University).
- xvii. The Scottish Government has set out a number of specific commitments to facilitate participation in the 100,000 Genomes Project and in research, including the development of online application processes and a register for those wishing to be involved in research. Northern Ireland will establish a regional GMC, which will provide the conduit to participation in the 100,000 Genomes Project and scope for potential collaborations with the Republic of Ireland.
- xviii. **Section 7** of the report highlights new issues for consideration and identifies where further work is needed. Important developments include the 100,000 Genomes Project and the establishment of regional GMCs. The EU Cross-Border Healthcare Directive will lead to the establishment of European Reference Networks (ERNs) for rare diseases. A call for first bids to establish ERNs will take place in 2016 and the UK is expected to play a key role.
- xix. The 100,000 Genomes Project, Genomic Medicine Centres and the Genomics England Clinical Interpretation Partnerships (GeCIPs) are still in their early stages but already they have the potential to become the principal drivers in the improved understanding and treatment of rare diseases. It is essential that the project delivers a lasting legacy for rare disease patients and is sustained and developed into a truly ground-breaking, world-leading research and healthcare delivery collaborative to tackle the hardest rare diseases questions.
- xx. Public Health England has begun to establish the UK's first comprehensive rare disease registry. However, for the benefits to be fully realised, there needs to be clear connectivity and interoperability of data at national level. Implementing the recommendations of the National Information Board is a key challenge which will require all rare diseases stakeholders to work together to achieve a world-leading data platform for the UK.
- xxi. The UK benefits from the unique position of having integrated healthcare provision. The four countries of the UK have taken different approaches to addressing the recommendations in the Strategy in response to the different challenges they each face. Some of the commitments in the UK Strategy are best delivered by the four countries of the UK working collaboratively. The Forum believes that increased collaborative working would help to advance the interests of rare disease patients. The UK Strategy can act as a catalyst for this by facilitating a cohesive, collaborative and effective delivery framework for rare diseases research, diagnostics and treatment pathways.

1. Introduction

- 1.1** The UK Strategy for Rare Diseases was published in November 2013. The Strategy includes a total of 51 commitments (listed in Annex A) that cover five specific areas:
- empowering those affected by rare diseases
 - identifying and preventing rare diseases
 - diagnosis and early intervention
 - coordination of care
 - the role of research.
- 1.2** The **UK Strategy for Rare Diseases** forms the basis for work across the four UK countries to improve services, support patients and promote the role of research to help us better understand the nature of rare diseases and how they might be treated. In recognition of the fact that healthcare delivery is handled differently in each country, a commitment was made at time of publication to develop separate implementation plans for England, Scotland, Wales and Northern Ireland. The draft strategy was shaped following a consultation by the four UK health departments on the first-ever UK Plan for Rare Diseases.
- 1.3** The UK Rare Disease Forum was established following the publication of the UK Strategy for Rare Diseases to monitor implementation across the UK and formally report back every two years (for Terms of Reference see Annex B). The membership of the Forum includes representatives from all four UK countries, NHS England, healthcare professionals, industry, professional bodies, patient interest groups, researchers and funders. The complete membership is detailed in Annex C.
- 1.4** Diseases that affect fewer than 5 people in 10,000 are described as rare. At least 80% of rare diseases have an identified genetic origin and the total number of rare diseases continues to steadily increase, with estimates ranging from 6,000 to 8,000 different conditions. Some 1 in 17 people will suffer from a rare disease at some point in their lives, with 75% of all rare diseases affecting children.
- 1.5** Living with a rare disease can involve complex condition management and has impacts beyond those directly affected, including siblings, parents and healthcare professionals. Diagnosis, treatment and support for those with rare diseases requires considerable funding from both the health and social care budgets.
- 1.6** Patient support groups play an important role in raising awareness and driving improvements in treatment and research. However, the vast number of different conditions means that, for many extremely rare diseases and also for those without a definitive diagnosis, there is no defined support network.
- 1.7** Despite the hugely diverse nature of rare diseases, patients and families often face very similar challenges within the healthcare system. The need to address these issues was a key driver for the development of the overarching framework set out in the UK Strategy for Rare Diseases.
- 1.8** The importance of rare diseases goes far beyond the relatively small number of patients with each condition. There is an increasing appreciation that rare diseases may each offer a unique and important insight into human biology. These insights are likely to have a much

wider relevance to other diseases affecting many more individuals.

- 1.9** This report represents the first opportunity to review progress to date against the 51 recommendations in the UK Strategy for Rare Diseases. The report also discusses the other, complementary, initiatives and technology advances that have emerged since publication of the Strategy and how they are helping to shape the future treatment of rare diseases. Given the number and breadth of the commitments, it has been difficult to systematically measure progress against each one. It was never going to be the case that all the commitments would be acted on at the same time. Instead, the purpose of the Strategy was to see the vision for rare diseases in place by 2020.
- 1.10** Improving the experience and treatment options for NHS patients affected by rare diseases remains the primary objective of the Forum and patient-centred care is at the core of the UK Strategy. Case studies in this report provide examples of good or innovative practice being put in place by healthcare providers across the UK.
- 1.11** When the UK Strategy was published in 2013, healthcare ministers stated that each country would need to develop its own plan to implement the Strategy to reflect its specific healthcare delivery models and approach to service improvement.
- 1.12** The Welsh **Implementation Plan for Rare Diseases** was published in February 2015 alongside and with equal status to plans for major conditions. The plan emphasises the importance of the patient experience. It recognises that patients and families are often the most knowledgeable about their conditions and need to be empowered so they can manage as much as possible of their own care. The implementation of the plan is supported by a national Implementation Group and an update on the progress made by the Welsh Government and NHS Wales will be presented publically on Rare Diseases Day 2016, a written report will then be made available in line with the commitment in the plan.
- 1.13** In June 2014 the Scottish Implementation Plan **It's Not Rare to Have a Rare Disease** was published. The implementation of the plan is overseen by the Scottish Rare Disease Implementation Oversight Group (RDIOG), which advises the Scottish Government. The aims of the Scottish Implementation Plan are closely aligned with those of the UK Strategy.
- 1.14** The Department of Health, Social Services and Public Safety (DHSSPS), Northern Ireland, has been leading the development of the Northern Ireland Implementation Plan in association with the Northern Ireland Rare Diseases Stakeholder Group (NIRDSC). **The Northern Ireland Implementation Plan for Rare Diseases** was published in October 2015 and is viewed as an integral part of the Health and Social Care Board's Specialist Services Commissioning Plan for 2015/16. The plan was seen as a pragmatic and outward-looking approach to improve cooperation between policy makers at all levels.
- 1.15** In England, the implementation of the recommendations in the UK Strategy falls within the remit of a number of organisations including NHS England, the National Institute for Health and Care Excellence (NICE), the National Institute for Health Research (NIHR), Public Health England (PHE) and Health Education England (HEE).
- 1.16** The Health and Social Care Act 2012 created the platform for NICE to take over the development of guidance for highly specialised technologies. NICE formally took over responsibility from the Advisory Group for National Specialised Services in April 2013. The highly specialised technology evaluation process is designed to evaluate the benefits and costs of technologies for rare diseases and conditions. It produces recommendations on when and how a highly specialised technology should be commissioned for use in the NHS in England.

- 1.17** NHS England is responsible for the delivery and day-to-day operation of the commissioning of specialised healthcare in England and therefore has a key role to play in many aspects of implementing the recommendations. The Highly Specialised Commissioning Team in NHS England is responsible for leading the overall response to the UK Strategy. In February 2014, NHS England published a **Statement of Intent** that sets out how NHS England would play its part in delivering the UK Strategy in England.
- 1.18** The UK Strategy for Rare Diseases is mentioned in the **Five Year Forward View** which sets out a shared vision for the future of the NHS in England based on new models of care. However, there is considerable concern that the lack of an England implementation plan makes it difficult to link any improvements directly to the objectives of the UK Strategy.
- 1.19** NHS England has established the Rare Diseases Advisory Group (RDAG), comprising representatives from the Royal Colleges, commissioners, patients, and the public and professionals. RDAG is responsible for making recommendations to NHS England, Scotland, Wales and Northern Ireland on the development of services for people with rare diseases and/or who need access to highly specialised services. Progress on implementing the UK Strategy is discussed at the group and is included in its Terms of Reference. In this respect, RDAG plays a particularly important role for NHS England where there is no published implementation plan. Given the wide and comprehensive remit of RDAG and its role in considering progress against the UK Strategy, there should be consideration of how RDAG could work more closely with the UK Rare Disease Forum, including the sharing of papers as appropriate.
- 1.20** As well as the progress being made in each of the four countries, there are also excellent examples where activity is coordinated at a UK level. The UK Genetic Testing Network (UKGTN) works with genetic testing laboratories across the UK and has a Clinical and Scientific Advisory Group that meets twice a year; the group includes the NHS England Medical Genetics Clinical Reference Group Chair and colleagues from the three devolved administrations. The working group has a particular focus on quality and equity of services for patients with rare diseases. The work of PHE on expanding its development of the National Congenital Anomaly Register into a UK Rare Diseases Registry is a welcome initiative, and responds directly to the UK Strategy.
- 1.21** The work of Genomics England on the Department of Health's 100,000 Genomes Project places rare diseases at the very forefront of innovative technology adoption and will deliver great benefits, especially, it is hoped, in the length of time to receive a diagnosis. Other parts of the 100,000 Genomes Project should also see huge benefits for rare diseases. HEE's training and education programme on genomics is setting down the foundations to promote better understanding of genomics, and thus rare diseases, among healthcare professionals. It will also see the emergence of a new cadre of clinical bioinformaticians who will be in the vanguard of genomic technology adoption and spread in the NHS.
- 1.22** NHS England is the driving force for genomics in the NHS. In supporting the delivery of the 100,000 Genomes Project, it has put in place a network of GMCs that will be central in the mainstreaming of whole genome sequencing as part of the diagnostic pathway. The development of GMCs will also involve other countries. It is essential that work on rare diseases and the development of genomic technologies and other advanced therapies are not confined by national boundaries. NHS England has also started work on formulating a Personalised Medicine Strategy, encompassing all aspects of the patient pathway, that promises to deliver real improvements to the experiences of those affected by rare diseases.

1.23 The need to develop new therapies remains critical for many rare diseases, particularly where they are life-limiting or severely debilitating. Organisations such as the Medical Research Council (MRC) and National Institute for Health Research (NIHR) and initiatives with all the UK health departments are supporting research related to rare diseases. The pharmaceutical industry also has a major role to play in the treatment of rare diseases. The Association of the British Pharmaceutical Industry (ABPI) includes many research-based biopharmaceutical companies working across the UK to develop novel therapies. The strength of the pharmaceutical sector underpins the world-leading position of the UK in the development of new treatments for rare diseases and the industry is also a major contributor to the economy.

1.24 The UK pharmaceutical industry operates in the rare diseases arena across the four nations of the UK and is well placed to highlight the differences in approach that positively or negatively impact on timely diagnosis and treatment. In addition, the global nature of pharmaceutical companies means that industry can provide a perspective on developments at the European and global levels.

1.25 The UK Strategy for Rare Diseases described a vision of how patients would be treated and supported, and research strengthened, by 2020. A significant amount of good work has been completed or is under way, but it is beyond question that there is much more to be done. As well as noting progress, this report also highlights some of the issues still to be addressed. Comparisons between different nations are probably best avoided at this stage. The four nations of the UK have begun to implement the recommendations in the Strategy from different starting points and with distinct circumstances.

1.26 The report does not make further recommendations but, in its final section, looks

to the future and offers thoughts on emerging initiatives in the area of rare diseases and their potential implications for policy development. Further progress reports are planned for 2018 and 2020.

1.27 Each of the four countries has adopted different approaches to implementing the UK Strategy. Good practice exists in each of the countries and some of the challenges differ. These differences can be reduced if there are clear mechanisms for spreading learning and good practice and for taking action on those commitments in the Strategy at a UK-level.

2. Empowering those affected by rare diseases

Commitments 1–8

- 2.1** The complexity of rare diseases and their management means that patients and their families become highly expert in their conditions, and are often more engaged with their clinical care than those with more common conditions. The consideration of patients' experiences, knowledge and understanding of what it is like to live with a rare disease is therefore essential if patient services are to be fit for purpose.
- 2.2** Patients affected by rare diseases and their families have been important champions of the need to develop specialised services. They are also acutely aware of the need for research to improve the understanding of rare diseases and thereby develop new treatments. A recent survey of **patient experiences** by Genetic Alliance UK showed how important increasing understanding of rare diseases is to patients, with 80% of respondents expressing an interest in research participation.
- 2.3** The opportunity for patients to register and record their experiences on rare diseases databases is an important tool for supporting patient empowerment. Comprehensive records of rare, genetic and undiagnosed conditions are key evidence in estimating the full scale of the unmet need. In partnership with the Department of Health and in direct response to the UK Strategy, Public Health England (PHE) has established the **National Congenital Anomaly and Rare Disease Registration Service** (the Registry). This builds upon and complements **Orphanet UK** which sits within NCARDRS and is a European reference portal for information on rare diseases and orphan drugs.
- 2.4** The Registry was formally launched on 1 April 2015 and is being developed with the aim of collecting data from the whole care pathway, in near real time. It will bring together data from nine existing registers and will mean that data collection is extended to the 51% of England where it has not previously been collected. The technology, data collection processes and quality assurance mechanisms can all be applied to the devolved administrations to ensure that UK-wide data is available on all these disorders. Exploratory discussions have already begun to consider the data-sharing issues between jurisdictions and the resource implications.
- 2.5** Patients can access their own data on the Registry via their GP, which ensures that the information is given only to the patient. Future plans include a secure patient portal which will allow patients to view and annotate their information. Rare disease patients are usually very willing to share their medical data to help develop better understanding of their condition and for the common good. The aim is that the coverage of the Registry should be as complete as possible; however, all patients retain an absolute right of opt-out.
- 2.6** The capture of robust, quality-controlled data is a key priority for the UK Government and its push to harness the intelligence this data can deliver when developing future therapies and healthcare services. It is essential that the work on the Registry, being led by PHE, complements and is connected to other initiatives, such as the 100,000 Genomes Project, Genomic Medicine Centres (GMCs) and the NHS Personalised Medicine Strategy, and responds to the recommendations of the National Information Board on data connectivity and interoperability.

- 2.7** The effective management and use of data is important to both present healthcare and the development of new therapies and healthcare tools. It is the view of both UK Government and industry that its development has the potential to significantly change the rare diseases technology landscape. Industry has successfully collaborated in similar initiatives, for example the Systemic Anti-Cancer Therapy (SACT) dataset website, and consideration should be given to how industry might engage in a similar manner with the initiative. It is not just industry that sees the potential benefit; patient organisations also believe that the development of a national rare diseases registration service holds great potential to influence the commissioning of services and their delivery.
- 2.8** Many patients with rare diseases do not have access to effective treatments and therefore look to research as a source of new therapies. This is particularly the case for diseases that affect only a small number of patients. These issues were investigated by Genetic Alliance UK in a programme – **'My Condition, My DNA'** – funded by the British In Vitro Diagnostics Association (BIVDA), the Medical Research Council (MRC) and the Wellcome Trust.
- Case study: My Condition, My DNA**
- Genetic Alliance UK has worked to understand and highlight the patient and family perspective on the ethical and societal issues surrounding genomic sequencing in advance of its uptake in the NHS. This project led to the development of a patient charter that makes 15 recommendations. These stress the need for patients to receive as much information as possible through the support of a trained professional. While patients are keen for their data to be used for research purposes, they are concerned that the information should be safely stored and obtained with suitable ethical consent. Patients also feel that the healthcare system will need to be prepared to take full advantage of the benefits of this new technology.
- 2.9** The availability of accurate and impartial information is essential to enable patients to make informed choices and, where appropriate, to manage their own care effectively. However, it is obviously critical that specialist information extends to those directly involved in the process of clinical care.
- 2.10** Information about genetic testing and the UK laboratory network is freely available on the website of the **UK Genetic Testing Network (UKGTN)**. UKGTN works to promote equity of access to genetic testing for rare conditions. The UKGTN website provides full details of the recommended genetic tests available from member laboratories, as well as contact details for regional genetic testing centres and specialist laboratories, treating patients and clinicians as equal partners.
- 2.11** Health Education England has developed the Genomics Education Programme (GEP). The primary purpose of the GEP is to support the understanding and training of healthcare professionals in genomic medicine; however, as much of the training resources are provided on an open access basis they may also become an important resource for patients. Examples of other initiatives include the creation of a Centre for Excellence in Teaching and Learning in Genetics in Leicester that includes the **GENIE** (Genetics Education Networking for Innovation and Excellence) project. This has involved the recruitment of patient advocates from the Asian population and provision of online genetic resources in a number of languages.
- 2.12** The provision of good information and opportunities to contribute to the discussion of the future of rare diseases service development is only part of patient empowerment. All Governments of the UK and their healthcare providers have a long-established and successful tradition of placing patients at the heart of healthcare decision making. It is something that we have become used to but it is worthwhile remembering that this involvement of patients

at nearly every level is something to be proud of and built upon.

- 2.13** Patients have had, and continue to have, representation in the development of the UK Strategy, the country implementation plans and the delivery of services. For example, the delivery of the Strategy in Wales is supported by an Implementation Group that includes a number of stakeholders including Genetic Alliance UK in Wales. Similarly in Scotland, the Rare Disease Implementation Oversight Group includes wide representation including patient representation through Genetic Alliance UK and Specialised Healthcare Alliance and other patient groups.
- 2.14** In Scotland, patients are involved in the drug approval process through the Patient and Clinician Engagement (PACE) process. This gives patient groups and clinicians a greater influence on the rare and end-of-life medicines that are approved by the Scottish Medicines Consortium (SMC) for use in the NHS. Pharmaceutical companies are also encouraged to submit additional evidence to help the SMC the impact of a new rare disease medicine in the round. The initiative has been seen as a positive development and a system has been piloted in Wales by the All Wales Medicines Strategy Group where the Clinician and Patient Involvement Group (CAPIG) considered the wider benefits of providing a medicine.

Case study: Patient empowerment – Scotland's National Managed Clinical Networks

Managed Clinical Networks (MCNs) are linked groups of health professionals and organisations from primary, secondary and tertiary care, which focus on coordinated service planning, provision of information for professionals and families, the collection of data to support improved care and engaging with patients, families and carers to shape services.

An example is the Scottish Muscle Network, which has produced guidelines, patient care cards and information for families and carers about living with a neuromuscular condition.

- 2.15** Industry has welcomed the introduction of PACE and CAPIG and sees them as significant developments that offer practical and flexible methods of delivering informed decision making. These innovations are important in that they involve patients in decisions about access to new treatments and they promote an understanding of the challenges faced when making such decisions.
- 2.16** In Northern Ireland, the Northern Ireland Rare Disease Partnership (NIRDP) has worked with the support of the Public Health Agency (PHA) to capture the patient experience through the 'Living Every Day with Rare Disease' survey. The survey identified isolation and difficulties in obtaining information as key problems. To begin to address the issues identified, NIRDP and PHA have established local groups to facilitate access to information and provide support for those living with rare diseases. In addition, PHA has supported a seminar series 'Rare Disease and Research', offering an opportunity for mixed audiences including patients, carers and healthcare professionals to hear from internationally acknowledged experts.
- 2.17** The NICE highly specialised technology (HST) evaluation process recognises the need to consider evidence from patients and carers as part of the evaluation process. The limited evidence base for many rare diseases means that patient evidence is particularly important. The HST process proactively identifies and supports patient groups to capture experience that can inform decision making based on the fact that patients are uniquely placed to contextualise the purported effects of the new technology beyond the direct health benefits. Other types of information patients are able to contribute can include the nature of the condition and its

effects on the lives of patients and their carers and the impact of the new technology.

2.18 NHS England directly involves patients in the decisions related to services provided for patients with rare diseases through the Rare Diseases Advisory Group (RDAG) and other governance structures such as the multidisciplinary Clinical Reference Groups (which advise NHS England on commissioning specialised services). NHS England recognises that the process by which medicines are identified, assessed and eventually approved is not always clear to patients. A recent public consultation on the principles and processes by which it will invest in specialised services, including rare diseases, identified a number of themes around rare diseases:

- that the NHS England prioritisation process would benefit from the principles and criteria previously used by the Advisory Group for National Specialised Services
- that NHS England might agree to fund interventions for rare conditions where there is limited evidence
- that rarity in itself should not give a greater priority to patients while acknowledging that there might need to be a separate process for rare conditions
- that consideration needed to be given to ensuring there was equitable access for patients where concentration of expertise meant that the number of specialist centres was likely to be small.

Case study: Engaging patients with the development of the National Congenital Anomaly and Rare Disease Registration Service

The National Congenital Anomaly and Rare Disease Registration Service has involved substantial engagement with the patient community since its conception.

Consultations began in July 2014 and, as the project has developed, the team has continued to receive valuable input using various methods including focus groups and patient-led seminars.

The Patient Empowerment Group, run as part of the Rare Disease UK project by Genetic Alliance UK, continues to provide advice and a patient voice as the project moves forward.

Case study: Birmingham Children's Hospital NHS Foundation Trust – Engagement with patients and families affected by rare diseases

Birmingham Children's Hospital (BCH) treats approximately 9,000 children with more than 500 different rare diseases each year. BCH is developing a paediatric rare diseases centre, the first of its kind in the world, to deliver care through coordinated multidisciplinary and multispecialty clinics where children and their families will be able to access peer support, gain information from patient support groups, access available research and be provided with the best care available anywhere in the world.

Patients have been involved in all aspects of the centre's design to ensure it meets their needs. This includes providing a large waiting area where families can interact with each other and patient support organisations, a kitchen so any special foods can be prepared, a sensory room and a separate 'chill out' room.

Roald Dahl's Marvellous Children's Charity funds two posts at BCH that coordinate children's care. The centre is also engaged in the 100,000 Genomes Project and with SWAN UK to develop a bespoke clinic at BCH for children with syndromes without a name.

BCH believes that this holistic paediatric rare diseases centre will help to reassess the way care is delivered to patients from 'one-size-fits-all' to a patient-centred approach.

3. Identifying and preventing rare diseases

Commitments 9 and 10

3.1 Systematic population-based screening programmes can offer early diagnosis and treatment for some rare diseases. The UK National Screening Committee (UK NSC) is the expert scientific advisory committee in the UK with responsibility for gathering evidence, consulting with users and other stakeholders and advising ministers about improvements to screening programmes. Recommendations from the UK NSC about screening for specific conditions are based on a rigorous assessment process and a set of internationally recognised criteria.

Case study: Recent advances in screening – a UK-wide approach

Following an evaluation by UK NSC, screening for maple syrup urine disease, isovaleric acidaemia, glutaric aciduria type 1 and homocystinuria is being implemented across England, Wales and Northern Ireland, and is under consideration by Scottish ministers. Screening for these conditions will help early detection, facilitate earlier treatment and improve long-term outcomes.

A more coordinated approach to the UK-wide implementation of screening tests, particularly where tests offer the opportunity for early diagnosis and the avoidance of preventable harm, would help alleviate the concerns of patients, especially the parents of young children.

3.2 Screening not only promotes early identification and treatment of disease but also plays an important role in providing parental choice and allowing parents to make informed decisions. Advances in screening technology and particularly non-invasive prenatal testing (NIPT) are likely to be increasingly used in

conjunction with other more established forms of prenatal screening.

3.3 However, while screening is important, the majority of cases of rare diseases are likely to be identified through the work of specialist centres or units. There have been considerable advances in genetic services in the UK in the last few years, providing more accurate genetic information through improved testing, support and counselling to patients and their families. The rapid pace of technology has seen the field of genetic testing move from single gene tests to the frequent use of whole exome sequencing and the development of new gene panel testing. Also, it must be remembered that an estimated 20% of rare diseases do not have a specific genetic cause. Instead, they may be caused by infections, allergies or the failure of some tissues and organs or through the exposure of unborn children to substances that interfere with normal development. Testing services are commissioned in various ways across the UK healthcare services, supported by regional genetics centres and specialist pathology services.

3.4 The 100,000 Genomes Project is changing the face of genomic services across the whole of the UK. The creation of Genomic Medicine Centres (GMCs) has the potential to transform how services are delivered and will lead to further integration of patient diagnostic and treatment services, education and training, and research.

3.5 While the initial focus of the 100,000 Genomes Project has been on developing these new service delivery models and discovery pathways in England, supported by funding from the Department of Health and the National

Institute for Health Research, similar complementary and directly connected services are being put in place across the UK. In Northern Ireland, a regional GMC has been announced and is being established. In Scotland, genomic testing capacity is being developed within the Scottish Genetics Laboratory Consortium, with discussions being held about establishing the Consortium as a GMC.

3.6 The introduction of panel tests has been very helpful in identifying and treating rare disease co-morbidities. For example, in Northern Ireland, an in-house panel test for hypertrophic cardiomyopathy (HCM) has been introduced that includes identified gene mutations from a number of families with HCM, allowing for predictive testing for at-risk family members. In addition, samples have also been sent to many centres in other parts of the UK to enable further research into the condition. Another example is the 106 gene congenital cataract panel offered by the Manchester Regional Genetics Laboratory, which identified a disorder that also causes epilepsy. In this particular condition, the frequency of epilepsy can be reduced by the introduction of a ketogenic diet.

3.7 Another initiative is Genomics England's PanelApp, which relies upon crowdsourcing to build 'panels' consisting of lists of genes involved in a wide range of rare diseases. Crowdsourcing offers a way to triangulate scientific and professional opinion. The use of PanelApp will replace the inconsistent sets of genes currently used by regional genetic laboratories and hospitals for diagnostic purposes. The aim is to develop a UK asset of global significance that will be communicated to the clinical and academic community after being formally approved by the Genomics England Scientific Advisory Group.

3.8 In summary, the delivery of genetic services across the UK is being transformed. The GMCs are playing a key role in this reconfiguration, and are likely to also become specialist centres for the diagnosis of rare diseases including those without a clear genetic origin.

4. Diagnosis and early intervention

Commitments 11–22

- 4.1 Diagnosis remains a key issue for patients with rare diseases. Delays in diagnosis are frustrating for patients and expensive for the healthcare system and can mean that opportunities for effective intervention are missed.
- 4.2 As part of its delivery of the UK Strategy recommendations, the Department of Health commissioned a report from the Policy Innovation Research Unit, London School of Hygiene & Tropical Medicine *Diagnostic Odyssey for Rare Diseases: Exploration of Potential Indicators*. The report reviewed the medical journey taken by patients with rare diseases and their families from the earliest stage to a final diagnosis. It is clear that this process frequently involves serial referrals to different specialists and a battery of diagnostic, often invasive, tests.
- 4.3 The *Diagnostic Odyssey for Rare Diseases* report highlights that measuring the diagnostic experience of rare disease patients may be an effective method of evaluating the impact of interventions and policies. One complication is that there needs to be clear understanding of what is meant by diagnosis, as patients often receive an initially broad diagnosis that is then progressively refined. The Department of Health is considering how to address the issues raised in the report as part of its wider work on genomics futures policy.

Case study: Eileen and Sophia's story – the importance of diagnosis

When she was just two and a half, Sophia was diagnosed with Myhre-LAPS syndrome, an extremely rare inherited developmental disorder affecting many systems and functions of the body. The diagnosis came through participation in the Deciphering Development Disorders (DDD) study. Before diagnosis, her mother, Eileen, had thought Sophia was the only child in the UK with the syndrome. However, the NIHR Rare Diseases Translational Research Collaboration (RD-TRC) put Eileen in touch with a small support group, with one other child in the UK and six in America.

Eileen found it very valuable to finally get a name for Sophia's delayed development and to be able to research her syndrome with the help of the Myhre-LAPS syndrome support group. Through participation in the group, Eileen now knows of new research on potential life-limiting complications of the syndrome, which appear to have significant implications for Sophia's treatment. She then shares this information with her geneticist, and also connects her geneticist with experts on the syndrome from around the world.

- 4.4 Education is key to reducing the diagnostic odyssey. General practitioners will always have difficulties in identifying a particular rare condition that they may see only once in their entire careers. In response to the UK Strategy, the Department of Health has worked with Health Education England (HEE), the National School of Healthcare Science and a sub-group of the UK Rare Disease Forum to produce two videos. One describes the problems faced by

families with a child with an undiagnosed disease: **Rare Disease: A Family's Journey**. The second video is aimed at GPs and the importance of considering the possibility that their patient may have a rare condition: **Rare Disease: The GP's Role**.

- 4.5** HEE has also played an important role in the development of general training in genetic medicine through the Genomics Education Programme (GEP), which aims to support the 100,000 Genomes Project. This programme was established in 2014 to embed genomics into the education of the current and future healthcare workforce. The objective is to develop sufficient capability in the workforce to allow a world-leading response to the revolution in genomic medicine. Delivery to date has included the production of a video to introduce the 100,000 Genomes Project: **Introducing Genomics in Healthcare**.
- 4.6** Other education materials are available, ranging from introductory online courses to a Master's in Genomic Medicine – with almost 2,000 individuals registered for the online courses and more than 200 applying to join the master's course. There are also Higher Specialist Scientist Training (HSST) and Scientist Training Programmes that include workforce training for the genetics scientific workforce about rare diseases, including training positions in Genomic Medicine Centres (GMCs) spread across England.
- 4.7** The Royal College of General Practitioners, in conjunction with the Motor Neurone Disease Association (MND Association), has developed resources that support GPs in diagnosing specific rare conditions that are particularly difficult to diagnose. This is supported by a **Red Flags Toolkit** that highlights the key features of MND that should be considered when a GP is struggling to diagnose a patient with odd progressive symptoms. The College has also developed, in collaboration with Muscular Dystrophy UK, an **e-learning**

package to support the diagnosis of neuromuscular disorders.

- 4.8** In Wales, a system for reviewing and approving new genetic tests has been developed and is being commissioned by the Welsh Health Specialised Services Committee (WHSSC). This system was created following a review by the All Wales Medical Genetics Service, working with the Wales Gene Park and the WHSSC, of the resources available for local genetics and the UK Genetic Testing Network (UKGTN) services. The review included a consideration of equity of access and aimed to improve the consistency of services through clear commissioning and oversight arrangements.

Case study: Evaluation of clinical exome sequencing for patients with rare diseases – Wales

As part of the Welsh response to the UK Strategy, the All Wales Medical Genetics Service, with support from the National Institute for Social Care and Health Research (now Health and Care Research Wales), is investigating whether exome sequencing, which allows many genes to be tested at once, can improve outcomes for patients with rare diseases as well as providing a cost-benefit to the NHS.

Patient members on the study steering group have contributed to the study design and lay summary and will guide the ongoing management of the project. This will include the design of a questionnaire examining the acceptability of genomic sequencing and issues related to incidental findings.

- 4.9** In Scotland, to increase awareness among clinicians of criteria for patient referral to diagnostic pathways for Scottish or English specialist centres, dedicated websites for all National Managed Clinical and Diagnostic Networks have been set up.
- 4.10** Scotland has reviewed the input of diagnostic specialties to rare disease diagnosis with a long-term goal to develop defined patient

pathways for specific diseases. Priority has been given to pathways for patients with acute porphyria, vasculitis (including Behçet's syndrome) and metabolic conditions.

- 4.11** The benefits of effective communication between those involved in diagnosis and treatment of patients with rare diseases have been clearly demonstrated in Northern Ireland. At the clinical level, blood samples from patients with a suspected lysosomal disorder are collected by the local team and sent to Willink Biochemical Genetics Unit in Manchester for enzyme testing. A close working relationship means that positive results can be acted upon quickly so that patients see a metabolic paediatrician more rapidly. These patients are then able to have their cross-reactive immunologic material (CRIM) status tested more quickly, allowing them to receive the most appropriate form of treatment. Improved communication between clinicians and commissioners means that where enzyme therapy is appropriate, it can be provided more quickly.
- 4.12** In England, work is being carried out in partnership with the medical Royal Colleges to identify the 20 conditions where a delay in diagnosis has the largest impact on prognosis.
- 4.13** NHS England is also working with the National Institute for Health and Care Excellence (NICE) to take forward the formal appraisal of technologies, particularly through the NICE highly specialised technologies (HST) programme. This work is focused on how NHS England can best accommodate the requirements set out in NICE appraisals within the healthcare system. The type of challenge this can involve is illustrated by the fact that a NICE HST appraisal may include conditions requiring a technology to be delivered at a number of expert centres. The NICE HST evaluation process takes account of factors that determine the need for the technology. These factors may include that the target patient group for the

technology in its licensed indication is so small that treatment will usually be concentrated in very few centres in the NHS. Alternatively, the target patient group may be distinct for clinical reasons or there may be a significant need for national commissioning of the technology. Concentrating expertise in a few centres supports the delivery of the technology in an environment that has the appropriate infrastructure and expertise to deliver the technology and care that patients with a rare condition need.

- 4.14** UKGTN holds a publicly available directory of genetic tests recommended for clinical use (the *NHS Directory of Genetic Disorders/Genes for Diagnostic Testing*). An important part of the UKGTN evaluation process for genetic tests has been the development of specific testing criteria for the use of individual tests. Testing criteria have been included in the evaluation process since 2005 and a total of 500 testing criteria have been developed. Testing criteria provide referral guidance for genetic testing, including clinical features, and the types of referrers expected to order the test. The criteria ensure that each test is used appropriately and targets those patient groups that will derive the most benefit.
- 4.15** Currently, NHS approved genetic testing is available for more than 1,000 rare disorders and, taken together, NHS laboratories have the ability to test more than 4,800 clinically relevant genes. Since the evaluation process was established in 2003, UKGTN has evaluated a total of 530 new test applications (gene dossiers) and approved 428 tests.

Case study: Advantages of using gene panels

An 8-year-old girl was referred to the Belfast regional genetics service; she had clawing of her toes and found walking difficult – both characteristic features of Charcot-Marie-Tooth disease (CMT). Since her father had similar feet, it seemed reasonable to diagnose CMT.

Initial genetic testing showed that the gene most commonly associated with CMT appeared normal. A review of the family history revealed both clinical signs of CMT and evidence of inherited kidney disease.

A reanalysis of the father's and daughter's DNA using a panel test, available through the UK Genetic Testing Network, was based on a panel of 54 genes associated with hereditary motor and sensory neuropathies. This revealed that father and daughter carried the same mutation known to cause kidney problems and in about one in eight patients also leads to CMT.

The panel test showed the clinical team how the two conditions were linked and they therefore could understand that features of CMT could not be used to identify those family members at risk of kidney problems. Instead, accurate screening was possible based on the actual mutation. This was especially important as several family members were considering acting as living donors for relatives requiring a transplant, and potential donors needed to ensure they did not share the same inherited kidney condition.

4.16 UKGTN reviews the take-up and costs of new recommended tests that have been approved and implemented by the NHS for at least two years. To evaluate if the genetic tests for inherited disorders are provided in an equitable way across the UK, UKGTN collects genetic test activity data from member laboratories. These are then analysed to provide rates of genetic testing per 100,000 residents. This approach aggregates all inherited genetic test activity irrespective of their frequency on the basis that clinical need is likely to be broadly similar across the UK. The data, which is set against the healthcare commissioning populations, has been used to inform levels of provision and future service developments. The most recent report on genetic testing rates available is from 2011/12. The process of data collection is due to recommence in 2016.

4.17 To ensure consistency in service specification for contracted activity, UKGTN has developed a measure of activity termed a Genetic Unit (GenU). The GenU consists of a maximum of nine weighted bands to which laboratory reports can be assigned. It has been agreed by the Medical Genetics Clinical Reference Group that the **GenU** system should be adopted for all activity relating to clinical genetics.

4.18 Industry has an important role to play in improving the diagnosis of rare diseases both in supporting the development of tests to identify rare diseases and the subsequent testing for stratified medicines for treatment. Companion diagnostics for treatments play, and will increasingly play, a pivotal role in accelerating access to innovative treatment for people with rare diseases.

4.19 The scientific advances in diagnosis continue at a rapid pace. The ability to test for an increasingly large number of genetic conditions is likely to be driven in the next few years by the work of the 100,000 Genomes Project in particular. Comparative data on the use and availability of genetic tests will be an important way to demonstrate that these tests are available to those most likely to benefit. The work being undertaken by Genomics England through the cross-cutting Clinical Interpretation Partnerships (GeCIPs) and UKGTN has immense potential for patients with rare diseases and those without a diagnosis. However, the ability to test is only part of the problem and work continues to raise awareness of the importance of considering rare diseases when assessing patients with complex and unusual symptoms.

5. Coordination of care

Commitments 23–30

- 5.1** The UK Strategy recognises that patients and families affected by rare diseases often face particular issues in obtaining coordinated and clear evidence-based care pathways. The nature of rare diseases makes it impossible to generalise or define clear pathways for care that will encompass all such diseases. However, some common themes emerge. These centre on the need for clear patient pathways, the provision of specialist clinical centres when appropriate and the need to coordinate care across the healthcare system.
- 5.2** The small number of patients affected by a specific rare disease, coupled with their probable broad geographical distribution and the requirement for specialist care, means that existing models to deliver healthcare are not always suitable. It has to be recognised that expertise is not available everywhere and patients may have to travel to other parts of the UK in order to be treated at specialist centres of expertise.
- 5.3** There is still progress to be made in this area, although thought has been given to how care pathways could develop. In Scotland, through work carried out by the National Managed Clinical Networks, an approach has been taken which involves patients in the decisions made about their clinical care. In Dundee, 'virtual clinics' for photosensitive skin disorders are planned to allow expert staff in the specialist service to provide clinics remotely, reducing the need for patients to travel. This is particularly important where exposure to sunlight can aggravate a condition.
- 5.4** Work is also being taken forward on developing patient pathways in Scotland and funding has recently been announced to develop a patient pathway for Huntington's disease.
- 5.5** In Northern Ireland, the development of new and innovative models of care, including in collaboration with other parts of the UK, is an important theme.
- 5.6** The success of multidisciplinary clinics in Northern Ireland has led to the development of other clinics, including the combined Genetic Cardiac Clinic for Fabry disease patients. These clinics provide an opportunity for patients to be scanned and see the genetics team, who can manage other Fabry-related issues, all on the same day. The clinics also provide a chance to meet a Fabry advocacy officer from the patient organisation to consider other aspects of daily life, including education and employment. Feedback from patients and families suggests that these clinics are a very successful innovation. They also appear to be a cost-effective way to deliver highly specialised care and to support clinical communication in a joined-up way.

Case study: Mucopolysaccharide (MPS) clinic – Northern Ireland

The clinic was established over 20 years ago at the instigation of the patient organisation and is led by Dr Simon Jones, who is based at the Willink Biochemical Genetics Unit in Manchester. Two clinics are run each year at the Royal Belfast Hospital for Sick Children. Travel expenses are met by the Society for Mucopolysaccharide Diseases and often allow one of the specialist nurses from Manchester to join the clinic. The local clinical lead is Dr Siobhan O'Sullivan, a consultant metabolic

paediatrician, and the clinic aims to be a one-stop-shop for patients' clinical and other needs. It is a multidisciplinary clinic with input from other specialties including orthopaedics, respiratory and dentistry, plus a psychologist and a social worker. The patient's GP, paediatrician and any other appropriate professionals involved in their care (e.g. a palliative care nurse) are invited to the clinic. An advocacy officer from the MPS Society is present to deal with issues such as education, benefits and housing.

The clinic means that patients do not have to leave Northern Ireland to get specialist expertise from a tertiary centre; clinicians have the chance to liaise directly with the tertiary specialists, which supports shared learning; hospital trips are reduced; and families have an opportunity to discuss issues or just catch up over tea and coffee.

- 5.7** England continues to refine the processes by which it assesses the costs and benefits of treatment for patients with rare diseases and then prioritises these for investment. NHS England has an annual and rolling programme of developing clinical commissioning policies and service specifications. All of these documents undergo public consultation.
- 5.8** A rare diseases annex to be incorporated into all relevant NHS England service specifications is also under consideration.
- 5.9** Improvements in paediatric care now mean that many more children with complex multi-system disorders survive into adult life. A majority of these conditions are of genetic origin, involve several organ systems and do not fit well into the traditional model of clinical care provided in secondary or tertiary adult services in the NHS. Although individual numbers are small, cumulatively these patients represent a substantial and increasing patient cohort. Often they experience uncoordinated, less than ideal, care and can find it difficult to access the expertise and research that could improve their prognosis.
- 5.10** To address the issues of fragmented care, the UK Strategy for Rare Diseases recommended the creation of specialist centres. These are well placed to deliver the expert care required and through the creation of a critical mass can support research (see section 6). The Birmingham Centre for Rare Diseases is an example of the way one hospital has created a specialist centre for treating patients with rare diseases (see case study).

Case study: Birmingham Centre for Rare Diseases (CfRD)

The CfRD links seamlessly with the rare diseases services at Birmingham Children's Hospital.

The model is that of a 'one-stop-clinic' for each disease, bringing all the relevant specialists to the patient. All necessary diagnostic tests are arranged to take place on the same day.

Patients are asked for consent to be approached for research studies, including to bank biological samples such as DNA, blood and urine. It is expected that the creation of a large number of well-characterised clinical cohorts with samples bio-banked will make the centre an attractive place for both academic and pharma-led research.

All clinics in the CfRD are equipped to allow remote consultation using secure video-conferencing, and patients have secure online access to their health records and other relevant information.

- 5.11** The UK Genetic Testing Network (UKGTN) supports the collation and sharing of information about centres offering specialist genetic services across the UK by publishing a guide to services. The information in the guide illustrates the complexity of the genetic testing landscape and the specialised nature of the services on offer. Less than 10% of disorders can be tested for at more than three laboratories; similarly, 27 laboratories offer tests for which they are the sole UK provider.

- 5.12** These single provider tests represent 69% of all the genetic disorders where testing is available.

The arrangements for genetic testing continue to evolve and are regularly published by UKGTN.

- 5.13** Since genetic tests need to be considered against measurable clinical outcomes, UKGTN continues to work with the Health & Social Care Information Centre (HSCIC), clinical professionals and the Medical Genetics Clinical Reference Group to identify relevant clinical outcomes.
- 5.14** The National Institute for Health and Care Excellence (NICE) has always considered orphan medicinal products as an integral part of its technology appraisal programme. Standard processes and methods used for other medicinal products and health technologies can often be applied to rare diseases as there is sufficient flexibility in these methods to account for the special nature of rarer diseases. However, it has become clear that rare disease medicines, or highly specialised technologies, need to be considered differently for funding or national commissioning.
- 5.15** The regulations underpinning the Health and Social Care Act 2012 specifically identify the arrangements for NICE to develop mechanisms for the evaluation of interventions for small populations with complex needs. NICE published its first piece of guidance from the highly specialised technologies evaluation in January 2015. Health Technology Assessments (HTAs) will no doubt become increasingly important as we see more targeted therapies and tools developed as precision medicine comes to the fore. This poses great challenges for all – industry, government, healthcare services and patients – as there will be difficult decisions to be made about resource allocation for what are likely to be very expensive therapeutics. Many of these concerns were raised in the report *Patient Perspectives and Priorities on NICE's Evaluation of Highly Specialised Technologies: Patient Charter*, published by Genetic Alliance UK and, while some of the issues have been addressed, there is still a great deal of thought
- needed about how we handle access to advanced therapies.
- 5.16** Industry has raised concerns that NICE faces significant capacity issues since it is only able to undertake three highly specialised technology reviews per year. In 2013 industry forecasted that the next five years would see almost a doubling in the specialty and rare diseases medicine sector.
- 5.17** NICE HST evaluations are time consuming and resource intense, which reflects the time and resources needed for the committee to consider all evidence submitted. The need to weigh up and understand a range of data relevant to the rarity of the condition and its associated technology explains why NICE is currently constrained in the number of appraisals it can complete each year. The HST Committee is mindful that rarity means that the weight of evidence is not the same as for conventional diseases, and seeks to assure stakeholders that all elements presented have been given due consideration before a decision is given.
- 5.18** It is often the case that new technologies and medicines for rare diseases struggle to develop a sufficient evidence base to allow a normal appraisal process. In these cases Managed Access Agreements offer one possible way to allow access to technology and at the same time generating valuable evidence through research and collection of 'real-world' data directly relevant to patients. These agreements involve reaching a compromise regarding value for money set against the level of uncertainty regarding clinical benefit. An important feature is that these agreements encompass all relevant stakeholders including patients. A Managed Access Agreement can therefore allow innovative technology in rare diseases to be utilised and the real-world data collected within a pre-agreed timeframe that can then be used to inform future appraisal guidance.
- 5.19** The UK Government has instigated the Accelerated Access Review (AAR). The AAR is

intended to address many of the issues around access to innovative therapies. The interim report, published in October 2015, clearly highlights these issues and specifically asks how we can accelerate and manage emerging products in our health system. The UK Rare Disease Forum looks forward to the publication of the full AAR report and hopes that it will be the catalyst for a national discussion, involving all stakeholders, on how we face these challenges as a society.

5.20 Further links will also be developed during 2016 with the highly specialised team and the Rare Diseases Advisory Group in NHS England.

5.21 Although there is much good practice across the UK, the question of funding and configuration of services for patients with rare diseases will always be a difficult issue. The view of the **Specialised Healthcare Alliance** is that proposals for devolving health-related budgets under the Cities and Local Government Devolution Bill are likely to impact on delivery of the Strategy. Wider reforms to the planning system in Wales, including the Welsh Health Specialised Services Committee, may also affect the delivery of the Strategy. Changes to the way in which services are planned and configured across the UK will therefore need to be kept under careful review in terms of the potential impact on patients with rare diseases.

Case study: Specialist clinics for patients with tuberous sclerosis complex – Wales and Northern Ireland

Tuberous sclerosis complex (TSC) can lead to non-cancerous growths in vital organs of the body resulting in severe complications, particularly in the kidneys and brain, and patients require a multidisciplinary and coordinated approach to management and treatment.

In May 2015, a new specialist clinic for TSC was launched in Cardiff led by Professor Julian Sampson. The first of its kind in Wales, it enables patients to receive specialist care and benefit from the latest research.

The Northern Ireland Regional Genetics Department has a well-established multidisciplinary TSC clinic offering access to a consultant geneticist, a consultant paediatrician and a genetic counsellor. The clinic delivers an inclusive approach by providing management, treatment and support for patients, families and carers. The TSC clinic can liaise and refer patients for expert advice and care and is ideally placed to enrol patients into research studies.

The Tuberous Sclerosis Association funds two advisers who deal with more complex cases, working closely with NHS staff to bridge the gap between home and hospital.

6. The role of research

Commitments 31–51

- 6.1** The UK continues to be at the forefront of research into rare diseases. Here, the move to a research and clinical environment where there is more focus on collaboration and joint working is a welcome development for rare diseases. The support from rare disease patients for research and their willingness to be involved in research remain high, as seen most recently in the response to the 100,000 Genomes Project. However, defining the boundaries between diagnosis, the delivery of clinical care and research can be difficult.
- 6.2** Rare diseases offer an unparalleled insight into human biology which may be relevant to a wide number of treatments. For the many rare disease patients with no informed diagnosis and where no effective treatments are available, research not only responds to unmet medical need but can be a real positive when so much else seems inconclusive. For many patients, participation in a research programme is seen as an important part of being able to manage their condition.
- 6.3** Research collaboration is essential in rare diseases, particularly if the prevalence means there are only comparatively small numbers of patients being treated in a number of hospitals and possibly in a number of countries. Unless it is a specialist centre, most hospitals will only have a very small number of patients with a rare disease. While the introduction of better governance arrangements has provided clarity about ethical considerations and appropriate experimental design, it has also made the administration of projects involving patients scattered across different institutions more difficult.
- 6.4** Action has been taken to address this issue and the National Institute for Health Research (NIHR) UK Rare Genetic Disease Research Consortium Agreement (known as the 'Musketeers Memorandum') is now in place. The Agreement allows research and development teams, supported by their NHS Trust, to develop a non-CTIMP (Clinical Trial of an Investigational Medicinal Product) project for rare diseases that can be automatically accepted by other regional genetics centres. The benefit of the Memorandum is that it promotes research into rare diseases and removes unnecessary bureaucracy without compromising patient safeguards. The portfolio currently includes 17 national rare diseases projects with another seven at the approval stage. Further streamlining of the research approval process is detailed in 6.33.
- 6.5** Wales has a global reputation for its genetic research in relation to rare diseases. **The Wales Gene Park** was created by Health and Care Research Wales in 2015 to provide leadership in rare genetic diseases research. In Wales, patients have been involved, with the support of Genetic Alliance UK, throughout the research pipeline – from setting research priorities and study design through to input into health and social policy.
- 6.6** The Wales Gene Park Education and Engagement team also plays an important role in the delivery of education and training programmes. These are designed to enable health and social care professionals to better identify rare diseases to help deliver faster diagnoses and access to treatment pathways for patients, supporting directly the objectives of the Welsh Implementation Plan for Rare Diseases.

- 6.7** Scotland is also an active partner in rare diseases research across the UK and internationally. Rare diseases are supported within the reorganised clinical research infrastructure in a way that is recognised by NHS Scotland. Involvement with research is an important way to empower patients. Therefore, the Implementation Plan for Rare Diseases in Scotland aims to encourage staff involved in the care of people with rare diseases to signpost them to appropriate sources of information about research, clinical trials and opportunities to participate.
- 6.8** To support those with rare diseases in participating in research, Scotland is currently exploring the development of an online application process and related patient registers.
- 6.9** In Northern Ireland, the existing research networks have facilitated the recruitment of patients to a number of other studies and collaboration with colleagues in centres outside Northern Ireland. Since Northern Ireland is the only UK partner to share a land border with another EU member state, this offers unique opportunities for cross-border collaboration in the field of rare diseases. Discussions have been instigated by the respective health departments in Northern Ireland and the Republic of Ireland to scope the potential to develop shared services, given the relatively small populations in both jurisdictions, where they can demonstrate improvement in quality of care and cost-effectiveness. The development of international collaborations was an element included in the Northern Ireland Implementation Plan for Rare Diseases.
- 6.10** An example of this type of partnership is the establishment of the all-island Congenital Heart Disease (CHD) Network Board in April 2015 to oversee the implementation of an all-island service model for patients born with heart conditions. Some of these conditions are classed as rare diseases.
- 6.11** Opportunities for collaboration will further expand now that Northern Ireland has formally joined the 100,000 Genomes Project's UK network of Genomic Medicine Centres. This will allow the establishment of the Northern Ireland Genomic Medicine Centre (NIGMC), which will focus on delivering accurate new genomic diagnoses for patients with rare diseases of unknown origin and cancer. The development of this centre was a major element of the Northern Ireland Implementation Plan for Rare Diseases.
- 6.12** The UK also continues to play a major role in rare diseases at the European level. The EUCERD Joint Action, coordinated by Newcastle University, has supported the work of the European Commission Expert Group on Rare Diseases. This has resulted in a number of recommendations to the European Commission on topics such as patient registration and data collection, European Reference Networks (ERNs), cross-border genetic testing, core indicators for national plans and strategies, and the clinical added-value of orphan medicinal products information flow. The UK continues to provide policy leadership in the new Joint Action 'RD-Action' which runs from 2015 to 2018.
- 6.13** Clinical trials are a key element of the research process and this is reflected across the UK as the UK Clinical Research Network (UKCRN). This network includes the relevant networks across all four nations. The NIHR will shortly be launching an update of the UK Clinical Trials Gateway (UKCTG), which will include the functionality to enable the public to volunteer and register their willingness to be contacted about participation in clinical trials. The system is built to NHS Security Standards, and will only allow contact between volunteers and approved researchers. As part of the secure registration process, the volunteer will have the option to include any information they feel might be relevant to them participating in a study, which could include rare disease.
- 6.14** The UK Strategy noted the absence of robust epidemiological data relating to rare disease patients. This lack of good data has been a

significant barrier to assessing the natural history of many rare diseases. It also makes it very difficult to assess progress in improving the diagnosis of patients with rare diseases, which was highlighted as a key issue in earlier sections of this report.

- 6.15** The value of patient registries in research has been clearly demonstrated in rare diseases and cancer. Incorporating existing sources of data held across England within the **National Congenital Anomaly and Rare Disease Registration Service** (the Registry) is an early goal of the project. In addition, the project will provide comprehensive coverage across England, replacing the patchwork of regional registers that gave only partial coverage. The Registry will increasingly play an important role in supporting rare diseases research, including provision of the longitudinal data associated with the individuals who are part of the 100,000 Genomes Project. Its data and patient monitoring function will be fundamental to supporting the objectives of Genomics England, especially during the long-term follow-up that will be required to fully deliver the benefits of this initiative.
- 6.16** The pharmaceutical industry has a pivotal role to play in the development of new medicines and treatments for rare diseases and is keen to encourage collaboration at the UK level. This is particularly important for rare diseases research where small patient numbers create very particular challenges to the industry with respect to clinical trial design and recruitment.
- 6.17** In September 2014, Health Education England (HEE) published a Research and Innovation Strategy, which sets out how it will create an education and training system that is evidence based and underpinned by research and innovation. This strategy will also build the capacity and capability of the current and future workforce to embrace and actively engage with research and innovation. To support this, HEE has developed a Clinical Academic Careers Framework, which proposes an overarching structure to develop the clinical academic workforce and a consolidated programme for all healthcare professions outside medicine and dentistry, including healthcare scientists. Working with NIHR, the HEE/NIHR Integrated Clinical Academic Programme (ICAP) has been developed; it contains five schemes from internships to senior clinical lectureships, plus a mentorship scheme.
- 6.18** The Department of Health, through NIHR, has invested £800 million over five years (2012–17) in NIHR Biomedical Research Centres and Units within leading NHS and university partnerships. These drive progress in translational research in biomedicine for the benefit of patients and the NHS, undertaking research in priority areas of high disease burden and clinical need.
- 6.19** The NIHR Biomedical Research Centres and Units have considerable expertise, capacity and activity in research for rare diseases. The NIHR is a member of the International Rare Diseases Research Consortium (IRDiRC). IRDiRC was launched in April 2011 through discussions initiated by the European Commission and the US National Institutes of Health; it coordinates international collaborative efforts to speed up the development of diagnostic tests and therapies for rare diseases.
- 6.20** In support of the UK Strategy for Rare Diseases, in October 2012 NIHR launched a themed call for Applied Clinical Research on Very Rare Diseases, as part of the researcher-led funding streams across six of the NIHR programmes. The call responded to the need for increased high-quality evidence on the organisation of super-specialised services and their commissioning, and the need to improve the health outcomes for sufferers of rare diseases. In total, over £5 million has been committed to research through this call, across seven projects, a large investment by NIHR in this area.
- 6.21** In parallel with the launch of the UK Strategy, NIHR established the NIHR Rare Diseases Translational Research Collaboration (RD-TRC),

with an initial investment of £20 million over four years. The NIHR RD-TRC provides world-class NHS research infrastructure to support translation from fundamental discoveries into translational research on rare diseases; increasing research collaboration to lead to improved diagnosis, treatment and care; and supporting deep phenotyping of people with rare diseases. At its core, it is formed from the NIHR Biomedical Research Centres and Units and Clinical Research Facilities, all with world-leading research expertise into rare diseases.

- 6.22** The NIHR RD-TRC aims to harness and develop the existing NHS research infrastructure to support patient-centred research into rare diseases, to facilitate tangible, rapid and efficient collaboration between NIHR-funded infrastructure, clinical researchers, NHS organisations, other research funders and life science companies; and to provide a greater understanding of the mechanisms underlying rare diseases by increasing the volume of in-depth phenotyping and linkage to data on genomic abnormalities.
- 6.23** The involvement of patients, their families and the public is central to the NIHR RD-TRC and the initiative actively supports patient involvement and awareness across centres carrying out rare diseases research. As well as hosting a range of activities to raise public awareness on Rare Diseases Day, it has recruited more than 6,500 patients to support 46 ongoing projects across 14 themes; each theme is focused on specific groupings of acquired and inherited rare disorders.

Case study: Involving patients from the word go

Involving and engaging patients are core to the work of the NIHR Rare Diseases Translational Research Collaboration (NIHR RD-TRC).

The overall activity of the programme is directed by the Strategic Oversight Group. This group includes two lay members, as well as patient representatives. The role of the group is to oversee the fundamental values and ethical principles of the NIHR RD-TRC. The involvement of lay members and outpatients helps the group to champion patient and public views regarding topics for research and makes sure that the most relevant research gets funded.

Researchers applying for funding must specify how patients have been involved in the research proposals and their plans for future patient and public involvement in the proposed work. Monitoring this activity is part of the regular reporting that researchers need to submit.

- 6.24** The NIHR RD-TRC also actively engages with industry partners, consulting with them on the selection of rare disease therapeutic themes and the individual awarded projects for deep phenotyping. It announced an opportunity in 2014, calling for expressions of interest in collaboration with NIHR-funded infrastructure and industry. To date it has received 22 expressions of interest, 13 of which were invited to submit a full application and six have been funded. This has resulted in £200,000 of industry funding for collaborative studies with the NIHR RD-TRC.
- 6.25** NIHR is a world leader in promoting and advancing active patient and public involvement, resulting in high-quality health and social care research. Over almost a decade, patients, carers and members of the public have contributed to the work of NIHR by helping it to decide what research to fund and how it should do this. They help to review and shape research projects and proposals and actively collaborate with researchers, clinicians and other health professionals to deliver and disseminate research

results. Their knowledge and insight play a vital role in helping the UK to recruit hundreds of thousands of volunteers to clinical studies every year.

6.26 NIHR recognises that patient involvement is integral to research. As such, all research projects, programmes and infrastructure supported by NIHR must have active patient/public engagement and involvement in their design and conduct. The 'Ok to ask' campaign was launched in 2013 to raise awareness about clinical research opportunities among the public and health professionals. These campaigns run annually. The 2015 campaign was highly successful in getting the message across that it is 'Ok to ask' about research.

6.27 In May 2014, NIHR published a five-year strategic plan, **Promoting a "Research Active" Nation**, setting out a new programme to encourage public engagement and participation in health, social care and public health research. NIHR organisations have been asked to incorporate it within their public involvement, participation and engagement plans. This includes a Year 1 pledge to publish exemplars of good and effective practice in a number of areas, including rare diseases.

6.28 NIHR also publishes guidance regarding patient involvement in research, both through INVOLVE and the Research Design Service. Through INVOLVE, NIHR recently undertook the Breaking Boundaries review, which examined future options for building an active collaboration with the public and making best use of their skills, knowledge and experience in the work of NIHR.

6.29 An important element of rare diseases research is the availability of biological samples in addition to genetic data. NIHR has supported two related initiatives in this area – the NIHR National Biosample Centre and the NIHR BioResource.

6.30 The NIHR National Biosample Centre was launched in January 2015 to provide high

throughput and high-quality biosample processing, storage and retrieval services, with the capacity to store up to 20 million samples. It will provide services to support NIHR-supported research, and research funded by partners including the Medical Research Council, charities and industry. This represents a significant national health research resource for the UK and will enable researchers to make use of modern genomics and other omics technologies in the diagnosis of rare diseases as well as gene discovery. The Centre will manage all the samples for the 100,000 Genomes Project and for the NIHR BioResource – Rare Diseases projects.

6.31 The Department of Health launched the NIHR BioResource in March 2014. It provides a national cohort of healthy volunteers, patients and their relatives who are willing to provide clinical information and samples that will enable them to be recalled by genotype and phenotype to participate in early translational research studies and early phase trials. NIHR BioResource – Rare Diseases was established specifically to identify the genetic causes of rare diseases, improve rates of diagnosis and to enable studies to develop and validate treatments, thus improving care for sufferers and their families. It works closely with other parts of the NIHR Infrastructure and Genomics England to support research into rare diseases. NIHR BioResource has eight centres across England and has recruited approximately 8,600 patients and their relatives; research and development (R&D) approval for rare diseases has been granted in 37 NHS hospital Trust sites.

Case study: The BRIDGE Project

This is a consortium that has been established as an umbrella for NIHR BioResource-funded next-generation sequencing (NGS) projects that aim to discover the genetic sequence variants that underlie unresolved inherited disorders and improve the sensitivity and specificity of approaches to identify variants that are more likely to cause the signs and symptoms of a rare disease. BRIDGE projects cover a variety of rare disease research areas, including cardiovascular, infection and immunity, and neuroscience. The consortium aims to sequence 8,000 samples from across the different projects by 2017. Analysis has already begun on the first BRIDGE projects – those that have led the way for recruitment, sequencing and phenotype capture – and initial genome sequencing has begun for the others.

- 6.32** A particular complexity of rare diseases resources is that projects often involve a large number of different organisations. The Health Research Authority (HRA) is in the process of implementing a significant and radical simplification of the process for setting up health research in the NHS in England. The revised process will eliminate the need to obtain individual permissions from all NHS organisations hosting research. The streamlined system of HRA Approval will comprise a review by a research ethics committee as well as an assessment of regulatory compliance and related matters undertaken by HRA staff. The new arrangement will allow study teams to focus on working with NHS organisations. Existing arrangements with other regulatory bodies allow HRA to confirm to researchers that all relevant approvals are in place. This is particularly beneficial to some of the more complex rare diseases research where the approvals pathway has been difficult to navigate.
- 6.33** The revised HRA Approval process will have particular benefits for rare diseases research but will apply to all health research in NHS England. HRA Approval is being rolled out in phases by
- study type. The next cohort will include studies involving analysis of data and tissue samples, and the subsequent cohort includes clinical trials.
- 6.34** The NIHR Biomedical Research Centres and Units have considerable expertise, capacity and activity in research for rare diseases. NIHR is a member of the International Rare Diseases Research Consortium (IRDiRC). IRDiRC was launched in April 2011 through discussions initiated by the European Commission and the US National Institutes of Health; it coordinates international collaborative efforts to speed up the development of diagnostic tests and therapies for rare diseases.
- 6.35** Collaboration across the UK is exemplified by the Deciphering Developmental Disorders (DDD) study. The project was jointly funded by the Health Innovation Challenge Fund (NIHR and Wellcome Trust), and aimed to find out if using new genetic technologies can help clinicians understand why patients get developmental disorders. It brought together clinicians in the 24 Regional Genetics Services throughout the UK and the Republic of Ireland, with scientists at the Wellcome Trust Sanger Institute. When recruitment of new patients ended in April 2015, more than 12,000 undiagnosed children (and their parents) and adults in the UK with developmental disorders had become involved. The work of the DDD team continues with the aim of ongoing analysis of the genetic information obtained. The experience of the DDD project has been an important factor in the development of plans by Genomics England in the 100,000 Genomes Project.

Case study: A journey to a diagnosis

When Zoe was born in 1995, everything appeared perfectly normal but by eight months her mum, Rhonda, had begun to think things were not quite right. At 20 months, when Zoe had her first paediatric appointment, her developmental delay was much more pronounced. A battery of tests revealed very little. In 2013 still without a clear diagnosis, Rhonda was keen to take part in the Deciphering Developmental Disorders (DDD) study.

As a direct result of the DDD study, Rhonda finally received a clear diagnosis in June 2015, identifying the faulty gene and thereby ending years of isolation and uncertainty. It turned out that Zoe was only the fourth person to carry this particular mutation in the DDD study. A diagnosis offered a chance to contact and support families in similar situations. It also made it possible to find out if Zoe's brother was a carrier and understand how Zoe had inherited the mutation. Identifying a clear genetic cause removes a huge burden from families that often see themselves as responsible for their child's condition.

It should not be forgotten how important a diagnosis is to parents – as Rhonda puts it, 'Trying to get answers has been frustrating and emotional but well worth every tear. Having a diagnosis is an immeasurable relief.'

licensing mechanisms administered by the European Medicines Agency (EMA).

Case study: Turning complex study summaries into plain English

The National Institute for Health Research (NIHR) Rare Diseases Translational Research Collaboration (RD-TRC) supports research programmes in a wide range of rare diseases. This research is complex and often seeks to integrate large quantities of phenotypic data with genomic analyses.

To make it accessible to people without any great knowledge of the conditions being studied or the methods being used, the RD-TRC has produced study **summaries** in plain English for the lay reader.

6.36 The true value of rare diseases research will be the development of novel treatments and medicines. Since many patients with rare diseases currently have no effective available treatment, making new treatments available as rapidly as possible is a key priority. The Early Access to Medicines Scheme (EAMS) offers a pathway for some medicines to be made available for patients in the UK in advance of licensing approval. EAMS is designed specifically for medicines that treat life-threatening or debilitating conditions, particularly where there is a clear unmet need. This scheme is therefore particularly suitable for improving access to rare diseases medicines and is distinct from adaptive

7. Next steps

- 7.1** There has been significant progress made in the field of rare diseases since the publication of the UK Strategy for Rare Diseases in 2013. The Strategy served to highlight those areas where improvements and changes were needed and has encouraged key delivery partners to take action. This report has detailed much of the good work that has been undertaken to date in all countries of the UK. However, to gain a better understanding of the direction of travel for rare diseases, their treatment and future patient services, it is good to reflect on how the issue of rare disease has moved ever higher up the agenda of policy makers across the world.
- 7.2** At the end of the last decade, the Council of the European Union made a recommendation that, in order to improve the coordination and coherence of national, regional and local initiatives addressing rare diseases and cooperation between research centres, relevant national actions in the field of rare diseases could be integrated into plans or strategies for rare diseases. It went on to further recommend that member states establish and implement strategies for rare diseases at the appropriate level, to ensure that patients with rare diseases have access to high-quality care, including diagnostics and treatments.
- 7.3** In 2009, the Chief Medical Officer's (England) annual report included the chapter '**Rare is Common**' that made recommendations on areas such as: better coordination of specialist services, including the transition from paediatric to adult services; the development of clear standards and pathways for the treatment and surveillance of rare diseases, with national registers to support service planning and delivery as well as research; strengthening research, including translational research with economic incentives, to develop and market medicines for the 'orphan diseases'; and supporting international collaborative efforts to share information and resources for rare diseases. In 2012, the International Conference on Rare Diseases and Orphan Drugs (ICORD) published *The Need for Worldwide Policy and Action Plans for Rare Diseases* as part of the Yukiwariso Declaration, reflecting the emergence of rare diseases as a prominent international issue.
- 7.4** While the formal development of a UK Strategy was a defining moment for rare diseases and meant that the UK had a clear overarching point for rare disease policy, it was born from more than the need to improve the lives of those affected by rare disease. It was also based on the outcomes of national and international discussions on the importance of rare diseases as a health and social care issue and agreement that action was required.
- 7.5** The UK Rare Disease Forum believes that the Strategy has played, and continues to play, a positive role in improving the lives of patients and helping to maintain the UK's position at the forefront of tackling rare diseases. It remains an important reference document for other advances and initiatives in related areas.
- 7.6** One key initiative has been 100,000 Genomes Project. Rare disease is a core pillar of its programme. It is likely that, as the project develops, it will become the principal driver in improving the understanding and treatment of rare diseases. The project will deliver potentially the world's biggest genomics knowledge base

and important 'spin-outs' from Genomics England. These will include the Genomics Clinical Interpretation Partnerships (GeCIPs), and the Genomic Medicine Centres (GMCs) in the NHS.

- 7.7** The GMCs are designed to build upon and develop further the existing network of genetic testing laboratories within the NHS and act as centres of excellence for treatment and research. Ensuring that the project leaves a lasting legacy will be increasingly important as it progresses. The Forum is encouraged by the way that all UK health services are moving to become fully involved with genomic technology. It is also welcomed that the role of industry in developing new technologies and therapies, based on genomics data, is recognised and is an integral part of the initiatives strategy.
- 7.8** The establishment of a national rare disease register by Public Health England is also welcomed by the Forum. The sharing of quality, standardised data is invaluable for improving treatment and research into rare disease. The experience of the Deciphering Developmental Disorders project clearly demonstrates the value that this type of data can play both for research and service improvement. To exploit the value of data to the fullest extent, barriers that might hinder connectivity and interoperability between the different databases must be addressed. The Forum hopes that the National Information Board strategy 'Personalised Health and Care 2020' could make a particular contribution in this area. We encourage all partners to work together to achieve a world-beating data platform for the UK.
- 7.9** Each of the four nations has a single national healthcare provider. We have a facilitating and permissive regulatory system and, by grace of the UK's mixed economy healthcare provision and separate governance structures in each country, we are well versed and experienced in delivering services through the networking of providers and experts. In addition, our academic, life science industry and research base mean that the UK has much to offer. Going forward, the Forum believes that all four countries of the UK should work more closely with each other to advance the interests of rare disease patients at all levels.
- 7.10** The need for cooperation to tackle rare diseases extends far beyond the UK. In the European Union there is a keen focus on rare diseases by organisations such as the European Organisation for Rare Diseases (EURORDIS) and the European Platform for Rare Disease Registries (Epirare). These programmes have been driving collaborative pan-European work on rare diseases. The establishment of European Reference Networks, as part of the EU Cross-Border Healthcare Directive, facilitates multiple work streams and programmes that are rare disease focused. The Forum believes that the UK is in a highly advantageous position when it comes to engaging on rare diseases issues at an EU level.
- 7.11** The delays often encountered by patients with a rare disease in obtaining a clear diagnosis represent an inefficient use of resources. The collective impact of rare diseases on health and social care is considerable and delivery of improved treatments will result in clear economic benefits. Developing better, higher quality services will include specialist centres, with continued access to expert knowledge from multidisciplinary teams. These in turn can support better quality primary care. Overall the aim will be to streamline services and make sure that more patients receive the most appropriate treatment as their first option.
- 7.12** The objectives for rare disease patients are closely aligned with the objectives of the Accelerated Access Review (AAR). The review takes a holistic approach and may identify packages of measures to promote faster uptake and adoption of new medicines and medical technologies including diagnostics. The expansion of diagnostics, particularly those

based on genomic technologies are likely to see rare disease patients as early beneficiaries. The AAR builds on the existing life sciences industry interest in precision medicine and companion diagnostics. Depending on its outcomes, the AAR recommendations could help reduce the length of the diagnostic odyssey for rare diseases patients. Better diagnosis will support the development of clearer care plans that enable patients to better manage their condition and improve their quality of life. While noting that many elements of the pathway are devolved, the review's ambition is to develop a joined-up, globally competitive landscape across the whole of the UK. The Department of Health will work with the devolved administrations where appropriate in order to do this. Issues related to regulation will be addressed on a UK-wide basis, while cost effectiveness and adoption will focus on England.

7.13 Therefore, as we look towards the next two years of implementation for the UK Strategy for Rare Diseases, the UK Rare Disease Forum believes the key issues to address should be:

- Evaluation – implementation of the UK Strategy for Rare Diseases should not be done blindly and by rote. The Forum will seek to develop clear metrics against which to measure implementation of the UK Strategy for its next report. The diagnosis and treatment of rare diseases is a rapidly changing landscape. Implementation of the strategy needs to reflect this, adapting and adjusting its goals in order to deliver the best outcomes for those living with rare diseases.
- Consolidation – building and transforming the best of existing provision to fully realise the potential of initiatives such as the 100,000 Genomes Project, GeCIPs, molecular pathology transformation and the reconfiguration of NHS England genomics pathology services to ensure they deliver the best possible outcomes for rare disease patients.
- Collaboration – at every level, across the UK and internationally. Tackling rare diseases relies upon high-quality collaboration for research and discovery, bringing on new therapies, service improvement and data sharing. Across the spectrum, the most important collaboration is the one with the patient, as an equal and expert partner in the process.

Useful information sources

Section 1

UK Strategy for Rare Diseases

www.gov.uk/government/uploads/system/uploads/attachment_data/file/260562/UK_Strategy_for_Rare_Diseases.pdf

Welsh Implementation Plan for Rare Diseases

<http://gov.wales/topics/health/nhswales/plans/rare/?lang=en>

The Implementation Plan for Rare Diseases in Scotland – ‘It’s Not Rare to Have a Rare Disease’:

www.gov.scot/Publications/2014/07/4751

Northern Ireland Rare Disease Implementation Plan

<https://www.dhsspsni.gov.uk/sites/default/files/publications/dhsspsni-rare-diseases-implementation-plan-oct-2015.pdf>

NHS England Statement of Intent

www.england.nhs.uk/wp-content/uploads/2014/02/rare-dis-stat-intent.pdf

Five Year Forward View

www.england.nhs.uk/wp-content/uploads/2014/10/5yfv-web.pdf

Section 2

Orphanet UK

www.orpha.net

Genetic Alliance Survey of Patients

<http://www.raredisease.org.uk/documents/Patient-Experiences-2015.pdf>

PHE National Congenital Anomaly and Rare Disease Registration Service

www.gov.uk/guidance/the-national-congenital-anomaly-and-rare-disease-registration-service-ncards

My Condition, My DNA

<http://www.geneticalliance.org.uk/docs/patient-charter-genome-sequencing-what-do-patients-think.pdf>

UK Genetic Testing Network

<http://ukgtn.nhs.uk/>

GENIE

www2.le.ac.uk/departments/genetics/genie?url=4ffa8258

Section 4

Diagnostic Odyssey for Rare Diseases: Exploration of Potential Indicators

www.piru.ac.uk/assets/files/Rare%20diseases%20Final%20report.pdf

Health Education England

Rare Disease: A Family’s Journey

https://www.youtube.com/watch?feature=player_embedded&v=nO_Hl065ZBE

Rare Disease: The GP’s Role

https://www.youtube.com/watch?v=1CNGk5lovv4&feature=player_embedded

Introducing Genomics in Healthcare

https://www.youtube.com/watch?feature=player_embedded&v=KiQgrK3tge8

Royal College of General Practitioners – Red Flags Toolkit

<http://www.rcgp.org.uk/clinical-and-research/~/~~/media/Files/CIRC/Rare-Diseases/RCGP-Red-Flags-Final-Nov-13.ashx>

Royal College of General Practitioners and Muscular Dystrophy UK: e-learning package

<http://elearning.rcgp.org.uk/course/info.php?popup=0&id=183>

The GenU

<http://ukgtn.nhs.uk/our-work/ukgtn-reportsguidelines/genetic-units-genus/>

European Reference Networks – European Commission guidance

http://ec.europa.eu/health/ern/implementation/index_en.htm

Section 5

Patient Perspectives and Priorities on NICE's Evaluation of Highly Specialised Technologies: Patient Charter

http://geneticalliance.org.uk/docs/hst-patient-charter_final.pdf

Specialised Healthcare Alliance – Minutes October 2015

http://shca.info/shca_reports.php

Section 6

Wales Gene Park

www.walesgenepark.cardiff.ac.uk/rare-diseases/

National Congenital Anomaly and Rare Disease Registration Service

www.gov.uk/guidance/the-national-congenital-anomaly-and-rare-disease-registration-service-ncards

NIHR Promoting a 'Research Active' Nation

www.nihr.ac.uk/documents/get-involved/Promoting%20A%20Research%20Active%20Nation_NIHR%20Strategic%20Plan_May%202014.pdf

NIHR Rare Diseases TRC research summaries

<http://rd.trc.nihr.ac.uk/study-summaries/>

Section 7

Annual Report of Chief Medical Officer (England) including the chapter 'Rare is Common'

http://www.sthc.co.uk/Documents/CMO_Report_2009.pdf

UK European Reference Network approved provider – information for applicants

<https://www.england.nhs.uk/commissioning/spec-services/latest-news/>

ANNEX A: Rare disease UK commitments

Empowering those affected by rare diseases

1. Strengthen the mechanisms and opportunities for meaningful and sustained patient involvement in rare disease service provision and research, recognising patient groups as key partners – including in the development of the four country plans to implement the Strategy.
2. Improve awareness amongst service providers and others of the effects that rare diseases can have on a person's education, family, social relationships and ability to work.
3. Encourage effective and timely liaison between the NHS and other public service providers, and encourage providers to consider the effects of rare diseases on people's lives when they are developing and managing services.
4. Make sure that patients and their families have a say in decisions about treatment and in the planning, evaluation and monitoring of services.
5. Consider how to give all patients with a rare disease clear and timely information about: their condition and its development; treatment and therapy options; practical support.
6. Improve access for patients (or where appropriate their parents or guardians) to their personal data.
7. Support patients to register on databases, where these exist.
8. Help patients to contribute to research and other activity related to rare diseases.

Identifying and preventing rare diseases

9. Continue to work with the UK National Screening Committee to ensure that the potential role of screening in achieving earlier diagnosis is appropriately considered in the assessment of all potential new national screening programmes and proposed extensions to existing programmes.
10. Initiate action to ensure carrier testing approved by the appropriate commissioning bodies, where the associated molecular tests are evaluated and recommended by UKGTN, is accessible for at risk relatives.

Diagnosis and early intervention

11. Work to achieve reduced times for diagnosis of rare diseases, whilst acknowledging that more needs to be done to ensure that undiagnosed patients have appropriate access to coordinated care e.g. to help disabled children who are thought to have a genetic syndrome or condition that science has not yet identified.
12. Work with the NHS and clinicians to establish appropriate diagnostic pathways which are accessible to, and understood by, professionals and patients, by
 - establishing clear, easily accessible and effective pathways between primary care, secondary care, regional centres and specialist clinical centres, as appropriate
 - putting protocols in place to identify patients with no diagnosis, ensuring that a lack of

diagnosis does not create a barrier to treatment

- drawing on patients' ability to help inform decisions about referral and diagnosis
 - creating effective clinical networks to support this process
 - making high quality diagnostic tests accessible through common, clinically agreed systems or pathway
 - embedding appropriate information in national data systems including measuring equity of access to molecular tests to maintain UKGTN diagnostic studies.
13. Ensure that there are appropriate procedures for evaluating the costs and benefits of treatments for patients.
 14. Where appropriate, support the availability of computerised prompts to help GPs diagnose a rare disease when a rare disease has not previously been considered.
 15. Improve education and awareness of rare diseases across the healthcare professions, including:
 - involving patients in the development of training programmes
 - encouraging medical, nursing and associated health professionals to get hands-on experience in specialist clinics
 - ensuring awareness of methods and clinical techniques used in differential diagnosis.
 16. Monitor the development of ICD-11 in preparation for its adoption.
 17. Work with colleagues in Europe on the development of the European Orphanet coding system and considering the adoption of Orphanet coding and nomenclature.
 18. Standardise data collection, building upon existing NHS data standards, and develop standards where they do not exist, increasing

the reliability of information for use in providing or commissioning care.

19. Explore options to improve the link between existing patient data and electronic health records.
20. Assess the potential for rare disease databases where they do not exist.
21. Agree international standards, building on existing NHS standards.
22. Support international links to UK databases and build on the work of current funded programmes that aim to link rare disease research internationally.

Coordination of care

23. Continue to develop service specifications for rare diseases. This will include country specific care pathways and a 'generic' care pathway that sets out best practice that can be applied to all patients with rare diseases in the UK (particularly where there are no disease specific pathways). The generic care pathway will include:
 - an appropriate care plan for all patients with a rare disease
 - clearly stated principles around the standards of care which patients with a rare disease can expect, including patients with no diagnosis
 - the development of seamless pathways for transition, from childhood to adolescence, and on to adulthood and older age
 - access criteria and measures of quality and outcomes.
24. Agree that specialist clinical centres should as a minimum standard:
 - have a sufficient caseload to build recognised expertise
 - where possible, not depend on a single clinician

- coordinate care
 - arrange for coordinated transition from children's to adults' services
 - involve people with rare conditions, and their families and carers
 - support research activity
 - ensure their expertise is available to families and their healthcare teams.
25. Ensure that the relationship between the specialist clinical centres and science and research is explained to and understood and put into practice by: practitioners delivering local health and social care; the research community; industry; academia.
 26. Set out clearly the connections to, and communications with specialist clinical centres in molecular diagnostics and other forms of diagnostic support.
 27. Ensure that specialist clinical centres are as concerned with research as with health and social care support, and that they develop networks that provide professional to professional dialogue and collaboration across a wide range of experts, including internationally (especially for those conditions that are ultra-rare).
 28. Work with international partners wherever possible and develop UK-wide criteria for centres to become part of an expert reference network to increase the flow of information between patients and professionals in a range of disciplines.
 29. Improve systems to record genetic and other relevant information accurately to record the incidence and prevalence of disease and support service planning and international planning.
 30. Identify how they can change systems to hold information about rare diseases, including information about the uptake of treatments.

The role of research

31. Look at how the four UK countries develop, change or expand information systems to capture, connect and analyse data about clinical and social care pathways.
32. Work together to identify a selection of the rare diseases most suited to the development of best-care pathways and propose other rare diseases for possible pathway development, taking on board the needs of patients and carers and the challenges faced during delivery of the first set of pathways.
33. Examine how they can encourage service providers to involve patients in research and to ensure appropriate funding for excess treatment costs for research in rare diseases.
34. Make better use of online applications to give patients information about their condition so that they can develop a personalised care path plan with their clinical and social care team.
35. Use portals to connect patients and relatives to enhance research participation and, where appropriate, promote self-enrolment to approved research studies with online consenting, self-reporting and use of social media.
36. Encourage patient groups to get involved with regulatory bodies.
37. Help patient organisations and community engagement events develop more formal partnerships with the NHS research-active organisations.
38. Explore the feasibility of the UK Clinical Trials Gateway including experimental medicine trials for rare diseases to provide information for patients and their families about research trials.
39. Work with the research community, regulators, providers of NHS services and research funders to develop risk-proportional permission systems.

40. Encourage researchers to use current guidance to produce generic participant information leaflets and consent forms and participate in future guidance reviews.
41. Promote good practice and the use of systems which facilitate a consistent and streamlined process to local NHS permissions of publicly, charitably and commercially funded research with an aim to reduce timescales.
42. Begin and complete next-generation sequencing (NGS) demonstration projects to: evaluate their usefulness, acceptability and cost-effectiveness; develop effective health economic assessments (for example through Health Technology Assessments) and similar initiatives.
43. Evaluate different NGS platform configurations, for example:
 - NGS for clinical condition-specific sets of genes (such as 100–200 of the 22,000 genes)
 - whole exome sequencing (2% of the entire genome)
 - whole genome sequencing.
44. Support the introduction of NGS into mainstream NHS diagnostic pathways, underpinned by appropriate clinical bioinformatics, including clinical bioinformatics hubs supported by high performance computing centres, where appropriate.
45. Ensure that training and education are available to the NHS workforce, highlighting the importance of NGS to all aspects of rare disease care, including support for evidence based local counselling for patients and their relatives who receive NGS results.
46. Work with industry to set priorities and determine how best to support research into rare diseases and promote research collaboration.
47. Support initiatives to facilitate engagement between patients, clinical care teams, researchers and industry wherever practical.
48. Set out the benefits of collaboration (besides producing specific treatments) for all stakeholders.
49. Continue to build a cohesive infrastructure for implementation and coordination of rare disease research in the NHS.
50. Encourage major research funders to use current structures to coordinate strategic funding initiatives in rare diseases.
51. Improve engagement between key stakeholders, including:
 - patients and relatives
 - main funding providers
 - healthcare commissioners
 - NHS hospitals and specialist care units
 - industry (pharmaceutical, biotechnology, IT, diagnostics).

ANNEX B: UK Rare Disease Forum

Terms of Reference

The UK Rare Disease Forum has a remit to monitor how the vision and actions outlined in the UK Strategy for Rare Diseases are being responded to across the UK. It will focus on the five sections of the Strategy:

- Empowering those affected by rare diseases
- Identifying and preventing rare diseases
- Diagnosis and early intervention
- Coordination of care
- The role of research.

The Forum will have an interest in the development work in all four countries of the UK, including what efforts are being made to promote collaborative responses to shared problems. However, the Forum will not duplicate the work of others.

The Forum will report progress on implementation of the UK Strategy for Rare Diseases to the health ministers of the four UK countries every two years. In carrying out its role, it will be important that the Forum maintains awareness of new opportunities, developments and knowledge that might have a bearing on the Strategy's implementation.

The specific areas of interest for the Forum include:

- how each country is progressing with its national plan
- appropriate consideration of EUCERD recommendations on core indicators for rare diseases national plans/strategies and how they could be used to monitor the implementation of the Strategy

- formally reporting back on implementation of the UK Strategy to ministers in the four UK countries by March 2016 and thereafter every two years
- what evidence or indicators could be used to assess that the Strategy commitments are being translated into services and support in practice (e.g. improved diagnosis, more integrated information and support, and coordinated care)
- consideration of what benchmarking information could be used, or easily established, to measure progress in specific areas
- promoting collaborative working on rare diseases, including at UK, European and international level.

Membership

Membership of the reconvened UK Rare Disease Forum will reflect the Forum's role focused on monitoring the implementation of the Strategy throughout the UK. Members will include representatives from all four UK countries, NHS England, healthcare professionals, industry, professional bodies, patient interest groups, researchers and funders. The membership of the forum is detailed in Annex C.

ANNEX C: UK Rare Disease Forum members

Alastair Kent OBE	Genetic Alliance UK – Chair
Kate Bushby	Newcastle University – Vice Chair
Colin Pavelin	Department of Health (Health Science and Bioethics)
Mark Bale	Department of Health (Health Science and Bioethics)
Tony Soteriou	Department of Health (Research Infrastructure and Growth)
Louise Knowles	Department of Health (Research Infrastructure and Growth)
Fiona Marley	NHS England
Edmund Jessop	NHS England
Maxine Foster	Health Education England
Jem Rashbass	Public Health England
Christine Collins	Northern Ireland Rare Disease Partnership
Veronica Gillen	Health and Social Care Board, Northern Ireland
Fiona Stewart	Northern Ireland Regional Genetics Service
Frances Martin	Department of Health, Social Services and Public Safety, Northern Ireland
Deirdre Evans	NHS National Services Scotland
Gus Black	Scottish Government
Elizabeth Porterfield	Scottish Government
Geoffrey Carroll	Welsh Government
Chris Dawson	Welsh Government
Andrew Wilkinson	Specialised Healthcare Alliance
Sheela Upadhyaya	National Institute for Health and Care Excellence
Willem Ouwehand	National Institute for Health Research
Sir John Burn	Newcastle Biomedicine
Phil Beales	Great Ormond Street Hospital
Graham Lipkin	Birmingham Health Partners
Charles Craddock	Birmingham Health Partners
Natalie Fine	General Medical Council
Tom Fowler	Genomics England Ltd
Audrey Duncanson	Wellcome Trust

Anne Mackie	UK National Screening Committee
Jacquie Westwood	UK Genetic Testing Network
Nick Meade	Genetic Alliance UK
Janet Hall	Royal College of General Practitioners
Imran Rafi	Royal College of General Practitioners
Joe McNamara	Medical Research Council
Mike Ringe	Association of the British Pharmaceutical Industry

Department of Health secretariat

Paul Jeff

Ian McKay

Dorothy Francis

Sylvia Pratt

