UK Departments of Health: Consultation on the United Kingdom Plan for Rare Disease

Response by the Wellcome Trust

June 2012

Key Points

- The UK is in a uniquely strong position to set the standard for patients with rare diseases, as provision of the best clinical care is deeply linked with research. Leading clinician scientists in the NHS, undertaking innovative research into rare diseases, can also provide the best possible care.
- We have seen an incredible rise in our ability to recognise rare diseases and the UK is home to world-leading genetic research in this area. As we understand more about the underlying genetics, there is a real possibility that many 'common diseases' will be found to be divided into a number of genetic subtypes, many of which may actually be 'rare diseases' too – with implications for both diagnosis and care.
- A national strategy for implementing clinical genomic technologies should form a cornerstone in the UK Plan for Rare Disease. This would support innovative research and integrate genetic testing into regular clinical practice to improve diagnostic processes.
- Electronic patient records and improved access to clinical data will be essential to enable researchers to investigate rare diseases, develop new diagnostics and therapies, as well improving access to clinical trials for patients.

Introduction

1. The Wellcome Trust is pleased to be able to respond to the consultation on the UK Plan for Rare Diseases (UKPRD). Rare diseases are those which affect fewer than 1 in 2000 people, but patients with rare disease are not rare, with 1 in 17 people in the UK estimated to be affected at some point in their life.[1] This places a large burden on patients, families and the NHS and we therefore welcome the development of the UKPRD. Given the Trust's remit and expertise, our comments focus primarily on the research perspective, diagnosis, use of patient information and collaborative networks. We also include details of relevant research that the Trust has funded.

[1] http://www.rarediseases.org.uk/documents/RD-UK-Strategy-Report.pdf

Speedy diagnosis and early intervention

Speedy diagnosis

2. Designing diagnostic services for patients with rare diseases should follow the model adopted by those centres currently providing the best practice in delivering innovative research-led care to patients. Examples of this are detailed in paragraph 16 and include the Wellcome Trust Centre for Mitochondrial Research in Newcastle and Andrew Hattersley's group at the University of Exeter working in monogenic diabetes (a rare and underdiagnosed form of diabetes).

3. Clinical care and research into rare diseases are deeply linked. There is often no distinction between clinical care and research in the diagnosis and care of people with rare diseases, as many facets of gold standard care may actually be part of research activities, for example a new genetic test or linking phenotypic data to the underlying genetic sequence. Furthermore, the best care for patients with rare disease is often delivered by clinicians who have developed the expertise, skills and knowledge through their research in that area. This close integration of research and clinical care allows innovative practice to be quickly delivered to patients while enabling researchers access to patients to further develop new approaches.

4. Many rare diseases have a strong genetic basis and providing a genetic diagnosis via genome wide sequencing or exome sequencing has the potential to be cost effective as the price of such techniques comes down – as well as providing greater certainty in the diagnosis. The Wellcome Trust Sanger Institute in their response to this plan discuss their ability to sequence a whole genome for the same price the NHS currently pays for one gene. We believe that access to genetic testing can play a key role in reducing the 'diagnostic odyssey' that patients faced by patients with rare disease.

5. Reducing the time to diagnosis will produce better medical outcomes for the patient, by avoiding exposure to unnecessary treatments while an understanding of what is happening to them can have an impact on psychological and social well-being, ideas of identity and not least, the health of any (potential) children if the condition is inherited.

6. One way of encouraging early appropriate referrals is for laboratories which run genetic tests to suggest a referral to an appropriate specialist centre on their results slips, a system already being trialled in Newcastle. The potential for computer prompts for GPs and clinicians, such as those already used in electronic prescribing, is an interesting idea that will require comprehensive electronic patient records to be implemented in secondary care systems in order to be a useful tool.

Training

7. Increasing the presence of rare diseases in specialty medical training is perhaps best addressed through a focus on diagnostic skills, including the use of information technology, and emphasising the importance of more generalist clinical skills. Most doctors do not need to be able to diagnose a rare disease but they do need the expertise to be able to recognise a collection of symptoms, signs and results as indicative of a possible rare disease and refer the patient appropriately.

Screening

8. The UK National Screening Committee requires randomised control trial (RCT) evidence before implementing screening programmes. While it is important we maintain screening programmes that have a strong evidence-base, it must be acknowledged that RCTs are not always possible or appropriate in rare disease research and there are other valid sources of strong evidence which could be utilised. There is a significant risk that a conservative approach by the National Screening Committee will cause harm to patients with rare diseases and their families by slowing the implications of important screening tests.

Coding and classification

9. In developing the 11th revision of the International Classification of Disease (ICD), the categorisation of rare and very rare diseases and those 'without a label' must be taken into account. The ICD does not encompass phenotypic information well. Given the highly evolving nature of our knowledge of both rare diseases and increasingly subtypes of common diseases, it might be argued the ICD should be more flexible to incorporate developments between revisions.

10. Given this, researchers at the Wellcome Trust Sanger Institute have been using the Human Phenotype Ontology (HPO) which is an ontology of clinical *observations* as distinct from the ICD coding system of clinical *inferences*.[2] The HPO is a useful pre-diagnosis tool and allows for more flexibility than the ICD which is only helpful for those with a diagnosis. More accurate classification of *observations and inferences* will have a positive effect on the dissemination of information and professional guidelines as data become more standardised and comparable across international networks.

11. As well as issues of classification, the curation, analysis and interpretation of this data is paramount in utilising for research or clinical practice. The Human Genomics Strategy Group (HGSG) recommended to the Government in January 2012 that a central repository should be created to store patient genetic and relevant phenotypic data, with the capacity to provide informatics services to the biomedical sector and researchers to support the development of new clinical tools.[3] A bioinformatics institute would provide interpretation and translation of the data, which is increasingly the most time and resource consuming element of genetic testing. We believe such an institute is important and would play a role in both clinical provision and research, establishing greater inter-operability of data and the dissemination of best practice in genetic testing across the clinical community.

12. Projects such as those at Sage Bionetworks which is providing an open repository for data on human disease biology, are aiming to create a common standard for computational disease models based on the largest possible set of data on human disease.[4] The importance of the ICD11 and systems such as the HPO, is highlighted by

[2] http://www.human-phenotype-ontology.org/

[3] http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_132369

[4] http://www.sagebase.org/commons/background.php

the need for accurate and powerful classification systems in order for these disease models to function.

Research

13. The UKPRD is right to recognise the strength of the UK biomedical research base which places us in a uniquely strong position to provide a model for best practice in supporting research into rare diseases and disseminating innovative clinical practices. As such, the UKPRD should build on the strengths of the NHS and UK biomedical sector in promoting innovation and collaboration between the NHS, academia and industry, as championed by the NHS Innovation Review in 2011.

14. One of the ways in which we have seen a rise in our ability to recognise rare diseases is through the advances in genetics pioneered by researchers such as those at the Wellcome Trust Sanger Institute. As we study the underlying genetics of more common diseases we are discovering that there is often a large spectrum of genetic subtypes of disease, many of which are rare. There is a real possibility that many more conditions will actually be found to be heterogeneous groups of rare diseases and that our approaches to caring for those with rare diseases today, will inform how we deliver care for more 'common diseases in the future.

15. We believe some of the best clinical care provided by the NHS is underpinned by those centres with a strong research base and that this integrated model of research-led care encourages innovation and propagation of best practice. The consultation asks how NIHR biomedical research centres can best translate research into clinical practice. As the NIHR's Collaboration for Leadership in Applied Health Research and Care (CLAHRC) aims to accelerate research into better care for patients and is responsible for developing models for the conduct and application of health research that is transferable across the NHS, it would seem appropriate that they could play a role in rare disease research and spreading best practice in care.

16. Encouraging translation of innovative research into clinical practice outside of the NIHR should also be supported and requires collaboration across public, private and philanthropic sectors. It should be recognised that research can benefit patients in other ways, for example it is currently often the only way for patients with a rare disease to get a genetic diagnosis and being involved in research can empower patients to learn more about their condition.

Examples of Wellcome Trust funding

17. The Wellcome Trust places great value in both basic and clinical research in contributing to improving human health, and the importance of clinical care underpinned by research. Examples of our funding focused on rare diseases includes:

    - The Wellcome Trust Centre for Mitochondrial Research funded by a £5.8 million Strategic Award to Doug Turnbull's group at Newcastle University. This Centre exemplifies the integration of clinical services and academic research and is

producing pioneering work in techniques which have the potential to eradicate mitochondrial diseases.[5]

- Andrew Hattersley's group at Exeter University is funded by a joint Department of Health and Wellcome Trust Health Innovation Challenge Fund (HICF) award of £1.2m, to develop diagnostics and care pathway for patients with a rare form of diabetes which is often under-recognised and is treatable with oral medication instead of insulin injections.[6]

- Dr Nigel Carter of the Wellcome Trust Sanger Institute received an £8.8m HICF award from the Department of Health and the Wellcome Trust for the Deciphering Developmental Disorders (DDD) project.[7] They are working with all 23 NHS regional Genetic Services to sequence the genomes of 12,000 children with developmental delay, in order to develop a unique online catalogue of genetic changes linked to symptoms that will enable clinicians to diagnose developmental disorders. They also aim to design more efficient and cheaper diagnostic assays for relevant genetic testing to be offered to all such patients in the UK, transforming the diagnostic pathway for children with abnormal development.

- Dr Matthew Wood at the University of Oxford and Dr Francesco Muntoni at the UCL Institute of Child Health are leading a £2.5m HICF awarded by the Department of Health and the Wellcome Trust to focus on the development and optimisation of a safe new generation of drugs for Duchenne muscular dystrophy.[8]

- The UK10K project, is a £10.5 million Strategic Award to the Wellcome Trust Sanger Institute to sequence the genomes of 10,000 people in the UK.[9] Data from 4,000 individuals in the TwinsUK and ALSPAC (Avon Longitudinal Study of Parents and Children) cohorts will be analysed along with information gathered from a second component of 6,000 people who have a severe condition thought to have a genetic cause, many of which are likely to be rare diseases. Understanding the underlying genetics and linking this to phenotypic information will be very powerful in advancing our knowledge of disease.

Use of patient information for research

18. As our knowledge of rare diseases increases, the importance of linking genetic and phenotypic data becomes pivotal in understanding the relationship between the clinical picture and the molecular basis of diseases. Being able to access accurate phenotypic data is important for geneticists in order to create appropriate diagnostic and therapeutic pathways. Gaining access to this information is not just a technical issue but an issue of

[5] http://www.ncl.ac.uk/iah/about/news/item/wellcome-trust-centre-for-mitochondrial-research-launched
[6] http://www.wellcome.ac.uk/Funding/Technology-transfer/Funded-projects/Health-Innovation-Challenge-Fund/index.htm
[7] http://decipher.sanger.ac.uk/
[8] http://www.wellcome.ac.uk/Funding/Technology-transfer/Funded-projects/Health-Innovation-Challenge-Fund/index.htm
[9] http://www.uk10k.org/

communication and clinical practice. UK Biobank[10] is paving the way in dealing with large genetic and phenotypic information and the technical, legal and ethical challenges involved with dealing with 500,000 participant's data. This £61 million project co-funded by the Wellcome Trust, the MRC and the Department of Health will help elicit factors involved in the development of rare disease.

19. The Scottish Health Informatics Programme (SHIP) is an ambitious national research platform for the collation, management, dissemination and analysis of Electronic Patient Records (EPRs) funded by the Wellcome Trust, the MRC and ESRC[11]. SHIP aims to provide access to an exciting new national research facility, create a research portal for EPRs already held by NHS Scotland, and develop and evaluate systems that work across institutional boundaries.

20. Scotland's early adoption of a unique patient identifier which is used across primary, secondary and tertiary care systems means that wide ranging health, demographic and social information can be linked together in research to improve population health. We welcome the Government's commitment in the Department of Health's new Information Strategy to move towards a single patient identifier for all patients in England by 2015.

21. Patient records can be an extremely valuable resource for research, and this is particularly true for rare disease research. The benefits of electronically held patient records are huge, allowing data to be used for epidemiological research, to monitor the safety and efficacy of drugs, and to study the effectiveness of treatments and interventions.

22. The Trust welcomes the launch of the Clinical Practice Research Datalink (CPRD) on 29 March 2012. Enabling researchers access to such a large and growing clinical database with the potential to link to local and specialist datasets could be very useful in rare disease research. It will also enable researchers to access information about small patient groups in a much more efficient way, and help to ensure that all eligible participants can be identified and invited to take part in relevant clinical trials.

23. Wherever possible, researchers use anonymised, non-identifiable information. However, sometimes researchers will need to access data from which it may be possible, directly or indirectly, to identify a patient. As it becomes increasingly possible to link different datasets, there is also greater likelihood of identifying individuals. This is more likely for patients with rare diseases because of the small numbers involved. The current regulatory framework is complex and confusing. There is urgent need for clarification of the data protection legislation so that patients and researchers conducting research into rare diseases can have confidence that data is protected appropriately.

24. The use of 'safe havens' such as the CPRD, a system of 'approved researchers', and professional standards for researchers that prohibit re-identification are all possible approaches to safeguarding pseudonymous data. We welcome the Government's commitment to review this area, and look forward to seeing the report of the Caldicott Information Governance Review. The proposals to amend the NHS Constitution also have significant potential to unlock patient data for research. Patients with rare diseases

[10] http://www.ukbiobank.ac.uk/
[11] http://www.scot-ship.ac.uk/

should be encouraged to respond to the consultation later this year to make their voice heard in the discussions.

Orphan Drugs and the Regulatory Environment

25. Orphan drug schemes run in the EU and the US provide good incentives for the development of drugs for Rare Diseases, however accessing these medicines remains a problem in many EU countries never mind the developing world. A level of financial risk-sharing with pharmaceutical companies has been trialled for some drugs, where providers only pay for therapies which have been shown to produce 'patient benefit'. However this approach is only feasible when there are clear biomarkers to show response to treatment, highlighting the importance of studying the underlying genetics and biology of diseases, to aid in identifying such markers.

26. The UKPRD does not discuss the regulatory difficulties in conducting multi-site research. In order to recruit enough patients to research, it is often necessary to include many centres nationally and internationally, particularly in rare diseases where the patient numbers are low. While ethical approval processes have been resolved it remains a major challenge to obtain the appropriate permissions from the NHS R&D offices of the devolved administrations in the UK and we believe this needs to be addressed if research into rare disease is to be supported. We are aware the Government is currently reviewing this area and we look forward to seeing how this progresses.

Centres of Expertise and networks

27. The plan lays out some high level criteria for 'Centres of Expertise' but the process for designating a Centre is unclear. Enabling new institutions to become 'Centres of Expertise' will encourage innovation, however this should not be at the expense of existing Centres, which must be supported to continue to develop expertise, people and resources. Given the breadth of rare diseases the focus should not just be on 'Centres of Expertise', but also on providing innovative care for patients with a rare disease and supporting individual clinicians conducting research, wherever they may be based.

28. The sharing of information between Centres of Expertise, local and primary care providers as well as relevant social services and the patient/carers themselves remains a huge problem. Addressing this challenge would have huge enormous potential benefits for the delivery of effective coordinated care. Given this, we are pleased that the new Department of Health Information Strategy[12] highlights the potential for 'joined-up' care and outlines steps towards achieving this, which must now be implemented.

29. The plan recognises that collaborative networks can form the foundation to enable prompt appropriate care. Academic Health Science Centres and the formation of Academic Health Science Networks in 2012/13 are further examples of how research and care can be integrated and we look forward to seeing how these develop and inform the evolution of 'Centres of Expertise'.

12 http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_134181

30. These collaborative networks, registries and centres need to be focused not just on UK integration, but should also participate in international partnerships to share knowledge, practice and research, especially important for very rare diseases with few patients. Ensuring that access to data, data standards and recording of phenotypic information is interoperable between centres in the UK, EU and globally will facilitate research and access to the best care for patients.

Empowering those affected by rare conditions

Patient information and support

31. Patient and carer groups are often useful sources of expert information for clinicians as well as patients. Empowering them to be involved in the commissioning of the pathways and services at a local and national level will be important.

    - The Wellcome Trust provides funding to Genetic Alliance UK, a charity representing over 150 patient organisations for those with genetic, often rare, diseases.[13] Genetic Alliance has also established Rare Disease UK and continues to be the main driving organisation for this umbrella group for rare disease patient organisations. Supporting these groups in producing information and resources for patients and clinicians will have a large impact on patient empowerment.

    - Initiatives such as EUPATI (European Patients Academy on Therapeutic Innovation) will also enable patients to be involved with creating educational materials.[14]

    - The Expert Patients Programme started by the NHS in 2002 should be extended to those living with rare diseases to enable the empowerment of patients and a louder voice for the rare disease groups.

32. Given that one of the main challenges of care and research into rare diseases is the rarity of each individual condition, an open collaborative-culture within the NHS, academia and industry is vital to support and encourage the sharing of information and involve patients in research. Such a culture requires engagement with patients and carers at a high level within commissioning and planning of services, research and information provision.

33. The plan discusses patients' enthusiasm to be involved with research. This engagement should be encouraged and facilitated, ensuring patients and clinicians are aware of opportunities to take part in research. The Trust welcomes the proposed amendments to the NHS Constitution, signalled by the Government in December 2011, would open the way for patients to be approached about research studies for which they may be eligible, with the opportunity to opt-out.

[13] http://www.geneticalliance.org.uk/
[14] http://www.patientsacademy.eu/index.php/en/

Orphanet

34. The consultation document questions whether the UK should continue to participate in Orphanet which has proved a useful tool for clinicians, patients and researchers alike. We would like to see the experiences and challenges faced by Orphanet in providing high quality information feed into the development of patient information and the commissioning of services in the UK.

Registers

35. In the absence of a reliable integrated electronic patient record system, disease registries have proved a very powerful tool in rare disease research, for example research into Sudden Infant Death Syndrome (SIDS). While we support the use of these tools when appropriate, registries are expensive to create and maintain, limited in the data they provide and should not replace a push to provide access to better integrated clinical records with accurate recording of disease and health attributes, such as through the CPRD.