



All Party Parliamentary Group
for Muscular Dystrophy

Access to high-cost drugs for rare diseases

SEPTEMBER 2013

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Foreword

There are over 60 different forms of muscular dystrophy and related neuromuscular conditions. All are rare, and some so much so that just a handful of people are affected in the UK. What they all have in common is a devastating effect on the body's muscles, increasingly compromising mobility, and often breathing and heart function. They all lead to progressive disability and this is something I myself understand, having lost my brother, sister, a nephew and a niece to myotonic dystrophy.

For decades the Muscular Dystrophy Campaign and families affected by muscle-wasting conditions have funded pioneering research. Basic laboratory research has developed potential therapeutic approaches, some of which, following extensive pre-clinical testing, are now being tested in clinical trials for several muscle-wasting conditions such as Duchenne muscular dystrophy. The prospect of these treatments becoming available may at last be within our reach.

However, as we have seen with other rare and complex diseases, successfully developing an effective treatment is far from the end. Following completion of clinical trials, pharmaceutical companies must apply to regulators for permission to market a treatment. Once received, the drug must still go through a lengthy appraisal and commissioning process before it becomes available to patients.

This is why the All Party Parliamentary Group for Muscular Dystrophy has conducted an inquiry into the provision of low-volume, high-cost drugs in England, while also considering the situation for patients in Scotland, Wales and Northern Ireland.

The link between good care and research is a vital one. Continued UK-wide investment into services for rare diseases will enable research to be conducted in a standardised and consistent environment. 'Centres of Excellence' for muscular dystrophy and related neuromuscular conditions are crucial for harmonising care to ensure that all clinical trial participants are treated in the same way. The Centres give patients and families access to specialist support from expert consultants and health professionals, which may include diagnostics, ongoing physiotherapy and integrated cardiac and respiratory services.

We have heard compelling and instructive oral and written evidence from researchers in the neuromuscular field, the pharmaceutical industry, the key organisations in the regulation, assessment and funding process, charitable organisations, and above all patients and their families. I thank everyone who has taken part in the inquiry for their invaluable contributions which has helped to inform the thoughts of myself and parliamentary colleagues in the Group.

This has enabled us to formulate a focused set of recommendations for several organisations to consider. We would like to see the 'bench to bedside' approach take place in an optimum, swift and streamlined way. It is equally essential that the newly-reformed NHS assesses rare diseases drugs in an efficient and fair manner.

For children and adults with life-threatening and life-limiting conditions, every day is vital and we are committed to ensuring urgent action is taken to implement the recommendations set out in this report.



Dave Anderson, MP for Blaydon

Chair, All Party Parliamentary Group for Muscular Dystrophy

Muscular Dystrophy Campaign

The Muscular Dystrophy Campaign is the leading UK charity focusing on muscular dystrophy and related neuromuscular conditions and is dedicated to beating these conditions by finding treatments and cures and by improving the lives of everyone affected by them. Founded in 1959, the Muscular Dystrophy Campaign takes the lead in investing in world-class research to find treatments and cures. People rely on the charity to provide expert information, advocacy and community support, and to signpost them to effective specialist services.

The charity also campaigns and works with parliamentarians and clinicians across the UK to ensure all people living with neuromuscular conditions have equal access to high-quality health and social care services.



The All Party Parliamentary Group for Muscular Dystrophy

The All Party Parliamentary Group (APPG) for Muscular Dystrophy, chaired by Dave Anderson MP, is a cross-party group of MPs and Peers, which raises the profile of muscular dystrophy and related neuromuscular conditions in Parliament.

The Secretariat of the group is provided by the Muscular Dystrophy Campaign.

Acknowledgements

Below are the Twenty Qualifying Members of the All Party Parliamentary Group, as well as Parliamentarians who received oral evidence submissions:

| | |
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| Dave Anderson MP | (Labour, Blaydon) (Chairman) |
| Clive Betts MP | (Labour, Sheffield South East) |
| Steve Brine MP | (Conservative, Winchester) |
| Russell Brown MP | (Labour, Dumfries and Galloway) |
| Mark Durkan MP | (Social Democratic and Labour Party, Foyle) |
| Graham Evans MP | (Conservative, Weaver Vale) |
| Tim Farron MP | (Liberal Democrat, Westmorland and Lonsdale) |
| Dr Hywel Francis MP | (Labour, Aberavon) |
| Pat Glass MP | (Labour, North West Durham) |
| Mary Glindon MP | (Labour, North Tyneside) |
| Rt Hon George Howarth MP | (Labour, Knowsley) |
| Barbara Keeley MP | (Labour, Worsley and Eccles South) |
| John Leech MP | (Liberal Democrat, Manchester Withington) |
| Stephen Lloyd MP | (Liberal Democrat, Eastbourne) |
| Baroness Masham of Ilton | (Crossbench) |
| Paul Maynard MP | (Conservative, Blackpool North and Cleveleys) |
| John McDonnell MP | (Labour, Hayes and Harlington) |
| Anne Marie Morris MP | (Conservative, Newton Abbot) |
| Dan Rogerson MP | (Liberal Democrat, North Cornwall) |
| Alison Seabeck MP | (Labour, Plymouth Devonport) |
| Lord Smith of Clifton | (Liberal Democrat) |
| Baroness Thomas of Winchester | (Liberal Democrat) |
| Lord Walton of Detchant | (Crossbench) |

The All Party Parliamentary Group (APPG) for Muscular Dystrophy wishes to thank the Muscular Dystrophy Campaign for its administrative support in the organising and staging of evidence sessions, gathering written evidence and producing a draft of this report.

Methodology

We held four evidence sessions to the APPG for Muscular Dystrophy between February 2013 and July 2013. Appendix 1 provides information on those who submitted evidence at each session. We also received written evidence from over 50 individuals and organisations with a specific interest in the inquiry's work.

The Muscular Dystrophy Campaign also provided considerable research analysis of the regulatory and commissioning process which contributed to this report. We are grateful to all those who assisted in our work.

Executive Summary

Patients with neuromuscular conditions and their families are waiting desperately for a cure or treatment to slow down the progression of their conditions. This wait is exacerbated by a fear that when medical breakthroughs are made, they may still be denied life-extending treatments.

In a comprehensive inquiry, the All Party Parliamentary Group for Muscular Dystrophy examined the needs of patients with rare diseases such as muscular dystrophy and related neuromuscular conditions to access potential treatments without delay if they become available. We heard about the stages before the licensing of treatments and the importance of streamlining and speeding up the process from basic research to clinical trials.

Evidence was heard about the low number of people affected by these rare diseases, the difficulties in attracting and securing funding, the need for international collaboration on research developments, translational research and the impact of NHS reforms and cost-saving requirements.

Evidence was taken from leading clinicians and researchers in the neuromuscular field and representatives of the pharmaceutical industry. We heard about barriers to treatments and the challenges of moving promising treatments into clinical trials – and then the approval of such treatments by regulatory authorities.

People with muscle-wasting conditions and their families gave powerful accounts, both during evidence sessions and in written evidence, about their fears that inconsistency of specialist care across the UK could delay – or even prevent – the NHS delivering therapies effectively once they become available.

These fears could be assuaged. Leading figures involved in the regulation, appraisal and funding processes gave encouraging indications that there are ways in which processes can be streamlined and simplified. We were keen to pursue how earlier access to medicines and adaptive licensing approaches could be accelerated. To ensure that patients with rare diseases are not denied vital and cost-effective treatments we need to see the NHS develop a new model with regulators and the industry. We also received valuable contributions from charitable organisations and alliances who stressed the importance of NHS care delivery and an inclusive and efficient appraisal process which takes full account of patients' needs.

The APPG for Muscular Dystrophy is calling on:

- the Government to establish a ring-fenced fund for rare disease drugs to ensure that patients affected by rare diseases are not denied treatments
- NICE to assess treatments for rare conditions in a different way from less rare conditions – ensuring an appropriate and effective cost benefit analysis
- the Medicines and Healthcare Products Regulatory Agency, NICE and NHS England to speed up access to life-changing drugs after final stages of clinical trials to ensure there are no major delays in treatments reaching children
- NHS England to ensure specialist centres are equipped with an appropriate range of health professionals to deliver treatments

The All Party Parliamentary Group for Muscular Dystrophy calls on the Government, devolved governments and organisations identified in the recommendations to take swift and effective action to ensure that the required standard of care is delivered and that access to high cost treatments is not denied.

Recommendations

1. Pre-trial/supporting trials

- (a) There is a pressing need to develop the clinical trial infrastructure with additional centres in the UK to enable more patients with rare neuromuscular conditions to participate in clinical trials. This will in turn help to hasten the development and introduction of new treatments. We were concerned to learn that the cutting of administrative support by some hospital trusts is having a detrimental effect on patient registries. As a result of these cuts some health professionals no longer have the capacity to upload patient details on to those databases which are important for clinical trials and translational research. **We therefore call on NHS England and the devolved health authorities to ensure muscle centres and clinics across the UK have the resources required to participate in patient registries and clinical trials.**
- (b) The Government must identify ways in which the UK can become a more attractive place for clinical trials in order for the UK to be at the forefront of technological development and innovation. We acknowledge the Department of Business, Innovation and Skills' Strategy for Life Sciences as a catalyst of UK growth. **We call on the Medicines and Healthcare Products Regulatory Agency and NHS England to consider a process for study approval whereby the various stages can be conducted in parallel to each other rather than as a more lengthy sequential approval process. To cut red tape around new clinical trials, we also recommend a simplified ethical approval process for multi-centre trials.**
- (c) Patient registries are central to developing clinical trials for rare conditions. However, currently they rely heavily on the financial support of the charitable sector. For the UK to be at the forefront in developing trials into new medicinal products for rare conditions, **we recommend that the National Institute for Health Research support the development of additional patient registries through statutory funding, as well as national clinical trial networks for rare conditions.**
- (e) **We urge the European Medicines Agency to include patient-reported outcome measures in the assessment of the benefits of drugs and treatments.** Regulators must recognise quality of life issues and take into account factors relating to daily living, which make a huge difference to individuals with rare conditions such as muscular dystrophy. We need a dialogue to ensure patients let the regulators and researchers know the most important things that would make the greatest difference to their lives.
- (f) We welcome the duty in the Health and Social Care Act aimed at ensuring research remains a core role of the NHS. This places a strong duty on the Secretary of State, NHS England and the Clinical Commissioning Groups to promote research. However, we were shocked to learn that effective promotion of research and clinical trials is still lacking in parts of the NHS and in the devolved countries. **We urge Clinical Commissioning Groups, hospital trusts, and health boards in the devolved countries to ensure health professionals promote research and share details about clinical trials among patients and families with rare conditions.**
- (g) It is essential that best practice standards of care are implemented in order to ensure a 'level playing field' so that the UK is a more attractive place for clinical trials for rare conditions. **We therefore call on National Institute for Health and Clinical Excellence to adopt quality standards for rare neuromuscular conditions and to implement current guidelines of best practice.**
- (h) In light of the French government's announcement of a seed fund to invest in biotherapeutics for rare diseases, **we recommend that the UK Government follows suit and builds on its own existing incentivised initiatives for innovation such as the Research and Development tax credit system and Patent Box which enables the UK to remain an attractive proposition for research into rare diseases.**

2. Speeding up access to treatments during later clinical trial stages and obtaining a licence

- (a) In order for the Government to fulfil its commitment to 'creating a more progressive environment that supports and promotes innovation with a view to providing faster access to new medicines for patients', **we recommend that it bring forward the Earlier Access to Medicines Scheme.** The scheme would be of real value to patients affected by muscular dystrophy and other rare diseases as it would allow faster access to emerging treatments which have shown clear scientific clinical benefit to patients and a positive risk profile. **We call on the governments in each of the UK countries to support this approach and for the Medicines and Healthcare Products Regulatory Agency to publish the findings of their recent consultation on such a scheme.**
- (b) We support the efforts of the pharmaceutical industry and the regulators to try to reduce the timeframe of clinical trials for future molecular patches with the potential to treat Duchenne muscular dystrophy, while maintaining standards of quality, safety and efficacy. The development of these so-called personalised medicines requires a re-assessment of approval protocols to avoid delays for patients with rare mutations. **We call on regulators to consider class approval and a fast-track approach for drugs with the same mechanics of action treating different mutations of conditions such as Duchenne muscular dystrophy.**

- (c) We look forward to the publication of the European Medicines Agency's findings into the utilisation of current licensing schemes and their recommendations for adaptive licensing. **We call on the European Medicines Agency to bring forward the publication of their recommendations into adaptive licensing [see page 28] sooner than 2015, following discussion of this approach for a number of years. We also recommend that the European Medicines Agency support an approach around adaptive licensing which would support drug development, licensing and patient access to innovative medicines in a managed and responsible way.**

3. The appraisal process and commissioning decisions

- (a) **We call on the National Institute for Health and Clinical Excellence to build on the framework established and validated by the Advisory Group for National Specialised Services, which accepts that highly specialised services should be appraised using a separate evaluation framework to ensure that vulnerable patients with very rare conditions are not denied treatments on the grounds of cost following an inappropriate cost benefit analysis.**
- (b) The Advisory Group for National Specialised Services had previously only appraised treatments for patients where the condition affected fewer than 500 patients in England or which involved services where fewer than 500 highly specialised interventions were undertaken each year. This rather ambiguous definition did not consider that some highly specialised treatments (including medicinal products) may benefit only a proportion of patients with an orphan disease. **We call on the National Institute for Health and Clinical Excellence to reconsider this approach and consider a more relevant and useful definition which accounts for the highly specialised technology.**
- (c) We welcome the leadership shown by the NHS in their appraisal process for Kalydeco (a new drug for cystic fibrosis) and in particular their determination to communicate effectively with patient organisations. We recommend that the National Institute for Health and Clinical Excellence uses this same rigour to ensure that patients are at the heart of the decision-making process. **In their assessment of treatments for rare diseases, we call on the National Institute for Health and Clinical Excellence, NHS England and the devolved health authorities to draw on the expertise from relevant patient groups and neuromuscular clinicians – and not to settle only for lay members on the emerging committees involved in assessment procedures.**
- (d) **We call on the Government to re-establish a ring-fenced fund for highly specialised technologies (formerly administered by NHS Specialised Services) to ensure that patients affected by rare diseases are protected and not denied treatment.** We believe a new model is required to reimburse medicines in line with patient numbers, given the aim to treat over 200 rare conditions by 2020.
- (e) **We call on the Scottish Medicines Consortium to review the way in which they assess treatments for rare diseases, following evidence received that many vulnerable patients with life-limiting conditions are being denied essential, life-changing drugs.**

4. The NHS: delivering effective treatments from the laboratory to the patients

- (a) **We call on NHS England and the devolved health authorities to ensure Muscle Centres and clinics are able to deliver forthcoming treatments for neuromuscular conditions and are equipped with adequately trained staff and multi-disciplinary teams of health professionals to deliver treatments and monitor disease progression.**
- (b) Future treatments for neuromuscular conditions are likely to extend lives and delay the progression of these often debilitating and life-limiting conditions. **We call on the NHS and devolved authorities to provide individuals and families affected by these conditions with essential services to aid mobility and to support independence – such as access to ongoing physiotherapy and hydrotherapy.**
- (c) We were pleased to learn about the new 'Innovation Fund' of £50million, which is open to applications from the new Clinical Reference Groups established for rare conditions and specialised services. **We call on the Clinical Priorities Advisory Group and the Rare Diseases Advisory Group to consider applications focused around innovative approaches in delivering care to patients and families affected by neuromuscular conditions.**
- (d) **It is clear that, should future treatments for neuromuscular conditions emerge, then the relevant Clinical Reference Groups (CRGs) would then have a role to play in providing advice to NHS England on funding and delivering treatments. We are concerned that, without a 'neuromuscular CRG', it is unclear which of the current CRGs will consider these important issues: Paediatric Neurosciences, Neurosciences, or the Multi-system Disorders CRGs. We call on NHS England to support the establishment of a 'neuromuscular CRG', which could be best placed as part of the current Multi-system Disorders CRG given the number of relevant neuromuscular clinicians currently on this particular CRG.**

Summary of Evidence

The patient experience

1. As part of this inquiry, we heard from a number of individuals and families living with rare, muscle-wasting conditions. Their powerful testimonies underline why it is so important for industry, regulators and the government to do all they can to speed up access to potential treatments in a responsible way.

2. Emily Crossley, from London, whose son Eli has Duchenne muscular dystrophy, commented on the current regulatory process for market authorisation which could limit her son's ability to access new treatments:

GlaxoSmithKline has a drug in a phase three trial to treat one subsection of boys affected by Duchenne muscular dystrophy. The current regulation would demand that every single drug [for exon skipping], even though it has a similar chemical background, will have to go through the same trial process for it to come to market.

The terrible thing for parents of sons with Duchenne is that we simply do not have that time. We are racing against time every single day. My son's muscles are dying on him and I don't have the luxury of being able to wait until he's 15 or 16.¹

3. This was echoed by another parent who emphasised the rapid progression of muscular dystrophy:

Time is running out. Please help my family – every day I witness my son struggle and every day we live in fear of the future.²

4. One parent contacted the group to emphasise that delays will have a devastating impact:

Duchenne muscular dystrophy is a progressive condition that my two sons suffer from. The condition causes worsening muscle wasting meaning that their ability to follow full lives is gradually compromised. There are no treatments and no cure. But there are very promising gene therapy and other novel treatments in development. Children deteriorate at an alarming pace and the earlier treatments can be provided the better the chance they have of leading full and normal lives. Slow assessment of treatments [after the licensing stage], that show massive potential, means that lives are lost during this process. There are no ifs and buts with Duchenne – without a treatment our children will die young having spent their last years completely dependent on others.³

5. Allan Muir's son, Jamie, has Pompe disease. At the APPG evidence session he spoke about their experience of diagnosis, clinical trials and the benefits of the treatment, enzyme replacement therapy, which is funded nationally in England:

Our son was diagnosed with Acid Maltase Deficiency at the age of two, with muscle weakness and sleep apnoea. It took a fair while and a referral to Great Ormond Street Hospital before we got a diagnosis. It was a difficult time but we got there. Some adults have to wait up to 10 years before they get a full diagnosis. After that, it was a matter of managing it, he had problems with scoliosis, and had scoliosis correction when he was 14, and it was quite severe.

At the age of 15 a drug trial had started at Rotterdam which he was involved in. We spent 18 months travelling for one or two weeks at a time for an enzyme replacement therapy, which was eventually commercialised in 2006.

Our son is now 23, he's stable, in pretty good shape, carries camera equipment up and down tall buildings and is doing incredibly well. The drug works perfectly.⁴

6. Anne Marie Groves from Great Yarmouth commented in written evidence:

Knowing that something will help gives hope; communication with the patient gives information. Both make the never-ending struggle with muscular dystrophy bearable.⁵

7. Another written evidence submission emphasised the recent developments of treatment and techniques and their potential impact:

This is an incredibly exciting time to be involved with muscular dystrophy research. New treatments and techniques are being developed and are really giving hope for the first time for those living with muscular dystrophy, and their friends and relatives. However, unless swift action is taken regarding patient treatment, a whole generation will

miss out on potentially life-saving treatment. My brother suffers from muscular dystrophy. In about a year he is likely to deteriorate from walking with the aid of a stick to being wheelchair-bound. He has a four-year-old daughter. Any treatment which could prolong the use of his legs would mean a great deal to our family.⁶

8. Phillippa Farrant, whose son Dan has Duchenne muscular dystrophy, made the following point to the inquiry:

As more and more young men with Duchenne reach adulthood, it's important that researchers also take into consideration this population when devising clinical trials. For instance, loss of arm and hand function is a devastating blow to independence and quality of life. My son Dan can still just use his powered chair with his thumb – it's essential that this small muscle function can be maintained.⁷

9. The powerful oral and written evidence that we have received has highlighted the urgency with which key organisations, starting at the pre-clinical trial stage to the licensing and approval stage, need to act in order to ensure that patients affected by muscular dystrophy and related neuromuscular conditions do not experience delays in accessing vital treatments when they become available.

Supporting the development of clinical trials for rare neuromuscular conditions

Clinical trials

10. The UK is an attractive place to carry out clinical trials given that there are a number of designated clinical treatment centres that provide a wealth of experience and knowledge as well as the depth of patient numbers needed to commence a clinical trial. However, we also heard about significant barriers in developing clinical trials for rare conditions.

11. Paul Humphrey, Marketing Manager UK and Ireland in the Rare Diseases Division at Genzyme, commented on the development of research into Lysosomal Storage Disorders in the UK. He said:

I think a strength the UK has is a very strong network of designated treatment centres, and what that allows to happen is a concentration of what are very rare individuals – 500 in the UK – into a number of small treatment centres.... I think for organisations seeking to set up clinical studies, they look to the UK, to these treatment centres with large populations, as their first port of call because they do have the experience and depth of patient numbers to start clinical studies.⁸

12. We heard that research is important not just for the development of a specific treatment but also for the facilitation of future research. Brendan Martin, General Manager, Genzyme UK and Ireland, illustrated this point:

The value of innovation is important to understand. Statins are generally recognised as having made an enormous contribution to society over the last 20 years with the reduction of risk of heart disease but the initial research which led to their discovery was in a rare disorder so there have been instances where research in rare disorders has opened a window that has led to an enormous contribution.⁹

13. Professor Dominic Wells, from the Neuromuscular Disease Group in the Department of Comparative Biomedical Sciences at the Royal Veterinary College, commented on different parts of the clinical trial process:

There are very promising things in clinical trials at the moment but it is not an empty pipeline in terms of some other things that are progressing. I'm fortunate enough to belong to the Therapeutic Advisory Committee for TREAT-NMD, which I now chair. TREAT-NMD is an international alliance of clinicians, scientists and patient groups affected by neuromuscular diseases. The Therapeutic Advisory Committee comments on pre-clinical data and plans for clinical trials, or plans for extending clinical trials. And we have an independent body of people covering the entire range from drug development, pre-clinical models and clinical expertise. And I think it's fair to say that there are a number of small companies that have some very promising products that will go into clinical trial very shortly.¹⁰

14. There is a pressing need to develop the clinical trial infrastructure with additional centres in the UK to enable more patients with rare neuromuscular conditions to participate in clinical trials. This in turn will help to hasten the development and introduction of new treatments. We were concerned to learn that the cutting of administrative support by some hospital trusts is having a detrimental effect on patient registries. As a result of these cuts, some health professionals no longer have the capacity to upload patient details on to those databases that are important for clinical trials and translational research.

We therefore call on NHS England and the devolved health authorities to ensure Muscle Centres and clinics across the UK have the resources required to participate in patient registries and clinical trials.

15. PTC Therapeutics outlined the challenges for companies and drew European and international comparisons in written evidence to the inquiry:

It can be challenging for companies to secure the investment needed to perform pioneering research into therapies for which there is such a small market, following approval. Without such funding, research and development of promising potential drugs will not be progressed to full development and ultimately licensing. In recognition of this, direct government grants can facilitate the necessary research, thus accelerating access to these novel therapies for patients. There is a precedent for the direct grant system, with such funding available in the United States and the Netherlands. A similar system in the UK would provide an incentive for organisations to take the risk of developing new therapies for orphan diseases and would be beneficial to the rare diseases community.¹¹

In light of initiatives in the United States and the Netherlands and the French government's announcement of a seed fund to invest in biotherapeutics for rare diseases, we recommend that the UK Government follow suit and builds on its own existing incentivised initiatives for innovation such as the Research and Development tax credit system and Patent Box which enables the UK to remain an attractive proposition for research into rare diseases.

Barriers to research development

16. We learned that the current regulatory arrangements for trial approval make it difficult for the UK to realise the full potential of scientific development and inhibits patients from benefiting from new medicines.

17. We heard from Professor Francesco Muntoni, Chair of Paediatric Neurology at the Institute of Child Health, Dubowitz Neuromuscular Centre, University College London, about his frustrations at different stages of the process:

The amount of bureaucracy that has been building up in the UK in the last 20 years is phenomenal... you may have a study which has been MHRA approved, that has been ethically approved, for which the company has the funding, but will be sitting around in the office for two or three months, and that happens after you have done everything.¹²

18. GlaxoSmithKline and Prosensa Therapeutics shared their concerns about the length of time it takes to set up a trial from the point of seeking study approval to the point of commencement of the clinical trial, particularly when compared to other European countries. Allison Morgan, Vice President, Clinical Research and Development at Prosensa Therapeutics, commented:

I am in the thick of clinical trials on a daily basis and, from my perspective, the UK compared to its European counterparts is bureaucratic and expensive. I can take Belgium as an example: I can get a study (approved) from start to finish within two months; and in the UK that might be five months.¹³

19. Speaking about the process, Allison Morgan from Prosensa added:

The MHRA is the regulatory body that approves the protocol, then it has to go to the Central Ethics Committee in the UK, then sometimes the hospital committee, then a local research unit, and then we have to negotiate the contract. All of this takes a lot of time.¹⁴

20. In addition, if a trial involves centres in Birmingham, Manchester, Newcastle and London, then each centre would have to apply for separate ethical approval despite its being for the same study. This is a lengthy and costly process.

21. In July 2013, the House of Lords Science and Technology Committee published a report on Regenerative Medicine. Their report highlighted problems with the UK's regulatory arrangements – described as 'labyrinthine' – as well as a lack of co-ordinated leadership on this issue.¹⁵

22. It was made clear by the experts giving evidence to the APPG that if the stages of the approval process ran in parallel to each other, this would save considerable time and allow the UK to reach more competitive levels.

In order for the UK to be at the forefront of technological development and innovation, the Government must identify ways in which the UK can become a more attractive place for clinical trials. We call on the Medicines and Healthcare Products Regulatory Agency and NHS England to consider a process for study approval whereby the various stages can be conducted in parallel to each other rather than as a more lengthy sequential approval process. To cut red tape for new clinical trials, we also recommend a simplified ethical approval process for multi-centre trials.

Patient registries

23. It is of critical importance that care and research are integrated, as to do so would improve access to clinical trials and patient outcomes.

24. Patient registries are vital in attracting support from the pharmaceutical industry in developing clinical trials, as well as being an important way for patients to access them. There are a number of UK patient registries for specific neuromuscular conditions, which contain information about individuals affected by the particular condition. TREAT-NMD is a network of excellence funded by the European Union and has been a driving force for the

establishment of patient registries. It aims to stimulate the development of national registries in each country. The Healthcare Quality Improvement Partnership provides the following description:

Clinicians in those disciplines covered by such specialist databases know these databases have considerable value for commissioning, service planning and public health, as well as clinical care. Registers are often the lifeblood of clinical knowledge in these areas, alongside audit and research. They are often rated highly as part of the network of information sources by National Clinical Directors and the Department of Health. They are usually supported by specialist societies and royal colleges, although these registers have typically been set up by either an individual clinician or a group of committed specialists in their disciplines.

They detail care provided for their client groups, the incidence and outcome of specific conditions and procedures, and organisational responses and treatments provided for specific conditions. They often gather information on clinical outcomes of patients, and form sources for audit and research into the causes of variance in outcomes and other research projects. They do not usually measure performance against standards, nor do they necessarily drive improvements in an explicit way, yet some have strongly 'audit-like' features, or can be developed into clinical audits.¹⁶

25. Dr Liz Philpots, Head of Research at the Association of Medical Research Charities (AMRC), highlighted the importance of patient information in order to conduct clinical trials:

I think access to patients is probably the first big barrier if you wanted to conduct a clinical study of patients with a particular condition; how do you access clinical patients, how do you know they'll be at that particular centre, how do you know the study is designed for them?

I think we are doing a lot in the UK around ethics, around NHS approvals, around getting that better because there is obviously a lot more to do to make that a lot smoother, so when a study wants to start it can start immediately and get going.¹⁷

26. Professor Muntoni from the Dubowitz Neuromuscular Centre underlined the importance of patient registries in the facilitation of standards of care and clinical research:

I know there is a lot of discussion about the NHS and networks and I hope this can be facilitated. The reality is at the moment, there is some funding provided by the Muscular Dystrophy Campaign and a lot of goodwill of a lot of people. There is already a good infrastructure, but I think it could be consolidated. It would mean that firstly, the current standard of care applied in the best possible way, meaning everybody will win who has muscular dystrophy today, because there is nothing wrong with being very precise in applying the standard of care. Also there will be perfectly trial-ready children, meaning if a drug comes, instead of only the children I see at Great Ormond Street Hospital or somewhere, the entire population of children would be easier to involve when I'm being contacted and asked how many children with Duchenne in the country would meet the inclusion criteria for this particular study.¹⁸

Patient registries are central to developing clinical trials for rare conditions. However, currently they rely heavily on the financial support of the charitable sector. For the UK to be at the forefront in developing trials into new medicinal products for rare conditions, we recommend that the National Institute for Health Research support the development of additional patient registries through statutory funding, as well as national clinical trial networks for rare conditions.

NHS promoting research

27. Dr Liz Philpots from the AMRC underlined the importance of research as a part of patient care. She spoke about the AMRC's document, 'The Vision for Research within the NHS', which looks at how you make research as a duty of the NHS into a reality. She said:

It's partly about making patients aware that research is available to them so they begin to understand research; it's about making clinicians on all levels aware. So it's not just the research active consultant, it's about making the GP, the nurse and the health professional know that they can be involved in research.¹⁹

28. She went on to say:

Research needs to be seen as part of care. That in order to have good care and new ideas, new treatments coming through that are therapies for individuals with conditions, the research needs to be seen as part of that, so there's an opportunity with a specialised centre to have research as part of that. And given that we have research

as a duty of the NHS, now to really push to say that you must make sure the centres allow research to happen, and that that research evidence is the right research and it then becomes part of standard practice both in that specialist unit and in a wider sense.

'The Vision for Research within the NHS' which is a larger document that looks at how you make that duty into a reality and partly it's about making patients aware that research is available to them so they begin to understand research, it's about making clinicians on all levels aware.²⁰

29. The AMRC's written evidence stated:

Over 90 percent of healthcare professionals told us (the AMRC) that they have experienced barriers in taking part in medical research over the last two years.²¹

30. Colin Pavelin, Head of Genomics and Rare Diseases at the Department of Health, stated that the Government has recognised the importance of research in promoting better patient outcomes and stressed that there is huge support for the belief that research must be a part of the healthcare pathway, notably with the Government's Life Sciences Strategy. He admitted, however, there is still a long way to go. Mr Pavelin said:

We do have a long way to go to ensure that there's awareness at an adequate level not just about rare disease but about the importance of patients being introduced and guided and facilitated to join a research clinical trial.²²

31. He added:

It is our intention that we make a plan and we research progress in neuromuscular diseases, of which muscular dystrophy is one, and that they will be integrated up to the service and we'll be hoping to do that across the format as far as possible with research.²³

We welcome the duty in the Health and Social Care Act aimed at ensuring research is a core role of the NHS. This places a strong duty on the Secretary of State, NHS England and the Clinical Commissioning Groups to promote research. However, we were shocked to learn that effective promotion of research and clinical trials is still lacking in parts of the NHS and in the devolved countries. We urge Clinical Commissioning Groups, hospital trusts, and health boards in the devolved countries to ensure health professionals promote research and share details about clinical trials among patients and families with rare conditions.

Facilitating clinical trials in the UK

32. We heard how important it is to ensure optimum levels of care are provided in order that those wishing to take part in a trial are on a 'level playing field'. This would ensure a standardised and consistent environment, both in relation to the treatment and care provision such as physiotherapy, in which the trials could take place, therefore yielding the most effective results.

It is essential that best practice standards of care are implemented in order to ensure a 'level playing field' so that the UK is a more attractive place for clinical trials for rare conditions. We therefore call on the National Institute for Health and Clinical Excellence to adopt quality standards for rare neuromuscular conditions and to implement current guidelines of best practice.

33. One of the many challenges in designing and conducting trials for muscular dystrophy and related neuromuscular conditions has been the lack of 'validated endpoints' to assess function for those individuals who cannot walk – or who are 'non-ambulant'. For Duchenne muscular dystrophy, the only endpoint that has been widely used is the six-minute walk test. We heard from a number of families affected by Duchenne muscular dystrophy who are concerned that this sole endpoint excludes a large section of their community – those who are non-ambulant – meaning that many are unable to take part in clinical trials.

We urge the European Medicines Agency to include patient-reported outcome measures in the assessment of the benefits of drugs and treatments. Regulators must recognise quality of life issues and take into account factors relating to daily living, which make a huge difference to individuals with rare conditions such as muscular dystrophy. We need a dialogue to ensure patients let the regulators and researchers know the most important things that would make the greatest difference to their lives.

Speeding up access to treatments

Clinical trials for Duchenne muscular dystrophy

34. We received detailed information about the latest clinical trials into the potential exon skipping drug which is a molecular patch for exon 51 of the dystrophin gene, which we were told could benefit 13 percent of the Duchenne muscular dystrophy population with certain specific mutations. Lord Walton of Detchant described recent developments at the first evidence session as ‘immensely exciting’.
35. Dr Rohit Batta, Global Medical Leader – Neuromuscular Disorders at the GlaxoSmithKline (GSK) Rare Diseases Unit, provided us with more details about the Phase 3 clinical trial:

GSK and Prosensa are now conducting a Phase 3 clinical trial, involving over 180 boys. This is a truly global study with various sites in Europe, South Korea and Chile. The results of the trial will be available in September this year.²⁴

36. Clinical trials have also begun to test molecular patches with the potential to treat rarer mutations that cause Duchenne muscular dystrophy. **Prosensa believes that with their discovery pipeline they might be able to treat up to 80 percent of boys affected by Duchenne muscular dystrophy.**
37. The question is whether the regulatory and commissioning arrangements are ready and prepared to bring forward such exciting and innovative developments surrounding Duchenne muscular dystrophy and other types of muscular dystrophy and related neuromuscular conditions.
38. Professor Muntoni from the Dubowitz Neuromuscular Centre commented:
- I will probably describe all of these [for Duchenne muscular dystrophy] as very high-tech and very focused therapeutic intervention. The exon skipping is quite unique because it is an intervention that is very tailor-made to an individual or groups of individuals with Duchenne which is, I suppose, useful to discuss at some point later on, as a disadvantage, because you do not have a single molecule that will treat 100 percent of boys with Duchenne. You will have a molecule, for example the one we develop in the UK, and that has been developed also by Prosensa/GSK, that will address a single molecule for approximately 13 percent of boys with Duchenne, and then you will have to develop another one to treat another 10 percent of Duchenne boys and so on and build the portfolio until we can treat every single group.²⁵*
39. With potential treatments on the horizon, we explored the possibilities of early access to medicines and flexible approaches to licensing, also establishing the extent of extrapolation for authorisation of molecular patches for Duchenne muscular dystrophy and the research and regulatory processes.

The market authorisation of new medicines to treat rare diseases

40. The European Medicines Agency (EMA) is responsible for evaluating applications for licences for drugs within the EU. There are seven committees within the EMA. The European Committee for Medicinal Products for Human Use (CHMP) is responsible for medicines for human use. We heard from Dr Ian Hudson, Head of Licensing at the Medicines and Healthcare Products Regulatory Agency:
- In practice, however, how it actually works is that in individual member states authorities like the MHRA provide resources to do the assessment within the EMA, so we all work in an integrated network that most products will go through in a centralised route.²⁶*
41. Under existing legislation, certain drugs which are being developed by the pharmaceutical industry for rare diseases can be granted by the European Commission orphan status. These are referred to as ‘orphan medicinal products’. Once orphan status has been granted, the licensing fee can be waived and the product is given market exclusivity for 10 years once approval has been given.
42. Baroness Thomas of Winchester pointed out that the time factor was critically important when saying:

Three or four years is a long time in the life of a boy with Duchenne.²⁷

43. The APPG supports the House of Lords Science and Technology Committee’s calls for the Health Research Authority to simplify the regulatory route.²⁸
44. Although unusual, applications for market authorisation can also be made directly to MHRA by a pharmaceutical company seeking a UK-only licence. In this situation, the Committee of Safety Medicines (part of the MHRA) would consider their application.²⁹ If this committee recommend that the drug should not be licensed, the pharmaceutical company can appeal to the Medicines Commission. Although not a long process, a product is not given market authorisation until it is ‘launched’. Generally though, Dr Ian Hudson at the MHRA told us that the most innovative products go through a centralised procedure operated by the EMA.

Are there opportunities for early access?

45. Despite the exciting developments in clinical trials into potential treatments for Duchenne muscular dystrophy, we heard concerns about the market authorisation process of approval of the drug.
46. One particular concern related to the time taken to achieve market authorisation. The EMA market authorisation process takes 210 days, which can only be shortened with accelerated review to about 150-120 days. This is still a long time for a patient awaiting treatment for a life-threatening disease, especially when you consider that this is just one step towards patient access.
47. The UK Government has shown support for innovation and is taking steps to ensure accelerated patient access to medicines for life-threatening and debilitating diseases through its *Strategy for Life Sciences*³⁰ and a commitment to consulting on an *Earlier Access to Medicines Scheme*.
48. It is the intention that ‘the scheme should be available for promising new medicines that will treat, diagnose or prevent life-threatening, chronic or seriously debilitating conditions without adequate treatment options. Data will be required that indicates that the benefit:risk profile of the medicine is positive. The scheme will be limited to medicines representing a significant advance in treatment in an area of unmet need, and we expect that one or two medicines per annum could qualify under this scheme.’³¹
49. The Muscular Dystrophy Campaign responded to the MHRA Early Access Scheme consultation and welcomed their intention to ensure swifter access to promising treatments for patients with debilitating and/or life-limiting conditions such as muscular dystrophy. **The MHRA is yet to publish the findings of their consultation.** It would be up to Scotland, Wales and Northern Ireland to determine if they should be part of this scheme.
50. The consultation for an Earlier Access to Medicines Scheme was in October last year. So far, the MHRA has not reported their findings. There was considerable consensus among our panellists and written submissions to bring forward this scheme. The UK Bio Industry Association commented:

Such a scheme already operates in France and has included within it a number of Orphan Medicinal Products. A similar scheme in the UK therefore might benefit patients by providing earlier access to truly innovative medicines in areas of severe unmet medical need. Provided this does not detract from the recruitment and conducting of clinical trials in the UK (which the experience of France shows that it can avoid) it could allow for earlier access to products in the rare disease space.³²

In order for the Government to fulfil its commitment for ‘creating a more progressive environment that supports and promotes innovation with a view to providing faster access to new medicines for patients’, we recommend that it bring forward the Earlier Access to Medicines Scheme. The scheme would be of real value to patients affected by muscular dystrophy and other rare diseases as it would allow faster access to emerging treatments which have shown clear scientific clinical benefit to patients and a positive risk profile. We call on the governments in each of the UK countries to support this approach and for the Medicines and Healthcare Products Regulatory Agency to publish the findings of their recent consultation on such a scheme.

The authorisation of future molecular patches for Duchenne muscular dystrophy

The UK Bio Industry Association has told us that It takes on average 10 to 15 years to develop this product from basic research, through the robust regulatory environment, to patients.³³

51. It is unclear whether the development of future molecular patches for other specific mutations which cause Duchenne muscular dystrophy will have to go through the same lengthy research and regulatory process.
52. Delays to accessing treatments are a constant concern for people affected by neuromuscular conditions, as one written evidence contribution highlights:
- It would be tragic and devastating for our family to encounter any barriers to access of future treatments.³⁴*
53. We were very interested to learn from Prosensa that with respect to the rarer mutations which cause Duchenne muscular dystrophy, negotiations are taking place between Prosensa and the EMA and FDA to carry out more innovative trial designs which can utilise the data from the exon 51 trials and thus be completed in a shorter time frame while maintaining safety standards for the patient.
54. We heard from Prosensa about their proposal for one study which would cover the entire programme for the next two exons, 45 and 53. We were informed that they have already started the exon 45 study in Belgium and they envisage that it will take just two years to complete.
55. Allison Morgan from Prosensa commented on the study design for the next exons, 45 and 53:
- The entire programme will be approximately two years, which is very, very short for the pharmaceutical industry. We have been able to do that on the back of the programme (exon 51) because the data from the programme will drive a pan portfolio approach as the concept from molecule to molecule is exactly the same.³⁵*
56. Our panel of experts emphasised the importance of clinical work in order to determine the correct dosage and ultimately the safety of the drug for patients. Allison Morgan from Prosensa commented on the challenge and importance of getting the therapeutic window correct:
- ... it's a bit the same with oligonucleotides; you have to be very careful when you put one in a child, and we do very, very safe, controlled dose escalation and then we look for a molecular response to make sure that we have the therapeutic window correct.³⁶*
57. We also heard from Allison Morgan from Prosensa about their work to identify a biomarker which could be used to assess disease progression and the effectiveness of new potential treatments. Referring to Duchenne muscular dystrophy, we learnt that if levels of dystrophin protein could be shown to be a good indicator of disease progression or severity, then this could be used in a clinical trial as a measure of the effectiveness of a new drug. Providing substantial evidence of effectiveness and safety has been gained in previous clinical trials of drugs in the same class, it could be the case that follow-on drugs would not require such a lengthy clinical trial.

We support the efforts of the pharmaceutical industry and the regulators to try to reduce the timeframe of clinical trials for future molecular patches with the potential to treat Duchenne muscular dystrophy, while maintaining standards of quality, safety and efficacy. The development of these so-called personalised medicines requires a reassessment of approval protocols to avoid delays for patients with rare mutations. We call on regulators to consider class approval and a fast-track approach for drugs with the same mechanics of action treating different mutations of conditions such as Duchenne muscular dystrophy.

58. We also discussed with our experts whether current EMA and MHRA licensing schemes allow for the licensing of follow-on drugs where a shorter clinical trial had demonstrated safety and efficacy or whether a new adaptive licensing scheme was needed.
59. We asked the regulator whether the requirements of market authorisation could be adapted so that the existing data from the same class of drug (such as drisapersen) could be utilised in the approval process. Dr Ian Hudson from the MHRA responded:
- I think first of all we would want the first drug to go through, to show safety, quality and efficacy. The standards required to do that for the first drug – the principle would need to be established. The question would then be: would a second one, a follow-on for a different mutation, require a reduced requirement? I think the answer is 'yes'.³⁷*

60. He went on to say:

There still needs to be some work to develop it but it may not need to be as elaborate as the first one. I think we would be open to discussions on that with people who have follow-on or different mutations to see how much can be inferred from the first drug to support the second.³⁸

61. We were concerned to learn from our experts that the EMA's conditional market authorisation (CMA), a scheme set up specifically for medicinal products to treat life-threatening conditions, is being used less often than it might have been. Given that there is currently no cure or treatment for Duchenne muscular dystrophy, CMA might provide the necessary framework for molecular patches as their use would be conditional on clinical work showing the benefit:risk balance is positive and the completion of ongoing studies.
62. We were therefore pleased to learn that as a result of the **Strategy for UK Life Sciences**, an expert working group has been set up by the MHRA to report on whether the current regulatory schemes (such as CMA) can be better utilised by industry to inform UK and EU policy. The same working group will also report on the development of an adaptive licensing project.

Adaptive licensing

63. Adaptive licensing (AL) is a 'prospectively planned, flexible approach to regulation of drugs' which is achieved through 'iterative phases of evidence gathering'. It is not about reducing the level of scientific thoroughness required for drug approval but to try and balance 'timely access for patients with the need to assess and to provide adequate evolving information on benefits and harms so that better-informed patient care decisions can be made'. AL differs from CMA as it can be applied more generally to a greater number of conditions. With AL, a plan for licence is agreed in advance by all – that is the sponsors, regulators, payers and patients.³⁹
64. Dr Ian Hudson from the MHRA informed us about adaptive licensing. He said:
- It is defined as a prospectively planned, adaptive approach to the regulation of drugs through iterative phases of evidence gathering followed by regulatory evaluation of licence adaptation. Adaptive licensing seeks to maximise the positive impact of new drugs on public health by balancing timely access for patients with the need to provide adequate evolving information on benefits and harms.⁴⁰*
65. We learned through our research that within the concept of adaptive licensing is the underlying rule that "all stakeholders will need to accept that initial approval is not just early but also conditional."⁴¹
66. In written evidence received we understand that discussions around AL have been around for some time. In evidence received by the Science and Technology Committee's report, *Bridging the Valley of death: improving the commercialisation of research*, Sir David Cooksey, Chairman of the Francis Crick Institute, said:
- Everybody welcomed it [AL] in 2006 as a concept. There have been lots of discussions, conferences etcetera about it; but, somehow, because it requires bureaucrats to take more risk and use new techniques, which are not necessarily proven to the last 'i' dotted and 't' crossed, you have a situation where that whole process of trying to shorten the approval cycle for drugs has run into a snowdrift because bureaucracy is standing in the way.⁴²*
67. Our panellists were supportive of an AL approach. Colin Pavelin, Head of Genomics and Rare Diseases at the Department of Health, saw adaptive licensing as an opportunity to bridge the gap between research and care and to enable the market authorisation process to bring more innovative medicines to the market. He said:
- I think it does open a window of opportunity for playing right through where we can start to take a slightly different approach to engaging with patients... whilst avoiding the gap we were just talking about, about patient safety. It is a wonderful way forward.⁴³*
68. Patient engagement is especially important for research into rare diseases as it is crucial to have a sufficient patient mass to be able to take forward clinical research.
69. We were shocked that the findings of a Muscular Dystrophy Campaign survey⁴⁴ for the inquiry uncovered that:
- Eighty-five percent of people with muscle-wasting conditions who responded to the survey have a poor or only partial understanding of how regulators assess new treatments.*

70. John Murray, Director of the Specialised Healthcare Alliance (SHCA), an organisation of over 80 patient-related organisations with an interest in rare conditions, also commented:

You obviously need to have sufficient data before you even go as far as adaptive licensing but I think there is a lot to be said, in principle, for looking at ways you can get treatments to patients sooner, in a managed context rather than, as has happened historically in the past, where once you're licensed you can just go hell for leather.⁴⁵

71. We learned that adaptive licensing is not only being considered by the working group set up by the MHRA but also by the EMA who will make recommendations for AL in 2015. In their written evidence, the UK Bio Industry Association said:

So-called adaptive licensing or staggered approval approaches are being discussed at European level through the EMA which is the proper place for such approaches to be considered as they are an EU competence. The UK Medicines and Healthcare products Regulatory Agency (MHRA) is a well-respected and high value regulatory body that can add much expertise to these discussions. Such approaches can learn from rare diseases which already utilise many flexibilities provided for within the regulatory landscape.⁴⁶

We look forward to the publication of the European Medicines Agency's findings into the utilisation of current licensing schemes and their recommendations for adaptive licensing. We call on the European Medicines Agency to bring forward the publication of their recommendations into adaptive licensing sooner than 2015, following discussion of this approach for a number of years. We also recommend that the European Medicines Agency support an approach around adaptive licensing, which would support drug development, licensing and patient access to innovative medicines in a managed and responsible way.

The appraisal and commissioning of drugs and technologies for rare diseases in England and Wales

72. In England and Wales, once a medicinal product for use by the NHS has received market authorisation, it will be appraised to evaluate its effectiveness (including cost-effectiveness).

73. We heard from the panel and in written evidence concerns about the decision to give the National Institute for Health and Care Excellence (NICE) the authority to evaluate new highly specialised technologies (including new medicines). This role had previously been carried out by the Advisory Group for Nationally Specialised Services (AGNSS).

74. We learned that prior to AGNSS there had been wide variation of how drugs for rare diseases were being commissioned. As a result of the Carter Review of 2006, AGNSS was established in 2010 to give independent oversight and advice to ministers on which highly specialised services (those with fewer than 500 patients or 500 or fewer procedures a year) should be commissioned nationally (in England). Dr Tony Hockley, former Department of Health Advisor and now at the CIVITAS Policy Analysis Centre, pointed out in written evidence:

At the end of 2011 in its Annual Report the new Group (AGNSS) reported that Ministers had agreed with all of the seven recommendations for national commissioning that it had recently made.⁴⁷

75. We heard from our experts that AGNSS was a well-respected body which facilitated the views and evidence from a wide network of patient groups, industry, clinicians, commissioners and other interest groups. Colin Pavelin from the Department of Health said:

AGNSS was very much respected as a group running specialised services and I think that's recognised.⁴⁸

76. In each session we heard concerns from our experts about the impact the termination of AGNSS would have on drug approval for orphan diseases if the standard evaluation process for common diseases would be used and applied to highly specialised technologies for rare diseases.

77. John Murray from the SHCA said:

As far as the evaluation of technologies specifically is concerned, well I can say that the interim technology which is basically agreed for the year end to March, is very closely aligned with the AGNSS frameworks so that is good news. It remains to be seen a) whether that is adopted for the longer term and b) how it is applied in practice, because you can have any kind of framework on paper but it's how the different criteria actually weigh up and a decision is taken in practice.⁴⁹

78. He added:

Our concern otherwise, as an alliance, is that you will have within NICE, if it sticks to that type of framework, two very divergent approaches: one for the generality of medicines and treatments, and one for highly specialised treatments. My worry is that that might make the former harder to defend against the latter because people with, I don't know, diabetes who can't get access to something, well that's because it doesn't meet the cost-effectiveness threshold but you have just passed something down the road for a very rare condition with a cost-effectiveness threshold that is ten times as great and I think that's the reason historically why there has been reluctance to bring it all together under NICE's auspices.⁵⁰

79. PTC Therapeutics added a call for clarity in its written evidence submission:

To minimise potential delays in access to effective treatments by UK patients with a high unmet need, it is important that there is additional clarity on the criteria that will be applied for assessing new treatments for rare diseases with limited data sets; the process for securing funding for a new treatment; and how implementation will occur.⁵¹

80. NICE describes in detail the process used for their technology appraisals in their 2013 online guide. Assessment of a drug for significant health benefit if given to patients for whom it is indicated is one of the central criteria for a referral for NICE appraisal:⁵²

The assessment process is a systematic evaluation of the relevant evidence (see section 3) available on a technology. The aim is to assess a technology's clinical and cost-effectiveness for a specific indication, taking account of uncertainty, compared with the appropriate comparator(s) listed in the scope. Assessment has 2

components: a systematic review of the evidence and an economic evaluation. Assessment, therefore, consists of an analysis of the quality, findings and implications of the available evidence (mainly from research). Strengths, weaknesses and gaps in the evidence are identified and evaluated.

Decisions on clinical and cost-effectiveness are made on evidence gathered for treating an indication of a drug rather than the population with a certain disease.⁵³

81. We have included in Appendix 4 of this report the case study of eculizumab, a treatment for atypical haemolytic uraemic syndrome (aHUS), which is a rare blood disorder. We noted with interest that Earl Howe, Parliamentary Under-Secretary of State at the Department of Health, in responding to a Written Parliamentary Question by Lord Walton of Detchant, referred to the affordability of the treatment in seeking further advice on its suitability:

Ministers accepted the view of the Advisory Group for National Specialised Services on the clinical effectiveness of eculizumab for the treatment of atypical haemolytic uraemic syndrome (aHUS) but wanted further advice on its suitability for direct commissioning taking account of its cost, benefit and affordability.

The department has asked the National Institute for Health and Clinical Excellence to develop guidance on the use of eculizumab for aHUS as the first topic to be evaluated through its highly specialised technologies programme.⁵⁴

82. Asked whether the NICE process would vary from the AGNSS process, Dr Alastair Fischer, Health Economist from NICE, told us:

I don't expect so, the whole thing will be done by the usual way of having an independent committee, which people can apply to and there will of course be a selection process determined within NICE to ensure that all the bases and opinions are covered. As far as the timings, it is expected that it will take either 24 weeks or 14 weeks depending on whether there is public consultation. And some of that can be within the timeframe, and it looks like that it's going to go ahead and go straight through. There can be a bit of collapsing of that time.⁵⁵

83. We also heard from the BIA that in a 2005 publication, 'Appraising orphan drugs', NICE called for a programme of orphan medicinal products that requires a special approach. Colin Pavelin from the Department of Health said:

I know that the Department of Health is starting to develop the plans for what the committee will look like; it is committed to ensuring that the quality and standards that AGNSS provided are replicated in the committee's remit.⁵⁶

We call on the National Institute for Health and Clinical Excellence to build on the framework established and validated by the Advisory Group for National Specialised Services which accepts that highly specialised services should be appraised using a separate evaluation framework to ensure that vulnerable patients with very rare conditions are not denied treatments on the grounds of cost following an inappropriate cost benefit analysis.

84. John Murray from the SHCA drew our attention to the definition of ultra orphan conditions and the subsequent evaluation and assessment of treatments:

I think there is potentially a problem around what you might describe as a population cliff in medicines evaluation, in other words if the patient population concerned is less than 500, then it goes into highly specialised technologies; if it's more than that it goes into the mainstream process and that seems to me a bit arbitrary.

85. Rare Disease UK (RDUK) has welcomed the consideration of the benefits to patients and promotes value-based pricing to address the relative patient populations of rare and very rare conditions:

RDUK supports efforts to facilitate better, more equitable access to effective medicines which improve patient outcomes and to improve the process for assessing new medicines for rare diseases. This includes consideration of a wider range of benefits to the patient alongside clinical effectiveness.

A caveat to this is that this framework is only used for medicines to treat very rare diseases affecting 500 or fewer patients. A single rare disease could affect up to approximately 26,000 people in England (most rare diseases will affect far less than this amount). As a result there is currently a significant gap between those medicines for less than 500 patients which could be eligible for AGNSS assessment and those medicines for between 500 and 26,000 patients which frequently fall to Individual Funding Request (IFR) panels. A considered approach to value-based pricing has the opportunity to rectify this situation.⁵⁷

86. The APPG supports the House of Lords Science and Technology Committee's recommendations on NICE's models for

evaluation, NICE's value-for-money consideration and that the UK Government's pricing and reimbursement systems should be fit for purpose:

We consider the NICE model for evaluating innovative treatments and cures to be inappropriate. It must devise suitable models that give appropriate consideration to the long-term savings sometimes offered by high up-front cost treatments.

Part of its [NICE] value-for-money consideration should be that early investment in this field could unlock other treatments with significant economic impact, both in terms of savings to the health system and increased potential work productivity.

The UK Government must ensure that its pricing and reimbursement systems are fit for purpose otherwise companies will base themselves in other countries.⁵⁸

Given that a number of very rare conditions affect more than 500 patients across the UK, we urge that NICE reconsider their approach in defining ultra-orphan and orphan conditions along these lines. As so-called personalised medicines develop, we seek clarification as to whether NICE will assess treatments relevant to total patient populations, or whether they would assess numbers affected by specific mutations.

87. Concerns were also raised about how patients with rare diseases and patient organisations would be represented in the appraisal process of NICE, which were emphasised by the Muscular Dystrophy Campaign's survey⁵⁹ revealing:

Ninety-five percent of patients say they want to play a part in the decision-making process when it comes to assessing new treatments.

Case study – kalydeco for cystic fibrosis

88. We heard details from NHS England about the success of the appraisal process which resulted in the commissioning of **Kalydeco** (Ivacaftor) for patients with cystic fibrosis.

89. The approval process around a new cystic fibrosis drug called Kalydeco (Ivacaftor) is a useful example of the potential challenges which may be ahead for rare and very rare conditions. The process took place under the guidance of the then NHS Commissioning Board during a time in between the old NHS and the new NHS system. Appendix 3 illustrates the different stages of approval for the new drug and also the uncertainty in Scotland and Wales regarding the rejection of the drug, creating inconsistency across the UK.

90. Paul McManus, Lead Pharmacist for specialised services, South Yorkshire and Bassetlaw, NHS England, was involved in the Kalydeco approval process within the NHS. He informed the APPG about the process and the learning points which can be extrapolated:

This is an area that I was involved in as part of a small team. We went through the process for the approval of Ivacaftor providing access under the NHS for patients with cystic fibrosis. It was quite a successful process – we ensured access for patients with cystic fibrosis at the beginning of this year even though the drug was only launched in July last year.

So it was quite a quick process to make a decision and that decision was made nationally, without any variation in access. It was successful in terms of communication with stakeholders – the Cystic Fibrosis Trust, the company, to clinicians at the beginning of last year about what was needed for the licensing process.

We had good co-operation from the company - the pharmaceuticals – providing the information needed to develop the health technology appraisal. We established that it wasn't on the NICE work plan and it wasn't going through the other process – the AGNSS process. We had to come up with a process which would allow the Specialised Commissioning Groups working on behalf of the PCTs to come up with a national decision.

Early communication and good communication with stakeholders was important, making sure patients were aware each step of the way – who is making the decision, what the decision will be – more the type of decision that was expected and communicated throughout.

One of the key learning points was responding to a unique situation and we had to set up a process to deal with that. Ideally we would want to look at and assess a high-cost drug within a framework and in the context of high-cost medicines for rare diseases in the pipeline and that's where we see the benefit of NICE looking at that whole range of medicines with a common framework.⁶⁰

91. John Murray from the SHCA further commented on the approval process for Kalydeco. He said:

I think it shows precisely...that NHS England does have this potential, if it chooses to use it, to show leadership in the field of rarer conditions and treatments for them.⁶¹

92. NICE made clear that there were a number of ways for patients to be involved but we felt their role would be more general rather than as a key part of the decision-making process. For instance, lay members are assigned to the new Highly Specialised Technologies Evaluation Committee, including at least one with an interest in ethics, with a proven track record of contribution to public discussion of ethical issues. Patients and patient organisations would have an opportunity only at the consultation phase to make their views known.

We welcome the leadership shown by the NHS in their appraisal process for Kalydeco and in particular their determination to communicate effectively with patient organisations. We recommend that the National Institute for Health and Clinical Excellence use this same rigour to ensure that patients are at the heart of the decision-making process. In their assessment of treatments for rare diseases, we call on the National Institute for Health and Clinical Excellence, NHS England and the devolved health authorities to draw on the expertise from relevant patient groups and neuromuscular clinicians – and not to settle only for lay members on the emerging committees involved in assessment procedures.

The commissioning of highly specialised technologies and specialised services

93. A number of panellists expressed concern about the decision to merge the ring-fenced funding for highly specialised services, which had previously been commissioned nationally by NHS Specialised Services, into the general NHS England budget. Paul Humphrey from Genzyme commented:

We did used to have a very functional and a very good system for the funding and treatment of patients with rare diseases...50 or so diseases were funded through that process (of national commissioning)... I think what we see now is the potential for very rare conditions being commissioned in the same way that the more common conditions are, and competing for the same funds, and just as Lord Walton says, it could be a situation where the loudest voice will secure the funds, and I think that offers a great potential risk to patients with extremely rare diseases and having rare disease services.⁶²

94. Lord Walton of Detchant shared similar concerns:

...the rare disease problem is going to grow and grow and grow, and the need for funding for these orphan and ultra-orphan drugs is going to increase steadily, and I think that if there was a possibility of getting a fund for the funding of drugs for rare diseases, orphan and ultra-orphan drugs, then that would be a great help. Now, I hope that our colleagues in the Commons would think about it.⁶³

We call on the Government to re-establish a ring-fenced fund for highly specialised technologies (formerly administered by NHS Specialised Services) to ensure that patients affected by rare diseases are protected and not denied treatment. We believe a new model is required to reimburse medicines in line with patient numbers, given the aim to treat over 200 rare conditions by 2020.⁶⁴

Importance of NHS care for research and delivering therapy

95. The inquiry focused on the vital link between high quality standards of specialist care for people with muscular dystrophy and related neuromuscular conditions and the research which can be conducted into these conditions.

96. We heard from Khurm Arshad about how the foundations need to be put in place on a consistent basis across all parts of the country:

Although we would like treatments to become available to patients when they come out on the market, there is no point in those treatments being purchased if there are gaps in care around the regions, because, if you've got children who are being given drugs and you've got no psychology provision or care advisors to monitor that, then we are going to take ten steps forward and we are going to take ten steps back at the same time. So, let's get involved quickly in terms of getting access to drugs and trying to streamline this process, but also at the same time, let's not forget there are gaps in care that need to be filled quite quickly in order for these two to work together.⁶⁵

97. We received several powerful testimonies of increasing concerns about the future management of muscle-wasting conditions, particularly focusing on access to specialist physiotherapy and hydrotherapy.

98. Mark Creswick told us about the uncertainty over future specialist physiotherapy for his son, Harley:

Before Harley started school he used to go to the Ryegate centre on a monthly basis to have physiotherapy to check on the flexibility of his muscles and they also showed him the different exercises to do on a daily basis to keep his legs as flexible as possible. Since he started school last September, the ways that the system works in the Sheffield area at the moment that you have to wait for the community physiotherapist to contact you. They contacted the school after chasing them in January, to say that they would try and come out to see them to explain what they can and can't do in school with PE and stuff like that, but they are not sure whether it will be this year, this school year, or when he starts into year one.⁶⁶

99. Emily Crossley highlighted the patchy provision of accessing services to support and manage her son's condition:

When we first received a diagnosis they didn't have one occupational therapist for the whole borough for 18 months, not one. When I applied for hydrotherapy someone just said to me, don't even bother fighting that battle because we are never going to get it. He has physio once every 12 weeks, it's really disgraceful. I feel very sorry for parents who are not in a Centre for Excellence as the local provision is negligible.⁶⁷

100. In our session about the patient experience, we heard about a top-down approach in which the patient still awaits information from their consultant about a potential clinical trial. Khurm Arshad, whose brother Auzair has Duchenne muscular dystrophy, said:

Our route to accessing clinical trials has always been through our paediatric consultant. I know there are various registries, like the Duchenne registry, which you can register on to but we've always seen it as a kind of top-down approach from our consultant really, and he's not been asked to participate in trials, but if he was we would consider it.⁶⁸

101. In the APPG's *Walton Report* into access to specialist neuromuscular care in 2009, Professor Kate Bushby from the Newcastle Muscle Centre explained how research and clinical expertise can be combined in a specialist centre:

If you have an area, e.g. Birmingham, where there are clinicians to look after both children and adults with neuromuscular diseases, and you had a push to build up a research team around them plus extra capacity for these clinical people to have academic time, you could see that building into a centre which is able to operate very effectively quite quickly and I think that model would work quite well.⁶⁹

We call on NHS England and the devolved health authorities to ensure Muscle Centres and clinics are able to deliver forthcoming treatments for neuromuscular conditions and are equipped with adequately trained staff and multi-disciplinary teams of health professionals to deliver treatments and monitor disease progression.

Future treatments for neuromuscular conditions are likely to extend lives and delay the progression of these often debilitating and life-limiting conditions. We call on the NHS and devolved authorities to provide individuals and families affected with essential services to aid mobility and to support independence – such as access to ongoing physiotherapy and hydrotherapy.

We were pleased to learn about the new ‘Innovation Fund’ of £50m which is open to applications from the new clinical reference groups established for rare conditions and specialised service. We call on the Clinical Priorities Advisory Group and the Rare Diseases Advisory Group to consider applications focused around innovative approaches in delivering care to patients and families affected by neuromuscular conditions.

It is clear that, should future treatments for neuromuscular conditions emerge, then the relevant Clinical Reference Groups (CRGs) would have a role to play in providing advice to NHS England on funding and delivering treatments. We are concerned that, without a ‘neuromuscular CRG’, it is unclear which of the current CRGs will consider these important issues: Paediatric Neurosciences, Neurosciences, or the Multi-system Disorders CRGs. We call on NHS England to support the establishment of a ‘Neuromuscular CRG’, which could be best placed as part of the current Multi-system Disorders CRG, given the number of relevant neuromuscular clinicians currently on this particular CRG.

Devolved countries

102. We explored the different methodologies used for appraisal of orphan diseases throughout the UK.

103. We noted with interest the comments on the process in Scotland by Brendan Martin from Genzyme:

In Scotland they took a different view, they wanted to use the uniform health technology appraisal across the board, and be completely consistent with one disease against another. The experience tells us that, of the orphan diseases, they tend to reject a higher proportion of drugs than they do drugs for common diseases. When it comes to the ultra-orphans, they reject 90 percent of them; it is a much, much higher proportion of ultra-orphan drugs that get rejected by the Scottish Medicines Consortium (SMC).

In our experience, for example, myozyme was rejected by the SMC, and we dreaded the day when a child in Scotland was going to be diagnosed with infantile onset Pompe disease, because we knew they had a very limited time window that they could survive, and we knew that it was going to be immensely difficult to get treatment made available to them. That day came, and it turned out that a decision was made to set aside the SMC recommendation and make treatment available to the child and since then, with the isolated three cases that have arisen in Scotland eventually, provision has been made through individually requested patient treatment support.⁷⁰

104. Dr Liz Philpots from the AMRC also commented on the need for a streamlined process between different countries in the UK:

As I understand, the fact is that you’ve got, in England and Scotland, two different regulators who are looking at a piece of evidence and possibly coming to two different conclusions. It shows that we need to have real clarity on how decisions are made and what regulators are looking for in order that when you’re devising a clinical trial and study to provide that evidence, you know what you’ll be marked against.⁷¹

105. Dr Rohit Batta from GSK informed us of the experience in Scotland where they sought uniform health technology appraisal of all diseases. He said:

The experience tells us that, of the orphan diseases, they tend to reject a higher proportion of drugs than they do for common diseases. When it comes to the ultra-orphans, they reject 90 percent of them.⁷²

106. There appeared to be a more positive perspective in Wales and Northern Ireland from the evidence which we gathered, with Brendan Martin from Genzyme also pointing out:

[In] Wales [they] have the All Wales Medicines Strategy Group, and they have tended to approve ultra-orphan diseases, although sometimes in more limited circumstances than is the case in England. Northern Ireland tend to adopt the English guidelines, although they don’t always have funding available to treat a patient immediately and there certainly is a formal waiting list system, that’s managed by a very smart and helpful geneticist in Northern Ireland who triages patients across the landscape, and makes sure that the greatest need is served with the money that is available. So it’s a more informal system, but so far it seems to work.⁷³

We call on the Scottish Medicines Consortium to review the way in which they assess treatments for rare diseases, following evidence received that many vulnerable patients with life-limiting conditions are being denied essential, life-changing drugs.

Common questions and answers

What is an orphan disease?

Orphan disease implies a rare disease. The EU defines an orphan disease as a disease of fewer than five per 10,000 population.⁷⁴ In the UK, a rare disease may affect up to about 30,000 people. The majority of rare diseases will affect far fewer than this – perhaps just a handful, or even a single person throughout the UK.

Eighty percent of rare diseases have a genetic component; they can be caused by a mutation in a single gene, by the action of a combination of different genes, or by chromosome abnormalities. There are around 7,000 known rare diseases. It is known that around seven percent of the population will be affected by a rare disease at some point in their life.⁷⁵

What is an ultra-orphan disease?

An ultra-orphan disease has no formal legal definition. Nevertheless, it has come to describe a very rare condition.

In the UK, there is no formal legal definition for an ultra-orphan disease and services are not commissioned as such. Instead, services are commissioned as being for specialised and highly specialised services. For example, previously, the National Specialised Services commissioned 70 highly specialised services nationally. Generally, these were services that affected fewer than 500 people across England or which involved services where fewer than 500 highly specialised services were undertaken each year.⁷⁶

About muscular dystrophy and related neuromuscular conditions

There are more than 60 different types of muscular dystrophy and related neuromuscular conditions. It is accepted that approximately 1,000 children and adults for every one million of the population are affected by muscle-wasting conditions in the UK. It is therefore estimated that some 70,000 people are affected by a neuromuscular condition in the UK.

Many neuromuscular conditions are orphan conditions and indeed some are very rare and are regarded as ultra-orphan. Neuromuscular conditions can be genetic or acquired and, with few exceptions, there are no effective treatments or cures.

Are there treatments available for neuromuscular conditions?

With few exceptions there are currently no known treatments or cures for muscular dystrophy or related neuromuscular conditions.

Pompe disease is caused by a lack of the acid alpha-glucosidase enzyme (which breaks down glycogen in muscle) which leads to a build-up of glycogen which in turn causes muscle weakness. The condition can be treated using an enzyme replacement therapy called myozyme. Because the drug must be given by infusion, in the UK, myozyme can only be administered at certain specialist centres.

Myasthenia gravis is caused by the body's immune system mistakenly attacking a protein which is needed to convey the electrical signals from the nerves to the muscles. There are an estimated 9,000 people in the UK affected by myasthenia gravis. The condition can be managed using immune-suppressants and drugs which stop the targeted protein being broken down by our body. This can improve muscle contraction and strength but can cause side-effects such as cramps. More severe myasthenia gravis can be treated with techniques called plasma exchange or intravenous immunoglobulin treatment. While these treatments can quickly control more severe symptoms they are short-lasting – only a few weeks – and are only used to treat the more severe cases.

What is a clinical trial?

A clinical trial is a type of clinical study which involves using volunteers to test potential treatments.

*'In a clinical trial (also called an interventional study), participants receive specific interventions according to the research plan or protocol created by the investigators. These interventions may be medical products, such as drugs or devices; procedures; or changes to participants' behavior, for example, diet. Clinical trials may compare a new medical approach to a standard one that is already available or to a placebo that contains no active ingredients or to no intervention. Some clinical trials compare interventions that are already available to each other. When a new product or approach is being studied, it is not usually known whether it will be helpful, harmful, or no different than available alternatives (including no intervention). The investigators try to determine the safety and efficacy of the intervention by measuring certain outcomes in the participants.'*⁷⁷ **US National Institute of Health**

Are there any treatments for muscular dystrophy and related neuromuscular conditions currently in clinical trial?

A number of clinical trials of potential treatments for certain types of neuromuscular conditions are underway and it is hoped that these will lead in time to the introduction of new treatments that can slow down or arrest the progressive nature of these often devastating conditions.

Perhaps the most notable is exon skipping technology, a potential treatment for some boys affected by Duchenne muscular dystrophy. We received detailed information about the latest clinical trials into the potential exon skipping drug drisapersen. Drisapersen is an antisense oligonucleotide (or molecular patch) for exon 51 of the dystrophin gene, which we were told could benefit up to 13 percent of the Duchenne muscular dystrophy population who have certain specific mutations. We heard encouraging results of a Phase 2 clinical trial which were reported by GSK in April 2013. GSK and Prosensa are now conducting a Phase 3 clinical trial of drisapersen, involving over 180 boys. This is a truly global study with various sites in Europe, South Korea and Chile. The results of the trial will be available in September this year.

PTC Therapeutics are currently starting a phase 3 international trial of the potential drug, ataluren, and are also in discussions with the regulatory authorities in the EU to try to reach an agreement on the path they should take towards getting ataluren approved. In the Phase 2b trial a low dose of ataluren increased the distance boys with Duchenne muscular dystrophy in the early stages after diagnosis could walk in six minutes.

Sarepta Therapeutics has announced that they plan to submit a licensing application for the exon skipping drug, eteplirsen, early in 2014. If the application is successful, Sarepta could be given permission to market eteplirsen in the USA. The company has also announced further details of a Phase 3 trial being planned for next year and given an update on the results of the Phase 2b trial that is ongoing.

Last year, clinicians in France undertook a Phase 1 clinical trial of a gene therapy for limb girdle muscular dystrophy type 2C (LGMD2C). The trial organisers used a virus to introduce a functional copy of the gamma-sarcoglycan gene – which is mutated in LGMD2C – into one wrist muscle of nine people with LGMD2C. Participants were monitored for up to six months and researchers found that all three participants who received the highest gene therapy dose and one patient from the middle-dose group had gamma-sarcoglycan protein (produced from the functional gene) present in the injected muscle. Importantly, none of the participants suffered from any serious side-effects.

This trial provided proof of principle that a virus could be used to deliver a functional copy of the gamma-sarcoglycan gene into muscle to treat LGMD2C. However, this trial was primarily aimed at testing the safety of the therapy and further trials will be needed to determine if the gamma-sarcoglycan that is produced has a positive benefit for muscle strength or function.

How do you obtain approval of a clinical trial for medicines for human use in the UK?

In accordance with The Medicines for Human Use Regulations (2004)⁷⁸ and subsequent amendments⁷⁹, researchers wishing to conduct a clinical trial for medicines for human use must gain ethical approval from the National Research and Ethics Service; authorisation from the Medicines and Healthcare Products Regulatory Agency and approval from the host organisation – if the research is NHS-based then it requires NHS Research and Development approval.

Researchers may also require approval from other authorities, such as the Human Tissue Authority licences, which regulates the use of human tissue, and, the Human Fertilisation and Embryology Authority, which regulates the use of material derived from human embryos. Individual submissions have to be made to each agency in order to gain approval and authorisation for a clinical trial. Submissions cannot be made in parallel but in a sequential process over time.

Are there any ways of speeding up access to new medicines?

EU Schemes

The EU has regulated for a number of schemes to support drug development, licensing and patient access. They are conditional approval, exceptional circumstances and accelerated assessment.⁸⁰

Market authorisation under exceptional circumstances is granted when comprehensive data including a positive benefit:risk balance based on scientific data cannot be provided. Specific reasons have been legislated for exceptional circumstance, such as 'it would be contrary to generally accepted principles of medical ethics to collect such information.'⁸¹ Decisions made under this scheme are reviewed annually and do not usually lead to 'normal' market authorisations as the necessary scientific data cannot be provided.

Conditional market authorisation (CMA) was developed by the EMA for medicines of orphan diseases which were seriously debilitating or life-threatening. A conditional authorisation may be granted without all the clinical data required for a full

licence but where the benefit:risk balance is positive and other requirements are met. Conditional market authorisation is also subject to specific obligations including the completion of ongoing studies and is valid for one year on a renewable basis. CMA can become a 'normal' market authorisation once the incomplete studies are provided.

Accelerated assessment reduces the assessment process from 210 days to 120-150 days. A sponsor would apply and be considered for accelerated review when the medicinal product is '*of major interest from the point of view of public health and in particular from the view point of therapeutic innovation*'.⁸²

UK Schemes

Individual patient supply: In EU regulations, compassionate use refers to the provision of a drug to patients before marketing authorisation (a 'licence') has been granted.⁸³ Compassionate use is covered by strict regulations; the drug company can only supply the product to named patients (and not for example give a supply to a hospital for use in any patient).

Fast Track Assessments: The MHRA provides a fast track procedure for specific new medicines with which there are convincing reasons for believing that the medicine would provide a major breakthrough in the treatment of patients for certain conditions.⁸⁴

The proposed UK Earlier Access Scheme: As part of the Government's Strategy for UK Life Sciences, the MHRA undertook a public consultation last year (July-October 2012) on proposals to introduce an earlier access to medicines scheme in the UK with the aim of increasing 'the speed and efficiency of routes to market approval for certain innovative, breakthrough medicines'.⁸⁵

The Muscular Dystrophy Campaign responded to the MHRA Early Access Scheme consultation and welcomed their intention to ensure swifter access to promising treatments for patients with debilitating and/or life-limiting conditions such as muscular dystrophy. **The MHRA is yet to publish the findings of their consultation.** It would be up to Scotland, Wales and Northern Ireland to determine if they should be part of this scheme.

Adaptive Licensing: Although not currently available as a regulatory scheme, adaptive licensing is being considered by the MHRA and at an EU level. Work to better understand adaptive licensing and how it might be used has received Ministerial support through the Strategy for UK Life Sciences.

We learned through our research that within the concept of adaptive licensing is the underlying rule that 'all stakeholders will need to accept that initial approval is not just early but also conditional'.⁸⁶

What is the appraisal process for highly specialised drugs and technologies in England and Wales?

Once market authorisation has been granted, a drug can only be accessed by patients through the NHS in England and Wales once it has been appraised by NICE and then approved for commissioning by NHS England and for Wales, the Welsh Specialised Services Committee (see arrangements for Scotland and Northern Ireland below).

In 2010, the Advisory Group for Nationalised Specialised Services (AGNSS) was set up to advise ministers on which highly specialised services should be commissioned nationally, the centres that should provide them and the annual budget for new and existing nationally commissioned specialised services.

One of the key criteria for assessment by AGNSS was 'that a drug's patient's [sic] population should be less than 500 across England'.⁸⁷ In its 2011 Annual Report, AGNSS reported that Ministers had agreed and supported all of the seven recommendations for national commissioning that had recently been made.⁸⁸

In a House of Lords debate on 18 July 2012, the Parliamentary Under-Secretary of State for Department of Health, Earl Howe, announced that NICE would 'take on the assessment of very high-cost, low-volume drugs from April 2013'.⁸⁹

AGNSS ceased to exist from 31 March 2013. NICE is currently recruiting for professional and lay members of their Highly Specialised Technologies Evaluation Committee.⁹⁰ The Committee will have responsibility for evaluating the benefits and costs of a small number of medicines aimed at treating patients with very rare diseases and very complex healthcare needs. Their evaluation will be considered within the context of national commissioning by the National Commissioning Board.

The Welsh Assembly Government has an agreement in place with NICE covering the Institute's technology appraisals, clinical guidelines and interventional procedure guidance, which all continue to apply in Wales.⁹¹

Value-based pricing: The value of medicine should not only be measured in relation to the disease itself, but also the value it can bring to healthcare system as a whole and to wider society.

The commissioning of highly specialised services in England

From the 1 April 2013, NHS England (formerly the NHS Commissioning Board) is responsible for commissioning all specialised services. Clinical Reference Groups 'will be responsible for providing NHS England with clinical advice regarding specialised services, and for the delivery of key 'products', such as service specifications and commissioning policies, which enable NHS England to commission services from specialist service providers through the contracting arrangements overseen by its area teams'.⁹²

Previously, NHS Specialised Services had a separate, ring-fenced fund to commission about 70 highly specialised services that affected fewer than 500 people across England or which involved services where fewer than 500 highly specialised procedures were undertaken each year.⁹³ This fund has been merged into an overall budget for all NHS services commissioned across England.

The appraisal process of highly specialised services in Scotland

The Scottish Medicines Consortium is responsible for advising NHS boards and their Area Drug Therapeutics Committees across Scotland about the clinical and cost-effectiveness of all newly licensed medicines, all new formulations of existing medicines and new indications for established products (licensed from January 2002).

The commissioning of highly specialised services in Scotland

National Services Division (NSD) is responsible for the commissioning of nationally designated highly specialist services and screening programmes that are generally concerned with the diagnosis and treatment of very rare diseases. NSD receives top-sliced, ring-fenced funding from the Scottish Government Health Directorates (SGHD) to commission and performance-manage these services.

In January 2013, the Scottish Government launched a £21m fund to cover the cost of 'orphan' medicines, which is active from March 2013 until April 2014. The fund is specifically used for drugs to treat diseases affecting fewer than 2,000 people. The fund only covers the cost of those treatments which have not been approved by SMC. For instance, it was reported that the drug Kalydeco which did not receive approval from SMC will now be funded for patients living in Scotland using this fund.⁹⁴

Witnesses

Tuesday 26 February 2013 – First inquiry session

Oral evidence was provided by:

Dr Rohit Batta, Global Medical Leader – Neuromuscular Disorders, GlaxoSmithKline Rare Diseases Unit

Paul Humphrey, Marketing Manager, UK and Ireland, Rare Diseases Division, Genzyme

Brendan Martin, General Manager, Genzyme UK and Ireland

Allison Morgan, Vice President, Clinical Research and Development, Prosensa Therapeutics

Professor Francesco Muntoni, Chair of Paediatric Neurology, Institute of Child Health, Dubowitz Neuromuscular Centre, University College London

Professor Dominic Wells, Neuromuscular Disease Group, Department of Comparative Biomedical Sciences, Royal Veterinary College

Tuesday 23 April 2013 – Second inquiry session

Oral evidence was provided by:

Khurm Arshad, whose brother has Duchenne muscular dystrophy

Mark Creswick, whose son has Duchenne muscular dystrophy

Emily Crossley, whose son has Duchenne muscular dystrophy

Allan Muir, Development Director at AGSD-UK, whose son has Pompe disease

Tuesday 18 June 2013 – Third inquiry session

Oral evidence was provided by:

Dr Alastair Fischer, Health Economist, National Institute for Health and Clinical Excellence

Dr Ian Hudson, Head of Licensing, Medicines and Healthcare Products Regulatory Agency

Paul McManus, Lead Pharmacist – specialised services, South Yorkshire and Bassetlaw, NHS England

Tuesday 9 July 2013 – Fourth inquiry session

Oral evidence was provided by:

John Murray, Director, Specialised Healthcare Alliance

Colin Pavelin, Head of Genomics and Rare Diseases, Department of Health

Dr Liz Philpots, Head of Research, Association of Medical Research Charities

Purpose of the inquiry

The inquiry was launched in February 2013 to carry out an in-depth investigation into the future of access to high cost drugs and therapies for orphan and ultra-orphan diseases and the challenges of market approval, regulation and reimbursement. This arose at a time of significant structural changes within the NHS, as well as a drive towards cost saving measures.

Through the Strategy for UK Life Sciences, the Government has shown its commitment for scientific innovation and to making innovations available to patients as quickly as possible. Yet, just last year, patients with cystic fibrosis experienced first-hand the challenges of the regulatory and commissioning process as they tried to seek access to a new medicine, Kalydeco. Access was eventually granted but required significant determination and pressure by patients and patient organisations.

We also heard of the recent move by the Government to reject advice on the commissioning of a new and potentially life-saving drug, Soliris (eculizumab), to treat a rare blood disorder – atypical haemolytic uraemic syndrome (aHUS). Ministers declined to implement the recommendation of the Advisory Group for National Specialised Services (AGNSS) that Soliris (eculizumab) be made nationally available on the NHS.

Barriers to scientific innovation into treatments for rare diseases can arise at a number of levels: from clinical trial approval to the appraisal and commissioning of new medicines for rare diseases. The process is even more uncertain for innovative medicines with the potential to treat only a subset of people with a rare disease. Exon skipping technology for Duchenne muscular dystrophy, for example, is currently in Phase 3 clinical trial. Each potential exon skipping drug (or molecular patch) will only treat certain specific mutations that cause Duchenne muscular dystrophy and under current procedures, it is uncertain whether future molecular patches for rarer mutations would have to go through the same lengthy regulatory requirements.

Until recently, the Advisory Group for National Specialised Services (AGNSS) had responsibility for the appraisal of ultra-orphan drugs, while NHS Specialised Services had responsibility for the commissioning of services for ultra-orphan diseases as well as a ring fenced fund to subsidise treatments for the drugs to treat these diseases.

Earlier this year, AGNSS and NHS Specialised Services were disbanded. The work of AGNSS to appraise ultra-orphan drugs will now be taken up by the National Institute for Health and Clinical Excellence (NICE), which is already responsible for the appraisal of drugs for common conditions. NHS England will take on the duties of the NHS Specialised Services to commission services for these conditions. The disbanding of the specialised organisations has caused considerable anxiety among the patient, clinical and scientific community, especially at a time when new potential therapies are showing considerable promise for some neuromuscular conditions. Until now there has been little clarity on what the new appraisal and commissioning processes will look like.

The parliamentary inquiry has received both written and oral evidence that underlines the need for urgent action to clarify the regulatory and commissioning processes of high cost drugs and therapies for this vulnerable group of patients with rare and very rare diseases.

Terms of Reference

The terms of reference for the inquiry are as follows:

“To determine the future of access to high cost drugs for orphan diseases in the NHS; the regulatory and reimbursement environment for orphan drugs; and the future of funding arrangements for research into treatments for children and adults with rare diseases”.

Written Evidence and Additional Evidence

All Party Parliamentary Group for Muscular Dystrophy, *Access to specialist neuromuscular care: The Walton Report, August 2009*

Association of Medical Research Charities, *Vision for Research in the NHS*, May 2013

BioIndustry Association, *Response to the All Party Parliamentary Group for Muscular Dystrophy Inquiry*, May 2013

Genetic Alliance UK, *Submission to the All Party Parliamentary Group for Muscular Dystrophy Inquiry*, July 2013

Muscular Dystrophy Campaign, *Survey*, June 2013

PTC Therapeutics, *Response to the All Party Parliamentary Group for Muscular Dystrophy Inquiry*, July 2013

Rare Disease UK, *A new value-based approach to the pricing of branded medicines*, March 2011

Dr Tony Hockley, *One small step for the NHS, but one giant leap for its principles?*, CIVITAS Policy Analysis Centre, May 2013

Parent Project Muscular Dystrophy (PPMD), United Parent Project Muscular Dystrophy (UPPMD), PTC Therapeutics, Prosenza – *Duchenne muscular dystrophy film*

46 patient and family testimonies, provided to the Muscular Dystrophy Campaign in June 2013

Case Study: Kalydeco

[Kalydeco treats the fundamental defect in people with cystic fibrosis and a specific mutation called G551D which affects about four percent of the CF population in the UK. A series of studies show that it has a major impact on a range of symptoms. It is the first drug that treats the root cause of cystic fibrosis, and further trials using Kalydeco in combination with a substance called VX-809 have shown a potentially positive impact on the more common F508del mutation.]

Timeline of key decisions:

- January 2012: the European Medicines Agency (EMA) started the fast track process to review Kalydeco for licensing in the EU and UK. This news was mirrored in the US where the Food and Drug Administration (FDA) agreed to fast track Vertex's application to have Kalydeco licensed in the US.
- 1 February 2012: The US Food and Drug Administration approved Kalydeco. It was approved for use in people with CF aged six and older who have at least one copy of the G551D mutation. The CF Trust said they wanted to ask the European Medicines Agency (EMA) to push the approval process in the EU through more quickly, to allow this medicine to become available for patients with CF in the UK.
- 25 May 2012: Kalydeco passes the first European regulatory hurdle. The European Committee for Medicinal Products for Human Use (CHMP) recommended that Kalydeco should be approved within the EU for people with CF aged six and over and who have at least one copy of the G551D mutation. The final decision to approve the treatment rests with the European Commission which generally follows the recommendations of the CHMP. Marketing approval is typically approved within three to four months.
- 22 June 2012: It was announced that a decision on marketing approval should be made by late August 2012. For patients and families, final decisions on the availability of the drug to NHS patients by prescription will be taken by NHS commissioners following negotiations with the manufacturer Vertex.
- 27 July 2012: Kalydeco receives approval from European regulators —the European Medicines Agency (EMA) approves Kalydeco. The decisions about whether Kalydeco will be available to the four percent of patients in the UK with this G551D mutation rests with the NHS.
- 7 August 2012: The Clinical Reference Group (CRG) for Cystic Fibrosis —made up of NHS clinicians, a commissioner, a public health professional and patient representatives – was asked to advise on the drug which received regulatory approval by the European Medicines Agency.
- 20 August 2012: Statement from North of England SCG on behalf of the four Specialised Commissioning Groups in England:

“A new medicine for the treatment of cystic fibrosis (CF), called Ivacaftor, has now received European approval and will be launched in the UK over the next few weeks.

While Ivacaftor will not be appraised by NICE, a robust clinical and economic evaluation of the medicine has been commissioned on behalf of the four Specialised Commissioning Groups (SCGs) in England from the NHS National Institute for Health and Research, Health Technology Assessment programme at the University of Southampton.

This work is being co-ordinated by the Yorkshire and the Humber office of the North of England Specialised Commissioning Group, which is the national commissioning lead for cystic fibrosis.

The draft evaluation report has been discussed with members of the national Clinical Reference Group (CRG) for cystic fibrosis, which includes patient, clinician and NHS commissioner representatives. The final report, together with recommendations from the CRG, will inform a single national decision on the funding of Ivacaftor in England, anticipated in autumn 2012. This decision will be taken by the four regional SCGs.”
- 25 September 2012: The Clinical Priorities Advisory Group (CPAG) met.
- 27 September 2012: The Cystic Fibrosis Trust called on the NHS and Vertex to speedily resolve all outstanding cost issues relating to Kalydeco, to ensure patients with the G551D mutation in cystic fibrosis (CF) benefit from this groundbreaking treatment as soon as possible. The call comes after this week's meeting of the Clinical Priorities Advisory Group (CPAG), set up by the NHS in England to assess Kalydeco. The CPAG agreed that Kalydeco provided

clinical benefit but deferred discussion of the drug's cost effectiveness to a further meeting with Vertex in a month's time. This meeting then made recommendations to commissioners to take a final decision about funding in December 2012.

- 19 December 2012: Decision by the NHS to fund Kalydeco from 1 January 2013. This is for patients in England with cystic fibrosis (CF) aged six and over and who have at least one copy of the G551D mutation.
- 14 January 2013: After rejection by the Scottish Medicines Consortium, the Scottish Government set up the Rare Conditions Medicines Fund of £21m to include Kalydeco running from March 2013 to April 2014.
- 30 April 2013: Kalydeco could be denied to people in Wales if a Preliminary Appraisal Recommendation by the All Wales Medicines Strategy Group (AWMSG), is accepted on 8 May.
- 10 May 2013: After a recommendation from the AWMSG not to fund Kalydeco, Welsh Assembly Government Health Minister, Mark Drakeford AM, announced that Kalydeco will be funded in Wales.
- 12 June 2013: Scottish Medicines Consortium again rejects funding for Kalydeco in Scotland but Kalydeco remains funded under the Rare Conditions Medicines Fund.

Case Study: aHUS

'Atypical haemolytic uraemic syndrome (aHUS) is a rare blood disorder that is often, but not always, inherited. Prior to the licensing of eculizumab, there was no treatment available to prevent death or organ damage, and up to 25 percent of patients would die following their first attack. The total number of patients in England in 2012 was 140 and at any one time in England there will be between 2.7 and 5.5 cases per million population with a confirmed diagnosis. Eculizumab therefore falls into the category of an 'ultra-orphan drug' for an 'ultra-rare disease'.

In the case of eculizumab, the decision to recommend national commissioning of the treatment appears to have been relatively straightforward, with almost universal support among the 17 participating members. AGNSS assessed, for example, that:

"It seems clear from the evidence presented that the drug is effective in halting the disease process. It is close to the top end of the scale of effectiveness. Preventing the disease process, which is active throughout the body, improves quality of life in patients with long-term aHUS. In newly diagnosed patients, a particular benefit is in preventing kidney damage, so that newly diagnosed patients will not go on dialysis. The drug will also enable patients already on dialysis to receive a transplant."

With regards to the cost of treatment with eculizumab the AGNSS assessment concluded that the cost per QALY:

'is in the lower end of the range of costs per QALY which have been estimated for the ultra orphan drugs, which is as expected if the drug is highly effective.'

The Group, therefore, recommended to ministers that as the number of patients rises owing to the national commissioning of an effective treatment then the price of the treatment should be renegotiated with the manufacturer. AGNSS initially assumed that as a result of its recommendations a national service for the management of patients with aHUS and the commissioning of eculizumab for such patients would be available from October 2012, although this was revised to 1 January 2013 by the hospital that would act as the national centre for this service.

But after several months of delay, the Health Minister, Earl Howe, announced in January 2013 that eculizumab would be subjected to a second assessment, under a new system for specialised services to be established within NICE sometime after the NHS reforms of April 2013.⁹⁵

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