WHY MEDICINES MATTER

IMPROVING ACCESS TO MEDICINES FOR RARE CONDITIONS IN SCOTLAND

GENETIC ALLIANCE UK

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WELCOME

Access to effective, often life transforming or life changing treatments for people living with a rare condition form a significant part of the approach to providing good care. In a climate where 5% of known rare diseases have a licensed treatment, it is essential that these treatments are available and accessible to clinicians as part of the holistic care package they provide to people living with a rare condition.

The Scottish Government has embraced the call from the rare conditions community to provide greater access to innovative treatments. Over the past decade policies and processes have been implemented to address the frequent challenge of the gap between the data requirements of regulatory bodies such as the European Medicines Agency (EMA) and the Medicines Healthcare Regulatory Agency (MHRA) and the Scottish Medicines Consortium (SMC) who are responsible for ensuring Scotland provides the best value to the whole population within a finite resource.

However, people living with a rare condition are often left frustrated when their clinician is unaware or unable to access the newest innovation that has the potential to change the course of their disease. Despite changes implemented in 2016, resulting in an overhaul of the SMC processes for reviewing medicines for rare conditions, recent statistics suggest that only 47% of the 47 medicines approved by the EMA between 2016 and 2019 were routinely reimbursed in Scotland on the 1st January 2021. This is in comparison to England where 72% of these medicines were reimbursed.

'Why Medicines Matter' provides a useful insight into the challenges and experiences of all stakeholders involved in ensuring medicines for rare conditions are accessible in a timely fashion. One thing that has been clear throughout the project is the positive intent that exists to improve care for people living with rare conditions even when challenges exist.

With that in mind, it is hoped that this magazine and the work of the 'Why Medicines Matter' project will set the tone for future conversations amongst key stakeholders, as Scotland develops its Action Plan in response to the UK Rare Diseases Framework. This tone needs to be one of collaboration and engagement and a plan that recognises the challenges each other face in bringing access to medicines in rare diseases and seeks solutions that deliver improved access for those who need it the most – people in Scotland living with a rare condition!

WHY MEDICINES MATTER TO ME

No one ever envisions their future and thinks 'hey, maybe one day I'll be a patient.'

It's a raffle of the worst kind, the one no one wants to enter and, after admiring the prize selection, no one wants to win. Aged five, someone must have bought me one of those little paper tickets and I won. I won a future of emergency admissions, ambulances, A&E, waiting rooms, appointments, prescriptions, repeated pneumonias, major operations, IV antibiotic and liquid diets. It really was the prize that just kept on giving.

Every day I rattled with 30+ tablets as more parts of my body began to fail; meds for pain, meds to stop me being sick, meds for skin reactions, meds to treat infections, meds to help me sleep, meds to control my heart, meds to support my lungs, meds to make my tummy work.

'It's beyond me', 'I can't help you I'm afraid', 'If my clever colleagues haven't worked it out, I don't think I'll be able to'.

When they couldn't find the answer, the doctors passed me on. I was sent from 'ologist' to 'ologist' like a hot potato.

'It won't be that it's very rare,' doctors said to me again and again over the years.

'If it wasn't rare, wouldn't we have found it already?' I posed.

In 1940, medical researcher, Theodore Woodward stated 'When you hear hoofs, think horse, not zebra.' The odds are patients have common diagnoses rather than rare ones. Day one, I understood Theodore Woodward's sentiment but 13 years down the line, his theory was proving to be a real barrier. I was facing the hard truth that I was 100% zebra. This came with another hard truth; most medics prefer horses.

Just at the point when the pneumonias were spiralling out of control, the IV antibiotics were no longer working and I was told there was nothing the medics could do, I tested positive for Tuberculosis. It eventually turned out I'd been living with 13 years of undiagnosed active M. bovis Tuberculosis from drinking unpasteurised milk (from my great aunt's farm when I was five years old). Yes, a cow, quite literally, ruined my life. I commenced 18 months of lifesaving chemotherapy and antibiotic treatment.

When I thought I'd finally got rid of that 'patient' label and had my life back, in 2018 I went into my first life-threatening adrenal crisis (turns out having TB for that long can really mess up your body). Throughout my twenties I have now found myself back in the healthcare system, I so wanted to leave behind. For the last four years I have been navigating life with adrenal failure; four years of ambulances, life-saving emergency injections and now a hydrocortisone pump injecting steroid through a cannula into my body 24/7 to keep me alive.

With both of my conditions, it hasn't just been a case of being ill, it has been a constant battle; a battle to be believed, a battle to be diagnosed and, eventually, a battle to be treated. I have never fitted the medical textbook and this has proven a vulnerable, scary and lonely place to be. My journey is proof that diagnoses and treatments are out there but it will sometimes require more time, thought and energy to uncover and access them.

Follow Tilly's journey on Instagram @thattillyrose

REFLECTIONS ON THE REVIEW OF ACCESS TO NEW MEDICINES IN SCOTLAND

The need for NHS Scotland's Review of Access to New Medicines published in December 2016 reflected in part, the challenge of reconciling increasing therapeutic opportunities and expectations with a healthcare system constrained by finite resources.

Healthcare funding continues to increase year on year however the increase does not and never will keep pace with the growing number of options in drug and non-drug therapies and the increasing range of complex and sophisticated investigations.

The potential for healthcare to consume resources will always outstrip the resources which are available. The resources are not only financial. This was the case in 2016 and arguably since then the gap between the pace of expansion of options and the resource shortfall has widened further. COVID-19 serves as a powerful example of an unanticipated impact requiring vast resources.

When RANMed was published it was heartening that the Cabinet Secretary for Health accepted all the recommendations as several were far-reaching and challenging. The Review highlighted difficulties with data sets and data collection not just in relation to access to medicines but to benefit gained from access. It also highlighted the challenges posed by low-volume high-cost medicines targeted at small numbers of people with rare and often highly complex conditions and in some instances offering treatments where none had previously existed.

A major conclusion of the Review was that while the processes of the Scottish Medicines Consortium (SMC) were robust and effective for the majority of medicines, they worked less well with the newer low-volume high-cost medicines which had specific considerations requiring a modified approach to their evaluation.

The considerations included the small numbers of people likely to be treated, the use of traditional measures of cost-effectiveness and value, the difficulties establishing evidence of efficacy and the need for on-going evaluation. In response to the Review work has been done by SMC, NHS Scotland, the Scottish Government, the pharmaceutical industry and representatives of patients and families. This has included refining definitions, particularly as they relate to orphan conditions and medicines, establishing better data sets and data collection systems and introducing mechanisms which allow medicines to continue to be evaluated and reviewed after SMC publishes its advice.

The impact of these measures has been not just to increase people's access to new medicines, including those for rare conditions, but to give those people, their families and the professionals involved in their care, confidence that the increased access is resulting in benefit through improved health outcomes and quality of life. Looking forward, the challenge is only likely to intensify as more therapeutic options emerge for more people with more conditions.

It will be important therefore that the collaboration between the various stakeholders continues to both reflect and meet the nature of the evolving challenge.

DRIVING CHANGE THROUGH PERSONAL EXPERIENCE

By Lesley Loeliger, PNH Scotland

Having been a very busy wife, mother of two and electronic engineer, taking ill in 2005 was a bit of a shock. I started to feel very run down with constant headaches and sore throats. It then took almost 2 years for me to be diagnosed with Paroxysmal Nocturnal Haemaglobinuria (PNH), an ultra-rare blood condition which causes blood cells to be attacked by the body's own immune system. These destroyed cells result in a very poor quality of life and the risk of a fatal blood clot. By the time I was diagnosed my health had deteriorated considerably. Severe exhaustion meant I had to be carried upstairs, needed help getting dressed and spent most of my time in bed. Not being a proper mother to my young children was the hardest, most upsetting part of the whole process.

Once diagnosed I discovered there was a drug available that could give me my life back. The drug was extremely expensive and, as such, would never meet Scottish Medicines Consortium (SMC) cost guidelines. Without access to the drug, blood transfusions and blood thinners were my only treatment options. Neither protected me from the chance of a fatal blood clot and neither gave me any improved quality of life.

In July 2011 I was one of three petitioners who called on the Scottish Parliament to review the SMC's methods for appraising medicines for rare diseases. As a tiny charity, the concept of giving evidence to the Health and Sport Committee was terrifying but, in reality, the process was remarkable. The committee listened, took time to understand, and developed recommendations that were beyond what I could have hoped. The resulting action by the SMC was extraordinary and extremely gracious. In particular, the introduction of the Patient and Clinician Engagement (PACE) process, to allow patient representatives to share what life is really like with a rare disease, was hugely helpful. The subsequent improvement of the PACE system, following the Montgomery review, was paramount in improving transparency in the SMC's decision-making process.

Early diagnosis and access to the right treatment plan is key to ensuring the best possible outcome for patients with rare diseases. Long diagnosis times are mentally and physically exhausting and damaging to patients and their families. As PNH patients we are extremely fortunate to have an amazing centre of excellence within Scotland where our care is coordinated and we know we can trust the expertise and specialist knowledge of our consultants and nurses. Having the correct treatment and emotional support is crucial to giving patients their lives back and allowing them a chance to work, socialise and, most importantly, spend time with their family. The work of the Health and Sport Committee, the review by Dr Montgomery and the extraordinary changes made by the SMC have definitely led to positive and, it would appear, sustainable changes in the way patients with rare diseases in Scotland are treated. There will always be more that can be done to hone the process but, as a PNH patient, I have seen a life-changing treatment made available that would never have been thinkable in the past and for that I am extremely grateful.

INDUSTRY PERSPECTIVE:

NAVIGATING THE APPRAISAL PROCESS IN SCOTLAND

Spinal muscular atrophy (SMA) Type 1, is a rare and devastating neuromuscular disease which impacts three new-borns in Scotland every year. Without treatment, most infants with Type 1 SMA do not reach their second birthday. Early diagnosis is crucial as motor neurons are rapidly and irreversibly lost after birth with devastating effects; only with early treatment can maximal benefit be achieved from therapeutic intervention.

In 2020, we provided a submission to the Scottish Medicines Consortium (SMC) for a new treatment for SMA. Patients recognise that new rare disease therapies often face additional approval hurdles due to their high cost, complexity and lack of long-term clinical data. Despite these challenges, our treatment was accepted for restricted use by NHS Scotland in just 7 months. We achieved this outcome by working collaboratively with the SMC, communicating clearly and deploying common sense in the right areas.

Throughout the assessment process, the SMC was pragmatic and successfully balanced clinical uncertainty and financial risk. Key to this was the inclusion of expert clinical opinions and patient voices through the Patient and Clinician Engagement (PACE) process, which is particularly important for rare disease treatments and gene therapies.

In our experience, a partnership approach with patients at the centre is required to successfully navigate the Health Technology Assessment (HTA) process and our recommendations include early engagement, managing expectations on data availability, keeping the submission simple and conducting additional healthcare resource utilisation studies if required.

Finally, the introduction of a newborn screening programme at the time of SMC decision would have enabled Scotland to get better value and this would also benefit patients though earlier diagnosis and improved access to treatment. After all, we must focus on delivering the right treatment to the right patient at the right time.

People living with rare diseases should expect the same quality of care as any other patient, and access to treatment is a fundamental part of this equation. It's for these people, and the thousands yet to receive a diagnosis, that the decision-making process must continually evolve.

By Imran Kausar, Novartis Gene Therapies

WHY MEDICINES MATTER:

IMPROVING ACCESS TO MEDICINES FOR RARE CONDITIONS IN SCOTLAND

In Scotland, over 400,000 people will be affected by a rare condition at some point in their lives. For the majority of those with a rare condition, accessing medicine is a challenge. Many conditions have no known cause and even more have no ongoing research into medicine or a medicine in development. Only around five percent of rare conditions have a licenced treatment but even then, this does not guarantee that a person will have access to that medicine.

A culmination of systemic and fundamental issues has meant that ensuring speedy access to medicines for rare conditions has long been an issue. In Scotland, this was recognised by an independent inquiry led by Professor Brian Montgomery which led to the introduction of the Scottish Medicines Consortium's ultra-orphan pathway and Patient and Clinician Engagement (PACE) processes, widely considered to have been a success.

Now is the time to consider what more can be done. The UK Rare Diseases Framework, published in January 2021, commits to 'improving access to services, treatments and drugs' and this presents an opportunity to explore what reasonable steps can be taken to further improve access to medicines for rare conditions in Scotland.

The Why Medicines Matter Project

The 'Why Medicines Matter Project', delivered in collaboration between Genetic Alliance UK and CRD Consulting, has sought to understand the views of three key stakeholder groups with an interest in access to medicines in Scotland.

Through a programme of engagement with support organisations representing people with rare conditions, health professionals and industry we have identified areas where further improvements could be made.

It is important to be clear that our work was not designed with an expectation of significant review of the processes for accessing medicines in Scotland. Rather, we hope that the findings, which reflect the perceptions of the stakeholder groups and their suggestions for improvement, can be used to inform future discussions that will inform the delivery of priority four of the UK Rare Disease Framework by the Scottish Government.

Findings

Interestingly, even although the three distinct stakeholder groups were consulted separately, there were many areas of consensus. In broad terms, stakeholders had high praise for the changes that have been implemented since the 2016 Montgomery Review, but were aware that medicines for rare conditions, including cell and gene therapies, will continue to pose a challenge for Health Technology Assessment (HTA) bodies and so urgent consideration must be given to ensure Scotland's processes are fit for the future.

While there was broad support for the ultra-orphan pathway and interim acceptance decision options, with both seen to have increased fairness by all stakeholders, there was also recognition that both could be improved. Stakeholders spoke of the limitations of the ultra-orphan pathway, with specific reference to the requirement for a specialist service and there were calls for a review of the suitability of the criteria. With regards to the interim acceptance decision options, this was considered to have facilitated earlier access, but greater transparency and guidance on data collection requirements are required.

Access to medicines not approved for routine use by the Scottish Medicines Consortium (SMC) remains uncertain. It is unclear what impact the refreshed approach to Individual Patient Treatment Request and Peer Approved Clinical Systems has had. Published data on rates of success would increase transparency, but clearer guidance and a Scotland-wide approach to the IPTR and PACS processes is required to improve access and address the continuing risk of 'postcode lotteries'.

Information for clinicians and healthcare professionals on rare conditions must be improved. We heard consistently throughout the project that there was a need for better access to rare conditions expertise and good quality information, not just about available treatments but about rare conditions in general, clinical management, research and clinical trial opportunities.

In the context of SMC decision making, all stakeholders indicated that there was insufficient rare conditions expertise around the table. It was recommended that at least two clinicians with rare conditions expertise (one specialising in paediatrics and one in adult care) should be included as standing members of the SMC committee.

And whilst there were high levels of satisfaction with SMC's PACE process, support organisations indicated that the process could be improved if they were able to nominate expert clinicians, including those practising outside Scotland, to participate.

For support groups participating in the PACE process, there was admiration for the support offered by SMC's Patient Involvement Team and all stakeholders recognised that the PACE process had successfully brought the voice of people with lived experience to the heart of the discussion. What was less clear however was the impact of PACE on decision making, with some participants describing feeling buoyed by their experience at SMC, only to be disappointed by a decision that they felt wasn't reflective of the discussion. Academic research to understand the true impact of PACE on decision making would be welcomed.

Support organisations indicate that they remain happy to participate, and that the Patient Involvement Team provides excellent support to allow them to do so. That said, more could be done to address the burden of participation on smaller, under-resourced organisations. Suggestions included introducing a grant scheme to support data collection and ensuring sustainable funding for the Patient Involvement Team to allow them to expand the support they offer.

Support organisations spoke of their willingness to be involved in the development of new treatments and in particular, called for early engagement with industry to support the development of clinical trials and to identify meaningful patient outcomes. Support organisations also advocated for early access to medicines and for industry to ensure that they engage with SMC at the earliest opportunity, offering the best possible price.

Looking to the future, all stakeholders recognised the challenges that new innovative (and often

high value) treatments will bring to increasingly pressured health budgets and were clear that stakeholders must work together, in collaboration with SMC, NHS Scotland and Scottish Government, to ensure that Scotland's approach to new medicines is fit for the future.

Conclusions

What is clear from our work, is that there is broad consensus amongst the three stakeholder groups on the key underpinning principles that access to medicines and decision making must be transparent, there must be equity of access (not just across Scotland, but in the UK) and processes must have sufficient flexibility to respond to unique challenges presented by rare conditions medicines now and in the future.

As the Scottish Government works to implement the UK Rare Disease Framework priority for improving access to services, medicines and treatment, it would do well to keep those principles in mind.

Our project recognises that, to achieve the goal of the UK Rare Diseases Framework to improve access to services, treatments and drugs, this discussion must continue. We have recommended a short life working group be established by the Scottish Government's Rare Disease Implementation Board to consider the findings of the Why Medicines Matter project and to progress discussion around how improved access will be achieved.

Why Medicines Matter Recommendations

The Why Medicines Matter Project has identified areas where stakeholders see opportunities for improvement. We recommend that work be undertaken to continue this conversation and explore the recommendations from this project. To achieve this, we recommend that the Scottish Government's Rare Disease Implementation Board establish a Short Life Working Group to consider how access to medicines for rare conditions can be improved in Scotland and ensure that the findings of the Why Medicines Matter project are reflected and addressed in the Scottish Rare Disease Action Plan.

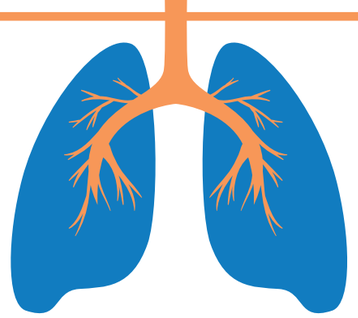
The table below outlines further recommendations for improvement.

Theme	Recommendations
Key recommendation	1. The Scottish Government's Rare Disease Implementation Board should: – Form a Short Life Working Group to consider how access to medicines for rare conditions can be improved in Scotland – Ensure that the findings of this report are reflected and addressed in Scotland's Rare Disease Action Plan
Progress since the 2016 Montgomery Review	2. The Scottish Government should conduct an impact assessment and produce a report which describes the impact of changes that have occurred since the Montgomery Review. This report should include: – Data on how many orphan and ultra-orphan medicines have been assessed by SMC and have been made available since 2016. – Details of how many Individual Patient Treatment Requests (IPTR) and Peer Approved Clinical System (PACS) requests for orphan and ultra-orphan medicines have been made, and the outcome of decision making. This information should be presented as a breakdown by NHS Scotland health board to understand equity of access across Scotland. 3. A Scotland-wide approach to the Individual Patient Treatment Request (IPTR) and Peer Approved Clinical System (PACS), including standardised processes and templates, should be implemented.
Interim acceptance decision routes	4. SMC should consider the extension of the interim acceptance decision option to a wider range of medicines. 5. Clear and transparent guidance on the requirements for data collection for medicines approved through the interim acceptance decision option should be published. This guidance should address how support organisations can be involved in the process and include guidance on support available to assist clinicians.
Ultra-orphan pathway criteria	6. A review should be undertaken to determine whether the criteria used for the ultra-orphan pathway are proportionate.
Rare conditions expertise at Scottish Medicines Consortium	7. Consideration should be given to developing a compulsory short training session on rare conditions to be delivered as part of the induction for new members of SMC. 8. Widen the SMC Committee membership to include at least two standing members with expertise in rare conditions.
System preparedness	9. Scottish Government should ensure genomic policy developments facilitate access to high cost, one off treatments such as cell and gene therapies. 10. Consideration must be given as to how system readiness can be ensured at the point of a new treatment's approval. Diagnostic pathways, including screening and companion diagnostics, service development and delivery pathways, all need significant planning to be available at launch. 11. The SMC's appraisal process should reflect and consider a medicine's impact beyond clinical and cost effectiveness, for example, impact on mental wellbeing. 12. An assessment of SMC's capacity and workforce should be undertaken to identify resources required to ensure SMC can keep pace with developments in rare condition medicines. If necessary, funding for SMC should be increased.
Pricing and Infrastructure	13. Establish dedicated infrastructure to support commercial negotiations with NHS Scotland and pharmaceutical companies. 14. Engage academia to conduct research and understand the views of the Scottish Public on funding high cost medicines for rare conditions.
Enhancing the role of the clinician	15. Further engagement is required with clinicians to understand their needs with respect to information, resources and support to manage the care of people with rare conditions. 16. Improve access to information and resources on rare conditions, medicines and clinical trials within NHS Scotland to aid the clinicians in their care of rare conditions. A central hub of signposting information relating to rare conditions, including details of managed clinical networks, in Scotland should be developed. 17. Consideration should be given to establishing formal mechanisms for industry to support training for clinicians on new innovative therapies, particularly cell and gene therapies.
Enhancing the role of people living with rare conditions and the organisations that support them	18. Consideration should be given to creating a funding infrastructure to ease the time and financial burden on organisations supporting people living with rare conditions. 19. Undertake a funding review of the Patient Involvement Team and ensure sufficient funding and resource is available for the team to continue to sustain and expand the support offered to support organisations.
Maximising the impact of PACE	20. Consideration should be given to undertaking and publishing research on the impact and weighting of PACE statements on decision making at SMC. 21. Consideration should be given to reviewing the scope of the PACE to determine whether further information and evidence not captured by the QALY could be used to help resolve uncertainties in the evidence base. 22. The PACE statement should be published in full alongside the published decision on the SMC website. 23. Guidance on the steps taken by SMC to identify appropriate clinical expertise to participate in PACE and SMC meetings should be made publically available. This should include information on how organisations that support people with rare conditions can nominate clinical experts to take part.
The role of industry	24. Mechanisms should be put in place to facilitate early engagement between SMC, organisations supporting people and industry to ensure data collected during clinical trials is representative of the priorities of people living with rare conditions. 25. Companies must ensure that they make a submission to the SMC as early as possible and that they give the best price on their first submission.

The full summary report of the Why Medicines Matter project, and the projects recommendations, can be read and downloaded from the Genetic Alliance UK website.

CYSTIC FIBROSIS:

HOW NEW MEDICINES ARE MAXIMISING THE BENEFITS OF PHYSIOTHERAPY



The introduction of highly effective CFTR modulators Kaftrio+Kalydeco®, has brought significant improvement in the physical health of people with Cystic Fibrosis (CF). Fewer respiratory infections, meaning fewer hospital admissions has impacted on the way physiotherapy is delivered.

As modulators were introduced during the pandemic, physiotherapists had been unable to review all people with CF face to face and limited the analysis of improvement experienced. There has been a noticeable upward trend in respiratory function, but the accuracy of home spirometry has not facilitated a direct comparison with pre modulator values. Evaluation of change in exercise capacity has relied on people with CF's subjective descriptions of an enhanced ability to participate in physical activity and improved energy levels.

As we move forward we are now in a position to conduct face to face clinical reviews, either via home visits or indeed in hospital. This allows us to fully appreciate the impact the CFTR modulators have had.

Improvements seen in our recent annual reviews for both exercise tolerance testing and indeed lung function have been remarkable.

People with CF have recognised that they can now focus attention on particular aspects of their CF care rather than feeling overwhelmed with the multi factorial nature of the disease. This has supported optimisation of some physiotherapy treatments, for example sinus management and physical activity.

Energy levels have increased and we have been able to empower people with CF to participate in Live online activity sessions. This was previously unachievable as face to face group meetings remain prohibited due to cross infection. Digital advancement has enabled us to offer online activity and education for groups of people with CF which has created peer support and opportunities to realise exercise goals. This has the positive effect of improvement in overall physical and mental health.

These opportunities have also been provided to those people with CF who cannot access the modulators and we have seen similar positive results in mental and physical health.

In the future, we see our role as physiotherapists being in health and activity promotion and management of exacerbation, with continued optimisation of care in those who remain unable to access the CFTR modulators.

A VIEW FROM A PHARMACIST:

HOW CFTR MODULATORS HAVE TRANSFORMED THE CARE OF PEOPLE WITH CYSTIC FIBROSIS

At Biogen, Cystic fibrosis (CF) is a devastating life-limiting genetic condition, characterised by a progressive decline in lung function, repeated respiratory infections, and premature death. This is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) protein.

In recent years, novel treatments for CF have been developed called CFTR modulators which target the dysfunctional CFTR protein. Clinical trials have shown that these medicines improve lung function, reduce the number of respiratory infections and improve nutritional status.

In 2020, the latest CFTR modulator, Kaftrio+Kalydeco® was licensed for use in the UK. Kaftrio+Kalydeco® has been shown to be effective in approximately 90% of patients with CF. A pricing agreement between the Scottish Government and the manufacturer of Kaftrio+Kalydeco® was reached in order to allow CF clinicians to prescribe this medicine to eligible patients from the day it received its product license. This meant that patients attending our CF unit could access a potentially life changing medicine quickly.

For the majority of patients who have received treatment with Kaftrio+Kalydeco®, the medicine has brought great improvements to their health.

We have observed that patients are having fewer respiratory infections, meaning fewer hospital admissions and fewer courses of antibiotics.

Patients' lung function has improved, along with their energy levels and patients feel more able to work, study and exercise.

Of course, this medicine is not a 'magic bullet' and patients with CF still require the care and support of the CF multidisciplinary team.

We still need to monitor lung function and nutritional status; give advice about physiotherapy and exercise; and monitor for and give advice about side effects of medication. Some patients have also required additional psychological support as they adjust to the positive changes in their body since starting treatment with Kaftrio+Kalydeco®. And we must remember that not all of our patients are eligible for this medicine and these patients still require intensive support to manage their condition.

In terms of my job role as a specialist pharmacist, access to new medicines has changed my role considerably. I have had a major role to play in initiating patients on these medicines – prescribing; providing patient education before and after initiation; monitoring for and reporting side effects; and providing ongoing support with adherence to medication regimes. It has been an extremely rewarding time for me professionally, observing the huge improvement in patient health and wellbeing that these medicines have brought.

FIGHTING FOR FAMILIES IN THE UK:

A VIEW FROM THE PKU SOCIETY

By Kate Learoyd, NSPKU

People with the rare condition PKU (phenylketonuria) have a single genetic fault; unlike most people their bodies do not process protein properly. An amino acid found in protein called phenylalanine builds up in the blood causing permanent damage to the brain. The condition is discovered at birth by the heel-prick newborn screening test. About 1 in 10,000 people have the condition – and it's slightly more prevalent in Scotland.

It is devastating news for families to be told their baby has the condition, as they will be told that almost all normal foods can cause brain damage. Mums and dads get the stressful job of feeding their kids 'safe' foods –

basically fruit, salad and prescribed medical foods from the doctor – and stopping their kids from eating the tasty foods they see all around them. It's a struggle for most to manage the punishing and complex dietary treatment and hunger, stress and guilt are common issues. Many adults don't manage to completely control their PKU and suffer from cognitive impairments and mental health issues as a result.

The rest of the world has had access to a medicine called sapropterin (brand name Kuvan) which was licensed in 2008. Kuvan has been widely used across Europe for more than a decade. As the national charity for PKU we have been fighting to bring this treatment here too – the drug boosts the ability to metabolise phenylalanine in responsive PKU patients, allowing them to have safer and healthier lives.

In 2018 the Scottish Medicines Consortium reviewed sapropterin and concluded that it was not cost effective. This was crushingly disappointing for our Scottish families; as the drug was already widely used across Europe at this stage. However the company BioMarin promised to resubmit in Scotland with more evidence – a promise which was never fulfilled.

This year NICE approved the drug for all patients up to the age of 22. This was a welcome step in the right direction; but patients with PKU are all too aware that the condition doesn't disappear at any age and do not support the imposition of an arbitrary age limit. We expect to see the treatment to start rolling out in England and Wales for children and young people before Christmas.

For Scottish families it will be extremely difficult to see the drug being offered across the border in England without hearing a plan on how the access issue will be solved in Scotland.

There is a tantalising hope on the horizon. As Kuvan is such an old drug, the manufacturer's marketing exclusivity has expired and cheaper generic versions are expected to be licensed imminently. I hope the Scottish government can make a swift and pragmatic deal to solve the access problem by commissioning these cheaper generic versions of sapropterin for all PKU patients in Scotland with no age restrictions. This could be the news ever for families across Scotland that live with this lifelong condition.

Meanwhile we must also confront the systemic issues as to why PKU patients in the UK have been left without access to a medicine for so long.

APPROVAL ISN'T THE SAME AS ACCESS

By Michaela Regan, MDUK

Muscular Dystrophy UK
Fighting muscle-wasting conditions

In the last few years, five new treatments for neuromuscular conditions have become available to patients in Scotland. These treatments have either been the subject of an Early Access to Medicines Scheme; approved by the Scottish Medicines Consortium (SMC); or access has been allowed through the ultra-orphan pathway. These fast-tracking schemes have helped address common barriers in rare disease appraisals – such as uncertainty and cost effectiveness.

Having new treatments is incredible progress considering they are the first to tackle the underlying cause of disease rather than symptom management.

It is clearly vital that access to these treatments is secured in the first place; but consideration as to how a treatment will be rolled-out if it is made available is essential so that services can be effectively resourced to ensure that people can truly benefit from access.

A prime example is Spinraza (also known as Nusinersen), a treatment by Biogen for Spinal Muscular Atrophy (SMA), which is administered through intrathecal injection. As such, administering this treatment requires a neuromuscular consultant, a theatre list space (with an anesthetist if sedation or anesthesia is required), a post-procedure day bed, and a neuromuscular physiotherapist for assessing and monitoring the patient for any benefit or adverse side effects. This places pressure on an already over-stretched workforce to juggle this extra demand.

As part of the Scottish Medicines Consortium's approval process, we would recommend considering ways to support a Scotland wide roll out plan in collaboration with the relevant clinical specialists to enable delivery of new treatments across paediatric and adult services. Such a plan would help ensure the specified timeframes for the roll out is feasible within the current capacity, support clinicians in conversations with Scottish NHS Trusts and Health Boards regarding resource requirements, and help to manage expectations of those patients eligible for the treatment.

WHY GENERICS MATTER

By Jess Hobart, UK Mastocystosis Support

UK masto

Imagine you have spent years trying to identify what's wrong with you and have finally found a doctor who has recognised your rare disease. People nearly always feel a sense of relief in having a name to put to their condition. But then comes the key question! Is there anything you can do to help me? In the case of mast cell diseases (mastocytosis, mast cell activation and hereditary alpha tryptasaemia) there is no cure. What we are able to do, is stabilise those mast cells, and try to stop the downstream effects of the chemicals released by those mast cells with a cocktail of medications. With them we can often keep people from having frequent life-threatening anaphylaxis (with epi-pens on hand for when needed), keep them from having diarrhoea on a daily basis, help children attend school and adults in work by damping down the reactions to difficult-to-avoid triggers like cleaning chemicals, perfumes, temperature extremes and stress.

All of these ingredients of the meds cocktail are available as generic medications, and none is terrifically expensive; even GPs are usually happy to prescribe them. So, off the patient goes to the pharmacy, only to discover that one or several medications are simply not available. This happens over and over again. As patient advocates, a lot of our time is spent on the phone to people at all points in the supply chain trying to understand why the medication has gone missing, when it might be back, whether there is an importable alternative, whether the national health services have shared information about the shortage and how to address it. Over and over. Right now, it's sodium cromoglycate, ketotifen, and the alcohol-free liquid cetirizine that are in peril. While the specific reasons for the outages have varied over time, the underlying drivers are the same. These are medications for which there is relatively small demand and the margin for generics producers is narrow, which seems to mean they don't prioritise making our medicines. Additional companies aren't keen to bother with entering our market given the cost of entry and the small potential profit! Often (but not always) there is just one license holder for the generic medicine in the UK. Where there is more than one license holder, the problem can be that our community needs a particular formulation (e.g. a liquid for children, but not alcohol because that can cause anaphylaxis) and the one company doesn't have supply.

One possible solution to this problem is to develop domestic capacity to produce generics for situations where the market is failing us. Endocrinologist colleagues in England are proposing the development of such government-led domestic capacity to produce generics to address situations where the price of a generic rises rapidly with no underlying reason such as cost of inputs. We believe there may be a shared solution for our rare disease community, where the size of the market means that there are few incentives to produce our generics (as there has been with orphan drug incentives to promote development of new medications for rare diseases where the market fails.) These endocrinologists have started a petition to begin the conversation about solutions to generics pricing and supply issues, and it is a conversation that would be welcome in all four nations.

GENERICS

INDUSTRY PERSPECTIVE:

BIOGEN

Scotland led the way to become the first country in the UK to grant access for this medicine to all eligible patients. Biogen welcomed this demonstration by the SMC of flexibility, collaboration, and leadership throughout the appraisal process.

At Biogen, defeating devastating neurological diseases has been our focus for more than 40 years. As a company that has introduced several pioneering treatments to patients, we believe that clinicians and patients should have freedom to receive the treatment most appropriate to them. We are constantly inspired by the campaigning efforts of patient advocacy groups driving change in the area of rare disease, and by those in charge of healthcare systems who are prepared to adapt and provide flexibility to meet the needs of patients.

Spinal Muscular Atrophy (SMA) is a debilitating and life-threatening muscle-wasting rare disease, which takes away a person's ability to walk, eat and ultimately, breathe.

In 2018, the Scottish Medicines Consortium (SMC) recommended the routine funding of our treatment Spinraza® (nusinersen) for the treatment of symptomatic Type 1 5q Spinal Muscular Atrophy (infantile onset). Following this, nusinersen was one of the first treatments to undergo the Ultra-Orphan (UO) pathway for Type 2 and 3 SMA paediatric and adult patients.

It was also encouraging to see the steps taken to ensure that medicines for very rare diseases were assessed in an appropriate manner. It meant ultra-orphan medicines, such as nusinersen, could be made available on the NHS in Scotland for at least three years while further efficacy data are gathered, ahead of a final decision on routine availability.

Biogen commends the Scottish government's innovative approach to ensuring access to rare disease treatments through the UO pathway, which has been ground-breaking both in its approach to data collection, as well as its understanding of the unique challenges around appraising orphan medicines.

This makes Scotland stand out from the rest of the UK, in sending a clear signal to industry, and the patient community, on its commitment to rare disease.

We have learned that alongside the reimbursement process, it is crucial to work collaboratively with the NHS in Scotland to ensure the new pathways and specialist services are in place to administer the treatment where there are high levels of unmet need.

It is important that this happens early in the process between all parties to ensure services are set up and prepared for patients.

This success, of course, would never have been achieved had not been for the forward thinking of the SMC and its willingness to collaborate with Biogen on bringing a treatment to SMA patients, and the determined campaigning of patient advocacy groups to drive change. It is these collaborative, risk-sharing approaches that will make access to advanced therapies for patients with high unmet needs not just a vague possibility but a concrete reality.

UNDERSTANDING CELL AND GENE THERAPIES:

HOW GENETIC ALLIANCE UK ARE INFORMING THE RARE CONDITIONS COMMUNITY

Developments in cell and gene therapies, also known as Advanced Therapy Medicinal Products (ATMPs), have shown great potential to be a miracle cure for certain genetic conditions over recent years. However, these therapies are complex, not just in how they function but also in their delivery to patients, as they are not simple 'off the shelf' type of medicines. The UK needs to ensure that its systems and processes are ready so that patients don't face delays in accessing life-altering treatments.

Towards the end of 2020, Genetic Alliance UK organised a series of workshops for a small cohort of the rare disease community to learn more about cell and gene therapies; what they are, how they work, why they are important and what the challenges are around regulating and delivering these types of therapies in the UK. An increasing number of cell and gene therapies are in development and people affected by rare genetic conditions are most likely to benefit from these new therapies. Therefore it is essential that we prioritise educating and informing the rare community to empower decision making down the line. These workshops highlighted that there is a great appetite for learning about cell and gene therapies within the rare disease community and that many have complex scientific questions relating to associated long-term risks, longevity of effectiveness and when the appropriate time is to receive a therapy you can only have once in a lifetime. The science is still too young to be able to answer these longer term questions but researchers need to be aware that these are some of the things that matter most to future potential patients.

Genetic Alliance UK are hoping to build on these findings by developing a Cell and Gene Therapy magazine that will lay out the current landscape of ATMPs and, two years after the workshops, attempt to find answers to some of the complex questions asked by members of the rare community.

PROJECT HERCULES:

A MODEL OF COLLABORATION & COOPERATION

I set up Duchenne UK with my co-founder, Alex Johnson, after our sons were diagnosed with Duchenne muscular dystrophy (DMD), a rare life-limiting muscle wasting condition mainly affecting boys. From the start we have had one aim: to end Duchenne, and we began by funding and accelerating research into DMD.

We wanted to find promising new treatments, and get them into the clinic and given to patients as soon as possible.

We built relationships with charities internationally, successfully campaigned for the Early Access to Medicines Scheme at home, and with an innovative pump-priming model we invested millions to sustainably fund doctors, nurses and physiotherapists in the NHS to deliver clinical trials for patients.

But we quickly learned that navigating the reimbursement stage of new treatments was just as important as discovery and research.

An example is Translarna, a DMD drug given conditional market authorisation by the EMA in 2014. Parents in the UK were celebrating that there was, finally, a new treatment for their sons, only to see them become ineligible for treatment in the time it took for NICE to decide to pay for it in 2016.

I realised there was something far worse than there being no treatment for your disease – one where there is a medicine which is proved safe and effective, but is sitting on a shelf because the people in charge can't agree how it will be paid for.

Fortunately, I met another mother of a boy with DMD, Fleur Chandler, who worked in health economics for a global pharmaceutical company. We founded a new Duchenne UK initiative at the end of 2017, Project HERCULES, to address a significant barrier for companies seeking to bring their treatment to the NHS: health technology assessments.

Each company must reinvent the wheel every time they bring a new medicine to NICE. It is expensive, time consuming, and often trial and error is the best way to navigate the process. But that's too long to wait for young people with DMD, as the disease progresses over time.

Project HERCULES brought together all the leading pharmaceutical companies working on DMD as well as patients, clinicians, academics and – most crucially of all – the regulator, NICE. From the bottom up, it produced an economic model which could be adapted to different treatment options, a Burden of Illness study to investigate evidence gaps, a Quality of Life metric, and a Natural History model of the disease which identified a new stage in DMD. It used what is probably the largest set of clinical data available, and interviewed hundreds of families.

This last point is important. Before Project HERCULES, companies would ask our community the same questions each time they went before NICE. It can be an exhausting and upsetting experience. Our hope is that by asking the questions once, and allowing anyone to access the answers, this onus on patients and their families is drastically reduced.

We believe Project HERCULES is a model of collaboration and cooperation.

Everyone involved 'wins'; it saves time and effort for companies, patients and NICE, and already we are seeing the initiative bear fruit. The new Quality of Life metric – the DMD QoL – has been published by Oxford University Innovation and is ready to be used by companies and academics. We look forward to the new stage identified in DMD – the Transfer Stage – leading to new research and targeted treatments.

The work of Project HERCULES isn't over, but it offers a blueprint which can be copied by any disease area.

MANAGING RARE CONDITIONS:

A CLINICAL PERSPECTIVE

As a paediatric nephrologist, I am privileged to be part of a team looking after children and young people with renal conditions including many rare renal diseases throughout Scotland. Rare diseases not only affect the patient, but also the whole family and none more so than in the case of a child or young person, when parents, siblings and other family members are also indirectly affected.

Optimum management of rare diseases involves up to date knowledge, provision and access to new or existing medication or therapies, along with appropriate pharmacy and dietary advice and adequate psychology and social support. Our team strives to provide a holistic package of care delivering this no matter the underlying condition or geographical location of the individual.

As a national service rare drugs or treatments, if available, are accessed then initiated according to due processes in place, on our advice primarily in our centre but also locally if possible. In paediatrics many medicines are unlicensed; however, processes have been simplified and in easily accessing new medicines, we have been able to put our patients foremost. Appropriate formulations of drugs may not be readily available for our patient group and medicines may have to be sourced centrally rather than locally. If and when new child friendly preparations are readily available, one element of the management burden for the individual becomes less.

Ongoing and targeted research with genetic advances are vital to tackle rare diseases.

More investment in this area would be welcome with industry, in general, perhaps being less keen to invest in orphan drugs research. New medicines may be limited and often are expensive treatments which may lead to inequality in provision due to funding, adding to the challenges faced.

Ultimately, in managing rare diseases, our ethos should be equity in treatment research and provision of holistic care, no matter the condition or location of the individual patient, minimising the isolation a rare disease brings.

Then we can look forward to facing our patients with rare diseases, bringing more hope and sense that indeed we are all valuing the individual and recognising their condition as much as any other.

WHY RAISING AWARENESS OF RARE CONDITIONS MATTERS

Priority 4: improving access to specialist care, treatment and drugs is probably the most challenging priority of the Rare Disease Framework. Just under half a million people in Scotland across all 14 Health Board areas are affected by a rare condition. From remote islands to busy cities, ensuring equitable access to high quality care and medicines is a formidable task for all healthcare professionals in Scotland. Approximately one fifth of Scotland's population live in poverty which increases marginalisation. Not only are new rare conditions being discovered every day but new and exciting therapies, including cell and gene therapies, are being developed and offered more quickly than is possible to keep pace with.

Scotland has many National Networks and Specialist Services which provide care for families affected by rare conditions, but these often focus only on one illness or body system. They are also only helpful once a diagnosis has been reached. The Scottish Medicines Consortium are the national source of advice on the clinical and cost-effectiveness of all new medicines for NHS Scotland. They have approximately 1700 medicines on their website and have recently developed a pathway for the assessment of ultra-orphan medicines. Again, this is only helpful once a diagnosis is reached and a treatment sought for that particular condition.

For clinicians prescribing new medicines for those affected with rare conditions there are several challenges. Firstly, there needs to be an awareness of what therapies are currently available and then consideration needs to be given to availability, access, cost and administration. Specialist pharmacists can be a great help in these situations but again they are not always readily available. Medicines are often prescribed unlicensed or 'off-label' and this can cause anxiety for those not familiar with these therapies.

Other challenges lie with a lack of awareness of rare conditions or even remembering to 'think rare' when facing an unusual clinical presentation. It can be difficult to know where to go to find reliable and up to date information. There is a lack of education and training on rare conditions in general for healthcare professionals. Good communication and co-ordination of care are key for our patients and yet they report we are still not good at delivering this.

The Office for Rare Conditions, funded by Glasgow Children's Hospital Charity, is working tirelessly to address these challenges. We aim to raise awareness and educate through our open access Webinar Series in Rare Conditions which occur every two months. These are recorded and are freely available on our website. We run an annual education day for staff working in Neonatal Units to encourage all healthcare professionals to 'think rare'. We engage with all healthcare professionals and run various events attended by those in Scotland and beyond. We also directly supervise medical students undertaking a Student Selected Component in the field of rare conditions. We promote general awareness of rare conditions by our presence within the hospital with visual prompts on digital screens and posters, publishing a regular newsletter highlighting current issues in rare conditions and government actions, distribution of information leaflets and other appropriate resources, hosting stands to provide information, resources and signposting for patients and families.

HEARING THE VOICE OF PEOPLE LIVING WITH RARE CONDITIONS

Cystinosis Foundation UK (CFUK) was invited to make a patient group representation for a re-submission to the Scottish Medicine Consortium for a slow-release form of a drug that all patients with Cystinosis take as their primary medicine. As the only Scotland based trustee I represented CFUK in this process, and happily partnered with Metabolic Support UK for a joint representation.

Having been a trustee for CFUK for 18 months and a mother to a daughter with Cystinosis for 11 years, I felt well placed to be able to write this submission for the wider community, all bolstered by the input of Metabolic Support UK, including results from a survey they ran about patient experiences. Summarising the effect of living with the condition on patient and carer's day to day lives, and the impact that this new formulation of the medicine would have, in a few hundred words is challenging. As much as you tell yourself that there are many more influential factors than the patient group submission, such as the pharma company's submission and the economics, it's hard not to feel like you have to do your utmost for all those patients and carers who are relying on you.

The weight of feeling like you, personally, are responsible for the outcome of the decision is heavy.

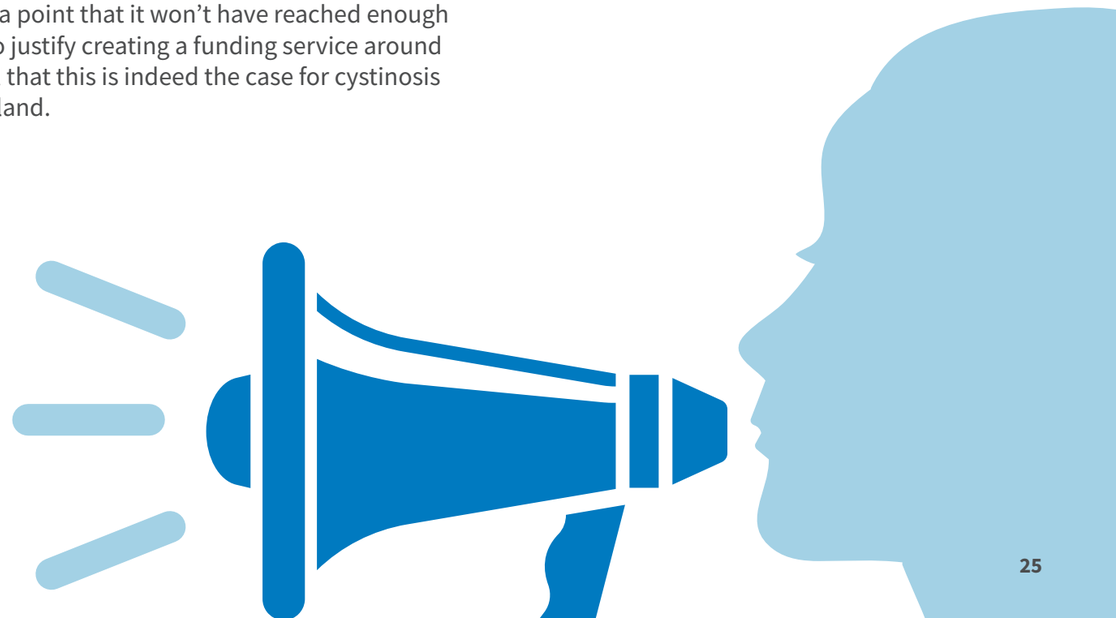
The whole process is really well supported by the contacts at SMC who explain the protocols in thorough detail and make themselves available for questions, comments and feedback.

Written guidance is extensive, explanatory meetings are well thought through and plenty of notice is given. The format of the committee meeting itself is equally well communicated in advance. We were one of four medicines being discussed in a four-hour virtual meeting.

However, I must raise the issue of the new methodology to assess whether a drug is 'ultra-orphan' or not. This determines whether the drug is subject to a different pathway than other submissions. The rules for ultra-orphan criteria changed in 2018 meaning Procysbi was no longer considered an ultra-orphan drug. There are four criteria to assess whether a drug is ultra-orphan – and Procysbi sails passed three of those criteria. The fourth criteria deems the condition must have 'highly specialised management' – i.e. a nationally funded service. For me, this feels contradictory. On the one hand we're saying this must be very rare, but on the other we're saying that it must have enough patients to warrant a lengthy and costly process of building up a funded service to support it. Surely if something is so rare then there will be a point that it won't have reached enough scale to justify creating a funding service around it. I feel that this is indeed the case for cystinosis in Scotland.

And as a result I'm sorry to say that I feel like we haven't had a fair shot at the process.

Unfortunately, the submission wasn't successful, with the feedback to the pharmaceutical company noting that it was mainly based on the economic modelling. All in all, well done to the SMC for running such a clear, supported and transparent process. However, in the sphere of rare disease, I have to raise a red flag on fairness.



WORKING COLLABORATIVELY:

HOW THE PHARMACEUTICAL INDUSTRY CAN HELP DRIVE CHANGE

The pharmaceutical industry is determined to make a difference for people with rare diseases. It is useful to remind myself of the stats: rare diseases affect approximately 8 percent of the population in Scotland. That means approximately 437,000 out of a population of 5,463,300 have one form of rare disease or another.

In terms of scale, that's more than the number of people in Scotland that have diabetes, cancer or dementia.

Most rare diseases still have no treatment, and we in the life sciences community are determined to change that and bring innovation to the people and families affected.

Here are two key areas where the ABPI and pharmaceutical companies are pushing to make a difference.

Data

To create the latest innovations in rare disease, as well as any other area of healthcare, Scotland needs to be able to unlock its healthcare data.

The data already exists, what is now needed is to create a national NHS data infrastructure that joins all the anonymised patient data currently sitting in regional safe havens – all backed by the right privacy safeguards, security and regulation.

We're pressing for the creation of a joint NHS Scotland and pharmaceutical industry data steering group to deliver advances in the use of healthcare data which will benefit research for not only rare diseases but for all diseases.

Making Scotland a go-to research destination for companies

In 2018, the pharmaceutical industry in Scotland spent £165m on R&D. We're working with other stakeholders to substantially build on this to create an environment where collaboration between industry, academia and the NHS is the norm.

ABPI Scotland facilitates Global Showcases, providing a platform for leaders in Scottish medicines innovation programmes to highlight the opportunity Scotland offers for collaboration and investment by global pharmaceutical companies.

The ABPI is also part of the Scottish Government's Life Sciences Industry Leadership Group and secretariat to the Cross-Party Group on Life Sciences – forums where advances in medicine research and development are discussed, which provide opportunities to build closer relationships for the ultimate benefit of patients.

We want to see people and families affected by rare diseases in Scotland get the same levels of treatment and care as people with more common diseases. The ABPI, on behalf of the pharmaceutical industry, is determined to play its part to make that happen.

BRINGING INNOVATION TO PEOPLE LIVING WITH RARE CONDITIONS IN SCOTLAND

Treating rare diseases is a global challenge that requires concerted action across borders. Huge strides have been taken in recent years, but we know that 95% of rare diseases still lack an approved treatment.

True transformation cannot be delivered in isolation but the forward thinking approach taken in Scotland to supporting patient access to rare disease medicines is a great exemplar for what can be achieved through partnership.

As part of our commitment to improving the lives of patients living with rare diseases in Scotland, Members of the Ethical Medicines Industry Group (EMIG) are engaged in a number of partnerships with the NHS and academia in Scotland in the field of rare diseases. This includes a number of initiatives to research, develop and trial new medicines.

Bringing this innovation to patients takes time but we're currently experiencing a revolution in the way we diagnose and treat disease. Whole genome sequencing offers the potential to expand our understanding of rare diseases, while the advancements in cell and gene therapy can transform patient outcomes.

However, our commitment runs much deeper than launching new medicines and includes a wide range of other activities such as supporting patient identification and disease awareness, co-designing and implementing new referral pathways, providing clinical education programmes and sharing best practice between centres.

It is hugely welcome that our ambition to level up outcomes for all rare disease patients in Scotland is being matched by the commitment shown by the NHS and SMC. There are a number of initiatives adopted in Scotland that the rest of the UK could learn from:

- The ultra-orphan medicines pathway has enabled conditional access to transformative rare disease products and products that are identified as innovative or promising can benefit from 'interim acceptance'.
- Where a medicine receives an initial draft negative recommendation, a Patient and Clinical Engagement (PACE) meeting can be convened to understand whether there are any benefits associated with the medicine that may not be fully captured within the conventional assessment process. The output from PACE meetings is often a major factor in the SMC's decision-taking.
- The Peer Approved Clinical System (PACS) also enables access to treatments without positive SMC guidance.

Industry has played no small part in influencing this forward thinking approach and patients are the beneficiaries.

However, we all can't afford to rest on our laurels. There are huge opportunities to revolutionise outcomes in the coming years but this will require industry, the NHS, and government to redouble our partnerships.

DEVELOPING A FAIR AND CONSISTENT APPRAISAL PROCESS FOR RARE DISEASE TREATMENTS

Orphan Medicinal Products (OMPs) are challenging to appraise given the limited clinical knowledge about most rare diseases, small clinical studies that can be conducted and high prices of innovative treatments. This leads to major 'uncertainties' in evaluation of their benefit and value for money, for example, as undertaken by the Scottish Medicines Consortium (SMC). SMC has recognized these issues and implemented adaptations to create more flexibility in decision-making for OMPs, but could more be done?

Tools could be taken from the European Commission funded IMPACT HTA project to develop an appraisal framework suitable for OMPs. IMPACT HTA explored how different forms of evidence and inputs are obtained, assessed and appraised to inform recommendations that govern access to OMPs. SMC generously contributed to this research by allowing observations of how the evidence and inputs for several OMPs and ultra-OMPs were considered by its various committees. With such information from NICE, SMC and CADTH in Canada, it was possible to explore the nuances of these complex processes that involve critical assessment of evidence, stakeholder inputs and multi-stakeholder deliberation to come to a judgement on value.

IMPACT HTA concluded that a fair appraisal process for OMPs requires:

- leniency in critical assessment to recognise the inherent limitations in clinical evidence
- flexibility in process to support determination of value
- consistency in application of leniency and flexibility

The IMPACT HTA appraisal framework goes beyond clinical and cost effectiveness to include domains such as nature of condition, patients' aspects, organisational issues, ethical issues, along with modifiers that deliver levels of flexibility for specific products, such as severity of disease, children etc. The decision-making framework and modifiers need to drive all parts of the process so that stakeholders and appraisal committee members can contribute relevant evidence and inputs for each domain of the framework. On this basis, eight recommendations have been developed that are built on a foundation of iterative clinical and patient involvement throughout the process.

Separate guidance has been developed on disease-specific Patient-Reported Outcomes. Such evidence is particularly important for severe, disabling rare diseases, where there may be no universally agreed clinically relevant outcome, where the nature of the condition is poorly understood. However, critical assessment of evidence from patient-reported outcomes needs to recognise the challenges of developing these measures and collecting the evidence in these small, heterogeneous populations. For some diseases carer quality of life is key. In addition, to such quantitative information, robust qualitative research about patients' and carers' experiences and perspectives is needed.

Evidence Submission and Critical Assessment processes address all dimensions of value and identify uncertainties	**Appraisal Deliberation considers all dimensions of value**
The entire Health Technology Assessment process is shaped around clearly defined decision-making domains and any decision modifiers	Appraisal committees are bespoke for rare disease treatments, or general appraisal committees include several rare disease specialists
All relevant evidence is obtained for each domain of decision-making and all decision modifiers	The deliberative appraisal discussion is driven by the domains of decision-making, and use of modifiers is clearly understood
Critical assessment of clinical evidence explicitly considers what evidence could have been generated in the rare condition	Uncertainties are characterised in terms of form, extent and implications for decision-making
Critical assessment of economic models takes account of paucity of knowledge in rare diseases and judges whether the model is sufficient for decision-making	Outcomes-Based Managed Entry Agreements may be used to resolve decision-relevant uncertainties, if collection of sufficient data is feasible
Clinical and patient experts are involved iteratively throughout the appraisal process to explain context of condition, existing care pathway and help resolve uncertainties related to determination of treatment value	
Delivering fair appraisal of Rare Disease Treatments through consistent flexibility	

Outcomes-Based Managed Entry Agreements, called Complex Patient Access Schemes by SMC, are one way to allow access to OMPs, when there are major uncertainties in the determination of value that could be resolved by additional data collection within the re-appraisal period. Data collection plans that are agreed by all stakeholders should be published. Then data collection should be carefully monitored to ensure all eligible patients are offered entry and sufficient data of good quality is collected. Various tools have been developed to support this process including a patient group submission form for re-appraisal. Given the lack of transparency of the data collection schemes in the Scottish Ultra-OMP pathway, these tools would be an important addition to the Scottish and UK-wide determination of value of OMPs.

DRUG REPURPOSING – THE INNOVATION WE NEED

Rare diseases lack treatments. This leaves millions of patients with no medical intervention to address complex, life limiting conditions. They are left without hope.

Those rare disease treatments that do exist are almost invariably expensive. At worst, this means patients are denied access to treatment all together. At best, it slows the delivery of life changing drugs to those who need them most.

How do we tackle these challenges? How do we find a way to deliver equitable care to those affected by a rare disease? The answer I always hear is 'innovation' – a buzzword that invariably means delivering gene therapies, gene editing, or other personalised medicine.

I'm all for such treatments, but it is naive to assume that these innovations can be either rapid or cheap. The unmet need is real and must be addressed now.

Why can't we look at innovation differently? To innovate is to do something in a new way. What those affected by rare diseases need are faster and less expensive routes to develop treatments.

Drug repurposing – the use of old drugs for new conditions – has huge potential in this regard. Repurposing uses the simple idea that existing drugs have multiple effects on the body. With careful research, we can exploit this to treat a wider range of diseases. This has a number of advantages:

- We remove the costly process of creating new drugs.
- We understand the safety of these drugs.
- Many such drugs are widely produced, readily available, and low priced.

This means that repurposing existing low-cost generic drugs could help to meet the huge unmet medical need of rare diseases. This innovation could be delivered more quickly than safe and effective gene therapies, and at a significantly lower cost.

However, there is a problem: companies have no belief that they can recoup their investment in developing and licencing a new use for an existing generic drug. Furthermore, as a general rule, academics and clinicians lack the funding, expertise, or manufacturing capabilities to convert their research into an approved treatment. This leaves the majority of research either stalled or treatment accessible only off-label.

There have been a few notable successes in rare repurposing that demonstrate its potential. Most excitingly nitisinone recently received approval for a second rare condition, alkaptonuria (AKU), after the trail-blazing work of the AKU Society. This patient group was at the heart of an international EU-funded collaboration that ran a clinical trial. After years of work, this research resulted in the first licenced treatment for AKU that showed the ability to halt, or even reverse, disease progress.

So, how do we create more nitisinones? We need to provide more training, funding, and regulatory pathways to drive academic repurposing to produce licenced medicines. We need to create new incentives to help industry, particularly generic drug manufacturers, benefit from selling licenced repurposed medicines at a low cost.

Achieving this will require innovative thinking, flexibility, and prioritisation of rare patients. The recently established NHS England Medicines Repurposing Programme is a positive sign of a new approach in the UK, but time will tell whether it is given the power and investment to deliver the change needed. If the programme is a success, we could soon see the innovative use of some of the world's most common drugs repurposed to help its rarest patients.

THE ROLE OF ARTIFICIAL INTELLIGENCE

Equitable access to rare disease medicines across Europe remains a challenge despite great advances in research and development and a number of approved innovative therapies in recent years.

Barriers to equitable access may include differences in national policies on pricing and reimbursement and medication expenditure, but also disparities between the evidence required to support drug marketing authorisation, e.g. drug efficacy and safety, and that required to inform health technology assessment (HTA) and payers' decision making, which includes other criteria such as health-related quality of life and comparative effectiveness to existing therapies.

Drug development for rare diseases is particularly complex due to scarcity of data, small patient populations, lack of age-appropriate disease-specific validated and meaningful endpoints.

Both digital technologies for remote patient monitoring and artificial intelligence (AI) analytics methods may change the landscape of rare disease drug development. They enable more continuous, systematic and objective patient data collection and the analysis of complex data captured through video, audio, wearables and sensors, allowing better characterisation of disease hallmarks. AI could advance the understanding of the disease's natural history and predict progression, both fundamental to developing effective treatments.

Rare disease patients have a crucial role in the design of digital endpoints that capture outcomes that matter to them and identify efficient real-world data (RWD) collection methods that do not pose additional burdens to already complex disease management.

Remote patient monitoring allows RWD collection in the home, reflecting the impact of the disease or treatment on patients' daily life more accurately than traditional in-hospital assessments. The COVID-19 pandemic has accelerated the uptake of digital technology and shown its feasibility in capturing patient-generated data.

Real-world evidence (RWE) has the potential to reduce the uncertainty associated with the approval of highly innovative health technologies for chronic complex conditions. Therefore, both HTA and regulatory agencies worldwide are increasingly accepting RWE as part of their evaluations.

However, issues around data transparency and reproducibility, appropriate study designs and methodologies for RWD collection and analysis still prevent the systematic use of RWE in HTA and payer decision making. RWE4Decisions, a multi-stakeholder initiative commissioned by the Belgian National Institute of Health and Disability Insurance, has recently called all stakeholders to support the generation, analysis, and interpretation of RWD to inform decision making. Cross-border collaboration among payers, HTA bodies and regulators will be key to agreeing on RWD requirements and analysis methods, hence linking regulatory approvals and reimbursement decisions to ensure timely access to medicines.

PUBLIC ATTITUDES TO RARE DISEASES:

THE CASE FOR EQUAL ACCESS

By Joe Smale, BioIndustry Association (BIA)

Living with a rare or ultra-rare disease is incredibly tough for patients and their families, and though rare diseases affect over 3.5 million people in the UK (1 in 17 people), only 5% of rare diseases have treatments currently available.

Rapid scientific advancements are enabling the UK's life sciences sector to develop innovative life-changing and potentially curative treatments for rare and ultra-rare diseases (often referred to as orphan and ultra-orphan medicines). This is cause for optimism, but even when these treatments are licensed, patients face an uphill battle trying to access them through the NHS.

Rare and ultra-rare diseases create a set of unique considerations that need to be taken into account when evaluating the clinical and cost-effectiveness of such treatments. Unfortunately, the current appraisal process in England is not adequately equipped to address these factors. Despite the introduction of an evaluation process in 2013 specifically designed for treatments for very rare diseases, the strict entry criteria for this process means that many orphan medicines and even some ultra-orphan medicines fall into the standard process designed to evaluate medicines for common diseases. This process is completely unsuitable for these treatments which are unable to demonstrate their cost-effectiveness. Orphan medicines assessed via this process are often not recommended for use by the NHS and patients are unable to access them.

From inception, the NHS has been predicated on the idea that people should have equal access to healthcare and treatment regardless of the level of need. To ensure that the aspiration for equal access for people with rare diseases is borne out in reality the appraisal of orphan medicines needs to be reconsidered. The introduction of specific measures to tackle rarity within the evaluation system is crucial to addressing the unique challenges faced by rare and ultra-rare diseases during the evaluation process.

To understand whether people would be open to specific measures to support access to medicines for people with rare diseases, the BIA carried out a public attitudes survey on rare diseases and access to medicines.

The survey found that 79% of respondents agreed that people living with a rare disease should be able to access medicines on the same basis as people living with more common conditions. Similarly, 78% agreed that the NHS should ensure access on the basis of clinical need even if this would be more costly to the NHS because of a disease's rarity.

These findings represent a reaffirmation of public support for equitable healthcare. They also show that there is broad interest in and support for protecting the universality of access to medicines through the NHS for rare diseases (in comparison to more common ones) even where this would require extra spending.

It is crucial that NICE and other HTA bodies in the UK consider the societal value for equitable healthcare and adapt their evaluation processes to level the playing field for orphan and ultra-orphan treatments so that patients can quickly and fair benefit from them.

ARTICLES AND CONTRIBUTORS

Genetic Alliance UK and CRD Consulting would like to thank those who contributed articles to the Why Medicines Matter magazine. A full list of articles and contributors is provided below.

Why Medicines Matter to Me
Article written by Tilly Rose
Tilly Rose is an author and activist, championing patient advocacy. Last year, Tilly made the decision to share her patient journey on Instagram and saw first-hand how her experiences resonated with followers. Being a 'medical mystery' means she has carried out on-the-ground research into the medical community for 18 years. She is currently writing her memoir, Be Patient.
Instagram: @thattillyrose

Reflections on the Review of Access to New Medicines in Scotland
Article provided by Dr Brian Montgomery, Independent Healthcare Consultant
Dr Brian Montgomery was asked by the Cabinet Secretary for Health and Sport to undertake an independent review of access to new medicines in Scotland in 2016. Dr Montgomery brought to the review his experience and perspectives as a practising clinician, Territorial Health Board Medical Director.
gov.scot/publications/review-access-new-medicines/

Driving change through personal experience
Lesley Loeliger, PNH Scotland
Lesley lives with the rare condition Paroxysmal Nocturnal Hemoglobinuria (PNH). In 2011, Lesley petitioned the Scottish Parliament for improved access to medicines for rare conditions in Scotland. She is the founder of the PNH Scotland support group.
pnhscotland.org.uk

Navigating the Appraisal Process in Scotland
Article written by Imran Kausar, General Manager, Novartis Gene Therapy
Novartis gene therapy is dedicated to developing and commercialising gene therapies for patients and families devastated by rare and life-threatening neurological genetic diseases.

Why Medicines Matter
Article co-written by Natalie Frankish, Policy and Engagement Manager for Scotland, Genetic Alliance UK
Natalie Frankish has been responsible for delivering Genetic Alliance UK's work in Scotland for over a decade, providing opportunities for people with rare, genetic and undiagnosed conditions in Scotland to have a say in the development of policies and services that impact them. Natalie has developed a Virtual Involvement Panel for people living with rare, genetic and undiagnosed conditions in Scotland and is responsible for developing the Rare Resources project designed to raise awareness and improve access to information on rare conditions. Natalie provides the Secretariat to the Cross Party Group on Rare, Genetic and Undiagnosed Conditions and is a member of the Rare Disease Implementation Board for Scotland.
geneticalliance.org.uk

Why Medicines Matter
Article co-written by Michelle Conway, Director, CRD Consulting
Michelle Conway is a freelance consultant and the founder of CRD Consulting Ltd. Her work spans across Industry and the third sector to support improved care and access to effective treatments for rare conditions. Originally trained as a nurse, Michelle has pursued a successful career spanning two decades in the pharmaceutical industry, spending a significant proportion of this time developing strategies to create improved market access for ultra-orphan medicines.
Recently graduating with a Master's in Public Policy, Michelle combines her knowledge and experience with a passion to remove barriers to effective care and treatment for those living with a rare condition by influencing policy to change the landscape. Using her excellent networking skills to engage key stakeholders from across industry, government and the third sector on priorities important to the rare disease community.

Cystic Fibrosis: How new medicines are maximising the benefits of physiotherapy

Article written by Lisa Morrison, Physiotherapist

Lisa Morrison is a physiotherapist with NHS Scotland and supports people living with cystic fibrosis.

A view from a pharmacist: How CFTR Modulators have transformed the care of people with cystic fibrosis

Article written by Iona Paterson, Pharmacist

Iona Paterson is a pharmacist working with NHS Scotland.

Fighting for families in the UK: A view from the PKU Society

Article written by Kate Learoyd, Campaign Manager, NSPKU

Kate Learoyd provides patient advocacy help to people living with Phenylketonuria. Kate manages campaign work for the National Society for Phenylketonuria. Kate has a son with PKU.

nspku.org

Approval isn't the same as access

Article written by Michaela Regan, Head of Policy and Campaigns, Muscular Dystrophy UK

Muscular Dystrophy UK (previously known as the Muscular Dystrophy Campaign) is the charity bringing individuals, families and professionals together to fight muscle-wasting conditions.

musculardystrophyuk.org

Why generics matter

Article written by Jess Hobart, Chair and Trustee, UK Mastocytosis Support

Jess has been learning from and helping people with mast cell diseases since 1995 when she first found other patients on the internet, several years after she was diagnosed with indolent systemic Mastocytosis. In the late 1990s she served as a co-chair and trustee of The Mastocytosis Society, in her native United States. In 2008 Jess moved with her husband and two sons to London and in 2014 began volunteering for The UK Mastocytosis Support Group. She holds masters degrees in public health and public policy and takes the lead with the group's research and advocacy branches.

ukmasto.org

Industry perspective: Biogen

Article written by Jonathan Randell, Senior Director, Biogen

Jonathan Randell is Senior Director at Biogen. Biogen is a biotechnology company specialising in the discovery, development, and delivery of therapies for the treatment of neurological diseases to patients worldwide.

Understanding cell and gene therapies: how Genetic Alliance UK are informing the rare community

Sophie Peet, Policy Analyst, Genetic Alliance UK

Sophie has a scientific background with a MSci degree in Natural Sciences which includes a major in Biochemistry and a minor in Chemistry. As Policy Analyst, Sophie supports the Policy team at Genetic Alliance UK and covers a wide-range of policy topics including but not limited to, genomics, UK rare disease policy, the regulation and development of innovative medicines, health technology appraisals of treatments and reproductive choice.

geneticalliance.org.uk

Project Hercules: A model of collaboration and cooperation

Emily Crossley, CEO and Founder of Duchenne UK

Emily is the co-founder and CEO of Duchenne UK. She graduated from Oxford University with a degree in modern history, and had a successful career as a reporter and anchor for Channel 4 News and CNN International.

After her eldest son was diagnosed with Duchenne muscular dystrophy (DMD), she established the Duchenne Children's Trust. The charity joined forces with Joining Jack and is now Duchenne UK. Since 2012 they have spent more than £17 million on accelerating the search for treatments and a cure for DMD, and have set up groundbreaking and award-winning collaborations, turning Duchenne UK into the UK's largest funder of DMD research.

www.duchenneuk.org

Managing rare conditions: a clinical perspective

Dr Deepa Athavale, Scottish Paediatric Renal Urology Network

Dr Deppa Athavale is a Consultant Paediatric Nephrologist at the Royal Hospital for Children in Glasgow. Dr Athavale is the Lead Clinician for the Scottish Paediatric Renal Urology Network (SPRUN). SPRUN is a National Managed Clinical Network working towards improving the overall standard of care for children and young people in Scotland with kidney and bladder related health care issues.

sprun.scot.nhs.uk

Why raising awareness of rare conditions matters

Dr Martina Rodie, Clinical Lead for the Office for Rare Conditions (Glasgow)

Dr Rodie is a neonatologist at the Royal Hospital for Children in Glasgow and is the Clinical Lead for the Office for Rare Conditions in Glasgow. The Office for Rare Conditions provides people living with rare conditions with information, signposts to appropriate resources and other organisations and connects people with rare conditions to each other. Working with health care professionals, the Office assists clinical services to provide information events for patients and families and education events for professionals.

officeforrareconditions.org

Hearing the voice of people with rare conditions

Alex Hutchinson, Trustee, Cystinosis Foundation UK

Alex is a Trustee with Cystinosis Foundation UK and has a daughter, Morven, diagnosed with nephropathic cystinosis in 2010, at 9 months old. Cystinosis is a rare inherited disease occurring in about 1 in 200,000 births within developed countries. It occurs when the mechanism removing excess cystine (an amino acid) breaks down. It is the Foundation's aim to aid researchers and the cystinosis community to strive for continued improvements to care.

cystinosis.org.uk

Working collaboratively: how the pharmaceutical industry can help drive change

Article written by Alison Culpan, Association of the British Pharmaceutical Industry (ABPI)

Alison Culpan is the Director of ABPI Scotland and is responsible for leading government affairs activity for the regional office. Alison has worked in a number of capacities in the pharmaceutical industry in the UK including sales and marketing, project management, communication and external affairs. She has also gained global experience through her roles in GSK as the Director for Global Issues working with WHO, IFPMA and as Government Affairs Director for China.

abpi.org.uk

Bringing innovation to people living with rare conditions in Scotland

Article written by Leslie Galloway, Ethical Medicines Industry Group

Following a successful career in senior management roles in both the pharmaceutical and medical device industries, Leslie Galloway was elected EMIG Chairman in 2005 and has been instrumental in developing EMIG into an influential trade association with over 300 member companies.

emig.org.uk

Developing a fair and consistent appraisal process for rare disease treatments

Article written by Karen Facey PhD CStat HonMFPH, Visiting Senior Research Fellow, University of Edinburgh

Karen Facey is a Senior Research Fellow at the Usher Institute of Population Health Sciences and Informatics at the University of Edinburgh (Edinburgh, UK). In her current role, Facey acts as the lead researcher for the IMPACT Health Technology Assessment Workplace-10 Appraisal of Medicines for Rare Diseases.

impact-hta.eu/work-package-10

Drug repurposing: the innovation we need

Article written by Rick Thompson, CEO, Beacon

Rick joined Beacon (previously known as Findacure) as the charity's third member of staff and first-ever Scientific Officer. His aim was to drive forward the charity's work in drug repurposing.

Rick became CEO in 2017, and is responsible for the organisation's growth and strategy.

rarebeacon.org

The role of artificial intelligence

Article written by Dr Elisa Ferrer Mallol, Patient Advocacy Manager, Apirito

Dr Elisa Ferrer Mallol is the Patient Advocacy Manager at Aparito. Elisa holds a Pharmacy degree and a PhD in physiology. She has broad experience in different areas of the healthcare industry, such as drug safety, medical publishing and research project management. In the last few years, she worked in the rare disease patient advocacy space, first at EURORDIS, the European umbrella of rare disease patient organisations, and now at Aparito managing the Patient Group Accelerator, a programme to help co-design digital endpoints in partnership with patient groups.

aparito.com

Public attitudes to rare disease: the case for equal access

Article written by Joe Smale, Senior Policy and Public Affairs Executive, UK Bioindustry Association

Joe Smale is Senior Policy and Public Affairs Executive for the UK BioIndustry Association (BIA). The BioIndustry Association (BIA) is the voice of the innovative life sciences and biotech industry, enabling and connecting the UK ecosystem so that businesses can start, grow and deliver world-changing innovation.

bioindustry.org

References for research used in articles can be provided on request.

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