Making the Unseen Seen

Rare disease and the lessons learned from the COVID-19 pandemic
Executive summary

Making the Unseen Seen

At the beginning of the COVID-19 pandemic of early 2020, a group of concerned advocates came together to take Action for Rare Disease Empowerment. The aim was to shed light on the unseen impact of the pandemic on people living with rare conditions in order to protect their existing services and for lessons to be learned.

Following cross-sector stakeholder discussion, three priority themes were identified under which evidence would be collated. These have subsequently been included as three of the four priorities highlighted by the UK Rare Diseases Framework.

Priority 1: helping patients get a final diagnosis faster
Priority 2: coordination of care
Priority 3: improved access to specialist care, treatment and drugs.

Information was gathered by a review of the published literature, grey literature review (including government documents, patient advocacy and public health documents) and interviews with key stakeholders, including patients, healthcare professionals, researchers, industry and advocacy groups. Although the focus of this review was the UK, the information search was not restricted to the UK.

This report reveals the impact of the pandemic on every stage of the patient journey, from diagnosis to eventual management. It catalogues the re-assignment of specialists away from rare disease, the fear of infection, the closure of clinics, the fracture of coordination of health and social care, and the delay or termination of clinical studies.

At the same time, the pandemic has accelerated the evolution of remote monitoring, the adoption of video calling and virtual appointments.

Finally, this report makes recommendations that should bring patients with rare disease into the light and make their management more robust for the future.
Foreword

Region-by-region, 2020 saw the world close its doors as a global pandemic ripped through communities. Its inhabitants were told to, ‘Stay at home. Protect the NHS. Save lives.’ History books will record this as a defining moment, one that all humankind experienced simultaneously. But, as the race for a vaccine won through and science delivered a light at the end of a year no one will ever forget, one thing is clear – while we were all in the same metaphoric storm, by no means were we all in the same boat. Lessons need to be learnt for those for whom the life raft was found to be inadequate – the rare disease community.

The inordinate strain on health and social care systems has meant that almost overnight those living with rare and complex health conditions felt set adrift, and with access to family, friends and neighbourhood support systems severed by lockdown restrictions, the short- and long-term consequences have been stark. Substantial additional pressures on existing charities, many of whom are staffed by volunteers (now juggling home schooling, working and care responsibilities), have meant their ability to respond to the crisis and provide that lifeline to bridge the ever-widening gap, was significantly compromised at this time of greatest need.

Despite these challenges, the spirit of ingenuity and resilience of all involved in this fight is beyond parallel. So too and in equal measure to the adversity faced, has opportunity emerged. New ways of thinking have led to unprecedented upscaling of specialist medical services within the NHS; fast-tracked drug development and approvals have set a new standard, and a true spirit of collaboration has shown just what is possible when we work together for a shared common vision.

So, as we lift our heads and look forward to brighter skies, now is the time to forge ahead and learn the lessons so to capitalise on the emerging opportunities.

It is time to use this lived experience borne by our rare disease community to build a legacy for future generations as we seek to protect this community through progressive regulatory, strategic and practical action.

And now is the time for that action – from grass roots to legislators we can all play our part – and play our part we must because if we do not, we effectively ignore diseases that affect over 3 million people in the UK and that cannot be acceptable.

Nicola Miller
Creative Director and Editor-in-Chief RARE Revolution Magazine
Co-founder, Teddington Trust SCIO
Headline findings

Markers for rare disease diagnosis demonstrate that the pandemic has exacerbated diagnostic delay. Individuals were reluctant to seek professional consultation, resulting in late presentations. There was a reduction in primary care capacity and referrals to secondary care. Requests for investigations pivotal in many rare diagnoses were reduced, and face to face surveillance of children aged 0-5 was impacted. All of which could add years to the diagnostic odyssey.

83% of people living with rare disease experienced delays or cancellations in diagnostic testing, transfusions, surgeries, scans and routine appointments. 66% stated disruptions negatively impacted their wellbeing, with 30% reporting disruptions were ‘definitely’ or ‘probably’ life-threatening. Deterioration of patient health was particularly notable in neurological diseases, where absence of therapies as opposed to natural disease progression was responsible.

Safety considerations, travel restrictions, shielding, trial-sites being repurposed to Covid wards and research staff either being called to the front-line, or called to replace others who were, have compounded the already fragile world of clinical development for Rare Diseases. In some cases, the result has been profound, with the termination of the only study for that disease.

The pandemic has exacerbated diagnostic delay

The pandemic has compounded existing inadequacies in health and social care

The pandemic has exposed the fragility of rare disease drug development
The three founding organisations of ARDEnt: Medics4RareDiseases, Cambridge Rare Disease Network and Rare Revolution Magazine, are grateful to all the organisations and individuals who joined us in our quest to protect rare disease patients and the services and organisations they depend on.

This has been a truly collaborative project from concept to delivery. We are indebted to all who took part for their contributions in bringing this report to fruition and to the attention of the public and policy makers.

We are especially grateful to the team at InterComm for their pro bono support in compiling this report and to Keele University interns, Himani Sehgal, Nicholas Graves and Caitlin Hampson for their invaluable support. Appreciation also to Sheela Upadhyaya, Rare Disease Expert Advisor; Dr Lara Menzies, Clinical Genetics Registrar, Great Ormond Street Hospital; Mary Bythell, National Disease Registration Service, Public Health England; Dr Kate Baker, University of Cambridge and Dr Gisela Wilcox, Honorary Senior Lecturer and Consultant in Metabolic Medicine, University of Manchester and Salford NHS Foundation Trust.

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Introduction

Rare diseases, defined as affecting fewer than one in 2,000 individuals, are individually rare but collectively common with an estimated combined prevalence of 3.5 – 5.9%. Approximately 3.5 million people in the UK live with a rare condition, but the rarity of each condition has, historically, left this large population overlooked. In recent years, however, positive change has been welcomed and 2013 saw the UK Government address rare disease as a key health priority with the publication of the first UK Rare Disease Strategy.

This strategic vision called for the best quality evidence-based care and treatment for those living with rare conditions, and concerted efforts have been made across sectors to achieve this. However, there is much work still to be done. Over the past decade the voices of the rare disease community have been gathered in a series of reports that form the backbone of the new UK Rare Diseases Framework, launched in January 2021 and bringing four areas for improvement into sharp focus.

Priority 1: helping patients get a final diagnosis faster
Priority 2: increasing awareness of rare diseases among healthcare professionals
Priority 3: better coordination of care
Priority 4: improved access to specialist care, treatment and drugs

These high-level priorities are major concerns for the rare disease community but the framework fails to fully capture the learning from the COVID-19 pandemic, which continues to make far-reaching changes to our world and our health and social care delivery.

This Action for Rare Disease Empowerment (ARDEnt) report is the product of a cross-sector collaboration of rare disease experts and includes the collation of published data on the impact of the pandemic on the rare disease community alongside insights from a range of interviewees in order to identify the post pandemic risks and opportunities in this field.

COVID-19 swept the globe during 2020 leading to significant morbidity and mortality, impacting all aspects of life, including the provision of health and social care.

Suddenly all people had to calculate risk, isolate themselves, prioritise needs and live with the uncertainty of contracting an illness with little known natural history, no robust treatment base and an uncertain prognosis. It was akin to the whole world experiencing the reality of living with a rare disease.
As the authors of this ARDEnt report observed the unfolding pandemic, it became apparent that the rare disease community may be disproportionately by COVID-19 and by the interventions implemented to hinder its transmission. Negative impacts were easily recognisable; many rare conditions render those clinically vulnerable to contracting the virus as well as to the complications of COVID-19. In response, shielding was recommended for many patients with rare diseases. This, in turn, has psychosocial effects on patients and their families: a community already reporting feelings of isolation and depression becomes further isolated. However, amidst the detrimental impacts, the authors recognised areas of opportunity, which can provide hope for the future: the rapid uptake of telemedicine and the pace at which clinical trials for vaccines were taking place. Could such adaptations be harnessed to make better progress in rare diseases?

Working to capture the risks and opportunities for rare diseases posed by the COVID-19 pandemic, and to learn from these findings, ARDEnt, a cross-sector multi-stakeholder coalition, was formed. ARDEnt comprises over 30 individuals and organisations including patients, advocacy, healthcare practitioners, industry representatives, scientists and data specialists. The principal aim of this group was to collate readily available information in order to inform the national action plans outlined in the new UK Rare Diseases Framework, and suggest best practice for rare disease patients post-pandemic. During an initial open consultation with the stakeholders, three themes were identified as being the most critical in terms of risks and opportunities for people with rare diseases. The themes are,

- Diagnostic delay
- Coordination of health and social care
- Clinical trials, research and access to treatment.

Though decided upon in May 2020 they echo those of the recent UK Rare Diseases Framework.

A major challenge of living with a rare disease is receiving a speedy and accurate diagnosis. In the UK, a person with a rare disease can expect to wait several years for an accurate diagnosis and receive a number of misdiagnoses along the way. Delayed diagnosis can lead to significant morbidity, loss of treatment or research opportunities and can be fatal. Many rare diseases result in premature deaths of infants and young children or are fatal in early adulthood. With reduced access to health services and the
halting of some diagnostic services, there was concern that the diagnostic odyssey would be further protracted.

The often complex and multi-system nature of rare conditions means that many of those are frequent users of health and social care services. Patients are often required to travel long distances to major urban areas for consultations with rare disease specialists. A person living with a rare condition is likely to have fragmented care across local and national services, and across primary and secondary care. Too frequently, coordination of this care falls to the patient or their family. The already delicate spider web of care felt even more fragile when the pandemic led to a ‘Stay at home. Protect the NHS. Save lives’ order from the UK Government.

In addition, a complex landscape surrounds the development of treatments for rare conditions. From small patient populations and lack of real-world evidence to the challenges of applying the NICE Impact model (Quality - Adjusted Life Years, QALY) to rare diseases and big price tags, taking a drug from compound to patient is an enormous challenge. The vast majority of rare conditions do not have an effective disease-specific treatment. However they are often chronic and disabling, can be life-limiting and invariably profoundly impact the lives of those and their families. Therefore research and drug development is essential for improving the lives of those with rare conditions. In a pandemic situation, with pre-clinical and clinical research halted or limited, opportunities for advancing disease understanding and treatments are further curtailed.

In this report, the ARDEnt group present learnings from how the pandemic affects those living with rare conditions and the services they rely on. We include risks that need mitigating and opportunities that need embracing with recommendations for each of the three themes.

Method

Following stakeholder discussion, three priority themes were identified under which evidence would be collated. These have subsequently been included as three of the four UK Framework for Rare Disease priorities.

Theme 1: Diagnostic delay
Theme 2: Health and social care coordination
Theme 3: Research and drug development including access to treatment

Information was gathered by the following methods: a review of the published literature, grey literature review (including government documents, patient advocacy and public health documents) and interviews with key stakeholders, including patients, clinicians, nurse specialists and representatives of patient groups and clinical trial specialists. Although the focus of this review was the UK, the information search was not restricted to the UK.
Diagnostic delay

Introduction

If you have a rare disease, the odyssey from first symptoms to diagnosis can take years. Patients often undergo multiple referrals, investigations, incorrect diagnoses and the frustration of unanswered questions. Their condition may deteriorate unaddressed during this time. Reduced access to health services and halted diagnostic services have further exacerbated diagnostic delay.

The team has addressed five core stages in the diagnostic pathway and, separately, children aged 0–5 years, a stage identified by NHS England (NHSE) as critical to prevent serious disease and promote lifelong health (Figure 1).

Because of the challenges in collecting absolute numbers of people diagnosed with a rare disease in a given time period, four rare liver disorders were examined as a proxy. These conditions were chosen as the diagnosis is made as an inpatient associated with a liver biopsy, enabling robust identification in HES (Hospital Episode Statistic) data. The average number of diagnoses per month in January to September 2020 showed a reduction of 36% in comparison to the same months in 2019, suggesting the pandemic caused an exacerbation of delay.

Confirmatory evidence came from a specialist nurse who recorded new presentations of one rare metabolic condition to specialist services dropping from an average of 13 per year in 2017–2019 to only seven in 2020, four of whom were diagnosed in January or February.

Patient groups have also noted the decline in the number of newly diagnosed families requesting information and registering for services. One group reported a 33% decline in 2020 compared to 2019. SWAN UK reported a 52% reduction in online registrations in 2020 compared to 2019.
How was pre-engagement with healthcare?

‘Stay at home. Protect the NHS. Save lives’ messaging by the UK Government from March 2020, resulted in 4 people in 10 feeling too concerned about burdening the NHS to seek help from their GP in April 2020. People were confused about what services were still available and concerned about the danger of going to hospitals. Emergency department (ED) attendances reduced by approximately 25% across the UK In a survey conducted in April 2020, one third of paediatricians working in EDs or paediatric assessment units witnessed delayed presentations.

What happened in Primary Care?

Diagnosis of a rare condition often depends on multiple consultations and a holistic view of the patient. This was very challenging even before the pandemic. The number of primary care appointments fell from 6,026,140 in the first week of March 2020, to 4,225,502 in the last week. Even December 2020 figures were still 11% below January. Of these, the number of face-to-face consultations declined from 80% to 60%, replaced largely by telephone consultations and video consults.

Were referrals to secondary care?

Referrals to specialist services fell during the pandemic; this is reflected in data from Clinical Genetics services which show that in some areas referrals fell by >50% during April-June 2020.

How were secondary and tertiary care?

Outpatient appointments, inpatient and diagnostic services changed significantly, especially during the peaks in COVID-19 cases. The Clinical Genetics Society Telemedicine Survey 2020, captured 2,204 responses highlighting some of the challenges in maintaining services during the pandemic (Table 1).

Was there an impact on diagnostic services?

The most frequently requested investigations fell from 1,967,376 per month in 2019 to 1,521,507 per month in 2020. This was reflected in the investigations most commonly used in rare disease diagnostics. When comparing the average for April–December 2019 to April–December 2020, there was a 40% reduction of gastroscopies, 30% reduction in echocardiography and 24% reduction in radiology with contrast.

“As a dermatologist video consultation was unexpectedly disappointing. We do close examination of the skin, so essentially, we could not do most of what we need to do”

Dr Robert Sarkany, Consultant Dermatologist and Head of UK National Xeroderma Pigmentosum Service

Table 1: Sample of challenges and advantages identified with remote consulting from The Clinical Genetics Society Telemedicine Survey 2020.

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<thead>
<tr>
<th>Challenges</th>
<th>Advantages</th>
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<tr>
<td>Examining patients through video/photography</td>
<td>No travel required</td>
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<td>Establishing rapport</td>
<td>Avoids hospital anxiety</td>
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<td>IT problems</td>
<td>Quicker results and disease management</td>
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<tr>
<td>Adapting to user needs e.g. sensory or cognitive impairments</td>
<td>Shielding/self-isolating maintained</td>
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<tr>
<td>Explaining complicated concepts</td>
<td>Potential for virtual specialised, multi-disciplinary services and diagnostic work-up</td>
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Genomic testing, key for most rare diseases, was rationalised with guidance on testing prioritisation issued by NHSE in March 2020. Genetic laboratories were instructed to reduce testing to urgent services only, to release capacity to support COVID-19 testing. Requests for microarrays, the first line genetic test for many patients suspected of having an undiagnosed rare disease, substantially reduced (Figure 2).

**How were children aged 0–5?**

75% of rare conditions present in childhood and 30% of people with a rare condition die before their fifth birthday. Infant Physical Examinations (one element of NIPE) were delayed two weeks and performed at single consultations with first immunisations, reassuringly without impact on NICE KPIs. Data for how one- and two-year checks have been impacted will be available in November 2021.

The ‘Babies in Lockdown’ report presented an online survey of 5,474 expectant mothers, parents of infants and toddlers, of whom fewer than one in ten had seen a health visitor face to face in the 103 days of the first lockdown. The ‘working for Babies Report’ identifies ‘threats to physical health as a result of lockdown, reduced health services and parental reluctance to access them’ as a key hidden harm of lockdown on young children. Restrictions in social interactions have seriously reduced the number of people young children encounter in their family, society and healthcare. This has left parents to oversee their children’s developmental progress without external support from experts from healthcare professionals or extended family members. A nurse specialist highlighted the case of an infant who received a diagnosis of a rare metabolic condition during the first national lockdown because his condition was identified by his grandmother. She recognised the enlarged abdomen when changing his nappy as similar to that of her late child who had died 30 years previously. With this knowledge she demanded that he was seen in A&E urgently, where he received his diagnosis. Had this child not lived with his grandparent the diagnosis may not have been made.

**Discussion**

The limits of coding for rare diseases and the inability to use routinely collected data for rare disease identification rendered it very challenging to compile this report. However, surrogate markers of rare disease diagnosis rate, including routinely collected data from four rare liver conditions, have demonstrated that rare disease diagnosis has been dramatically by the pandemic.

“Many of the labs and a lot of geneticists were redeployed, resulting in dramatic reductions in diagnosis”

CEO of umbrella organisation for rare genetic conditions

![Figure 2: Number of microarray requests over a 16 month period from 2019 to 2020.](image)
Recommendations

Remote clinical consulting should be optimised

This must include appropriate triage to identify when face-to-face consultation is preferable, and to ensure patients are not disadvantaged by whichever form of consultation is chosen. Local community services need to be able to support such working with improved remote access to testing.

The use of clinical informatics in rare disease is enhanced

Healthcare data can support the understanding of diagnostic trends, natural history and service planning. To enable this we advise improving rare disease clinical coding and resource commitment to rare disease data infrastructure.

Actions are taken to identify undiagnosed rare disease patients missed due to the pandemic

Proactively seek out the undiagnosed, including a face-to-face assessment for every child 0–5 not seen since March 2020. Further, a plan for the investigation and referral backlog to include bringing diagnostics earlier in the patient workup.
02
Coordination of health and social care

Introduction

Rare disease before the pandemic

For those with a rare disease, a lifetime of complex health and social care coordination awaits. Generally degenerative in nature, rare diseases often affect multiple body systems, resulting in an increased disease burden during the person’s lifetime. Healthcare coordination frequently becomes disjointed as patients must collaborate with specialists across disciplines, often in different locations.

Rare Disease UK’s ‘Rare Reality Report’ highlighted that 83% of those surveyed said they do not have an appointed care coordinator, while a third visit three or more separate clinics, with some attending up to ten. Over 50% attend one or more clinics every three months for condition-specific appointments.

Additionally, families struggle to access Education Health and Care Plan (EHCP) and specialist support and equipment, which then falls to caregivers to coordinate. COVID-19 has exacerbated these extensive demands.

What follows highlights the disproportionate impact of COVID-19 on people living with rare diseases: they experienced disruption to and the loss of health and social care services, which will be felt long after the pandemic ends.

Impact on access to healthcare and social services

Throughout the pandemic those with rare diseases faced significant disruption to access to health and social care. 83% of people living with rare diseases experienced delays or cancellations in diagnostic testing, transfusions, surgeries, scans and routine appointments. Treatments which healthcare services considered ‘non-essential’ and ‘elective’ were cancelled or postponed; however, patients see these as vital for the management of their conditions. Some appointments were delayed between one and six months, whilst others were cancelled indefinitely. Due to the nature of rare diseases, pauses in treatment can cause rapid progression of the disease and severe deterioration of health.

We are seeing a negative impact particularly for people who have neurological conditions. The closure of day centres and respite services and the cancellation of physiotherapy, speech and language and other services has been really devastating for some. Some have taken significant steps backward, which is being noted by our neurologist, who is seeing severe neurological degeneration which is not disease progression, but the loss of all those therapeutic inputs

Dr Robert Sarkany, Consultant Dermatologist and Head of UK National Xeroderma Pigmentosum Service

Sixty six per cent of rare disease patients stated disruptions negatively impacted their wellbeing. 30% reported it was ‘definitely’ or ‘probably’ life-threatening.
In young patients who require orthotics, these need replacing regularly as they grow. With services cancelled this year, these patients are now without orthotic support, further exacerbating their conditions.”

Consultant Specialist Paediatrician at Tertiary Hospital

Forgotten and alone – mental health impacts

COVID-19 restrictions on healthcare left the rare disease community feeling forgotten and unheard. They felt disproportionately; a feeling compounded for some by the psychological burden of knowing they have a higher risk of mortality than the general population were they to contract COVID-19. 50% of respondents to a CDH UK survey reported feeling ‘extremely worried’ at the beginning of the pandemic. Anxieties over receiving equal care should they contract COVID-19 were also apparent, acting as a driving force in families who continued to shield long after restrictions lifted.

Services or closed during the pandemic:

- Paediatric services have been limited
- Outpatient services were paused or went online
- Elective surgery stopped
- Face-to-face multidisciplinary clinics stopped

“Our professionals are just monitoring, rather than making any intervention. Our appointments were cancelled multiple times, but these appointments are a priority in keeping my daughter’s condition stable. We don’t have any dates or any idea when they will resume.”
A physical and psychological burden

Alongside disruption to healthcare, social care disappeared overnight, leaving families unable to access carers, therapies and respite care because of closure of units and limited availability of PPE and difficulty accessing it.\(^5^1\)

The SHARE study, led by Southampton researcher Professor Anne Sophie Darlington, established that 95% of respondents were apprehensive about allowing carers into their homes due to the risks posed and confusion over social distancing rules. Care, therefore, became the parents' responsibility, which alongside the isolation of shielding, led to a damaging impact on families' mental health.\(^5^5\)

This strain negatively impacted the symptoms of those with rare diseases, inducing further stress, and thus forcing them into an endless cycle of fear, isolation and exhaustion.\(^3^5, 4^0\)

“Where home services were available, families were anxious about the risk of contracting coronavirus from additional people coming into the home, even though they were desperate for support. Many were told ‘if you are saying no to the services now you will need to reapply if you want to pick them up again.’ This is a real worry as these services are often hard fought for and risk of losing them causes significant distress.”

Leading genetic charity

Attrition of and changes to NHS services

‘The Rare Reality of COVID-19’ report highlighted that of the 80% of those receiving NHS support for their rare disease, 40% reported closures of the units providing their care. Clinicians were redeployed, while resources and funding were redirected to treat COVID-19.

When rare disease patients did attend hospital, sometimes there were no protective protocols in place, and 16% reported an absence of crucial equipment due to priority being given to COVID-19 wards.\(^5^2\) As the rare disease population became increasingly aware of the risks, they became fearful of attending hospitals, leading to delays in the presentation of symptoms.

“We found families delayed in seeking care, not because we couldn't see them but because they either feared coming or didn't want to disturb us because we were busy. This meant when we did see people there were some delayed presentations.”

Consultant Specialist Paediatrician

Both paediatric assessment units and emergency departments observed a decline in the number of children attending hospital; 241 paediatricians witnessed delayed presentation of symptoms, and suggested this delay was significant in nine deaths.\(^5^3, 5^4\)

Furthermore, clinicians have indicated that reduced clinic attendance influenced treatment decisions, as they were unable to initiate or switch treatments without testing. In some cases, patients were obligated to continue with current treatment plans to avoid intolerance-related appointments.

As departments and facilities tried to cope with the increasing demands of COVID-19 and physicians were redeployed, new and improved services were almost impossible to implement.\(^5^2, 5^3, 5^5-5^7\)

“It's had a big impact on morale. For colleagues, who are keen to get new and improved services working, the disruption has been completely devastating. Working conditions have also been tough. And the frightening nature of intensive care has been a bruising...
experience for some people redeployed to it.”
Dr Robert Sarkany

Failure to meet educational needs

Rare diseases can coincide with Special Educational Needs and Disabilities (SEND). Children with SEND will either attend specialist schools or require additional support within mainstream school settings.

School closures and the Coronavirus Act 2020 suspended the legal responsibilities of local governments to provide support for children with SEND. Education, alongside healthcare, now solely fell into the hands of parents.

Twenty per cent of parents of children with rare diseases reported ‘extremely severe’ or ‘severe’ stress, a greater percentage than that found in the general population.

There were positive outcomes – some individuals reported ‘enjoyed spending more time with family’ and there was ‘less running around’. Additionally, some with sensory disorders found the home routine easier to cope with and felt calmer as a result.

However, further anxiety arose with the return to school as parents debated whether they should allow their children to return after shielding due to a lack of information on the potential risks.

“The lack of information on the return to school for children who had been shielding has meant we have been inundated with calls from fraught parents.”
Consultant Specialist Paediatrician

Patient group organisations stepping into the breach

The pandemic has had considerable impact on the charitable sector. Overnight, finances were put at grave risk, and the strain of maintaining operations when both staff and vital volunteers were juggling home-schooling or caring responsibilities often resulted in a reduced ability to carry out core activities.

This was accompanied by a surge in demand for information and support from the community and, from the outset, rare disease organisations were at the core of this frontline response. These organisations provided those living with rare diseases with PPE, supplementary information specific to their condition and mental health and social care support.

Lacking clear guidance from healthcare professionals (HCPs) and with the closure of many healthcare services, families turned to support groups. Staff also found the pressures of trying to reassure families stressful, particularly at the start when so little was known about the virus.

“We found it difficult because we were getting lots of phone calls from a lot of very concerned people. I think people expected us to have more knowledge and connections than we do, especially early on.”
Patient Group Leader

www.istock.com/jacoblund
Utilising technology

One opportunity that has arisen from the pandemic is the adoption of telemedicine. Prior to COVID-19, 81% of routine appointments were face-to-face; by April 2020, 71% were virtual.67

Telemedicine has both benefits and limitations for the rare disease population. Previously, patients could be faced with substantial journeys in order to attend specialist clinical appointments; this was both expensive and physically and emotionally demanding. Telemedicine helps to eliminate these burdens.52

“Families appreciated being able to have their multidisciplinary meetings through Zoom. It’s easier being able to have an appointment with lots of medics at once. Whereas, before it was so difficult for people, going back and forth to hospital to see each doctor individually.”

Charity leader

Telemedicine is, however, reliant upon communication and is more effective in some medical disciplines than in others. Thirty-five per cent of patients had difficulty effectively describing symptoms.68

Limitations of video consultations and the use of home photographs were also highlighted as problematic, with some HCPs finding these much less successful than expected. Digital exclusion and privacy issues have also been raised, so whilst telemedicine is a solution for now, rare disease patients would like the option of returning to face-to-face appointments post-pandemic.69-71

I worry about the families that are digitally excluded or even just excluded by language where they might normally use an interpreter.

Consultant Specialist Paediatrician

Case study

I’m David. I’m the only person in the UK diagnosed with occipital horn syndrome, along with POTS (postural orthostatic tachycardia syndrome), long QT syndrome and a few others. Pre-COVID, I had regular physio, occupational therapy, hydrotherapy, clinic appointments, procedures and operations. Although more physio and pain management would have been good and I would have loved a dedicated care coordinator, I felt I was being looked after, given the complexity of my conditions.

When COVID struck, I got a letter advising that I use my discretion about shielding. Uncertain, I chose not to shield – to look after my mental health.

Lockdown has been difficult and frustrating. Accessing my GP has been a nightmare – hard to get appointments, no regular tests, poor communication and everything blamed on COVID. So many appointments were cancelled. It felt like the world decided COVID was the only thing that exists. Having a rare disease comes second.

My mental health has really suffered; it’s been horrendous – we live in a small one-bedroom flat with no garden or balcony. I cope with my rubbish health by getting out and about and living an active ‘normal’ life – lockdown has been a reminder that I am ill and that I can’t escape it.
We’re coping, but we’re struggling. Now in 2021, I’m worried about the backlog of appointments that I will face. I’m grateful that I have just had a small operation and I am starting to have a few more (hopefully), so I’ll be ‘shielding’ to some degree. But I feel okay with restrictions being lifted.

One positive is telemedicine – video calls for my rare disease mental health sessions have been great. Telemedicine should be a choice though and not remove all patient contact with clinicians.

Recommendations

**Expert mental health support should be part of the care pathway for people with rare conditions and their carers**

Research demonstrates that living with a rare condition has a significant negative impact on the mental health of patients and their families. The current pandemic has further exacerbated this issue and highlighted the woeful lack of relevant services. Leading mental health charities and NHS services should collaborate with patient organisations and support groups, pooling resources so that patients can access tailored mental health support.

**People with rare disease should have their treatments, therapies and care, essential for halting disease progression, protected**

Viable models for cross-discipline care coordination in rare disease to better treat, support and protect standards and continuity of care. The pandemic has highlighted even more that access to and coordination of care for rare conditions is fragile and difficult - to make a success of the UK Framework for Rare Diseases, we need to get this challenge right.

**NHS and Government support for crucial patient organisations**

Patient organisations currently fill a vital role in supporting the NHS to serve people living with rare conditions. We recommend closer collaboration between the NHS and support organisations to foster improved support and more equitable and sustainable funding models for service delivery.
Obtaining a diagnosis is just the start for someone by a rare disease. Once diagnosed, it is of little comfort to discover there is probably no treatment or cure and frustrating for the healthcare professionals involved that no-one seems to care. Little incentive has been provided for pharmaceutical companies to develop specific therapies.

However, the past 20 years have seen several important developments, including European Medicines Agency (EMA) Guidelines for Rare and Orphan Diseases in 2000; the Human Genome project (more than 80% of rare disease have genetic origins); the rise of real-world evidence as an alternative to traditional clinician studies and the 2009 EMA guidance ‘Better Medicines for Children’ (75% of rare diseases impact the paediatric population).

And then in February 2020, COVID-19 appeared.

As a result, worldwide more than 2,500 trials were terminated or withdrawn between the end of 2019 and May 2020, double the same period in 2019. Almost 45% gave COVID-19 as the reason.

Four months into the pandemic, 70% of clinical trials and studies – funded by the Association of Medical Research Charities (AMRC) members – had been stopped, paused, or delayed. Early-stage trials were impacted most severely, as new recruitment almost stopped completely. Over 1,000 charity supported clinical research staff were seconded to front-line patient care.

Although a search of the impact on rare diseases through the ClinicalTrials.gov website was confounded by the different definitions of disease, 404 UK rare disease studies were identified. Of these 404 studies, 157 were focussed on 5 rare conditions - Cystic Fibrosis, Haemophilia, Duchenne Muscular Dystrophy, Fabry Disease and Sickle Cell Anaemia. The other 247 studies spanned 115 different rare diseases. Some patients found that the sole UK trial for their condition was negatively impacted.

The metadata study of the ClinicalTrials.gov website demonstrated that trail sponsors were slow to update their trial status. As a result it was difficult to ascertain the number of trials stopped, suspended, continued or completed.

A more realistic insight into the impact of the pandemic on UK rare disease trails was captured through interviews with a selection of physicians, patient organisation representatives, and pharmaceutical executives involved.
Negative impacts of COVID-19 on rare disease clinical trials

Termination of the sole clinical trial
For some ultra-rare disease patients, the sole clinical trial investigating their condition was halted by COVID-19, including Alström Syndrome (AS) - where all clinics had been cancelled by July 2020.

Redeployment of NHS staff
Trial procedures were stopped when staff were re-deployed. The metaphyseal chondrodysplasia type Schmid (MCDS)-Therapy trial into skeletal dysplasia (SD) could not obtain scans nor gather sleep study data. Similar scenarios were experienced within the Motor Neurone Disease-Systematic Multi-arm Adaptive Randomisation Trial (MND-SMART) and Tay–Sachs disease (TSD) studies.

Impacted recruitment
Many studies were required to temporarily halt recruitment, including the TUDCA-ALS (Tauroursodeoxycholic Acid-Amyotrophic Lateral Sclerosis) Trial for MND. Aiming to repurpose a drug for MND treatment, the TUDCA-ALS trial had reached 40% of its recruitment target when COVID-19 hit. After months of delay, recruitment recommenced in August 2020 but has since progressed more slowly than in countries outside the UK.

Disruption of monitoring
Patients already on essential treatments could often continue, but with gaps in monitoring of biomarkers (leading to protocol deviations). There has been a lack of validated biomarkers and a subsequent loss of valuable data. The Duchenne Muscular Dystrophy Hub (DMDH) reported an inability to monitor trial efficacy, in addition to the MICROCAL trial for MND. The DMDH reported difficulties in obtaining remote consent from patients, compounded by protocol complications. Six-month gaps in SD patient natural history created protocol deviation, subsequently requiring feasibility, screening, and patient eligibility to be revisited.

Access to trial sites and treatment centres denied
It became almost impossible to visit trial sites due to safety considerations, travel restrictions, shielding, trial-sites being repurposed to COVID-19 wards and research staff either being called to the front-line, or called to replace others who were. The MND-SMART trial, announced on the BBC news, aimed to slow, stop or reverse the progression of MND. MND has an average life expectancy of 18 months (post-diagnosis) so MND-SMART clinicians sadly anticipate losing a significant proportion of their recruited participants during COVID-19. The DMDH reported the loss of their animal colonies due to researchers being unable to access the laboratories, causing delays of at least six months in-order to rebreed the animals.

Significant confusion as to who should be shielding
Most rare disease clinicians and specialists spoke of a lack of swift communication from the UK Government and reported discrepancies amongst their patients as to who had been advised to shield. The resulting confusion studies on mucopolysaccharidosis and AS, among others. Simultaneously, concerns arose on how to monitor patient safety, then for example at the DMDH.

Staff were redeployed and the pharmaceutical company terminated the only Alström Syndrome trial
Funding has dried up

This has been a particularly problematic issue for rare disease clinical trials due to the multi-faceted impact of continued trial costs alongside an estimated cash shortfall from medical research charities in 2020 of £310 million (reported by the AMRC). In addition, there has been ambiguity over whether university researchers and PhD students were eligible for furlough. During 2020, many clinical trials were informed of previously dependable financial sources would be diminishing or stopping completely, including grants already committed to. Financial impacts will likely continue for the foreseeable future as many large fundraising events have not yet recommenced.

Dislocation with other study countries

Several rare disease clinical trials reported knock-on effects to European or other international partners as well as major gaps within their data. The MCDS trial for SD – a multicentre international trial, with partners in Europe and Australia – aimed to finish simultaneously across all centres, but the UK’s timeline has become mismatched with the other partners, causing detrimental effects throughout the whole study.

Positives of COVID-19 on RD clinical trials

Adaptation from clinicians and enthusiastic uptake of remote patient monitoring

Uptake of remote patient monitoring has been rapid and enthusiastic. Despite numerous delays caused by the COVID-19 restrictions, a great deal of patient monitoring and data collection has switched to virtual alternatives, including patient-clinician consultations via video link, telemonitoring, test procedures performed by home visit nurses and wearable devices that can supply 24–7 information on a patient’s condition.

Clinical trials moving towards a more patient-centric approach

Most of our interviewees related a shift of clinical trials and sponsors to a patient-centric approach, primarily resulting from a need to perform trial procedures and patient monitoring that is much less dependent on clinic/hospital attendance. This has reduced the travel required, and inconvenience experienced by patients, as well as reducing trial costs and the proportion of clinician time devoted to data collection. This has the potential to significantly decrease patient attrition in scenarios where patients become increasingly disabled within short-time frames.

Speeding up of ethics and R&D approvals

Processes relating to ethics and R&D approvals have become more efficient, moving away from being complex and time-consuming procedures. Similar improvements have occurred between trials and relevant trusts, prompting many to question why it took such extreme circumstances for progress to be made.

Rare disease clinical trials may receive more funding due to ‘spotlight effect’ resulting from COVID-19. Correlations between COVID-19 risk and rare disease populations have shone a spotlight on rare disease, emphasising the need for further clinical trials into these conditions. Small pharmaceutical companies and investors are currently attracted to the field of rare disease thanks to recent offers of financial backing should they commit to rare disease research.

“We have identified opportunities for home based trial procedures, which are much more patient-centric.”
Recommendations

Decentralised trials and remote monitoring need to be implemented widely, both as default and to some extent as backup.

Some biomarkers can be measured at home by patients, carers, or technology; others could be done by healthcare professionals visiting the home setting.

Virtual site visits to be encouraged.

This will allow research to continue seamlessly during pandemic situations, but also significantly reducing burden on patients and families during all times.

Encouragement for real world evidence to be included as an option within regulatory studies in the rare diseases.

Real world evidence gathering may be less susceptible to the impact of a pandemic; a focus on real world evidence could, in some circumstances, reduce the damage caused by disruption or loss of clinical trials.
Recommendations

Diagnostic delay

Remote clinical consulting should be optimised
This must include appropriate triage to identify when face-to-face consultation is preferable, and to ensure patients are not disadvantaged by whichever form of consultation is chosen.

The use of clinical informatics in rare disease is enhanced
Healthcare data can support the understanding of diagnostic trends, natural history and service planning. To enable this we advise improving rare disease clinical coding and resource commitment to rare disease data infrastructure.

Actions are taken to identify undiagnosed rare disease patients missed due to the pandemic
Proactively seek out the undiagnosed, including a face-to-face assessment for every child 0–5 not seen since March 2020. Further, a plan for the investigation and referral backlog to include bringing diagnostics earlier in the patient workup.

Coordination of health and social care

Mental health support should be part of the care pathway for people with rare disease
Research demonstrates that living with a rare disease has a significant negative impact on the mental health of patients and their families. The current pandemic has further exacerbated this issue and highlighted the woeful lack of relevant services. Patient organisations and support groups need to collaborate with leading mental health charities and NHS services, pooling resources so that patients can access tailored mental health support.

Treatments, therapies and care for people with rare disease and which are essential for halting disease progression should be protected in law
A robust set of guidelines to ensure those with rare disease are not disproportionately disadvantaged. Recognition that some treatments and therapies for those with rare diseases cannot be deemed ‘elective’ and are essential for maintaining minimum health. Recognition that to withhold these treatments and therapies results in negative impacts upon health and quality of life, which often cannot be reversed and that may lead to avoidable disease deterioration and, in some cases, loss of life.

Support group funding models need urgent assessment to ensure stability
The current pandemic has irrevocably highlighted the precarious sustainability of rare disease support groups. Support groups play an essential role in the practical, emotional and educational support of individuals and families by rare disease. A service not currently met by either health- or social care settings and bodies. It is our recommendation that a thorough consultation on the future of financial support of these groups should be undertaken to deliver a robust and sustainable future for their services.
Access to treatment and productive research and drug development

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References - Endnotes


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