2021: A year in review

2021 has been another year of confusion and contradiction … but it has also been a year of united action by communities, a year when new legislation has been brought forth, and a year when healthcare started to change.

As 2021 comes to a close, we'd like to take the time to think back on the year it has been. Not dwell on the ongoing scientific details of Covid-19 itself, but to appreciate some of the many things we have achieved together because of, or despite, the pressures of the pandemic. We truly believe that this year is one we can all be proud of for the way we have supported each other during hardship, built on successes, and made changes needed to achieve even more in 2022.

Community power

It is right to start our reflections by recognising the unique and powerful contribution that the people who live and work in rare disease have made during the ongoing pandemic. Much of the genetic techniques underpinning vaccines like Pfizer-BioNTech's or Moderna's were refined when trying to tackle the genetics underpinning over 70% of rare conditions[1]. In addition, many of the widespread adaptations necessary for the restart of some routine healthcare during 2021 were already recognised and called for in our community. The skills and experience - in linking geographically remote individuals, building capability teams from very few experts, and delivering in uncertainty, has proven to be invaluable to leaders as we try to tackle the consequences of the pandemic.

People living with rare conditions have been disproportionately affected throughout the pandemic with severe disruptions in essential care occurring for 84% in Europe, with 33% of these interruptions being life-threatening[1,2]. Yet, despite this, our networks and communities have shown their united strength, built on the shock of 2020, and adapted fast to the digital world. An example of this is the Rare Disease Day that happened at the start of the year[3]. Despite being virtual, this

managed to unite experts from around the world, including patients, caregivers, medical specialists, academics, regulators, and clinical researchers such as ourselves. It provided an excellent platform for discussions, awareness, and advancing the rare agenda. It also provided the springboard for many national awareness-raising activities in communities across the globe. This enormous achievement, despite the ongoing pandemic, demonstrates that we can do it. Not everyone likes communication to be virtual, but we are on the front edge of exploring what is possible. We're taking steps to figure out how to blend international, and national approaches so that we can begin to link together communities the right way, as well as to support every individual optimally. And, as shown this year, we're doing it together.

Evolving frameworks

Many of the frameworks and platforms supporting the development of new medicines for people with rare conditions have been advanced during 2021. We begin with the publication of the Rare 2030 Foresight Study Recommendations[4]. These are proposed policy recommendations to support those with rare conditions. They provide the 10-year roadmap for integrated European- and national-implementation and were developed with input from a large group of patients, practitioners, and key opinion leaders. Essential areas discussed include earlier and more accurate diagnosis, access to high-quality person-centred healthcare and affordable treatments, partnership with patients, innovative, focussed clinical development, and optimisation of data for patient and societal benefit. Previous policy frameworks have achieved so much in the past, but 2021 is the year that people have come together to take ownership this new, modern framework to build the community future.

> "The health of 30 million people living with a rare disease in Europe should not be left to luck or chance. Rare 2030 prepares a better future for people living with a rare disease in Europe with foresight."
>
> ***Rare 2030 Foresight Team***

The UK also released its diseases framework published at the start of the year[5]. This focusses on several priority areas, many of which were also reflected by the community itself in its own report on pandemic impacts and priority improvement areas (ARDEnt Report[2]). These were

- **Faster diagnosis:** Outlining aims for programs such as enhanced screening, diagnostic tools, and better ways for doctors to spot when someone should undergo advanced genetic testing.
- **Increased awareness of rare conditions in healthcare professionals:** The healthcare professionals people turn to in times of need often don't have sufficient awareness of rare diseases to know how to provide optimal support. Such healthcare workers need training in genomics, particularly in rare diseases, and excellent examples already exist in many patient organisations.
- **Better coordination of care:** Many rare conditions affect multiple systems in the body, all of which are treated by different experts. This creates a time consuming and complex logistical burden for families, as well as poor communication and coordination between specialities.

The aim is to adopt the advances in technology to improve information-sharing, condition-monitoring, and remote service-access required.

- **Improving access to specialist care, treatment, and drugs:** The UK is aiming to support the NHS in adopting more innovative new treatments and methodologies. During 2021, funds such as the Early Access to Medicines Scheme (EAMS), the Accelerated Access Collaborative (AAC) and the expansion of the Innovative Medicines Fund have all been open to public consultation, and NICE has been re-evaluating the way it reviews data for health technology assessments.

Strong themes run throughout all areas, including highlighting the importance of co-creating improvements with patients themselves (particularly from under-represented communities), international collaboration (especially in the wake of Brexit regulation changes), adopting new digital and data inventions (e.g. telemedicine, or improving the data sharing between databases), and the fundamental recognition that we all need to work together to make change happen.

United States have also made many strides forward in 2021. One of these was the initiation of a partnership between the FDA and public, private, and non-profit sectors to foster development of gene therapies in rare genetic conditions affecting populations too small for viable commercial development[6,7,8]. The group is called the Bespoke Gene Therapy Consortium (BGTC), and its aims are to make adeno-associated virus (AAV) technology more accessible to a broader range of diseases; to streamline preclinical and product testing, to facilitate novel scientific and regulatory advances, and to bring gene therapy to a wider range of people who need it.

Another exciting development was the FDA-funded delivery of the 'Rare Diseases Cures Accelerator-Data and Analytics Platform' ((RDCA-DAP®) initiative[9]. This platform will give the community the centralized and standardized base to host and share de-identified rare diseases data that is needed to support increased treatment innovation. It was created through a partnership between Critical Path Institute (C-Path), the National Organization for Rare Disorders (NORD®) and the U.S. Food and Drug Administration (FDA) and has grown to include many others throughout the rare disease community.

> "There is a lot of enthusiasm for seeing this platform become all it can be for patients and drug developers. It is not just about the data. This is a place to generate solutions in a highly collaborative way."
>
> ***Jeff Barrett, Ph.D., F.C.P., C-Path Senior Vice President and RDCA-DAP Lead.***

Embedding innovation in rare disease trials

The delivery of clinical trials for rare diseases has always required specialist focus and skills (see our previous white paper: Key considerations when conducting rare disease paediatric trials). However, even on this background, the impact of Covid-19 shook the very foundation of clinical research in 2020. Many of the challenges that were recognised have continued in 2021 – for example, families are still having to be guided through Covid restrictions and implications for their care during trials. The transition period for Brexit also ended this year and the consequences have also hit any clinical

trials involving UK clinical sites and/or UK-based patients, with extra approvals required, documentation to support the import/export of pharmaceuticals and logistical supply chain issues[10].

It is, however, not all doom and gloom. Telehealth, digital healthcare practice, and remote/home sampling approaches that the rare disease community have requested for many years are now increasingly normal within the healthcare service. This familiarity in many regions across the globe is creating a step-change for those of us working in rare trials. It is no longer normal for sites to assume that everyone will come into the clinic for every visit. Instead, our discussions with new sites about decentralised trials is met with familiarity. People are more open about technologies and data gathering practices that support people in their own homes. This means that specialists in rare can instead focus energy on moving the field forward rather than persuading the majority to adopt what – for us – has seemed achievable for a long time. Even the inclusion of representative patient voices in trial design, set up, and delivery has, in some ways, become easier during this year. Instead of spending hours travelling to a face-to-face patient engagement event with a clinical development team, patients can now achieve this in a relatively quick virtual discussion[12]. This is a step towards broader access. However, as pointed out by patient experts themselves, it is only the start - even greater variety of approaches will need to be built on this foundation to encourage more diversity in patient representation[11].

Preparing for 2022

We have ourselves gone through some change in 2021 with Orphan Reach and Emmes merging to create an international specialised rare disease centre[12]. This consolidates our expertise in delivering trials that support rare conditions and provides even greater resources to help even more rare disease families. As discussed during our launch at the World Orphan Drug Conference[13], this sets us up for the challenges ahead – innovating further in paediatric rare disease trial design and delivery and adopting novel technological solutions that improve patient experience.

Another example of the centre's united strength is the increase in our ability to identify novel trial endpoints by linking Emmes' strong biostatistical function and ability to collect and analyse real-world evidence with our engagement of patients and expertise in rare (see our previous white paper: Rare trials you can trust: Biostatistics). Such advances not only help with monitoring disease progression, but they also ensure that trials are more feasible and faster than ever before – speeding up the time it takes to get new medicines to those who needs them most. Rapid uptake in decentralised trials around the globe can also be better supported with the wider roll-out of patient and trial-staff education that is going to become so important. Our 'Clinical Outcome Assessment' and 'Patient Reported Outcomes' training has been established and honed through years of use. As people begin to complete these activities on their own, in remote locations, the need for such established training packages to support those individuals will also increase. The merger gives us a greater global scale and resource to deliver and ensure that the quality of information collected in our trials, regardless of which innovative study design approach we use, is of the highest, and most useful, standards.

As 2022 arrives the focus on integrated patient voices in rare disease trials continues to grow. With patients at the centre of everything we do, our studies are designed with ever more engaging ways for people to access services, support and trials. As Liz Curtis, Chief Executive Officer and Founder of The Lily Foundation said:

> Here at the Lily Foundation we think that orphan drug developers are becoming increasingly aware of the importance of patient involvement in trial design, especially as badly designed trials wont retain the numbers that are needed to gain valuable results. We are asked more and more frequently to look and give feedback in the early process of trial design to make sure trials are realistic for patients.

We want to work with the communities to tackle key areas such as how to increase the diversity of backgrounds and culture in patient engagement and participation in studies[14,15]. The ongoing advancements in decentralised trials will help, but without the patient community engagement and novel approaches that form the backbone of specialist centres like ours, it can only do so much. Through true partnership, the world of clinical trials can help people with rare conditions more, providing new treatments and support paths that matter for those involved, whatever their background may be.

Together we can support the patient-driven research that is needed to provide data for new endpoints that our biostatisticians can work to get approved, and our trial staff can effectively implement them when developing new treatments for those involved. As a global specialist centre working in partnership with the community, we can jointly tackle some of the key challenges that 2022 will send our way and develop medicines that matter.

> My hope for 2022 is that we will be able to apply lessons learned from the past almost 2 years we had to live in a global pandemic. Clinical trials in general faced huge logistical challenges, not only affecting orphan drug R&D. We indeed had to think outside of the box on top of the existing extra challenges affecting rare disease clinical trials. Combining our valuable past experience with our team's relentless efforts to reduce the time to market, I feel that we are in a strong position to make things happen for our clients and the patients.

Thomas Ogorka, Managing Director of Orphan Reach- Emmes' Rare Disease Centre.

Coming up in 2022: Our White paper series will focus on 4 key therapy areas across the year, starting with neurology in Q1. If you would like to get involved, please contact us at info@orphan-reach.com.

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