

Rare disease research: What challenges have presented in a global pandemic?

When I first heard that the university genetic laboratory was going to be repurposed for COVID-19 research, I was surprised. It was still the beginning of March 2020 and the false sense of security that we would be out of the woods by summer still prevailed in my mind. I remember thinking *'surely, the lab does not need to be repurposed... we probably won't even end up using it because they will have the vaccine figured out in a few months'*. Naive old me did not realise that the effort, collaboration and funding required to develop a vaccine from scratch, would take a minimum of a year even on an accelerated timescale.

It is now simple to understand why my university was suddenly reallocating funding and resources to COVID-19 research. It was and is, after all, the more pressing research problem to be solved. But what does this mean for all of the patients with rare, genetic conditions who were relying on the university laboratory for a diagnosis? What challenges are they now facing because of a lack of rare disease (RD) research?

Challenge 1 – Suspension of clinical trials and delay in research

As a direct result of COVID-19, most clinical trials have been paused and ongoing trials have stopped recruiting [1]. Over the course of 2020, enrolment to clinical trials across the world has decreased by 65% [2] and the number of clinical trials classed as 'suspended' on the US National Institute of health's registry has skyrocketed [3]. Clinical trials require regular in-person visits to hospitals alongside therapeutic administration of the intervention being studied from trained professionals. This is not possible in the current situation where government guidelines have been applied to stop social interaction and prevent foot traffic in hospitals and other public settings.

For RD patients who rely on clinical trials for access to treatment therapies, this is a devastating prospect. 24% of participants in the EURODIS Rare Barometer Covid-19 survey said that they have had to discontinue one of their medicines or treatments due to unavailability since the pandemic began [4]. As Rich Horgan, the founder of Cure Rare Disease (CRD) says "for rare patients with progressive diseases, a halt in drug development progress is effectively a regression in progress" [5]. Patients for whom time is a limited resource may feel hopeless after finding out that a clinical trial where they could have received life-saving therapy has been cancelled. For a mother on the news who fought tooth and nail for her child to receive an experimental drug treatment, it has been disheartening to hear that the research has been suspended [6].

Similarly, for a family with 3 young children diagnosed with GM1 gangliosidosis, a rare and life-threatening disease which affects the central nervous system, the pandemic meant they had to rush from Sweden to the US to be included in a gene therapy clinical trial [7]. If they were just a day late, they would not been allowed into the US due to border restrictions.

The best solution to this problem would be to re-establish clinical trials as soon as possible to prevent long-term health repercussions for RD patients. It is important to think of strategies which follow government guidelines. One creative solution to the problem has been the rise of 'virtual trials' where clinical trial data is collected using technology. Trial design is reshaped to allow for therapies to be administered at home with training provided to caregivers to administer the interventional therapy. Pfizer, the biomedical corporation who is responsible for the current vaccine breakthrough, also pioneered the first virtual trial [8].

There are multiple benefits to this trial design. There is the potential to save money, prevent face to face contact and overcome geographical barriers – something which is useful when studying just a

handful RD patients dotted around the globe. However, we still need data to see how effective results from virtual trials can truly be e.g. there may be a lot of bias which goes unrecorded. Nevertheless, virtual clinical trials can be a tactic that could be successfully implemented in future RD research, even after COVID-19 cases decline.

Challenge 2 – Funding and fundraising

Although RD research is slowly becoming more of a public health priority with increased funding from public bodies towards RD related initiatives e.g. 100,000 genomes project, a significant proportion of research funding comes from non-profit organisations. Much of the money raised by non-profits comes through gathering financial contributions from businesses and the general public.

I am grateful to have been given the opportunity by the Student Voice team to speak to the European board representative of the International WAGR syndrome association (IWSA) – a non-profit organisation dedicated to raising awareness of, stimulating research and supporting families affected by WAGR syndrome. WAGR syndrome is a rare condition which increases patient risk of developing a **W**ilms tumour. Patients also generally have other cardinal features such **A**niridia (absence of the iris), **G**enitourinary problems and a **R**ange of developmental abnormalities [9]. The representative and I discussed the challenges of IWSA no longer being able to have in-person meetings and fundraising events. In 2019, the overall income of IWSA was \$70,000 – more than half of which was raised by in-person family fundraisers and projects. In 2020, the projected income of IWSA is 25% less than the previous year, a result of COVID-19. This will directly impact the research into WAGR syndrome that IWSA finances.

We also spoke about the options of virtual fundraising during ‘WAGR awareness day’ which occurs annually every November 13th. Although fundraising is still active and running, the representative expressed worries that the reach of the campaign will not be as large as previous years.

However, the financial problem for RD research lies on a deeper scale than in-person fundraising. It should not be the job of the patients and their families to fundraise money for their own treatment (which usually is priced at extortionate amounts). In a fair world, all RD research funding would be covered by the public sector. For many years, groups like the European organisation for rare diseases (EURORDIS) and rare diseases international (RDI) have been lobbying for RD to be considered an imperative public health priority [10]. RDs individually affect less than 1 in 2000 people but when they are all collectively added together 1 in 17 people of the population are affected – no small number.

Many RDs are degenerative and life-threatening conditions which can lower the quality of life of persons affected. Including this, RD patients are a frequently neglected population that face many inequalities in access to healthcare and social opportunity. It is important that RD gets more recognition and awareness. In September 2019, the UN states accepted a milestone declaration to include rare diseases as part of the universal healthcare coverage (UHC) [11]. The main principle of UHC is to be able to provide all vulnerable individuals equitable access to healthcare when necessary. Additionally, the EU has invested more than €1.4 billion to support rare disease research to more than 200 collaborative research and innovation projects [12]. These breakthroughs show us that awareness of RD is increasing, and how important it is to keep urging for the government to allocate more funds to RD research.

Challenge 3 – The importance of genomics research and diagnosis

Nearly, 80% of RD conditions are genetic and a large proportion of RD research is related to genomics. In the past 20 years, next generation sequencing (NGS) technologies have revolutionised the field of research by providing a quicker, cheaper and high-throughput alternative to traditional sequencing methods like Sanger sequencing. Genetic sequencing has been very useful in the field of RD diagnosis through looking for specific gene variants/mutations [13].

Because of COVID-19, 6 in 10 patients have not been able access testing for their genetic condition either through genetic sequencing or other methods [14] This has a direct effect on patient empowerment as they are left feeling poorly informed, which is often compounded by misdiagnoses and poor co-ordination of care. This is an area that needs more creative solutions to fix so that patients have better access to testing.

What have we learnt from the current situation to carry into the future?

The pandemic has helped to emphasize the importance of raising awareness for RDs. There is a risk of the COVID-19 situation discriminating against vulnerable RD patients from receiving equitable holistic care. Part of that care involves implementing RD clinical research as so much is still left to be discovered in this diverse field. With the application of creative strategies such as virtual trials alongside lobbying for more funds to be allocated by the public sector towards RDs, we can hope to improve the delivery of RD research in the future.

1. Weiner, D.L., Balasubramaniam, V., Shah, S.I., Javier, J.R. et al. 'COVID-19 impact on research, lessons learned from COVID-19 research, implications for pediatric research', *Nature pediatric research*, 88, pp.148-150.
2. *COVID 19 and Clinical Trials: The Medidata Perspective Release 2.0.* (2020).
3. *Search of: Suspended Studies - List Results - ClinicalTrials.gov.* (n.d.). Retrieved November 16, 2020.
4. Moore, D. (2020) *THE RARE REALITY OF COVID-19 ABOUT GENETIC ALLIANCE UK.*
5. *Surviving as a rare disease biotech during COVID-19* -. (n.d.). Retrieved November 15, 2020, from <https://pharmaphorum.com/r-d/views-analysis-r-d/surviving-as-a-rare-disease-biotech-during-covid-19/>
6. *The Coronavirus Pandemic Has Stopped Research Into Treating Rare Diseases.* (n.d.). Retrieved November 16, 2020, from <https://www.buzzfeednews.com/article/danvergano/coronavirus-rare-disease-children-research>
7. *Their three children have a fatal disease, and they refused to let the coronavirus take away their only chance at saving them - The Washington Post.* (n.d.). Retrieved November 15, 2020, from https://www.washingtonpost.com/local/their-three-children-have-a-fatal-disease-and-they-refused-to-let-the-coronavirus-take-away-their-only-chance-at-saving-them/2020/04/24/87124d46-865b-11ea-ae26-989cfce1c7c7_story.html#comments-wrapper
8. Roehr, B. (2011). Pfizer launches virtual clinical trial. In *BMJ (Clinical research ed.)* (Vol. 342). British Medical Journal Publishing Group. <https://doi.org/10.1136/bmj.d3722>

9. *International WAGR Syndrome Association*. (n.d.). Retrieved November 16, 2020, from <https://wagr.org/>
10. *UN Member states include rare diseases in political declaration on universal health coverage*. (n.d.-b). Retrieved November 16, 2020, from https://www.eurordis.org/sites/default/files/publications/princeps_document-EN.pdf
11. *UN Member states include rare diseases in political declaration on universal health coverage*. (n.d.-b). Retrieved November 16, 2020, from https://www.eurordis.org/sites/default/files/publications/princeps_document-EN.pdf
12. *Rare diseases, European Commission* (no date). Available at: https://ec.europa.eu/info/research-and-innovation/research-area/health-research-and-innovation/rare-diseases_en (Accessed: 15 November 2020).
13. Liu, Z. *et al.* (2019) 'Toward Clinical Implementation of Next-Generation Sequencing-Based Genetic Testing in Rare Diseases: Where Are We?', *Trends in Genetics*. Elsevier Ltd, pp. 852–867. doi: 10.1016/j.tig.2019.08.006.
14. *Not leaving Rare diseases in COVID-19*. (n.d.-a). Retrieved November 16, 2020, from https://www.rarediseasesinternational.org/wp-content/uploads/2020/07/RDI-STATEMENT-Not-leaving-behind-RDs-in-COVID-19_Final.pdf