OVERCOMING OBSTACLES IN RARE DISEASE CLINICAL TRIALS

With an urgent need to develop new treatments for people with rare diseases, the University of Birmingham's Professor Timothy Barrett explains how a new consortium will provide a step change in the delivery of rare disease clinical trials

Amina was diagnosed with diabetes when she was four years old. Her parents were told she had type 1 diabetes, the commonest form in childhood, and learnt to inject her with insulin several times a day. They had many sleepless nights checking her blood glucose in case it went too low. Unfortunately, aged ten years, she began to lose her vision, and family photos showed her on holiday at the seaside using a white stick. She was diagnosed with Wolfram syndrome, a rare genetic disease. This is a progressive degenerative disorder without treatment, and people die prematurely from complications.

Rare disease challenges

In 2021, the UK Government published the UK Rare Diseases Framework, a national vision to improve the lives of the approximately 3.5 million people in the UK living with a rare disease. There are over 7,000 rare diseases, each affecting less than one in two thousand people but collectively accounting for illness in 6% of the UK population. 30% of these affect children, of whom half will die before five years of age. Over 95% have no cure or treatment, illustrating the scale of the public health challenge.

In 2022, England's first Rare Disease Action Plan was published, transforming the priorities of the framework into actions.

One of the underpinning themes was to deliver pioneering research. Despite progress being made, there are still major challenges in researching new treatments for People Living With Rare Conditions (PLWRC), as described in the O'Shaughnessy report. In this article, I will highlight some of those challenges and outline some potential solutions we are exploring at the University of Birmingham.

The need to improve rare disease clinical trials

The roadmap to getting a new treatment to a patient with a rare disease requires a clinical trial or fair test of a proposed treatment. This has traditionally involved comparing people receiving treatment to those receiving a placebo (inactive, dummy treatment) – the randomised controlled trial. While these are the gold standard for common diseases involving large numbers of participants, this is unfeasible for rare diseases due to the rarity of each disease.

Medicines regulators are concerned with the robustness of conclusions drawn from clinical trial data, and PLWRC deserve the same quality of evidence as those with common conditions. Regulators have traditionally required evidence from 'gold standard', double-blinded randomised controlled trials to prove the safety and efficacy of treatments. However, due to the challenges described above, such trials are not often feasible or acceptable in rare diseases.

There is a critical need to design 'one-stop shop' trials that will collect all the information required for regulatory authorisation and licencing a new treatment, with limited participants, and to be acceptable to diverse communities, regulators, and policymakers. This will require innovation in regulatory science to accelerate the pathway from medicine development and evaluation in clinical trials to patient access as standard of care.

Health inequality exists in all diseases but is particularly prevalent in rare diseases and clinical trials, where ethnic minority communities are often underrepresented. Moreover, the small numbers of people living with any individual rare condition are often widely dispersed geographically, which requires trials to be delivered across multiple centres. There is a lack of robust natural history data for most rare diseases, which complicates the design of clinical trials in these populations. It is challenging to select appropriate outcome measures relevant to PLWRC that are validated and acceptable to medicines regulators and health technology assessment bodies.

There is, therefore, a need to reach out to and identify eligible trial participants from diverse communities and exploit real-world data to enhance clinical trial design in rare diseases.

Participation in any clinical trial is onerous (for example, travel to various locations, caring responsibilities, time off work/study, and discomfort of interventions). This is particularly true for patients whose conditions are life-limiting or progressive, who may be allocated a placebo from which they will derive no benefit. Unfortunately, there has been a historical notion that investigators do not need to seek input from PLWRC, carers, and support organisations when running their clinical trials, nor do they understand how to do this.

We need to ensure that PLWRC are involved early in protocol design to prevent wasted time and resources on trials that are unacceptable to PLWRC and to help justify innovative trial design to regulators.

Rare Diseases Translational Acceleration Programme

In Birmingham, we are addressing these challenges through the creation of a Rare Diseases Translational Acceleration Programme (RD-TAP), putting PLWRC at the heart of our work to deliver a step-change in the volume, variety, and speed of delivery of treatment trials for rare diseases. Our consortium comprises expertise from the University of Birmingham, Birmingham Women's and Children's Hospital (BWCH) and University Hospitals Birmingham (UHB) via Birmingham Health Partners (BHP) strategic alliance.

Together, this consortium has the expertise and track record in coordinating national clinical trials initiatives; supporting regional, national, and international rare disease networks; driving government policy change through regulatory science; and most importantly, working in partnership with our patients and communities to move forward the implementation of the UK Government's Rare Disease Strategy.

Specifically, in trial design, our CRUK Clinical Trials Unit is implementing an integrated phase or 'one-stop shop' clinical trials to be used for supporting regulatory submission for marketing authorisation: the 'fit for filing' (new compound) and 'pivotal' (repurposed medicines) trial approaches. This means that one trial will satisfy all the data requirements for regulatory authority approval of a new treatment.

In our University of Birmingham Centre for Rare Disease Studies, we are exploring the potential to reduce regulatory barriers to trials through local agreements between NHS hospital trusts that will allow investigators to rapidly enable set-up for a rare disease treatment trial, which can then be delivered across multiple rare diseases sites with accelerated local approvals. This will allow national delivery of trials that might not have otherwise been able to recruit sufficient numbers of patients, speeding up the delivery of rare disease clinical trials.

Through our Centres for Rare Diseases at Birmingham Women's and Children's Hospital and University Hospitals Birmingham, we are working with national patient registries, bringing patients together and collecting real-world data on outcomes that are relevant to PLWRC and acceptable to medicines regulators. This will yield an integrated, national patient data asset to enable the timely identification of trial-eligible participants across the UK.

Learning from COVID and informing future rare disease clinical trials

Finally, we are implementing our learnings from the COVID pandemic, when some clinical trials were paused for face-to-face study visits and exploring ways to extend remote study visits by using video consultations, home health monitoring, and remote blood sampling via finger prick, to reduce the burden of hospital visits.

Amina was referred to the NHSE Highly Specialised National Wolfram multidisciplinary team service in Birmingham and introduced to the patient support group, WS-UK. Working with WS-UK as partners, our Cancer Research UK Clinical Trials Unit, and the Medical Research Council, we were able to recruit her into an international pivotal clinical trial of a repurposed medicine to slow the disease progression (TREATWOLFRAM ClinicalTrials.gov NCT03717909).

This clinical rare disease clinical trial addresses many of the issues described above and is due to report in 2024. We, and Amina, hope this trial will provide a much-needed treatment for her condition and serve as a valuable template for accelerating the delivery of treatment trials for other rare diseases.

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