Clinical trials for rare and ultra-rare diseases

Summary of FORUM workshop held on Thursday 24 March and Wednesday 30 March

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Executive Summary

A rare disease is defined as affecting fewer than 1 in 2000 people. Collectively, rare diseases affect 1 in 17 people – over 3.5 million people in the UK - and yet few have available treatment options. However, the rarity of these conditions presents specific challenges to running clinical trials and generating enough robust evidence to prove safety and efficacy, meaning development of treatments for rare diseases can be difficult. Innovations to improve recruitment of trial participants, reduce the burden of trial participation, and enable more efficient generation and analysis of trial data would help to alleviate these challenges and deliver on the priority of the UK Rare Diseases Framework and the wider rare diseases community to ‘improve access to specialist care, treatments and drugs’.

In March 2022, the Academy of Medical Sciences and the Faculty of Pharmaceutical Medicine (FPM) held a two-part FORUM workshop to identify innovations to overcome challenges to clinical trials for rare diseases, to explore the practicality and acceptability of those innovations to different stakeholders, and propose next steps. The workshop convened experts from a wide range of disciplines and backgrounds, including people living with rare conditions (PLWRC)\(^1\) and those who care for them, triallists, regulators, researchers, and healthcare professionals. Participants felt there were significant opportunities to make it easier to run clinical trials for rare diseases and discussed innovations and proposed next steps to do this.

### Improving recruitment of trial participants

The rarity of these conditions makes efficient recruitment of trial participants essential to ensure clinical trials can collect enough data to prove safety and efficacy of rare disease medicines. However, a lack of awareness of ongoing trials, reluctance of healthcare professionals to refer PLWRC to trials, and restrictive, time-limited eligibility criteria make this difficult. Participants discussed approaches to improve trial recruitment, including:

- **Making clinical trials more discoverable** by developing a centralised clinical trial repository with broader coverage and accessibility, building on existing repositories such as ScanMedicine.\(^2\)

- **Engaging PLWRC and those who care for them directly about referral for clinical trials**, through platforms such as the Scottish Health Research Register,\(^3\) patient registries, or with assistance from rare condition support organisations.

- **Making PLWRC more findable** using real-world data, including in patient registries, and by linking rare disease services, such as the NHS highly specialised services, with clinical trial infrastructures.

- **Ensuring participant-facing information about clinical trials is presented accessibly** to give confidence to participate and enable truly informed consent.

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1. In this document, the term ‘people living with rare conditions’ or PLWRC is generally used to mean people with acute and/or chronic rare diseases – they may currently be patients of the healthcare system or managing their condition themselves. It can also include those who are indirectly affected, such as family or carers.

2. [https://scanmedicine.com/clinicaltrials/](https://scanmedicine.com/clinicaltrials/)

3. Note that this specific example was not directly discussed by workshop attendees. [https://www.registerforshare.org/](https://www.registerforshare.org/)
Reducing burden of trial participation
While offering access to potentially beneficial experimental treatments, trial participation can greatly impact the quality of life of PLWRC and their families. Clinical trials for rare diseases often need to recruit PLWRC from large geographical areas, presenting significant logistical and administrative challenges to trial participants and their families. Furthermore, sometimes painful, invasive treatment administration and time-consuming trial assessments can take a toll on participants’ physical and mental health. **This burden of participation can lead to trial participants dropping out before the end of the trial, and the physical and mental health impacts can compromise the validity of trial assessments.** Workshop attendees discussed ways to reduce burden of trial participation:

- **Provision of effective logistical, financial and administrative support to trial participants** was highlighted, for example by specialist, patient-centred organisations with the relevant expertise, such as Rare Disease Research Partners.  
- **Improved communication between trial staff, routine care staff, PLWRC and carers** (e.g. via a specific triallist staff member as point of contact).
- Innovations for **trial participation from home** where appropriate, such as home delivery of medications, remote monitoring and wearable technologies. However, end-user engagement and flexibility are key as there is no ‘one size fits all’ approach.
- **Development and selection of endpoints that are meaningful to PLWRC and their families,** validated using real-world evidence, including from patient registries.
- **Involvement of PLWRC and their families while designing the trial** to help reduce the burden of participation.

Making the best use of trial data
The limited number of PLWRC available to participate in a clinical trial due to the rarity of conditions means it is essential to make the most efficient use of data that are gathered to determine safety and efficacy of medicines. Innovative data sources, trial designs and data analysis were discussed. These included:

- **Registry-based studies:** Answering experimental questions using pre-existing data or data that are already being collected in patient registries could save PLWRC and triallists time and resources. To facilitate this, data collected by registries should be meaningful to PLWRC, and acceptable to regulators.
- **Alternative sources of control data** – such as control data from previous studies, pre-treatment data, or synthetic, digital control data generated from natural history data – could be used to overcome practical and ethical concerns of using standard randomised controlled trial designs in rare diseases. However, care will need to be taken to make sure data are representative of the target population for a treatment to ensure conclusions are valid and avoid worsening inequalities.
- Consider using **platform trials** to improve trial efficiency, to centralise and improve recruitment, and to reduce the number of trial participants needed to produce robust results. This might include evaluating multiple treatments alongside each other – an umbrella trial – or investigating the effects of one treatment on multiple different diseases or disease subtypes – a basket trial. **Adaptive trial design,** changing in pre-defined ways in response to data as they are gathered, could also lead to more informative and efficient trial outcomes. However, novel trial designs and innovative methodologies may not be appropriate in every situation and should be **applied cautiously to avoid unintended consequences** that worsen challenges (e.g. by increasing the number of trial participants required to ensure statistical power).

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4 https://rd-rp.com/
• Improving understanding of innovative trial designs will be key to ensure acceptability to trial participants, regulators, healthcare professionals, and health technology assessors.

The value of patient registries for rare diseases research is clear, for recruiting trial participants, as a source of natural history data, for validating elements of trial design, and for registry-based studies. Integrating patient registries, with and across borders, and linkage with other health data repositories would multiply these benefits. However, not every rare disease has a patient registry. Organisations planning to set up a registry should learn from others’ experience to maximise their efforts.

Harnessing the full potential of the innovations discussed at this workshop, without duplicating effort, will require collaboration and co-operation between the different sectors and companies in the precompetitive space. In particular, the involvement of PLWRC and those who care for them is essential to running successful clinical trials for rare diseases.
Introduction

There are more than 7000 distinct rare diseases – defined as affecting fewer than 1 in 2000 people in the general population.\(^5\) Collectively, rare diseases affect 1 in 17 people in their lifetime – over 3.5 million people in the UK. 75% of rare diseases affect children and many can prove fatal in early life.\(^6\) Rare diseases often require complex care throughout life and have a massive impact on the lives of people living with rare conditions (PLWRC) and those who care for them, including on their financial stability, education, independence, and physical and mental health.\(^7\)

Despite the life-limiting and life-threatening nature of rare diseases, only 1 in 20 of these diseases currently have specific treatment options.\(^8\) Where treatments are available, they can be life-changing – improving prognosis and/or quality of life. In recognition of this unmet need, the UK Rare Diseases Framework (published in January 2021) set out an ambition to improve access to specialist care, treatments and drugs for PLWRC.\(^9\) Each of the four UK nations are developing rare disease action plans to achieve this and other priorities.

Challenges of running clinical trials for rare diseases

The development of medicines for rare diseases remains challenging, in part because the rarity of individual rare diseases makes it more difficult to gather enough evidence to prove the safety and efficacy of medicines in clinical trials, presenting challenges for how trials are designed and run. The geographic distribution of PLWRC often requires multinational trials, meaning trial sponsors need to navigate the different regulations and healthcare systems of participating countries. Furthermore, the symptoms and young age of many PLWRC can make the practicalities of participating in such rare disease clinical trials, such as travelling long distances to trial centres, particularly burdensome and disruptive for them.

The vision and phase 1 implementation plan for the Future of UK Clinical Research Delivery (published in 2021) set out a strategy to create an efficient, resilient and effective clinical research ecosystem that patients can participate in and benefit from.\(^10\) The England Rare

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Diseases Action Plan (published in March 2022) recognises that to include PLWRC in this vision, special considerations and innovative approaches will be required to address the challenges outlined above. The Plan calls for exploration of the particular challenges facing rare disease clinical research delivery, including barriers to entry and innovative approaches to trial design. The delivery of this and some of the themes explored in this report are aligned with actions and commitments in the Future of UK Clinical Research Delivery: 2022 to 2025 implementation plan (published in June 2022). The Northern Ireland Rare Diseases Action Plan and the Wales Rare Diseases Action Plan also have targets for improving the awareness and participation of PLWRC in clinical research for rare diseases. Although the Scotland Rare Diseases Action Plan is not yet published, the Scottish Cross-Party Group of Rare, Genetic and Undiagnosed Conditions has declared similar intentions to improve access to information on rare disease clinical trials and research to facilitate participation.

**Challenges in other parts of the drug development pipeline**

In addition to challenges in clinical trials, rare diseases pose challenges at other stages of drug development. For example, drug discovery is more difficult because the lack of research into many rare diseases means that the underlying biological mechanisms are often not well understood, and it is difficult to find biological targets for novel treatments. Challenges and delays in getting the right diagnosis, often termed the ‘diagnostic odyssey’, make it difficult for PLWRC to get the right treatment, and prevents their recruitment to clinical trials. At the other end of the drug development process, achieving equitable access to rare disease medicines is a global challenge, with developing countries often neglected in rare disease drug development and access. In the UK, there is a patchwork of processes for assessing rare disease medicines, and uptake of approved treatments into the clinic for use by PLWRC is varied.

The challenges posed by rare diseases at each stage of the drug development pipeline are related. For example, the requirements for getting regulatory approval for a medicine for a rare disease filter back and heavily influence the decisions made earlier in the process of drug development, when identifying potential treatments and conducting clinical trials. Despite this interdependence, the challenges of running clinical trials for rare diseases are distinct and warrant individual consideration, while taking into account the context of the wider drug development pipeline.

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14 Note that this was published after the workshop took place. NHS Wales Health Collaborative (2022). Wales Rare Diseases Action Plan 2022 – 2026. https://collaborative.nhs.wales/implementation-groups/rare-diseases/wales-rare-diseases-action-plan-2022-2026/ (Actions 1.4 and 1.5)
FORUM workshop on clinical trials for rare and ultra-rare diseases

To discuss the challenges and opportunities facing clinical trials for rare and ultra-rare diseases, the Academy convened a two-part FORUM workshop in partnership with the FPM on Thursday 24 March and Wednesday 30 March 2022. The workshop was co-chaired by Professor Alan Boyd FMedSci, Chief Executive Officer at Boyd Consultants, and Dr Zoya Panahloo, Chair of the FPM Rare Diseases and Gene Therapy Expert Group and Senior Medical Director for Rare Disease at UCB.

Workshop attendees included representatives from academia, industry, healthcare and the NHS, rare condition support organisations, regulators, and health technology assessors. We would particularly like to thank the PLWRC and carers who attended for their generosity in sharing their lived experience and opinions during the workshop.

In Session 1 of the workshop, attendees identified innovations to overcome challenges of running clinical trials for rare and ultra-rare diseases (Annex 4). These challenges were divided into four overlapping themes, listed below, and each group was given one theme to discuss and identify innovations for. The themes are listed below:

1. Barriers to recruitment of trial participants (including at the point of diagnosis) and participation.
2. Defining relevant and acceptable outcome measures (including biomarkers and patient reported outcome measures) and endpoints.
3. Innovative and adaptive clinical trial design.
4. The use of real-world evidence and natural history data.

In Session 2, the acceptability and practicality of a subset of these innovations to different stakeholder groups were discussed by a subset of workshop attendees. (For details about sectors represented in the breakout group discussions of each innovation in Session 2, see Annex 5.)

This report summarises the key points from the discussion, shares the innovations identified, and proposes next steps. Many of the innovations would be beneficial to all clinical trials, as reflected by the inclusion of similar themes in the subsequently published Future of Clinical Research Delivery: 2022 to 2025 implementation plan. However, workshop participants felt that the unique challenges faced by PLWRC meant that the innovations and next steps discussed in this report would be particularly beneficial for this group.

In addition to the executive summary of the workshop above, a summary targeted to PLWRC, based on input from some of the PLWRC and carers who attended, can be found Annex 1. The workshop agenda, attendee list and a list of innovations identified in Session 1 can be found in Annex 2, Annex 3, and Annex 4, respectively. A glossary of some of the key terms used in this document can be found in Annex 10.

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Lessons learned from the TREATWolfram Trial – a case study

Clinical trials for rare and ultra-rare diseases face many challenges and there is significant opportunity to innovate to improve the efficiency and acceptability of trials. In his opening talk, Professor Timothy Barrett, Director of the Centre for Rare Disease Studies at the University of Birmingham, used the TREATWolfram Trial to illustrate some of these challenges and opportunities.

Wolfram syndrome
Wolfram syndrome is a genetic condition typically associated with childhood-onset insulin-dependent diabetes and progressive vision loss due to atrophy of the optic nerve at the back of the eye. Affecting 1 in 500,000 people worldwide, it is an ultra-rare neurodegenerative disease that is life-limiting with no specific treatments.

The TREATWolfram Trial
Sodium valproate, a drug typically used to treat epilepsy, has shown promise as a repurposed drug candidate for treating Wolfram syndrome in preclinical models of the disease. Professor Barrett and his team are currently running the ‘TREATWolfram’ Trial – an international, Medical Research Council-funded, randomised controlled pivotal trial in 63 people living with Wolfram syndrome to see if the drug is effective in slowing the neurodegeneration. In his talk, Professor Barrett reflected on some challenges and opportunities that were highlighted by this trial.

Recruitment of trial participants was challenging
As is the case with many rare and ultra-rare diseases, there were not enough people living with Wolfram syndrome in the UK for the TREATWolfram Trial. Therefore, the trial also recruited from France, Poland and Spain. Professor Barrett highlighted a few challenges this posed:

- The burden of long-distance travel for people living with Wolfram syndrome with multisensory deficits and mobility issues.
- Each country had different regulatory requirements and satisfying these was difficult and took time.
- The lack of a central pharmacy responsible for dispensing and quality assurance to act as a competent authority to help UK trial centres collaborate with trial centres in the European Union (EU) post-Brexit.

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18 https://www.birmingham.ac.uk/partners/enterprise/wolfram-syndrome.aspx
19 University of Birmingham (2018). Efficacy and Safety Trial of Sodium Valproate, in Paediatric and Adult Patients With Wolfram Syndrome. ClinicalTrials.gov Identifier: NCT03717909
https://www.clinicaltrials.gov/ct2/show/NCT03717909
Selecting outcome measures relevant to PLWRC
Professor Barrett reflected that the outcome measures of a trial that were originally considered by researchers to make the most significant impact are not necessarily those most important to the lives of people living with Wolfram syndrome and their families. In this study, although researchers were initially interested in preventing diabetes, improvement in vision was uniformly highlighted as the most important outcome measure for people living with Wolfram syndrome and so the trial pivoted to adopt this as the primary endpoint. This example emphasises the importance of involving PLWRC in trial design and the flexibility needed by the research community to investigate outcome measures relevant to PLWRC.

Innovations in trial design
Professor Barrett raised the question of whether innovative regulatory mechanisms are needed to conduct clinical trials in very small populations and noted that regulatory agencies are beginning to consider more innovative trial designs. However, in 2016, the European Medicines Agency (EMA) required the TREATWolfram Trial to be a ‘gold standard’ double-masked randomised clinical trial with little flexibility. This can pose difficulties for recruitment to clinical trials for rare diseases and raises ethical questions around giving placebo to people with progressive diseases, especially given the burden of trial participation. Professor Barrett suggested giving access to the active drug for trial participants in the placebo arm at the end of the trial or designing crossover studies – where trial participants taking placebo ‘cross over’ into the treatment arm halfway through the trial – as happened in the Luxturna® development programme (Annex 6: case study 2).

Further opportunities: real-world evidence and drug repurposing
Professor Barrett discussed the opportunity presented by real-world evidence (Box 1) in Wolfram syndrome. One of the challenges is that it is unusual for the collection of routine clinical data in healthcare systems to be standardised to the extent that it would be directly useful in a clinical trial. For example, different hospitals across the country use different techniques to measure vision. He also pointed out that many people living with Wolfram syndrome (as with many other rare diseases) do not have comprehensive natural history data, though this would be useful.

Sodium valproate is a drug licensed for use in another condition, meaning the safety and toxicity profile of the drug was known already. Professor Barrett highlighted the opportunity presented by drug repurposing in the field of rare diseases but pointed out that there is currently little incentive for pharmaceutical companies to support clinical trials for products whose patents have expired.
The use of real-world evidence and natural history data has been proposed to reduce the burden on PLWRC of participating in clinical trials and to increase the range and relevance of evidence collected by small studies. The US Food & Drug Administration (FDA) defines real-world evidence as:

‘the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of real-world data’.\(^\text{20}\)

Real-world data can be collected from a variety of sources including patient-generated data in home settings (e.g. from smartphone apps or home testing), patient health records, patient and product registries, specific programmes such as the yellow card scheme,\(^\text{21}\) and other data sources relevant to health status. Such data have been critical for pharmacovigilance and is now being used to extend indications, or remove contraindications, post-licensing, particularly for groups that are often not included in pre-licensing studies such as pregnant women.\(^\text{22}\)

Natural history data are information about a disease over time in the absence of an intervention, typically from disease onset until either its resolution or the individual’s death. Instead of giving some trial participants a placebo treatment or routine care, clinical trials can use natural history data as a ‘historical control’ to see if the drug being tested has an effect. This reduces the number of trial participants needed and can lead to faster trial completion. In this way, natural history data are one kind of real-world data that can be used in clinical trials for rare diseases. However, it is important to be aware of and account for variability that can potentially be introduced by use of natural history data from the past – for example, the effect of improved quality of medical care over time might mean outcomes differ irrespective of the treatment under investigation.

How one collects and uses real-world evidence depends on the research question, the clinical context, and the decision to be made. Examples of application of real-world evidence in clinical trials include:

- Research fully embedded in care settings (so that no data are wasted)
- Integrated quality control mechanisms
- Flexible and linkable on-demand data compilation from databases/registries (e.g. for natural history data as a historical control in a clinical trial);

\(^\text{21}\) https://yellowcard.mhra.gov.uk/
\(^\text{22}\) Academy of Medical Sciences (2018). Next steps for using real world evidence. https://acmedsci.ac.uk/file-download/7021031
- Stakeholder engagement, including potentially increased patient engagement with mobile technologies or data capture.

Real-world evidence can also be used after a treatment has received regulatory approval to provide additional information about safety and/or efficacy in particular populations (e.g. pregnant women). However, discussions in this workshop focused on clinical trials pre-approval, while acknowledging that different stages of the drug development pipeline are interrelated.

A 2018 FORUM workshop on ‘next steps for using real-world evidence’ highlighted the importance of case studies to improving the acceptability of real-world evidence and the need for building capacity and capability in the health system to routinely collect high-quality, standardised real-world data. Participants in the 2018 workshop widely agreed that traditional hierarchies of evidence should be revised, instead selecting the type of evidence based on the methods and evidence most relevant for answering the research question. To achieve this, more research into the strengths and limitations of different kinds of evidence is required, including of real-world evidence generated by different methods.

Patient and carer experiences

PLWRC face specific challenges when trying to access and participate in clinical trials for their disease. Marina Leite Brandão, patient contributor and Vice-Chairperson of Retina International Youth Council, shared some of the barriers to participating in clinical trials that she and other people living with her condition have experienced.

Ms Brandão has a rare genetic disease called Stargardt disease that affects vision. She began to lose her eyesight aged 8 and today is legally blind. There is currently no approved treatment for Stargardt disease, but Ms Brandão discussed the recruitment process for a currently ongoing, multinational, multicentre clinical trial of an oral drug, emixustat. Ms Brandão herself applied to participate in the trial but was not selected due to the characteristics of her disease not satisfying the eligibility criteria. Based on her experience and her efforts with local and national rare condition support organisations to help recruit people living with Stargardt disease in Brazil to the trial, Ms Brandão highlighted four barriers to effective recruitment of participants to the trial:

- **The mental and emotional burden of pursuing clinical trial participation.** People may feel unsure and afraid of participating but also hopeful about the opportunity. She noted the importance of effectively managing expectations of what trials are aiming to achieve to avoid disappointing people. She highlighted the need to address the lack of mental health support for PLWRC and their carers, during the recruitment process, while participating in a trial, and after the trial has completed.

- **Restricted time for recruitment is a challenge, particularly for multicentre clinical trials.** Due to regulatory restrictions and delays, the time window for recruitment of trial participants in the relevant trial centre in Brazil was very short. Therefore, despite having a cohort of people living with Stargardt diseases available and willing to participate, they did not have the time to include many of that group.

- **Lack of awareness and understanding of clinical trials among PLWRC.** Complex academic language is a barrier to understanding. Ms Brandão noted that often potential participants would claim they understood in conversations with researchers and trial staff, but then return to patient representatives and rare condition support organisations with questions. She highlighted the important role of engaged rare condition support organisations in helping to answer such questions and to improve communication between researchers and healthcare professionals working on the trial and PLWRC.

- **Many PLWRC either do not have or have poor-quality information on their own disease history.** Many people living with Stargardt diseases enquiring about trial participation did not have up-to-date medical history of their disease as they may not have visited the ophthalmologist since diagnosis, or they may not have taken the required genetic tests to validate their diagnosis. Ms Brandão underlined the importance of building

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26 The rare condition support organisations involved were Retina Minas and Grupo Virtual Stargardt.
awareness with people about their disease and encouraging personal medical care, so that they have the necessary details available when a clinical trial starts recruiting.

Despite living on different sides of the globe, Helen Beveridge and her daughters, Kelsie and Shona Beveridge, experienced some similar difficulties finding out about and accessing a clinical trial for Kelsie and Shona’s condition. Alongside her daughters, Mrs Beveridge also explained the burden and impact of participation once Kelsie and Shona were accepted on to a trial.

Kelsie and Shona live with Niemann-Pick’s Type C (NP-C), a neurodegenerative metabolic disease that affects 1 in 120,000 people. The disease affects walking, talking and eating, and impacts the brain. NP-C is genetically determined; Helen, her husband and her third daughter, Tally, are all carriers of the genetic mutation but do not have the disease.

Kelsie pointed out that NP-C is often misdiagnosed. Shona spoke about how it was initially thought that she had ataxia until genetic tests showed she had NP-C. Age of onset and symptom severity of NP-C varies; Kelsie’s symptoms are milder than Shona’s, and Kelsie was only diagnosed at the age of 14, because of a specific genetic test following Shona’s diagnosis.

Finding out about clinical trials and being referred to take part was a challenge

After being told that Shona would not survive past the age of 20, Helen and her husband were grieving for her lost future and looking for hope, so they started to look for potential clinical trials. There was not much information about NP-C on the internet or in the media, and Helen highlighted the lack of local advice and information about clinical trials and clinical trial participation. Fortunately, Helen heard about a promising clinical trial in conversations with other parents of people living with NP-C around the globe. The treatment being investigated was fortnightly intrathecal infusions of an uncomplexed cyclodextrin.\(^{27}\) However, their paediatric neurologist had no experience with multinational trials and little experience with NP-C; because of this, the clinical team were reluctant to refer Kelsie and Shona to the trial. With persistence, Helen managed to get the referral in time for Kelsie and Shona to get the last two places on the trial.

Participating in the clinical trial impacted hugely on the physical and emotional health of Kelsie and Shona, was associated with significant logistical challenges, and had a large impact on family life

The first 12 months of the trial, ‘part B’, were double-masked so neither trial participants nor trialists were told whether they were taking the active drug or the placebo. Helen highlighted that the double-masking was not effective because, based on differences in effects of the drug, the family deduced early on that Shona was receiving the active drug and Kelsie the placebo. At the end of part B, the trial was unmasked and the family’s suspicions were correct. All trial participants were moved on to ‘part C’ of the trial with no endpoint specified. At this point, Kelsie also started receiving the active drug.

Travel to and from the trial centre was logistically challenging and required significant commitment of time and energy. As the trial centre was in Birmingham, participating in the trial meant travelling 450 miles each way for two nights every fortnight (by car, plane, train, and with some walking). The company organising and paying for their travel arrangements

often made mistakes, adding to the administrative burden. The travel had a significant impact on Kelsie and Shona’s education as both were in exam years, though Shona pointed out that her teachers were often helpful and gave her work to do while she was in hospital. Helen and her husband took turns accompanying Kelsie and Shona to the appointments. Both have full-time jobs and had to take time off work. They used up their annual leave so family holidays during this period were not possible.

The drug was delivered by lumbar puncture and both Kelsie and Shona experienced severe side effects during the trial that affected their quality of life. After the first administration of the drug (by lumbar puncture in those in the treatment arm only), Shona experienced debilitating migraines and other side effects. She was admitted to a local hospital but, because of the double-masking, Helen was unable to give clinicians any information about the medication Shona was on or how it had been administered. This made working out what care Shona needed difficult. Migraine is one side effect of lumbar puncture, but trialists were unable to share that Shona had received a lumbar puncture due to the double-masking, with one member of the trial’s clinical team suggesting to Helen that the migraine was unrelated to her participation in the trial. Kelsie had no side effects during the first 12 months (likely because she was receiving placebo during this time), but had bad reactions to lumbar puncture in part C of the trial until a different kind of needle was used. After the second dose and just before her exams, she suffered catastrophic hearing loss – a side effect related to the drug being tested – and is now reliant on hearing aids.

As an alternative to lumbar puncture, Shona had an intrathecal port fitted at the end of part B of the trial, but it failed. In discussion with other people living with NP-C, they heard that 5 out of 12 ports had failed and so decided against having another fitted. Subsequently use of the port was suspended. Shona shared that she struggled emotionally when the port failed and saw a counsellor.

The EMA put the trial on hold to revaluate the benefit/risk ratio, so Shona and Kelsie missed a few doses. Once the trial restarted, the drug stock at the centre was out of date, resulting in another enforced break. From when they joined, the trial was passed between three or four different pharmaceutical companies. After three years on the trial, given there was no endpoint in sight, the family decided to withdraw; although they believed that the drug provided some benefit (reducing or delaying some symptoms of NP-C), this was not enough to offset the negative impacts of the significant travel required and the side effects of the lumbar punctures on the overall quality of life of the family.
Challenges and opportunities for clinical trials for rare diseases

As illustrated by the experiences and case study shared above, there are many challenges to running clinical trials for rare diseases. Most of these challenges stem from low numbers of people living with any particular rare condition.

The small populations eligible for clinical trials in rare diseases mean that clinical development programmes involving large numbers of participants are not feasible. However, conclusions based on limited data are more susceptible to variability and more affected by missing data. This causes challenges for regulators and health technology assessment bodies, as discussed below.

The low numbers of people living with any particular rare condition also poses significant problems for participant recruitment. If there is more than one drug candidate for a particular disease, trials are sometimes in ‘competition’ for a small number of eligible PLWRC, with PLWRC considering the impact of participation on their eligibility for other trials. This is a particular consideration for trials of gene therapies that may change the underlying genetics of the participant, potentially affecting their involvement in future trials. Often trials must be multinational, with trial sites around the world to recruit enough participants. Satisfying the requirements of regulatory agencies in many different countries is complex and time-consuming for trialists.

There is less awareness and expertise around rare diseases compared to more common conditions, both among researchers and healthcare professionals. This compounds the difficulty of identifying and recruiting PLWRC and of running geographically distributed clinical trials.

Furthermore, most rare diseases lack natural history data, meaning the selection of appropriate endpoints that are relevant to PLWRC, measurable, validated and acceptable to regulators and health technology assessment bodies is particularly challenging.

As vividly illustrated by the experiences of the Beveridge family, the burden of taking part in clinical trials on PLWRC is heavy. The predominantly hospital-based clinical assessments are often long and sometimes invasive. Frequently, PLWRC and their families are required to travel long distances to trial centres, which is particularly difficult as many PLWRC have debilitating symptoms and/or are children. These challenges decrease recruitment and retention rates of the participants in trials.

Producing sufficient evidence to satisfy regulators and health technology assessment bodies is made more difficult by these challenges. They also increase the cost of developing treatments for rare diseases above what would traditionally be recovered in expected sales, disincentivising companies from developing drugs in this space. Interventions, such as those discussed in Box 2 and Box 3, aim to incentivise the development of drugs for rare diseases,
including by improving the return on investment.

**A regulatory perspective**

Regulators are concerned with the robustness of conclusions drawn from clinical trial data. As in the TREATWolfram Trial, regulators may require evidence from ‘gold standard’, double-masked randomised clinical trials to prove safety and efficacy of medicines. However, due to the challenges described above, such trials are often not feasible or acceptable in rare diseases. Innovations in study design and methodology are required. Regulators and health technology assessment bodies have to carefully balance the need for more evidence and greater certainty with the practical difficulties of running clinical trials big enough to produce such evidence in rare diseases.

Attendees noted that regulators are becoming more flexible in their approach to clinical trials for rare diseases. In his talk, Dr Daniel O’Connor, Expert Medical Assessor, the Medicines and Healthcare products Regulatory Agency (MHRA), noted that PLWRC are entitled to the same quality of treatments as other patients. He discussed some of the challenges and outlined some of the regulatory mechanisms in the UK that support clinical trials for rare diseases. These include orphan drug designation (Box 2) and the Innovative Licensing and Access Pathway (Box 3). Dr O’Connor also mentioned the Early Access to Medicines Scheme, which aims to give access to medicines before it receives market authorisation and to create a framework for the collection and consideration of real-world evidence of the safety and efficacy of these medicines.28 He began and ended by urging trialists to engage with regulators as soon as possible to discuss the design of their trial and get scientific advice.

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**Box 2: Orphan drug designation in the UK**

In Great Britain, ‘orphan drug’ designation is given to a drug developed to treat a rare disease (affecting fewer than 1 in 2000) that will significantly improve the current standard of care for that disease, according to criteria set out in the Human Medicines Regulation (as amended in 2021). Incentives based on orphan drug designation help to stimulate the development and marketing of drugs in the rare diseases space.

While describing orphan drug designation, Dr O’Connor raised the issue of how a rare disease is defined. With the advent of personalised medicine, common diseases are being subdivided by biomarkers into rarer subsets. Currently, drugs targeting rare subsets of a common disease would not be considered for orphan drug designation unless the subset displayed specific and unique characteristics that were required for the drug to carry out its action.

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28 [https://www.gov.uk/guidance/apply-for-the-early-access-to-medicines-scheme-eams](https://www.gov.uk/guidance/apply-for-the-early-access-to-medicines-scheme-eams)
Box 3: Innovative Licensing and Access Pathway: a rare disease perspective

The Innovative Licensing and Access Pathway (ILAP) was launched in 2021 with the ambition to deliver safe, early and financially sustainable patient access to innovative medicines.\(^{29}\) It is run by a partnership between the MHRA and three health technology assessment bodies – the National Institute for Health & Care Excellence (NICE), the Scottish Medicines Consortium, and the All Wales Therapeutic and Toxicology Centre – and with input from a patient reference group. ILAP includes:

- Innovation passports, which link the medicine to the development of a Target Development Profile.
- A Target Development Profile: a UK-specific roadmap to deliver patient access with sustained multistakeholder collaboration.
- A toolkit: to drive efficiencies in the clinical development programme. The toolkit includes a novel methodologies tool to establish a culture that is receptive and supportive of novel methodologies, such as innovative clinical trial designs and endpoint development, in both the clinical and preclinical space to develop new medicines.

While ILAP is not a rare disease-specific programme, rare diseases are one of the special areas to which ILAP applies. The first innovation passport was issued for a drug for a rare disease.

Digital endpoints to improve clinical relevance and reduce burden of trial participants

The rapid adoption of digital technologies during the COVID-19 pandemic presents opportunities to make things more convenient for trial participants and their families, for example, by remote health visits or clinical assessments.

Dr Elin Haf Davies, Chief Executive Officer at Aparito, discussed how patient-driven, technological innovation could be used to develop digital endpoints that are relevant to participants, measured in the comfort of their own homes, and acceptable to clinicians, trialists, regulators, and the health technology assessment body.

Many traditional clinical outcome assessments (COAs) used in trials are time-consuming, hospital-based and can be painful. This burden on the participant means that frequently the results are not representative of day-to-day life of the patient, and retention of participants in the trial is often low. An optimal COA should:

- Be relevant to how participants feel, function, and survive
- Minimise participant burden (e.g. by being measurable from home)
- Be accurately and consistently measurable

• Produce evidence that answers the scientific questions and gives confidence to regulators when judging whether a drug is safe and effective.

Dr Davies pointed out that introducing such optimal COAs enhances clinical trial design and reduces clinical trial waste, regardless of what design is being used. She described Atom5™, Aparito’s clinical trial software platform that enables hybrid and decentralised clinical trials and assessments at scale, including using machine learning and artificial intelligence (AI) to measure digital COAs from videos of trial participants. Based on this software platform, Aparito works with rare condition support organisations through its Patient Accelerator Program to co-design disease-specific digital endpoints. This can include designing alternatives to flawed endpoints (Box 4), supporting rare condition support organisations to collect natural history data to inform endpoint selection (Box 5), and developing novel endpoints for understudied stages of a disease (Box 6).

**Box 4: An alternative to the 6-minute walk test in Duchenne muscular dystrophy**

Duchenne muscular dystrophy (DMD) is a genetic disease that causes progressive muscle degeneration and weakness over time. The 6-minute walk test (6MWT) uses the distance walked in 6 minutes as a measure of performance capacity and is a commonly used primary endpoint in DMD, among other diseases. High variability in patients’ changes in the 6MWT over time have complicated clinical trials and treatment efficacy in DMD. These challenges are increasingly recognised by patients and their families, rare condition support organisations, clinicians, and regulators.

An alternative endpoint has been developed. The Stride Velocity 95th Centile (SV95C) is an objective, real-world digital ambulation measure of peak performance, representing the speed of the fastest strides taken over a recording period of 180 hours in the patients’ home environment. SV95C is measured using wearable technology and is the first wearable-derived digital endpoint for DMD; it was qualified by the EMA in 2019 for use as a secondary endpoint in DMD and is currently under review for becoming a primary endpoint.  

**Box 5: GARDIAN, the neuronopathic Gaucher registry**

The Gaucher Registry for Development, Innovation & Analysis of Neuronopathic disease (GARDIAN) is an international, patient-led registry owned by the

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31 https://gardianregistry.org/
International Gaucher Alliance (IGA).

Gaucher disease is caused by build-up of fatty substances in certain organs. Neuronopathic Gaucher disease types 2 and 3 are characterised by early onset brain involvement, which affects cognitive function.

GARDIAN is designed to study people with neuronopathic Gaucher disease in a standardised and systematic way with the aim of advancing disease management, designing safer treatments, and improving patient outcomes, while understanding what is important to people with neuronopathic Gaucher disease and their families. The registry will include both patient-reported data and clinically reported data in a format acceptable to regulators, and include disease-specific patient-reported outcomes and observer-reported outcomes developed specifically for GARDIAN. It is currently translated into seven languages and, three years after the feasibility project was conceived, the registry recently recruited its first person with neuronopathic Gaucher disease.

Collaboration with organisations with expertise in data analysis and learning from the experience of other rare condition support organisations who had set up registries was key to setting up GARDIAN as the IGA did not have all the necessary skills in-house. GARDIAN partners include Aparito and Cerner Enviza. Gaining funding for the registry was another challenge; many experts had to donate their time for free to help set the registry up and funding was eventually sourced from a few different pharmaceutical companies.

Box 6: Video-based assessment of limb use in DMD

The trajectory on which people living with DMD lose use of their limbs, including loss of ambulation and of upper limb strength, is not well characterised as a continuous measurement by traditionally used COAs. Working with Duchenne UK, Aparito developed an app to perform home-based video assessments of limb functionality along with a quality-of-life assessment. Four tasks to assess limb functionality were chosen: walking, hands-to-head while sitting, hands-to-head while standing, and sit-to-stand then hands-to-head while standing.

In a feasibility study, 12 participants produced 62 videos, 52 of which were suitable to apply machine learning to. The app uses OpenPose software to track parts of the body as they move in the videos and measure different characteristics of the movement, including smoothness, velocity, symmetry, and effort of the movement. The validation of these digital biomarkers is now underway.
The importance of patient and carer involvement

Attendees reflected that seeking input from PLWRC, carers, and rare condition support organisations is essential to running successful clinical trials in the rare disease space, particularly given the lack of natural history data. In addition to developing outcome measures relevant to PLWRC as highlighted by Dr Davies and Professor Barrett, it was noted that such input would be important for developing trial protocols acceptable to PLWRC and designing understandable participant-facing materials to effectively communicate about the trial. Dr O’Connor reflected that involving PLWRC early on prevents time being wasted on trial designs that are unacceptable to the PLWRC community, such as randomisation, and can help to justify elements of trial design to regulators.

There was discussion about the representation of PLWRC on research ethics committees. Some attendees argued that including representatives with lived experience of a rare disease was important to ensure the committee had access to expertise provided by such a person. Others raised the concern that it would be difficult for such a representative to be able to remain objective. One approach suggested to achieve a balance between objectivity and relevance of expertise was to have a PLWRC on the committee with a rare disease other than the one under discussion who could provide a rare disease-relevant perspective. The Heath Research Authority (HRA) maintains a cohort of volunteer research ethics committee members and co-opts members with relevant expertise for the review of relevant applications. To include individuals with expertise in rare diseases, that expertise would need to be represented in the cohort of research ethics committee members. The HRA are currently recruiting new expert and lay research ethics committee members and are open to applications from the rare diseases community (including clinicians, allied health professionals, researchers, PLWRC, and carers).

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32 The HRA was not represented at the workshop but has since shared more detail about how research ethics committees are formed. They are currently recruiting for more research ethics committee members and encourage individuals in the rare diseases community (including clinicians, allied health professionals, researchers, PLWRC, and carers) to volunteer where possible to ensure that expertise was available to call upon. Note that this is not a rare diseases-specific role.

Improving recruitment of trial participants

Given the small numbers of PLWRC for any particular rare disease, optimising recruitment for clinical trials for rare diseases is particularly important to make sure enough evidence is gathered to prove the safety and efficacy of a treatment. However, there are a variety of challenges.

Attendees, including the Beveridge family, highlighted that it is difficult to find out about clinical trials, or even about relevant rare condition support organisations, from the perspective of PLWRC. As highlighted by the Genetic Alliance UK’s recent report on ‘good diagnosis: improving the experiences of diagnosis for people with rare conditions’, an optimal time for PLWRC to receive this kind of information would be at the point of diagnosis. However, most clinicians are unlikely to be experienced with rare diseases or aware of relevant clinical trials and relevant rare condition support organisations. This can also mean that they are reluctant to refer PLWRC to trials.

Alternative places for PLWRC to find out about clinical trials are rare condition support organisations and other PLWRC. However, not all rare diseases have rare condition support organisations and it can be hard to connect with other PLWRC given the rarity of the conditions.

PLWRC may also find out about trials from the internet; for example, in trial registries such as ClinicalTrials.gov. However, attendees pointed out that most, if not all, existing trial registries are public-friendly, and that the quality and completeness of entries is variable.

The result is a lottery of access to this information, where finding out about clinical trials relies on word of mouth between clinicians, PLWRC and rare condition support organisations; PLWRC who happen to be in hospitals that have expertise in their condition often end up with better access to clinical trials.

Attendees reflected that, from the triallists’ point of view, raising the profile of a clinical trial can be a challenge because there are regulations/restrictions on how trials can be advertised, including in patient networks.

Eligibility criteria for clinical trials are often restrictive, which makes it more difficult to recruit enough trial participants. Attendees expressed concern that some exclusion criteria are arbitrary, making recruitment of the required number of PLWRC more challenging. One example given was the restriction to an age range between 18 and 65 for participants in a trial studying a rare disease that involves flare-ups of a condition that can happen at any age. Eligibility criteria may also exclude PLWRC who have been part of other clinical trials.

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35 https://www.clinicaltrials.gov/
the pool of people with a particular rare disease is small, PLWRC are more likely to have previously taken part in a clinical trial, so such criteria can significantly restrict the pool of PLWRC eligible for participation. Because rare diseases are rare, attendees highlighted that eligibility criteria should be as broad as possible while still reducing variability as much as is feasible to enable meaningful results to be collected.

Frequently there is also time pressure for trial recruitment. This may be because of a deadline set by the regulators, as in the example given by Ms Brandão, or it may be because of time pressure built into the eligibility criteria (e.g. needing PLWRC in a narrow age bracket, as in Box 7, or at a particular stage of the disease). Proposals by the MHRA to make changes to clinical trials legislation in the UK suggest the introduction of ‘a sunset provision on approvals’, such that the approval will lapse if no participant is included within a specified period. As highlighted by the Academy’s response to the MHRA call for evidence on the subject, to avoid unintentionally making recruitment for clinical trials for rare diseases more difficult, it will be important that any legislative change allows for exemptions where good rationale is provided.

Box 7: Time pressure for recruitment in a trial for spinal muscular atrophy
Spinal muscular atrophy (SMA) is a rare genetic neurodegenerative disease characterised clinically by progressive muscle weakness. Attendees discussed examples of trials for SMA treatments with eligibility criteria that required babies with SMA less than 6 months old (e.g. trials of Risdiplam). However, SMA is usually not diagnosed until the baby is 5 months old, leaving a short window for the parents to find out about the trial, be referred, assessed, and recruited.

In this case, the role of rare condition support organisations (in this case SMA Europe) to signpost parents of newly diagnosed babies to clinical trials was highlighted. The company running one particular trial under discussion also designated one person who, unusually, had access to all patient data for the trial and coordinated logistical, financial and administrative support for trial participants. This point of contact helped improve the successful recruitment of participants to the trial and also to conduct a coherent approach to reducing the burden of trial participants throughout.

Making clinical trials more findable
To tackle some of the challenges of recruiting trial participants described above, attendees identified two innovations in Session 1 to help make clinical trials more findable and

37 Academy of Medical Sciences (2022). Academy of Medical Sciences’ response to the MHRA’s consultation on legislative changes for clinical trials. https://acmedsci.ac.uk/file-download/83223772
accessible to PLWRC, for which practicality and acceptability were discussed in Session 2. Other innovations discussed included developing national rare disease networks to help reduce the postcode lottery.

**Innovation 1: Building a centralised national database of ongoing rare disease trials and their locations from already existing platforms.**

The concept of a centralised national database on rare disease trials was highly acceptable to attendees. It was noted that building such a database would be challenging practically and there were questions around ownership and maintenance. Therefore, there was a strong consensus that such a database should not be built from scratch but based on a pre-existing database. One such centralised database that was highlighted was the National Institute of Health Research (NIHR) repository of trials, ScanMedicine (Annex 7). One suggestion was to supplement pre-existing registries such as ScanMedicine or ClinicalTrials.gov with a public interface.

**Innovation 2: PLWRC could refer themselves to clinical trials (potentially with the support of rare condition support organisations) to help overcome the reluctance of some healthcare practitioners to refer PLWRC to trials, even after diagnosis.**

There was general agreement that the referral system needed to be improved, as referral often involves multiple people, each of whom might have a slightly different interpretation of the eligibility criteria. In addition to reducing access for PLWRC, this increases the effect of selection bias and attendees commented that it is one of the reasons the results of clinical trials do not reflect the real world. There were concerns about the lack of support for PLWRC in deciding which clinical trial to be a part of (for diseases where there were multiple trials) and about managing the expectations of PLWRC to safeguard their mental health.

It was suggested that PLWRC (or their families) could refer themselves to clinical trials. This was highly acceptable to PLWRC and carers. Where appropriate, self-referral to approved research studies is promoted by the Scottish Health Research Register (SHARE). SHARE is an NHS Research Scotland initiative that has been established to allow people aged 11 and over and resident in Scotland to register their interest in participating in research. Participants agree to allow SHARE to use their anonymised NHS records to check whether they might be suitable for health research studies.

Further discussions revolved around the role of rare condition support organisations in referral of PLWRC to trials, rather than self-referral. Attendees considered that rare condition support organisations could signpost available trials [using resources such as ScanMedicine (Annex 7)], help PLWRC understand clinical trial materials, and potentially provide support to PLWRC in deciding whether to participate in a clinical trial and which to participate in if there were more than one.

Attendees pointed out, however, that not every rare disease has a rare condition support organisation, and many rare condition support organisations are not well resourced enough to provide such support.

An alternative is for NHS highly specialised healthcare services and other rare disease services in the UK to have research coordinators to monitor research opportunities and work

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closely with PLWRC communities to inform and promote the benefits of research. This is consistent with the ambitions for the Rare Conditions Coordination Service for Scotland proposed by Scotland’s Cross-Party Group on Rare Genetic and Undiagnosed Conditions, and for the national rare disease care centre in Northern Ireland proposed in the Northern Ireland Rare Diseases Action Plan.

**Proposed next steps:**
- A mapping exercise of existing repositories from a rare diseases perspective to identify where the gaps are and raise awareness of resources already out there, such as ScanMedicine (Annex 7).
- The similar digital recruitment services in other UK nations, such as the NIHR BioResource and Find, Recruit and Follow-up service, should follow the example of SHARE of giving people the power to self-refer to clinical trials where appropriate.
- For rare diseases with clinical trials, rare condition support organisations might consider appointing a member of staff or trustee to provide information and advice about available trials to PLWRC and act as a point of contact with the trialists, if there are sufficient resources. Sharing the costs associated with such a role between relevant companies, funders and rare condition support organisations would be important to avoid overburdening rare disease support organisations, which often have limited resources.
- Appoint research coordinators for NHS highly specialised services (HSS) for rare diseases and other services for rare conditions.

**Making PLWRC more discoverable**

Another approach to improve recruitment of trial participants could be to make PLWRC more discoverable by trialists and sponsors.

Attendees discussed the practicality and acceptability of three innovations to help trialists and researchers identify PLWRC to recruit to clinical trials. Other innovations highlighted in Session 1 included stratification of patient groups to make sure the most appropriate patient groups are targeted for a trial.

**Innovation 3: Formally link NHS HSS for rare diseases and other specialised rare disease services in the UK to clinical trial infrastructure to allow easier recruitment of trial participants and facilitate collection of biomarker samples and communication on care.**

The NHS’s HSS in the UK were described as a highly valued service for the rare disease community. Linking HSS to clinical trial infrastructure would be in line with requirements laid out in the Health and Care Act 2022 for leaders within the NHS to ‘actively facilitate’ research and was generally acceptable to PLWRC, carers and trial sponsors. Co-location would allow

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44 Note that the Find, Recruit and Follow-up service was not directly discussed as an example in the workshop.

45 Note that the Health and Care Act 2022 was enacted in April 2022 after the workshops took place and not directly discussed at the workshop. *Health and Care Act 2022*. Available at:
trial participants to receive specialist care during trials and ensure there was sufficient expertise in the relevant rare disease at the trial site.

PLWRC are often required to travel long distances to HSS and clinical trial sites. Co-locating services would hopefully reduce the travelling PLWRC and their families are required to do overall. However, such co-location should be coupled with efforts to better enable local/home participation in clinical trials, such as remote monitoring approaches (see Innovation 9). One suggestion was a hub-and-spoke model with the main clinical trial site at the HSS and satellite sites in areas local to participating PLWRC.

Attendees strongly recommended that any changes in infrastructure should be co-designed with PLWRC and their families, and with clinical research networks. It was noted that only a minority of rare diseases benefit from an NHS HSS.

**Innovation 4: Using real-world data to help make PLWRC discoverable for trial recruitment.**

Real-world data were highlighted as an asset for identifying PLWRC. For example, the Find, Recruit and Follow-up service aims will enable electronic health information to be used to identify sites with suitable PLWRC, to offer PLWRC opportunities to participate in clinical trials, and to follow up research participants. Participants were generally supportive of linkage between different platforms, particularly where this resulted in an improved joined-up experience for PLWRC, as long as data usage was transparent. Therefore, the phase 2 commitment of the Future of Clinical Research Delivery: 2022 to 2025 implementation plan for the Find, Recruit and Follow-up service to work across the four UK nations to increase opportunities for people to quickly and easily access research of relevance to them is likely welcome.

Rare disease-specific services were discussed. For example, the National Congenital Anomaly and Rare Disease Registration Service (NCARDRS) (Box 8) has demonstrated that analysis of linked sources of healthcare data, including routinely collected health data, is a powerful tool to build cohorts of people with particular rare diseases. The approach used in exemplar studies in certain rare diseases such as haemophagocytic lymphohistiocytosis (HLH) (Box 8) could be applied to other conditions. Advanced analysis may even be able to identify PLWRC prior to diagnosis. Such methods could be a powerful way of improving recruitment of participants to clinical trials and/or could help rare condition support organisations set up patient registries. There are plans to establish a similar database in Northern Ireland (NI), the NI Rare Disease and Congenital Abnormality Registry.

Questions were raised around the difficulty of working with real-world data for diseases that are not currently coded for (e.g. in ICD-10 or ICD-11 – see discussion of Innovation 10). Attendees were also concerned that consent procedures covered processing of data by

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services such as NCARDRS and emphasised that people should be adequately informed about how their data are being used, particularly since the data are personally identifiable.\textsuperscript{48} It was felt that consent to be contacted subsequently for potential involvement in research should also be explicitly consented for, and there was concern that, without going through their clinician, there would not be sufficient support in place to help with their decision-making. The importance of the application of national opt-outs and the availability of the Caldicott Guardian to people in NCARDRS databases was emphasised.

The possibility of previously undiagnosed PLWRC being identified by analysis of NCARDRS data raised ethical questions. For example, whether or not it would then be appropriate to contact the person to recommend taking a diagnostic test was discussed, particularly in cases where the rare disease may not yet have a treatment.

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Box 8: The National Congenital Anomaly and Rare Disease Registration Service\textsuperscript{49}

The National Congenital Anomaly and Rare Disease Registration Service (NCARDRS) collates, validates and registers data at local, regional and international level at various stages of a patient’s life. Data comes from a variety of sources including routinely collected health data from hospitals, clinically reported data, specialised centres, prescribing data, patient registries, and genomic data. This comprehensive approach enables NCARDRS to achieve the highest possible ascertainment and completeness of cases in the population.\textsuperscript{50} The aim of NCARDRS is to use the data ‘to inform and improve the diagnosis and treatment of patients’.\textsuperscript{51} Collaborations with organisations collecting and managing this data is essential.

This rich source of linked data can be used to identify cohorts of people with a rare disease. For example, one recent study validated the accuracy of routinely collected electronic healthcare data in identifying people with a rare systemic inflammatory syndrome, haemophagocytic lymphohistiocytosis (HLH), by comparing with clinically reported data.\textsuperscript{52} Subsets of data are also validated with condition-specific measures. One attendee shared that recently a cohort of people were contacted to validate results of an NCARDRS investigation, and only a very small number wrote back to say that they did not have the disease identified by the analysis.

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\textsuperscript{49} https://www.ndrs.nhs.uk/

\textsuperscript{50} Pericleonous M, et al. (2021). Defining and Characterising a Toolkit for the Development of a Successful European Registry for Rare Liver Diseases. Orphanet Journal of Rare Diseases. [pre-print] https://doi.org/10.21203/rs.3.rs-400211/v1

\textsuperscript{51} https://www.ndrs.nhs.uk/about-us/how-information-is-collected/

Advanced methods to analyse the data can further be used to find additional people with a disease that may be difficult to find otherwise. In one example shared by an attendee, language processing software was used to find mentions of Alpha-1-antitrypsin deficiency in associated documents (e.g. lab reports, hospital letter, etc.) and significantly increased the cohort compared to looking at the hospital records alone. The NCARDRS is starting to explore the use of AI to predict who might have a rare disease though not yet diagnosed.

NCARDRS could be useful for rare condition support organisations looking to set up patient registries. It could also be used by triallists to see the geographical distribution of people with a rare disease to help plan where to set up trial centres.

Proposed next steps:
- Any new service for rare conditions, such as the Syndromes Without A Name (SWAN) clinic being piloted in Wales, should incorporate capacity for research and clinical trials for rare diseases into the design of the service.
- Linking HSS and other rare disease services with clinical trial infrastructure could involve having a member of healthcare staff who is a point of contact for PLWRC wanting to take part in relevant clinical trials and triallists wanting to recruit trial participants. This role could be fulfilled by an already existing healthcare professional (e.g. a research nurse, clinician, clinical academic), or it could form its own role. The individual performing this function will require protected time to do so to avoid adding a burden to an already stretched healthcare workforce.

Truly informed consent
To be recruited to a trial, a trial participant must be provided with enough information to enable them to give informed consent. ‘Informed consent’ requires that a prospective trial participant understands what the research is and what they are consenting to. There were concerns from Ms Brandão and others that often information about a trial and the clinical assessments performed are not presented to PLWRC in such a way that they can understand and appreciate the potential impact on their lives.

Innovation 5: Ensuring information for PLWRC about what is involved in clinical trial participation is accessible so that they can provide informed consent.
Participant-facing information might include participant information leaflets and entries in clinical trial repositories. It needs to be accessible while retaining sufficient detail about benefits and potential harms to enable informed consent. However, often participant-facing

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54 https://researchsupport.admin.ox.ac.uk/governance/ethics/resources/consent#:~:text=Informed%20consent%20is%20one%20of%20the%20research.
information is technical and held in excessively long documents, which presents a barrier to making informed decisions about trial participation, particularly for sick PLWRC with reduced capacity due to their symptoms. Furthermore, often participant-facing information focuses on the risks of participation and underemphasises the benefits. In evidence gathering for its response to the MHRA consultation on changes to clinical trials legislation, the Academy heard some evidence that this can reduce the diversity of trial participants.\(^{55}\)

Ensuring information is presented to prospective trial participants in an accessible and understandable way can be particularly challenging in rare diseases. Many of the investigational treatments use advanced therapies (e.g. gene or cell-based therapies) that are more challenging to understand and explain and may have repercussions for the eligibility of a trial participant to participate in future trials. Furthermore, clinical trials for rare diseases are often multinational and so there may be cultural and language barriers to gaining informed consent. However, as the pool of eligible trial participants for clinical trials for rare diseases are restricted, it is particularly important to ensure a PLWRC is fully committed to a trial when they sign up, with full knowledge of the potential impact on their lives, to reduce the likelihood and expense of them dropping out during the trial. There was a strong feeling that effective communication of information about a clinical trial to prospective trial participants had potential to save both time and money for both the PLWRC themselves and the trialists.

Participant-facing information should be accessible. Attendees emphasised that there is no ‘one size fits all’ approach, and organisations should take into account the needs of the target audience when writing the information, considering both language and format; for example, avoid giving small text to people with visual impairment. Electronic consent forms could be used to enable prospective trial participants to read them multiple times, though there was concern about the digital exclusion of participants not able to engage with or access such technologies. It was noted that regulatory requirements sometimes present a challenge to writing accessible patient information leaflets and the need to engage regulators early was reiterated.

Smaller pharmaceutical companies and other trial sponsors may not have the expertise in-house to develop accessible materials. Attendees highlighted the value and importance of collaborating with PLWRC, carers and/or rare condition support organisations in the design of accessible patient information leaflets. This is consistent with the recommendation from the Academy’s report on ‘enhancing the use of scientific evidence to judge the potential benefits and harms of medicines’ that regulators work with pharmaceutical companies, PLWRC, and carers to improve the comprehension and readability of patient information leaflets such that they present a clearer, more simplified and balanced appraisal of the benefits and potential harms of the medicine.\(^{56}\) However, rare condition support organisations may not have the resources or expertise to drive the process themselves and it was suggested that they be thought of as consultants rather than contractors.

Attendees pointed out that a lot can be learned from best practice of producing patient information materials to aid shared decision-making and consent procedures in healthcare settings. For example, the charity Salivary Gland Cancer UK recently published patient leaflets

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\(^{55}\) Academy of Medical Sciences (2022). *Academy of Medical Sciences’ response to the MHRA’s consultation on legislative changes for clinical trials.* https://acmedsci.ac.uk/file-download/83223772

\(^{56}\) Academy of Medical Sciences (2017). *Enhancing the use of scientific evidence to judge the potential benefits and harms of medicines.* https://acmedsci.ac.uk/file-download/44970096
about tumour profiling that were co-created by patients and oncologists. 

Proposed next steps:
- Make clinical trial repositories dynamic and easily accessible to patients and the public.
- Share best practice about how to get meaningful informed consent for advanced therapies.
- Involve PLWRC, their families, and rare condition support organisations in the co-creation of accessible participant-facing informational materials with support and guidance from regulators.

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57 This example was highlighted to us following the workshop and not directly discussed by workshop attendees. [https://www.salivaryglandcancer.uk/treatment-options/gene-profiling-or-tumour-profiling-or-genomic-testing/](https://www.salivaryglandcancer.uk/treatment-options/gene-profiling-or-tumour-profiling-or-genomic-testing/)
Reducing participation burden

Participating in clinical trials for rare diseases comes with significant burdens, which can make PLWRC reticent to participate or force them to drop out before a trial is completed. The burdens can also affect the physiology and mental health of trial participants, confounding trial results.

These burdens include:
- PLWRC are often required to travel (or even relocate) long distances, sometimes internationally, to trial centres. The administrative burden of arranging travel and accommodation is significant, with one attendee describing it as ‘paralysing’. One example issue highlighted was that NHS expenses procedures were set up with staff in mind and not designed well for volunteers and trial participants. Attendees generally agreed that support provided for PLWRC participating in trials was not sufficient.
- Treatment administration can be invasive and painful. The interventions can sometimes cause debilitating side effects, as with the lumbar punctures administered to the Beveridge sisters. The treatment being investigated itself may also have serious side effects.
- Trial assessments are often time-consuming and exhausting. Some can also be distressing, painful and invasive (e.g. needing to have tissue samples taken many times). Attendees expressed that sometimes clinical assessments and endpoints were chosen without thinking carefully about the impact on the trial participant or the usefulness of the result for effectively measuring outcomes that are meaningful to PLWRC and their families.

These stressors are particularly challenging because PLWRC are often already suffering from debilitating symptoms of their condition, and many are children.

The burden, and also the hope, of taking part in clinical trials can also affect the mental health of trial participants and their families. Attendees agreed that it was essential to communicate effectively with trial participants, including making sure they understand the purpose of tests they were taking, to manage their expectations concerning the outcome of the trial, and to answer questions that arise regarding their health throughout the trial.

In addition to affecting the quality of life of trial participants, attendees pointed out that the effect of these stressors on the physiology and mood of trial participants often significantly affects the results of their clinical assessments, undermining the validity of the clinical trial results.

To help manage and reduce the burden of clinical trial participation in rare diseases, attendees discussed innovations to provide additional support for trial participants and design more accessible clinical trials, including selecting clinical assessments and endpoints that reduce the burden for, and are meaningful to, PLWRC and their families.

Regarding all the innovations listed below, attendees emphasised that different things work for different people; a personalised approach to introducing innovations should be used, with involvement of PLWRC and their families to avoid unintentionally increasing the burden to certain groups of PLWRC.
Support during the trial
Attendees described examples both where burden was increased due to a lack of support and communication during clinical trials, and exemplars where the experience of trial participants was improved by provision of support in consultation with rare condition support organisations. In addition to increasing the burden of participation for all PLWRC, a lack of logistical, financial and administrative support is likely to exacerbate inequities, as PLWRC with less time and resources are less able to participate.

Innovation 6: Better administration and support of trial participants, especially coordinating travel and accommodation.
Provision of more support for trial participants and their families, and in particular logistical support, was highly acceptable to attendees. However, it was recognised that this requires understanding of the needs of individual PLWRC, knowledge of the disease, and sufficient resources to do so in an effective and timely manner.

As such a service would require significant input from the PLWRC themselves and their families, the role of rare condition support organisations was discussed. It was pointed out that many rare condition support organisations do not have the resources or expertise to provide this service in addition to their other activities, but that in some cases they could advise as consultants.

An alternative is for the service to be provided by a specialist organisation. One such organisation providing clinical trial support services is Rare Disease Research Partners (RDRP).58 RDRP provides personalised logistical support for PLWRC and their families so they can participate in clinical trials worldwide. This includes support with travel and accommodation, relocation, reimbursement and 24/7 assistance. They partner with rare condition support organisations to ensure they can cater for disease-specific needs. Providing such support not only improves the experience of trial participants and their families but also improves retention of trial participants.

There was also discussion around the role of ethics committees in ensuring support is in place for trial participants when approving a trial design and what expertise they would need to make that judgement.

Innovation 7: Improving communication between trial staff at centres running clinical studies (including medical monitors) and routine care staff (e.g. local hospitals, GPs, etc.).
Frequently the routine care of a PLWRC is not joined up with their participation in a trial. In addition to the difficulties this can cause for PLWRC, as described by the Beveridge family, variability in standard of care between different regions and countries can affect the results of a trial. There was concern that sometimes triallists do not consider this source of variability. Therefore, attendees agreed that improving communication between trial staff running clinical trials and healthcare professionals providing routine care to the PLWRC is very important. One suggestion was to have a key contact in the trial staff, both for the trial participant and any healthcare professionals involved in their routine care, who could answer questions.

Proposed next steps:
• Triallists should ensure that sufficient logistical, financial and administrative support for

58 https://rd-rp.com/
Design of the trial
When designing a clinical trial, it is important to ensure the burden of participation on PLWRC and their families is manageable so that they can participate from the beginning to the end of the trial.

Innovation 8: Involve PLWRC and other relevant stakeholders to reach a consensus on the design of clinical trials.
PLWRC and rare condition support organisations are the experts in their disease and are the target consumers of the treatment. This expertise is particularly important given many rare diseases are not well studied and there is not a large amount of natural history data. Meaningful patient and public involvement (PPI) can reduce unnecessary or overly burdensome procedures, improve recruitment of trial participants, retention, and experience, and reduce cost. Attendees agreed that there is a lot to be gained from involving PLWRC and rare condition support organisations in trial design and that currently their input is undervalued or tokenistic. The recommendation from attendees was to involve PLWRC early in clinical trial design.

Attendees highlighted that there are strict regulations about how industry can engage with PLWRC and that pharmaceutical companies may be concerned that they will be seen as trying to influence patient groups. Rare condition support organisations can help industry feel more comfortable by convening discussions with senior leaders, regulators, researchers and PLWRC. The Association for British Pharmaceutical Industry (ABPI) has produced a sourcebook with guidance to support pharmaceutical companies and rare condition support organisations to collaborate successfully in a manner compliant with the law and the ABPI code.

The importance of managing the expectations of PLWRC at every stage was emphasised. It was pointed out that sometimes PLWRC may not want to be involved.

A recent consultation from the MHRA on changes to clinical trials legislation suggested a legislative requirement for the involvement of people with relevant lived experience in the design, management, conduct and dissemination of a trial. The Academy and the FPM

60 Academy of Medical Sciences (2022). Academy of Medical Sciences’ response to the MHRA’s consultation on legislative changes for clinical trials. https://acmedsci.ac.uk/file-download/83223772
responses to the consultation both reflected the opinion of some attendees that any changes should allow triallists to justify where PPI is not appropriate or possible. Without this, a legal requirement for PPI at every trial stage risks creating unnecessary challenges or delays, adding work and economic costs (to both sponsors and patient and public contributors), and resulting in tokenism or a tick-box approach to PPI, without proportionate meaningful benefit. The HRA is further exploring this in a cross-sector project, co-produced with public contributors, to collect evidence about how high-quality, people-centred clinical research can be done well.

Innovation 9: Better enabling of home/local participation in trials – e.g. delivery of trial medications at home or locally where possible or remote monitoring.

During the COVID-19 pandemic, many trials had to use remote monitoring and other interventions to allow better local/home participation in clinical trials. This could include delivery of the trial medication at home, or performing clinical assessments locally or remotely (e.g. by video or with wearable technologies as discussed in Box 6). Such interventions were generally considered to be acceptable by attendees with caveats.

Enabling home/local participation in trials has the potential to lower the burden on trial participants by reducing travel, improve the quality of the data collected, and improve access to trials for geographically dispersed populations of PLWRC. Attendees felt that data collected in the home environment could give regulators and assessors better insight into the effects of the treatment as the stressors involved in travelling to the trial centre would not be confounding the data.

Attendees warned that some triallists are doing remote monitoring in addition to, rather than instead of, onsite assessment, meaning that the burden on trial participants increases rather than decreases. Guidance should be put in place by regulators to give triallists the confidence to incorporate remote monitoring into their trial designs in ways that reduce participant burden.

A balance should be struck between what needs to be done in a clinic and what can be done at home. In one example shared, despite initial misgivings from triallists, monthly subcutaneous injections of the trial medication at home, monitored by triallists by video, significantly reduced the burden on trial participants as they did not have to travel. However, more complex, invasive drug delivery mechanisms such as lumbar puncture would not be suitable for a home environment. There was concern that the home of PLWRC should not be turned into ‘mini-clinics’ and that PLWRC would feel pressured into being monitored at home.

The incorporation of remote monitoring into a trial’s design should be done in collaboration with rare condition support organisations to avoid unintended adverse consequences. PLWRC will face different challenges, depending both on the challenges of their particular disease and their personal preference. Attendees emphasised the importance of using remote monitoring technologies to personalise interactions rather than depersonalising them.

Home or local participation in clinical trials frequently rely on the PLWRC or their carer actively participating in their clinical assessment or drug delivery. To do this effectively, they

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63 Academy of Medical Sciences (2022). Academy of Medical Sciences’ response to the MHRA’s consultation on legislative changes for clinical trials. https://acmedsci.ac.uk/file-download/83223772
64 Note that this article was published after the workshop took place and attendees did not directly discuss this example. HRA (2022). Can you help us put people first in research? https://www.hra.nhs.uk/about-us/news-updates/could-you-help-us-put-people-first-research/
should receive training and/or support from a local healthcare professional. There were concerns about a lack of research nurses to provide such support. Therefore, the phase 2 commitment for NIHR to provide investment to increase research capacity including nurses and allied healthcare professionals, as indicated in the Future of Clinical Research Delivery: 2022 to 2025 implementation plan, is likely welcome.\(^{65}\)

Technological solutions may be useful to enable home participation in clinical trials. These might include apps or online platforms to enable remote monitoring and assessment (e.g. Box 6), or wearable technologies to collect data. Wearable technologies should capture features that are clinically meaningful, both from a regulatory perspective and from the perspective of PLWRC and their families (e.g. Box 4).

In some cases, the symptoms or inclinations of a PLWRC may make them less able to interact with a technology. For example, many boys with DMD also have attention deficit hyperactivity disorder and could not cope with an asymmetric design of wearable technology so the design had to be changed.

This illustrates the importance of thinking carefully of the needs of the end-user and involving them throughout the design process. Technologies should be made accessible, simple, and understandable. PLWRC are often geographically dispersed and may speak different languages and have different amenities in terms of access to the internet. This should be accounted for during the design process to avoid the unintentional exclusion of certain groups of PLWRC.

During a trial, a dedicated tech support team should be engaged to help with problems as PLWRC and their carers will likely need support; it was pointed out that having medical staff trying to provide tech support would not be an efficient use of their time.

**Proposed next steps:**
- Detailed guidance and best practice examples of involving patients and the public in clinical trial design should be developed by regulators in consultation with relevant stakeholder groups, to help avoid a tokenistic approach to PPI.\(^{66}\)
- Guidance should be co-developed by regulators and other stakeholders (including members of the public) to give triallists the confidence to incorporate remote monitoring into their trial designs in ways that reduce participant burden.
- Triallists should provide PLWRC and their families with necessary training and support (e.g. tech support) to enable trial participation from home where appropriate.
- Collaboration between rare condition support organisations, triallists, medical technology companies and regulators will be important to develop and validate wearable technologies and meaningful endpoints based on them.
- Researchers and tech developers should involve PLWRC and rare condition support organisations early in development of products.

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\(^{65}\) Note that this report was not published at the time the workshops took place and its contents were not directly discussed by workshop attendees. This statement is speculation by the author and workshop chairs. DHSC (2022). The Future of Clinical Research Delivery: 2022 to 2025 implementation plan. https://www.gov.uk/government/publications/the-future-of-uk-clinical-research-delivery-2022-to-2025-implementation-plan/the-future-of-clinical-research-delivery-2022-to-2025-implementation-plan

\(^{66}\) Academy of Medical Sciences (2022). Academy of Medical Sciences’ response to the MHRA’s consultation on legislative changes for clinical trials. https://acmedsci.ac.uk/file-download/83223772
Selection of meaningful endpoints

Selecting meaningful clinical endpoints is a challenge in rare diseases. This is because of the lack of natural history data, the slow progression of many diseases, and the variability of age of onset/flare-up of some rare diseases. Even among people with the same rare disease, symptoms and how they are experienced are often different. This means PLWRC often do not feel that outcome measures capture change in their disease state or that outcome measures are significantly influenced by other factors, meaning any effects of a drug can be missed. Attendees discussed examples such as the 6MWT, often used as an outcome measure in DMD, which is not considered by patients or clinicians to effectively capture the features of the disease (Box 4).

Many endpoints are based on improvement in disease symptoms. Attendees pointed out that, as many rare diseases are progressive, a drug that can halt disease progression and maintain a patient’s current state of health is of significant value. Therefore, endpoints based on maintenance of a patient’s current state of health should be considered.

Where clinical endpoints are hard to measure, one option is to measure biological markers that act as surrogate markers for clinical endpoints. However, it is difficult to find biological markers that map to clinical endpoints that PLWRC consider to be meaningful. Attendees also highlighted that identifying such biomarkers can be a challenge because of barriers to access and analysis of biological samples.

Attendees highlighted the importance of using outcome measures that are important to PLWRC. These might include patient-reported outcome measures on factors such as concentration or fatigue. However, these are often difficult to reliably measure; data are noisy, meaning more trial participants are required to find a meaningful result, which is a challenge given the small populations of PLWRC.

Despite the challenges, new approaches and technologies present opportunities to improve endpoint and outcome measure selection for rare diseases. As discussed by Dr Davies in her talk, wearable technologies present an opportunity to design alternatives to flawed endpoints (Box 4) and capture stages of a disease not revealed by current outcome measures (Box 6).

Qualitative, text-based data collection can also be a rich source of information about patient experience of an investigational medicine. Attendees highlighted that there is a need to upskill the clinical trial workforce to use the tools needed to analyse qualitative data. Despite qualitative data collection already being used routinely in social sciences, the perception around such data among many researchers, triallists, regulators and health technology assessors is that it is ‘anecdotal’ and ‘difficult to quantify’. If such techniques are to be used to their full potential, perceptions around them need to be changed.

Alongside the specific innovations discussed below, there was general consensus that there should be better collaboration and active coordination between organisations in the precompetitive space to help explore the natural history of a rare disease and select appropriate endpoints. To this end, it was suggested that different organisations with an interest in the same rare disease, including pharmaceutical companies, rare condition support organisations, regulators, and health technology assessors, could run joint workshops for this purpose.

Innovation 10: International and interdisciplinary collaboration to allow international integration of patient registries and biomarkers to provide natural history data.

Patient registries can be used to identify novel outcome measures and biomarkers that are relevant and acceptable to PLWRC. However, currently, data are fragmented into smaller
registries, meaning data are not necessarily standardised and are difficult to access and use. Furthermore, many rare diseases do not have patient registries.

The concept of international integration of patient registries was highly acceptable to attendees, though considered to be challenging. An integrated international registry could provide a rich source of natural history data to help select outcome measures that are meaningful to PLWRC, design trials and recruit trial participants. One recently established international patient registry is the GARDIAN registry (Box 5) and attendees discussed how the model could be applied to other diseases.

One of the challenges to setting up patient registries is resourcing. Often patient registries are owned by rare condition support organisations. However, it can be difficult for rare condition support organisations to source and maintain the funding required to develop and maintain an international registry. Attendees suggested registries could be set up and maintained by collaboratives including national funding bodies and pharmaceutical companies as well as rare condition support organisations. Attendees raised the challenge of justifying investment in large-scale data collection before it is clear how that data are going to be used or useful in the future.

Another practical challenge highlighted was the need for better codification of rare diseases by registries and the healthcare system to help identify records for inclusion in an international registry. The International Classification of Diseases (ICD) system only codes for relatively few rare diseases; ICD-10 only codes for ~200 rare diseases and the updated ICD-11 only codes for ~2000 (of an estimated 7000).67 Orphanet has developed a classification system for rare diseases. Although Orphanet is beginning to be incorporated into the internationally recognised structured clinical vocabulary for electronic health records, SNOMED CT,68 uptake has broadly been limited and patchy.69 Programmes like NCARDRS (Box 8) that use analysis methods that do not necessarily rely on disease coding could present a way of building cohorts of people with a specific rare condition, despite issues with disease coding.

In addition to discussing disease-specific registries, attendees also discussed the concept of an international database of all PLWRC that could enable a coordinated effort to develop therapies for rare diseases; for example, to help identify similarities between different disease pathologies that could be amenable to the same drug. The scale of such a project would be large but it could build on the work of already existing international platforms such as the RDCA-DAP (Annex 8).

Innovation 11: Develop a common set of outcome measures or endpoints, with input from PLWRC, that are broadly applicable to all (or a subset of similar) rare diseases – walking, sleeping, eating, pain, particular biomarkers, etc. – and validate them in common diseases. This will likely include repurposing endpoint measures for different diseases.

Developing and validating outcome measures for rare diseases can be challenging because there are many rare diseases and not many people living with each. Although rare diseases may have different causes, some rare diseases may have symptoms or pathological

68 Note that this example was not directly discussed by workshop attendees. SNOMED International (2021). INSERM and SNOMED International release SNOMED CT to Orphanet map supporting representation and use of rare disease content in electronic health records. https://www.snomed.org/news-and-events/articles/INSERM-SNOMED-Intl-SCT-Orphanet-Map
mechanisms in common. The suggestion was made that PLWRC populations could work together to develop a common set of outcome measures and define potential molecular pathways for drugs to target. In addition to helping with the selection of meaningful outcome measures, there was suggestion that these could be used to test the same drug in multiple rare disease populations with similar symptoms, as discussed in Innovation 15. Such an approach could be useful for diseases without a single genetic cause, such as scleroderma or mitochondrial diseases.

The concept of targeting a particular symptom, rather than a specific disease, was acceptable in theory. However, attendees pointed out that this would cause licensing issues in the current system as drugs are traditionally targeted to a disease first and then a symptom within that disease. Furthermore, there was scepticism among attendees about feasibility as there is significant heterogeneity both between people living with the same rare disease and between different rare diseases.

Attendees concluded that this innovation poses a challenge and would require more explorative research. There was some discussion of the potential for registry-based cluster analysis to identify similarities between different rare diseases, upon which a common set of outcome measures could be based.

Proposed next steps:
• Joint workshops bringing together different stakeholders to explore the natural history of a rare disease and select appropriate endpoints would be beneficial.
• Funders should consider their role in supporting patient registries for rare diseases in collaboration with other relevant organisations.
• The development of case studies to demonstrate the value of patient registries would be useful to help justify funding for registries for other rare diseases.
• The development of case studies of how to set up patient registries, such as GARDIAN (Box 5), would be useful to share best practice.
• Organisations building patient registries for rare diseases should involve PLWRC and their families during the design process.
• The Orphanet definitions for rare diseases should be incorporated with current international systems for diseases classification.
Innovating clinical trial design to make best use of data

Clinical trial design for rare diseases needs to satisfy a number of practical, scientific and statistical requirements to prove that a medicine is safe and effective. These requirements are often in competition with each other, which may disincentivise trial sponsors from developing treatments, discourage PLWRC from taking part, and provide challenges for regulators. For example, the limited number of PLWRC available to participate in a clinical trial means that recruiting sufficient participants to achieve statistical power may be more challenging. Therefore, in addition to ensuring that as many PLWRC are recruited and able to participate in clinical trials as possible (as discussed in the previous two sections), it is important to design clinical trials for rare diseases to make the best use of the data that is gathered.

To achieve this, attendees discussed alternatives to the randomised, double-masked controlled clinical trial. They considered alternative approaches to the control/placebo arm, different structures of clinical trial, and ways of improving the robustness of conclusions drawn from clinical trials. Attendees pointed out that complex clinical trial designs, particularly multi-arm and/or responsive trial designs, require advanced statistical methods and expertise, and recommended statisticians be brought into relevant clinical trial teams.

In addition to the innovations highlighted below, attendees discussed the use of real-world evidence to validate elements of clinical trial design, such as the selection of endpoints or the baseline level of symptoms observed in the PLWRC population (as in Annex 6: case study 3).

Innovation 12: Registry-based treatment studies.
In some cases, it might be possible to answer experimental questions with pre-existing data or using data that are already going to be collected by patient registries. This would save PLWRC and triallists time and energy.

A registry-based study is an investigation of a research question using the systems of new or existing patient registries for recruitment of trial participants and data collection. To be used for this purpose, the registry must collect data that are useful to triallists, meaningful to PLWRC (including patient-reported outcome measures), and acceptable to regulators. This might include information about the clinical status, quality of life, comorbidities, and treatments of PLWRC over time. Therefore, it is important that patient registries are built in collaboration with relevant PLWRC, triallists and regulatory bodies. The GARDIAN registry is

an example of a patient registry set up with registry-based treatment studies in mind (Box 5). Guidance from regulators, such as the EMA’s ‘guideline on registry-based studies’, are important to help organisations running registries know what regulators will accept. However, it was noted by attendees that registries already in existence may not have been developed to answer the questions of regulators and triallists and retrofitting such registries for use in registry-based treatment studies would be a separate challenge to building new ones.

The concept of registry-based treatment studies was generally acceptable if registries involved were co-designed with PLWRC and their families, and if consenting procedures robustly cover use of registry data for this purpose.

Registry-based treatment studies are only as representative as the data that are in the registry, and attendees highlighted the need to be aware of the bias between and within different registries. This includes the ethnic diversity of individuals represented in the data and the potential variability over time or between individuals, such as might be introduced by different standards of medical care in different regions or countries. However, if this is taken into account, registries can be a useful tool for making sure cohorts of trial participants are more representative.

Practically, attendees noted that the quality and completeness of data in patient registries is often not uniform, and data are not collected in a standardised way. Sharing data from national registries across borders can be difficult and multinational registries must satisfy data access and approval processes of many different countries to collect data. One suggestion was that clinical academics could be required to report their data to a registry to get funding.

Proposed next steps:

- Further guidance from other medicines regulators on registry-based treatment studies would be welcome.
- A workshop bringing together relevant stakeholders, including medicines regulators, trial sponsors, PLWRC, rare condition support organisations, and researchers to discuss and share best practice on use of real-world evidence for rare disease registrational purposes would be useful.
- Triallists should make use of patient registries for recruitment and to help ensure trials are representative.
- Funding bodies should consider requiring clinical academics to report their data to an appropriate registry as a condition of funding.

Control/placebo arms in clinical trials for rare diseases

In a randomised, controlled clinical trial, the performance of an investigational medicine taken by trial participants in the treatment arm is compared to the performance of the current standard of care plus a placebo in the control or placebo arm. Establishing control or placebo arms in a clinical trial for a rare disease medicine is challenging due to ethical concerns over giving a placebo drug to someone with a progressive disorder and the lack of incentive for PLWRC to participate.

To overcome some of these issues, the Luxturna® trial used a ‘cross-over’ trial design (Annex 71).

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6: case study 2). PLWRC were reluctant to take part in the phase II/III trial if they would not receive the investigational drug because Phase I trials had produced compelling data that the treatment was effective as well as safe. To address this, the trial was designed such that the participants in the placebo arm of the trial were crossed over to the investigational arm of the trial after 12 months.

Alternatively, natural history data or control data from previous studies of a rare disease could be used as control data (as discussed in Box 1). However, many rare diseases do not have comprehensive natural history data or previous clinical trials to draw upon. Another approach suggested was to use a PLWRC’s own data before treatment as control data. However, as highlighted by Ms Brandão in her talk, many PLWRC may not have detailed records of the natural history of their condition.

**Innovation 13: Use of synthetic, digital control groups**

Instead of having trial participants in a control group in a trial, attendees discussed using machine learning and/or AI to generate a set of synthetic control data based on historical data. Such historical data could include control data from early phase/preclinical research, a trial participant’s own data before they received the treatment, and/or real-world evidence synthesised from multiple sources of real-world data. For those rare diseases with patient registries, those registries could have a role in collecting and curating data for this purpose, and therefore it is important for patient registries to ensure the format and type of data collected are acceptable and useful to regulators, as mentioned above. Attendees also suggested a mapping exercise to determine what real-world data are already available that could be used to generate synthetic control data. Also, as discussed in Innovation 12, it is important to be aware of and account for bias and variability present in sources of historical data used to generate the synthetic control data.

One barrier to the adoption of synthetic control groups identified was mistrust and lack of understanding in AI and machine learning techniques among clinicians, triallists, regulators and health technology assessors. Transparency, responsible behaviour and accountability will be essential to build trust if such techniques are to be adopted and accepted by the sector.

Proposed next steps:
- Develop positive case studies of synthetic control data generated by machine learning and/or AI being used alongside and validated against non-synthetic control groups, to demonstrate the potential and reliability of the technique. Such proofs of concept might need to be performed in more common conditions.

**Clinical trial platforms**

A platform trial is a clinical trial with a single master protocol with multiple experimental conditions being considered. This might include evaluating multiple treatments alongside each other – an umbrella trial – or investigating the effects of one treatment on multiple different diseases or disease subtypes – a basket trial. Trial design may also be adaptive, changing in pre-defined ways in response to data as they are gathered. Depending on the experimental question being asked, platform trials have the potential to improve the efficiency of the trial, centralise and improve recruitment, and reduce the number of trial participants needed to produce robust results.

**Innovation 14: Clinical trial platforms that test multiple drugs against one control arm (umbrella trials)**

To make the best use of control data, one option is to test multiple drugs against one control arm – known as an umbrella trial. High-profile umbrella trials include the UK RECOVERY trial,
which was set up to test a range of potential treatments for COVID-19. This could be a useful approach in rare diseases with multiple investigational treatment options as trials are often competing for a small pool of PLWRC and it can be difficult for PLWRC to decide which trial to participate in. The choice is particularly challenging given taking part in certain trials can preclude a PLWRC’s ability to take part in future trials, because of the reticence of companies to confound their results. Including investigational treatments in one umbrella trial can help make the best use of trial participants’ time. Attendees also pointed out that many drugs may not be curative alone and that umbrella trials can be a useful approach to testing drugs in combination.

**Innovation 15: Clinical trial platforms that test the efficacy of one drug at treating multiple diseases (basket trials)**

An umbrella trial is an example of a multi-arm trial. Another type of multi-arm trial considered during discussions was a ‘basket trial’. A basket trial is a clinical trial platform that tests the efficacy of one drug at treating multiple diseases, with each arm of the trial being a different disease. This could be particularly useful when applied to rare diseases with similar symptoms or pathological mechanisms. Recent research has clustered diseases according to their genetics, proteins present in the blood, and symptoms, sometimes identifying genes that play roles in multiple clinical scenarios. There could be scope to use techniques such as these to identify clusters of diseases with similar underlying pathological mechanisms that might be suitable for basket trials.

The benefit for triallists is that there is a larger pool of PLWRC to recruit from. However, attendees highlighted a variety of practical challenges. As discussed above, finding an outcome measure that is relevant to different rare diseases is challenging. From the perspective of regulators and assessors, approval is currently based on disease indications rather than symptoms. Therefore, to robustly determine efficacy for any one disease indication for regulators, there need to be enough trial participants for each disease, increasing the necessary sample size. Finally, orphan drug designation cannot be given to a drug being tested in a group of diseases so it could change how the trial is regulated.

Attendees suggested that pursual of the application of basket trials in rare diseases should involve engagement with regulators and assessors to ensure acceptability.

**Innovation 16: Prioritisation of treatments for investigation and/or coordination of the efforts of different pharmaceutical companies**

Conducting multi-arm platform trials would need to involve coordination of different organisations, including multiple pharmaceutical companies, PLWRC and regulators. There may also be a need for prioritisation of the treatments under investigation to minimise the burden of trial participation and maximise the chances of completion. However, attendees highlighted that getting different pharmaceutical companies involved in collaborative projects, such as umbrella trials, is challenging as companies often feel they are in competition with each other. Any prioritisation of treatments could affect this. However, stratifying PLWRC (e.g. based on their symptoms or genetics) and allocating them to the most appropriate treatment arm could maximise the chance of success of a treatment without favouring any particular drug – a similar approach was taken in the National Lung Matrix Trial (Annex 9).
Attendees highlighted that risk taking is more acceptable to PLWRC, rare condition support organisations and academics than for industry and that therefore risk-sharing and collaboration are important to ensure clinical trial platforms are acceptable. Having non-industry partners such as rare condition support organisations or academics lead on collaborative projects can provide important reassurance to industry partners that they are not in competition with each other. However, attendees highlighted that it is important to be aware of the different interests of participating organisations. Industry partners were considered by attendees to be more conservative and demanding during contract negotiations in terms of confidentiality and access to data. It was pointed out that rare condition support organisations or academics may not have the in-house expertise and support to deal with complex contract negotiations.

It should be noted that most rare diseases do not have enough (or any) candidate treatments available for investigation and so Innovation 14 and Innovation 16 are not broadly applicable to all rare diseases.

**Innovation 17: Adaptive trial design (e.g. early futility analysis) to allow changes to be made to the trial protocol during the trial based on the data as they are collected.**

**Innovation 18: Advanced methods for improving the quality of analysis of clinical trial data (e.g. using Bayesian methods, which allow for more frequent monitoring and interim decision-making during a trial, and/or AI).**

Traditional clinical trials directly compare data collected over the course of a clinical trial once complete. In contrast, an adaptive approach allows certain modifications, planned before the trial starts, to be made to the trial design after the trial has started, based on the data generated during the trial while maintaining the trial’s validity and integrity. If done correctly, this added flexibility to modify certain elements of the trial design during the trial can lead to more informative and efficient trial outcomes. The flexible features of an adaptive clinical trial might include stopping the trial early if the drug is not expected to show an effect, and, in the context of umbrella trials, dropping treatments that are not having an effect and moving trial participants to ongoing experimental arms, or adding in new treatments during the course of the trial.

Adaptive clinical trial designs have been used extensively in medical device development and the lessons learned from those studies are now being applied to drug development. Adaptive trials could be particularly useful in rare diseases where less is known about the disease beforehand, and where the low number of people living with a particular rare condition means making the best use of the time of trial participants and data produced are even more important.

Taking an adaptive approach to clinical trial design requires use of advanced methods to analyse clinical trial data, to enable more frequent monitoring and interim decision-making. Bayesian methods of analysis, for example, allow data generated during the trial to update assumptions made at the beginning of the trial so the trial design can be revised accordingly. One example is futility analysis – a statistical procedure for stopping the trial early if it appears that the experimental arm is unlikely to be shown to be definitively better than the control arm if the trial is continued to the final analysis.

Attendees highlighted that an adaptive approach, including one using Bayesian methods, requires deep understanding and careful planning to help make the most of the data and to ensure that the results reflect the ‘real’ effect of the intervention. This is particularly important because more powerful analytical techniques have the potential to magnify flaws in the input data.
Adaptive approaches were generally acceptable to attendees in theory as a way of reducing the required number of trial participants for faster trials while maintaining the robustness of the results. However, it was pointed out that adaptive approaches can result in the number of trial participants required increasing during the trial, depending on the data, which could pose problems in rare diseases. As discussed below, clearly communicating the ways the design of an adaptive clinical trial might change during the trial to potential trial participants is more challenging. However, it is essential to ensure that they can understand how participation may impact their lives and make an informed decision about participation.

Because of these challenges, attendees felt that adaptive analytical approaches to trials such as Bayesian analysis have significant potential, but more work is required to make them acceptable before they could be adopted more widely, as discussed below.

**Innovation 19: Improving the understanding of funders, research ethics committee members and PLWRC about the advantages and limitations of different clinical trial methods (including the limitations of traditional randomised clinical trials in rare diseases).**

When discussing adaptive approaches to clinical trial design and other innovative clinical trial designs, there was concern the complexity could make them difficult to understand. This means that gaining informed consent from potential trial participants is more challenging and the results are hard to interpret for trialists, regulators, and health technology assessors. Therefore, improving the understanding of and engagement with different stakeholders about adaptive and other innovative clinical trial designs are important to ensure acceptability. Conversely, attendees felt that the limitations of traditional randomised clinical trial designs were not widely appreciated, meaning undue preference is given to traditional trial designs.

For some attendees, including PLWRC and carers, the acceptability of a particular innovative clinical trial design depended on whether it was communicated clearly. Accessible language and explanations of data are important for non-specialists to help them make decisions, including to help PLWRC make informed decisions about the implications of trial participation on their lives. This is particularly important for adaptive approaches where the trial design will change depending on the interim results of the trial.

**Proposed next steps:**

- The development of positive use cases to help raise awareness and understanding of the benefits and limitations of multi-arm and/or adaptive trial designs would be useful. These use cases could be embedded into training (for trialists, research ethics committee members, and research-active healthcare professionals), included in patient information leaflets, and/or provided alongside applications for ethics approval to provide context.
- Train more statisticians equipped to manage the complex requirement of clinical trial development and design as well as analysis, particularly where innovative methodologies are concerned.
- A workshop to bring stakeholders together and share experience of running multi-arm and/or adaptive clinical trials and to explore how they could be usefully applied in rare disease would be useful. Sharing practice for innovative clinical trial designs is essential to make the best use of resources.74

• Regulatory guidance co-developed with relevant stakeholders, including PLWRC and their families, about how such clinical trial platforms can be used in rare diseases would be valuable.
• Exploratory research would be useful to identify groups of rare diseases with similar pathological mechanisms.
Conclusions

Developing safe and effective treatments to improve the lives of people living with rare conditions (PLWRC) requires innovation to overcome the challenges of conducting clinical trials for rare diseases. In his concluding remarks, Professor Boyd emphasised the importance of listening to and supporting PLWRC who participate in trials, being flexible and open-minded to novel, evidence-based approaches, and collaboration between different organisations and different sectors.

Living with a rare disease can bring many challenges. While joining a trial can have advantages for PLWRC as they have the chance to receive a potentially useful medicine, it also has drawbacks, including significant logistical, financial, administrative, physical and emotional burdens for PLWRC and their families. Providing support for PLWRC taking part in trials, including for travel and accommodation, will remove unnecessary barriers to trial participation and improve quality of life to improve trial participant recruitment and retention. Ways of enabling PLWRC to take part in trials locally or from home, such as remote monitoring, may also be considered. It is important to acknowledge that there is no ‘one size fits all’ and the needs of each individual must be considered.

Professor Boyd also highlighted the importance of communication. This includes communication with PLWRC about the trial so that they can make informed decisions, and communication between often remote trial sites and local healthcare providers to ensure care decisions are well informed.

Patient registries are rich sources of patient-relevant information and can be used to define patient-relevant clinical endpoints, validate elements of trial design, provide natural history data as a control group, identify potential trial participants, and even to run registry-based studies. New patient registries should be built with input from regulators with clinical trials in mind.

In addition to patient registries, effective linkage of other data sources and infrastructure can be used to improve recruitment and reduce the burden of participants. For example, Professor Boyd points out that linking current and future diagnostic infrastructure (such as the Genomics England Newborn Screening Programme)75 with both clinical trial infrastructure and clinical rare disease services (such as the NHS HSS) would help ensure families are put in touch with the correct clinical support and given the opportunity to participate in any ongoing clinical trials as soon as possible.

Innovative clinical trial designs, including adaptive approaches and multi-arm trials, and new sources of data, such as wearable technologies and real-world evidence, have the potential to solve some of the challenges for running clinical trials for rare diseases. The development of positive case studies and joint workshops to share experience will be important to improve the understanding of and confidence in such innovations of PLWRC;

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regulators, companies and health technology assessment bodies.

Harnessing the full potential of the innovations suggested during this workshop without duplicating effort will require **collaboration and co-operation between the different sectors, including industry.** In particular, the **involvement of PLWRC and those who care for them is essential** to running successful clinical trials for rare diseases. **Rare condition support organisations** can play an important role in convening and **facilitating** these discussions but may require resources and support to do so.

Listening to and supporting PLWRC to participate in clinical trials, open collaboration between relevant stakeholders, and embracing innovation in research-enabled services can help to create an environment for the development of safe and effective medicines to improve the lives of PLWRC.

"**The message is clear: we can’t carry on as normal, we need to learn from experience, to think differently and change our approach.**"

Professor Alan Boyd FMedSci, Chief Executive Officer, Boyd Consultants.
Annex 1: Summary for people living with rare conditions

A rare disease is defined as affecting fewer than 1 in 2000 people. Collectively, rare diseases affect 1 in 17 people – over 3.5 million people in the UK – and yet few have available treatment options. However, running clinical trials to develop safe and effective new treatments can be a challenge for rare diseases. In March 2022, people living with rare conditions and those who care for them came together with organisations that run and regulate clinical trials to discuss ways to overcome some of these challenges in a workshop run by the Academy of Medical Sciences’ FORUM and Faculty of Pharmaceutical Medicine. This summary highlights elements of the workshop discussions thought to be important and relevant by some of the people living with rare conditions/carers who attended the workshop.

**What is a clinical trial and why are they important?**
Clinical trials test new treatments in multiple people to help decide whether the treatments are safe, have the desired effect on a disease, and are an improvement on the current standard treatment for that disease. Clinical trials also teach us important information about a specific drug (for example, the most effective dose that minimises any side effects) and/or the disease in question. To find out more about clinical trials, watch this video, read this article, or see the ‘find out more’ box at the end of this summary.

It is important that clinical trials produce enough relevant, high-quality evidence for medicines regulators to make this judgement and approve the treatment for use in patients. The low number of people living with a particular rare condition often makes it difficult to recruit enough people to take part in a clinical trial to gather this evidence.

People living with rare conditions and their carers/families who contributed to the workshop talked about some of the benefits of participating in clinical trials. They felt clinical trials enabled them to:
- Have access to a new treatment that might improve their quality of life
- Meet relevant researchers, healthcare practitioners and other people living with their condition
- Contribute to clinical research that will benefit the wider community living with the condition (even if the treatment did not work as expected)

76 The Academy of Medical Sciences’ FORUM provides an independent platform for senior leaders from across academia, industry, government, and the charity, healthcare and regulatory sectors to come together with patients and take forward national discussions on scientific opportunities, technology trends and associated strategic choices for healthcare and other life sciences sectors.
- Take action, giving hope and motivation for the future, particularly where a condition has no existing treatment.

They also talked about challenges of participating in clinical trials for rare conditions, including:
- Difficulty finding out about relevant clinical trials
- Strict eligibility criteria
- The administrative, financial and logistical burden of participating in trials
- The lack of communication between trial staff and those involved in the routine care of trial participants
- The mental and physical load of participation whilst managing their condition.

During the workshop, attendees discussed how to overcome and reduce some of these challenges.

**Finding clinical trials to participate in**

People living with a rare condition often do not know how to find out about relevant clinical trials once diagnosed. Because the conditions are rare, clinicians (and other healthcare professionals) are often unfamiliar with the condition and relevant ongoing clinical trials, and so less able to help.

The low numbers of people living with a particular rare condition means it is particularly important that all people eligible to take part in a clinical trial for a rare condition are aware of the options available to them. Suggestions of how you can find out about ongoing clinical trials are in the ‘find out more’ box at the end of this summary.

Most clinical trials have criteria people must meet to be allowed to participate. These are usually published online but clinical trial staff and some healthcare professionals will be able to give advice about whether a person is eligible.

To ensure the results of a clinical trial are valid and complete, it is important (where possible) for trial participants to continue participating to the end of the trial. To help with this, clinical trial staff should work to make participation as manageable as possible and ensure potential participants carefully consider what is involved with the trial beforehand. Workshop attendees pointed out the importance of making information leaflets for potential participants easily understandable and accessible, including the language and format used.

**Reducing the challenges of participating in a clinical trial**

Participating in a clinical trial for a rare condition can come with specific challenges. Workshop attendees strongly felt that trial participants should be provided with more support to overcome these so that they can continue to participate in a trial.

Clinical trials for rare conditions can often involve more travel to reach trial centres than other kinds of clinical trial. This is because the organisation running the clinical trial needs to recruit people with rare conditions from a large area, often from many countries, to ensure there are enough trial participants. This travel can pose significant administrative, financial, and logistical challenges for people living with rare conditions and their families, affecting their quality of life and their ability to participate. Organisations such as the Rare Diseases Research Partners provide support for people, including by helping to organise their travel and accommodation.

Another way of reducing the amount of travel is to allow for trial participation from home or locally; for example, administering the treatment being investigated at home or using virtual communication methods such as video calls to monitor and assess trial participants. However,
trial participants would need expert support and training, and care should be taken to avoid excluding people not able to use the technologies needed for home participation.

Usually, the healthcare professionals looking after a person’s participation in a clinical trial are not the same as the healthcare professionals providing their routine care. A lack of communication between these groups, and also with the trial participant themselves, can lead to uncertainty and distress when dealing with potential side effects of the treatment being tested. Communication is made more challenging because, often, neither the participant nor the trial staff they interact with know whether the participant is receiving an active drug or an inactive drug (placebo). Usually, this information is only revealed at the end of the trial, to avoid biasing the results. Workshop attendees suggested that a named member of trial staff be appointed as a main point of contact with trial participants and relevant healthcare professionals to answer questions, provide information, and help support trial participants.

**Nothing about us without us – clinical trial design**

Consulting with people living with rare conditions and their carers/families is essential when designing and conducting a clinical trial to ensure that the results will be relevant to them, and that the clinical assessments will be manageable for trial participants.

Workshop attendees also discussed novel clinical trial designs that could help make clinical trials for rare conditions more informative and more efficient. These included:

- ‘Umbrella’ trials, where multiple new treatments are tested in the same trial
- ‘Basket’ trials, where the efficacy of one new treatment is tested on multiple diseases
- ‘Adaptive’ clinical trials, which change in pre-defined ways in response to data as they are gathered – for example, stopping a clinical trial early if the treatment does not seem to be having the expected effect.

Clear communication of the advantages and disadvantages of novel clinical trial designs will be essential to make sure they are understood by and acceptable to people living with rare conditions and their families.

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**Find out about ongoing clinical trials for your condition**

In addition to asking your doctor or healthcare professional, you can:

- **Search for** clinical trials online: There are databases that collect ongoing clinical trials (such as ClinicalTrials.gov) but many of them are not written in easily understandable language or are difficult to navigate. One useful new website is ScanMedicine, which gives patients, healthcare professionals, and researchers easy access to information about clinical trials and medical devices brought together from over 11 databases.
- **Join a national register:** Increasingly, there are registers that – with permission – use coded information in the various health data records to find and contact people who are eligible to take part in clinical trials. Such registers include the National Institute for Health and Care Research

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77 The Academy is not responsible for content of third-party websites.
BioResource and the Scottish Health Research Register & Biobank. In some cases, the register gives people the power to self-refer for clinical trials where it is safe and appropriate. Other similar digital recruitment services are being set up across the UK and/or linked to pre-existing services.

- **Contact a rare condition support organisation**: Many rare conditions have groups or charities run by and for people living with a particular rare condition and their families. (The umbrella organisation for all rare conditions is Rare Diseases UK for the UK and EURORDIS for Europe.) These organisations can often help people living with rare conditions find out about clinical trials.

- **Join a patient registry**: A patient registry is usually run by an organisation that collects data over time about a group of people living with a particular condition, with their permission. They are sometimes used to find people to take part in relevant clinical trials. The data in these registries can also become part of the evidence base considered in a clinical trial, reducing the number of people needed to participate. Some kinds of clinical trials – registry-based studies – can be carried out using only data collected in a patient registry, reducing the time and money needed to complete the trial. You can ask the relevant rare disease support organisation or your clinician if you want to find out whether there is a patient registry you can join.
Annex 2: Workshop agenda

Workshop 1, Thursday 24 March (am, GMT)

<table>
<thead>
<tr>
<th>Time</th>
<th>Start</th>
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<tbody>
<tr>
<td>9.00</td>
<td>Opening remarks from co-chairs</td>
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<tr>
<td></td>
<td>Professor Alan Boyd FMedSci, CEO, Boyd Consultants</td>
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<td></td>
<td>Dr Zoya Panahloo, Chair of the FPM Rare Disease and Gene Therapy Expert</td>
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<td></td>
<td>Group &amp; Senior Medical Director Rare Disease, UCB</td>
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<tr>
<td>9.05</td>
<td>Overview: opportunities and challenges facing clinical trials for rare diseases</td>
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<tr>
<td></td>
<td>Professor Timothy Barrett, Leonard Parsons Professor of Paediatrics and Child Health &amp; Director, Centre for Rare Disease Studies, University of Birmingham</td>
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<tr>
<td>9.20</td>
<td>The experience of patients and carers</td>
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<td></td>
<td>Short talks from patients and carers living with a rare condition to highlight their experiences trying to participate in clinical trials.</td>
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<tr>
<td></td>
<td>- Marina Leite Brandão</td>
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<td></td>
<td>- The Beveridge family</td>
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<tr>
<td>9.35</td>
<td>Regulation of medicines for rare diseases</td>
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<tr>
<td></td>
<td>Dr Daniel O’Connor, Expert Medical Assessor, The Medicines and Healthcare products Regulatory Agency (MHRA)</td>
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<tr>
<td>9.45</td>
<td>Q&amp;A with speakers</td>
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<tr>
<td>10.00</td>
<td>Break</td>
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</tbody>
</table>

**Session 1: Scene-setting talks**

10.10 Breakout session: to identify tractable advances or innovations in clinical trials for rare diseases

*A breakout session involving all attendees to allow smaller-group discourse to identify tractable advances or innovations to overcome challenges and barriers to clinical trials for rare diseases in one of four areas.*

Each breakout group will discuss one of the four workshop themes*.

1. Barriers to recruitment (including at the point of diagnosis) and participation in clinical trials
2. Defining relevant and acceptable outcome measures (including biomarkers and patient-reported outcome measures) and endpoints in clinical trials
3. Innovative and adaptive clinical trial design
4. The use of real-world evidence and natural history data in clinical trials

*Organisers will do their best to allocate participants to breakout groups based on their theme preference expressed in the pre-workshop survey.

For their given theme, each breakout group should:

- Consider rare disease-specific barriers and challenges for a given theme
- Identify innovations and advances to overcome some of the barriers and challenges discussed
- Reach a consensus about 2-4 innovations and advances to consider for discussion in Session 2 of the workshop
Discussions can draw on the background information and case studies provided in materials provided in the run-up to the workshop.

There will be a 5min break halfway through the breakout group session.

11.15 Break

11.25 Voting

Interactive ranking of innovations and advances for each theme (e.g. with Mentimeter) accompanied by discussion.

11.55 Closing remarks and introduction of what will be done in the next session by the Co-chairs.

12.00 Event close

Workshop 2, Wednesday 30 March (pm, BST)

<table>
<thead>
<tr>
<th>Time</th>
<th>Start</th>
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<tbody>
<tr>
<td>13.30</td>
<td>Opening remarks from chair and introduction about how the meeting will run Professor Alan Boyd FMedSci, CEO, Boyd Consultants Dr Zoya Panahloo, Chair of the FPM Rare Disease and Gene Therapy Expert Group &amp; Senior Medical Director for Rare Disease, UCB</td>
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</tbody>
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**Session 1: Scene-setting talks**

<table>
<thead>
<tr>
<th>Time</th>
<th>Start</th>
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<tbody>
<tr>
<td>13.35</td>
<td>Bringing clinical trials to patients remotely Dr Elin Haf Davies, Founder and CEO, Aparito</td>
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</tbody>
</table>

13.45 Short summary for each theme from breakout group discussions in Session 1.

14.05 Break

**Session 2: Breakout groups**

<table>
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<tr>
<th>Time</th>
<th>Start</th>
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<tbody>
<tr>
<td>14.15</td>
<td>Breakout session: Considering the practicality and acceptability of innovations in clinical trials for rare diseases to different stakeholder groups. A breakout session involving all attendees to allow smaller-group discourse to consider the acceptability and practicality of innovations/advances identified in Session 1 to different stakeholder groups. For each advance/innovation and with respect to each stakeholder group, the groups should discuss:</td>
</tr>
</tbody>
</table>

- The acceptability of the innovation
- Practical considerations, changes and reassurances needed for implementation of the innovation
- Next steps to implementing each innovation. |

There will be a 5min break halfway through the breakout group session.

15.20 Break

**Plenary discussion**

<table>
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<th>Time</th>
<th>Start</th>
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<tbody>
<tr>
<td>15.35</td>
<td>High-level feedback from the breakout groups The facilitator from each breakout group will feedback 1-2 high-level reflections about the discussions in their group.</td>
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</table>

15.55 Plenary discussion A whole-delegation discussion, led by the co-chairs, to identify the next steps for the sector and the potential leads and actors for these.

16.25 Closing remarks by the co-chairs

16.30 Event close
Annex 3: Attendee list

The workshop comprised two sessions. In Session 1, attendees identified innovations to help overcome challenges to running clinical trials for rare diseases. In Session 2, attendees discussed the practicality and acceptability of a subset of innovations identified in the previous sessions.

Steering committee
Professor Alan Boyd FMedSci, Chief Operating Officer, Boyd Consultants (co-chair)
Professor Sophie Hambleton FMedSci, Professor of Paediatrics & Immunology, Newcastle University (attended Session 2 only)
Dr Nick Meade, Joint-Interim Chief Executive and Director of Policy, Genetic Alliance UK (attended Session 2 only)
Dr Zoya Panahloo, Chair, Faculty of Pharmaceutical Medicine Rare Diseases and Advanced Therapies Expert Group (co-chair)

Speakers
Professor Timothy Barrett, Leonard Parsons Professor of Paediatrics and Child Health & Director, Centre for Rare Disease Studies, University of Birmingham (Session 1)
Helen Beveridge, Parent and Carer (Session 1)
Kelsie Beveridge, Patient Contributor, Niemann-Pick type C Patient and Student (Session 1)
Shona Beveridge, Patient Contributor, Niemann-Pick type C Patient (Session 1)
Marina Leite Brandão, Patient Contributor, Vice-Chair of Retina International Youth Council; & MPA Student of Innovation Public Policy and Public Value, University College London (Session 1)
Dr Elin Haf Davies, Chief Executive Officer, Aparito (Session 2)
Dr Daniel O’Connor, Expert Medical Assessor, The Medicines and Healthcare products Regulatory Agency (attended Session 1 only)

Attended both sessions
Georgina Abbott, Public Contributor
Dr Kate Adcock, Director of Research and Innovation, Muscular Dystrophy UK
Richard Ballerand, Lay Lead, Technology Appraisal Committee, National Institute for Health and Care Excellence
Dr Bridget Bax, Reader in Rare Diseases and Deputy Head of Cell Biology, St George’s University
Dr Emma Blamont, Head of Research Scleroderma and Raynaud’s UK
Mary Bythell, Head of Rare Disease Registration, National Disease Registration Service, NHS Digital
Dr Michelle Campbell, Senior Clinical Analyst for Stakeholder Engagement and Clinical Outcomes, Division of Neurology Products, Food & Drug Administration
Linda Chicout, Public Contributor
Tanya Collin-Histed, Chief Executive Officer, International Gaucher Alliance
Dr Catriona Crombie, Associate Director, Technology Transfer, LifeArc
Tansy Donovan-Rodriguez, Medical Lead for Pulmonary Hypertension, Janssen UK
Dr Marc Dooms, Senior Orphan Drug Pharmacist, University Hospitals Leuven
Dr Richard Evans, Programme Manager, Medical Research Council
Professor Grainne Gorman, Professor of Neurology, Director of Wellcome Centre for Mitochondrial Research, Newcastle University
Nadine Grossmann, Public Contributor and Doctoral Candidate, Freie Universität Berlin
Dr Anthony Hall, Gene Therapy Clinical Development, Healx
Dr Virginie Hivert, Therapeutic Development Director, EURORDIS
Dr Suvi Hokkanen, Real-world Evidence Expert in Rare Diseases and Neurodegeneration, UCB
Professor Penny Jeggo FMedSci, Senior Scientist, University of Sussex
Professor Fiona Karet FMedSci, Professor of Nephrology, Honorary Consultant in Renal Medicine, University of Cambridge
Hameed Khan, Public Contributor
Graham Kirk, Public Contributor
Dr Anthony Lockett, Co-Founder and Principal Investigator, MEDQP
Magdalena Martinez Queipo, Clinical Project Manager, CTI Consulting
Susan Mechan, Solicitor, England & Wales/Scotland
Dr Penny Morton, Programme Manager for Translational Research, Medical Research Council
Will Pender, Senior Policy Manager, Duchenne UK
Dr Sinisa Savic, Clinical Associate Professor, University of Leeds
Hannah Stark, Operations Lead, NIHR BioResource for Translational Research
Bob Stevens, Group Chief Executive, The Society for Mucopolysaccharide Diseases (MPS Society)
Katy Styles, Carer Contributor
Mark Styles, Person living with Spinal and Bulbar Muscular Atrophy
Dr Ana Lisa Taylor Tavares, Senior Clinical Research Fellow in Rare Disease Genomics, Genomics England
Tony Thornburn OBE, Chair of Behçet’s UK
Professor Mark Turner, Professor of Neonatology and Research Delivery, University of Liverpool
Russell Wheeler, Trustee, Leber’s Hereditary Optic Neuropathy Society UK
Lucy Wilson, Research Policy Officer, Department of Health and Social Care

Attended Session 1 only
Professor Eric Alton FMedSci, Professor of Gene Therapy and Respiratory Medicine, National Heart & Lung Institute, Imperial College London
Gareth Baynam, Medical Director, Rare Care, Perth Children’s Hospital
Oliver Buckley-Mellor, Policy Advisor, Cancer Research UK
Professor Patrick Chinnery FMedSci, Professor of Neurology & Head of the Department of Clinical Neurosciences at University of Cambridge, and Chair of the National Core Study on Clinical Trials and of the UK COVID-19 Therapeutics Advisory Panel
Dr Cristina Dias, Consultant in Clinical Geneticist and Genomic Medicine, King’s College London, Clinician Scientist, King’s College London and Francis Crick Institute
Dr Munya Dimairo, Research Fellow, University of Sheffield
Dr Cheryl Hemingway, Consultant Paediatric Neurologist, Neuroinflammatory Service Lead, Great Ormond Street Hospital for Children
Dr Larissa Kerecuk, Rare Disease Lead, Birmingham Women’s and Children’s Hospital
Dr Peter Lanyon, Rare Diseases Clinical Lead, National Disease Registration Service, NHS Digital and Consultant Rheumatologist, University of Nottingham
Professor Francesco Muntoni FMedSci, Professor of Paediatric Neurology, Great Ormond Street Hospital, Director of The Dubowitz Neuromuscular Centre
Nuru Noor, Doctoral Candidate in Clinical Trials Methodology, University College London
Dr Christine Patch, Principal Staff Scientist Genomic Counselling, Engagement and Society, Wellcome Connecting Science
Kacper Rucinski, Public Contributor and Board Member, SMA Europe
Dr Tom Siddons, Clinical Research Manager, Actelion
Dr Frank Tenniglet, Senior Director (Pediatric Development Rare Diseases), UCB
Attended Session 2 only

Professor Claire Booth, Professor of Gene Therapy and Paediatric Immunology, University College London Great Ormond Street Institute of Child Health
Dr Simon Day, Director, Clinical Trials Consulting and Training
Victoria Hedley, Rare Disease Policy Manager, John Walton Muscular Dystrophy Research Centre, Newcastle University
Professor Pamela Kearns, Professor of Clinical Paediatric Oncology, University of Birmingham
Dr Su Lwin, Dermatology Registrar, Honorary Clinical Research Fellow, King’s College London
Sheela Upadhyaya, Rare Diseases Strategic Advisor, National Institute for Health and Care Excellence
Dr Lauren Watson, Rare Disease Lead, Genomic Science and Emerging Technologies Team, Department of Health and Social Care

Secretariat

Rachel Bonnington, Public Engagement Officer, the Academy of Medical Sciences
Melissa Bovis, Public Engagement Manager, the Academy of Medical Sciences
Teteh Champion, Policy Officer, the Academy of Medical Sciences
Ben Cottam, Head of Policy and Communications, Faculty of Pharmaceutical Medicine
Dr Alice Fletcher Etherington, Policy Officer, the Academy of Medical Sciences
Dr Anna Hands, Policy Officer, the Academy of Medical Sciences
Izabela Koni, Digital Communication Assistant, Faculty of Pharmaceutical Medicine
Ania Kordala, Policy Intern, the Academy of Medical Sciences
Joe Meredith, Policy & Press Coordinator, Faculty of Pharmaceutical Medicine
Sarah Porter, Head of Fundraising, Academy of Medical Sciences
Dr Maria Magdalena Razalan, Grants Manager, the Academy of Medical Sciences
Dr James Squires, Head of Policy, the Academy of Medical Sciences
Rosanna Tabor, Fundraising Officer, Academy of Medical Sciences
Julia Turan, Digital Communications Manager, the Academy of Medical Sciences
Angel Yiangou, Policy Manager, the Academy of Medical Sciences
Annex 4: Innovations identified in Session 1

In Session 1 of the workshop, each of the eight breakout groups was given one of the four themes and asked to identify 2-4 innovations. At the end of Session 1, a rough poll was taken to gauge the preference for some of the innovations within each theme amongst all workshop attendees. This was used to help decide which innovations to take forward to Session 2. Within each theme, the innovations are listed in order of poll results with the most popular at the top.

Many of these innovations were taken forward into Session 2 to explore practicality and acceptability, though not all received the same depth of discussion. Some were not taken forward for discussion in Session 2 because they were felt to be either too vague or to be describing desired outcomes rather than innovations on how to achieve the outcome – these are indicated with an asterisk

1. Barriers to patient recruitment (including at the point of diagnosis) and participation in clinical trials for rare diseases

- **Better administration and support of trial participants**, especially coordinating travel and accommodation. Patient organisations can be used to coordinate and administrate this.
- **Building a centralised national database of ongoing rare disease trials and their locations** from already existing platforms [e.g. National Institute of Health Research (NIHR) repository of trials].
- Formally link the highly specialised services for rare diseases in the UK to clinical trial infrastructure (e.g. the NIHR repository of trials) to allow easier patient recruitment and facilitate collection of biomarker samples.
- Improving communication between trial staff at centres running clinical studies and routine care staff (e.g. local hospitals, GPs etc.).
- **Patients could refer themselves to clinical trials (potentially with the support of patient organisations)** to help overcome the reluctance of some healthcare practitioners to refer patients to trials, even after diagnosis.
- Better enabling of home/local participation in trials.
- Delivery of trial medications at home or locally where possible.
- **Ensuring information for patients about what is involved in clinical trial participation is accessible** so that they can provide informed consent (e.g. by involving patients and patient groups when making patient information leaflets).

2. Defining relevant and acceptable outcome measures (including biomarkers and patient-reported outcome measures) and endpoints in clinical trials for rare diseases

• International collaboration and collaboration between people working on different diseases to allow international integration of patient registries and biomarkers to provide natural history data. To share ownership, setting up such registries could be paid for with a combined pot of money contributed to by patient advocacy groups/charities, the NIHR, pharmaceutical companies etc.
• *Invest in biomarkers and in endpoint development, including qualitative endpoints.
• Create a framework where stakeholders feel comfortable to work together in the precompetitive space (e.g. different pharmaceutical companies/organisations could run joint workshops to develop endpoints together).
• Develop a common set of outcome measures or endpoints, with patient input, that are broadly applicable to patients across all (or a subset of similar) rare diseases – walking, sleeping, eating, pain, etc. – and validate them in common diseases. This will likely include repurposing endpoint measures for different diseases.
• *Drive trust of artificial intelligence in clinicians and regulators.
• *Go to where it is hardest – geographically, socially, language etc. – learn from these experiences and work to provide trials closer to home.

3. Innovative and adaptive clinical trial design for rare diseases

• Adaptive trial design (e.g. early futility analysis) to allow changes to be made to the trial protocol during the trial based on the data as they are collected.
• Clinical trial platforms that test the efficacy of one drug at treating multiple diseases (basket trials).
• **Involve patients and other relevant stakeholders to reach a consensus on the design of clinical trials** (e.g. to make sure burden is manageable and patients can participate from beginning to end of the trial).
• Education of funders, ethics committees and patients about the advantages and limitations of different clinical trial methods (including the limitations of traditional randomised clinical trials in rare diseases).
• Registry-based treatment studies.
• Clinical trial platforms that test multiple drugs against one control arm (umbrella trials).
• **Use of synthetic and/or digital control groups** – Instead of having patients in a control group in a trial, machine learning/AI can be used to generate a set of control data based on historical data (e.g. either control data from previous studies or from a patient’s own data before they received the treatment).
• For rare diseases with quite a few treatments on offer but not many patients, **prioritisation of drugs on offer or coordination of the efforts of the different pharmaceutical companies** by the regulator (or the companies themselves) to minimise patient burden and maximise the chance of completing.

4. The use of real-world evidence and natural history data in clinical trials for rare diseases

• **Methods to validate the accuracy of real-world data to help make patients findable for trial recruitment.** E.g. the National Congenital Anomaly and Rare Disease Registration Service (NCARDRS, NHS Digital) has undertaken ground-breaking work to validate the accuracy of using routinely collected healthcare data to identify people with rare diseases, enabled by data sharing agreements between NCARDRS and different healthcare organisations (e.g. NHS Trusts). This has been undertaken for some exemplar rare diseases (in particular, rare autoimmune, non-genetic conditions) and could be expanded to other rare disease areas.
• Use of real-world data to validate elements of clinical trial design (e.g. make sure endpoints chosen are useful).
• *Making data more accessible by reducing the unnecessary legal hurdles.
• **Advanced methods for improving the quality of analysis of clinical trial data** (e.g. using Bayesian methods, which allow for more frequent monitoring and interim decision-making during a trial, and/or AI).

• **Wearable technologies** (e.g. for remote monitoring).

• Create a framework where stakeholders feel comfortable to work together in the precompetitive space (e.g. different companies/organisations could run joint workshops to co-develop endpoints).
Annex 5: Practicality and acceptability discussion – sector breakdown

In Session 2, attendees were split into eight breakout groups and each group was given 2-3 innovations identified in Session 1. They were asked to discuss the practicality and acceptability of those innovations. It was not possible for every innovation to be discussed by representatives from every sector and opinions of individuals do not necessarily represent the consensus in their sector. The approximate representation of different sectors discussing each of the innovations is indicated below.

<table>
<thead>
<tr>
<th>Innovation</th>
<th>Sectors(^79) represented in breakout groups that discussed the practicality and acceptability of each innovation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Academia, industry, healthcare (including allied health professional), rare condition support organisation/charity, PLWRC,(^80) relevant professional/membership organisation, and health technology assessor</td>
</tr>
<tr>
<td>2</td>
<td>Academia, industry, healthcare,(^81) PLWRC, rare condition support organisation/charity, research infrastructure, and rare disease policy</td>
</tr>
<tr>
<td>3</td>
<td>Academia, PLWRC, healthcare, rare condition support organisation/charity, and rare disease policy</td>
</tr>
<tr>
<td>4</td>
<td>Academia, PLWRC, research infrastructure, funder, and industry</td>
</tr>
<tr>
<td>5</td>
<td>Industry, rare condition support organisation/charity, and PLWRC</td>
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<tr>
<td>6</td>
<td>Industry, rare condition support organisation/charity, and PLWRC</td>
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<tr>
<td>7</td>
<td>Academia, PLWRC, research infrastructure, funder, and industry</td>
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<tr>
<td>8</td>
<td>Industry, healthcare (including allied health professional), PLWRC, law, and academia</td>
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<tr>
<td>9</td>
<td>Academia, healthcare, PLWRC, industry, and rare diseases policy</td>
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<tr>
<td>10</td>
<td>Industry, regulator, funder, rare condition support organisation/charity, academia, and healthcare</td>
</tr>
<tr>
<td>11</td>
<td>Academia, industry, healthcare (including allied health professional), rare condition support organisation/charity, PLWRC, relevant professional/membership organisation, and health technology assessor</td>
</tr>
<tr>
<td>12</td>
<td>Academia, PLWRC, research infrastructure, funder, and industry</td>
</tr>
</tbody>
</table>

\(^79\) Note that trial sponsors from academia and industry were included.

\(^80\) Includes people living with rare conditions and their carers/families in this context.

\(^81\) Note that many of the clinicians who attended were clinical academics.
<table>
<thead>
<tr>
<th></th>
<th>Industry, regulator, funder, rare condition support organisation/charity, academia, and healthcare</th>
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</thead>
<tbody>
<tr>
<td>13</td>
<td>Academia, healthcare, PLWRC, industry, and rare diseases policy</td>
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<tr>
<td>14</td>
<td>Industry, rare condition support organisation/charity, and PLWRC</td>
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<td>15</td>
<td>Industry, healthcare (including allied health professional), PLWRC, law, and academia</td>
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<td>18</td>
<td>Academia, industry, healthcare, PLWRC, rare condition support organisation/charity, research infrastructure, and rare disease policy</td>
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<tr>
<td>19</td>
<td>Academia, industry, healthcare, PLWRC, rare condition support organisation/charity, research infrastructure, and rare disease policy</td>
</tr>
</tbody>
</table>
Annex 6: Case studies

This section includes three case studies relevant to some of the workshop themes, provided to the workshop attendees prior to the sessions to help stimulate discussions in the groups.

Case study 1: the DMD Hub – a patient-led ‘pump prime’ model to expand clinical trial capacity

Duchenne muscular dystrophy (DMD) is a rare muscle-wasting condition affecting around 2500 people in the UK, with the symptoms usually manifesting in infancy. It almost exclusively affects males, and is a progressive and debilitating disease, resulting in loss of limb function and full-time ventilator reliance. It is often fatal by 30 years old.

There is no cure, and very few dedicated treatments. The DMD patient community is very keen to take part in clinical trials, but before 2015 there were only 2 trial sites in the UK, and just 13 active trials. Many patients missed out on participation and there were huge differences in access between different regions. A patient-led medical research charity, Duchenne UK, founded the DMD Hub in 2015 to help those patients who want to take part in clinical trials by increasing capacity.

By 2021, Duchenne UK, the DMD Hub and its partners had invested £3M into the project, funding 34 posts through an innovative ‘pump-priming model’ at 11 trial sites across the UK, resulting in 437 extra patients on trials. There are now 20 active clinical trials in the UK, with 8 new trials opening in the UK in 2021 alone.

The pump-priming model means that income generated from trials is invested back into the neuromuscular teams at clinical trial sites, making them self-sufficient and a source of revenue for NHS Trusts. By funding key junior doctor roles for clinical trials through a tapered funding model, the DMD Hub also helps develop the next generation of consultants.

Case study 2: Use of a control in clinical studies in rare diseases is not always as straightforward as you might think – as illustrated by the Luxturna® story.

Before a new medicine, treatment or intervention is approved by the various medicine regulatory agencies for use by patients, several clinical studies are performed to confirm the safety of the medicine in question and check its ability to produce the required result. These studies are often referred to as the ‘pivotal’ or main studies. In the rare disease situation, it is

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82 https://www.duchenneuk.org/
83 https://dmdhub.org/
not always possible to have multiple different studies with different patients participating due to the limited number of patients with the condition being investigated. Regulators are aware of this problem and will usually only require a single, high-quality clinical study. The gold standard is a randomised controlled trial, in which similar numbers of patients are randomly allocated to either an ‘experimental’ group, receiving the novel intervention, or a ‘control’ group, receiving either an alternative intervention, a dummy intervention (placebo) or no intervention at all. However, other issues often arise in the design and conduct of a clinical study in a rare disease that make even the inclusion of a control group difficult.

This is illustrated by the development of a therapy to treat rare disease patients with progressive visual problems and subsequent blindness, caused by a mutation of a particular gene (the RPE65 gene) in the retina (back) of the eye. The safety and effectiveness of this therapy, called Luxturna®, were assessed in three clinical studies.

The endpoints used to determine the effectiveness of Luxturna® were common to all three studies. These included a Multi-Luminance Mobility Test (MLMT), which was designed to measure changes in vision that affect everyday life. Specifically, MLMT measures the ability of a patient to navigate an obstacle course accurately and at a reasonable pace, plus assessments of visual fields (the area that can be seen by a stationary eye) and visual acuity (the ability of the eye to distinguish shapes and details at a given distance).

Two initial phase 1* clinical trials were conducted (on 11-12 patients) to test the safety of Luxturna® and find the best dose of the drug. In the first study, 12 patients received the treatment in one eye; in the second study, 11 of the same patients received the treatment in the other eye. In addition to demonstrating that the treatment was safe, these studies showed that Luxturna® treatment improved navigational ability as well as visual field and acuity assessments at one year after treatment.

However, the positive results of the phase 1 tests presented a challenge for planning a randomised, well-controlled phase 3* study. Patients were not likely to want to be in the control group of a study, not receiving the Luxturna® treatment, when they know there is evidence that the treatment works. Since there are currently no approved treatments for this disease, this also creates ethical concerns. These concerns were raised with the sponsor of the study, Spark Therapeutics Inc., by patients and their caregivers, patient groups and healthcare professionals. In discussions with these groups and the regulators, a variation on the standard design of the pivotal study was developed. It was agreed that:

- The control group would not initially receive treatment, but would benefit from the same assessments as the patients in the treatment group.
- After 12 months, all patients would be given the opportunity to receive treatment with Luxturna® and would be followed up for an additional 12 months. This was called a ‘cross-over’ approach because the control group crossed over into the treatment group.
- Twice as many patients (21/31 patients) would be randomly assigned to the treatment group than the control group (10/31 patients).

At the end of this additional follow-up period, all the ‘cross-over’ patients who received Luxturna® 12 months later showed a similar response to the patients who initially received Luxturna® in the treatment group.

Summary: In taking this approach of allowing all the patients in the control group to subsequently receive the investigational treatment as well, this allowed a randomised, well-controlled pivotal study to be performed as part of the development programme. This pivotal study satisfied the requirements or the regulators and Luxturna® subsequently received
regulatory approval from the FDA in December 2017 and from the EMA in November 2018.

**Case study 3: Using real-world evidence to determine whether a potential side effect of the treatment was caused by or unrelated to treatment.**

Several new treatments have recently been developed to treat multiple myeloma and non-Hodgkin’s lymphoma, two types of cancer. Clinical trials of these treatments are ongoing, but there is concern that these treatments may be causing a side effect, the development of ‘second primary malignancies’ (SPMs) – new tumours unrelated to the cancer the patient already has.

However, the number of patients in the trials, and the relative rarity of SPMs mean that each individual trial is not providing enough data to conclude whether the treatments are causing these side effects or not. Specifically, there was not enough information about the ‘baseline’ rate of SPMs, i.e. how many people would develop SPMs even if they had not received the treatments being studied.

Therefore, researchers used real-world data from the Cancer Analysis System (CAS), a population-level cancer database in England for patients diagnosed from 2013 to 2018, to determine this ‘baseline’ rate of SPMs in a much larger population of patients with either multiple myeloma or non-Hodgkin’s lymphoma.

This allows the researchers to provide greater clarity on the expected rates of SPMs in clinical trials for new treatments, so that those clinical trials can determine whether the rates of SPMs they observed were abnormal or to be expected, and therefore if the treatment was causing the SPMs.

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85 https://www.annalsofoncology.org/article/S0923-7534(21)02352-8/fulltext
Annex 7: ScanMedicine, NIHR’s repository of clinical trials

ScanMedicine is a comprehensive database of clinical trials launched in 2021 by the NIHR Innovation Observatory, based at Newcastle University. ScanMedicine is a free resource for researchers, clinicians and the public that draws from 11 of the world’s leading clinical trials databases and pulls information on medical devices, diagnostics and digital applications from the American Food and Drug Administrations (FDA) database.

Users have access to up-to-date information about what clinical research is ongoing in their area of interest. Data are presented by the tool in an accessible format and results are searchable by trial type, phase, registry, status regarding recruitment, and more. Collating the data in one place removes the need to search different databases or check for duplicate trials.

86 https://scanmedicine.com/clinicaltrials/
Annex 8: the Rare Disease Cures Accelerator-Data and Analytics Platform (RDCA-DAP)

RDCA-DAP is an integrated database and analytics hub that houses patient-level data from a variety of sources, including clinical trials, longitudinal observational studies, patient registries and real-world data (e.g. electronic health records) contributed from organisations around the world, across a multitude of rare diseases. It is being developed by the Critical Path Institute (C-Path) and National Organization for Rare Disorders through a collaborative grant from the FDA.

It is designed to accelerate drug development for rare diseases by sharing existing patient data and encouraging the standardisation of new data collection, resulting in an improved understanding of a rare disease. The data are integrated in a format acceptable to regulators and can be used to improve understanding of disease progression, clinical outcome measures and biomarkers, and innovative clinical trial designs. The format can be used by rare condition support organisations looking to start a registry.

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[88](https://c-path.org/programs/rdca-dap/)
Annex 9: The National Lung Matrix Trial

In discussing the practicality of umbrella trials for rare diseases, attendees discussed the National Lung Matrix Trial (NLMT). The NLMT is an ongoing, large-scale phase II trial for finding treatments for non-small cell lung cancer (NSCLC). It should be noted that NSCLC is not a rare disease but some of the concepts discussed were useful.

The NLMT has multiple arms testing different drugs and the arm that trial participants are allocated to is based on the type of NSCLC they have and the genetic profile of their cancer cells.

Cancer Research UK funded the NLMT, and a variety of pharmaceutical companies, labs, medical centres and NHS Trusts are collaborators. Attendees highlighted the central importance of collaborating and managing relationships with different stakeholders involved during trials of this kind, including pharmaceutical companies and regulators.

Attendees pointed out the value of having a non-industry organisation as a broker in negotiations to help reassure companies that they are not in competition with each other. They also highlighted the importance of robust negotiating skills during contract negotiations. Regulators were generally accepting of the NLMT, but attendees noted the importance of managing expectations about not having real-time access to data during the trial.

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Annex 10: Glossary

More comprehensives glossaries can be found here:
- https://www.mrcctu.ucl.ac.uk/glossary/

Adaptive trial design
An adaptive design allows certain modifications, planned before the trial starts, to be made to the study design after the trial has started while maintaining the trial’s validity and integrity. If done correctly, this added flexibility to modify certain elements of the trial design during the trial can lead to more informative and efficient trial outcomes. Adaptive clinical trial designs have been used extensively in medical device development and the lessons learned from those studies are now being applied to drug development.

Artificial intelligence (AI)
The ability of a computer or a robot controlled by a computer to do tasks that are usually done by humans because they require human intelligence and discernment, such as visual perception, speech recognition, decision-making, and translation between languages.

Basket trials
A clinical trial design in which the efficacy of a treatment is evaluated on multiple diseases (e.g. diseases with a similar underlying biological cause or mechanism) or multiple different states of the same disease (e.g. different types of cancer).

Bayesian methods
Bayesian methods allow one to use new data produced during a trial to update assumptions made at the beginning of a trial and to update the trial design accordingly.

Biomarker
A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition. Also called molecular marker and signature molecule.

Clinical trials
Clinical trials are a type of clinical research designed to look at new ways to prevent, detect, or treat disease. Clinical trials rely on the participation of volunteers (participants) and follow a research plan or protocol created by the investigators running the study. Participants in a clinical trial may include people with a specific disease or condition and/or healthy volunteers. The goal of a clinical trial is to determine whether a specific diagnostic intervention, treatment, prevention, or behaviour approach is safe and effective.

Clinical trials infrastructure
The clinical trials infrastructure refers to the necessary resources (workforce, financial support, patient participants, information systems, regulatory pathways, and institutional commitment) and the manner in which they are organised and brought together to conduct a clinical trial.

Control arm or control group
In a clinical trial, the control arm is the group of participants that does not receive the therapy being studied. This control arm is compared to the group that receives the investigational therapy, to see if the investigational therapy works and is safe. The comparison of the investigational therapy arm against the control arm defines what the results of the trial actually mean and the context for how the results can be used in clinical practice.

**Dose-escalation study**
A study that determines the best dose of a new drug or treatment. In a dose-escalation study, the dose of the test drug is increased a little at a time in different groups of people until the highest dose that does not cause harmful side effects is found. A dose-escalation study may also measure ways that the drug is used by the body and is often done as part of a phase I clinical trial. These trials usually include a small number of patients and may include healthy volunteers.

**Futility analysis**
Futility analysis refers to a statistical procedure for stopping the trial early if it appears that the experimental arm is unlikely to be shown to be definitively better than the control arm if the trial is continued to the final analysis.

**Eligibility criteria**
In a clinical study, eligibility criteria are the requirements that must be met for a person to be included in the study. These requirements help make sure that participants in a trial are like each other in terms of specific factors such as age, disease or stage of disease, general health, and previous treatment. When all participants meet the same eligibility criteria, it is more likely for example that results of the study are caused by the therapy being tested and not by other factors or by chance. Eligibility criteria consist of both inclusion criteria (which are required for a person to participate in the study) and exclusion criteria (which prevent a person from participating).

**Endpoint**
In clinical trials, an event or outcome that can be measured objectively to determine whether the intervention being studied is beneficial. Some examples of endpoints are survival, improvements in quality of life or relief of symptoms.

**Health technology assessment body**
A public organisation that provides recommendations on the medicines and other healthcare interventions that can be paid for or reimbursed. These organisations look at the relative effectiveness and cost effectiveness of medicines that have been authorised.\(^{90}\)

**Highly specialised services**
Highly specialised services are provided by the NHS to a smaller number of patients compared to specialised services, usually no more than 500 patients per year. These are services for very rare and/or complex conditions. Because of the small number of patients the services are provided in a limited number of hospitals, which enables the clinicians to maintain their expertise.

**Historical data**
Data on disease progression from past studies and administrative databases (e.g. hospital databases, GP surgeries).

**Historical control data**
Historical control refers to the practice of using historical data to estimate potential response to placebo or standard-of-care treatment among patients in an ongoing study.

**Informed consent**
This refers to a participant in a research study agreeing to take part of their own free will after being given all the important facts about that study, and after they have had the chance to ask questions and have them satisfactorily answered and understood.

**Machine learning**
Machine learning is a branch of artificial intelligence (AI) and computer science that uses data and algorithms to imitate the way that humans learn, gradually improving the accuracy of a computer’s performance at a task.

**Natural history study**
A natural history study is a pre-planned observational study intended to track the course of the disease. Its purpose is to identify demographic, genetic, environmental, and other variables (e.g. treatment modalities, concomitant medications) that correlate with the disease’s development and outcomes. Natural history studies are likely to include patients receiving the current standard of care and/or emergent care, which may alter some manifestations of the disease. The natural history of a disease is traditionally defined as the course a disease takes in the absence of treatment in individuals with the disease, from the disease’s onset until either the disease’s resolution or the individual’s death.

**Observational study**
An observational study is a type of clinical research in which investigators assess health in groups of participants without the investigator changing the participants’ routine medical care or lifestyle. Similar to clinical trials, observational studies have a research plan or protocol created by the investigators. A registry and a natural history study are types of observational study.

**Orphan drug/medicine**
An orphan drug is a drug developed to treat medical conditions which, because they are so rare, would not be profitable to produce without government assistance. In the US and the EU, it is easier to gain marketing approval for an orphan drug. There may be other financial incentives, such as an extended period of exclusivity, during which the producer has sole rights to market the drug. All are intended to encourage development of drugs that would otherwise lack sufficient profit motive.

**Outcome measures**
Outcomes are measures of health, e.g. response to treatment, presence or absence of disease, a measure of well-being.

**People living with rare conditions**
People living with rare conditions (or PLWRC) refers to people who have an acute and/or chronic rare condition. They may currently be patients of the healthcare system or be managing their condition. The term may also be inclusive of those who are indirectly affected by a rare condition such as the carers or families of people with a rare condition, depending on context.

**Pivotal study**
A pivotal clinical trial is a clinical study seeking to demonstrate the ability of a new drug to produce the desired result in order to obtain its marketing approval by regulatory authorities.
Placebo
A placebo is a dummy treatment that is designed to be harmless and to have no effect. It looks, smells, and tastes like the treatment being tested, so that trial participants do not know if they are taking the dummy treatment or the treatment itself.

Platform clinical trial
A platform trial is a clinical trial with a single master protocol in which multiple treatments are evaluated alongside each other. ‘Adaptive’ platform designs offer flexible features such as dropping treatments for lack of effect, declaring one or more treatments better than the other, or adding new treatments to be tested during the course of a trial.

Precompetitive space
An arena in which ‘precompetitive collaboration’ is enabled and encouraged. ‘Precompetitive collaboration’ involves two or more companies within the same industry, coming together to address a shared problem that does not impact direct business competition and is often focused on joint social or environmental impacts (e.g. developing knowledge, expectations, standards etc.).

Protocol
A protocol is the plan for a research study. Protocols need to be approved by an ethics committee before the study begins to recruit participants. They provide information on the question being addressed by the study, the eligibility criteria, and the frequency of visits for trial participants.

Qualitative
Measuring the quality of something rather than its quantity. (The alternative to ‘qualitative’ is ‘quantitative’ – measuring the quantity of something rather than its quality.) In medical science, a lot of value is placed on repeatable, quantitative measures of outcomes. However, discussions are being had about how to reliably incorporate more qualitative outcome measures to make sure meaningful information that is difficult to measure quantitatively is not being missed (e.g. the emotional state of patients).

Standard of care
Treatment that is accepted by medical experts as a proper treatment for a certain type of disease and that is widely used by healthcare professionals.

Randomised clinical trial
In a randomised clinical trial, similar numbers of patients are randomly allocated to either an ‘experimental’ group, receiving the novel intervention, or a ‘control’ group, receiving either an alternative intervention, a dummy intervention (placebo) or no intervention at all. Information from the control group allows the researchers to see whether the new treatment(s) are more or less effective than the current standard treatment.

Rare condition support organisation
A rare condition support organisation is typically a not-for-profit organisation that represents the needs and interests of PLWRC and/or those who care for them. Many are led by PLWRC or PLWRC have a high degree of involvement in the running of the organisation. Rare condition support organisations vary greatly in size and resources. They include charities, groups begun by PLWRC and more.

Rare disease (or rare condition)
A rare disease (or rare condition) is a disease that affects fewer than 1 in 2000 of the general population.
**Real-world data**
Real-world data refers to data relating to a person's health status and/or the delivery of healthcare that is routinely collected outside of a research setting. Real-world data may be collected from a variety of sources including the patient, clinician, registries, or electronic medical records.

**Real-world evidence**
Real-world evidence refers to the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of real-world data.

**Registry-based treatment study**
A registry-based study is an investigation of a research question using the systems of new or existing patient registries for patient recruitment and data collection.

**Stakeholder**
A stakeholder is defined as an individual or group that has an interest in any decision or activity of an organisation.

**Trial arm**
Trial arm refers to one of the groups to which trial participants are assigned in a randomised controlled trial. The group of people receiving the current standard of care is usually referred to as the control arm.

**Translational research**
Translational research (also called translation research, translational science, or, when the context is clear, simply translation) is research aimed at converting results of laboratory research into results that directly benefit humans. An example of translational research in medical science might be taking a drug for a disease that works in mice and testing it in humans.

**Ultra-rare disease**
An ultra-rare disease is defined in Europe as a disease that affects fewer than 1 in 50,000 of the general population.

**Umbrella trials**
Umbrella trials evaluate multiple treatments for a single disease. The patients in the trial may be separated into subgroups and receive the treatments that are most appropriate based on the underlying cause or mechanism for their disease (e.g. by using genetic markers).

**Validate**
To check the accuracy or 'validity' of something or to check something is working as intended.

**Wearable technology or wearables**
Wearable technology, also known as 'wearables', is a category of electronic devices that can be worn as accessories, embedded in clothing, implanted in the user’s body, or even tattooed on the skin. The devices are hands-free gadgets with practical uses, powered by microprocessors and can be enhanced with the ability to send and receive data via the internet.