Clinical trials for rare and ultra-rare diseases: 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 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 (HSS), with clinical trial infrastructures.
- **Ensuring participant-facing information about clinical trials is presented accessibly** to give confidence to participate and enable truly informed consent.

Reducing burden of trial participation

While offering access to potentially beneficial experimental treatments, trial participation can

[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
[3] Note that this specific example was not directly discussed by workshop attendees. https://www.registerforshare.org/

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.[4]
- **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 is 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 is 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 is 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 it is 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).
- **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

[4] https://rd-rp.com/

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 cooperation 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.

Innovations and proposed next steps

Workshop attendees identified innovations and proposed next steps to overcome some of the challenges of running clinical trials for rare diseases. These are listed here in brief. For a full discussion of the practicality and acceptability of each innovation, please see the full report.

Improving recruitment of trial participants

Making clinical trials more findable

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

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.

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.[5]
- The similar digital recruitment services in other UK nations, such as the NIHR BioResource and Find, Recruit and Follow-up service,[6] 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 triallists, 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 HSS for rare diseases and other services for rare conditions.

Making PLWRC more discoverable

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.

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

Proposed next steps:

- Any new service for rare conditions, such as the Syndromes Without A Name (SWAN) clinic being piloted in Wales,[7] should incorporate capacity for research and clinical trials for rare diseases into the design of the service.

---

[5] https://scanmedicine.com/

[6] https://bioresource.nihr.ac.uk/participants/join-the-bioresource/; DHSC, Welsh Government, The Scottish Government, and Northern Ireland Executive (2022). *The Future of UK Clinical Research Delivery: 2021 to 2022 implementation plan.* https://www.gov.uk/government/publications/the-future-of-uk-clinical-research-delivery-2021-to-2022-implementation-plan/the-future-of-uk-clinical-research-delivery-2021-to-2022-implementation-plan Note that the Find, Recruit and Follow-up service was not directly discussed as an example in the workshop.

[7] Welsh Health Specialised Services Committee (2022). *Welsh health specialist services integrated commissioning plan (ICP) 2022-2025.* https://bcuhb.nhs.wales/about-us/governance-and-assurance/imtp/whssc-integrated-commissioning-plan-2022-2025/ Note that this example was not directly discussed in the workshop.

- 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

Innovation 5: Ensuring information for PLWRC about what is involved in clinical trial participation is accessible so that they can provide informed consent.

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.

Reducing participation burden

Support during the trial

Innovation 6: Better administration and support of trial participants, especially coordinating travel and accommodation.

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.).

Proposed next steps:

- Triallists should ensure sufficient logistical, financial and administrative support for trial participants is built into trial protocols, and research ethics committees should continue to hold them to account for this. Such support may be provided by engaging a specialist third-party organisations such as RDRP.
- The HRA should explore ways to better ensure research ethics committee members are aware of the specific challenges faced by people running and participating in clinical trials for rare diseases (e.g. training videos).
- Trial sponsors should have one member of the team responsible for being a point of contact with trial participants and relevant healthcare practitioners, either for individual trials or the whole trial portfolio of an organisation.

Design of the trial

Innovation 8: Involve PLWRC and other relevant stakeholders to reach a consensus on the design of clinical trials.

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.

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.[8]

[8] https://acmedsci.ac.uk/file-download/83223772

- 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, medtech 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.

Selection of meaningful endpoints

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

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.

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,[9] 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

Innovation 12: Registry-based treatment studies

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

Innovation 13: Use of synthetic, digital control groups

[9] https://gardianregistry.org/

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

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

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

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

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 it is 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)

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).

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 triallists, 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.[10]
- 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.

[10] Pericleous M, *et al.* (2022). *Defining and characterising a toolkit for the development of a successful European registry for rare liver diseases: a model for building a rare disease registry.* Royal College of Physicians: Clinical Medicine **22(4)**, 340–347. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9345223/