CLINICAL TRIALS RESEARCH NEEDS RECOMMENDATIONS

RARE DISEASE MOONSHOT

A paradigm change: optimising clinical trials design and conduct in Rare Diseases with Regulatory Science and collaboration

This paper provides recommendations to funders, researchers, patients, industry and other stakeholders on where public-private partnerships (PPPs) would bring most value in optimising clinical trials in small and very small populations and points to consider when setting up such collaborations.

To address the unmet needs of the Rare Disease (RD) community in a timely and meaningful manner, projects at all stages of the development need to contribute to regulatory approvals. To expedite clinical trial readiness of rare diseases and enable regulatory approval, public-private cross-sectoral collaboration is required to address key drug development challenges.

The key challenges are:

- **Bridging translation and regulatory approvals by using methods, materials, or measures that have the potential to facilitate drug development, such as Drug Development Tools (DDTs)**
- **Leveraging regulatory science for rare diseases by developing new trial designs to enable timely product development and regulatory submissions, building capacity for their implementation (infrastructure, skills), as well as scaling up and deploying drug development tools in R&D practice.**
- **Deploying and updating patient engagement resources and tools by using and developing solutions to overcome hurdles in cross-border patient participation (in particular remote approaches)**
- **Leveraging existing data, resources and infrastructure by maximising, generating or re-using data generated with patients, including standardisation, FAIRification of data, and integration/ exploitation of regulatory grade sources in R&D plans.**

When planning a research project in Rare Diseases, patient's engagement, existing tools, methods, technologies and infrastructures as well as gaps in knowledge, should be adequately considered. Additionally, appropriate skills such as regulatory science, quantitative medicine and data science strategies need to be planned at the design of a project ensuring that outputs can meet regulatory requirements and patients' needs, thereby reducing failure rates of therapeutic developments.

Introduction

The drug development process for rare diseases is known to present both opportunities and challenges. Because of the small patient pool available in these indications, there are challenges in designing and conducting clinical trials to generate the appropriate evidence, analyse and interpret the data, and ultimately meet the regulators' expectations. In rare diseases, academic teams and researchers face many challenges when designing and conducting clinical trials to develop safe and effective new treatments in small population. The top three main critical downfalls in the rare disease development of treatments are 1) a poor understanding of the disease process and natural history, 2) an incomplete understanding of clinically meaningful endpoints, and 3) the inability to assess the clinical benefit and achieve full approval. This leads to sub-optimal translation of outcomes into clinical development and subsequent implementation into healthcare. While some of the most promising approaches lie in using innovative clinical trial designs and making use of real-world data (RWD), it is key to not only use existing tools and methods as appropriate but also to identify and address regulatory, technical and operational gaps. This will help ensure that, from basic science to clinical trials conducted in rare diseases, trials quickly yield more effective, affordable, and safe medical products for patients.

Furthermore, there is the need for applied scientific work to create new tools, such as Drug Development Tools (DDTs) and technologies, to get fundamentally better answers about how the safety and effectiveness of new products can be demonstrated. This will also help to as well as to understand better how each disease progresses in faster time frames, with more certainty, and at lower costs to minimise patient burden.

To address some of those problems, those involved in the Rare Disease Moonshot initiative[1] which was officially launched in December 2022, have undertaken the initiative through collaborative efforts to support the use of existing tools, the development of a new generation of predictive tools and methods that would qualify as Drug Development Tools (DDTs), and the necessary research infrastructure to facilitate the optimisation of clinical trials designs and conduct in rare diseases. The Rare Disease Moonshot aims to be complementary to the upcoming European RD Partnership, foreseen to be launched in 2024. It will build on, contribute to, and directly accelerate the goals set by the International Rare Diseases Research Consortium (IRDiRC[2] and its Orphan Drug Development Guidebook).

This paper not only reflects the challenges and opportunities in rare diseases drug development that needs to be considered from the translational stage, but also provides points for funders, researchers, patients, industry and other stakeholders to consider when engaging in public-private partnerships (PPPs) in rare diseases (RD) to address the unmet needs of the rare diseases community.

Bridging translation and regulatory approvals

A marketing authorisation (MA) is granted based on the provision of adequate evidence on clinical efficacy and safety of medical products. Depending on a compound's therapeutic area and pharmacological parameters, evidence of efficacy might comprise demonstration of short-term effects, maintenance of effect, and / or effects on long-term clinical outcomes. While taking account of the regulatory and HTA framework in a global environment, these requirements, and the respective objectives regarding safety, are reflected as multiple specific research questions that need to be addressed in a clinical development programme.

In Rare Diseases, the low number of patients and limited understanding of the variability and progression of each disease frequently slow down the drug development process. This means that randomised controlled clinical trials, and endpoints that can reliably evaluate the efficacy and safety of a potential therapy are challenging to design and conduct. The draft Strategic Research & Innovation Agenda of the future European Rare Disease Partnership[3] identifies a gap in the generation of regulatory-compliant research results. Thus, the translation and uptake of academia-driven research are often compromised by lack of timely regulatory advice and interaction beforehand with regulators. The need to engage and boost regulatory science and data science strategies at the design and planning stage is also a gap that needs to be addressed in order to accelerate the implementation of novel technologies, innovative trial design and the use of Real-World Evidence (RWE) in study design and medicines developments.

Public-private partnerships could help pool resources to address these gaps promptly, by reducing fragmentation and scaling up existing initiatives making a real difference for patients. The 'Rare Disease Moonshot' coalition works together as an ecosystem of multi-disciplinary rare diseases experts and infrastructures. As a coalition, it aims to

1 https://www.rarediseasemoonshot.eu/

2 https://irdirc.org/

3 https://www.horizon-europe.gouv.fr/european-partnership-rare-diseases-33757

explore synergies and opportunities for collaboration, hereby supporting a range of public-private partnerships. Of particular interest are research projects aimed at developing new tools and treatments, expediting clinical trial readiness of rare diseases, and contributing to enable regulatory approval.

The coalition will collaborate with state-of-the-art infrastructures, services and support research that will be further advanced by the Rare Disease Partnership so that clinical and translational Rare Diseases research are highly productive to address the unmet needs of the rare diseases' community.

Research needs to address clinical trials gaps in Rare Diseases

Leveraging regulatory science for Rare Diseases

Multi-stakeholders' collaboration can be key to address challenges in designing, planning and conducting clinical trials in Rare Diseases. Such collaboration can help drive the use or modernisation of existing tools and the development of new tools and methods, optimising clinical trials in a meaningful way to patients.

The Innovative Medicines Initiative (IMI)[4], now Innovative Health Initiative (IHI[5]), the world's biggest PPP in the life sciences, has shown the value of multi-stakeholders' collaboration in the pre-competitive space over the years. Other PPPs are also of great interest, such as, the Critical-Path Institute in the US. With PPPs, it is possible to push the boundaries of science to develop faster, better and more personalised treatments and health innovations. Several IMI projects were set up with the goal to optimise clinical trial design features, ranging from operational aspects to trial methodology, while ensuring trials have a patient- and caregiver-centred approach. Many of these important IMI projects were designed to deliver important objectives, setting up sustainable clinical research networks for delivering clinical trials (c4c), transforming the way trials are designed, such as with the use of platform trials (e.g. EU PEARL), Modeling and Simulation (e.g. D-DMORE), RWD or other data sources (e.g. GetReal, EHDEN, H2O), developing new outcome measures (e.g. NECESSITY,), or using digital health technologies (e.g. Trials@Home; IDEA-FAST, MOBILISE-D) whether to generate real-life data or to be used as endpoints.

There is an urgent need for additional public-private collaborative work to further develop some IMI outcomes to be applied to the science of medical product development and clinical trial processes, including trial design, endpoints, and analyses. Further PPP work is also needed to increase the number and uptake of Drug Development Tools (DDTs) applicable to rare diseases. DDTs are methods, materials, or measures that have the potential to facilitate drug development. Having qualified DDTs that many sponsors can use will help optimise drug development and evaluation. The resources needed to develop a qualified DDT are often beyond the capabilities of a single entity. These collaborative efforts allow multiple interested parties to pool resources and data to decrease costs, expedite drug development, and facilitate regulatory review. Increased public availability of qualified DDTs is anticipated to benefit public health through (1) increased availability of effective drugs, (2) earlier access to medical therapies and (3) an enhanced knowledge of the drug under development and (4) increased quality of research and acceptability of its results.

Several DDTs already exist on the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) websites, including tools developed by patient organisations, that can be considered and leveraged when planning Rare Disease projects or used to create new DDTs.

By advancing disease aetiology, biology and natural history that are insufficiently understood, Regulatory science that allows to advance regulatory readiness levels, combined with quantitative medicines (quantitative methodologies in pharmacometrics, statistics, systems pharmacology, artificial intelligence, machine learning and digital data analytics) capacities and capabilities to develop DDTs, leads to better design and evaluation of clinical trials.

The European Commission, in collaboration with the EMA and the Heads of Medicines Agencies (HMA), have launched initiatives to boost the EU competitive centre for innovative clinical research. Those initiatives are: 1) The 'Regulatory science research needs' list[6] published in December 2021 by EMA who identified around one hundred topics with the hope to stimulate researchers and funding organisations to consider addressing these needs in their work and programmes, 2) the EMA Regulatory Science Strategy to 2025[7], and 3) the ACT-EU initiative[8] launched in January 2022.

4 https://www.imi.europa.eu/

5 https://www.ihi.europa.eu/

6 https://www.ema.europa.eu/en/documents/other/regulatory-science-research-needs_en.pdf

7 https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/ema-regulatory-science-2025-strategic-reflection_en.pdf

8 https://www.ema.europa.eu/en/news/accelerating-clinical-trials-eu-act-eu-better-clinical-trials-address-patients-needs

Deployment and uptake of patient engagement resources and tools

Patients' views and perspectives should continue to be increasingly included in all stages of both drug development and PPPs. This can be done through many patient engagement activities such patient and public advisory boards[9]. Moreover, solutions to overcome hurdles in the implementation of cross-border patient participation in clinical trials, e.g. using trials with remote elements, should be identified and proposed.

Leveraging existing data, resources and infrastructure for Rare Diseases

The Rare Disease Moonshot partners have existing state-of-the-art infrastructures, services and support that can be further advanced by the Rare Disease Partnership. However, those can already be leveraged in Rare Disease PPPs activities for clinical and translational RD research to be highly productive.

Particularly, there is an urgent need to improve the maximisation of patient-generated data and utilise these data for the development of accessible tools that optimise and accelerate drug development for rare diseases within the community. In order to ensure the quality of patients' data and enable the re-use of this data, such data should be gathered in a regulatory-grade format and FAIR (Findable, Accessible, Interoperable, Re-useable), suitable for analytics.

The C-Path Rare Disease Cures Accelerator-Data and Analytics Platform[10,11] (RDCA-DAP®), an FDA-funded initiative, provides a centralised and standardised infrastructure to support and accelerate rare disease characterisation, with the goal of accelerating therapy development across rare diseases. RDCA-DAP encourage sharing of data and foster regulatory-grade standardisation of new data collection for analytics. In so doing, the RDCA_DAP initiative further accelerates the understanding of disease progression (including sources of variability to optimise the characterisation of subpopulations), clinical outcome measures and biomarkers that capture clinically meaningful changes, as well as facilitates the development of mathematical models of disease and innovative clinical trial designs.

Recommendations

The IHI call 4, topic 4[12]: "Establishing novel approaches to improve clinical trials for rare and ultra-rare diseases and future calls in Rare Diseases" is an opportunity to generate high quality science, by having a variety of expertise and tools synergised to address a complex area relevant to public health needs. This call also offers an opportunity to share learnings educate and train all the relevant key players to find appropriate solutions to common issues in rare diseases, which will benefit everyone involved in the matter, including patients. Furthermore, this provides an opportunity to create synergies with other existing EU-funded projects (e.g., the RD Partnership), while avoiding work duplication.

To address the unmet needs of the rare diseases' community in a timely manner, all projects need to contribute to regulatory approvals. Therefore, the Rare Disease Moonshot recommends ensuring that patient's engagement, existing methodological tools and existing infrastructures are adequately considered and leveraged when planning a PPP research project in the Rare Diseases.

Moreover, to facilitate research, innovation and regulatory qualification, the Rare Disease Moonshot recommends that appropriate skills such as regulatory science, quantitative medicine and data science strategies are planned at the design of a project. This will ensure that regulatory research questions can be addressed accordingly.

To conclude, these recommendations aim at ensuring that research projects outputs meet regulatory requirements and patients' needs, thereby reducing failure rates of therapeutic developments.

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9 https://preprints.jmir.org/preprint/44206

10 https://portal.rdca.c-path.org/

11 https://c-path.org/fda-acknowledgement/

12 https://www.ihi.europa.eu/sites/default/files/uploads/Documents/Calls/FutureTopics/DraftTopic_TrialsRareDiseases_June2023.pdf