TRANSLATIONAL RESEARCH NEEDS RECOMMENDATIONS

RARE DISEASE MOONSHOT

Accelerating translational research for rare diseases white spots by bringing public and private partners together earlier, better, and more often to achieving a common goal in order to bridge the gap between scientific discovery and clinical application. White spots are known to be conditions for which there is no approved treatment option and where development is not currently commercially viable. This is the reason why this paper provides recommendations for a robust collaborative framework involving public-private initiatives to leverage the complementary strengths of various stakeholders, including patients, researchers, clinicians, regulatory authorities, industry and Health Technology Assessment (HTA) bodies. Recommendations for overcoming the barriers to successful translational research include developing a shared vision focused on patient-centric approaches, while ensuring structural access to comprehensive expertise across the value chain and investing in innovative methodologies alongside standardization and awareness efforts and a call for the acceleration of translational efforts through the establishment of cross-sectoral accelerators and the enhancement of Technology Transfer Offices to facilitate effective technology transfer and innovation processes.

This paper argues for a collective and strategic approach to translational research in rare diseases, emphasizing the necessity of integrating diverse perspectives and resources to address the formidable challenges inherent in bringing scientific breakthroughs to the bedside. By fostering deep collaboration and adopting targeted public-private interventions, the paper posits that we can significantly improve patient outcomes and navigate the challenging landscape of translational research more effectively.

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Introduction

Translational research is the process of development of scientific discoveries into practical applications to improve human health, in a bi-directional cycle known as "bench-to-bedside-and-back." Ideally, translational research in rare diseases is coordinated to build a deep understanding of the pathophysiology and utilises advanced analytical technologies and a keen insight into the patient journey to gain a deeper understanding of disease, while enabling the design of targeted new approaches to disease diagnosis and care. While it holds immense promise for advancing health in the era of personalised medicine, translational research is fraught with challenges that collectively form the metaphorical "valley of death." These challenges are particularly pronounced in rare diseases, in which small patient groups, limited clinical experience and gaps in scientific knowledge lead to so-called 'white spots.' These are areas with little or no ongoing research to further our understanding, resulting in groups of patients that are in high need of diagnostic and therapeutic options. Such white spots can best be successfully addressed by creating carefully planned public-private initiatives that utilises the strengths and expertise of each involved stakeholder, and specifically addresses the challenges in translational research for rare diseases. These specific challenges are further expounded below, and this paper concludes with concrete recommendations for public-private actions to overcome the barriers.

Understanding complex biology in rare diseases

Perhaps the most significant challenge is the inherent difficulty in developing an understanding of disease mechanisms and then translating this basic scientific knowledge into clinical interventions. The journey from laboratory findings to tangible therapies involves studying complex and heterogeneous biology within a maze of technical, regulatory, and logistical hurdles. The transition from preclinical studies - conducted in controlled laboratory settings - to human trials requires meticulous planning and adoption of validated methodologies. In rare diseases, it is important to gain a thorough understanding of the natural history of the disease and subsequently develop and validate clinical endpoints that allow robust evidence generation in small patient populations. In many rare diseases, researchers are faced with complete absence of appropriate endpoints, or existing endpoints completely unsuitable for the candidate therapy, which can be exacerbated because of the same disease may present quite differently across patients and change over time. Such knowledge gaps in a given disease area are strong disincentives for large or small companies to invest in that area, as the time and costs involved with developing a complete disease picture are punishingly high.

Lack of incentives

In the case of academia, where basic scientific discoveries are typically made, there is little incentive to navigate the complexities of applied translational research, due partially to a reward system that incentivises discovery - in the form of peer-reviewed publications - but not further development, which generally has a lower academic impact factor. As a result, academic institutions have not historically built the expertise and institutional apparatus to support early development, thereby creating a lack of awareness of the regulatory requirements, lack of knowledge of the existing infrastructures that can support them, and lack of access to industrial development expertise. These constraints reduce the entrepreneurial spirit of academic innovation and drive higher failure rates despite increasing public funding and policy attention for translational sciences. Consequently, smaller companies face similar challenges when working to translate academic discoveries into breakthrough therapies, requiring significant financial and expert support to create value and develop a commercially interesting proposition.

Cost of development

Financial constraints represent another important challenge in translational research. The costs associated with developing a medicine are staggering, encompassing preclinical studies, clinical trials, and regulatory approval. Securing funding for each stage is a persistent struggle, and many promising projects falter due to insufficient long-term financial support. This financial barrier is particularly acute during its early stages when a project lacks the robust evidence base necessary to attract major investments and is exacerbated by the lower expected financial returns associated with small patient populations. This challenge is even more acutely experienced in Europe due to a very fragmented and more conservative venture capitalist landscape compared to other regions such as the USA.

Life cycle management and medicines repurposing

The high development costs and failure rates paired with low patient numbers often result in prices that may create tension in health systems. One promising strategy with the potential to reduce costs is the development of secondary indications for already approved molecules or experimental medicines that already have been shown to have a suitable safety profile in clinical trials or in healthcare. This strategy of life-cycle management, often called drug repositioning or repurposing, receives a great deal of scientific attention in academic development

in rare diseases. Sadly, though, there is not a commensurately high proportion of secondary use label extensions reflecting this attention. Market failures related to pricing of a generic medicine in the new indication, difficulty in engaging companies to co-develop in new indications, and lack of awareness of the sometimes-complex regulatory requirements for successful label extension, are the primary drivers of failure. In recognition of this the European Commission committed EUR60 million in 2022-2023 to three projects dedicated to professionalising the repurposing eco-system[1].

Navigating regulatory steps

The regulatory landscape is complex and demanding for all stakeholders in the early development phases of a new technology, while the science is being developed. Clear regulatory and ethical considerations are essential for safeguarding patient well-being, while a lack of awareness of regulatory requirements within academia impedes the swift progression of research towards clinic. This is compounded by a lack of easy access to expert advisors that can provide support and facilitate dialogue with regulators. Regulatory agencies are generally flexible and open-minded when considering the evidence base for drug approval – obviously within the boundaries of patient safety and potential for real world efficacy – but are under-engaged in crucial early phases by academia.

Sprint race mindset

The journey from scientific discovery to efficacious treatment can best be visualised as a relay race with different participants in a large team, each working in synergy and with a common goal of transferring the 'baton' of knowledge towards the ultimate goal of creating patient value. However, currently, academic research and public funding instruments often fund research with a 'sprint-race' mindset – with the goal of peer-reviewed publication - in which the research project is viewed as a single initiative and conducted with little or no synergies with an overall disease area strategy. This often results in research that is scientifically interesting but does not meet the standards for contributing adequately to therapy development, and only rarely does it support educated investment decisions.

Leveraging public-private collaboration to solve challenges

The challenges of translational research in medicine are multifaceted, encompassing scientific, financial, regulatory, and enterprise aspects. The "valley of death" metaphor vividly illustrates the precarious nature of the transition from discovery to clinical application, emphasising the need for strategic interventions and systemic support to ensure that promising medical innovations successfully navigate this challenging terrain. Given the above, collaboration across sectors is essential if we are to successfully tackle the many white spots in rare disease research. This entails close cooperation between diverse stakeholders, such as patients, researchers, clinicians, supporting structures (e.g. research infrastructures and technology transfer offices), industry partners, and regulatory bodies is vital for successful translational research.

Coordinating these efforts is challenging, given the differing priorities and competing interests, communication barriers, and cultural disparities among these groups, but rewarding for organizations who embark into this common journey. An essential stakeholder is the patient, who rightfully can act as the key driver for research funding, policy, clinical excellence initiatives, as well as scientific partner and to support clinical trial design and execution.

Herein follow practical recommendations for targeted public-private interventions to improve patient outcomes through effective and collaborative translational research and development.

Recommendations

1. Develop a shared vision along the value chain with a patient-focused translational research approach

For rare disease white spots it is essential that investigators, their organisations and their funders have a clear understanding of the various phases of the knowledge journey, the relevant scientific and clinical questions to be answered, and how best to transfer knowledge between phases. By engaging patients and other key stakeholders, including biotech and pharmaceutical partners early in the research process, linking the steps and ensuring that all stakeholders understand the requirements to become 'clinical trial ready', each step can easily be designed to contribute more efficiently to the development of an integrated therapeutic strategy. Industrial expertise, resources and tools can provide key support in building a complete picture of a given disease, facilitating more effective academic discovery and transfer into the innovation pathway.

1 For more information please see the REMEDi4ALL, RePo4EU and Simpathic project websites - https://remedi4all.org/, https://repo4.eu/ and https://cordis.europa.eu/project/id/101080249

It is therefore imperative that research funders conduct multi-stakeholder dialogue with their scientific communities, healthcare sectors, patients, industry and investors, to cooperate in defining a common set of knowledge goals and quality standards, while understanding the knowledge requirements of each step in the development chain. This will further necessitate the coordination of funding and research activities, also in order to establish priorities so that resources are committed in areas of maximum potential impact.

2. Ensure structural access to expertise from the entire value chain

To conduct more coordinated research across organisational boundaries in a distributed approach, an overarching planning mechanism is essential that allows investigators and their funders to design research that is fit for exploitation and further development. There are various ways to establish coordination mechanisms with basic principles that drive a successful design, including:

a. **Define jointly the shared goals**, with agreement on phasing of milestones and go/no-decision-points for the overall development strategy. Dead-end confirmatory research projects that will not culminate in patient value should be re-focused or stopped to prevent resource waste and unnecessary patient burden.

b. **Ensure that experts from the different organisations throughout the value chain are represented and contribute to the planning and funding process** and that these experts do not have any conflict of interest. This principle will also ensure that all steps in the value chain are considered by the research funder.

c. **Install cross-disciplinary translational review processes** - access by public and non-profit funders to regulatory, scientific, industrial, clinical and patient expertise to ensure that early-stage investments are reviewed with later development steps in mind. Utilise existing research infrastructures whose mission is to support these processes[2].

d. **Co-create with patients** - whose involvement and insights are essential at all steps of the value chain.

e. **Engage with regulators, payers, and clinicians structurally and in a timely fashion**, to ensure that research design is optimised for translation into a healthcare setting.

f. **Create the minimum required control and oversight mechanism**, blending bottom-up research creativity with top-down selection mechanisms and quality control.

g. **Leave execution and control of individual research projects and programmes to the funders that finance them** and ensure that each has the tools and expertise to robustly validate the design and monitor the progress of their projects; the focus should remain on translatability of research findings.

During both design and implementation of research projects, ensure that researchers have structural knowledge of and access to relevant mentors and coaches, from expert domains that are scarce in academia, such as regulatory science, process development, scale-up and manufacturing, commercialisation, and intellectual property rights. In many instances there are local and international infrastructures that provide such support, but awareness of the opportunities remains lower than desired. Nonetheless with existing tools developed by the European Medicine Agency (EMA) specific to the academic sector[3]. Mentoring programmes are an efficient manner to achieve this, with differing approaches available[4] that facilitate varying intensity of contact and involvement of the mentors. An important element is that sufficient expertise is brought in during the research design phase, so that the research results – if successful – will be sufficiently robust to not only warrant publication but also further investment and development. Universities are encouraged to design incentives for investigators to take on this additional burden.

3. Invest in innovative methods as well as standardisation and awareness

In general, standards, reagents and technologies utilised in the non-clinical research process are often not suitable for translatability, scale-up or safe for use in humans. Moreover, complex Intellectual Property (IP) landscapes in key technologies such as gene therapy vectors and manufacturing or base editing technologies, and frequently inadequate patent applications prevent commercial development of scientific inventions. Awareness of issues around selection of reagents, validity of a chosen technology in context of use as well as freedom-to-operate evaluations are an essential part of good planning and future exploitability.

2 See for example https://eatris.eu/ and https://ecrin.org/

3 See for example https://www.ema.europa.eu/en/documents/leaflet/ema-tools-available-medicines-developers-academic-sector_en.pdF

4 See for example https://imt.ejprarediseases.org/collection/mentoring-packages/

Technologies form the backbone of high complexity translational research methods and clinical products – we must continue to develop new approaches that target rare disease (RD)-specific challenges - but they must also be validated in the specific context of use, scalable and qualified for unfettered development into clinical settings. We must thus define and validate key characteristics of Advanced Therapy Medicinal Products (ATMPs) and other innovative therapeutic modalities, as well as quality standards that are critical to later stages of their development, in particular those targeting rare diseases with no approved treatment option.

Novel approaches in statistical methodologies, real-world evidence use, innovative clinical trial design (such as platform trials) and more have the potential to increase success rates in RD research; this has been recognized[5] in flagship public-private collaborations, such as IMI/IHI, and work to validate and broadly disseminate and implement these approaches must continue apace.

4. Accelerate translation through public-private partnerships by creating cross-sectoral accelerators and strengthening existing innovation hubs

Lack of awareness of later requirements in development - such as scale-up, quality control, regulatory compliance to name a few - leads to a staggering attrition rate in early development stages, in particular for complex ATMPs. Structural dialogue and interaction between early-stage innovators/funders and later investors (industry and venture capital) will allow for earlier and enhanced de-risking and faster translation, with a focus on the common goal of patient benefit. The establishment and use of strong scientific and technical centres (ATMP hubs) that provide access and advance translatable, quality-controlled technologies will be of help to assist academic and potentially industrial developers of ATMPs.

In addition, the following should be considered: utilise proven existing frameworks and initiatives for maximum efficiency; leverage these resources and initiatives to develop a transversal value chain, and under it create disease-specific strategies that will tackle the white spots[6] in a coordinated manner, thereby breaking down institutional silos and reducing knowledge asymmetries.

5. Enhance and Utilize Technology Transfer Offices (TTOs)

Lack of critical mass and resources in TTO capacities leads to challenges in the technology transfer and innovation process. It is important to raise awareness of and enhance the role of TTOs in supporting translational research efforts and align them with the specific needs of rare disease patients and encourage them to seek critical mass. This can be done by increasing domain-specific knowledge and by encouraging and supporting multi-institutional collaboration of the TTOs in best practice exchange, knowledge pooling and training programmes. This can be efficiently achieved by utilizing existing TTOs with demonstrated excellence to lead this initiative.

5 See for example https://ec.europa.eu/info/funding-tenders/opportunities/portal/screen/opportunities/topic-details/horizon-ju-ihi-2023-04-04-two-stage; and Why EU-PEARL? – EU-PEARL

6 White spots: conditions for which there is no approved treatment option and where development is not currently commercially viable.

Suggested actions for implementation of the recommendations

Action	Owner	Who should be involved?
Mandate a public-private coordination body to bring together information and knowledge on current research efforts in RD, provides guidance on research programme planning and ensures that R&D within a given disease area is coordinated. Ensure timely engagement of all stakeholders during research execution.	ERDERA[7]	Industrial & public funders, research infrastructures, regulators, relevant existing initiatives
Create a public-private innovation accelerator and innovation marketplace utilising existing structures (such as EJPRD[8] and ERDERA), comprising financial and technical resources and expertise for effective development. Links to other incubators and accelerators is essential.	ERDERA, IHI[9]	Industry, venture capital, philanthropy, charities, patient organisations, research foundations, public funders
Support non-profit funders in coordinating and optimising their funding process to ensure projects are designed and executed with exploitation and later development in mind.	Public funders	Industry, research infrastructures, ERDERA
Include curricula in principles of translational medicine at all stages of tertiary biomedical sciences education and research; include more education offerings as part of research funding process, such as workshops for grant awardees. Create public-private PhDs and exchange programmes.	Academia	Public funders, industry, research infrastructures
Create a network of ATMP centres of excellence, tasked with methods development, standardisation, accessible facilities for collaborative R&D; engage regulators for collaborative regulatory science research.	Non-profit research institutions	IHI, industry, EU member states, research infrastructures, patient organisations, research foundations
Create a network of TTOs to provide best practice exchange, develop training curricula and provide consulting advice	Academia	Member states, European Commission

Conclusions

As described above, the importance of efficient translational research is even more pronounced in the rare disease space, due to the technical challenges and relative lack of resources. To be effective, the R&D community must come together from across all sectors in bringing attention to under-researched diseases and to drive innovation in the white spots. This entails deep collaboration among partners (including public funders) to monitor ongoing research and capture the opportunities to more quickly discover and address the gaps in the diseases research pipeline. Furthermore, collaborating to mobilise and educate the community by offering new opportunities such as industrial doctorate programmes or mechanism to enhance younger generations of scientists with patients and patient organisations, implementing a joint funding pipeline approach for specific goals, with the aim of decreasing the costs of development and thus the chance of uptake in healthcare settings.

By working together with all sectors - including regulatory agencies, HTA bodies and payers – and ensuring that each player has a clear understanding of how their work fits into the greater whole, we can increase efficiency, speed up innovation and reduce failure rates. We call upon the community to come together and develop practical solutions to the challenges enunciated above.

7 https://www.ejprarediseases.org/erdera/

8 https://www.ejprarediseases.org/

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