Monaco *et al. Rare Dis Orphan Drugs J* 2024;3:27
DOI: 10.20517/rdodj.2024.18

Rare Disease and Orphan Drugs Journal

Review

Open Access

The complexity of funding rare disease research: an IRDiRC assessment of the landscape

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How to cite this article: Monaco L, Letinturier MCV, Aketa N, Athanassiou D, el Hajjar J, Frost S, Granados A, Haight AR, Jonker AH, Kahn SR, Kang S, Kritikou P, Kyriakopoulou C, McMaster C, Parker S, Scherman D, Valentine N, Wiafe S, Hartman AL. The complexity of funding rare disease research: an IRDiRC assessment of the landscape. *Rare Dis Orphan Drugs J* 2024;3:27. https://dx.doi.org/10.20517/rdodj.2024.18

Received: 2 Jul 2024 **First Decision:** 1 Aug 2024 **Revised:** 22 Aug 2024 **Accepted:** 30 Aug 2024 **Published:** 9 Sep 2024

Academic Editor: David Pearce **Copy Editor:** Fangling Lan **Production Editor:** Fangling Lan

Abstract

The complexity of the funding landscape for rare diseases (RD) research is due to many factors. Each type of funder has strategic goals guiding its investments. The International Rare Diseases Research Consortium (IRDiRC) convened RD experts to explore contributing factors and investment principles in RD funding. This report includes the Task Force's findings. Similar to IRDiRC's previous work on motivating factors for company investments in RD research, the current Task Force found that return on investment (ROI) was a guiding principle. However, within the broader RD funding landscape, the definition of ROI varied between types of funders. While they shared funding requirements (e.g., scientific quality, health economics), funders employed both major investment and venture-type instruments, demonstrating the ongoing need for flexibility in supporting RD funding. These observations warrant further analysis of the interactions and partnerships among all actors of RD research and the sustainability of RD research funding.

Keywords: Rare disease research funding, rare disease advocacy groups, rare disease regulatory issues, venture philanthropy, venture capital, public-private partnerships

INTRODUCTION

Funding rare diseases (RD) research is a major challenge, even in high-income countries[1]. The International Rare Diseases Research Consortium (IRDiRC) is an initiative designed to positively impact the lives of people living with RD by supporting a multinational perspective and collaboration on RD research[2,3]. The recent IRDiRC Chrysalis Task Force identified financial and non-financial factors that make RD research attractive to companies[4]. One of the key factors identified in that study is the concept of ROI; however, the individual factors that converged into ROI were weighted differently by different types of companies and specific diseases. While analyzing the results of that study, it rapidly became apparent that a wider scope of investors (public funders, private investors, foundations, advocacy groups, partnerships and others) also needed consideration. The IRDiRC Funding Models for Rare Diseases Research Task Force was created to explore the larger funding ecosystem in RD research. Supported by a targeted literature review and interviews with key opinion leaders, the Task Force found that while the concept of ROI is still very central, its interpretation and the factors that contribute to it are even more diverse than when only companies are evaluated, partly because there is a greater number of interested constituents.

Key findings of the task force

Our analysis initially addressed a range of factors influencing the decisions to invest in RD research that are recognized by investors. The different types of funders were then investigated, in association with the key motivating factors for funding RD research and the stages of research to invest in, as well as the diverse partnerships between different kinds of funders. Ultimately, we analyzed the choice of funding instruments in support of RD research [Figure 1].

FACTORS INFLUENCING INVESTMENT DECISIONS

There are many factors that influence the decision to invest in a particular RD and contribute to the assessment of economic feasibility and potential ROI.

Scientific quality and innovation

An RD research and development program cannot succeed unless the underlying biology and intervention are aligned. Most funders and investors emphasize the need for scientific quality. The disease target needs to be valid and the therapeutic intervention needs to address major aspects of the underlying RD biology.

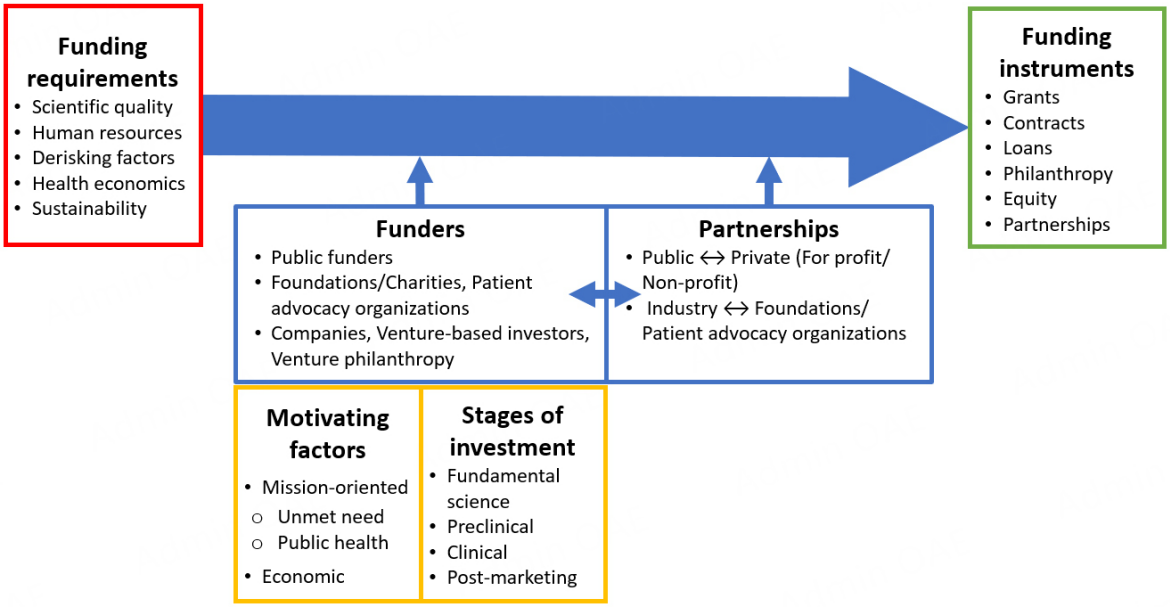

Figure 1. Elements addressed in the analysis of funding models for RD research.

In the RD funding landscape, innovation is a leading factor in ensuring that critical challenges are addressed to deliver the highest medical value to the public. Funding can play a pivotal role in propelling RDs during their initial development stages of new ideas for research and care, serving as a decisive evaluation moment for true innovation. Funders are integral to ensuring the public's accessibility to innovation. The impact of innovation goes beyond technological advancements; it makes cutting-edge RD solutions available to a broader audience, thereby transforming ideas toward access in healthcare.

Evidence assessment frameworks are used by regulators and health technology assessors to grade the merit, innovation, and quality of the RD research product. They influence the RD patient journey by highlighting the uncertainty associated with small sample size trials and clinical studies that may include heterogeneous populations. Newer techniques have also been employed, including epidemiological simulation models, real-world evidence, novel biomarkers, qualitative evidence, or patient-reported outcomes.

Human resources

In RD research and development, experienced professionals from academia, clinical settings and industry, and importantly, patient advocates can play a critical role in generating evidence that matters to key different stakeholders, especially when the scientific dialogue is undertaken early in development.

Scientific leadership is critical to safeguard scientific quality and to ensure that the proposed interventions are consistent with the biological mechanism and disease state; they also should translate to the desired therapeutic effect.

One cannot overemphasize the impact of the human factor. Every program needs a champion. Ideally, this person does not have competing interests but also has international recognition, enabling building from connections and experiences other than their own. Because of some unique characteristics of RDs, champions need practical development or clinical experience to anticipate and address the challenges that invariably arise in advancing a treatment or they need to be capable of engaging those with these skills in an appropriate manner.

Experienced regulatory affairs professionals play a critical role in communicating and coordinating with regulatory agencies while also taking advantage of special pathways, such as orphan drug designation, to expedite the availability of treatments.

Ideally, RD clinicians and clinical statisticians will be adept at managing interactions with regulatory agencies and overcoming the challenges unique to RDs, such as limited patient populations, gaps in disease understanding, and undefined endpoints. Their strategic foresight in development planning, coupled with a comprehensive grasp of RD-specific regulatory requirements, helps to anticipate and mitigate potential obstacles. This expertise ensures a streamlined development process, aligning closely with RD-specific regulatory demands to expedite the journey from concept to cure.

Derisking factors

In RD investment decisions, the significance of disease-specific and patient-intrinsic factors is paramount. The epidemiology of the disease in question and its burden are key considerations. The total size of the targeted patient population is a factor, with certain diseases receiving more funding due to higher prevalence or because they are associated with a significant societal burden.

Projects closer to clinical trials or with a clear path to translation into clinical settings may receive higher priority due to their potential for near-term patient impact.

Regulatory compliance and ethical standards are crucial in reducing risk. Examples of derisking strategies in RD include orphan drug designations and pathways for direct engagement of regulatory authorities (which can increase visibility and engagement and thereby increase the likelihood of project prioritization and success). Projects that offer solutions applicable across regions while adhering to these standards are viewed as lower-risk and are more likely to be prioritized.

Another example of derisking is the protection of intellectual property rights, which is an incentivizing factor for investment decisions because it increases the potential for financial returns and reduces the risk of competition.

Ultimately, the ability to reduce investment risk is directly linked to its chance of regulatory approval and commercialization success. The priorities also depend on the scope of a funder's mission and the stage of the funder's investments (e.g., from early research to commercialization). Some funding agencies focus their investments on particularly risky stages in development (e.g., translational aspects or first-in-human studies).

To summarize the importance of investment strategies, Levine and Stemitsiotis stated, "If biotechnology companies, investors, and pharmaceutical companies were to more effectively derisk RD acquisitions, greater capital will be available to help more patients"[5]. This paradigm might also be true at the early stages of RD drug development.

Health economics

As companies investing in RD consider their resource allocation as part of their investment decision-making process, they may prioritize investments where there is a higher likelihood of success in reaching the market[6]. However, when considering health economics, several challenges have been noted in the literature regarding RDs.

Health economics, including health technology assessment (HTA) in Europe, is important for new health technology to reach the market. Understanding what makes a positive health economics evaluation is, therefore, a crucial component of the decision-making processes of all investors. Previous experience with successful RD HTA evaluations could aid this process, while alternative payment models, including those linked to performance, are discussed for very high-cost drugs, which are becoming increasingly common with RDs[7].

HTA plays a key role in countries where reimbursement is conditioned upon it. It has been argued that economic evaluation methods for common diseases might not apply to RDs due to their intrinsic challenges (e.g., smaller populations, lack of evidence, high drug prices, *etc.*)[8]. The lack of evidence, such as the absence of a comparator arm in some studies, can pose a challenge for economic evaluations. In such cases, early engagement with HTA agencies to explore alternative methods of generating evidence securely might be helpful, even if it means creating an alternative but rigorous pathway[9] (e.g., through real-world evidence studies).

Other key health economics parameters to consider include the competitive landscape, incentives relating to market exclusivity, and expectations of a price premium[4]. This price consideration is associated with the type of disease, the required therapy, and its frequency of administration (i.e., whether it is a one-time treatment or a regular therapy regimen). Typically, high prices associated with new RD technologies might exacerbate the problem, as payers sometimes find it difficult to accept them[10].

Several suggestions on how to solve this problem include tying the payment model to the performance/effectiveness of the new treatment and payment with installments, as it might be unfeasible for payers to initially cover full payments of high-cost gene therapies[7]. Another suggestion has been to involve banks to finance the initial expenses and distribute the total costs over time (in some cases, total costs for new advanced therapies are not necessarily higher - they are distributed differently, with more substantial initial costs that decrease over time). Others are challenging the traditional financing system in the industry, proposing the utilization of innovative financing vehicles with different ROI expectations. One example is capital that is more patient-oriented, with an investment horizon extending beyond the typical five to seven years seen in venture capital, which, in turn, would allow for more long-term sustainable returns.

Sustainability

Funding for RD research from public entities hinges on the financial capacity at the national or supranational level, often competing with allocations for health-related needs linked to common diseases. Private foundations, on the other hand, depend on donations and fundraising, which can vary over time upon shifts in socioeconomic conditions. In both scenarios, the uncertainty surrounding sustained funding availability may hinder long-term funding initiatives and restrict the pursuit of more ambitious programs.

Raising capital for RD companies is a challenge because of the risk involved and the need for investors with financial goals to generate a financial ROI. In addition, there are challenges in raising funds in the current biotech market landscape. Venture capital partners are under immense pressure to provide early financial returns to their investors. During the early days of the SARS-CoV2 pandemic, there was a surge in optimism about the rapid development of drugs and vaccines. This led to non-specialists entering the biotech investment market, resulting in an oversaturation of funding for unrealistic projects. When these expectations proved unrealistic, many investors left the market, leading to a significant reduction in available funds. Additionally, interest rates rose significantly afterward, making biotech investments less attractive compared to safer options.

TYPES OF FUNDERS, KEY MOTIVATING FACTORS AND STAGES OF INVESTMENT

RDs are recognized as a compelling target of funding by a range of investors, spanning from public entities to private non-profit organizations, to biotech and pharmaceutical companies, and venture capital investors. Decisions to invest in one or multiple stages of the research and innovation life cycle are driven by each investor's institutional mandate or funding objectives encompassing progress in understanding RDs, development of innovative diagnostic methods and treatments, and financial ROI.

Classically, in the very early stages of a project, small investments (sometimes called "seed funds") are frequently obtained from private investments. One group is "family and friends" (which can include grateful patients or families). Another group is "angel investors", who typically have an interest in high-risk but potentially high-yield outcomes. Both invest their own funds and might acquire equity in the enterprise (more commonly seen with the latter than the former). Increasingly, other types of funders (discussed below) may provide seed funding. Later stages of support are provided by all types of funders, discussed in greater detail here.

Public funders

Funding by government entities plays a crucial role in supporting research and innovation activities in RDs[11-14]. The primary investment goal of most public funders is to improve the health of their constituents, and thus, the "return" of the ROI is the product of the research rather than financial considerations. Public funders provide support to almost all the constituencies involved in RD research and finance much of the RD biomedical research conducted at universities and academic medical centers, including the RD national centers of excellence[15] and multinational RD clinical networks[16]. Some public funders also support private non-profit organizations such as charities, foundations, and patient associations, including academic spin-offs and small and medium-sized enterprises (SMEs)[17,18].

A considerable share of public funding is invested in mission-oriented or challenge- and outcome-driven research approaches that are well suited for RD research. Such approaches are seen as a funding model that brings the necessary scale of collaboration and expertise for addressing the unmet medical needs of RDs. Typically, this research is carried out by diverse research consortia, spanning from academic centers to SMEs.

Public funding is also channeled to research infrastructures (e.g., biobanks) and to capacity-building for advanced data-driven approaches in RD research. Clinical trial preparedness is also fostered through the support to natural history studies and patient-centered registries, including undiagnosed RD programs.

Foundations and charities

Foundations have a strong philanthropic mission and, foremost, prioritize research projects that fulfill patient needs. In this respect, their ROI is similar to that of public funders. Patient representatives are integral members of decision-making boards within foundations, making substantial contributions to the development of investment strategies. Patient groups and foundations historically funded research with the goal of seeding critical, otherwise unfunded research, without seeking a financial return for their investments. That approach is changing because the investment landscape has changed. For example, some large foundations have a long-term outlook on bringing treatments to patients. Therefore, they have a diverse portfolio of funding instruments and the ability to connect with a broad industry network or form new companies.

Patient advocacy organizations (PAOs) play a crucial role in funding RD research and drug development, even though typically, they do not directly conduct the research themselves. Their investments, while infrequently direct monetary contributions, play a crucial role in propelling research and drug development forward. They play a key role in shaping policies that incentivize drug development for RD and may direct part of the money they raise toward research activities. Some of the investment opportunities for PAOs such as funding basic science research can lay the groundwork for future drug discovery; funding patient recruitment efforts or co-sponsoring clinical trials can expedite the development process; investing directly in promising biotech companies can accelerate progress and potentially yield financial returns to support further research; and investing in platforms facilitating data sharing and collaboration between researchers can streamline workflows and promote progress[19].

In general, non-profit organizations' roles in funding RD research have evolved, partially due to the large amount of capital needed to fund and develop therapies in general[20], and RD treatments in particular, and the high cost of capital. As this dynamic has shifted, non-profit organizations have also become more sophisticated in their funding approaches, such as sometimes seeking to monetize their assets (registries) and/or seeking a financial ROI to create a renewable cycle of funding. Although still not yet common, foundations are increasingly using a venture philanthropy approach (or similar/other approaches) to receive a financial ROI, which, in turn, will be reinvested in their research mission.

Venture investors and venture philanthropy

Venture capital investors occupy a crucial space in the RD funding landscape because they bridge the gap between public and non-profit funders and established companies. They typically invest and manage funds provided by others (but this varies). Their support to startup biotech companies is not limited to funding but often includes expertise in industrial operations and RD-specific regulatory procedures, strategic guidance, networking opportunities, and competence in risk mitigation.

Private investors with niche criteria can significantly shape the investment landscape for RD. For example, some investors focus on companies led by women with personal and professional experience in the space, recognizing their unique perspectives and insights. Such targeted approaches can reduce disparities in the playing field. Other investors prioritize companies that generate revenue within a particular range or employ a certain number of employees, allowing them to find opportunities aligned with their risk tolerance and growth expectations.

Altogether, niche investing can lead to valuable partnerships and collaboration opportunities, forge relationships with portfolio companies, and offer targeted support to help them succeed.

Venture philanthropy is a relatively new model that has already demonstrated success by bringing new treatments for a number of RD through early development, clinical trials, and ultimately for approval by regulators for access by patients[21]. The venture philanthropy concept rose from the venture capital model whereby investments are made in areas considered high-risk but with the potential for high rewards. A major difference between venture capital and venture philanthropy is that profit is not the primary motive. Instead, revenue generated from an approved treatment/cure is directed back to the philanthropic fund to be reinvested in activities aligned with the foundation's goals. In venture philanthropy, the major stakeholders (patients and families) are engaged at all levels, and by its nature, venture philanthropy has to be risk-tolerant.

As RD venture philanthropy is usually focused on a specific disease, benefits often go beyond providing investment. An RD-focused venture philanthropy fund offers scientific expertise, access to patient registries with patients that are often very well characterized over time (natural history is often a major criterion for many RDs as part of clinical trial outcomes), and an already existing clinical network. The regulatory process to enable a first-in-human trial for a RD, and clinical trials required for therapy approval, require sophisticated knowledge of these spaces, which might not be found within academia and patient foundations (companies and governmental institutions also have expertise in this domain, but this expertise might not be available to all interested parties). Beyond deep knowledge of the RD, a board of directors with investment and regulatory expertise are likely requirements for success through venture philanthropy. Some of these schemas can also bring long-term commitment, unlike most governmental agencies, which typically have limited funding timelines.

Companies

Pharmaceutical and biotech companies primarily focus their investments on RD translational research, often building upon foundational findings from non-profit organizations in the basic and preclinical research space. The aim of providing therapies to RD patients is balanced by the necessity to reach a financial ROI and is challenged by the economic viability of the programs. Financial ROI is a major motivator for companies funding research for RDs, as found by the IRDiRC Chrysalis task force[4]. The high costs usually involved in the development of specialized medicines for RDs (e.g., monoclonal antibodies, gene therapies, etc.) partly drive this approach[22,23].

PARTNERSHIPS

Recently, there has been a shift from research and innovation on RD involving individual investors to a multistakeholder open innovation and collaboration model with relevant actors in the research and development life cycle. Such collaboration aims to increase the effectiveness of RD research, share knowledge with the entire research community, and boost the translation of disruptive research from academia to the market.

Public-private partnerships

Public-private partnerships (PPPs) are designed to strategically bridge the gap between scientific research and commercial development in RD treatments. Many public funding initiatives strongly encourage or require the formation of PPPs, particularly targeting startups and SMEs engaged in RD research. For projects with shorter timelines, the emphasis shifts toward funding startups and small companies, with the generation and filing of patents being considered crucial indicators of progress and innovation.

PPPs typically bring all the relevant stakeholders together, including regulators and HTA bodies.

Industry partnerships with foundations and patient advocacy organizations

To pursue the development of promising therapeutic programs up to patient access, foundations and patient advocacy organizations may seek partnerships with pharmaceutical companies that can provide financial support and competencies in drug development. Conversely, companies may rely on academic discoveries and knowledge of RDs of interest to feed their drug development pipeline.

Programs are often co-developed or licensed by the foundation to the industrial partner, with shared revenues from commercialization. This kind of partnership bears the risk of subsequent disinvestment and withdrawal from the development programs due to revisions of the company's strategic objectives. In some cases, foundations have assumed the burden and responsibility to complete such programs up to patient access, possibly with the support of public funders.

Collaborative efforts may be established among foundations or patient advocacy organizations to pool resources to support impactful initiatives. Although many patient groups lack the size to provide significant research funding, in some cases, they have collaborated with international partner foundations to support large and expensive programs and developed innovative and sophisticated models, not only to jointly fund large and expensive programs, but also to leverage public funding, derisk the process, and deliver operational support on the field. Finally, some disease foundations have engaged in "advocacy partnerships" to strengthen their collective advocacy voice in addressing regulatory issues.

FUNDING INSTRUMENTS

Public funding is implemented primarily via grants or contracts by regional, national, international, and supranational organizations (e.g., the EU) through a combination of multi-level funding mechanisms, with most public funds allocated to single and multi-partner grants.

Single-partner grants are often the result of investigator-initiated competitive calls for disease-agnostic research proposals, with competition based on scientific excellence across common and RD, addressing disease mechanisms, natural history, trial readiness and clinical studies.

Multifaceted grants engaging multiple partners are frequently the result of mission-oriented annual or multi-annual competitive calls for high-impact research proposals in targeted clinical challenges/unmet needs that can be either disease-agnostic or RD-specific. Governments and public funders invest funds to support the research and technological basis of startups and SMEs in health research because these companies are often more innovative in early-stage research and development. They also represent governmental support for small businesses. Other initiatives provide grants to help startups and SMEs bring their innovations from technology readiness level (TRL) 5-8[24] and also provide direct dilutive funding (i.e., an exchange of partial ownership for equity in the company) for companies to transition from TRL 8 to TRL 9. Business loans, microfinancing, guarantees, and venture capital to SMEs are also offered.

Foundations and RD patient associations invest charity funds in grants to academic institutions to support basic research projects and translational preclinical studies. Many diseases increasingly see specific patient organizations/charities that initiate research into a dedicated disease. Advice on business and industrial know-how and support to innovation hubs may be supported.

RD foundations also support niche activities rarely funded by public funders, such as social science and humanities research for patients and families, and provide counseling and grant management support for patient advocacy organizations' specific scientific projects.

CONCLUSION

The funding landscape for RD research is wide-reaching, with a number of interested parties and decision points [Figure 1]. All investors need to address funding requirements like scientific quality, human resources, sustainability, and health economics upon articulation of their funding priorities and instruments. Decisions are made for mission-driven and economic factors that impact ROI. This includes consideration of which stage of product development is within the investor's expertise and based on the needs of the RD community. Despite the distinct institutional nature of each investor (public *vs.* private; non-profit *vs.* profit), there is no rigid separation between these factors. Investment strategies may involve partnerships between funders of different types, which are increasingly used because of shared risks and

Table 1. Knowledge gaps in the analysis of the RD funding scenario

Stakeholder interactions	Sustainability	Partnership impact
There is a gap in our knowledge of how researchers, funders, advocates, regulatory agencies, and policymakers interact in specific rare and ultra-rare diseases	Because of the high number of rare diseases, there is a gap in our knowledge of how costs at every stage of diagnostic and therapeutic development could be managed in a sustainable manner	The impact of partnerships between different interested parties in rare diseases is largely unknown

non-overlapping (or minimally overlapping) risk tolerance. The motivating factors and decision points partially overlap with those found by the IRDiRC Chrysalis Task Force[4]. This complex scenario reveals knowledge gaps [Table 1] to be addressed through targeted research. Taken together, funding becomes a catalyst for developments in economically challenging areas, turning unmet needs into opportunities. It is clear that people living with RD will benefit greatly from continued candid dialog and innovation in all respects between interested parties.

DECLARATIONS

Acknowledgments

The authors gratefully acknowledge the important participation and contributions of all the invited key opinion leaders for our online interviews: Yoshitsugu Aoki, National Centre of Neurology and Psychiatry, Japan; Christopher Austin, Flagship Pioneering, USA; Luca Benatti, Italian Angels for Biotech, Italy; Sam Blackman, Day One Biopharmaceuticals, USA; Jean-François Briand, AFM-Téléthon, France; Germano Carganico, Rare Partners, Italy; Pat Furlong, Parent Project Muscular Dystrophy, USA; Holm Graessner, Tübingen University, Germany; Florence Guillot, Agence Nationale de la Recerche, France; Barbara Handelin, The 90-10 Institute, USA; Joshua Henderson, Alexion Pharmaceuticals, Sweden; Emil Kakkis, Ultragenyx, USA; Peter Kolchinsky, RA Capital, USA; Kenjiro Kosaki, Keio University, Japan; Karl-Johan Myren, Alexion Pharmaceuticals, Sweden; Rieko Nakamura, Ministry of Health, Labour and Welfare, Japan; Irene Norstedt, European Commission, Belgium; Francesca Pasinelli, Fondazione Telethon, Italy; Damon Race, GeneVentiv Therapeutics, USA; Atsushi Unuma, Japan Agency for Medical Research and Development, Japan. The authors also thank Eileen Li, Chinese Organization for Rare Disorders, China, for her contributions. This manuscript was prepared by the authors in their personal capacity. The views and opinions expressed here are those of the authors and do not necessarily reflect the views, opinions, or positions of their employers, any subsidiary companies, or any government agency.

Authors' contributions

Proposed, developed, and led the related IRDiRC Funding Models for Rare Diseases Research Task Force, led the online interviews with the invited key opinion leaders, wrote multiple sections, and performed overall review, structuring, and editing of the manuscript: Monaco L, Hartman AL

Participated in the related IRDiRC Funding Models for Rare Diseases Research Task Force and contributed to its project management and coordination of the writing of the paper: Letinturier MCV

Are members of the IRDiRC Funding Models for Rare Diseases Research Task Force and contributed to the analysis of gaps and opportunities in rare disease research funding models, including running the interviews with invited key opinion leaders, and/or writing of the paper: Aketa N, Athanassiou D, el Hajjar J, Frost S, Granados A, Haight AR, Jonker AH, Kahn SR, Kang S, Kritikou P, Kyriakopoulou C, McMaster C, Parker S, Scherman D, Valentine N, Wiafe S

All authors read and approved the final manuscript.

Availability of data and materials
Not Applicable.

Financial support and sponsorship
The IRDiRC Funding Models Task Force was supported by the Scientific Secretariat of IRDiRC, funded by the European Union through the European Joint Programme on Rare Disease under the European Union's Horizon 2020 Research and Innovation Programme Grant Agreement N°825575. The Scientific Secretariat is hosted at the French National Institute of Health and Medical Research (INSERM) in Paris, France.

Conflicts of interest
Daniel Scherman is the editor-in-chief of *Rare Disease and Orphan Drugs Journal*, while the other authors have declared that there are no conflicts of interest.

Ethical approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

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