Copenhagen Economics

DEVELOPMENT OF NOVEL THERAPIES

How can Europe speed up development of therapies for the 95% of rare diseases with no authorised treatment?

Takeda
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Intended for EU Policy Stakeholders

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Executive summary

Today, a significant share of the rarest diseases lacks an approved treatment

Significant progress in the treatment of rare diseases has been made following the introduction of the OMP Regulation in 2000.[1] Today, approved treatments exist for around 5% of rare diseases. [2]

While this is a success, 95% of rare diseases remain without an authorised treatment.[1] The lack of authorised treatment mostly concerns the rarest diseases. In fact, 79% of rare disease patients suffer from 149 of the most prevalent rare diseases, with prevalence between 1 and 5 in 10,000.[3] Many of these diseases have an authorised treatment.[4] The challenge for the next two decades is continuing the positive path for all rare disease patients and developing treatments for those affected by the rarest diseases.

New technologies bring opportunities

Developing innovative medicines starts with science. Recent years' advances in gene therapy are particularly relevant for people living with a rare disease, with 71.9% of those being genetic and 69.9% with exclusively paediatric onset.[5] This has opened opportunities to treat, possibly cure, people living with rare diseases that previously were left without hope of improving their health status. This is promising but it comes with challenges.

But development times are inherently long

One key feature of these rare diseases is the small patient population. This means that fewer people with a rare disease can participate in clinical trials and contribute to the generation of data on clinical outcomes. The risk of failed trials increases.[6] In fact, just 1 in 10 phase 1 clinical trials for all medicines will eventually lead an approved medicine.[7] While still contributing to advancing knowledge on rare diseases, the remaining 9 failed clinical trials represent a lost opportunity to utilise scarce resources for clinical research.

Furthermore, with fewer patients the statistical power of clinical trial data decreases, which may reduce the relevance of the data in the eyes of regulatory authorities, HTA bodies and payers. Such data challenges will often lead to long development times because OMP developers need to produce additional data or change the trial design. An example is of an OMP, the first to treat a particular rare disease, that obtained Marketing Authorisation in 2022, 23 years after the first clinical trial was initiated.[8]

Developing a successful treatment, including for the rarest diseases where no authorised treatment exists, takes time and resources. While more resources are necessarily required to address unmet needs, there is a potential to speed up development through new ways of working together along the OMP development path from basic research to market authorisation.

Partnerships is the key concept

Partnerships is likely to be the most impactful concept to speed up the development of innovative medicines. Finetuning existing incentives within the legislative framework is needed but not sufficient. Instead, partnerships can move the needle towards treating all people living with a rare disease.

Traditionally, medicine development and approval have been characterised by a developer-approver relationship that is based on bilateral incentives and a transactional approach. It has worked well for the past 20 years, incentivising OMP developers through e.g. Orphan Market Exclusivity and Orphan Drug Designation. However, if we are to bring innovative medicines to those living with the rarest diseases faster, a more collaborative approach is needed. This is because as the complexity of medicines development grows, so does the impact of the actions of one party on the other party. Hence, a transactional approach will yield inferior outcomes, which in this context means lengthier and costlier development to the detriment of all involved.

The opposite model is one of partnerships. EMA, HTA bodies, payers, OMP developers and patients must approach each other with a common problem-solving mindset aiming to bring effective treatments faster through clinical trials, authorisation and HTA processes. For example, this can mean re-organising their procedures concerning data requirements. If such procedures were imbued with common problem solving and the intention to bridge the gap between data requirements and the data that can be collected, development times could be shortened.[9]

For faster innovative medicines development, we have identified two crucial partnerships:

Public-private partnership for basic research

The lack of basic research is a key barrier to development for the rarest diseases.[9] Boosting basic research requires more and smarter funding that leverages data and the integration of research communities across Europe. This ensures more effective and targeted research for every euro spent. An effective solution would therefore be a Private Public Partnership (PPP) fund focused on rare diseases to boost funding of basic research in underserved areas integrating learnings from platforms such as IMI, IHI and the European Joint Programme on Rare Diseases. Here, European Reference Networks (ERNs) have the potential of becoming an important platform.

Evidence partnership for better trial design

Another key barrier to innovation in rare diseases is the lack of clarity on requirements for the evidence needed to obtain approval by regulators and to demonstrate value with HTA bodies.[9] Early, iterative dialogues between developers, EMA, HTA bodies and payers that follow a partnership logic will allow making feasible plans for the evidence required early on, therefore informing a more efficient clinical development. In such a framework, adaptive pathways can support faster access to treatment by accelerating patient recruitment. Similarly, digital solutions can allow for the inclusion of more outcomes and continuous monitoring.

Notes: 1) European Commission (1999) / 2) European Commission (2020) / 3) 79% (mid-point between 77.3% and 80.7%) of rare disease patients suffer from 149 of the most prevalent diseases, with prevalence between 1 and 5 in 10,000, see Wakap et al. (2020) / 4) Out of the 142 EMA approved OMPs by 2017, 43% (61) are indicated for a rare disease with prevalence between 1 and 5 in 10,000, see European Commission (2000). The number of rare diseases covered might be lower since more than one OMP could be approved for the same indication. / 5) Wakap et al (2020) / 6) Aartsma-Rus et al (2021)/ 7) Sun et al. (2022) / 8) Marketing authorization was granted in 2022, clinical trials were initiated in 1999, see EMA, Link , and clinicaltrial.gov link. The first clinical trials concerned a different indication, see page 11 / 9) Aartsma-Rus et al. (2021)

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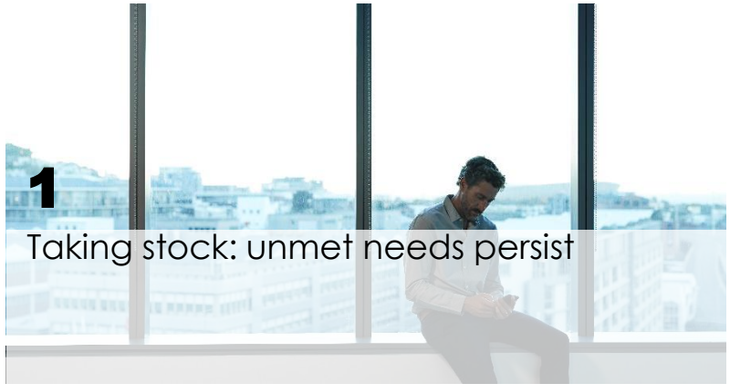


1
TAKING STOCK: unmet needs persist

People living with a rare disease are better off today than 20 years ago but unmet needs persist

Developing and bringing to the market medicinal products for rare diseases – Orphan Medicinal Products (OMPs) – is of crucial importance. While each rare disease affects a small number of individuals – no more than 5 in 10,000 in Europe[1] – they collectively represent a common health issue. In fact, current estimates indicate that 30 million EU citizens may be living with a rare disease.[2] This means that 1 in 17 individuals in the European Union suffers from one of the approximately 6,000[3] debilitating rare diseases.[4]

Rare disease treatment has improved drastically in the past 20 years

Today, the outlook for people living with a rare disease in Europe is more promising than it was two decades ago.

Following the introduction of the OMP Regulation,[3] R&D activities have intensified, leading to a significant number of orphan designations applications and orphan designations being granted, see Figure 1 and Figure 2.

These R&D activities ultimately lead to new OMPs becoming available to patients. In fact, the number of OMPs authorized by the EMA has increased from just three in 2001 to around 200 today, see Figure 2. In addition, rare diseases have received increased societal recognition of the existence of unmet needs and heightened clinical awareness.

Together with the involvement of key stakeholders, people living with a rare disease and researchers, the increase in the number of OMP-focused companies has supported the rise in development. In the year 2001, only three pharmaceutical companies had orphan-designated authorised products on the market. Since then, more than 120 unique sponsors have received marketing authorisation for OMPs in Europe[5].

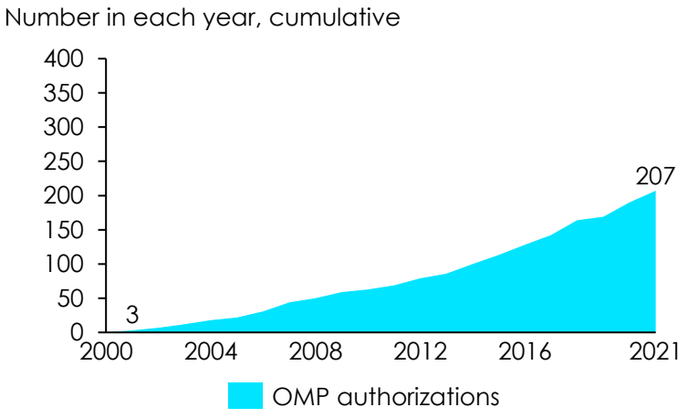
Lack of authorized treatment persists, especially for the rarest diseases

Despite the progress, unmet needs have been identified along different dimensions.[6] One of these is lack of authorized treatment.

In fact, 95% of known rare diseases remain without an authorised treatment.[7] However, this does not mean that the vast majority of rare disease patients still lack an authorised treatment. Many authorized OMPs are indicated for the most prevalent rare diseases, which affect a large share of rare disease patients. Roughly 80% of rare disease patients suffer from 149 of the most prevalent rare diseases, with prevalence between 1 and 5 in 10,000.[8] Many of these diseases have an authorised treatment[9].

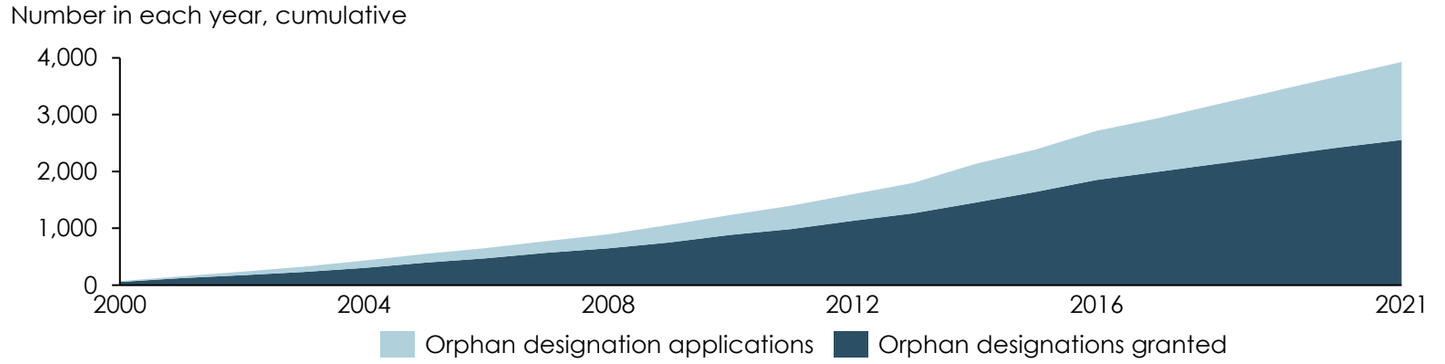
This means that the lack of authorized treatment mostly concerns the rarest diseases that affect few patients across Europe. Developing and bringing to the market treatments for all rare disease patients requires tackling areas where research and development is particularly difficult due to the extremely low number of affected patients.

Figure 2. OMPs authorized by the EMA



Source: Copenhagen Economics based on European Commission (2020); European Medicines Agency (2021a); European Medicines Agency (2021b).

Figure 1. Applications and designations granted by the EMA



Source: Copenhagen Economics based on European Commission (2020); European Medicines Agency (2021a); European Medicines Agency (2021b).

Notes: 1) European Commission (1999), article 3, recital 1(a) / 2) Wakap, et al. (2020). / 3) EURORDIS website, see liNnk, / 4) Zanello et al (2022) / 5) EURORDIS website, see link / 6) Copenhagen Economics (2021) 7) European Commission (2020) / 8) 79% (mid-point between 77.3% and 80.7%) of rare disease patients suffer from 149 (4.2% of rare diseases) of the most prevalent diseases, with prevalence between 1 and 5 in 10,000, see Wakap et al. (2020). Note that prevalence information was available for 3585 or the 6172 rare diseases. / 9) The number of rare diseases covered by the approved OMPs might be lower than the number of approved OMPs since more than one OMP could be approved for the same indication. For instance, the number of rare diseases with prevalence between 1 and 5 in 10,000 could be lower than 61 (the number of approved OMPs indicated for a rare disease with prevalence between 1 and 5 in 10,000) because more than 1 OMP might be approved the same indication, see European Commission (2020).

2

CHALLENGES: clinical development is a resource-intensive and long process

Clinical development in the OMP space is challenging for patients and investigators

Significant resources are needed to develop OMPs

The clinical development of a medicine and the process of bringing it to market and patients is a challenging endeavor, see Figure 3.

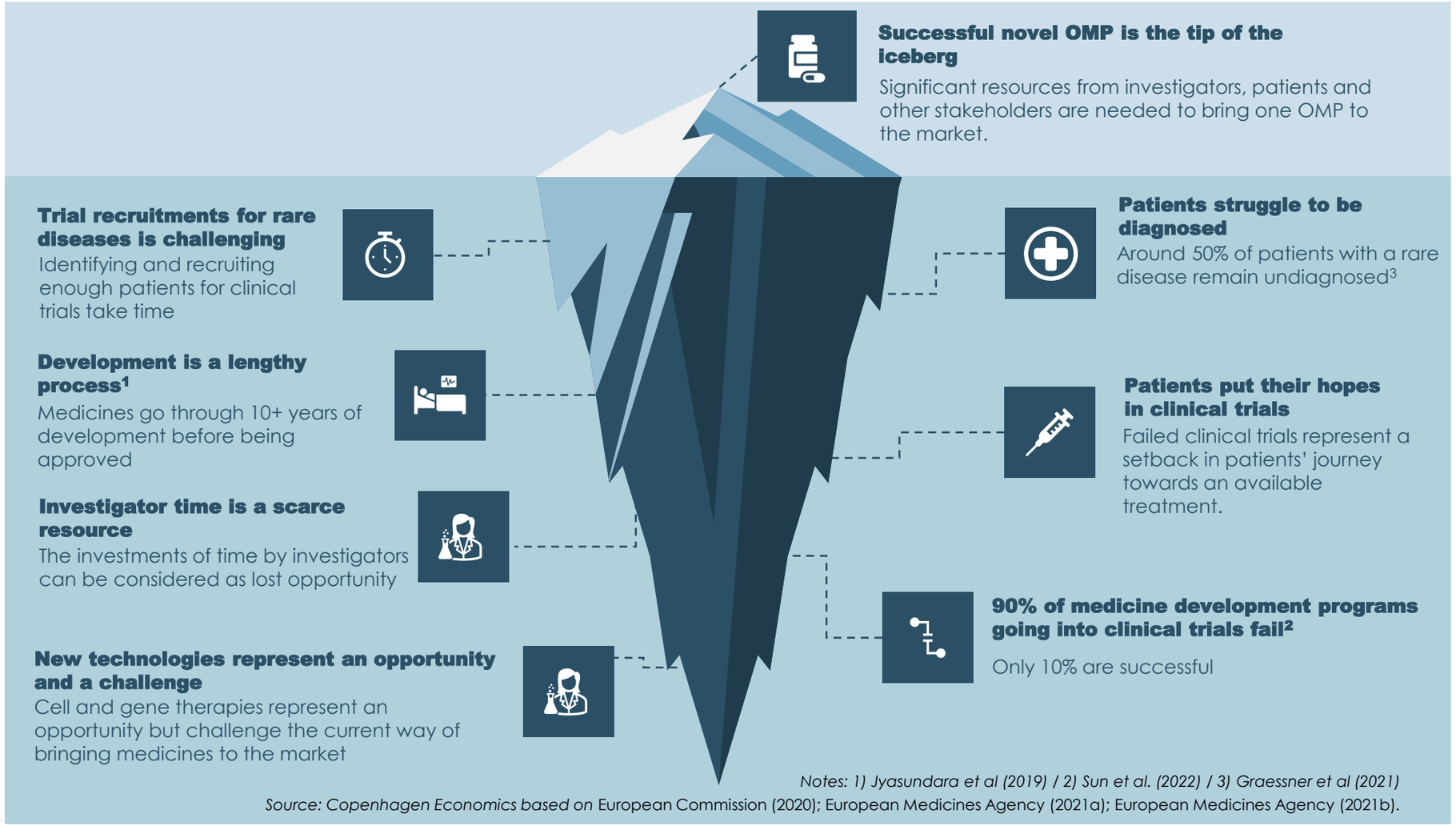
A medicine development program requires significant resources from all the many stakeholders involved, takes a long time and carries a high risk of failure.[1]

From the perspective of patients and caregivers, living with a rare disease imposes a significant burden.[2] Failed clinical trials can represent a setback on their journey towards receiving treatment. On the one hand, failed clinical trials are still a step towards improving knowledge of the disease. On the other hand, they push forward in time the moment when a treatment will be available.

Developing a treatment for the rarest of diseases is even more challenging due to, for instance, the small and dispersed patient population,[3] the little available basic research. [3]

In the following pages, we describe more in detail these key challenges.

Figure 3. A successful medicine development program for an OMP is just the tip of the iceberg



Notes: 1) Jyasundara et al (2019) / 2) Sun et al. (2022) / 3) Graessner et al (2021)

Source: Copenhagen Economics based on European Commission (2020); European Medicines Agency (2021a); European Medicines Agency (2021b).

Notes: 1) Aartsma-Ru et al (2021), Jyasundara et al (2019) and Wouters et al. (2020) / 2) See for instance EURORDIS (2017a). / 3) Aartsma-Rus et al (2021)

Many resources go into clinical trials for medicine candidates that ultimately fail

OMP developers invest time and resources in multiple trials, with a high risk of failure

From the perspective of an investigator, OMP developer or investor with a portfolio of novel therapies under development, 9 failed development programs across different diseases stand next to one successful medicine, see Figure 5.

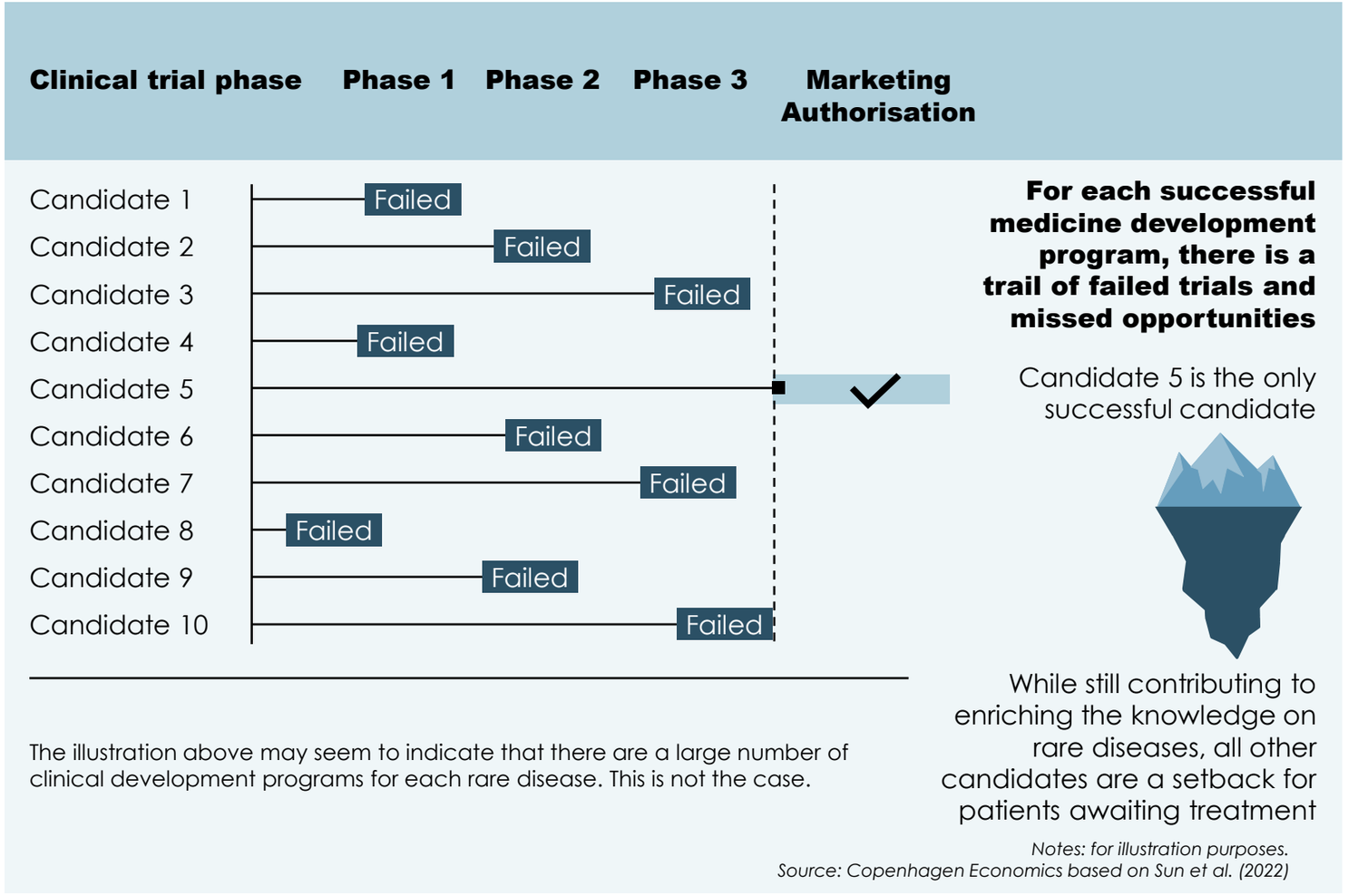
In addition, significant activities on drug discovery and pre-clinical research are required even before a candidate reaches phase 1 clinical trials. It is estimated that 80 to 90% of research projects fail before reaching clinical trials.[1]

Once a candidate reaches phase 1, the average success rate in receiving a marketing authorization is approximately 1/10, see Figure 4. This means that on average, out of 10 candidates that reach phase 1 across different diseases, only one will succeed and receive a marketing authorization. Many resources were employed in the 9 failed clinical trial candidates, not only from OMP developers. Clinical trials require a mix of healthy volunteers and patients, qualified research centres, training for clinicians, and specialized laboratories. These are just a few components of the complex ecosystem that is required to conduct clinical trials.

Many failed clinical trials represent a setback for patients

Living with a rare disease puts a significant burden on patients and their caregivers.[2] For a disease with no known treatment, OMP development programs represent a hope of improved quality of life for these patients. Failed clinical trials still contribute to advancing the knowledge of the disease and the hope for treatment in the future. At the same time, they do represent a setback for patients enrolled in the trials and currently awaiting treatment.

Figure 4. Only 1 in 10 phase 1 clinical trials will eventually lead an approved medicine



Notes: for illustration purposes.
Source: Copenhagen Economics based on Sun et al. (2022)

Notes:1) Seyhan, A.A. (2019) / 2) See for instance EURORDIS (2017).

Even when successful, clinical development of a breakthrough treatment is a lengthy process

Developing a breakthrough treatment takes a long time

One of the challenges for the development of medicines is the time it takes for the development. OMP developers face many challenges that increase the development time. For instance, trial amendments (50% of all rare disease clinical trials are amended[1]) and identifying and recruiting enough patients are two examples.

Previous studies found that it takes on average 12.3 years from the time of patent filing to the time of regulatory approval for OMPs.[2] This time goes up to 15.1 years when concentrating on first-in-class OMPs, i.e. OMPs representing the first treatment approved for a given indication.[3]

Based on a sample of 9 OMP cell and gene therapies approved by the EMA, we find that it takes on average over 14 years from patent filing to regulatory approval.[4]

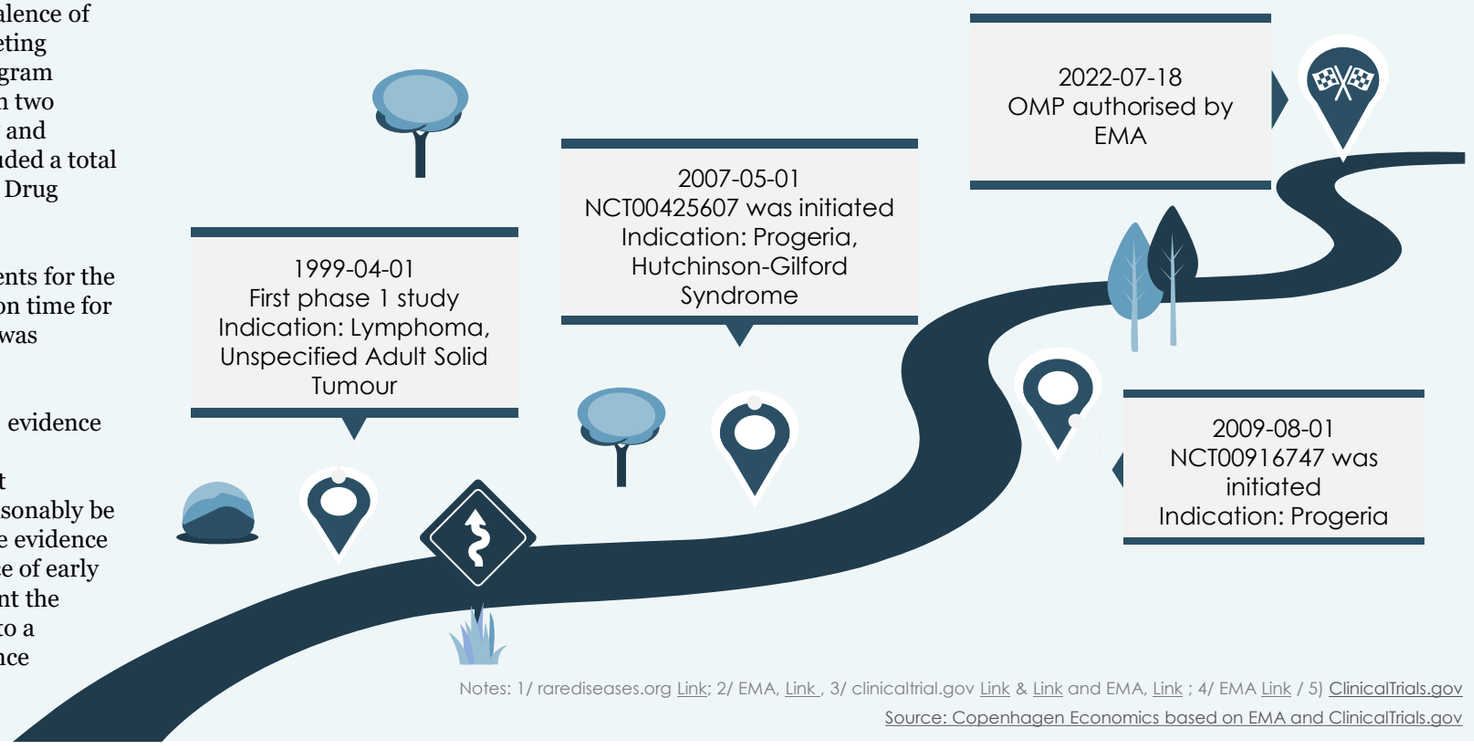
In some cases, development times may be even longer. For instance, the development of an innovative OMP, approved for an ultra-rare disease, took more than 20 years, see Figure 5. Such long development times are not unique and represent lost time for patients awaiting treatment.

Figure 5. The development program for an innovative OMP has taken more than 20 years

Hutchinson-Gilford progeria syndrome is a disease with only prevalence of approximately 1 in 20 million.[1] The new medicine received a Marketing Authorisation by the EMA on 18 July 2022.[2] The development program included 35 phase I, II, and III studies.[9] The approval was based on two studies on Hutchinson-Gilford progeria syndrome (NCT00425607 and NCT00916747). These two studies were initiated in 2009 and included a total of 29 and 85 patients, respectively.[3] The OMP obtained an Orphan Drug Designation on 14 December 2018.[4]

This example highlights one of the challenge of developing treatments for the rarest diseases namely long evaluation times. The longest evaluation time for a patient included in the two studies was 11 years.[2] The first study was initiated in 1999 and the last initiated study was in 2021.[5]

In addition, it highlights the challenge of collecting comprehensive evidence in the case of the rarest diseases. The EMA granted a marketing authorization under 'exceptional circumstances'.[2] This is because it recognized that the disease is so rare that the developer cannot reasonably be expected to provide comprehensive evidence. At the same time, the evidence collected showed a positive risk-benefit balance and the importance of early initiation of the treatment after diagnosis. This led the EMA to grant the marketing authorization under exceptional circumstances subject to a number of post-authorization obligations such as additional evidence collection.[2]



Notes: 1/ rarediseases.org Link; 2/ EMA, Link , 3/ clinicaltrial.gov Link & Link and EMA, Link ; 4/ EMA Link / 5) ClinicalTrials.gov

Source: Copenhagen Economics based on EMA and ClinicalTrials.gov

Notes: 1/ ICON (2022b) based on Tufts CSDD Impact Report (Jan/Feb 2022); 2/ Jayasundara et al (2019) 3/ Tufts Center for the Study of Drug Development (2018), based on US approvals; 4/ CE's calculation based on data from GlobalData. Drug development time is calculated following the methodology commonly used in the literature: we calculate the difference between application date of constraining patent in the EU and the date of the first EMA marketing authorisation for a given treatment. All cell and gene therapies for which information was available were included in the analysis. These were all approved by the EMA after 2017.

Gene therapies represent an opportunity for people living with a rare disease but clinical development faces significant challenges

Gene therapies contain genes that lead to a therapeutic, prophylactic or diagnostic effect by inserting 'recombinant' genes into the body, to treat a variety of diseases, e.g. cancer, genetic diseases, and infectious diseases.[1] These new technologies open up possibilities to develop innovative treatments for rare diseases. This is promising from a patient standpoint, but it comes with a unique set of challenges. For instance, animal models are often not suitable for pre-clinical studies [2] This means that preclinical studies are often limited, the first-in-human studies are performed on the target population and safety needs to be assessed without access to healthy volunteers.[2]

The pipeline for gene therapies has grown in the past years. In Q1 2022, there were 498 gene therapies in phase I and II, compared to 16 in phase III and in pre-registration.[3]

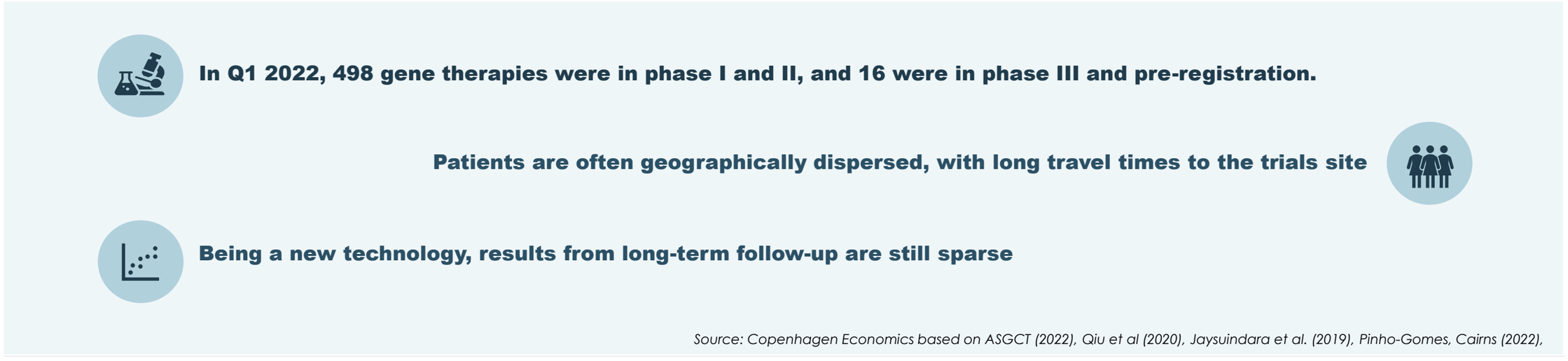
When conducting gene therapy clinical trials, three challenges arise when the diseases targeted are rare.

First, patient recruitment in clinical trials is challenging, costly, and time-consuming due to the small but geographically dispersed group of patients.[4] For some gene therapy clinical trials, patients often experience long travel times to the trials site.[5] Furthermore, identifying relevant patient populations may take a long time. To reduce the trial duration, the identification of patients through registries can be beneficial.[6] However, this is not possible in most disease areas as such registries do not exist.

Second, as the area is still relatively new, long-term follow-up results are still sparse.[7] Long-term follow-ups are important as both the EMA, HTA bodies, payers, patients, and developers require knowledge of the long-term efficacy and safety of the medicine. However, the lack of long-term results is not a hinder to a (conditional) approval of the medicine, and it may therefore enter the market despite the lack of long-term follow-up results. The better the alignment on data requirements between the different stakeholders, the faster an effective treatment meeting an unmet need can be made available to patients.

Third, to increase the speed towards approval, the trial design must be optimal from day one. To ensure this, EMA, HTA bodies and payers, patients and OMP developers should be included as early as possible to align on data requirements. The inclusion of several parties in the design of the clinical trial calls for partnerships across the board of parties.

Figure 6. Facts on gene therapy clinical trials



Source: Copenhagen Economics based on ASGCT (2022), Qiu et al (2020), Jaysuindara et al. (2019), Pinho-Gomes, Cairns (2022),

Notes: 1/ EMA see link/ 2) ICON (2022a) / 3)ASGCT (2022) / 4) Jayasundara et al. (2019) / 5) Qiu et al (2020) / 6) Boulanger et al (2020) / 7) Pinho-Gomes, Cairns (2022),

3 WAY FORWARD: partnerships for better patient outcomes

There is a trade-off between the rate of innovation and resources invested

There is an inherent trade-off between rate of innovation and resources employed

If the rate of innovation is to be accelerated to tackle the 95% of rare diseases without a treatment, a higher level of resource such as patient time in trials, qualified research centres, specialized labs is required. Illustrated in Figure 7 on the right, accelerating the rate of innovation happens along the current 'regulation' line, e.g., by moving from point A to point B, which is associated with higher usage of resources. More resources allocated to innovation will lead to a higher rate of innovation implying more authorised treatments. But the many failed trials and long development processes driven by e.g. small patient populations and the uncertainty of data inherent in small patient populations imply that much time and many resources are needed for even a limited number of new treatments. Hence, in the current environment, it will difficult to ease this trade-off. A higher rate of innovation requires a significantly higher level of resources by investigators, medicine developers patients. Reducing resources will decrease the rate of innovation. At the same time, policy makers, such as the European Commission, have the ambition to provide treatments for the remaining 95% of rare diseases without an authorised treatment *while* curbing pharmaceutical spending.[1]

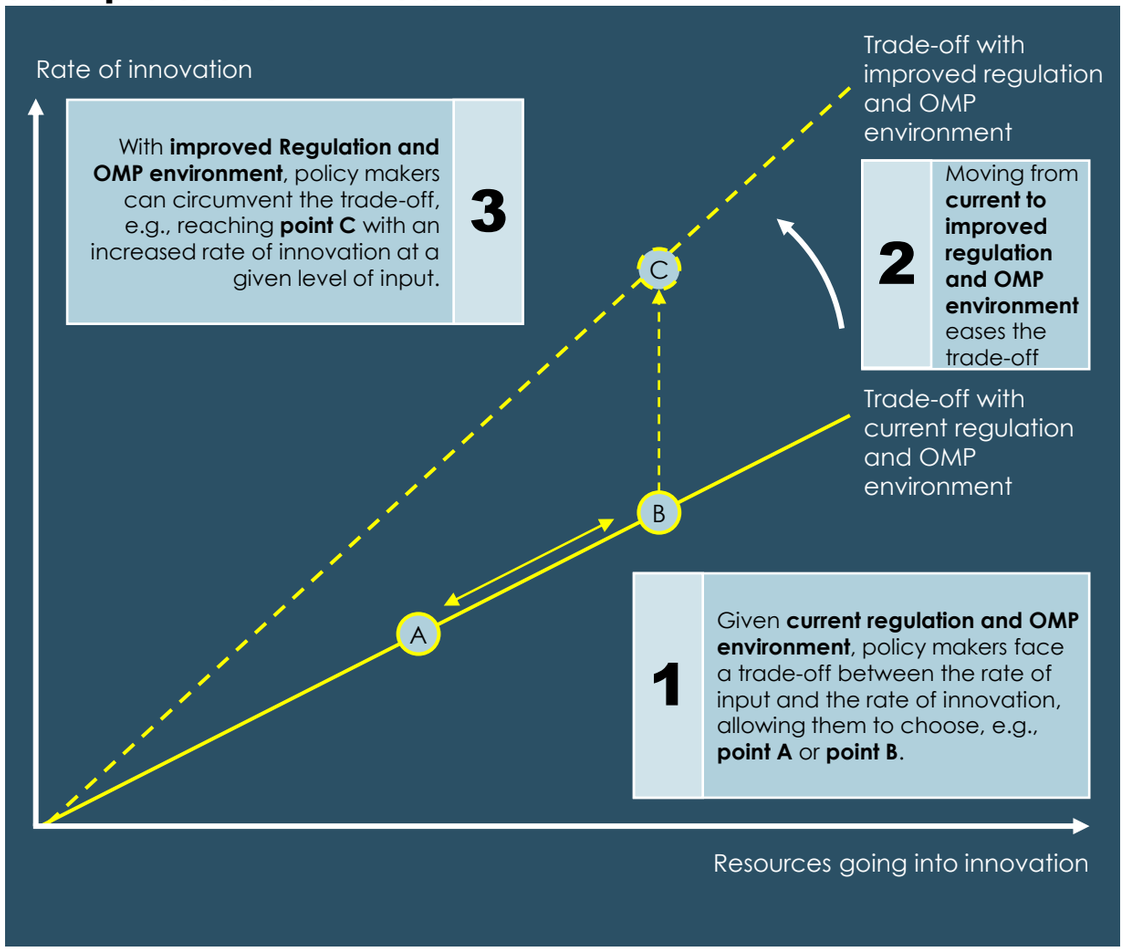
But this trade-off can be manipulated to speed up development

The current trade-off between the rate of innovation and resource needs reflects the world as it is. It is rooted in incentives such as Market Exclusivity and Orphan Drug Designation that has proven effective for getting more than 200 OMPs on the European market the past 20 years.[2] However, what worked in the past will not work in the future to tackle the rarest diseases.

With more complex technologies, sparse basic and translational research and longer development times, it is necessary to align all contributing parties around the same goal and with a common problem solving mindset. While this does not dissolve the relationship between rate of innovation and resource deployed, it holds the promise of accelerating pharmaceutical innovation for a given level of resources.

> Improving this trade-off can create a win-win-win situation for patients, healthcare sectors, and the pharmaceutical industry alike. It is not a zero-sum game: no one is worse off if we create the trust and work more efficiently together towards agreed goals

Figure 7. Circumventing the trade-off between the rate of innovation and input factors for innovation



Source: Copenhagen Economics

Notes: 1) European Commission (2021a) / 2) European Commission (2020)

Effective solutions require a partnership approach

Incentives within the legislative framework are needed but not sufficient

The current incentive system, relying on market exclusivity as the key incentive, has not spurred sufficient development for the rarest diseases.[1] Tweaking these incentives at the margin is not likely to be sufficient as it leaves major barriers in the ecosystem around bringing new therapies to patients untouched. For instance, additional market exclusivity years is a particularly useful tool when the developer is fairly knowledgeable about the inherent risks throughout the development value chain including what it takes to obtain the market authorisation and for HTA bodies and payers to recommend and reimburse the medicine. That is, however, rarely the case for treatments addressing the rarest diseases. In many cases basic and translational research is insufficient. Or the unknows cumulate through the lifecycle from translational up to HTA and payers' recommendation and reimbursement to an extent that length of protection is not a relevant mitigating tool. Hence, a small change in years of market exclusivity will not on its own be an effective tool to address the barriers to developing treatments for the rarest diseases.

Therefore, policy solutions need to go beyond the known tool of market exclusivity to direct investments towards the rarest diseases without authorised treatments.

Effective solutions require partnerships as an integral part of the OMP lifecycle

As we have previously highlighted,[2] most of the barriers along the OMP lifecycle seem to emerge in the interplay between two or more actors often with markedly different success criteria. This is also the case for basic research, clinical development and approval. As a result, the type of solution that will prove effective going forward completely changes. Effective solutions must bring several actors around one table, with a shared goal. Effective solutions therefore require partnerships.

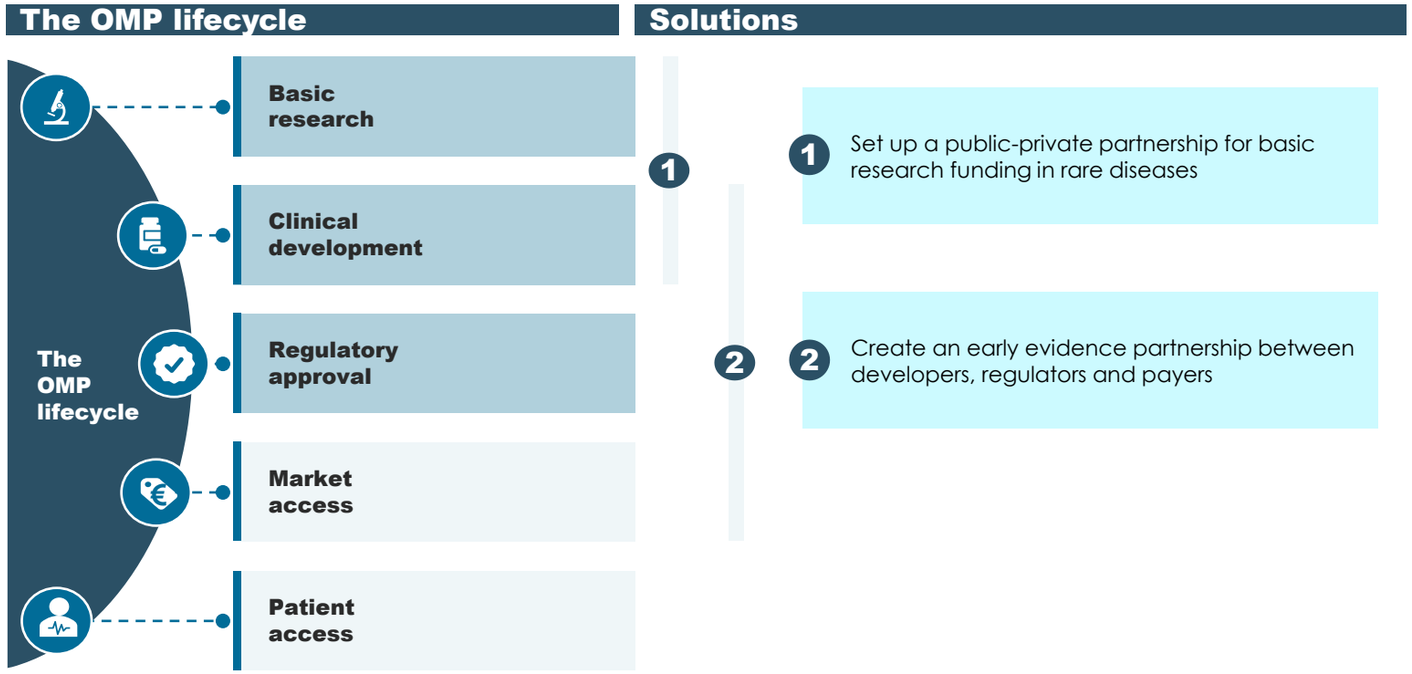
Partnerships are driven by the prospect of greater value creation for the individual party than an individual actor would be able to create alone. They are more complex to set up and maintain but have the potential to generate high impact. Partnerships are necessary to drive speedier innovation of treatments for the rarest diseases without authorised treatment.

Focusing on medicine development and approval, we have identified the following two partnership models, see Figure 8:

1. A public-private partnership for basic research funding in rare diseases
2. Early evidence partnership between developers, regulators and payers.

We describe these two partnerships and how they will support more efficient development of OMPs on the next pages.

Figure 8. Partnership-based solutions for more effective medicine development



Source: Copenhagen Economics (2021).

Notes: 1) European Commission (2020) / 2) Copenhagen Economics (2021)

Public-private partnership for basic research funding

Funding and collaboration for basic research are key pillars in addressing the rarest diseases

Basic research is the starting point of all OMP development and its funding is an important fuel to the European OMP ecosystem. Without basic research, there can be no clinical development, as OMP developers depart from it to investigate and develop targeted and novel treatments. The lack of (translational) basic research is an important explanation for lack of authorised treatments for the rarest diseases.[1] Basic research may not exist at all in a given disease area, or, if it exists, it is insufficiently evolved to be ready for OMP developers to take it up into clinical development.[1]

The scarcity and fragmentation of expertise in rare diseases makes basic research a prime example of an area that profits from increased scale by lifting both funding and collaboration to a European level.

Only a small number of European countries have funded research on rare diseases through very dedicated programmes[2]. The EU has supported these efforts in the rare disease field with more than EUR 2.4 billion attributed to over 800 research and innovation projects, the majority of which are collaborative.[3] Currently, the European Joint Programme for Rare Diseases (EJP RD), running until 2023, leads the most systematic and coordinated funding efforts for rare diseases basic research in Europe.[4] Moreover, programmes like the E-Rare Consortium[5] have enabled the collaboration of national funding organisations.

In addition to funding, research collaboration also benefits from scale. Today, the European Reference Networks (ERNs), adopted in 2017, have established a base infrastructure for pan-European collaboration in rare disease research and diagnosis. However, there are still some recognised issues with the ERN infrastructure, mostly concerning lack of legal basis and member state involvement, that challenge its sustainability and full use. Outside of the ERNs, rare disease knowledge and data still predominantly sit within geographically dispersed and disconnected research programs, disease specialists, and small biotech companies - and within different, non-standardised databases.[6] This makes it difficult to share and leverage existing resources in a systematic way, which leads to delays in for instance diagnosis and patient recruitment for clinical trials. Moreover, it is currently not possible for actors to have an overview of where research and development is already taking place and what areas remain unaddressed. Several Europe-wide initiatives aim at overcoming these challenges - one noteworthy example being the FAIR Virtual Platform,[7] driven by the EJP RD.

Fostering basic research requires larger scale and smarter funding

If Europe's ambition is to develop better treatments for people living with rare diseases, it needs to foster basic science in the areas where currently none or only insufficient basic research exists.

This requires two changes. First, Europe has to increase funding in this area. Without an increase in the level of funding, more basic research is not achievable. Second, Europe has to fund basic research in a "smart" and efficient way by leveraging data and the integration of research communities. This needs to be paired with more coordination of funding efforts, strategically directing funding into underserved areas and introducing more guidance and conditionality to achieve development-ready research.

Smart funding of rare disease basic research requires a high level of coordination, collaboration and sharing of resources. This requires all key stakeholders involved in basic research and development to play their part.

What next?

While a level of alignment and willingness to collaborate towards the goal of bringing treatments to all patients with a rare disease exists (see e.g. the Rare Disease Moonshot)[8], Europe should strive to organise rare disease funding for basic research in a single Public Private Partnership (PPP) funding entity, including joint financial and in-kind contributions of both public and private funders. This fund should rely on a European collaborative data infrastructure that connects today's scattered research communities in rare diseases on one network. Here, the ERNs have the potential of becoming an important platform and infrastructure.

The fund should target previously underserved disease areas following clear and transparent rules and continuously evaluate progress in order to re-allocate funds from those making less progress to those making more progress. Using the data infrastructure, funding can address disease areas with positive externalities, where results in one disease can be used to advance insights into another. This allows for exploiting both scale and scope of a data network.

Such a partnership has the potential to:

- Overcome fragmentation by creating a central overview and coordination of all European rare disease funding efforts,
- Flexibly direct funding in areas of most unmet need
- Make funding conditional on commonly set outcomes
- Overall, allow more effective research for every EURO spent.

This PPP for basic research funding could also spur the development of a broader PPP for basic research such as the Shonan Health Innovation Park, see next page.

Notes: 1) Aartsma-rus et al. (2021) / 2) CORDIS (2022)/ 3) European Commission (2021b) / 4) EJP RD (2023). See link / 5)ERA-LEARN (2022) / 6) Kodra et al (2018) / 7) EJP RD (2023). See link / 8) See EFPIA EURORDIS Joint Statement (2022)

Box 1. The Shonan Health Innovation Park as a powerful partnership for innovation step-changes

In 2018, Takeda transformed its Shonan Research Centre in Fujisawa City, Japan, to the **Shonan Health Innovation Park** (Shonan iPark) in an effort to establish a life science ecosystem open to the world. Bringing researchers, industry, venture start-ups, government and academia together, this initiative aims to form a true co-location ecosystem for collaboration and co-creation, resulting in the incubation and acceleration of research and transformation of cutting-edge science into impactful health solutions for patients around the world.

Today, bringing innovative medicines to the market is becoming increasingly difficult and there is a growing disconnect between the translation of basic science and technologies into applications for patients. The Shonan iPark aspires to overcome these challenges by forging partnerships in health innovation and commercialisation, where partners can optimise each others' technologies, expertise and resources through inter-business, interdisciplinary and international collaboration. Shonan iPark has already achieved a number of scientific and business milestones, including for instance an international partnership with National Horizons Centre in England and the launch of a new market access pathway in Japan for pioneering life sciences companies.

Since 2018, Shonan iPark has grown to more than 2,000 employees from over 110 partners. Takeda has signed its ownership rights to the Shonan iPark trust and currently engages in the partnership as a flagship tenant, committing to leading the development of the ecosystem.

Shonan iPark: ecosystem of inter-business, interdisciplinary and international collaboration

Sources: Takeda (2020) and Shonan iPark (2022)

Early evidence partnership between developers, regulators and payers

Lack of clarity early on concerning evidentiary requirements from regulators and HTA bodies/payers contributes to inefficiencies and failures

One of the single most important challenges for bringing innovative medicines to the market and innovating in areas where little R&D takes place is to collect the right type of evidence that can support success both at the regulatory stage (supporting positive risk/ benefit balance and significant benefit) and the market access stage (demonstrate value added to payers). This is particularly the case for the rarest diseases where the small patient population challenges the feasibility of the standard randomised control trial (RCT) set up. The following challenges can be observed across Europe:

First, evidentiary requirements differ between regulators and HTA/payers across Europe. In particular, across Europe, we observe a disconnect between the decision taken at the regulatory stage (e.g. where an OMP is considered to bring significant benefit or received conditional marketing authorisation) and the market access stage where that same benefit is not recognised or the evidence is deemed too uncertain.[1] These differences make navigating the European regulatory and access pathways more cumbersome, resource-intensive and often less efficient.

Second, the lack of clarity on the evidentiary requirements for stages early on in the development process drives high uncertainty and longer development and market access times.[2] Failing to agree on required evidence early can also cause (partial) failure of market access when HTA/payers requirements do not accept the evidence collected to obtain regulatory approval. This issue likely particularly concerns new treatments (new class of products, mechanisms of action, or gene therapy) whereby regulators and payers have to determine afresh which evidence should be considered.

Third, the issue for many OMPs is one of timing; the data to further improve the evidence base for efficacy, safety and relative clinical and economic value can only be collected once the medicine is delivered to patients[3], through patient registries. This means that decision-making processes both on approval and pricing and reimbursement need to become more dynamic, taking into account new evidence instead of one-off decisions based on a complete ex-ante evidence base.

Early and iterative dialogues on evidence requirements are needed

If Europe wants to drive more development of treatment for the rarest diseases, the hurdle of evidentiary requirements is a key one to tackle. The challenge is to re-think and co-design the OMP development pathway such that the right kind of dialogues happen with the right stakeholders at a sufficiently early stage to agree on a feasible pathway for evidence generation.

The improvement of clarity on the evidence base for different decision points requires all stakeholders (developer, EMA, HTA bodies payers) to engage in a dialogue that starts early (in time for clinical trial design) and continues as the OMP makes it through the lifecycle. Importantly, the patient perspective needs to be integrated throughout[3]. Such an early dialogue should support evidence development for the different decision-points along the OMP lifecycle.

Early dialogues therefore have the potential to increase efficiency of development, predictability of the approval and subsequent reimbursement processes, and overall lower the failure rate.[1]

In such a framework, adaptive pathways can support faster access to treatment by accelerating patient recruitment and the use of more flexible clinical outcomes. Similarly, digital solutions can be utilised to allow for the inclusion of more outcomes and continuous monitoring. We discuss these in the next pages.

What next?

EU policy makers should develop a forum for an early evidence partnership between regulators, HTA/payers and OMP developers. Such a forum should build on current formats such as PRIME, Impact HTA and EMA-EUnetHTA parallel consultation. Recent experience on the EMA-EUnetHTA pilot demonstrates the usefulness of this type of parallel advice. It also points, among other things, to the need for

- A sustainable financial framework increasing capacity to meet demand from developers
- Clear documentation of advice in a single document that is reused at different decision-points
- The need to involve all relevant stakeholders in a structured manner, especially payers.

Importantly, such a forum should go beyond a dialogue-format to include a partnership logic that aims at delivering tangible results for all involved. In practice, the outcome of these partnerships should be a development plan based on agreements on (i) relevant endpoints, (ii) the type of data (including RWE) that should be collected and how, (iii) the points at which different types of evidence can be expected and what that may mean for dynamic decision-making and the subsequent regulatory and market access pathway (e.g. conditional marketing authorisation, conditional reimbursement, the use of innovative payment models). The starting point for these discussions should be patients' needs and perspectives such that what is measured and assessed reflects what matters to patients and their experience.[4]

Notes: 1) EURORDIS (2017b) / 2) Aartsma-rus et al. (2021) / 3) Moseley et al (2020) / 4) Copenhagen Economics (2021).

Adaptive pathways can provide faster access to treatment for patients by accelerating patient recruitment and the use of more flexible clinical outcomes

Adaptive pathways is a scientific concept for medicine development and data generation which allows for early and progressive patient access to a medicine.[1] Through iterative phases of evidence gathering followed by regulatory evaluation and license adaptation, adaptive pathways seek to maximize the positive impact of new treatments on public health by balancing timely access for patients with the need to provide adequate evolving information on benefits and harms.[2]

The advantages of adaptive pathways lies in appropriate prospective planning that allows to avoid inefficiencies. They allow to incorporate multiple stakeholders' requirements upfront to avoid the need to request additional studies later in development, and they allow to exploit the full potential of utilising the real-world evidence generated in clinical practice to refine decisions by regulators and other stakeholders.[2]

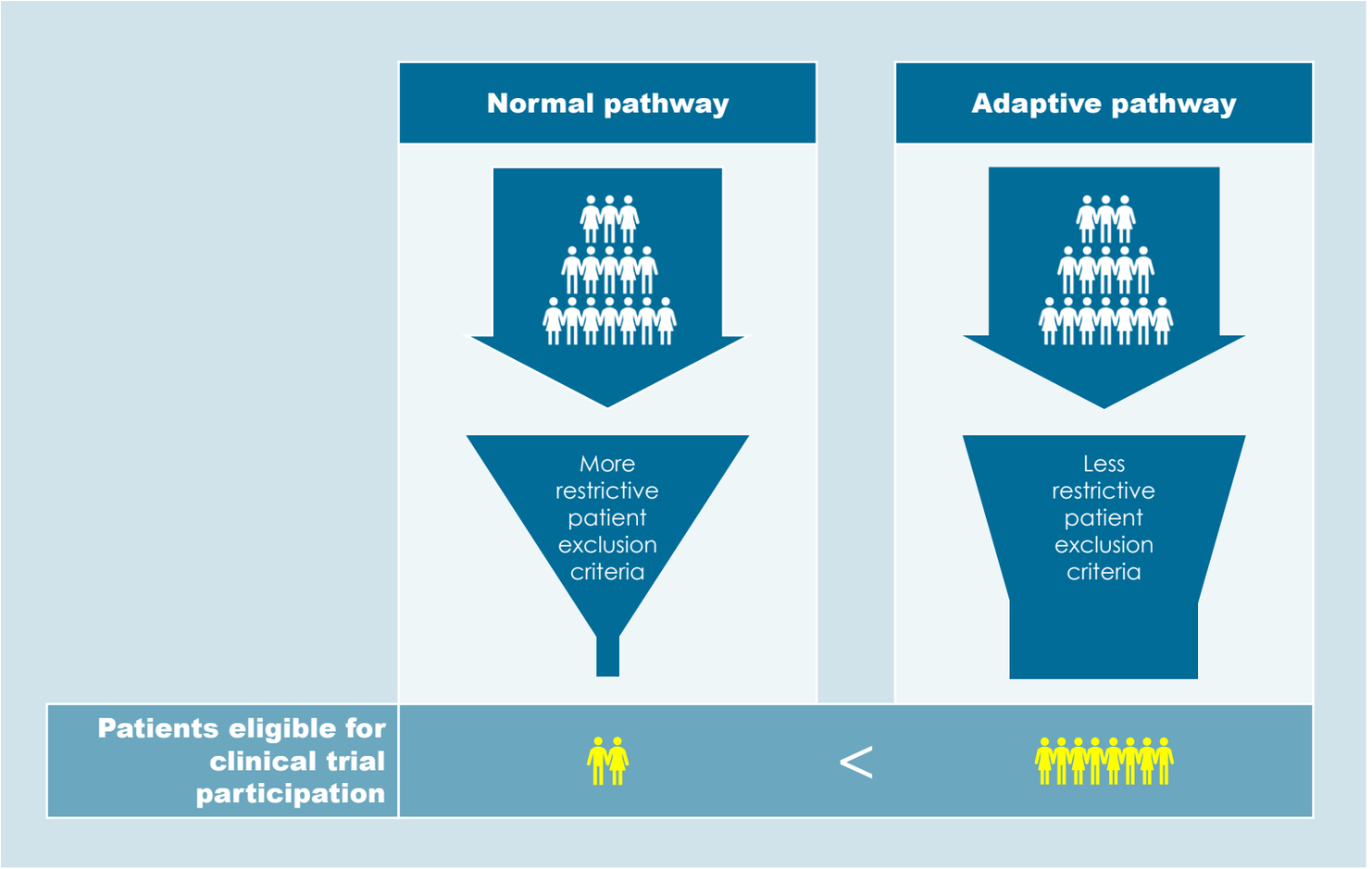
Adaptive pathways can accelerate patient recruitment in clinical trials

Adaptive pathways allow for less restrictive patient inclusion/exclusion criteria, making a larger share of patients eligible to be part of a clinical trial, see Figure 9 on the right. Patient inclusion/exclusion criteria can be relaxed when the clinical trial is continually evaluated during the study. Adaptive pathways enable more heterogenous patient recruitment.

Adaptive pathways enable the use of more flexible clinical outcomes

With adaptive pathways, stakeholders can reiteratively examine a treatment's preliminary results and its effects on relevant clinical outcomes. This allows OMP developers and regulators to relax the requirements on the clinical outcome upfront. The final evaluation of a new innovative medicine can be done in a real-world setting. This enables reduced efficacy and safety criteria at the time of approval and thereby reduces the time of development.

Figure 9. Adaptive pathways can help accelerate patient recruitment



Source: Copenhagen Economics

Notes: 1) EMA website, link. / 2) EMA (2012)

Digital solutions allow for the inclusion of more outcomes and continuous monitoring, hence accelerating the approval of innovative treatments

Digital solutions can improve the efficiency of clinical trials and accelerate the pace at which evidence is collected.[1]

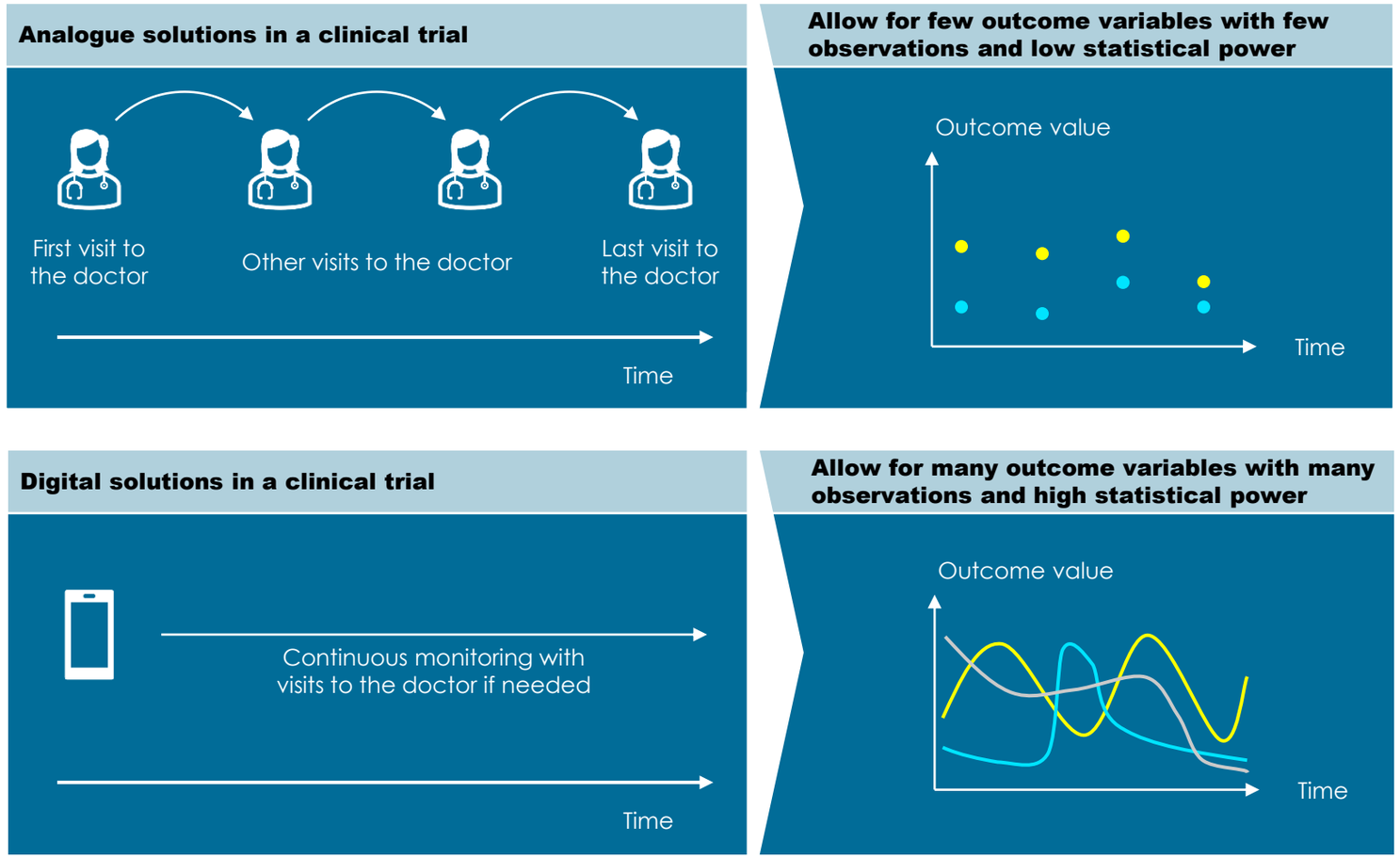
Digital solutions in clinical trials allow for better data on more clinical outcomes

When clinical trials utilise digital solutions, it becomes possible to increase the number of outcomes measured and the frequency of measurement. The insights generated by continuous monitoring provide a better overview of a treatment's effects, which may be hidden when using discrete measures. See Figure 10 for an example of continuous vs discrete measurement. Continuous measurement of clinical outcomes will enrich the data in the pivotal trials and will guide OMP developers' decisions regarding continuing the clinical trials or not, and regulators' approval decisions.

In the figure, lower right corner, let us assume that the most relevant clinical outcome turns out to be the grey line. If this was not clear from the outset, the grey outcome variable might have been excluded in the analogue clinical trial due to the limited number of possible outcome variables.

Even if the blue and yellow outcome variables are the ones of key interest, the figure demonstrates that continuous monitoring provides a much richer dataset compared to the analogue design. Further, if the aim of the clinical trial is to increase the blue outcome variable, then an increase in the dose of the treatment following the peak registered by continuous monitoring might be a way forward. That might would go undetected in the analogue clinical trial example due to the lower frequency of measurements.

Figure 10. Time saved due to digital solutions in a clinical trial



Source: Copenhagen Economics

Notes: 1) See for instance Tenaerts, et al. (2020)

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Development of novel therapies

How can Europe speed up development of therapies for the 95% of rare diseases with no authorised treatment?

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