Exploring Alternative Financing Models and Early Access Schemes for Orphan Drugs: a Belgian Case Study

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Research Article

Keywords: financing models, insulated fund, private insurance, early access schemes, compassionate use, medical need, off-label use

Posted Date: March 21st, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1454658/v1

Abstract

Background: Although some countries have made specific adjustments in their healthcare system to accommodate often-expensive orphan drugs, availability of these orphan drugs is still not evident. This study investigates alternative financing models and early access schemes for orphan drugs in the context of the Belgian healthcare system.

Methods: Three focus group discussions were held with a panel of eleven experts from the Belgian Drug Reimbursement Committee, the Colleges for Orphan Drugs, the pharmaceutical industry, physicians, ethicists and pharmacists. Retrieved data were pseudonymised, analysed and coded according to the Qualitative Analysis Guide of Leuven.

Results*:* Experts disfavoured an insulated orphan drug fund as well as private insurance, as isolation of a separate budget and a mostly profit-driven mechanism, respectively, would contradict the Belgian fundamental principle of solidarity. Moreover, an insulated fund could potentially reproduce the same budgetary constraints as the general reimbursement system albeit on a smaller scale. As the Special Solidarity Fund is intended for urgent care and exclusively accommodates eligible to the criteria, its design would not allow general financing of orphan drugs. Overall, implementation of an alternative financing model was not endorsed, instead, suggestions to improve the current reimbursement system were preferred; increased collaboration and transparency, robust and quality real-world evidence but also digitalization of data were elements mentioned. Alleviating administrative burden and simplifying the admission process for compassionate use program/medical need program and early treatment reimbursement should be prioritized to facilitate early access. Furthermore, a legal framework for off-label use could stimulate proper adoption. Efforts on collaboration of expertise centres and coordination of orphan drug databases across Europe could foster a robust data network to support orphan drug availability in individual countries.

Conclusions: This research reveals that reassessing current financing models and early access schemes by eliminating inadequacies, may be more conducive than establishing alternative systems to increase availability of orphan drugs in Belgium. Other jurisdictions may rely on this information to review their own models of early access and financing and cultivate a more sustainable delivery of orphan drugs.

1. Introduction

For more than 20 years, the US Orphan Drug Act and EU Regulation on orphan medicinal products have been effective at incentivizing development and increasing registration of orphan drugs for people living with a rare disease (1, 2). Yet, central market authorization in the EU does not guarantee national distribution or availability of a drug (3). In fact, pricing and reimbursement have been identified as key determinants of national access (4). This has led to the establishment of restricted and discrepant accessibility of orphan drugs among Member States (5). As of 2020, 96% of EMA approved orphan drugs were available to patients in Germany whereas, in Latvia, this was as little as 2% (6). Market authorization holders are, namely, not obliged to launch a drug in all EU countries and often focus on commercially viable and lucrative markets for high-cost and innovative orphan drugs (5). These are preferably countries with high GDP, willingness-to-pay and a large eligible population for the involved therapy (5). This strategic launching is a direct result of ‘external reference pricing’ and assures companies to obtain higher prices when delivering their orphan drug to wealthiest countries first (5, 7). Poorer countries that are unable to afford the suggested price experience delays in access to orphan drugs or do not offer them at all.

As orphan drugs are often disproportionally costlier than other drugs, people living with a rare disease rely on financial support to access these drugs (8–10). It is, therefore, essential to minimize patients’ co-payments or fully reimburse orphan drugs by national healthcare systems or insurance funds. Different factors contribute to a reimbursement decision, however, many countries adopt health technology assessment (HTA) as a means to evaluate a novel drug (7). Budget impact and cost-effectiveness are reoccurring components considered in HTA (11). Depending on the accounted elements in respective countries, orphan drugs are usually deemed not cost-effective and overtaxing for healthcare budgets (12). For that reason, some have implemented exceptional attention to foster access to these orphan drugs (13). For instance, England implemented a higher cost-effectiveness threshold whereas, in France and Germany, no economic evaluation is required for orphan drugs (13). Several studies reported on the fast-growing share of orphan drugs in healthcare budgets compared to other drugs (14, 15). In the period of 2010–2019 the share of orphan drugs sales worldwide grew from 10.5–16% (16). In this light, different systems are established to control budget spending and the opportunity cost associated with funding orphan drugs.

Multiple countries have implemented various financing models to pay for orphan drugs. For instance, in Italy, the Agenzia Italiana del Farmaco (AIFA) fondo 5% functions as a financial source for independent research and development but also funds treatment of people living with a rare disease for which the orphan drug has not yet been authorized (17–19). Monetary capital for the fund is raised through the contribution of 5% from pharmaceutical companies’ promotional expenses, otherwise intended for physicians. In Scotland, the New Medicines Fund is similar as it financed by a proportion of pharmaceutical companies’ earnings determined by their national pharmaceutical price regulation scheme (20). This fund is intended to accommodate high cost orphan drugs denied or recommended for reimbursement by the Scottish Medicines Consortium (21, 22). After extensive reform following stark criticism of their previous operations, the Cancer Drug Fund in

the United Kingdom was established as an annual fixed budget for temporary access to promising cancer drugs with remaining clinical uncertainties (23–25). During this period, data collection from the company is required, in turn, patients benefit from early access to these treatments (23). Since around 30–40% of current orphan drugs address oncological conditions, a large part of rare disease patients benefit from this fund (26, 27). Private health insurance is a well-known mechanism of financing drugs in the United States of America and Canada (28, 29). Although private health insurance may reach a wider audience, it is often subject to malfunction due to poor information dissemination, misuse of market power and, income and knowledge inequity (30).

With a view to address financing limitations and accelerate access to orphan drugs not yet authorized or under development, several countries have introduced alternative access schemes (31). Examples are, compassionate use programs (CUP), provided by pharmaceutical companies, and unmet medical need programs (MNP), such as the French 'Autorisation Temporaire d'Utilisation d'extension' (ATU) (32–34). In some instances, people living with a rare disease are treated with a medicinal product not yet indicated or authorized for their specific condition under, so-called, off-label use (35). Even if the situation is life-threatening and the drug has been labelled as safe, off-label use is often a last resort due to its inherent experimental character.

In this study, we aimed to explore health economic, ethical, legal, social and practical aspects of aforementioned access schemes and financing models for orphan drugs. Although these issues were investigated in the setting of the Belgian health care system, the analysis provides additional insights in trade-offs and (dis)advantages of alternative access schemes and financing models for orphan drugs that are likely to be relevant to other countries.

2. Belgian Financing Models And Access Schemes For (Orphan) Drugs: The Status Quo

In the current Belgian drug reimbursement procedure, orphan drugs benefit from a privileged position. These drugs are exempt from the claw-back measure which requires pharmaceutical companies to return a proportion of their revenues to the government when a certain threshold of budget spending is attained (36). Moreover, pharmaco-economic evaluations are not compulsory and allocation decisions are made despite limited data (13). Clinical uncertainties are often temporarily tolerated as long as evidence is collected within the context of a managed entry agreement. This signifies that, individual reimbursement of approximately 30% orphan drugs is conditioned by recourse to an assigned Orphan Drug College (37, 38). This College consists of expert-physicians who evaluate case-by-case eligibility and adoption rights of the orphan drug and advise the consultant physician of the sickness fund on its potential reimbursement (39). Additional responsibilities of the College involve evaluating the determined reimbursement conditions and the need of an Orphan Drug College for the specialty but also outlining an activity report gathering use, context and number of applications within 30 days of the orphan drug adoption (39).

In Belgium, there is also a Special Solidarity Fund (SSF) for non-traditional financing of urgent medical care (40). The latter concerns critical needs beyond rare diseases and covers treatment, medical devices or cross-border healthcare requested on individual basis (40, 41). However, access to the fund is strictly conditional and functions as a last resort in case other reimbursement options were unsuccessful. Ultimately, The College of Medical Doctors Directors decides on financing via SSF by considering urgency, safety, alternative treatments, critical medical need, scientific value and effectiveness (40). Noteworthy is that coverage through the SSF is often temporary and only partially covers expenses for adults. In 2010, the Belgian Health Care Knowledge Centre drafted recommendations to resolve burdensome administration and complex operations of the SSF (41). Improvements in terms of automatization and digitalization, oral communication with experts of the Orphan Drug College and also transparent follow-up of dossiers were addressed (41). An additional way of financing drugs in Belgium is through private health insurance. Unlike the North-American systems, private coverage in Belgium only exists complementary to the mandatory public health insurance and amounts to 5.1% of the current healthcare expenditure (42, 43).

Early temporary authorization (ETA) in Belgium forms the cornerstone of early access to orphan drugs within a regulated framework (36). Under ETA, an innovative drug, not yet approved by the European Medicines Agency or not available through the conventional reimbursement system, can be granted to patients with a seriously debilitating or life-threatening disease in critical medical need (44). However, some conditions need to be fulfilled. The involved disease should be included on the National Institute for Health and Disability Insurance's (NIHDI) 'Unmet Medical Need' list (45). A license for ETA can be requested by the pharmaceutical company and depending on prior authorization in another indication or not, respectively, a medical need program (MNP) or a compassionate use program (CUP) could be initiated (44). Furthermore, an application for market authorization or clinical trials with preliminary evidence of the drug should be ongoing. Optionally, the pharmaceutical company could also apply for monetary compensation, so-called, early temporary reimbursement (ETR), for offering the drug through CUP or MNP. Another way of early access to orphan drugs is through off-label use. Although, reporting of off-label use and side-effects to respectively, the issuing company and the FAMHP and approval from the Ethics Committee is required, only a handful of off-label treatments have official guidelines (35). Moreover, unless sponsored through charity, reimbursement of off-label treatments is not provided by the Belgian state.

3. Methods

3.1. Study design

Focus group discussions were chosen as a qualitative explorative research technique to enable in-depth information gathering and interactions between participants. In light of national healthcare measures, a total of three discussions, of two and a half hours each, were held through Zoom videoconferences between October 2020 and February 2021. The moderation was led by pharmacy students, LF and CC, and supervised by SS and KA. In the first session, conversations were initiated by presenting stakeholders with predetermined questions based on a literature review (see **Appendix 1**). In subsequent focus group discussions, key topics that were highlighted prior were elaborated further and posed questions were adjusted to stakeholders' previous remarks (see **Appendix 1**). The study was approved by the KU Leuven Ethics Committee on September 9th, 2020 (reference n^{o} MP015702).

3.2. Participants

Each focus group discussion consisted of eight to eleven representatives of the Belgian Drug Reimbursement Committee, the Colleges for Orphan Drugs, the pharmaceutical industry, physicians, ethicists and pharmacists. Candidates were selected based on Belgian nationality and expertise in payment and access of orphan drugs. Invitations were sent by e-mail followed by a reminder a week after. Respondents were provided with arrangements on the time and course of scheduled focus group discussions and were required to sign an informed consent form before attending the meetings.

3.3. Pseudonymization

Participants' opinions and perspectives were audio-recorded and transcribed verbatim, pseudonymized and numbered as follows: codes A1 and A2 were assigned to pharmacists, codes I1 and I2 to pharmaceutical company employees, codes E1 and E2 to ethicists, code D1 to a physician of the College for Orphan Drugs, code K1 to a representative of a patient advocacy group for cancer, code C1 to a member of the Belgian Drug Reimbursement Committee, code C2 to a health insurer and code C3 to a member of the healthcare policy cell of the Belgian Minister of Health and Social Affairs.

3.4. Data analysis

Data were analyzed according to the Qualitative Analysis Guide of Leuven (QUAGOL) which is a process consisting of two parts, each subdivided into five steps (46). In the first part, an iterative process was organized to familiarize with the acquired information and a code tree was constructed. In the second part, data was transferred into the QSR NVivo Release 1.3 qualitative software program and coded by linking quote to concept. All steps were discussed and validated amongst students and researchers before results were finally summarized in a framework matrix. The privacy and confidentiality were guaranteed throughout the entire process and data were stored in accordance to the five-year storage policy of KU Leuven.

4. Results

4.1. Exploring alternative financing models for orphan drugs

Ethicists unanimously agreed that financing orphan drugs requires a unique approach that considers inherent issues related to rare diseases which impede patients from receiving treatment. Having specific criteria for orphan drugs would prioritize equal access for all patients by counteracting these disadvantages. Therefore, irrespective of the financing model, some sort of exceptionalism should be incorporated into the design.

"If you start lumping orphan drugs together for reimbursement like the majority of drugs, you will not get anywhere. If you adopt one criterium, a one-size-fits-all, people with special health needs that often experience difficulties, for which they do not have any liability, will be excluded. Not due to their disease but by way of distribution. So, if you want to categorize that disease, you will have to approach it in a different way. Otherwise, they do not stand a chance." (E1)

The following sections describe the various orphan drug financing models and their operational preconditions (see Table 1) that were discussed by focus group participants.

Table 1
Preconditions for adoption of a financing model in Belgium

Financing Model	
For all models	• Exceptionalism in the form of specific criteria
Insulated OD fund	• Monetary contributions, as a proportion of drug prices, from pharmaceutical companies
	• Guarantee continuity in reimbursement in the form of a dynamic, inexhaustible source
	• Isolate a percentage from the overall drug budget of which the share would be determined as a function of disease rarity or health gains
	• Orphan drug prescription and treatment in a handful of expert centers could enable efficient data generation
Emergency fund (SSF)	• Only efficiently operate for bridging an exceptionally critical period for individuals and not as a standard reimbursement
Private insurance	• Solidarity could be upheld if genetic testing as a prerequisite for membership would be prohibited by law
	• Costs could be contained if a large population takes on private insurance

OD, orphan drug; *SSF*, Special Solidarity Fund

4.1.1. Insulated orphan drug fund

Based on Rawls's Maximin principle, that defines maximizing the minimal situation as morally responsible, ethicists conveyed their interest in an insulated orphan drug fund (47). Isolation of a predetermined budget in such fund would establish a distinct procedure that accounts for rarity, vulnerability and complexities associated with orphan drugs. According to a health insurer and an ethicist, monetary contributions as a proportion of drug prices from pharmaceutical companies could be legally enforced. Although, such fund would likely be most valuable in countries with restricted public resources.

"An insulated fund would allow separate rules, considering rarity and the challenges of orphan drugs. Is it the only way to do so? I am not yet convinced myself. But it is a way to deviate from the standard that is applied elsewhere and that is certainly not fitting for assessment of orphan drugs." (E1)

Conversely, most participants expressed that a fund would not necessarily equate to a solution. Excluding a vulnerable group from the standard procedure could also be considered ethically unsound. Discussion on contribution percentages would arise and, in case of private financing, patients would be relying on the industry's goodwill. Moreover, one physician expressed that in a previous civil society forum, civilians preferred not to separate orphan drugs from other medicines. Also, budgetary constraints and associated challenges such as, eligibility, budget size, allocation, disease heterogeneity and depletion would remain. As the Belgian healthcare system is founded on solidarity, an insulated fund would contradict this principle.

"If you consider a privately financed fund, you make patients dependent not on the government, something well-structured, but on the goodwill of the industry. You would wonder whether that is appropriate for the most vulnerable to be at the mercy of a private fund rather than public policy." (E1)

"How would you compare the reimbursement of a third-line oncologic that prolongs one patient's life with four months compared to another therapy with five candidates that would obtain a different life quality? Through the same fund? You would still have discussion, isn't it?" (D1)

"Does everyone get access to the fund or do people with five million euros in their bank account get the same treatment as someone who is unemployed?" (D1)

A fund implemented as a structural solution for financing orphan drugs, should ideally guarantee continuity in reimbursement in the form of a dynamic, inexhaustible source. An alternative would be to isolate a percentage from the overall drug budget of which the share would be determined as a function of disease rarity or health gains. However, participants preferred to maintain solidarity, through specific attention towards orphan drugs, within the standard reimbursement procedure and reform only that which requires it (cfr. infra). For instance, concentrating orphan drug prescription and treatment in a handful of expertise centers could enable efficient data generation on clinical uncertainties, alleviate workload of the Orphan Drug College and ameliorate quality care for patients.

"The core is that it is such a mixed population with variations of pathologies. Secondly, for rare diseases and their therapies, there are often many uncertainties. Those are two main elements that you should cover. That would be challenging with something that is fixed for ten years.

You will always need something dynamic." (D1)

"If an orphan drug is prescribed in two or three centers, the files are always complete. It becomes a problem when a particular orphan drug is prescribed in 40 to 50 centers, because then there are a lot of people who have little experience prescribing some of those drugs which makes the files worse. A mechanism should be thought of to limit orphan drug treatments to one or two centers." (D1)

However, some company representatives voiced that the current drug budget should be increased by generally re-evaluating current reimbursement of drugs. In contrast, ethicists expressed that a fair price system, in which a high, but reasonable price of an orphan drug is justified, could free up more financial capital.

"I don't think pharmaceutical companies would favour sponsoring such a fund. Instead, we should plead for an expansion of the medication budget to help as many patients through standard procedures." (I2)

"If you adopt a system of fair pricing, it would simplify making more budget available. If a disease is life-threatening and of high medical need, those fair prices could be set higher." (E1)

4.1.2. Emergency fund: The Special Solidarity Fund (SSF)

Stakeholders expressed that emergency funds such as the SSF could only efficiently operate for bridging an exceptionally critical period and not as a standard reimbursement procedure for orphan drugs in Belgium. Since access to the fund is tied to strict criteria and limitations, this type of funding is highly unreliable for patient and physician. Furthermore, adults are still faced with significant out-of-pocket costs since not all expenses are covered. It was also felt that the current operation of the SSF is characterized by tedious administration and complex registration. Even though, in 2010, the Belgian Health Care Knowledge Centre drafted recommendations to optimize the SSF, little is known about its realization.

"The SSF should remain an exception. It is case-by-case, so really not for everyone with a rare disease. It is to answer needs when there is no structural solution or to give access to medicines not yet registered. For adults with a rare disease, costs are never fully covered. It is also a limited budget that could run out." (C1)

"It is a very laborious administrative procedure. Patients need to apply, usually with help of the hospital's social services, but it is usually not applied for due to the tediousness and the significant delays." (I2)

4.1.3. Private insurance

The majority of stakeholders opposed the adoption of private insurance to finance orphan drugs. According to them, this system is profit-driven instead of needs-focused. Insurers would be prone to demand stellar prices for admission since accommodating orphan drugs is often linked to high costs. Furthermore, it would be highly inefficient for each insurance company to perform their own health technology assessment to determine which orphan drug to take on financially. Ethical debates could arise from admission requirements, such as genetic testing, which would reduce access to these insurances. The popularity of such a scheme for orphan drugs could also be questioned as incidence rates for rare diseases are generally low. Overall, stakeholders were of the opinion that private insurance, similar to an insulated fund, would be incompatible with the foundational belief of solidarity in Belgian healthcare.

"Access will not be uniform. Since, in Belgium, we highly consider the principle of solidarity, I do not think it is applicable in our country." (C1)

"This will de facto lead to a two-track policy. There would be decent public healthcare but the moment it becomes expensive and inaccessible, it would be handed over to private insurance. Making it accessible to only those who can afford it or who are administratively resilient enough to arrange it." (E1)

In contrast, ethicists conveyed that private insurance as an additional system could establish a competitive market that might provide accelerated access to orphan drugs. Solidarity could be upheld if genetic testing, as a prerequisite for coverage, would be prohibited by law. Current complementary insurance in Belgium demonstrates that it is possible to keep costs relatively low. Furthermore, costs could be contained if a large population takes on private insurance. In the end, people would rather have part of their orphan drug expenses funded, with or without a shorter delay, than assume full out-of-pocket costs.

"If everyone participated, that amount would remain relatively low, but if, for example, only 10,000 people register for it, that paints another picture" (E1)

4.2. Access schemes for fast-track delivery of orphan drugs

Focus group participants discussed a number of access schemes for orphan drugs and their operational preconditions (see Table 2) as described in the following sections.

Table 2
Preconditions for adoption of an early access scheme in Belgium

Early Access Scheme	
ETA	
→ CUP/MNP	• Reduce administrative burden and accelerate the process, parallel submission at FAMHP, NIHDI, the ethical committee and the Commission for Human Medicines • Legally extend responsibility to company and authorities to prevent decision fatigue of physicians • Implement these programs at European level instead of national level • Data capturing of clinical outcomes should be aimed for by fostering a legal framework with clear instructions • Raising awareness amongst people living with a rare disease • Agree on which parameters to analyze to ensure highest quality of real-world evidence; a first step would be to guarantee a well-structured list of reimbursed drugs requiring prior authorization • Current available information in databases should be gathered, pseudonymized, fine-tuned and electronically connected by experts • Automation (via wearables), digitalization and validation • People living with a rare disease could be closely involved during the application process and neglect could be avoided by creating patient-friendly, electronic dossiers
→ ETR	• Reform and simplify the ETR procedure (customized reimbursement amount) • Proposed to reimburse orphan drugs that are accessed through ETA subject to the condition of data collection • Suggestions from physicians, patient organizations and health insurance, beyond the industries requests, to the unmet medical needs list
Off-label use	• Improved regulations and stricter monitoring • Appoint specific expert facilities for: peer review, continuous evaluation, communication of clinical evidence and advice on usage • An independent scientific body or doctor's association to formulate guidelines or advice on use → alleviate medical liability of physicians • Financial responsibility distributed amongst company and health authorities • Effort towards valuable qualitative data collection - improved structuring of medical dossiers and referencing KCE trials for clinical evidence + data should be standardized, linked and centralized into a transnational register that is closely monitored • Stimulating drug-repurposing in a controlled environment to prevent soaring prices

CUP/MNP, compassionate use program/medical need program; *ETA*, Early Treatment Authorization; *ETR*, Early Treatment Reimbursement; *FAMHP*, Federal Agency for Medicines and Health Products; *KCE*, Belgian Health Care Knowledge Centre; *NIHDI*, National Institute for Health and Disability Insurance

4.2.1. Early Temporary Authorization (ETA)

4.2.1.1. Compassionate use program/medical need program (CUP/MNP)

In the context of orphan drugs, stakeholders were of the opinion that CUP and MNP are positive initiatives to provide patients with essential treatment at an early phase while generating clinical evidence. Besides, one third of drugs delivered through ETA receive orphan designation from the European Medicines Agency. Moreover, contrary to off-label use, more substantial preliminary evidence on the drugs exists. ETA is, namely, only approved under condition of ongoing clinical trials or market authorization application at the European Medicines Agency and after a benefit-risk analysis by the Federal Agency for Medicines and Health Products (FAMHP).

"We checked how many percent of the compassionate use programs were approved orphan drugs, and that was one third of the compassionate use programs approved by the agency of orphan diseases." (I1)

However, stakeholders argued that these programs in Belgium need improvement as some hurdles hinder their adoption. For instance, prior permission from the FAMHP and an opinion from the ethics committee and the Commission for Human Medicines is required in order to proceed to an application for CUP or MNP at NIHDI. Involving multiple government bodies in such a process is often considered expensive, tedious and time-consuming. Recent amendments to the CUP/MNP procedures following an update of the Royal Decree on medicines for human and veterinary use, have additionally complicated the process. Furthermore, physicians were often hesitant to decide on a specific company or clinical trial for ETA, as a variety of options often exist and the company should consent to initiating such program. Moreover, General Data Protection Regulation (GDPR) for ETA, in terms of confidentiality and data capture, is unclear. In turn, the collection of clinical evidence is currently uncoordinated and privacy issues remain unsolved. Redundant or inaccurate information is then assembled into multiple systems which makes data extraction complicated and burdensome.

"As of yet, there has also been a problem with the data collection associated with it.…I hear all sorts of things, I hear there are confidential issues involved. I also hear that the prescribers do not want to go to the trouble of collecting that data. Companies certainly do not want to go through all of that administration for data collection. There is a lot of ambiguity at the moment." (D1)

"It is necessary to decide who is responsible to collect data. So far, it is one that says, it is the companies, the other one says, it is the doctors and a third one says, it is the authorities but, in the end, insufficient data is collected. Until it is clear, maybe legally or another way, who is responsible for it, I am afraid nothing will happen…And also define who is the owner of the data…that owner also must be willing to share the data." (C1)

"In day-to-day practice, I don't think everyone uses the same measurements necessarily, so it's very difficult to compare results between patients and draw a conclusion about that kind of data. It is also a kind of real-world data, hey, there must be some form of standardization to be able to interpret this data." (C1)

To reduce administrative burden and accelerate the process, parallel submission at FAMHP, NIHDI, the ethics committee and the Commission for Human Medicines of the application dossier for CUP/MNP should be facilitated. Stakeholders suggest to legally extend responsibility of selecting an adequate program to company and authorities. This could stimulate CUP or MNP initiation by alleviating decision fatigue of physicians and leveling the playing field. Another remark was to possibly implement these programs at European level instead of national level. Increased efforts towards data capturing of clinical outcomes should be aimed for by fostering a legal framework with clear instructions. Raising awareness amongst people living with a rare disease on the value of information sharing for high-cost orphan drugs, could also increase informed consent rates for data capture during early access programs and generate additional clinical evidence. Prior to initiation of ETA, an agreement on which parameters to analyze should be reached to ensure highest quality of real-world evidence. However, a first step to defining these parameters would be to guarantee a well-structured list of current reimbursed drugs requiring prior authorization by a physician of the health insurance fund (this is known as Chapter IV reimbursed drugs in Belgium). Current available information in databases should be gathered, pseudonymized, fine-tuned and electronically connected by experts. To ease data collection, automation and digitalization should be prioritized while disease treatment and drug administration should be limited to selected expertise centers. Electronic devices such as wearables could further aid with collecting data, however both devices and data should be analyzed and validated by specialists, such as those from the Colleges of Orphan Drugs. People living with a rare disease could be closely involved during the application process and neglect could be avoided by creating patient-friendly, electronic dossiers.

"Well, it's actually more complicated, I mean we tried to make it easier, the intention is that a parallel submission will be made to the FAMHP and the RIZIV/INAMI. At the same level, in collaboration with the FAMHP, the ethics committee would also intervene. However, that is something new, why do I mention it, because we also proposed it at European level and there was quite a bit of interest shown for it." (D1)

"Yes, it would be important to have an electronic system. Also, for the orphan drugs with a College because we support the collection of wearables." (I1)

"If that data then plays a major role, then we also have to be sure that it is correct, right? Yes, those systems must be validated, otherwise they are really not valuable." (A2)

"But if you link that to conditional reimbursement, then maybe it could be implemented, huh. Maybe not such a bad idea, that you ask the patient to fill in data 2–3 times a year for 5 or 10 minutes and that that is one of the conditions that he/she gets his/her medication. I don't think these should be absolute conditions, but we should ask nicely anyway…a large framework has to be created to realize that, and if that is the case, I can imagine that the patient is invited to register data anonymously, of course. There needs to be a legal framework. Nowadays, it seems that there are mainly discussions since GDPR is unclear." (D1)

"I think with permission you never have problems, if the patient gives the informed consent. Suppose that something makes a real difference scientifically and as a society you invest disproportionate resources into it, then from an ethical point of view I think that is also a discussion

that you should dare to have in order to say that we expect something in return. I also think that if you use solidarity in the context of very expensive resources… if it is really essential to demonstrate whether something provides sufficient efficacy and return to pay for it as a society, then I think you can discuss it every now and then." (E1)

"I think the philosophy is also not to centralize it all, but to ensure that the databases that are available can communicate with each other." (K1)

"But I think one of those solutions that are shared and discussed nowadays, is that we would actually register real-world data so that a real analysis could be done after a certain duration of treatment so that a better decision could be made in the end…The Orphan Drug Colleges would be a good opportunity for that …Well, in fact, it has to be decided upfront what data should be collected, for how long, by who...so that we have quality data in the end that can be interpreted." (C1)

4.2.1.2. Early Temporary Reimbursement (ETR)

Pharmaceutical companies rarely apply for ETR when offering an orphan drug through CUP or MNP. Stakeholders were convinced that implementation of ETR is hampered by the complicated eligibility criteria for a positive reimbursement decision, the layered application process but also the lack of familiarization with the concept. Moreover, pharmaceutical company employees emphasized that the proposed compensation is a fixed and modest amount to cover logistic costs, which is negligible compared to the costs of offering the orphan drug.

"…the idea of choosing the amount was to cover the logistics costs…and that amount is relatively low, but is to compensate for the administrative burden of the industry …We would like to improve the ETR and make it more appealing. But now it's relatively burdensome and doesn't bring much more than a CUP or MNP, so if the companies have to choose now, it's easy in fact, CUP or MNP.." (I1)

"We have been very dynamic, in the beginning it was a compensation, a lump sum, which was initially seen as a kind of foreshadowing of the final reimbursement by the industry, it was then made clear that it was not the case and then it also disappeared…" (D1)

In this light, stakeholders supported the prospects by the Belgian Parliament to reform and simplify the ETR procedure. Some suggested to adjust the current ETR to the French ATU system that has well-established data capturing and provides the companies with a customized reimbursement amount, others did not support this idea as Belgian regulations do not allow any correlation of the temporary compensation with the final reimbursement amount paid by NIHDI. As an alternative, the physician proposed to reimburse orphan drugs that are accessed through ETA subject to the condition of data collection. One stakeholder voiced that research in other disease areas could be stimulated to add suggestions from physicians, patient organizations and health insurance, beyond the industries requests, to the unmet medical needs list. In case a developed drug addresses unmet medical need, an agreement with the company could more easily follow.

"Yes, I can only speak for the industry, we are of course in favor of quick and temporary reimbursement until a final decision has been made about reimbursement. So, the principle (of ATU) is something that we as an industry are advocating for. Of course, the scope has to be aligned. Which medicines are now eligible for this? It goes without saying that you cannot reimburse all medicines the same way." (I2)

"in ideal circumstances that (unmet medical need) list would not only be fed by the industry, but also by the unmet need defined elsewhere, but yes, as long as the minister does not define what unmet need is…" (D1)

"No, sorry to say, but I think yes, there should be suggestions but from the field, that is, from doctors, but also from the health insurance fund because they see what the medical need is in society." (C1)

4.2.2. Off-label use

Many orphan designations originated from off-label prescriptions, therefore, stakeholders were convinced that off-label use could be valuable to affordably accommodate unmet medical needs. However, improved regulations and stricter monitoring should be adopted. Reimbursement could also be requested without registration at EMA, if some evidence on small cohorts gathered by scientific institutions, such as the Belgian Health Care Knowledge Centre (KCE), is available.

"It is an increasing phenomenon…drugs that work via a certain pathway and if that pathway applies to a tumor in the lung or in the colon… doctors believe that if the pathway is the same for a tumor in a different location, I would like to try that (same medicine) with this patient, but there is no registration for it." (I2)

"Sometimes off-label use is already in the guidelines…then it is clear that everyone agrees with it." (A2)

However, it is clear that reimbursement of off-label use is not guaranteed. In turn, financial hurdles arise when requests are denied and patients are subject to full out-of-pocket costs. In those instances, real-world data is improperly followed-up and not digitally recorded into a register. This comes with a risk of infrequently reporting adverse events, not detecting abuse of practice, difficulties in evaluating efficiency of

the orphan drug, non-specialist' prescriptions and discrepancies in methods of data gathering as no consensus on GDPR currently exists. Although, the company is responsible for the conformity and quality of the product, physicians are fully liable for its prescription and are therefore hesitant to offer off-label use. Furthermore, a pharmacist emphasized the lucrative practice of drug-repurposing by pharmaceutical enterprises where drugs, that were relatively cheap and proven efficient in off-label use, turn extremely expensive after orphan designation.

"I think the NIHDI plays a big role in off-label use. Sometimes it is not reimbursed and sometimes it is. If it is not reimbursed, it is often financially difficult to establish off-label use." (A2)

"It will always be difficult to report the negative effects, but we actually need that." (A2)

"But not the off-label use and that is the problem…evaluations of all systems have to be made and again about GDPR…who should collect which data, who is allowed to…who is entitled to that data and who owns it and so on." (D1)

Similar to ETA, stakeholders expressed that management of off-label use should occur by appointing specific expert facilities for its adoption in therapy. This would enable peer review, continuous evaluation, communication of clinical evidence and advice on usage. Alternatively, a legal framework could be set up that would allow the FAMHP, an independent scientific body or a doctor's association to formulate guidelines or advice on use. The latter could alleviate the medical liability on physicians and yield valuable qualitative data. Off-label use could be further encouraged if financial responsibility is distributed amongst the company and health authorities. An effort towards data collection should be made nationally through improved structuring of medical dossiers and referencing KCE trials for clinical evidence, although these may be of limited power. Qualitative real-world data should be standardized, linked and centralized into a transnational register that is closely monitored. Finally, stakeholders advocated for stimulating drug-repurposing in a controlled environment to prevent soaring prices.

"…what we are reflecting about are those centers of expertise, reference centers, after the European example…for those kinds of very rare diseases off-label use could be permitted in only one or two centers in Belgium. This could be done with other people, so that there is peer control. There must be, so to say, a joint database. Or at least have some sort of yearly reporting in an expertise center." (D1)

"I think that there should be partial responsibility between authorities and companies…And, of course, you could also think about a shared responsibility for financing. Now, the doctor is completely dependent on the goodwill of the company and we are aware that some companies are more willing to participate than others." (I2)

"…evidence should also be collected, which could perhaps be part of the answer…So that, in case of off-label use, data is also produced by those doctors and that progress can be made, that evidence is created." (I2)

"This may be possible through the FAMHP. A legal framework can be drafted by the FAMHP in which, based on an evaluation, is determined which (off-label use) we now think is justified." (C2)

"But that's why it might not be a bad idea what C2 proposes, that is possibly one option. That the limited evidence that there may be of off-label use, because I think we agree that it is limited compared to when there is a market authorization, that you let an independent body judge it. When you talk about the FAMHP, I have my reservations since the FAMHP currently works on a fee for service basis…a fee of 11 000 euros should be paid for an evaluation, which is not free, I would say. Another option could be…similar to the Netherlands, that scientific associations would do that evaluation. For example, that doctors who prescribe off-label are evaluated for impertinence by scientific association…so basically, the peers. Then one would have to deal less with that financial element and perhaps be even closer to practice and the people who are really aware of the latest good practices, than when you would involve FAMHP." (I2)

"What is the representativeness if you have two patients in Belgium? It would be better to have an international registry." (I2)

"But then again, we have to be careful to do it in controlled circumstances, because that's the problem right now. Certain companies acquire those (smaller businesses), then re-exploit the monopoly position making it to become extremely expensive, whereas before, it could be used unnoticeably at a reasonable price." (C2)

5. Discussion

This qualitative study compiles multidisciplinary expert opinions on trade-offs between different access schemes (i.e. early access schemes and off-label use) and various financing models (i.e. insulated fund, private insurance, or emergency fund) for orphan drugs in Belgium. Stakeholders substantiated why alternative financing models would or would not be applicable in Belgium and also highlighted which and how processes for early access should be preserved and/or ameliorated.

Although ethicists found that an insulated fund would be able to highlight orphan drugs despite their usual neglected position amongst other drugs, it was generally determined that solidarity, the main principle of Belgian healthcare system, would be disregarded in such fund. Complete isolation of orphan drugs on a smaller scale would reproduce the same budgetary concerns, relating to budget size, depletion, allocation, disease heterogeneity and eligibility, as the conventional reimbursement system. These issues have already been encountered in countries like England and Scotland, that had to initiate several reforms of their insulated funds (20, 23). Another issue was whether the insulated fund needed to be funded by government (hence the general public), industry or both. Representatives of pharmaceutical companies conveyed that the industry would not be in favor of sponsoring such fund as discussion on contribution percentages would arise. This could be argued as in countries like Italy and Scotland, this system has been well-established by law (18, 21).

Private insurance was generally perceived as profit-driven, based on examples of its functioning in North-America, and thus, inadequate for a system based on solidarity (48). Experts were skeptical about membership requirements and related these to sensitive or personal information-sharing but also elevated fees, unless enough people would join the insurance. An emergency fund such as the SSF was considered incapable to be reformed into an insulated fund that would be fully responsible for the financing of orphan drugs. This emergency funding is unreliable (as it is often temporary), hindered by many restrictions and a fluctuating, limited budget, and can thus only operate on a small scale.

Overall, stakeholders believe that it would be better to improve the functioning of current established systems (in terms of efficient data generation, decreased administrative burden, more financial capital for orphan drug expenditure) instead of introducing new ways for financing orphan drugs. It could be argued that if this is the ideal approach towards orphan drugs, this thought process may be influenced by human tendencies to stick to the status quo (49, 50). It could, furthermore, also be that the proposed models were incompatible with compulsory social insurance in Belgium (51, 52). The insulated fund was, namely, based on examples in Italy and the UK, which have a general taxation system, and on the USA and Canada which have a strong private insurance system (28, 29, 51). However, optimization of current processes is not always evident as shown by the KCE initiative to improve the BSF more than ten years ago, with little to no implementation today (41).

This research additionally reveals insights on the implementation of early access schemes and their conditions, such as CUP/MNP with ETR and off-label use, for fast-track (usually temporary) delivery of orphan drugs to people living with a rare disease. Stakeholders unanimously consented that early access to orphan drugs is a benefit to the treatment of rare disorders that often need immediate attention. It was obvious that these schemes must be kept, however major reforms should be introduced. For CUP/MNP and ETR, the administrative burden should be reduced to make the programs more attractive. For off-label use, a legal framework should be defined to ensure its proper use in adequate instances. An overarching precondition that frequently reoccurred in the discussions, was the importance of quality, robust and digital data collection. This finding corroborates recent survey results of encouraging stakeholders to consult registries in decision-making (53). Prior to initiating therapy with an orphan drug, a protocol with clear questions and instructions on what evidence to collect should be drafted. Selecting a handful of expertise centers permitted to treat rare diseases with orphan drugs or experiment with off-label use, could foster a more coordinated environment for monitoring and data gathering.

Another important aspect that was mentioned, was the need for frequent and efficient communication through standardization of data measurement but also strategically linking current existing databases. The European Commission defined some common data elements for rare disease registries, however, practical actions are yet to be taken (54). The Danish Health Data Authority, which successfully established comprehensive and quality assured health data in Denmark, might serve as an example for future measures in setting up a centralized health data authority for rare diseases (55, 56). Upscaling these initiatives to European level would most probably increase the representativeness and meaningfulness of collected data for rare diseases often affecting just a small population nationally. These benefits of cross-country collaboration on healthcare have been shown by European establishments such as the International Horizon Scanning Initiative and European Reference Networks (57, 58).

Although this qualitative study evaluated financing models and early access schemes for orphan drugs from the perspective of the Belgian healthcare system, it has also produced some relevant take-home messages for an international audience. In the case of cross-country collaboration and healthcare, it will be important for all participating EU countries to have strong and coordinated data capture, regardless of the established financing models and access methods for orphan drugs, for seamless communication between healthcare systems. This may be especially relevant in the context of the often, small population suffering from a particular rare disease. Stakeholders outlined several suggestions to improve data collection. For countries such as Austria, France, Germany and Luxembourg with healthcare systems based on compulsory social insurance, similar to Belgium, an insulated funds or private insurance might not be the first choice (51). However, the underlying element of a separate approach in an insulated fund and the generation of more competition (and thus potentially improved access to orphan drugs) in the case of private insurances, are positive aspects that should be maintained or prioritized also in these systems with solidarity at the basis. In contrast, countries which finance healthcare through general taxation, such as England, Scotland, Italy or have a system of private insurance in places like Canada and the USA, can draw from the criticism stakeholders have expressed during the

discussions (28, 29, 51). Are current methods to counteract depletion or scarcities in resources within funds such as New Medicines Fund, Cancer Drug Fund and AIFA robust and sustainable on the long run? Are there ways to control price setting and prevent unaffordable prices of life-saving orphan drugs in a climate where private insurances predominantly finance healthcare?

For this study we were able to gather various experts on orphan drugs from different fields for three extensive focus group discussions, which provided relevant information on accessibility and funding of orphan drugs. However, the conduct of our study was also subject to some limitations as focus group discussions were held online due to the ongoing global health crisis. This meant that communication might have been affected by technical issues relating to quality of internet connection and recording devices. Moderating a discussion in such environment was also challenging. Some participants were generally more outspoken than others, which meant that not all perspectives might have been equally conveyed. Moreover, the output from the focus groups was partly determined by the posed questions but was naturally also limited by the knowledge of the involved experts. The pandemic might also have influenced responses as, for certain stakeholders, other priorities may have been at play. Finally, it is worth mentioning that the involved physician had already been retired at time of conduction of the research.

Future research should involve experts on orphan drugs from all over European countries to delve into formulating concrete and practical actions for a legal framework on cross-country collaboration at EU level. This orphan drug framework should address, inter alia, coordinated and digitalized data capture, GDPR, terms and conditions for off-label use and the possibility of a centralized early access scheme.

6. Conclusion

This study revealed that alternative financing models such as an insulated fund and private insurance for orphan drugs were perceived by stakeholders to conflict with the foundational principle of solidarity in the Belgian healthcare setting. It, furthermore, showed lack of adequate data collection, administrative burden and poor communication to be the main hurdles to early access, through compassionate use, medical need program or off-label use of orphan drugs. We believe that the concepts and gaps identified in this study, may stimulate other jurisdictions to review and improve their models of early access and financing to foster a more sustainable access to orphan drugs.

Declarations

Ethics approval and consent to participate

Statement on ethics approval and consent:

“The Research Ethics Committee UZ/KU Leuven hereby grants favorable advice to the proposed study, as it was described in the protocol. The Commission is of the opinion that from an ethical standpoint there are no objections to the proposed study. The study was approved on 09-09-2020.”

Committee’s reference number: MP015702

Consent for publication

Not applicable.

Availability of data and materials

Data are available upon request to the corresponding author.

Competing interests

Steven Simoens (SS) has previously conducted research about market access of orphan drugs sponsored by the Belgian Health Care Knowledge Centre and by Genzyme (now Sanofi), and he has participated in an orphan drug roundtable sponsored by Celgene. SS is a member of the ISPOR Rare Disease Special Interest Group’s Challenges in Research and Health Technology Assessment of Rare Disease Technologies Working Group, the International Working Group on Orphan Drugs, and the Innoval Working Group on Ultra-Rare Disorders.

Kathleen Claes has received consultancy fees from Alexion, Astellas and Sanofi. Isabelle Huys reports no conflict of interest.

Funding

This research was funded by grant G0B9819N received from the Research Foundation of Flanders (FWO, Fonds voor Wetenschappelijk Onderzoek). The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data;

preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Authors' contributions

KA, LF, CC, IH, KC and SS contributed to conception and design of the study. KA, LF and CC acquired the necessary data for the research that was analysed and interpreted by all authors. KA drafted the manuscript under supervision of IH, KC and SS. All authors critically revised the manuscript, read and approved the submitted version.

Acknowledgements

I would like to express sincere gratitude towards Lennert Follon and Charlotte Calis for their invaluable assistance during this study, and towards the focus group discussion participants for their willingness to share their expert opinions.

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- Appendix1FGDguide.docx