



# Design recommendations for a Romanian Innovation Fund for Medicines

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# Summary

## *The case for investment: high amenable mortality rates in Romania*

While health outcomes in Romania have improved significantly over the past 20 years, the country still has among the worst rates of 'amenable' mortality<sup>1</sup> in Europe: two to three times the EU average. This means that an estimated 60,000 deaths could be prevented per year if optimal quality health care were available to all. Strong cost-containment measures and restrictive patient access to innovative therapies contribute to the relatively low health spending in Romania, which accounts for 5.5% of GDP versus an EU average of 8.1%.

Given the strong association between low health expenditure and high amenable mortality, there is a strong case for increased investment in health in Romania. Investment in the population's health must be considered in its broadest sense, but a key part of this is keeping up with global advancements in innovative treatments. In recognition of the limited access to and slow uptake of innovative therapies in Romania, we outline key recommendations for the creation of a Romanian Innovation Fund which could provide earlier access to potentially life-saving medicines and improve population health.

## *What can we learn from other European Innovation Funds?*

We evaluated four European Innovation Funds which fall into three broad categories:

- Pre-EMA authorisation, accelerated access scheme (French Temporary Use Authorization (ATU) scheme)
- Parallel funding for high-efficacy drugs (Italian Innovative Drugs Fund)
- Access with evidence generation (Czech Highly Innovative Drugs Programme and English Cancer Drugs Fund (CDF))

By carefully assessing the core objectives, design, and operational practicalities of each of the funds, and considering these in relation to the prevailing conditions in Romania, we make a series of recommendations for the design of a Romanian Innovation Fund.

## *Key design recommendations for the Fund*

- **Timeline:** The Fund should principally seek to 'bridge the gap' between EMA approval and a Romanian health technology assessment (HTA), similar to the French post-ATU model.
- **Exit:** The exit mechanism from the Fund should be based on formal Romanian HTA. Mechanisms to ensure continuity of treatment for patients up until effective routine reimbursement (where relevant) should be agreed and developed. Equally, will be important to negotiate continuity of care for patients where a medicine is not approved for routine reimbursement.
- **Eligibility criteria:** Eligibility for the Fund should target serious conditions with recognized unmet medical need (consistent with EMA's PRIME criteria) and be based on specific, quantitative criteria tailored to local practice – particularly around amenable mortality in light of Romania's relatively poor outcomes in this area.
- **Financing:** The Fund should comprise a new, dedicated ('ring-fenced') budget to increase total healthcare resources whilst also facilitating transparency and budget predictability.
- **Institutional responsibility:** OHE recommends that the Fund should be administered by the social insurer (CNAS), with the Romanian HTA agency (ANMDDMR) being responsible

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<sup>1</sup> *Amenable mortality refers to avoidable deaths. i.e. deaths that could have been prevented with the provision of optimal quality health care (i.e. timely and effective medical treatment in the light of prevailing medical knowledge and technology)*

for the evaluation process for medicines eligibility. In general, we recommend that responsibilities within an Innovation Fund align as closely as possible with existing responsibilities for the general pharmaceuticals budget.

- **Reimbursement within the Fund:** alternative contracting approaches may be appropriate, particularly financial-based drug or patient expenditure caps, which would balance budget predictability, protection against budget over-runs, and minimal data infrastructure requirements.

### *Next steps*

Identifying new financial resources to dedicate to the Fund requires a collaborative approach, the result of which must inform eligibility considerations. In order to develop explicit eligibility criteria, we recommend further research into the key contributors of amenable mortality in Romania, including which can be best addressed with innovative medicines, to ensure clear rationale for the eligibility criteria and maximum impact on population health. The administrative responsibilities and timelines should be developed in collaboration with all relevant stakeholders and should rely where possible on current infrastructure and capabilities. In addition, the legal framework – and identification of legislation requiring amendment – must be investigated and developed to enable implementation of the Fund.

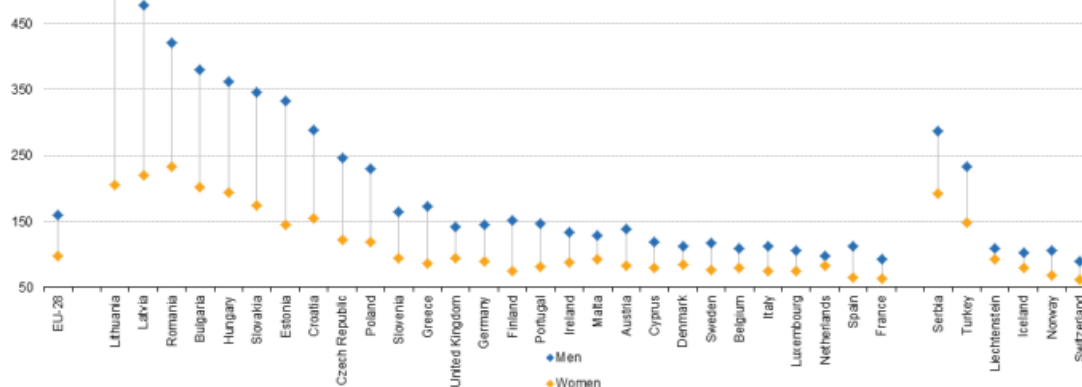
# 1. Introduction and context

Across the globe, the return on investment of a healthy, thriving population is well recognised. However, delivering this is hugely complicated and countries diverge significantly in their approaches, owing in part to their unique contexts. In Romania, spending on health is relatively low, and so too are the overall health outcomes of the population. Increased investment in the population's health must be considered in its broadest sense, but a key part of this is keeping up with global advancements in innovative treatments. The overarching goal of this report is to support the development of a system in Romania which recognises the role of innovative medicines can play in improving the health of the population, and considers how a cost-effective use of innovative medicines might be achieved through the creation of a medicines innovation fund.

## Poor health outcomes in Romania

As detailed in The Economist Intelligence Unit (EIU) report on financing health and medicines in Romania (2018), the country has seen significant improvements in health over the previous 20 years: life expectancy at birth has risen by 5.5 years since 1998, while the infant mortality rate has more than halved, from 20.6 deaths per 1,000 live births in 1998 to an estimated 9.3 deaths in 2017.

However, as illustrated in Figure 1, Romania still has among the worst rates of 'amenable' mortality in the EU, ranking only above Lithuania and Latvia out of the 28 countries of the EU. A death is considered to be 'amenable' if it could have been avoided through optimal quality health care (Eurostat, 2018), highlighting the importance of having sufficient health system resources and using them effectively. The amenable mortality rate in Romania is more than three times the EU average for males and two times the EU average for females.



Note: The figure is ranked by total amenable mortality rate.  
Source: Eurostat (online data code: hlth\_cd\_apr)

eurostat

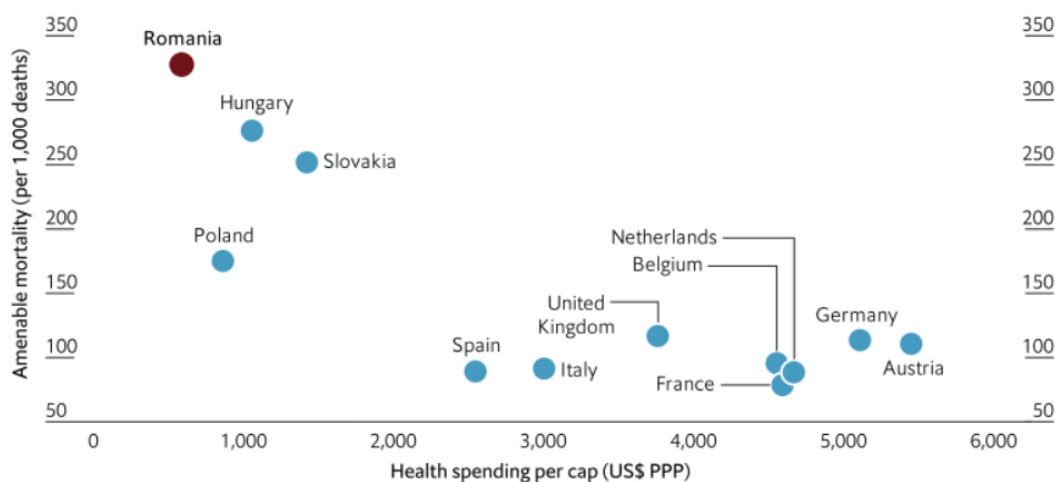
**FIGURE 1: EU AMENABLE MORTALITY RATES PER 100,000 BY COUNTRY AND SEX, 2015**  
(From Eurostat, 2018)

Based on these amenable mortality rates and the current Romanian population of 9.1 million males and 9.66 million females (Countrymeters, 2020), up to 45,500 male and 14,400 female amenable deaths could be avoided each year through the provision of optimal quality health care (i.e. the provision of timely and effective medical treatment in light of the prevailing medical knowledge and technology).<sup>2</sup>

*Romania spends significantly less on health than EU counterparts*

Health spending in Romania is among the lowest in the European Union<sup>3</sup> (EU), accounting for 5.5% of gross domestic product (GDP) in 2016 compared to an EU average of 8.1%. This relatively low overall spending carries over to pharmaceutical spending, where per capita spending on drugs is approximately US\$200 compared to a per capita average of US\$220 in Eastern Europe and US\$450 in Western Europe (The Economist Intelligence Unit, 2018).

The EIU report highlights the strong negative relationship between amenable mortality and health expenditure, at least in the lower ranges of expenditure per capita, illustrated in Figure 2.



Sources: Eurostat, The Economist Intelligence Unit.

**FIGURE 2: AMENABLE MORTALITY VS HEALTH EXPENDITURE, 2017**  
(From The Economist Intelligence Unit, 2018)

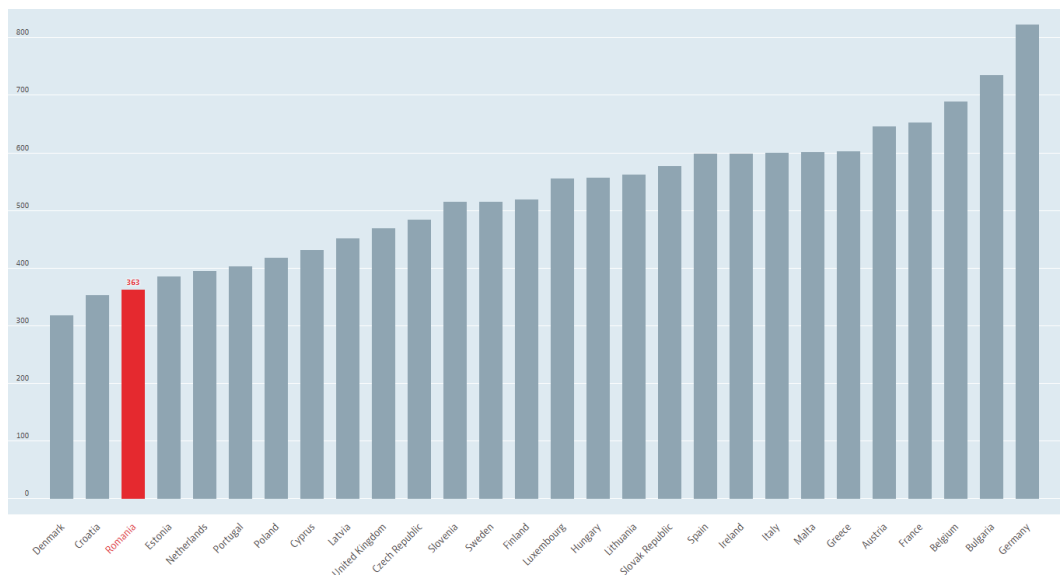
The relationship between lower health system expenditure and higher amenable mortality is perhaps most problematic around pharmaceutical expenditures, as Romania has among the lowest pharmaceutical sales per capita in the EU (Organization for Economic Cooperation and Development, 2020), illustrated in Figure 3 below (Romania in red). The EIU report suggests this low spending reflects low public coverage for drugs and an absence of a voluntary health insurance (VHI) market, leading to a high out-of-pocket burden on patients (The Economist Intelligence Unit, 2018).

<sup>2</sup> Avoidable deaths =  $\frac{\text{amenable mortality per 100,000}}{100,000} \times \text{population}$

<sup>3</sup> Throughout this report, European Union figures prior to 2020 include the United Kingdom.

### Emphasis on cost-containment in health expenditure

This low absolute spending is exacerbated by specific cost-control measures in Romania that meant the list of reimbursed drugs was not updated between 2008 and 2015, blocking patient access to new medicines over this period (The Economist Intelligence Unit, 2018). Cost-control objectives have also led Romanian pharmaceutical policy to focus on generics. By definition, this approach prioritises older medicines over the newest and most innovative products (The Economist Intelligence Unit, 2018).



**FIGURE 3: PHARMACEUTICAL SALES PER CAPITA, 2018**  
(From Organization for Economic Cooperation and Development, 2020)

### Restrictive patient access to innovative medicines

In Romania new medicines are assessed on the basis of cost-effectiveness and a positive health technology assessment (HTA) is required before a medicine can be publicly reimbursed. However, the average HTA decision in Romania can take almost a year from the time of submission (The Economist Intelligence Unit, 2018), adding an additional barrier to patients accessing new medicines. To some degree, the focus on cost-containment may also prioritise consideration of the budget impact of new medicines rather than their relative efficiency, and may fail to take into account their impact on broader and/or downstream health care costs .

The combination of low per capita drugs expenditure, a historic focus on generic medicines driven by cost-containment priorities, and greater concern for budget impact than the relative efficiency of new medicines has restricted access to the most innovative new medicines. This restriction precludes any improvements in the amenable mortality that could be achieved through the timely uptake of new medicines. Restricted access also limits efficiency gains that could be realised by reducing direct or indirect costs elsewhere in the in the system.

To address the challenge of ensuring timely access to innovative new medicines within the constraints of the Romanian health system, the EIU report recommends the introduction of a **Medicines Innovation Fund**. Such a fund, modelled on existing European funds, could accelerate

patient access to innovative medicines, improve health outcomes and reduce future healthcare costs.

Section 2 of this report summarises different medicines innovation funds in the United Kingdom, France, Italy, and the Czech Republic. Section 3 draws on the characteristics of these European innovation funds to make specific recommendations for a Romanian innovation fund, including the positioning of a Romanian Fund in the approvals timeline; medicines eligibility criteria; financing of the Fund; institutional responsibility for the fund; and pricing and reimbursement of medicines in the Fund. Section 4 provides a discussion of alternative contracting approaches for reimbursing medicines during their eligibility for the Fund. Finally, section 5 summarises the report and lays out next steps in the development of a Medicines Innovation Fund for Romania.

## 2. Summary of existing European innovation funds

To understand the options available to Romania for implementing an Innovation Fund, it is important to learn lessons from the funds currently operating in Europe. We undertook a search of the published and grey literature to understand the kinds of challenges that innovation funds aim to address in their respective health systems and how the design of these funds varies to meet these different objectives.

We found four innovation funds in Europe with enough published information to review: the Cancer Drugs Fund (CDF) in England; the Temporary Use Authorisation (ATU) scheme in France; the Innovative Drugs Fund in Italy; and the Highly Innovative Drugs (HID) programme in the Czech Republic. These funds are schematically illustrated in Figure 1 below with respect to their positioning relative to EMA approval, national marketing authorisation and national HTA review.

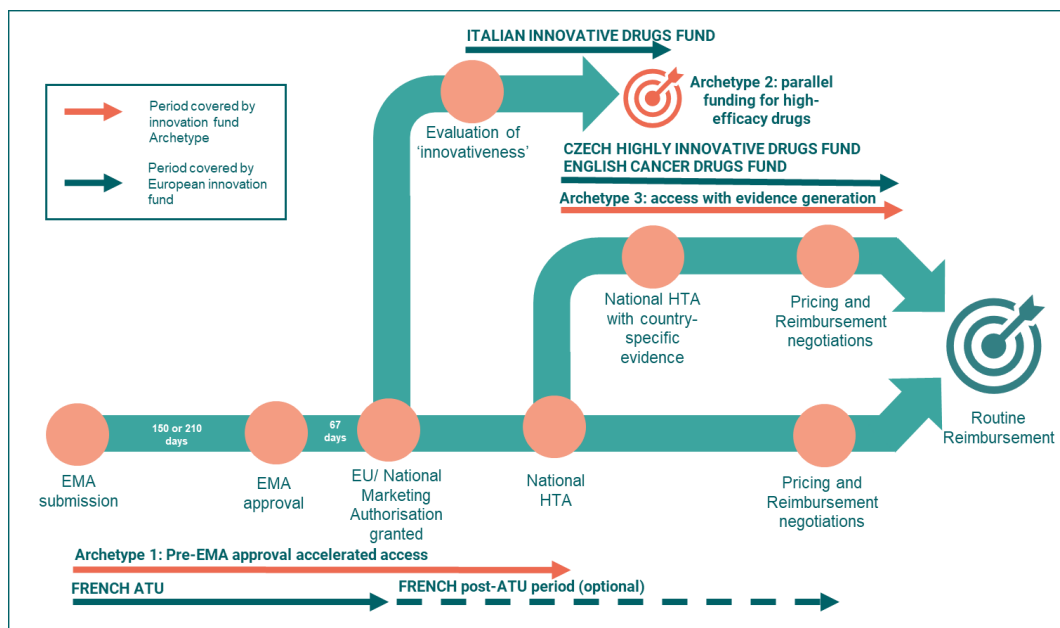


FIGURE 1: SCHEMATIC OF REVIEWED INNOVATION FUNDS

Broadly these funds conform to three general archetypes:

1. **A pre-EMA authorisation, accelerated access** scheme. The aim of this type of fund is to speed up access to drugs before they are formally licensed, and therefore before HTA and routine reimbursement decisions are finalised. This archetype is mainly followed by the French Temporary Use Authorization scheme.
2. **Parallel funding for high-efficacy drugs** to ensure dedicated funding is available for new, high-efficacy drugs and to reduce competition for limited national or regional pharmaceutical budgets. This type is analogous to the Italian Innovative Drugs Fund.
3. **Access with an evidence generation obligation** is used by both the Czech Highly Innovative Drugs Programme and the English Cancer Drugs Fund in slightly different ways. This type of fund combines *earlier* access with an obligation to generate additional evidence when uncertainties in the clinical or economic evidence prevent a final decision on value-for-money. Medicines are not available until the completion of the initial HTA and therefore access is later than pre-HTA funds (i.e. the French ATU) but it allows widespread access during real-world evidence generation and a follow-up HRA. In this sense, access is accelerated relative to medicines that must await final HTA approval.

Although the different archetypes are associated with different objectives, all the funds share four key considerations: the size and control of the budget of the fund; the eligibility criteria; the price setting mechanism and the exit criteria. The remainder of this section will explain and compare these key design considerations across the European funds. We present these funds for information purposes and note their specific strengths and limitations but do not suggest that any single fund should be adopted as a template for a Romanian fund. It will be more useful to incorporate aspects of each of the funds in a bespoke Romanian Innovation Fund.

## 2.1. Cancer Drugs Fund: England

The main objective of the Cancer Drugs Fund (CDF) is to accelerate access and support evidence generation for promising cancer medicines (NHS England, 2016). It was initially established as a temporary solution to increase access to cancer drugs that were not routinely available on the NHS and to act as a bridge to value-based pricing, which was subsequently not implemented. The CDF was revamped in 2016 to improve access to promising cancer medicines with incomplete clinical or economic evidence. A future iteration of the fund has been suggested to transition the Cancer Drugs Fund to become the Innovative Drugs Fund, which will also be available for non-cancer drugs.

The CDF is allocated an annual ring-fenced budget of £340 million making it one of the smaller innovation funds by budget of the four European funds. The increased scope of the Innovative Drugs Fund is likely to have an increased budget of £500 million/year to cover additional indications. In the pre-2016 fund, a major problem was significant budget over-spends. This led to the adoption of a net cost-correction mechanism in the revamped, post-2016 fund to avoid over-spend while ensuring that new drugs and patients can still access the fund. Under this cost-correction mechanism, if the annual budget is reached and another drug enters the fund, reimbursement is reduced proportionally for all companies receiving funding through the CDF. It has been termed a "haircut." Acceptance of this cost-correction mechanism is a pre-requisite for receiving funding from the CDF.

The CDF is the only fund among those reviewed that limits access to only one group of therapeutics based on disease. All new drugs, regardless of their indication, can be referred to the National Institute for Health and Care Excellence (NICE) for appraisal by Ministers at the

Department of Health and Social Care. For cancer drugs, NICE then undertakes an appraisal using the same process and criteria as for any other technology appraisal. The key difference is that if it is judged that there is 'plausible potential' for the drug to meet standard criteria for routine commissioning but there is too much uncertainty around cost-effectiveness to make a positive recommendation, then NICE can recommend the drug for use within the CDF instead of simply accepting or rejecting it at this stage. If a drug has been recommended for use within the CDF, NICE issues a Managed Access Agreement which specifies the necessary data collection required to resolve the areas of clinical uncertainty and defines the eligible patient population. In the proposed Innovative Drugs Fund, non-oncology drugs will also be eligible and this 'access with evidence generation' option will be more widely available. However, it is not clear whether the appraisal criteria will be adapted for the new Innovative Drugs Fund.

As well as the Managed Access Agreement stating the data collection requirements, a Commercial Agreement is signed as part of this, and is negotiated after NICE recommends the drug for use within the CDF. This determines how much the health service will pay for the treatment during its time in the CDF. One advantage of the CDF design is that this Commercial Agreement optionally can include a 'patient access scheme', which can offer an opportunity for industry to use non-standard contracting models (such as outcome-based pricing). In reality, however, non-standard contracts are rarely used and the NICE/NHS pricing committee responsible for price-negotiation for the CDF typically secures a large discount in exchange for faster access to the English market. The CDF price is not made public, unlike some of the other European funds who publicise the prices negotiated at this stage. Offering large discounts for access to the CDF is more likely to be tolerated by manufacturers because the Commercial Agreement is confidential and therefore prices cannot be used for referencing pricing by other countries.

The duration of funding in the CDF is set on a case-by-case basis and is defined in the Managed Access Agreement, unlike all the other European funds which define a set time for inclusion in the fund. This gives the CDF flexibility to address different types of clinical uncertainty and be responsive to the maturity of the clinical evidence base and the time of the initial appraisal but may add an administrative burden. The duration of data collection, and therefore the duration of inclusion in the CDF, is informed by the appraisal committee and finalised through discussions between NICE, NHS England and the manufacturer. NICE expects that normally CDF funding will last no more than 2 years, but this is not an upper limit and may be longer depending on the data collection required. The end of CDF funding is marked by NICE's final appraisal of the drug and a decision on whether the drug should be recommended for routine commissioning. The drug must exit the scheme at this point – either into routine commissioning or to be rejected for further NHS funding.

The main institutions involved in administering the CDF in England are the HTA body (NICE) the payer (NHS England) and the Ministry of Health, the Department of Health and Social Care. Ministers in The Department of Health and Social Care are responsible for referring drugs to ministers to be appraised by NICE. NICE conducts the initial HTA and its guidelines determine the eligible patient population and the data collection agreement is informed by the recommendations of the NICE appraisal committee and finalised through negotiation between NICE, NHS England and the manufacturer. NICE also conducts the final HTA and gives a recommendation on whether the drug should be routinely reimbursed. A joint NHS England/ NICE CDF Investment Group has an overseeing role including managing the overall budget, determining when the cost-control mechanism is applied and approving CDF Managed Access Agreements.

## 2.2. Temporary Use Authorisation: France

The French Temporary Use Authorisation (ATU) scheme is a combination of a Compassionate Use scheme and an innovation fund. The main aim of the ATU is to ensure quicker access to drugs not yet covered by a Marketing Authorization in France when there is unmet medical need (ANSM, 2015). The dual aims of this fund, Compassionate Use and innovative drug funding, are met through the two forms of the scheme: the nominative ATU and the cohort ATU. The nominative

ATU is a named patient access scheme while the cohort ATU grants access for a specific patient population. While the budget, process and eligibility criteria are similar for the nominative and cohort arms of the ATU scheme, it is the cohort ATU that is most similar to a conventional innovation fund. This report will therefore discuss the cohort ATU scheme only. Any mention of the nominative ATU arm will be flagged and is only used when required to explain the processes or limitations of the cohort ATU.

Unlike the CDF, the ATU scheme does not have a ring-fenced, fixed, annual budget and ATU drugs are reimbursed through the Social Security Pharmaceutical Innovation Fund which is part of the social insurance system. The scheme is said to exceed EUR 1 billion/year which makes it one of the biggest funds alongside the Italian fund. However, the majority of the patients and the budget of the ATU scheme is allocated through the nominative ATU arm – 217 drugs and 15,987 patients for nominative ATUs in 2018 compared to 20 drugs and 5,642 patients for cohort ATUs in the same year (Cosset et al., 2020). This suggests that the process for recruiting patients for a cohort ATU presents an administrative barrier that limits uptake. This may be because cohort ATU drugs can only be prescribed after the treating physician has sent a treatment access request to the manufacturer, who then sends the drugs to the hospital pharmacy on a case-by-case basis. To forecast demand for the ATU scheme, the manufacturer has to inform the French Medicines Regulator, ANSM, of the number of eligible patients and the number of patients expected to be included in each year of treatment.

Eligibility for the ATU is based entirely on unmet medical need and it is the only fund that gives access to drugs for the period before EMA authorisation. The cohort ATU covers drugs that meet the following subjective criteria for a defined cohort of patients:

- The medicinal product is intended for the treatment, prevention or diagnosis of serious or rare diseases,
- No other appropriate treatments are currently available for the indication in France
- Efficacy and safety in use are strongly presumed based on the results of clinical trials carried out with a view to submitting a MA application
- The medicinal product is likely to offer a real clinical benefit and the introduction of treatment cannot be deferred.

Drugs included in the scheme can only be prescribed in hospitals for either inpatient or outpatient use, with inpatient drugs funded from a different part of the existing pharmaceutical budget.

The cohort ATU is granted for a group or sub-group of patients. The eligible patient cohort is defined in the ATU application according to the protocol for therapeutic use and information collection (PTU). The PTU also defines the information that will be collected during the ATU period and can be used to inform the HTA after Marketing Authorisation has been granted. While there is an evidence generation requirement, it is not as strong a requirement as in the CDF and is limited by the timing of the scheme relative to the initial HTA. As the ATU is available before an HTA is completed, the areas of clinical uncertainty cannot be defined by the French HTA body and the PTU is submitted by the manufacturer. This is unlike the CDF, that runs after the initial HTA is completed, which allows NICE to set the data collection requirements based on the areas of clinical uncertainty that they identified during HTA. Because of this, or because of relatively low patient numbers using the cohort ATU scheme, the information collected during the ATU phase is often not used during HTA which reinforces the view that the ATU scheme is designed to address access rather than generating useful, real world evidence.

Free pricing applies to cohort ATU drugs whereby manufacturers set their own price for reimbursement during the ATU period and is generally regarded as an upper limit for reimbursement in France. If the reimbursed amount exceeds EUR 10,000 per patient per year, ATU holders must reimburse the difference to ANSM, excluding drugs with turnover of less than EUR 30 million/year during the ATU phase. This cap was introduced to control free pricing; however, this threshold is rarely reached. At the end of the ATU phase, if the routine reimbursement price negotiated with the reimbursement committee (CEPS) is lower than the ATU price, the manufacturer can be asked to pay back some or all of the difference between the ATU price and the reference net price. In addition, if CEPS decides not to reimburse the drug in France following

the HTA, then it can decide on a reference price and ask the company to reimburse the difference between the ATU price and the reference price for sales during the ATU period.

Despite this rebate obligation, there is suggestion that free pricing may make the ATU scheme unaffordable. Recent legislation (the 2020 French Social Security Financing Law) has removed free pricing for the nominative arm of the ATU for which prices will now be set by the Ministry of Health. While the cohort ATU was not included in this legislation, and free pricing is still used for the cohort arm of the scheme, the changes could be extended to the cohort ATU in the future.

The duration of eligibility for the cohort ATU lasts for one year with an opportunity to apply for an additional year. In addition, if the manufacturer has not already applied for Marketing Authorisation at the time of applying for a cohort ATU, it must do so within one year of obtaining a cohort ATU. The ATU scheme has an optional second phase of funding through the post-ATU stage which enables the drug to be funded while HTA and price negotiations are completed. The post-ATU phase is optional for ATU holders, and to receive reimbursement through the post-ATU phase, the manufacturer has to request reimbursement within one-month of receiving a Marketing Authorisation. The post-ATU phase has no time limit and is set by the length of the P&R negotiations.

The main administering body for the ATU scheme is the French Agency for the Safety of Medicines and Health Products (ANSM). ANSM is the French medicines regulator whose function is somewhat analogous to MHRA in the UK. Unlike the CDF, which is initiated by NICE, the manufacturer must apply to ANSM for a cohort ATU. The ATU application contains the PTU which defines the treatment protocol, the eligible patient population, and the number of eligible patients in France and the data collection plan. The ATU application is approved by the relevant disease area team in ANSM mainly based on the safety and pharmaceutical quality. The French Health Care Products Price Committee (CEPS), which sits in the Ministry of Health, has to be informed by the manufacturer of the price that will be charged during the ATU although there is no price negotiation at this stage.

### 2.3. Innovative Drugs Fund: Italy

The Italian Innovative Drugs Fund is very different from the French ATU and the English CDF in design as it offers an alternative funding route rather than transition funding until routine reimbursement. The main objective of the fund is to provide a source of funding for high-efficacy drugs: drugs that are deemed highly clinically beneficial and “cost-effective but unaffordable”, with the ultimate objective of ensuring equal access to innovative drugs across the country.

Like the CDF, the Italian fund has a ring-fenced, fixed budget of EUR 1 billion each year, with half earmarked for oncology therapies and the other half for all other indications. Unlike the CDF and the ATU, which are administered nationally, the Italian fund is divided sub-nationally and regions are allocated a fraction of the overall budget depending on their level of pharmaceutical spending per capita. If regions over-spend on their portion of the fund, they have to cover the over-spend from their own health budgets. There is an overall budget control mechanism which states that if spending on an individual innovative drug exceeds the budget, the overspend is compensated 20% by company concerned and 80% shared by other companies participating in the fund.

Eligibility for the Italian fund is dependent on a formal assessment of ‘innovativeness’, similar to the Czech fund. Drugs are assessed on three criteria: unmet therapeutic need, added therapeutic value and quality of evidence and can be graded as either Innovative, Conditionally Innovative or Not Innovative on the basis of the assessment. Innovative drugs are able to access the Innovation Fund and are immediately added to regional formularies, whereas Conditionally Innovative drugs are not able to access the fund but can benefit from being added immediately to regional formularies. Drugs that are found to be ‘Not Innovative’ cannot access the fund or be added to regional formularies. The HTA process and the assessment of the innovative status are based on similar evidence, but the procedures are separate and not necessarily sequential. There is no price-setting

implication if a drug has received Innovative status, however reimbursement is set through a Managed Access Agreement as is used in the CDF. The Italian Innovative Fund is the only European fund with no evidence generation expectation during the period of accessing the fund.

The process of moving from the Innovation Fund to routine reimbursement in Italy is not clear and these processes are not necessarily intended to be sequential. However, like the ATU scheme there is a time limit for inclusion in the fund, with 'first in class' drugs able to access the fund for up to 36 months. 'Follower' drugs that are categorised as Innovative benefit like First in Class drugs that are classed as Conditionally Innovative and are not able to access the fund but can benefit from automatic inclusion in regional formularies for the remaining duration of the original Innovative status award.

The Italian medicines regulatory agency, AIFA, is responsible to assessing the innovativeness of drugs and decides whether a drug can access the fund. They are also responsible for setting the criteria for Innovativeness which were most recently renewed in 2018. AIFA is also responsible for negotiating pricing and reimbursement for routine commissioning so is likely to have this role for drugs reimbursed through the Innovation Fund. Regional governments are responsible for managing their allocated portion of the fund and are liable to cover over-spends from their own budgets.

## 2.4. Highly Innovative Drug Programme: Czech Republic

The Czech Republic's Highly Innovative Drugs Programme is the only innovation fund we found to be operating in Central and Eastern European health systems. The objective of the Highly Innovative Drug Programme is to speed up access for patients to highly innovative drugs and to generate real world evidence for the use of the drug in the Czech population to inform national HTA (Ornstova et al., 2018; Skoupá, 2017). It is broadly similar to the CDF in the timing of the fund but has some similarities to the Italian Innovation Fund and the French ATU.

The main similarity with the ATU scheme is that the programme does not have a fixed, ring-fenced budget but is a mechanism for temporary reimbursement of innovative drugs through the same budget as routinely reimbursed drugs. In order to control the cost of the programme a risk-sharing agreement has to be signed by the manufacturer to limit the financial impact of innovative drugs on public health and much of the administrative burden (e.g. managing registries) is also covered by the manufacturer.

The temporary reimbursement mechanism offers time-limited reimbursement for drugs that are assessed to be Highly Innovative Drugs (HIDs). The criteria for innovativeness are based on drugs which show higher efficacy or improved safety compared to alternative treatments or drugs for diseases with no alternative treatments. Drugs that are judged to be HIDs but exceed the maximum acceptable cost-effectiveness threshold for permanent reimbursement can receive conditional reimbursement through the Highly Innovative Drugs Programme. This has similarities to the Italian Innovation Fund because of its focus on 'high efficacy' drugs and incorporation of an 'innovativeness rating'. However, unlike the Italian Fund, where Innovative status automatically allows a drug to access the fund, HIDs in the Czech Republic that are also found to be cost-effective following HTA enter straight into routine reimbursement instead of the HID Programme.

HID status can only be achieved if drug fulfils at least one of the three high-level HID criteria:

- Higher efficacy or safety compared with alternative therapies
- Current care lacks effective therapy and the drug has significantly higher efficacy
- It has proven higher efficacy but there is information lacking about cost-effectiveness or cost-effectiveness in real clinical practice

The quantitative interpretation of each of these criteria is presented in Table 1.

**TABLE 1: CZECH HIGHLY-INNOVATIVE DRUG FUND ELIGIBILITY CRITERIA**

<b>1. Innovative treatment provides significant efficacy relative to current SOC:</b>
<ul style="list-style-type: none"> <li>• <math>\geq 40\%</math> reduction in AEs, serious complications, drug interactions or drop-outs; or</li> <li>• Median survival gain <math>\geq 2</math> years (or <math>\geq 50\%</math> where expected survival <math>&lt; 24</math> months)</li> </ul>
<b>2. Current care lacks effectiveness. Innovative treatment provides:</b>
<ul style="list-style-type: none"> <li>• <math>\geq 20\%</math> reduction in mortality; or</li> <li>• <math>\geq 40\%</math> survival gain in patients with <math>&lt; 24</math> month expected survival; or</li> <li>• <math>\geq 30\%</math> extension in time to hospitalization; or</li> <li>• <math>\geq 30\%</math> reduction in serious clinically relevant symptoms</li> </ul>
<b>3. Innovative treatment has efficacy but uncertain effectiveness or cost-effectiveness and:</b>
<ul style="list-style-type: none"> <li>• No alternative treatment available; or</li> <li>• New concept of treatment and meets criteria of unmet need</li> <li>• Condition resistant to alternative treatments and innovative treatment meets criteria of unmet need</li> </ul>

*(Ornstova et al., 2018)*

As with the French fund, patients can only access the drugs included in the HID Programme at specialised health centres which control the budget and ensure good quality of data collection. Manufacturers must take on responsibility for running local patient registries to monitor outcomes and to verify results of pivotal clinical trials in the Czech context.

As the HID Programme is specifically available for drugs that do not meet the national cost-effectiveness threshold (CZK 1.2 million/QALY) which is strictly required for permanent reimbursement, prices are likely to be higher than for routine reimbursement. The temporary reimbursement price for the duration of the HID Programme is based on per-pack reference pricing across all European countries and the lowest per-pack price is used.

The minimum period for temporary reimbursement through the HID Programme is 2-years with an optional 1-year extension on the basis of additional information gathering through patient registries. At the end of the 2-3 year period, if the drug is found to be cost-effective in a second HTA, it will be added to permanent reimbursement mechanism, otherwise funding will be stopped and the drug will no longer be available. On joining the HID Programme, manufacturers must commit to cover ongoing treatment costs of existing patients if permanent reimbursement (i.e. cost-effectiveness) is not achieved at the end of the temporary reimbursement period. While the costs during the HID Programme are likely to be high, the Programme allows the Czech government to give access to high-efficacy drugs during the most 'expensive' period for that drug. It therefore enables them to delay routine reimbursement pricing decisions until reference pricing across Europe is likely to have significantly reduced the price of the drug while benefiting from generating real world evidence to inform their HTA process.

The main administering body of the HID Programme is the State Institute for Drug Control (SUKL) which is the regulatory body responsible for undertaking HTA and managing pricing and reimbursement of medical products in the Czech Republic. SUKL assesses whether a drug meets HID criteria and undertakes a cost-utility analysis. The temporary reimbursement agreement that allows drugs to be reimbursed under the HID Programme must be signed by the manufacturer which includes the risk-sharing agreement and an agreement to manage patient registries. Drugs are reimbursed through the public health insurance scheme and are only accessible at health centres contracted by public health insurance fund to manage the budget. The public health

insurance fund and SUKL are both supervised by the Ministry of Health but are different administrative bodies.

### *Summary of European Innovation Funds*

National health spending in the four European countries operating Innovation Funds is shown in Table 2 and the key characteristics of these funds are summarised and contrasted in Table 3 on the next page. The spending proportions in Table 2 imply that the Innovation Funds in UK, France, and Italy represent 0.01%, 0.03%, and 0.04% of national GDP, respectively.

**TABLE 2: SUMMARY OF HEALTH, PHARMACEUTICAL AND INNOVATION SPENDING BY COUNTRY**

	Innovation Fund annual budget	Health spending as % GDP	Pharmaceutical spending as % health spending	Pharmaceutical spending as % GDP	Innovation Fund as % Pharma spending
<b>France</b>	1 billion EUR	11.6	13.2	1.5	2.16
<b>United Kingdom</b>	350 million GBP	9	11.9	1.1	1.03
<b>Italy</b>	1 billion EUR	9.2	17.5	1.5	2.88
<b>Czech Republic</b>	Pending source	7.5	17	1.2	Pending source
<b>Romania</b>	NA	5.2	26	1.3	NA

(OECD, 2020)

**TABLE 3: SUMMARY OF EUROPEAN INNOVATION FUNDS**

	England Cancer Drugs Fund	French ATU	Italian Innovative Medicines Fund	Czech Republic Highly Innovative Drug Program
<b>Stated Primary Objective</b>	Enable access and support evidence generation for promising cancer medicines	Accelerated access for drugs addressing unmet need before and during MA and HTA review process	Exceptional funding for drugs deemed clinically beneficial and “cost-effective but unaffordable”	Enable access and collection of real-world evidence through a temporary reimbursement mechanism
<b>Access before or after EMA approval</b>	After	Before	After	After
<b>Access before or after HTA</b>	After	Before	Before	After
<b>Ring-fenced, Fixed budget vs open budget</b>	Yes (£340 million/year)	No (Estimated EUR 1 billion/year)	Yes (EUR 1 billion/year)	No
<b>Evidence generation requirement</b>	Yes, set by NICE based on first HTA	Yes, set by manufacturer before HTA	No	Yes, set by SUKL after first HTA
<b>Inclusion based on 'innovativeness'</b>	No	No	Yes	Yes
<b>Number of HTAs required</b>	2	1	1 (+ 'innovativeness' assessment)	2
<b>Transition to routine funding vs bespoke funding route</b>	Transition funding during evidence generation period	Transition funding to routine funding	Bespoke funding route	Transition funding during evidence generation period
<b>Fixed duration vs case-by-case duration</b>	Case-by-case	Fixed 1 year (with extension available)	Fixed 36 months	Fixed minimum 2 years with 1-year extension available

## 3. Key design considerations for a Romanian Innovation Fund

The following sections outline specific issues for consideration in the design of an Innovation Fund for medicines in Romania. These points will cover:

1. Positioning the Fund in the authorisation-approval timeline;
2. Eligibility period and exit process for medicines included in the Fund;
3. Specific definitions and eligibility criteria for including medicines in the Fund;
4. Pricing and reimbursement of medicines in the Fund;
5. Financing and budgeting of the Fund;
6. Institutional responsibility for the Fund.

The report will outline alternative courses of action for each point, with reference to the design of the other European funds outlined in section 2. It is important to note, however, that many of these issues are inter-related and adopting one design option can restrict the options available in addressing others. As a result of this 'path dependency' across different elements, it is difficult to make many concrete recommendations and this section will focus on enumerating alternatives and issues for discussion or negotiation between the LAWG and the Romanian government.

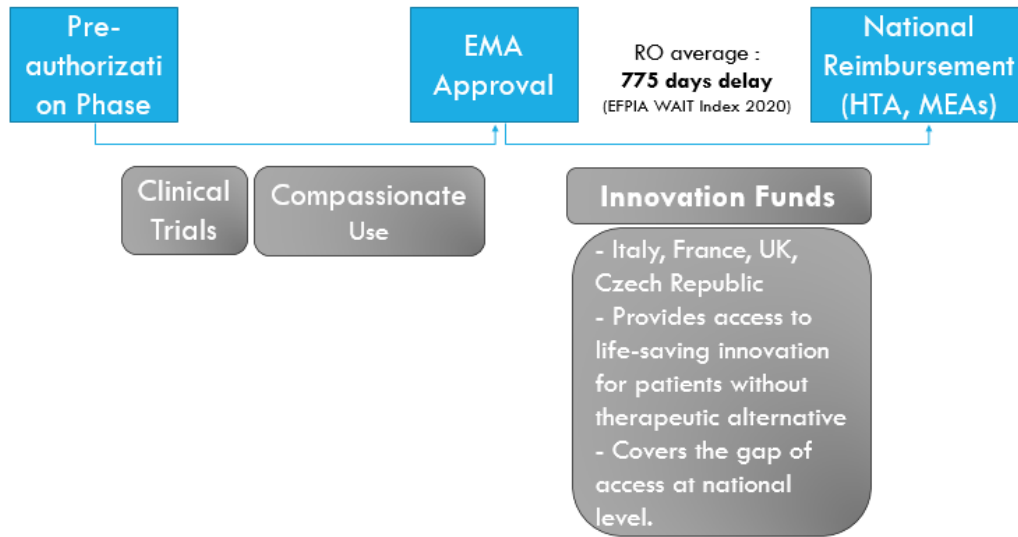
### 3.1. Positioning the Fund in the authorisation-approval timeline

The longer the gap between clinical development and routine reimbursement, the longer the delay in patients accessing innovative and potentially life-saving medicines. This is the access gap that an innovation fund can bridge, and the European funds reviewed above aim to bridge different parts of it. Broadly, funds either cover the gap pre-EMA authorisation (French ATU), or they cover the gap between EMA (or similar) authorisation through to national HTA (French post-ATU, Italian fund), or beyond initial HTA through to a follow-up HTA on the basis of a more mature evidence base (Czech HID and UK CDF).

A fund that gives access to patients before EMA authorisation must carefully manage the uncertainty around safety and efficacy at this early stage of the regulatory process. This can be done by limiting access only to the lowest risk patients (as in the case with the Czech HID where clinical trial eligibility criteria are used) and by closely monitoring individual patients for safety signals (which appears to be done for the French ATU). The implications of these measures for equity and access will be discussed in more detail in section 3.2. The other downside of a fund that gives access before EMA authorisation is that it has to offer funding for drugs for a longer period of time, with a correspondingly higher cost burden on the fund. While the French ATU scheme is technically a pre-EMA authorisation access fund, the post-ATU phase gives funding for the remaining time post-EMA authorisation before its assessment for routine reimbursement.

Most of the European funds provide for access post-EMA-authorisation and before national HTA and Pricing and Reimbursement (P&R) negotiations are finalised. This part of the access gap varies significantly between countries because of differences in resources and expertise in the HTA and P&R process, as well as national procurement processes.

## Access to innovation in Romania



**FIGURE 4: SCHEMATIC OF ACCESS TO INNOVATION IN ROMANIA**  
(SOURCE: LOCAL AMERICAN WORKING GROUP ROMANIA)

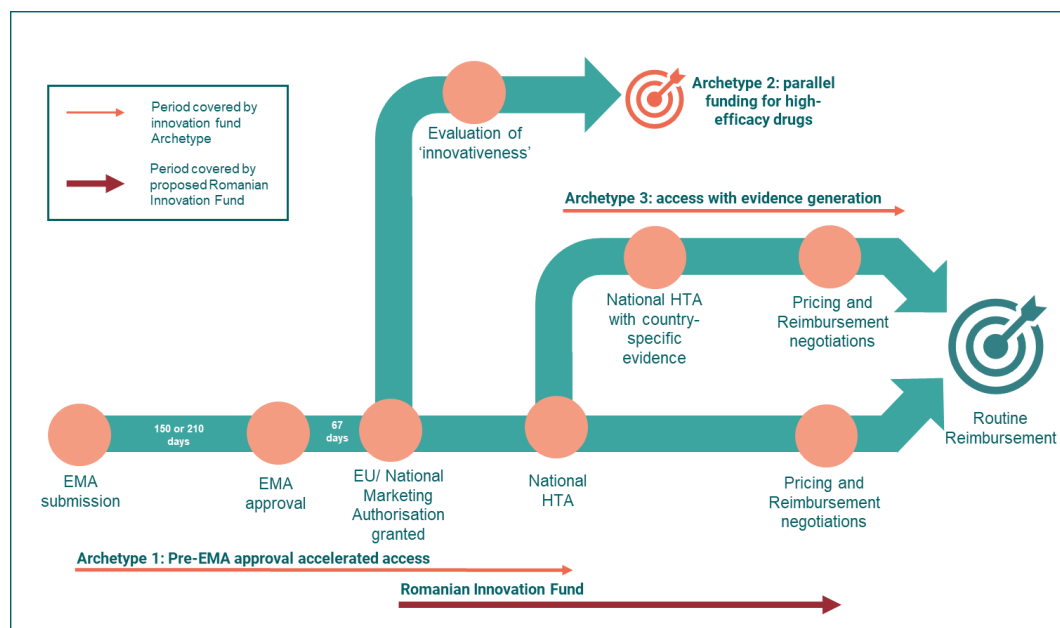
The EU “Transparency” Directive (directive 89/105/EEC) outlines a series of procedural requirements designed to ensure that national pricing and reimbursement decisions within the EU are transparent and do not create undue obstacles to pharmaceutical trade (Council Directive 89/105/EEC of 21 December 1988 relating to the transparency of measures regulating the prices of medicinal products for human use and their inclusion in the scope of national health insurance systems). A key requirement is that decisions be made within a specific timeframe: 90 days between the receipt of an application and a decision around price (Article 2), and 90 further days where relevant for a decision to be made on the inclusion of a medicinal product on a positive list covered by the national health insurance system. However, this timeframe does not include the time needed to prepare submissions under relevant national regulations (which may include pauses for the supply of additional information) or the time required to complete other formalities before a new medicine can actually reach a patient. Across Europe, the time delay between marketing authorisation and patient access varies greatly between countries, from an average of 119 days in Germany to over 900 in Serbia; the EU average is 445 days (IQVIA, 2019). Romania is not included in the EFPIA’s 2018 Patient W.A.I.T. Indicator survey, but according to the European Health Consumer Index (EHCI) 2018 report time to access is rated in the poorest category of >300 days for Romania (Bjornberg and Phang, 2019).

Whilst long processes of HTA review do delay patient access, it is not the only factor. In a joint initiative ‘Time to Patient Access’ by the EFPIA Oncology Platform, one of the key factors identified in delaying patient access to innovative therapies in Europe – which is particularly pertinent in the Romanian context – is the *late start* of the reimbursement process (EFPIA, 2020). This includes the late submission of reimbursement dossiers by pharmaceutical companies due to external reference pricing, as well as due to some countries requiring the input of the final reimbursement decisions of other countries, before starting their own HTA. For Romania, this includes the need to incorporate the HTA outcomes of France, UK and Germany, as well as achieving more “points” based on a medicine’s reimbursement status in other EU countries<sup>4</sup>. This leads to inevitable delays in Romania, and is only the first of many steps on the road to reimbursement, which involves:

<sup>4</sup> The scorecard is based on six criteria: HTA decisions from France, UK and Germany, the number of EU countries with reimbursement, the development of a local real-world data study, and a budget impact assessment.

- Time from EMA approval to HTA: applications to Romanian HTA require prior assessment in France, UK and Germany, as well as the completion of other criteria that must inform the submission for the scorecard assessment.
- Reimbursement process: the time for HTA evaluation of the submission
- Negotiation: cost-volume agreements by the social insurer (CNAS)
- Prescription protocol: publication of the prescription protocol by the Ministry of Health
- Reimbursement: update of the reimbursement list by Government decision (once or twice per year, without a predictable calendar).

The benefit of bridging the gap between EMA approval and national HTA and P&R negotiations is that the fund can be used to generate evidence that is needed to complete the final HTA. Evidence generation is a priority for the CDF (which is positioned after an initial HTA). The Czech fund also uses this period to generate real world evidence, but the evidence generation requirement is used as a risk sharing mechanism with the manufacturer in the Czech fund to a greater extent than in the CDF. An additional benefit of bridging this gap is that the fund can overcome limitations in HTA expertise when safety and efficacy are more certain (i.e. after EMA authorisation), and the clinical risks of granting access are lower. **Given the extended length of time between EMA approval and completion of the Romanian HTA process, and a relative scarcity of evaluative capacity, OHE recommends positioning the fund prior to the HTA, similar to the French model after EMA authorisation (i.e. French post-ATU).** The recommended positioning of a Romanian fund relative to other European funds is illustrated in Figure 5.



**FIGURE 5: SCHEMATIC OF INNOVATION FUNDS INCLUDING PROPOSED ROMANIAN FUND**

### 3.2. Eligibility period and exit process for innovative medicines

#### *Should exit be linked to HTA?*

One of the biggest challenges, alongside budget control (covered in 3.5), is managing the transition of drugs from the fund into routine reimbursement. The European funds have opted for a fixed inclusion duration or an exit criteria linked to a formal HTA. For the CDF, the duration of eligibility is

set within the Managed Access Agreement on the basis of the evidence generation required and drugs exit the funds after a final HTA. This is similar to the French post-ATU phase, which has no fixed time duration and ends when the drug enters routine reimbursement. However, the French ATU, Czech HID Programme and Italian funds all have set inclusion durations, with or without a possibility for extension. The French and Czech funds are notable for a redundant 'dual-exit' approach, with an HTA requirement as well as a maximum duration for eligibility. The justification for this approach is not clear. One explanation may be that the maximum duration is intended as an incentive for the completion of an HTA. Another is that a maximum duration may act as a clearing mechanism to ensure that unassessed medicines do not accumulate in the fund due to delays in the HTA process. This justification, though, seems to weaken the centrality of HTA and has the potential to exclude efficacious and potentially cost-efficient medicines from regular reimbursement for prosaic administrative reasons.

Under either a fixed eligibility period or an HTA-linked exit, it is likely that some patients will no longer be able to access beneficial medicines they started whilst it was covered by the fund. The French ATU has the post-ATU funding period to overcome this problem. A similar mechanism should be included in a Romanian Fund for the ongoing use of medicines that were initiated during eligibility for the Fund but expired or were not approved by an HTA.

A benefit of having a set inclusion duration is that there are no administrative barriers to clearing medicines from the fund, easily freeing budget for other products. The downside, however, is that by delinking exit from the final HTA, there may not be an incentive for the HTA body to formally evaluate medicines and allow them to expire from the fund rather than issue a formal rejection. This could lead to inconsistency and a lack of transparency in decisions, or the use of the HTA timeline for advantage in P&R negotiations. As importantly, an HTA will ensure that only the most cost-efficient medicines transition to regular reimbursement. **Therefore, OHE recommends that the exit mechanism from a Romanian Innovation Fund be based on a formal HTA.**

In cases where HTA results in a negative decision, funding from the innovation fund would cease but arrangements should be in place to ensure continuity of treatment for those patients already on therapy, for example with costs covered by the manufacturer (as is the case for other funds; this may require a pre-defined cut-off for enrolment of patients so it is clear to the manufacturer what their liability would be). For positive HTA decisions, the Innovation Fund should continue to pay for the therapy up until effective routine reimbursement (i.e. until the conclusion of pricing and reimbursement negotiations, including contracts and prescription protocols). Consideration could be given to specifying a time limit to negotiations between manufacturer and payer between the HTA decision and routine reimbursement, to avoid unnecessary delays that may arise from an incentive to prolong the "best deal" for either party (e.g. if the reimbursed price during Innovation Fund eligibility is particularly higher/lower than the final reimbursed price). Alternatively, a "claw-back" mechanism could be introduced which would involve a re-payment of the difference between the two prices over that period.

### 3.3. Specific definitions and eligibility criteria for including medicines in the Fund

In the following subsections, OHE discusses specific elements of overall eligibility for the proposed Innovation Fund.

#### *Existing criteria vs custom criteria*

One of most important design considerations for an innovative medicines fund is defining the eligibility criteria. The first consideration is whether the criteria are the same as for routine commissioning or whether they differ to specifically include certain kinds of drugs. The former is the model used by the CDF, whereby a fund is a bridging mechanism for cancer drugs that need some additional real-world evidence to inform cost-effectiveness calculations and routine reimbursement negotiations. The second mechanism, where inclusion criteria are more specific than the conditions

for routine reimbursement, are used by the other three European funds which allows them to specifically prioritise 'innovative' drugs. While they each use slightly different criteria, all the funds are based on addressing unmet medical need for diseases which cause serious morbidity or mortality. **Given the Romanian context, where the priority is to address amenable mortality, OHE recommends the use of specific criteria – particularly around mortality – to prioritise innovative drugs to address unmet need.**

### *Qualitative vs quantitative criteria*

The European funds which are available specifically for innovative drugs use subtly different eligibility criteria, with the main difference being the extent to which they rely on qualitative, expert deliberation versus more quantitative benchmarks. The French ATU is available for drugs for serious or rare conditions where there are no other appropriate therapies available for the indication in France and where efficacy and safety are 'strongly presumed' from the available data. The decision on whether a drug meets these qualitative criteria is taken by disease-specific expert teams within ANSM, the fund's administering body. This contrasts with the Czech HID Programme which has strict, quantitative criteria. For example, to show that a drug improves on existing therapies, it must be associated with at least a 20% improvement in survival or 40% fewer adverse events. The Italian Innovation Fund, which balances unmet medical need, added therapeutic value and quality of evidence, incorporates elements of quantitative assessment with expert opinion (Fortinguerra et al., 2020).

There are benefits and limitations to qualitative (e.g. French ATU) and quantitative (Czech HID Programme) eligibility criteria. The primary benefit of qualitative criteria is that there is more discretion and flexibility at the boundary to include drugs that are judged to be innovative but may not meet strict quantitative criteria for various reasons. Refreshed eligibility criteria for the Italian fund in 2018 which incorporated expert opinion and therefore added more flexibility were seen to be effective (Urbinati, Rova and Cioni, 2018) and may suggest a tendency towards more discretionary qualitative criteria as a fund matures.

Fewer discretionary quantitative criteria ensures that specific criteria are met and avoids spending resources on marginally innovative medicines. Quantitative criteria have the additional benefit of being very transparent, both to manufacturers and to citizens who are concerned about the risks of inconsistency or special treatment for some groups. However, quantitative criteria may make it difficult to address some qualitative objectives such as equity of access or outcomes.

Both qualitative and quantitative approaches require some technical and evaluative expertise to effectively assess drugs against defined eligibility criteria, but **given the relative scarcity of the evaluative capacity in Romania, OHE recommends the use of quantitative criteria as these are likely to be easier to implement; these could be combined with qualitative criteria either now or in the future if resources allow.** As in the Italian model, it would be possible to incorporate more qualitative criteria as Romanian experience with the Fund increases.

The Czech HID criteria outlined in Table 1 offers a template for a quantitative approach focusing on improvements in survival or a reduction in adverse events. A limitation of the Czech criteria is that they prioritise survival gains over quality-of-life improvements, although this is consistent with the earlier recommendation of focusing on reducing amenable mortality as the primary objective of the fund. The advantage of survival criteria is that they are relatively easily measured in clinical trials. Incorporating quality-of-life gains in the criteria will be difficult prior to a QALY-based HTA.

### *'Piggy-back' eligibility criteria*

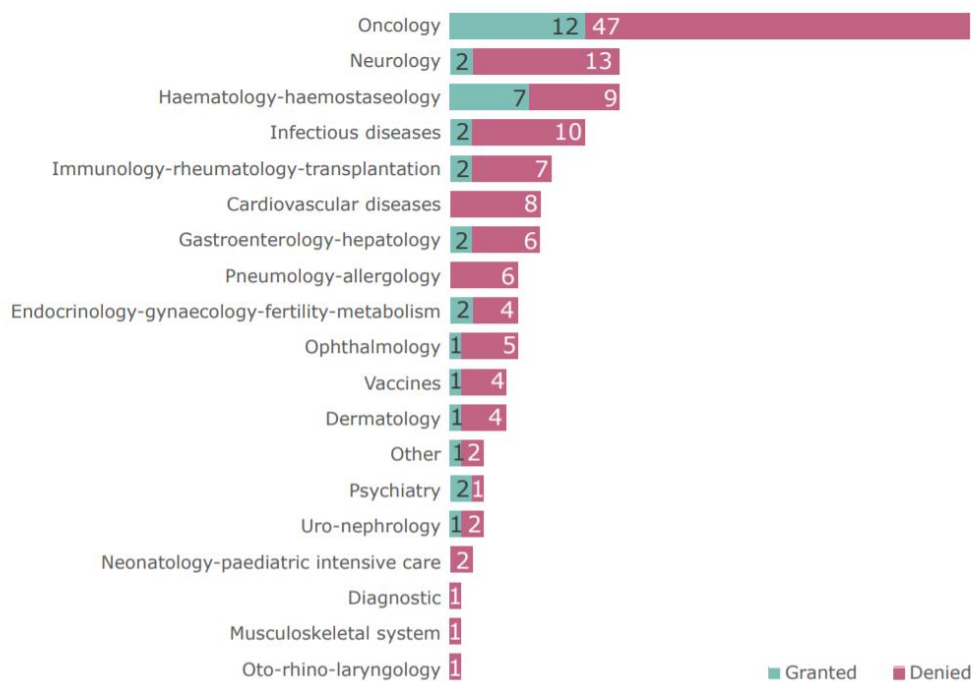
A Romanian innovation fund will need to use eligibility criteria that can be assessed effectively using existing resource and expertise within the country. To overcome limitations in national HTA capacity and to reduce the administrative burden of the fund, it may be possible to piggy-back on innovation criteria designated at the European level. The EMA has two programmes for accelerated access to drugs which address unmet medical need: the PRIME scheme and Orphan designation. The PRIME scheme gives regulatory support to drugs for conditions where there is unsatisfactory

diagnosis, prevention or treatment or for medicinal products which will be of major therapeutic advantage to those affected (European Medicines Agency, 2018a). To be eligible for PRIME, medicines must:

- Target conditions where there is an unmet medical need, i.e. for which there exists no satisfactory method of diagnosis, prevention or treatment in the Community or, even if such a method exists, in relation to which the medicinal product concerned will be of major therapeutic advantage to those affected;
- Demonstrate the potential to address the unmet medical need for maintaining and improving the health of the Community, for example, by introducing new methods of therapy or improving existing ones (European Medicines Agency, 2018a).

Within these criteria, approval is based on deliberative discussions amongst scientific experts.

The Orphan designation encourages the development of drugs for life-threatening or chronic diseases with a low prevalence in the EU (European Medicines Agency, 2018b). Notwithstanding the separate Orphan designation, the PRIME scheme is also heavily weighted towards medicines for rare diseases, with 30 of 36 approved medicines in the period between 2016 and 2018 for rare conditions (European Medicines Agency, 2018c). The majority of submitted and approved medicines were oncology-related.



**FIGURE 6: EMA PRIME SUBMISSIONS BY DISEASE AREA AND APPROVAL STATUS, 2016-2018**  
(FROM EUROPEAN MEDICINES AGENCY, 2018C)

While there are benefits to using the PRIME scheme or Orphan designation, a clear downside is that it is not possible to tailor the criteria to address the national context. Relying on these schemes would bias a Romanian innovation fund to disproportionately include Orphan medicines which, by definition, would only be available to very few patients and therefore would be unlikely to significantly reduce amenable mortality at a national scale. Indeed, cardiovascular disease appears to be the primary source of amenable mortality in Romania, and this condition is not typically

associated with orphan drugs. Orphan drugs are relatively over-represented in the Italian and French funds, whose eligibility criteria favour drugs for rare diseases. This is either explicit, as in the case of the French fund where 'rare' drugs are mentioned, or implicit, which is the case for the Italian fund where it is easier for orphan drugs with more uncertain evidence to get Innovative status (Fortinguerra et al., 2020).

**OHE recommends prioritising medicines that deliver meaningful innovation to all patients with unmet need, consistent with EMA's PRIME criteria.** To ensure that benefits accrue as widely as possible, orphan status should not be a primary eligibility criterion.

### *Which patients should be eligible for the fund?*

As well as specifying the inclusion criteria for drugs to enter the fund, all the European funds also specify the patient population eligible to access those drugs. When defining the patient population, there is a trade-off between cost-containment and maximising access. If the eligibility criteria are very broad, then total costs will be higher and average efficacy may be lower if patients who are relatively less able to benefit from a specific drug can access it. On the other hand, though, narrowly defining an eligible patient population will limit the population health impact. Stricter eligibility criteria may be necessary for funds like the ATU that provide access before EMA authorisation and therefore have greater uncertainties around safety and efficacy. The Czech fund also restricts access to patients meeting the eligibility criteria of the original clinical trials. The European funds use the patient population definition to control costs, at the expense of access, to varying degrees. In the CDF, NICE defines the eligible patient population in the Managed Access Agreement broadly by the indication of the drug. However, for the French ATU, the manufacturer has the responsibility for specifying the eligible patient population and an estimate of the number of patients expected to be treated in the ATU application. The eligible patient population for the Czech fund is set by SUKL (the administering organisation) and typically uses the eligibility criteria from the pivotal clinical trials. This reduces the administrative burden of setting bespoke eligibility criteria for each drug but comes with its own administrative burden by requiring prescribers to confirm and recording each patient's specific eligibility criteria. Adopting the eligibility criteria of clinical trials is also likely to have implications for fairness and equity of access to innovative medicines, as most trials restrict eligibility to younger participants with limited comorbidities. They also most often restrict the participation of pregnant women for safety reasons.

The French and the Czech funds also limit access by mandating that drugs be prescribed from hospitals. The Czech fund goes even further by limiting access to specific hospitals contracted by the public health insurance fund. The downside of limiting access to inpatient care is that treatment costs could increase by requiring patients to be admitted to hospital to access the drugs. It may also exacerbate inequality as it limits access for patients who live further from hospitals, which is an existing problem that limits healthcare coverage in Romania (The Economist Intelligence Unit, 2018).

Narrow eligibility criteria act as a cost-containment mechanism and ensure that medicines are used by those most able to benefit but come with additional administrative burdens. They may also restrict women and older patient groups from accessing a medicine if the restrictions are based on the clinical trial population. Hospital-based prescribing requirements may also be associated with unnecessary admissions as physicians seek to secure access for their patients. Eligibility must be balanced with defined criteria to ensure efficient and sustainable use of medicines in the Fund. **OHE recommends eligibility based on a medicine's indication in the EMA marketing authorization, not the eligibility criteria of the pivotal trial(s), with no artificial restriction on the location of prescribing.** The challenges of budgeting with this model of eligibility will be covered in section 3.4.

### *Appraising Innovativeness*

From the preceding discussion, it is clear that there are different approaches to appraising innovativeness with respect to eligibility for the Innovation Fund, from adopting external appraisals of innovation, to internal Romanian appraisals based on quantitative or more qualitative criteria.

- Fund any medicines approved by the PRIME EMA scheme (or one of the other European Innovation Funds). This would simplify evaluation but would not necessarily prioritise conditions associated with the greatest unmet need in Romania.
- Eligibility based on demonstrating defined survival gains or reductions in adverse events in pivotal clinical trials. This may or may not be restricted to defined priority disease areas (potentially based on amenable mortality). This is likely to favour specific classes of medicines – particularly those associated with survival gains rather than improvements in quality of life.
- Subjective expert appraisal based on clinical trial data as well as expert medical opinion. This is the most complex process and will require considerable expertise to synthesise and evaluate the available data. The advantage of a more qualitative approach is the ability to adapt to a greater range of medicines, including consideration of quality-of-life as well as survival.

It is essential to recognise that eligibility for a Fund intended to accelerate access to the most innovative medicines must necessarily be restrictive. If the threshold for “innovative” is set too low, the Fund will be overwhelmed with “new” rather than truly innovative medicines. A quantitative scorecard designed to prioritise conditions associated with high amenable mortality would provide an objective and defensible basis for eligibility to a new Innovation Fund in Romania, although it would be relatively inflexible in its ability to consider more subjective patient benefits such as improvements in quality of life. As the Fund matures and evaluative capacity in Romania increases, it may be appropriate to include more qualitative criteria in the appraisal of innovativeness.

### 3.4. Financing and budgeting of the Fund

#### *Ring-fenced vs not ring-fenced?*

The European innovation funds use both ring-fenced and non-ring-fenced budgets. Ring-fencing is process by which a portion of a larger budget is reserved for a specific purpose. In this case it refers to ‘ear-marking’ a portion of the pharmaceutical budget specifically and exclusively for the innovation fund. Whether the money that is reserved in this way is additional funding for the overall budget or just a portion of the same budget will not be discussed here. However, given the Romanian context of under-spending on pharmaceuticals relative to other European countries, it is assumed that an innovation fund would need to be financed through additional funding.

The significant benefit of a ring-fenced budget is that forecasting, and budget control are easier and more transparent. The downside of ring-fencing is that if the dedicated budget is reached, then access to the fund is closed to new patients and medicines. Funds with ring-fenced budgets therefore need mechanisms to maintain access to the fund when the budget has been reached, whereas funds that do not have ring-fenced budgets need mechanisms to control the budget to prevent over-spending.

The French ATU scheme and the Czech HID Programme are both non-ring-fenced funds i.e. there is no specified budget cap. The French ATU scheme allows manufacturers to set the price with the condition that they have to reimburse the difference when the final reimbursement price is negotiated. The ATU also asks the company to predict the number of patients treated under the ATU in their application. These two mechanisms are used to enable budget forecasting and cost-containment. Free pricing within the ATU is under review as costs per treatment are often very high, and the nominative ATU has ended free-pricing in March which may be extended to the cohort ATU in the future. This suggests that the rebate mechanism alone is a weak cost-containment measure. The Czech HID Programme takes a more substantial risk-sharing approach

with manufacturers than the French scheme. The Czech fund requires the manufacturer to sign a risk sharing agreement and manufacturers are expected to entirely fund data collection as well as the continued cost of patients already on treatment if at the end of the fund, a price cannot be negotiated that meets strict cost-effectiveness criteria.

The Italian fund and the CDF are examples of ring-fenced funds and both have a cost-containment mechanism to ensure that new patients and drugs can enter the fund after the fixed budget has been reached. Both funds have had issues with overspending in earlier iterations which demonstrates that ring-fenced funds can still overspend if there is no cost-containment mechanism. The CDF's cost-containment mechanism means that when a new drug enters the fund and the budget is already allocated, the prices reimbursed to the other drugs are all reduced proportionally to maintain the budget cap. Manufacturers have to agree to the mechanism before entering the CDF. The Italian fund has a similar mechanism whereby any overspend in the fund is reimbursed 20% by the company concerned and 80% by the rest of the companies in the fund. The downside of these mechanisms is that they need to be enforced through contracting and they have to be 'triggered' which adds an administrative burden.

**Given the notably low levels of per capita pharmaceutical spending in Romania, OHE recommends that the Fund should comprise 'new' health resources and not be 'carved-out' from the existing health budget.** To avoid resources being used to address short-term needs, it should also be dedicated (ring-fenced) for innovative medicines. A dedicated budget will also facilitate transparency and predictability.

### *Fund size and potential funding sources*

Setting the total budget of a Romanian Innovation Fund is a political matter and outside the scope of this report, but as an initial reference point we suggest that based on the funding of the UK, French and Italian funds as a proportion of national GDP (see Table 2), **a target amount for a Romanian fund could be between 30 and 100 million Romanian lei, or US\$6 to US\$24 million at current exchange rates.**<sup>5</sup>

Similarly, identifying the politically and economically optimal funding source(s) for a Romanian Innovation Fund is outside the scope of this report and requires detailed consideration of the efficiency impact of different funding and taxation options on health sector and the wider economy. To inform these considerations, the remainder of this section provides a brief overview of the Romanian fiscal situation and identifies different options and associated considerations.

Potential sources of financing were suggested by "Resources for Healthcare" Platform participants at LAWG Working Groups gathered in 2019. These suggestions are reported in LAWG's "White Paper on Innovation in Healthcare" and summarised below:

- Widening the contribution base and revising categories of persons exempt from healthcare contributions. The health system funding in Romania is particularly reliant on contributions from a relatively small portion of the population: only 1/3 of beneficiaries of the health systems are also contributors, which is unsustainable in the long term. However, there are potential negative equity implications associated with shifting more of the financing burden to older or sicker users of the healthcare system.
- Transfer of taxes (already in place) collected by the Romanian government for health purposes directly to the healthcare budget. In this approach, it will be important to identify corresponding priorities for disinvestment in order to free-up resources.
- Increased collection of existing taxes by the fiscal authorities.
- Development of Voluntary Health Insurance system, that could take part of the burden from the public health system.
- Non-reimbursable external funds, especially from the European Union. To this end, central health authorities need to develop their project management capability, including by setting up and staffing dedicated compartments.

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<sup>5</sup> [1 LEI = US\\$0.23 as of 25/06/2020](#)

- Analyse if a system similar to the pension funds could be considered for healthcare, in order to finance the Innovation Fund for Medicines. This would mean that a percentage of the mandatory contribution to public health would be directed to finance the Fund (as a second pillar, managed by the state).

### 3.5. Institutional responsibility for the Fund

Each of the European funds involve some collaboration between HTA agencies, national payers/insurers, and Ministry of Health:

- **HTA agency:** To ensure that scarce healthcare resources are used as efficiently as possible, as well as to ensure consistent and transparent reimbursement decisions, it is important for national HTA agencies to be involved in any innovation fund. These bodies provide expertise in assessment and are the gatekeepers to routine reimbursement and may also be responsible for price negotiations.
- **Payer/Insurer:** In multi-payer social insurance systems, including Romania, insurers generate the revenue used to fund healthcare providers. In single-payer, tax-financed systems such as the UK, this function is performed by the Treasury. These bodies have responsibility for generating resources for healthcare and, in some instances, will have responsibility for contracting provision.
- **Ministry/Department of Health:** In public healthcare systems, Ministries/departments of Health are responsible for monitoring population health needs and the provision of healthcare. In some systems the provider is also responsible for price negotiations. These bodies will have the most information on sources of amenable mortality.

In the case of the English CDF and the Czech HID fund, HTA agencies act as a gatekeeper for entry to and exit from the funds through a formal HTA, but the administration and pricing of the CDF is managed by the NHS, whilst the Czech fund relies on reference prices identified by the HTA body (State Institute for Drug Control). In the French ATU, the fund is administered primarily by the HTA agency (ANSM), which also conducts a formal HTA, but pricing is managed by the Ministry of Health. In the Italian Innovation Fund, the HTA agency (AIFA) assesses the eligibility of medicines on the basis “innovativeness” and conducts price negotiations but does not conduct a formal HTA.

In general, Ministries of Health are the most political of the organisations involved. To ensure the objectivity of the funds, their interaction with most of the European funds is minimal and typically limited to price negotiations following eligibility assessment by an HTA agency. HTA agencies are integrally involved in the administration of the other European funds, consistent their expertise in assessment and their perceived objectivity. HTA agencies act gatekeepers for entry and exit in most of the other funds, but given the limited capacity of the Romanian HTA agency, reflected in long HTA timelines, this agency may not be in a position to take on additional responsibilities in the short term. The involvement of payers/insurers in the other funds is mixed. The NHS is closely involved in the CDF, but insurers/providers play less of a role in the other funds. However, the critical role of insurers importance in securing funding for new healthcare initiatives, either through social insurance premiums or taxation, should not be underestimated. This is particularly true for lower-resource countries such as Romania where additional spending is tightly constrained and may require extensive political negotiation.

**Given capacity limitations with the Romanian HTA agency (ANMDDMR) and the political challenges of securing new funding, OHE recommends that the Fund should be administered by the social insurer (CNAS).** As funding becomes more secure and capacity within the ANMDDMR grows, it may be appropriate to re-assess this responsibility in the longer-term.

This would result in a split of administrative responsibilities:

- ANMDDMR would be responsible for the evaluation process to include medicines in the Fund, based on a dedicated and transparent methodology. It would also require a dedicated Department within ANMDDMR, with technical experts specialized on pharmacoeconomics. It is also important that the process of including and maintaining a product in

the Fund does not affect the ongoing process of HTA and does not delay access into reimbursement for medicines temporarily reimbursed through the Fund.

- National Health Insurance House (CNAS) would be responsible for the implementation of management entry agreements with producers, therefore covering the contracting phase of this temporary reimbursement process. The increased capacity of CNAS is also necessary, to better respond to the process needs.
- Ministry of Health would be responsible for developing and publishing the prescription protocols for the medicines approved by ANMDM for temporary reimbursement through the Fund.

Considering that the objective of the Fund is to make medicines available to patients with unmet medical needs as quickly as possible, it is important that timelines for evaluating eligibility, agreeing pricing, and developing a prescribing protocol should also be as accelerated as possible. In general, prescribing protocols must balance population health effects with cost control. OHE recommends prescribing eligibility should be based on a medicine's indication in the EMA marketing authorization rather than a location of prescribing or clinical trial eligibility criteria as in the Czech Fund.

As already described, many innovation funds in Europe also have a data collection function, offering a way to capture the real-world outcomes associated with the medicines administered through the fund. This could be a worthwhile future aspiration for the Romanian Innovation Fund, which would require investment in patient registry and other data collection platforms, as well as evaluative capacity within the HTA function of ANDMR.

### 3.6. Pricing and reimbursement of medicines in the Fund

The pricing of innovative medicines is inherently challenging (Cole et al., 2019), and this challenge is amplified by the temporary nature of the Fund and the accompanying uncertainty over long-term reimbursement. Manufacturers must be adequately compensated for the development of an innovative medicine, and to participate in a fund with attendant administrative hurdles, whilst the government must be satisfied that it will not overpay for a medicine that has not yet been evaluated and may not ultimately demonstrate acceptable clinical effectiveness or value-for-money.

The different European innovation funds have taken different approaches to the pricing of medicines:

- The English CDF allows for managed access agreements and other innovative contracting arrangements but most often simply negotiates a substantial discount on the manufacturer's price following an HTA evaluation with excessive uncertainty. Effectively, the medicine is priced to ensure that it will be cost-effective under conservative assumptions around the uncertain parameters. This price can be reset following re-assessment based on evidence generated whilst the medicine was in the CDF.
- The French ATU allows manufacturers to set their own price during a medicine's time in the fund, prior to an HTA, but if a lower price is ultimately agreed following the HTA, any excess revenue must be refunded by the manufacturer.
- Medicines are only eligible for the Italian Innovative Drugs Fund following HTA, consistent with the notion of funding medicines that can be deemed "cost-effective but unaffordable". Price setting, therefore, is based on some (but not necessarily strict) consideration of acceptable value-for-money, subject to considerations such as unmet need.
- Pricing of medicines in the Czech HID programme is based on per-pack reference pricing across all European countries, and the lowest per-pack price is used. A medicine's time in the HID is intended to generate evidence to inform an HTA and it is possible that the price may increase based on the value it demonstrates in a Czech setting.

To a large degree, these differences in pricing arrangements reflect differences in the timing of the funds (pre- or post-HTA). The English and Czech funds follow a formal HTA that can inform a price that leads to acceptable value-for-money, whereas eligibility for the French fund covers the period prior to formal HTA and therefore considerations of value-for-money cannot directly inform pricing.

The previous discussion of the timeline of the Fund and its recommended positioning prior to a formal HTA in approval process implies unrestricted pricing with a potential claw-back of any excess revenue relative to the acceptable price following HTA, as per the French ATU, or international reference pricing as per the Czech HID. Both approaches have challenges in the Romanian context. First, the earlier a drug is eligible for the Fund following EMA or FDA approval, the less likely it is that there will be other international prices to use as a reference. Second, unrestricted pricing can lead to difficulties around budget predictability and affordability, particularly in more resource-constrained systems such as Romania's. In addition, the mechanisms for retroactively recovering excess expenditure may be legally and administratively challenging.

**OHE suggests that alternative reimbursement models may provide more bespoke solutions somewhere between unrestricted pricing and external reference pricing.** A fuller discussion of potential reimbursement solutions are outlined in [Section 4](#) below.

## 4. Options for alternative reimbursement of medicines within an Innovation Fund

Payer reimbursement of medicines is typically based on a price-volume or 'per pill' payment model, where a fixed price is agreed between the payer and seller, and the seller is reimbursed based on a fixed price per unit multiplied by the quantity purchased. This model is straightforward to implement and minimizes administrative burden on both sides of the arrangement but has important limitations when there is uncertainty around the effectiveness of an innovative medicine or around its potential budget impact as payers seek to avoid over-paying for the benefits a new medicine provides. These uncertainties are likely to be substantial in the context of an innovative medicines fund as, by their nature, these medicines will not have an extensive history of use. The complexity and small patient populations associated with many new, innovative medicines also means there will inevitably be some additional uncertainty relative to older and more established medicines.

Attempting to resolve *effectiveness uncertainty* through additional evidence generation can lead to delays in widespread patient uptake, which can be associated with avoidable patient morbidity or mortality and excess healthcare costs. Alternative contracting, however, can mitigate against uncertainty-related over-payment in a more timely and often more effective manner by shifting some or all of the risk from the payer to the manufacturer. Alternative contracting can also mitigate against *budget uncertainty* and the risk of budget over-runs associated with uncertainty over patient uptake and total budget impact.

Broadly, there are four categories of alternative contracting options that could be used as the basis of a managed entry agreement (MEA) for a Romanian Innovation Fund: financial-based, outcomes-based, patient-based, and indication-based contracting. This section outlines the design of each category. At the end of the section, OHE concludes that a financial-based approach with a hard cap on expenditure per drug or per patient would be the most appropriate for a Romanian Fund, as it would balance budget predictability, protection against budget over-runs, and minimal data infrastructure requirements.

## 4.1. Financial-based contracting

Financial-based contracting mitigates against budget over-runs stemming from uncertainty over the uptake of a new medicine by limiting the total expenditure on one or more medicines. Financial-based contracting includes the following options:

- **Collective drug cap** – Aggregate drugs expenditure in a defined period is capped and manufacturers are collectively liable to reimburse some or all expenditure beyond this cap. Liability is typically shared based on each company's proportional share of total sales.
- **Individual drug cap** – a specific product is heavily discounted or free beyond an agreed volume or total expenditure
- **Tiered** – a refined drug cap contract by which a product is increasingly discounted as different volume or expenditure thresholds are met
- **Subscription** – a fixed amount is paid for unlimited consumption over a defined period (the "Netflix" model)

This form of contracting shifts the risk of excessive utilisation and budget over-runs from the payer to the manufacturer, although there is a risk of over-paying with a subscription model if uptake is less than expected. Implementation of these contracts is relatively straightforward. Drug cap and tiered contracts require agreement on key volume/expenditure thresholds and information on the aggregate prescribed volume or expenditure for a specific product. A challenge, though, can be in distinguishing between wholesale volumes purchased as inventory and the volume actually prescribed to patients. A subscription contract can be even simpler, requiring only agreement on the subscription price as volume information is not required. Subscriptions, though, have a risk of over-payment if less product is used than expected.

## 4.2. Outcomes-based contracting

Outcomes-based contracting mitigates against effectiveness uncertainty, or over-paying for the benefits a medicine provides in a real-world setting. Outcomes-based contracting can be patient level or population level:

- **Patient level** – a target is agreed for individual patient response to treatment and a payer is only reimbursed in full each patient achieving this target, e.g. 6-month cancer remission. Reimbursement may be pro rated for partial response/outcomes.
- **Population-level** – a target is agreed for a population outcome and reimbursement is pro rated according to this outcome, e.g. 80% of patients surviving to 1 year.

This form of contracting shifts the risk of over-payment for a medicine that is less effective than expected in a real-world setting from the payer to the manufacturer. Such a contract can be particularly useful in the context of an innovative medicine with limited real-world evidence. A challenge, though, is that there must be a data infrastructure that allows monitoring of patient-level outcomes and linking specific patients/outcomes to the medicine under contract. There is a similar challenge in linking population outcomes to a specific medicine, as well as around the timeframes required to track longer target outcomes.

## 4.3. Patient-based contracting

Patient-based contracting can mitigate against effectiveness or budget impact uncertainty and can take features of financial- or outcomes-based contracting. Patient-based contracting includes the following options:

- **Patient cap** – a product is fully reimbursed up to a fixed threshold, beyond which the price is free or heavily discounted. This is similar to a drug cap at the individual level.
- **Patient subscription** – a fixed amount is paid for every patient initiating treatment, regardless of outcome. This is, in effect, a subscription contract at an individual level.
- **N-cycles** – the n-cycles model can work in an increasing or decreasing manner. A greater number of cycles may be taken as an indicator of treatment success and the price increases over the number of treatment cycles. Conversely, additional cycles may be taken as an indicator of poor success (e.g. cycles of an antibiotic required to clear an infection) and the price declines beyond a defined number of cycles. This is similar to patient-level outcomes contracting.

Patient caps and subscriptions shift the risk of budget over-runs from the payer to the manufacturer and promote budget predictability. There is still a risk of paying for ‘unused’ product if an individual patient utilises less than expected, although the magnitude of this risk is arguably less than with product-level financial contracts. An n-cycles contract can be used to mitigate the risk of effectiveness uncertainty to the extent that the number of cycles is correlated with a positive or negative outcome. Patient-level financial contracting is likely to require more complex data infrastructure as it requires individual-level rather than population-level utilisation data. N-cycles contracting is arguably more straightforward than outcomes-based contracting but may not correlate perfectly with the desired health outcome.

### *Real-world examples of alternative reimbursement arrangements*

As noted above, alternative reimbursement mechanisms shift some the risk that is conventionally borne by the payers in terms of over-paying for real-world effectiveness and budget unpredictability or over-runs towards the manufacturer. The most appropriate mechanism will depend on the specific circumstances of the medicine to be reimbursed and the health system. Below we outline some examples of innovative contracting in a European context. There are undoubtedly additional examples in practice, but innovative reimbursement arrangements are often confidential and not in the public domain.

- Under the UK's Pharmaceutical Price Regulation Scheme (PPRS), implemented in 2014, the UK pharmaceutical industry agreed to cap the growth in total NHS expenditure on branded medicines at agreed rates. For the first two years of the agreement (2014, 2015), expenditure was capped at 2013 levels. For the years 2016-2018, agreed growth was between 1.8 and 1.9% annually. If this rate was exceeded in any year, the excess expenditure was collectively reimbursed by members of the Association of British Pharmaceutical Industries on a proportional basis relative to their total net sales (ABPI, 2014). The PPRS represents a **financial-based collective drug cap**.
- The PPRS was updated to the Voluntary Patient Access Scheme (VPAS) in 2019. The scheme caps growth in expenditure at 2% per year but includes exemptions for small and medium sized companies. ‘New active substances’ are also exempted from this cap for three years from the month of licensing, beginning in January 2018 (ABPI, 2020). Like the PPRS, the VPAS represents a **financial-based collective drug cap**.
- In 2017, France introduced a reimbursement cap of €10,000 per patient per year on drugs in the ATU with pre-tax sales of €30 million per year (Grubert, 2017). This scheme represents a **patient-based expenditure cap**.
- Sweden reached an agreement with the manufacturer of a new biological drug used to treat metastatic melanoma, which has a cure rate of 20%. The drug was provided free to all patients and the manufacturer was only reimbursed for patients who were cured (Economist Intelligence Unit, 2020). This represents **outcomes-based patient level reimbursement**.
- In Germany, pharmaceutical companies are free to set the prices of new medicines in the first year after launch but are liable to pay rebates if expenditure in that period exceeds

€250 million (Grubert, 2017). This scheme represents a **financial based individual drug cap**.

### *Summary of alternative reimbursement models*

In general, any of the alternative contracting arrangements outlined above can be used until there is a reliable understanding of the effectiveness and budget impact of a specific product, at which point contracting can shift to a standard price-volume contract. This evolution, from alternative contracting to a standard price-volume contract, fits well with an innovation fund aimed at ensuring timely but time-limited market access to innovative medicines prior to a formal HTA, followed by a shift to the general drugs budget. Each of the contract types outlined have specific advantages in terms of shifting risk from the payer to the manufacturer but generally require some investment in data infrastructure. In the Czech Republic, the need for investment in data infrastructure to support evidence generation has been shifted to the manufacturer and a similar approach could be adopted in Romania.

**OHE recommends an individual drug cap as an alternative contracting approach for an early-access Innovation Fund** as it balances budget predictability, protection against budget over-runs, and has minimal data infrastructure requirements. We suggest a model similar to the German example above, where each medicine in the Fund faces a fixed expenditure cap.

The key challenge will be setting an appropriate cap. The simplest solution would be for expenditure on each medicine in the fund to be capped at an equal share of the budget. That is, if there are 10 medicines in the fund, annual expenditure on each medicine would be capped at 1/10<sup>th</sup> of the Fund's annual budget. Should utilization of a particular drug be less than expected, the surplus should be re-invested in the following year's budget rather than transferred to the health budget or general revenue to ensure there is no incentive to intentionally underspend on medicines in the Innovation Fund.

There may be specific medicines or groups of medicines where a more complex approach would be appropriate. An alternative to the individual drug cap is a collective cap, as in the UK and Italian funds, where over-runs are shared across all drugs in the Fund through proportional refunds or reductions in reimbursement (i.e. a shared "haircut").

## 5. Summary recommendations for a Medicines Innovation Fund in Romania

Although there has been considerable progress over the last 20 years in the population health of Romania, there is still considerable room for improvement as amenable mortality (deaths that could have been avoided through optimal quality health care) is more than two times higher than the EU average. Whilst the relative wealth of a country has a big impact on the resources available to invest in and improve health care provision, Romania spends less of its total economic resources on health than the EU average (5.5% of GDP in Romania compared with an EU average of 8.1%). The low levels of Romanian investment in health is particularly stark with respect to pharmaceuticals as Romania ranks third from last among all OECD countries in per capita pharmaceutical sales.

Given a clear correlation between amenable mortality rates and health spend per capita, an increase in health investment is fundamental to avoiding unnecessary deaths in Romania. As the relative underinvestment in health is particularly stark around new and innovative medicines, OHE notes that increased spending on medicines is likely to be a key part of additional investment in a healthier Romanian population. Such investments could reduce mortality, improve quality of life, and potentially lead to longer term cost savings through a reduced need for healthcare. Given the pressures on health spending and resourcing it would make sense for additional spending on innovative medicines, at least initially, to be channelled through a specific innovation fund.

We have not as part of our remit been asked to comment on the appropriate size of the fund. OHE notes that the appropriate size of any fund will be a matter for agreement between the stakeholders. However, discussions on the size should be informed by an understanding of the various priorities for spending in health and the relative contribution they can make to improving amenable mortality in Romania.

In this report, OHE highlighted key design considerations for an innovation fund for medicines and outlined a series of recommendations for its design and implementation in a Romanian context. We also highlighted key issues that must be addressed in the formal design process and/or its ongoing review.

A brief summary of these recommendations and issues:

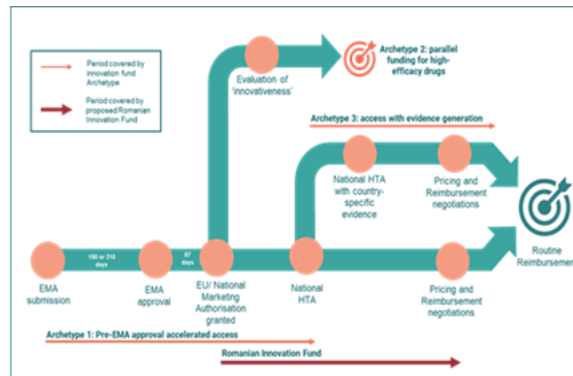
1. **The Fund should ‘bridge the gap’ between EMA approval and a Romanian HTA.** A key source of delayed access to innovative medicines in Romania is the lengthy period between central marketing approval and a local reimbursement decision, during which patients cannot access potentially life-saving medicines. Bridging this gap in access with an innovation fund has the potential to accelerate access and save lives.
2. **Exit from the Fund should be based on a formal HTA.** A set inclusion duration means that there are no administrative barriers to clearing medicines from the fund, easily freeing budget for other products. However, delinking exit from the final HTA could lead to inconsistency and a lack of transparency in decisions. An HTA will ensure that the most cost-efficient medicines transition to regular reimbursement.
3. **Eligibility for the Fund should target serious conditions with recognized unmet medical need (i.e. no therapeutic alternative or current ones lack effectiveness) and be based on specific, quantitative criteria tailored to local practice – particularly around amenable mortality – which address high unmet medical need, regardless of**

**orphan status.** Given high amenable mortality, the key ambition of the Fund should be to prioritise innovative medicines that address unmet medical need for diseases associated with substantial morbidity or mortality in Romania. Clear quantitative criteria tailored to local practice (such as applied in the Czech HID) will promote transparency, ensure that only those drugs offering substantial benefits are supported, and simplify/streamline an otherwise lengthy deliberative process. This final point is particularly important given Romania's relative scarcity of evaluative capacity. As experience with the fund and evaluative capacity grows, more qualitative criteria could be introduced to address objectives beyond amenable mortality, such as equity in access and health outcomes.

4. **The Fund should represent a new, dedicated ('ring-fenced') health resource and not be 'carved-out' from the existing health budget.** The proportion of economic resources devoted to healthcare in Romania is low relative to other EU countries and funding innovative medicines from the existing healthcare budget will take resources away from other critical functions. The Fund should be ring-fenced to avoid resources being used to address short-term needs or budget short-falls.
5. **In the short-term, the Fund should be administered by the Romanian social insurer, CNAS.** Given the limited capacity of the ANMDMR, reflected in long HTA timelines, this agency may not be in a position to take on additional responsibilities in the short term. In addition, the importance of CNAS in securing funding for the Fund should not be underestimated. As funding becomes more secure and capacity within the ANMDMR grows, it may be appropriate to re-assess this responsibility.
6. **Alternative reimbursement models should be considered, particularly financial-based drug or patient expenditure caps, to ensure accelerated access to innovative medicines whilst mitigating against risk of over-paying for benefits and budget over-runs.** Standard price-volume contracting will be difficult given inherent uncertainties associated with innovative medicines prior to a formal HTA, whilst early access means there will be few international examples to use for reference pricing. Unrestricted pricing can lead to difficulties around budget predictability and affordability, and mechanisms for retroactively recovering excess expenditure may be legally and administratively challenging.

We note above and in section 3.3 that eligibility for the Fund should be based on quantitative criteria focusing on addressing amenable mortality and high unmet need but we do not propose specific criteria. **OHE recommends research into key contributors to amenable mortality in Romania, including which can be best addressed with innovative medicines, to ensure clear rationale for the quantitative criteria and to ensure the Fund has the maximum impact on improving the population health of Romania.** We also reiterate that as the fund evolves, the inclusion of additional qualitative eligibility criteria could permit broadening the objectives of the fund to include addressing inequities in access and health outcomes.

A detailed breakdown of the precise steps and timeline associated with the Fund is difficult to specify in advance, as it will be the result of negotiation and agreement between the relevant stakeholders. However, below, we outline a potential framework based on the recommendations we have made. We recognise, though, that realistic timelines must take into consideration other timelines and processes in Romania.



	Marketing Authorisation granted	Application for access to fund	Time between fund approval and finalisation of HTA	HTA	Pricing & Reimbursement negotiations
Innovation Fund period covered					
Process [& timescale]	External decision-point	<input type="checkbox"/> Producer submits dossier <input type="checkbox"/> Evaluation of dossier by CNAS [30 days] <input type="checkbox"/> Positive/Negative decision <input type="checkbox"/> Negotiation of MEA [30 days] <input type="checkbox"/> Development and publication of prescription protocols and legal documentation [30 days]	<input type="checkbox"/> Submission of HTA dossier [timescale dependent on external (international) decisions] <input type="checkbox"/> HTA process [up to one year]	External decision-point	<input type="checkbox"/> Procurement: cost-volume agreements <input type="checkbox"/> Publication of prescription protocol <input type="checkbox"/> Patient access: inclusion in positive reimbursement list
Stakeholders	EMA, manufacturer	Manufacturer, CNAS, MoH	Manufacturer, CNAS, ANMDMR	ANMDMR	CNAS, MoH
Key considerations		<input type="checkbox"/> Establishing price <input type="checkbox"/> Quantitative criteria for eligibility <input type="checkbox"/> Preference for financial-based: per drug budget cap	<input type="checkbox"/> Packaging (akin to clinical studies?)	<input type="checkbox"/> For those that exit fund: manufacturer to cover cost for patients on therapy?	

**FIGURE 7: INNOVATION FUND - PROPOSED PROCESS**

In summary, OHE argues that high levels of amenable mortality, low levels of health spending – particularly on newer pharmaceuticals – and long delays in HTA approvals justify the development of an Innovation Fund for Medicines in Romania. Such a fund would provide early access to potentially life-saving medicines and improve population health. Appropriate design considerations would ensure that Fund eligibility is targeted to the most impactful medicines whilst ensuring financial predictability and sustainability as well as protecting against the risk of over-paying for innovative medicines with uncertain value-for-money.

*Some next steps in developing an Innovation Fund for Medicines in Romania*

- Develop explicit eligibility criteria for the Fund. As noted above, this may involve automatically funding medicines approved by other European funds (including PRIME), or a Romania-specific scorecard. This will require collaboration with the Romanian Ministry of Health (MoH) to ensure Fund aligns with MoH priorities.

- Agree a procedure with Fund administrator (recommended: CNAS) by which medicines accepted to the Fund, likely on favourable financial terms to the Romanian government, are protected against manipulations in HTA timelines to artificially extend favourable pricing arrangements. This may take the form a clause in any contracting arrangements which automatically increases reimbursement for a medicine beyond some defined period in the Fund.
- Agree a procedure with Fund administrator (recommended: CNAS) by which medicines that achieve positive HTA status transition to routine reimbursement in a timely manner (and/or a process to be agreed for claw-back of the difference between the Fund price and the final price, for the period between positive HTA and routine reimbursement, either from payer to manufacturer or manufacturer to payer, as appropriate)
- Development of the legal framework for implementation of the Fund in Romania (identification of the legislation that needs amendments and additions).
- Identify and secure new financial resources for the Fund. Likely to require collaboration with the Ministry of Health and/or Ministry of Finance.
- Recruit appropriate administrative and evaluative capacity in CNAS and ANMMDR.

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Founded in 1962 by the Association of the British Pharmaceutical Society, the Office of Health Economics (OHE) is not only the world's oldest health economics research group, but also one of the most prestigious and influential.

OHE provides market-leading insights and in-depth analyses into health economics & health policy. Our pioneering work informs health care and pharmaceutical decision-making across the globe, enabling clients to think differently and to find alternative solutions to the industry's most complex problems.

Our mission is to guide and inform the healthcare industry through today's era of unprecedented change and evolution. We are dedicated to helping policy makers and the pharmaceutical industry make better decisions that ultimately benefit patients, the industry and society as a whole.

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### **Areas of expertise**

- Evaluation of health care policy
- The economics of health care systems
- Health technology assessment (HTA) methodology and approaches
- HTA's impact on decision making, health care spending and the delivery of care
- Pricing and reimbursement for biologics and pharmaceuticals, including value-based pricing, risk sharing and biosimilars market competition
- The costs of treating, or failing to treat, specific diseases and conditions
- Drivers of, and incentives for, the uptake of pharmaceuticals and prescription medicines
- Competition and incentives for improving the quality and efficiency of health care
- Incentives, disincentives, regulation and the costs of R&D for pharmaceuticals and innovation in medicine
- Capturing preferences using patient-reported outcomes measures (PROMs) and time trade-off (TTO) methodology
- Roles of the private and charity sectors in health care and research
- Health and health care statistics

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