



Alternative access schemes for pharmaceuticals in Europe: Towards an emerging typology

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ABSTRACT

European governments employ sophisticated health technology assessment and regulatory procedures to identify which pharmaceuticals to fund publicly. However, there are persisting demands from patients for those drugs excluded from positive reimbursement lists, leading to the emergence of what are here termed “alternative access schemes”. This paper presents a purposive review of these schemes based on available scholarly and grey literature, illustrated with real-world examples from recent practice. It puts forward an original typology of alternative access schemes based on their marketing authorization (regulation) and reimbursement (redistribution) status. We describe the complex, multidimensional policy trade-offs between the principles of patient freedom of choice, clinical autonomy, encouragement of innovation, evidence-informed decisions on safety and quality, access to treatment, and financial sustainability, involved in marketing authorization and reimbursement decisions. We discuss the ways in which alternative access schemes differ and conclude that our typology can illuminate salient policy dilemmas raised by alternative access schemes in national drug reimbursement systems.

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1. Introduction

Health policy-makers in many countries have been creating mechanisms to determine how the limited funds for pharmaceuticals can be used most effectively. Health technology assessment (HTA) and drug pricing and reimbursement (P&R) procedures seek to provide high quality treatment to the maximum number of patients while ensuring the sustainability of public budgets [1]. Yet there are situations that pose specific challenges, relating to the particular combination of price, effectiveness, and target population. One well-known example is orphan drugs, where exceedingly high treatment costs combined with small patient populations typically generate prices that exceed standard cost-effectiveness thresholds [2]. Another dilemma arises where a medicine is expensive yet highly clinically effective, so that it may meet cost-

effectiveness criteria; however the high number of patients that may require treatment makes the budgetary impact prohibitive. Examples include novel drugs for hepatitis C [3–5] or high cholesterol [6]. For example, sofosbuvir-based treatments for hepatitis C have been subject to a variety of special funding arrangements, such as managed-entry agreements in France [7] or Germany [8]. Another challenge to HTA and P&R is where cost-effectiveness is low but there is popular or political pressure to fund the medicines, for example, for specific types of cancer or orphan drugs [9,10]. Indeed, a recent study showed that, in many countries, “market access for oncology products can occur outside the HTA process”, before or despite HTA recommendations [11]. These examples suggest that standard HTA and reimbursement procedures may have difficulties accommodating all potential issues relating to costs and benefits of new drugs [4].

Where treatment of specific diseases or particular classes of drugs is unavailable via standard reimbursement mechanisms, authorities have implemented a variety of bespoke arrangements to make them available. Some have been described in detail

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in the health policy literature, especially managed-entry agreements (MEAs), including performance-based reimbursement or coverage with evidence development [12–14]. However, less attention has been given to other non-standard routes delivering new drugs to patients, including the family of “early access programs” (“expanded use” in the US) [15], “compassionate use” [16,17] and “named-patient basis treatment” [18], plus other special funding schemes such as the Cancer Drugs Fund in England [19]. With the rising costs of new pharmaceuticals [20], this emerging practice is likely to grow in importance.

This paper takes a first step in systematizing the variety of *alternative access schemes*. It presents a purposive review of the various schemes mentioned in European scholarly and grey literature and provides illustrations of cases known to the authors. It then proposes an original typology of alternative access schemes based on their marketing authorization (regulation) and reimbursement (redistribution) status. Next, it discusses the policy tradeoffs involved in regulatory and reimbursement decisions. It concludes with a discussion of additional dimensions on which alternative access schemes differ and considerations for the future use of our typology.

2. An overview of alternative access schemes

Alternative access schemes are, in principle, any programs that seek to provide patients with access to treatment (in our case, drugs) that are not available to them via the main formulary of publicly funded medicines – the positive drug list (PDL). Based on a purposive review of existing literature and policy practice, we have identified the following types of alternative drug access schemes in the European Union (EU):

- 1 *Early access programs* are national programs for the provision of drugs in the process of, or shortly after obtaining marketing authorization, made available to a limited number of patients [15]. Depending on the particular arrangement, the drugs can be fully or partially reimbursed from public funds, although they are often provided directly by the manufacturer, who thus gains additional data for marketing authorization purposes [see e.g. 21]. An example of an early access program would be sofosbuvir-based treatment for hepatitis C in 2014–2015 in England [3].
- 2 *Compassionate use* concerns investigational medicines in development, which can be given, following a request to the European Medicines Agency (EMA), to a group of patients who have a disease lacking effective authorized therapies and where there are no ongoing clinical trials [22]. In this case, an EU member state may ask the EMA's Committee for Medicinal Products for Human Use (CHMP) to issue a non-binding opinion on conditions for use, the conditions for distribution, and the patients targeted by such program; where two or more member states notify an early access program, CHMP may issue an opinion automatically, which member states are required to consider [23,24]. The list of compassionate use programs with EMA involvement so far includes predominantly hepatitis C treatments [18]; their reimbursement status is determined nationally in the EU. However, EU member states are free to set their own rules regarding compassionate use and include broader definitions of medicines or potential uses in their national regulations. For example, Italy has recently broadened its understanding of compassionate use to include off-label use drugs (see below) and some drugs unavailable on the Italian market [25].
- 3 *Named-patient basis early access* is similar to the EU compassionate use program, but for designated individual patients [15,17,18]. Its rules are set by EU member states and decisions on the reimbursement status of drugs used on a named-patient

basis are, again, country-dependent. Note that some countries, for instance Hungary, use the term “named-patient program” to designate extraordinary funding, nominally granted to individual patients, for drugs that have marketing authorization but are not on the PDL. This is similar to the United Kingdom National Health Service (NHS) practice of “individual funding requests” where patients in “exceptional clinical circumstances” can ask for funding of drugs not routinely funded by the NHS [26].

- 4 *Off-label use* refers to “situations where a medicinal product is intentionally used for a medical purpose not in accordance with the authorized product information” [27,28]. This means that the drug is not authorized for the particular condition. Its reimbursement status is country-dependent. France has explicit reimbursement criteria for use of off-label drugs [29], while in other countries rules are less clear and off-label use may be an individual decision rather than a formal scheme. Nevertheless, off-label use is estimated to be “quite widespread” [29] and therefore, in the European context, often covered from public funds for a relatively high proportion of patients who need them.
- 5 *Coverage accompanied by evidence development, with conditional reimbursement and performance-based reimbursement* are examples of *non-financial MEAs* that typically concern authorized drugs (though perhaps with restrictions, reflecting uncertainty over their efficacy and safety). They typically restrict the number of patients who have access to them in time: for example, the well-known case of a negative cost-effectiveness evaluation at the end of the conditional reimbursement period for treatment for Pompe and Fabry disease in the Netherlands [30]. Pay-for-performance agreements have also been documented, for example in Spain [12].
- 6 *Special funds* are ear-marked budgets devoted to specific diseases. The best known example is the English Cancer Drugs Fund [9,19], but treatments for some communicable diseases are also sometimes financed via different routes than the PDL [31].
- 7 Finally, even for drugs on the PDL, HTA bodies, payers and other reimbursement decision-makers may decide to impose *restrictions on physician or provider specializations* allowed to prescribe them (e.g. only specialized centers), as well as limit their indication more narrowly than the marketing authorization label. This results in classes of drugs that are less available to patients than if they had been on the PDL. These practices are common in Central and Eastern Europe [32], but have been also known in more affluent countries, e.g. in the Netherlands [33].

In line with recently emerging research on the topic [15,34], we offer a tentative typology of the universe of alternative access schemes in Fig. 1 below. The following section elaborates on its conceptual rationale and empirical elements.

3. Towards a typology of alternative access schemes

To be available to patients, a drug needs to receive both a positive marketing authorization decision and a positive reimbursement decision. These two decisions serve as a basis for a simplified two-dimensional matrix on which we can position alternative access schemes. The decisions that must be made create multiple dilemmas involving trade-offs between numerous, sometimes competing objectives of health systems. Concretely, the decision by the regulator to grant marketing authorization should provide formal assurance of new drugs' quality (safety and efficacy), sanctioned by experts. However, the evidentiary thresholds used have sometimes been represented as barriers to innovation for researchers and businesses, clashing (at least in countries with a major pharmaceutical industry) with the industrial objective of the “health care state” – nurturing domestic pharmaceutical com-

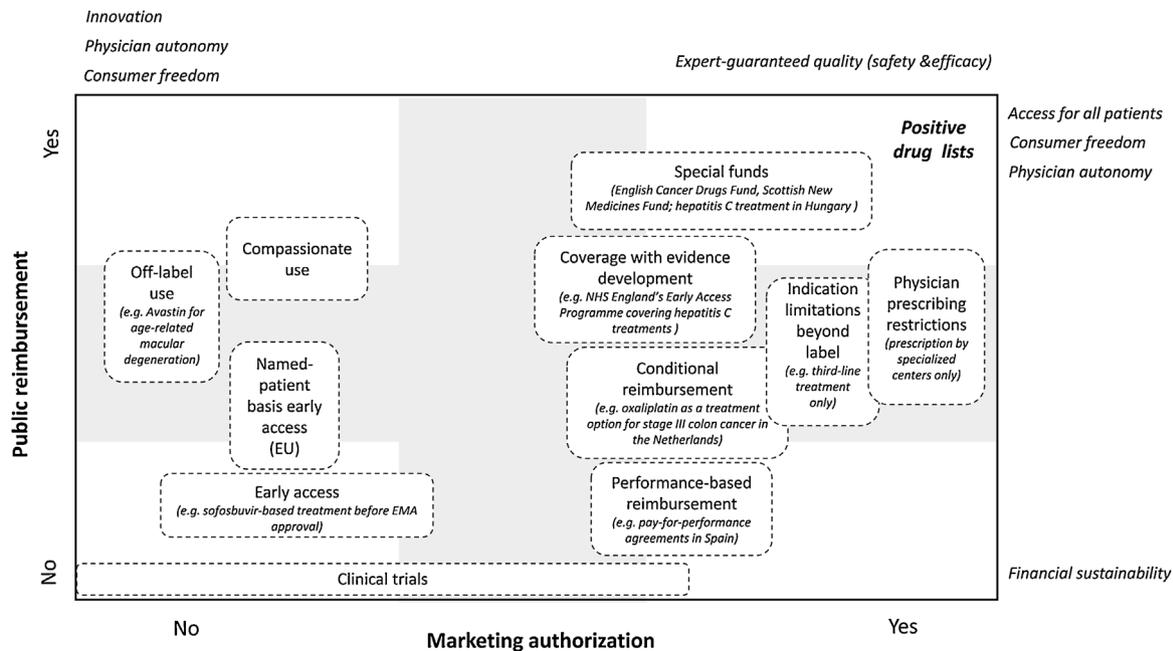


Fig. 1. The universe of alternative access schemes in Europe.

panies [35]. Simultaneously, by withholding drugs that have not been judged sufficiently safe and effective from the market, individual patients face limited access to the drug they believe they need, while physicians face limits on their autonomy to treat their patients according to their best professional opinion. These trade-offs might be considered to have been resolved in modern “risk societies”, which have tended toward accepting reduced freedom of choice as a price to pay for decreasing risk [36,37]. However, they have recently been resurfacing in academic critiques of libertarian paternalism [38], as well as longstanding industry campaigns on “access to innovation”, which view regulation as an unjustified restriction on the liberty of individuals and businesses [39] or as a barrier to innovation [40]. The recent United States “Right to Try” legislation is an example where these arguments have prevailed [41].

The reimbursement decision is, in turn, dominated by the redistributive welfare function of health care [35], making services available to all patients while keeping long- and short-term costs in check. Lowering costs may be achieved by limiting the scope of services (e.g. not reimbursing certain drugs at all), or by compromising on coverage (and often, in effect, equity) and providing treatment only to a limited number of patients. But those making decisions on reimbursement also consider some of the same objectives that emerge during marketing authorization. For instance, reimbursement decisions often rely on additional health technology assessments to re-evaluate efficacy and safety. Similarly, patients’ access to treatment and physicians’ autonomy to prescribe appropriate treatment are limited by negative reimbursement decisions (or lack of decisions). In short, the set of trade-offs involved in regulatory and reimbursement decisions is complex and multidimensional.

As a result, decision-makers negotiate the various trade-offs by treating marketing authorization and reimbursement decisions more as continua rather than binary categories. This has previously been noted in relation to drug reimbursement [42], but categories such as EMA conditional approval or additional monitoring suggest that even the regulatory dimension is less clear-cut. The agency’s controversial “adaptive pathway” [43] in particular exemplifies how policy-makers seek to balance the objectives of fostering innovation with mitigating risks for patients [44]. Inter-

mediate categories therefore emerge, manifesting in our matrix as the grey zones of marketing authorization and reimbursement status. Both dimensions can be operationalized as responses to the question: “Are drugs in the particular funding scheme available to all patients who can benefit from them?” In the grey zones the answer is: “only to some”.

The various alternative access schemes can be positioned on the two-dimensional matrix, creating the typology of schemes in Fig. 1, which includes selected examples of schemes known to the authors. The starting point is the PDL in the upper right corner – drugs in this scheme are available to everyone who needs or demands them, and are fully authorized by the regulator. Diagonally opposite them are drugs in clinical trials, which are not *per se* a funding scheme, but provide some access to treatment to a limited number of patients, in some cases even after the drug has received marketing authorization [e.g. 21]. Clinical trials can be a significant source of new treatment especially in low-resource countries [e.g. 45].

Several caveats with our typology need to be mentioned. First, the typology was developed based on real-world cases known to the authors. Given that reimbursement is jurisdiction-dependent, we expect that the list of schemes we include is not exhaustive. Second, the exact positioning of some common schemes is likely to differ by country, potentially spanning multiple cells within the matrix. Finally, we see the typology as dynamic – individual drugs may be subject to different arrangements over time, as illustrated by the example of sofosbuvir-based treatments for hepatitis C in Fig. 1.

4. Discussion: the many questions raised by alternative access schemes

Alternative access schemes share the common feature of addressing a perceived patient need or demand that is not being met by treatments on the PDL. Beyond that, however, alternative schemes differ in many respects. First, the drugs they cover may have different marketing authorization status. They may include drugs under investigation, but also approved drugs or drugs withdrawn in one jurisdiction but still approved in others – for instance, drugs not registered in one EU country but available in others only

via the mutual recognition procedure [46]. Second, the schemes may also differ in the number of patients they include: from a handful of individuals in named-patient programs to the entire patient population included in MEAs and similar schemes. Third, the quantity and strength of evidence available about the drugs may vary, with different degrees of certainty about their effectiveness, cost-effectiveness and budgetary impact. For instance, there are doubts about the effectiveness of drugs included in England's Cancer Drugs Fund [9], while concerns about sofosbuvir-based hepatitis C drugs focused on the size of eligible patient population and budgetary impact in rich and poorer economies alike [3,47]. Fourth, the degree of formality of the approach varies: the Cancer Drugs Fund is an official scheme with an allocated budget, but payment for off-label prescribing is, in most countries, a practice (variably tolerated) that may nonetheless fulfill the function of a specific disease fund for some patient populations.

Finally, the schemes differ in key governance aspects: who pays, who sets the rules and what the rules are. The source of funds for treatment may vary: early access programs may be provided by manufacturers free of charge [21], and even among publicly funded schemes, there are differences. For instance, in Scotland, the centrally allocated, ring-fenced New Medicines Fund offered additional funds to local health boards beyond their budgets for products on the PDL [48]. Who pays often determines who the rule-maker (or decision-maker) is concerning patient eligibility, leading to potential discrepancies in access. This has been at the core of a controversy in Slovakia, where a patient with a rare disease was denied an individual funding request treatment by his statutory health insurance fund, even though patients insured with a different payer had their requests approved [49]. The case exposed a lack of explicit eligibility and decision-making criteria in the Slovak named-patient procedure. The Slovak case may well be extreme, but decision-making rules in alternative access schemes are different from rules in the PDL in many other countries. Drugs on the PDL are typically subject to well-defined HTA processes. Criteria for alternative schemes are often more lenient, as in the case of the English Cancer Drugs Fund, or ill-defined and dependent on the circumstances of the individual patient or group of patients. In Scotland, for example, this has led to concerns that the special fund could undermine the authority of the Scottish Medical Consortium, the HTA body responsible for appraising new drugs [50]. However, some schemes have strict eligibility conditions for patients: access to hepatitis C treatment in Hungary is, for instance, governed by an explicit multi-criteria priority index [47].

These governance issues are far from trivial. On the one hand, alternative access schemes are useful, offering flexibility to accommodate patients whose treatment needs cannot be otherwise satisfied. Individual circumstances are therefore key, and rules require some discretion – off-label prescribing for pediatric patients is one case where a flexible, individualized approach is necessary. On the other hand, some alternative access schemes cover large groups of patients, sometimes similar to some patient populations eligible for drugs on the PDL. As the Cancer Drugs Fund debate shows, this raises questions of equity – why do drugs for some patient populations face lower evidentiary requirements than for others? Why do they have a dedicated budget which could otherwise be spent in a more evidence-based manner? As growth of alternative access schemes continues, these questions will become increasingly pressing.

Hypothesizing why we observe a multiplication of alternative access schemes in recent times is relatively straightforward: high prices of new drugs means they fail established HTA requirements of cost-effectiveness, budget impact or comparative effectiveness. Pricing is, indeed, a pivotal factor in reimbursement decisions, in many countries determining the default availability of a drug. Depending on the default, some of the schemes may be seen as

expanding patient access where the treatment would otherwise be unavailable to patients (e.g. early access or special funds). Others, on the other hand, can be interpreted as restricting access to drugs which would otherwise in principle be available via the PDL (e.g. physician-prescribing limitations or conditional reimbursement). Even these considerations are, however, context-dependent: in poorer countries where no reimbursement is the default, alternative access schemes may be providing at least some expansion of access, whereas in richer countries, where even expensive drugs have historically been funded, any limitation on prescribing may be perceived as restricting access. As even richer countries move towards more restrictive PDLs, no reimbursement may become the new normal, and alternative access schemes today considered as rationing or cost-containment tools (e.g. indication limitations beyond label restrictions) may become a standard way of getting expensive drugs at least to some patients. This has been the case for some time in Central and Eastern Europe [31] but has recently also been noted in the wealthier Western European countries [11].

Beyond rising drug prices, the reasons for growing alternative access schemes may vary by country, disease, or drug. The fact that these drugs manage to obtain “backdoor market access” via alternative schemes suggests a demand for them [20]. Whether the demand corresponds to genuine unmet patient need or is induced by industry supply is likely to be case-specific – the breakthrough hepatitis C treatment was generally seen as fulfilling an unmet need, but the jury is out on many cancer drugs that offer only small benefits compared to existing treatment. Similarly, for drugs available on the PDL in some countries but not in others (typically smaller, poorer markets), the question is less of need but of the country's ability to pay and the industry's interest in launching their products. In a context of international reference pricing, it may be more advantageous for some companies to provide some products via potentially opaque alternative schemes than to have a low list price [51]. This, again, points to the importance of governance and equity questions in alternative access schemes.

5. Conclusion

This paper set out to provide an overview of an increasingly important phenomenon – alternative access schemes: arrangements that seek to provide patients with access to drugs not available via the PDL. Our typology of alternative access schemes seeks to systematize the topic and provide an initial conceptual framework for future research and discussion. Since the typology was developed inductively based on the authors' knowledge, it is almost certainly non-exhaustive. It also leaves out many questions linked to alternative access schemes, notably ones of their desirability and efficiency. Perhaps drug companies take advantage of some schemes, or perhaps the incorporation of certain schemes under existing rules would drive drug prices up and alternative schemes are therefore a good thing. This is one empirical question calling for further research, along with many others.

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