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Medicines Evaluation: The "Simplified" Complexity

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The short-term economic survival of a health system, which we can call sustainability, depends on several factors. It is about maintaining the ability to pay personnel and maintain, renovate, expand, and build structures while buying technologies suitable for the provision of health care. However, the provision of health care must be affordable and effective, with anticipated and mitigated risks, while at the same time satisfying the users, the needy. Therefore, sustainability goes beyond financial considerations and assumes that it is the long-term maintenance of the ability to provide quality health care.

The provision of health care is dynamic. The needs of the populations are in continuous change as a result of modifiable demography, environmental conditions (climate, housing, work, etc.), and the "evolution" of the epidemiological characteristics of many pathologies. The available technology is also evolving, almost continually improving in terms of effectiveness and safety. In addition, the desires of potential users of health services, we all are, become more pressing and more demanding of effectiveness in the health response. Sustainability is under constant threat.

Therefore, we have the need to balance the response to people's needs and desires, with the use of the most appropriate technologies for each need. One can intervene in the sustainability of a health system through

1. concerted, multidisciplinary actions, involving all policies (Health in All Policies) and health impact assessment. These actions will be directed to populations and can be defined as those that fall within the scope of health promotion and prevention of diseases and disabilities. On the other hand, it is essential to educate populations about healthy living styles and about what people can and should do to maintain their state of physical, mental, and social well-being. Isolated individuals or families cannot do everything, they need help, but they can do more than they usually do.
2. And one must be very strict in choosing the technologies to be used for each situation, evaluating the patient, their personal circumstances, and the disease.

The most significant cause for the increase in healthcare spending is the rising technology prices. It is understood that health technologies comprise a vast group of equipment and processes, such as, all drugs, equipment, and medical or surgical procedures and the support and organization systems used to provide them, in the definition of the Office for Technology Assessment, now defunct. Of all these technologies, ranging from diagnostic and therapeutic equipment to various software and hardware, medicines (including genetically modified cells) are the most expensive and progressively more expensive. The prices for innovative medicines are consistently higher than their effectiveness and much higher than their production and investigation costs. Most Big Pharma buy molecules and other technologies from startup small companies, and some in academia and only pay for the registration studies and marketing. Simply, consumers and governments pay more than they should for the added health value of new medicines.

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It can be concluded that the unaffordable price of medicines is one of the most important, perhaps the most crucial threat to the sustainability of health systems. It may seem paradoxical that "medicines," the most essential sustenance for the effectiveness of health care, are the greatest threat to the sustainability of health systems. But they are!

The use of medications has risks of inducing adverse effects that must be controlled. The use of the "wrong" drug, not indicated for the person and pathology concerned, is another risk. The use of wrong or inappropriate routes, doses, rhythms, and schedules of administration is yet another risk. The persistence of medication beyond the time when it is necessary, or the subtraction of doses configures situations of overtreatment or undertreatment. Many medications, when combined, can be additive, synergistic, or antagonistic. Therefore, there is a potential for generating adverse events with the use of medications and also the risk of using one or more medications without achieving the desired effectiveness. Treating, and spending resources, without achieving the goal is a form of waste, a way of undermining the sustainability of a health system. It is money spent without being effective, eventually inducing complications and without obtaining patient satisfaction, that is, without quality. Of course, any intervention, such as prescribing a drug with no therapeutic effect, or of dubious consequences, is malpractice. Malpractice is, apart from the harm it causes to individuals, a loss of efficiency which is harmful to the sustainability of the health system. The induction of unbearable adverse events for the patient or the nonadherence to the treatment prescribed, but in the meantime purchased, is a loss of efficiency. It should be noted that the sustainability of the health system involves all payers, be they users, insurers, or the State.

At this point you can see how important it is to evaluate the drugs that are used to treat people, and the same arguments can be used for veterinary treatments, even more so when the use of veterinary drugs has a huge impact on human health, but this topic is for another time.

Primarily, medicines must show to be effective and safe and then show that they can be affordable. Affordability is, in essence, the ability and willingness to pay a certain price to obtain a certain effect. It turns out that the increase in the price that the sellers ask for new medicines threatens the sustainability and, therefore, the sustainability of health systems, in particular the part that has public funding through the State budget, such as the Portuguese National Health Service (NHS).

The evaluation of efficacy and safety is, in most cases of innovative medicines, carried out centrally, at the European Union (EU) level in the European Medicines Agency, EMA. Once approved, i.e., having an approved indication, each medicine can be used in label in all EU countries. The approved indication corresponds to what is called MA, Marketing Authorisation. The MA is reflected in the Summary of Product Characteristic (SmPC), which is valid for all EU countries. Having an approved SmPC is a different thing than having a buyer's price in each country, and it is the competence of each Member State to define the price they are willing to pay within the NHS. In Portugal, the competence to set prices is attributed to the Ministry of Health and, for this, it relies on the technical work of a specialized agency, INFARMED.

It seems simple, but it is not. Let's start with some of the EMA's problems. Pharmaceutical drugs, when they apply for an MA, have evidence of efficacy (if any at all) and not of effectiveness. This means that studies (clinical trials) have shown, after the relevant statistical evaluations have been made, that the medicinal product concerned, used alone or in combination, at a given dose and dosing regimen, achieves a certain beneficial effect (endpoint) when used in a population with very strict characteristics in terms of pathology, age, demographics, concomitant pathology, accessory medication, etc. This is the demonstrated efficacy. Efficacy may, or may not, correspond to effectiveness, i.e., obtaining the same effect in "real" populations not so well selected and in a real-life context, outside of clinical trials. Almost always, in terms of the probability of outcomes, effectiveness results are smaller than the expected efficacy. On the other hand, despite ongoing regulatory measures, most clinical studies exclude higher-risk populations, such as the elderly and frail or patients with severe organ damage, and have implementation (not only compliance) problems in children and the mentally ill. The marketing authorization, in accordance with the legal framework in force, is granted only for the specific therapeutic regime, namely combinations of medicinal products, and for very specific populations, those of the clinical trial. It may seem that this is reductive, but it is the way to minimize the risks of having an effectiveness that is lower than efficacy, ensure the containment of adverse effects, and guarantee the efficiency ratio of the drug, the ratio between its cost and likely benefit.

The concern with the safety of patients and the cost of medicines, seeking to avoid waste by ineffective therapeutic prescriptions, was one of the reasons for the proliferation of the use of Evidence-Based Medicine, the

conscious, explicit, and judicious use of the best evidence in making decisions about the treatment (or care) of individual patients. I will not be able to dwell on the issues of this excellent definition by Sackett et al., but I must point out that it is a matter of adapting the best evidence to each specific case. The EMA, seeking that the MA can be adjusted to the best cases, leaving the judgment of extrapolation of the results of the trials to the relationship of each doctor with his specific patient, uses the best available evidence, that of the clinical trial, to decide the text of the approved indication. Obviously, the marketing authorization is restrictive, not least because there is always the problem that not everything is the subject of clinical trials or clinical studies prepared in accordance with the standards required for submission to the FDA or EMA. Note that the MA in Europe may, and they do, sometimes differ from the FDA opinion. In addition, the Pharma Industries only pursue studies that may generate some financial gain, in general, avoid combinations using drugs from their competitors, and are not interested in far-fledged indications, i.e., illegal psychoactive drugs that are the talk of the town. Once there are generic drugs, the original patent owners do not seek new indications. So, there are many opportunities for off-label, that is, the prescription of a drug beyond the approved indication. Note that the trend toward rapid approval of drugs with the meager suggestion they may be effective for certain unmet needs, after noncomparative phase II studies, has led to an increase in conditional approvals that, in fact, are an aberration of the use of the best evidence, just when the best evidence has not yet been produced. And there are situations, in the field of fraud, where studies do not mention observed side effects, and the results are stilted by the effect of statistical manipulation. In any case, these cases of deliberate or accidental fraud are rare and the greatest difficulty is that the endpoints are not always the most appropriate and the comparisons are made with comparators that are outdated at the beginning of the study or, finally, when the results end up being published, years after the beginning of the trial.

Once the MA is obtained, the seller, who may be the manufacturer or the owner of the patent of the medicine, must obtain a reimbursement regime so that the medicine can be purchased in Portugal. Without this, considering the prices usually requested, most individuals or institutions would not be able to acquire them.

This process of economic evaluation is legally defined. It is the responsibility of INFARMED and obliges applicants to comply with a form of presentation and demonstration of specific criteria. It has two conceptual problems and one process. The first design problem is the requirement to repeat the demonstration of efficacy and therapeutic advantage. The first has already been evaluated by the EMA. The second should result from the anticipatory work of the national agency. INFARMED should be attentive to what is coming and what has been approved and make its own added-value judgments before pricing, without requiring the applicant to repeat the provision of data that has already been reviewed by the EMA. The second design problem is in drug-economics studies that require one or more comparators. Now, there are situations in which the best comparator does not exist because the clinical study was done against a comparator already outdated in clinical practice or the approval was made with a phase II study. The procedural problem is easier to understand and solve. INFARMED is too slow to decide because it does not have the permanent staff structure that it would need to resolve all the cases submitted to it. It reposes on a commission of external advisors, not all of them real experts. Therefore, my proposal is to eliminate the first part, that of the redemonstration of efficacy and therapeutic value, at least in the evaluation of medicines already approved by the EMA, and to provide INFARMED with sufficient and permanent human resources to be a health technology assessment agency comparable to NICE or, in part, to AHRQ. In fact, although this is a longer discussion, there is a misconception at the level of the elaboration of therapeutic guidelines, erroneously called therapeutic guiding norms (a huge paradox as a norm is not guidance or a guideline) by the DGS, which should be centered on INFARMED and coupled to the drug evaluation process. Not to mention the astonishment caused to me by the therapeutic "recommendations" that are elaborated in Portugal, namely by scientific societies or professional ruling bodies, without taking into account the approved indications or the medicines with approved national reimbursement.

Next, the whole process of price adjustment is full of deception and lack of transparency, with real prices confidential and different from published prices, by virtue of the blackmail that the pharmaceutical industry exercises on the Portuguese Government. From the Big Pharma point of view, either we accept a confidential price, to protect the calculation of the reference price in other Member States, or there is no marketing in Portugal and, being the medicine essential, we will buy at prices published for another country, usually very expensive. Of course, Portugal's negotiating capacity is always compromised because we have a monstrous rolling debt to the pharmaceutical industry. In short, obscene prices upfront and a compromised ability for the NHS to pay in time drag out the negotiations.

Innovative medicines sometimes, many times, arrive too late at the bedside. Please bear in mind that there is an implicit interest rate when the NHS pays late, albeit the Pharma can finance themselves at lower rates within their own main offices abroad.

It turns out that the price determination for NHS hospitals is even more complicated because there is a cashback system, in which the laboratory returns to the State any gain higher than a predetermined amount of expenditure or number of patients treated. There may even be cost-sharing situations in which the State only pays for the treatment of patients in whom there has been a therapeutic success, an innovative practice initiated when enzyme inhibitors for hepatitis were introduced. From this cashback system, calculated according to the estimated number of patients starting treatment each year (in Portugal, there is a lot of "fantasy" because the epidemiological records are poor), it results that the extension of the marketing authorization, i.e., including more potential patients in the calculations, leads to a new negotiation process. Therefore, we may have a situation in which the drug A + B can be used, but if it is A + B + C or A + C, even for the same disease, you already need special authorization that will have to be requested from INFARMED, regardless of whether C has already been approved for dozens of years. If the drug is generic, the situation is blurry and, obviously, as soon as A, B, and C lose patent protection and generic drugs emerge the whole pharmacoeconomic reasoning subsides to the generalized use. At this point, the regulatory authority (INFARMED) has no more saying, and the decisions go to the local formulary committees, normally with unequal perspectives on patients' access to treatments.

While the negotiations are going on, the drug can be used (I have already explained that the MA is for the whole of Europe) and even purchased. There is the figure of the AUE, special use authorization (a sort of expanded access program or compassionate use), which allows the authorization, by INFARMED, so that an NHS institution can buy a drug if there is no therapeutic alternative and, what is absurd, the patient's life is in immediate danger. On the one hand, the evaluation of the existence of a therapeutic alternative should not be made only in the light of the comparability of MA but also by the therapeutic need of each specific patient. On the other hand, the requirement that a patient be at the risk of death in the short term is subject to a subjective assessment of the probability of dying within an undefined length of time, and this risk of dying will certainly change over time. A few weeks ago, I received the indication that a certain drug that prevents the progression of a potentially deadly disease could not benefit from an AUE because the patient would not yet be at a high risk of dying. Therefore, it would be necessary to wait for the disease to progress until the patient is at foreseeable risk of dying, at which point it will no longer be worth requesting the said drug whose effectiveness has only been demonstrated in mitigating the evolution to a potentially fatal condition.

Also, as part of the current system, while negotiations are underway to assign price to an innovative drug (not necessarily new, because a new indication of an "old" drug is an innovation), INFARMED may require or approve an Early Access Program, PAP, in which the drug is dispensed free of charge under clinical conditions proposed by the seller and approved by INFARMED. Once the PAP is finished, even if the drug does not yet have an agreed-upon price, prescribers can ask for AUE, although the hospital will be buying the drug at the international price. There are also extended access programs in Europe, established by the seller prior to the approval of the MA by EMA, basically, a form of prescription induction that would deserve another approach. Back in Portugal, there is the ludicrous situation that if a medicine has requested PAP and this program application is refused, the AUE is no longer authorized. It makes no sense to link the two mechanisms of exceptional drug use for medicines with MA and not yet priced for the NHS. All medicines applying for NHS pricing should have an obligatory period of PAP, at the company's risk, for a limited time within which the price had to be granted or the application refused. PAP should be used to monitor needs and uses in Portugal. The implication of a negative final decision from INFARMED, because both parties could not agree on a fair price, would be the prohibition of that medicinal drug in the NHS. It has been done elsewhere.

If a drug has marketing authorization in a country outside the EU, for example, granted by the FDA, it can be imported upon request with the AUE mechanism. If a medicine is to be used in an off-label situation, i.e., outside the approved MA but with approval for another indication, if there is no need for importation, the process runs internally with Hospital Formulary Committee without the need for AUE and INFARMED authorization. This means that the phenomenon of "jump the gun", the use with presumed effectiveness or even before a price has been established for the NHS, can be done only with the authorization of the pharmacy and therapeutic commissions (CFT) – the Formulary Committees – of each institution. This is also true for medicines or combinations of medicines that have MA in Europe but have not asked for a price for the NHS. Sounds confusing? It is.

Further, it generates inequalities that should not exist. The solution would be the

1. simple withdrawal of all authorization for special use programs, with the regrettable consequences of having people without access to the best treatment because of INFARMED delays in negotiating prices, or
2. concentration of certain pathologies and treatments in selected centers of excellence and
3. the design, approval, and implementation of clear NATIONAL guidelines, conceived with INFARMED stewardship and direction (this would be an attempt to minimize conflicts of interest between pharma industry and experts), including medical doctors, pharmacists, hospital administrators, and patients in the guideline building and testing process. The national guidelines are also important because all previous effectiveness or pharmacoeconomic assessments cease to apply when there are generic drugs or full generic combinations.

Conflict of Interest Statement

Investigator for BMS/Celgene, Janssen, Sanofi and Takeda. Consulting for Amgen, Astellas, BMS/Celgene, Gilead Sciences, Janssen, OM Pharma/Viforpharma, Pfizer, Pharmamar, Servier and Takeda.

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