Health Policy xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Health Policy

journal homepage: www.elsevier.com/locate/healthpol

An ethical framework for the creation, governance and evaluation of accelerated access programs

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ARTICLE INFO

Article history:
Received 2 February 2017
Received in revised form 7 July 2018
Accepted 14 July 2018

Keywords:
Pharmaceutical funding decisions
Pharmaceutical regulation
Coverage with evidence development
Investigational drugs
Bioethics

ABSTRACT

There are increasing demands on regulators and insurers internationally to provide access to medicines more quickly, and often on the basis of less robust evidence of safety, efficacy or cost-effectiveness than have traditionally been required. These demands arise from a number of sources, including those advocating for access to medicines for patients with life-threatening diseases, rare diseases, or subsets of common diseases and where entire populations are threatened in the context of public health emergencies. In response to these demands, policymakers have instituted a number of initiatives aimed at speeding up access to medicines, which we refer to collectively as "accelerated access" programs. While there are strong arguments for accelerated access programs, these programs also raise a number of socio-political, epistemic and moral issues. Some of these issues are common to all types of accelerated access programs, while others are specific to particular types of accelerated access. Here, we offer a conceptual framework that highlights ethically relevant similarities and differences among different kinds of accelerated access processes for the purpose of enabling ethically and politically-informed policy making.

1. Background

Regulators and insurers around the world face the challenge of providing timely access to safe and effective medicines that both consumers and the community can afford. Current regulatory and reimbursement systems have been established in order to protect patients from harmful and ineffective treatments and ensure the sustainability of health systems. However, in recent years there has been increasing claims—particularly by industry and patient advocates—that these systems act as a barrier to patients receiving timely access to new medicines. Many people (often with the backing of the pharmaceutical industry) have begun to advocate for faster access to medicines, particularly for patients with life-threatening diseases, rare diseases and molecular subsets of common diseases, and where entire populations are threatened in the context of public health emergencies. Those with rare diseases, or rare subsets of more common diseases, argue that existing requirements for evidence of efficacy and cost-effectiveness are too rigid when research participant populations and markets are unavoidably small [1–3]. Patients with life-threatening illnesses are increasingly demanding the "right to try" experimental interventions [4]. In the setting of pandemics, such as the 2014 Ebola virus epidemic in West Africa, there has been intense debate about how safe and effective vaccines and therapies may be rapidly developed and disseminated [5–7].

A range of policy initiatives have been introduced in an attempt to address these concerns; collectively these are commonly known as "accelerated access" initiatives [8]. A number of taxonomies have been developed to characterise specific types of accelerated access initiatives and explore how they have been implemented across jurisdictions (see, for example [9–11], on managed entry agreements). While these taxonomies draw out the different approaches to registering and subsidising medicines and propose technical and economic principles for their application, there is currently no equivalent synthesis of the socio-political, epistemic and moral issues that they raise. In this article we address this gap by describing the main types of accelerated access to medicines (drawing on both our review of the literature and existing frameworks) and then offer a description of the socio-political, epistemic and moral issues that may arise in the context of different kinds of accelerated access. We focus on pharmaceuticals rather than, for example, medical devices, diagnostics and biological therapies because accelerated access programs have been instituted primarily for pharmaceuticals and distinct (and sometimes less stringent) systems exist for

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https://doi.org/10.1016/j.healthpol.2018.07.014
0168-8510/

the registration and subsidy of other technologies, potentially raising their own, unique set of socio-political, epistemic and moral issues.

2. Methodological approach

The approach we used was largely conceptual. Discussion amongst the authors was used to classify existing accelerated access programs and identify the relevant ethical issues and arguments that these raise. This was supplemented by a literature search to ensure that we had not missed any key program types or typologies thereof, or ethical arguments. The databases Google Scholar, MEDLINE, EMBASE and Web of Science were searched in January 2017 and June 2018 using terms such as "accelerated access", "accelerated approval" "conditional approval", "provisional approval", "conditional medicines authorisation", "notice of compliance with conditions", "managed entry", "coverage with evidence development", "access with evidence development", "compassionate use", "compassionate access", "expanded access", "special access", "early access", "medicines access program" and "right to try". We emphasise that this was not a systematic search; rather we aimed to recall as many articles as possible and we continued to collect articles until no new program types, typologies or ethical issues or arguments were identified.

3. Types of accelerated access to medicines

Accelerated access initiatives may speed up access to medicines at two stages in the medicines lifecycle: at the pre-marketing authorisation (henceforth registration) stage, or at the post-marketing authorisation (henceforth reimbursement) stage. Within each of these stages, accelerated access initiatives can be divided into those that simply speed up registration or funding processes (prioritisation initiatives), and those that bypass existing processes and/or change the evidentiary requirements and thresholds for regulatory approval and funding.

3.1. Prioritisation

Initiatives do not involve changes to usual measures, standards or processes for the registration or reimbursement of medicines. Instead, they involve a change in the resources devoted to the evaluation of a therapy for either registration or funding purposes in order to speed up the process. One example of a prioritisation initiative at the registration level is the US Food and Drug Administration (FDA's) priority review designation. This designation can be granted to drugs that, if approved, would offer significant improvements in the safety or effectiveness of the treatment, diagnosis or prevention of serious conditions when compared to standard applications. For products granted this designation, the agency's goal is to take action on applications within six months (compared to ten months under standard review) [12]. A similar scheme recently implemented by Australia's Therapeutic Goods Administration (TGA) aims to speed review of vital and life-saving medicines by up to 3 months [13].

3.2. Registration bypass or modification

Initiatives provide access to therapies that have not yet been approved by those responsible for those authorising the medicines. These initiatives can facilitate access to therapies that are not registered in any jurisdiction (either because they are investigational new drugs still undergoing clinical trials or because they are awaiting initial evaluation by regulatory agencies), therapies that have been approved in other jurisdictions, or therapies that have been approved in the relevant jurisdiction, but for other indications. For example, many jurisdictions (including Australia [14], Canada [15] and European countries including France, Germany and Sweden [16]) have "special access" schemes or "early access" programs which allow for the importation and supply of unregistered therapies at the request of the patient's physician. In the US, patients can also access investigational new drugs outside of clinical trials through "right to try" laws (which allow patients to request access to experimental therapies without the need for approval from the FDA) [17] and industry access schemes [18]. The latter are referred to as "compassionate use" and "expanded access" schemes [19], and may include access for individuals or groups of patients. The World Health Organisation's Monitored Emergency Use of Unregistered and Experimental Interventions program (MEURI), which made available experimental interventions to patients infected with Ebola virus disease both within and outside of clinical trials during the recent epidemic in West Africa [20,21], is an example of a pre-marketing authorisation initiative at the supranational level. Finally, some types of registration bypass or modification allow the registration of therapies on the basis of less complete or different types of data to that which is usually required and may require further data collection on safety or efficacy once the medicine enters the market. The US Food and Drug Administration's accelerated approval [22], the European Medicines Agencies conditional marketing approval [23], and the TGA's provisional approval process [24], are some examples of this.

3.3. Reimbursement bypass or modification

Initiatives refer to processes that allow for the subsidy of registered therapies outside of the usual reimbursement channels or using different criteria than is customary. This category includes special funds established to provide subsidy for specific classes of therapies that do not meet the usual cost-effectiveness criteria of the Health Technology Assessment agencies that provide advice to payers on whether or not a technology should be funded; examples include the Cancer Drug Fund in England and Australia's Herceptin and Life-Saving Drugs programs. An increasingly popular alternative to special funds is "Coverage with Evidence Development" (CED). This involves an agreement between a pharmaceutical company and a healthcare payer to provide provisional coverage of a therapy at a price justified by the evidence available when a decision is made. Ongoing coverage and the final price paid are then dependent on the collection of additional data (either through the completion of clinical trials or the collection of "real world" evidence once the therapy reaches the market place) in order to resolve uncertainties surrounding clinical or cost-effectiveness [25–28]. An example is the conversion of the Cancer Drug Fund in England into conditional reimbursement in 2016 after review of its performance [29]. Other adapted reimbursement mechanisms include hospital medicines access programs (MAP) and compassionate supply by pharmaceutical companies where the company provides the therapy to patients at a reduced or no cost, usually for a limited time, in order to cover the period between registration of a therapy and the provision of funding by public or private insurers.

4. Socio-political, epistemic and moral issues

Each type of accelerated access raises a range of socio-political, epistemic and moral issues. While all issues may be relevant to all forms of accelerated access, particular issues are more salient for particular types of accelerated access because of when they occur and who is affected by them. This is outlined in Table 1 and explored in more detail in the following sections.

Please cite this article in press as: Pace J, et al. An ethical framework for the creation, governance and evaluation of accelerated access programs. Health Policy (2018), https://doi.org/10.1016/j.healthpol.2018.07.014