



## ANALYSIS

# Demands for access to new therapies: are there alternatives to accelerated access?

Patients deserve timely access to new therapies, but the rhetoric surrounding accelerated access impedes rational policy making, argue **Jessica Pace and colleagues**

Jessica Pace *doctoral researcher*, Narcyz Ghinea *doctoral researcher*, Ian Kerridge *professor*, Wendy Lipworth *senior research fellow*

Centre for Values, Ethics and the Law in Medicine, University of Sydney, NSW, Australia

It is almost impossible to turn on the television or open a newspaper without hearing about the “miraculous” benefits of the latest medicines. The targeted cancer therapy idelalisib, for example, was touted as a revolutionary treatment that would “melt away” your cancer,<sup>1</sup> while the new leukaemia drug venetoclax has been described as being so innocuous that it is “like taking Panadol [paracetamol].”<sup>2</sup> While much of this rhetoric centres on cancer medicines, new treatments for other chronic and life threatening conditions such as diabetes,<sup>3</sup> cystic fibrosis,<sup>4</sup> and Duchenne muscular dystrophy<sup>5</sup> are also described as miracle cures.

The mass media is replete with stories of terminally ill patients who have been given a second chance by these new miracle drugs. However, alongside such stories of triumph are darker stories—of patients having access to these life saving drugs denied or compromised by excessively conservative regulators or cost conscious public or private insurers (payers). Headlines over the past few years include “Aussie patients denied funding for 30 life-saving drugs,”<sup>6</sup> “Dying mum fights for life-prolonging drugs the NHS won’t fund due to cost,”<sup>7</sup> and “Company denies drug to dying child.”<sup>8</sup>

This rhetoric is indicative of an increasingly pervasive social expectation, which we refer to as the access imperative. By this we mean the view that patients with severe or life threatening diseases should not have to wait (as long as they do) for regulatory approval or formal subsidy before they can access medicines. This access imperative seems to be gaining in strength, leading to numerous recent inquiries into the adequacy of existing regulatory and reimbursement systems including in the UK and Australia,<sup>9 10</sup> and calls to expedite access to promising new treatments.

Politicians across the political divide seemingly accept the need for faster access as truth. For example, US President Donald Trump recently labelled the US Food and Drug Administration’s (FDA) regulatory approval processes “slow and burdensome” and vowed to deregulate the drug industry,<sup>11</sup> while Obama’s vice president, Joe Biden, committed to speeding up the approval

of promising new cancer drug combinations.<sup>12</sup> In countries with publicly funded insurance programmes, politicians appeal to voters by promising to provide funding for medicines that have been rejected by payers. For example, New Zealand’s opposition Labour party committed to funding pembrolizumab for melanoma after it was rejected by that country’s public payer.<sup>13</sup> The drug industry and industry funded consumer groups across the globe also promote faster access, encouraging patients to demand access to timely and affordable medicines,<sup>14</sup> and advocate for the right to try experimental therapies without the usual regulatory oversight.<sup>15</sup>

## Global responses to demands for faster access

In response to this pressure, many countries have introduced formal programmes that provide earlier access to medicines, targeting both regulatory and reimbursement processes. Some of these accelerated access processes are relatively uncontroversial because they simply improve the efficiency of current decision making processes—for example, Europe, Japan, the US, and Canada require regulatory bodies to prioritise applications for marketing approval for drugs deemed to be potentially life saving or a significant improvement over currently available treatments for serious conditions.<sup>16–19</sup> Others, however, are more problematic, as they suspend or erode current standards of safety, efficacy, or cost effectiveness. Numerous jurisdictions have introduced systems that allow for provisional approval of medicines on the basis of less complete data (such as surrogate markers) on the condition that post-marketing studies are done to resolve any uncertainties about safety or clinical effectiveness.<sup>20–23</sup> Many countries also allow individual patients to apply to regulators for use of unregistered medicines through special access schemes or early access programmes.<sup>24–26</sup>

Several “managed entry” or “coverage with evidence development” schemes have also been established for therapies that have been approved by regulators but not (yet) funded. These schemes allow for funding of a therapy at a price justified

by the evidence available at the time a decision is made, with ongoing coverage—and final price—decided after the accumulation of data from clinical trials or “real world” use.<sup>27-30</sup> Formal programmes to fund therapies not deemed to be cost effective by health technology assessment agencies (such as the UK’s recently reconstituted Cancer Drugs Fund<sup>31</sup> and Australia’s Life-Saving Drugs Program<sup>32</sup>) have also been established. These formal schemes exist alongside “compassionate access” or “individual patient use” mechanisms, in which drug companies fully or partly subsidise medicines that have not been subsidised by public or private insurers.<sup>33</sup>

Such initiatives are not unique to the developed world. Programmes were introduced to facilitate rapid access to unapproved treatments during the recent Ebola virus epidemic in west Africa after a World Health Organization panel concluded that “it would be acceptable on both ethical and evidential grounds to use as potential treatments or for prevention unregistered interventions that have shown promising results in the laboratory and in animal models but have not yet been evaluated for safety and efficacy in humans.”<sup>34</sup>

## Effects of accelerated access

Good arguments exist for accelerating access to medicines. Patients in desperate situations—such as those with life threatening illness or rare diseases for which there is no available treatment—should have timely access to potentially beneficial therapies and be provided with hope of a cure.<sup>35</sup> It is asserted that it is up to these patients and their physicians, not regulators, to determine when it is reasonable to try a therapy.<sup>35</sup> In addition, many people believe that particular groups of patients, such as those with rare diseases, are disadvantaged because of the difficulties of conducting clinical trials in small patient populations and demonstrating cost effectiveness when drug companies need to charge more to recoup their investment.<sup>36</sup>

Existing regulatory and subsidisation processes may indeed be too slow to meet the needs of patients with limited life expectancy. For instance, a recent analysis found that average approval times of six major regulators ranged from 304 days for the US FDA to 511 days for Swissmedic.<sup>37</sup> Assessment by public and private insurers (payers) can further increase the time to access for more expensive medicines because of affordability.<sup>33</sup>

Rigid adherence to inflexible standards for safety, efficacy, or cost effectiveness (such as an emphasis on large phase III randomised controlled trials) may also prevent timely access to new therapies. Many drugs that were initially approved using accelerated pathways have subsequently become part of standard care, lending credence to the view that we need to modernise regulatory processes. Notable examples include bicalutamide for advanced prostate cancer, imatinib for chronic myeloid leukaemia, anastrozole and letrozole as adjuvant treatment for postmenopausal hormone receptor positive breast cancer,<sup>38</sup> and antiviral medicines for HIV/AIDS (including darunavir, raltegravir, and etravirine).<sup>39 40</sup>

However, failure to register or fund a drug does not necessarily mean the regulatory or reimbursement systems are cumbersome or unfair.<sup>41</sup> There may be too much uncertainty about a drug’s safety or efficacy, or it may have low cost effectiveness or be unaffordable.

Evidence is growing that accelerated approval of medicines may cause serious harm. For example, medicines approved since the US accelerated approval pathway was introduced are more likely to be withdrawn from the market or receive a new “black box warning” than those approved before its introduction.<sup>42</sup>

Similarly, drugs approved in Canada using its notice of compliance with conditions pathway are more likely to have a serious safety warning compared with those approved through a standard review process.<sup>22</sup>

Medicines made available via accelerated approval mechanisms may also prove to be ineffective. The independent drug bulletin *Prescrire* assessed all 22 drugs that had been granted conditional approval in the European Union since 2006, finding that less than 40% of these offered an advantage over current therapies, and there were insufficient data to make a judgment for nearly a third.<sup>39</sup> Similarly, most oncology drugs approved in the US between 2008 and 2012 were approved on the basis of surrogate endpoints, and further follow-up showed that more than half of these had no or unknown effects on overall survival.<sup>43</sup> Some, such as bevacizumab (Avastin) for breast cancer<sup>44</sup> and gemtuzumab ozogamicin (Mylotarg) for chronic myeloid leukaemia<sup>45</sup> also had serious side effects and were withdrawn from the market.

Although identifying more suitable surrogate endpoints could reduce these problems, we believe that negotiating lower evidence standards, whether in terms of endpoints or experimental design, to accelerate access to medicines can expose patients to futile treatments that, at best, provide false hope and, at worst, cause serious harm.

Changes to reimbursement systems that involve disregarding usual cost effectiveness thresholds for the subsidy of medicines also have serious consequences for healthcare systems by creating opportunity costs and overwhelming budgets. The recent changes to the UK Cancer Drugs Fund are a case in point. After the fund exceeded its budget by 50% in 2014,<sup>46</sup> and without assessment of the effect of the resources spent, in 2016 it was converted to a managed access programme that will provide funding for therapies for two years while further data are gathered.<sup>47</sup> More permissive cost effectiveness thresholds may increase not only overall expenditure but also the prices of medicines. In 2004, a report commissioned by the US Congress concluded that removing price controls (which includes cost effectiveness analysis) would greatly increase revenues from patented medicines—by, for example, almost 60% in Australia and more than 30% in the UK.<sup>48</sup>

## Countering the rhetoric

Speeding up access to medicines is clearly appropriate and beneficial in some cases. The problem is that the rhetoric surrounding accelerated access makes it difficult to assess the necessity and feasibility of such programmes. Combating this rhetoric will not be easy, as it is natural for researchers to want to promote their work to improve their status and chances of receiving lucrative research grants; for manufacturers to promote their product to increase their market share (and therefore the return on investment for shareholders); and for media outlets to tell emotive stories to sell papers. However, the following steps would go some way to controlling it:

- Ensuring that press releases of research groups make factual claims that do not overstate the evidence (this could be a responsibility of institutions such as universities that oversee research)
- Extending or more strictly enforcing regulations prohibiting the promotion of off-label medications by pharmaceutical companies
- Encouraging media outlets to report on both positive and negative trial outcomes and not to set unrealistic expectations when reporting the latest research through, for example the

introduction of media standards for the results of drug trials and provision of alternative messages such as the importance of social solidarity and preventing the exploitation of vulnerable patients by researchers, politicians and members of the pharmaceutical industry.

## Better response

It would be unrealistic, however, to believe that such strategies could ever fully stop the calls for greater access to medicines, which are underpinned by compassion and valid concerns such as inequities for people with rare diseases and promotion of biomedical innovation.<sup>35-49</sup> We therefore have to find different ways to respond. Perhaps the most obvious alternative—although it is often neglected—is to increase support for publicly funded clinical trials. Such trials, particularly if they allow for crossover and open label extensions, would provide patients with timely access to new therapies (without the public misconstruing them as proved therapies, which official regulatory and payer endorsements tend to imply). They would also protect patients from harm by providing adequate monitoring of both safety and efficacy and allow for further data collection before therapies are used more widely.

Although increasing publicly funded trials would demand substantial investment, experience from paediatric oncology shows that it is both feasible and can have groundbreaking results. Many cancer treatments are licensed only for adults,<sup>50</sup> but most children receive access through clinical trials. This has been credited with increasing the overall five year survival rate for childhood and adolescent cancers from about 60% in the late 1970s to more than 80% today.<sup>51</sup>

Another approach could be to use drug pricing as a lever for promoting access to medicines. Linking prices to demonstrable evidence of effectiveness could allow for lower cost effectiveness thresholds for drugs with the highest evidence and would encourage companies to conduct high quality research to improve their revenues, even after the medicine is on the market. More ambitious pharmaceutical price reform strategies would also increase access to medicines, although they are likely to be strongly resisted by industry.

We cannot simply reject calls for accelerated access as the values that underpin these calls are genuine and deeply felt. But accelerated access programmes are not the best way of respecting these values. Approaches to facilitating access to medicines need to be based less on rhetoric and more on reason, and need to remain cognisant of both the importance of maintaining standards of safety, efficacy, and cost effectiveness and the realities of finite health budgets.

Contributors and sources: JP is a doctoral researcher focusing on the ethics of debates surrounding accelerated access to medicines. NG is a doctoral researcher focusing on ways of improving decision making processes around high cost cancer drugs. IK has an international reputation in bioethics and the philosophy of medicine. WL's work focuses on the ethics of drug development and health technology assessment. IK and WL drafted the article and JP provided critical revision. All authors approved the final version.

Competing interests: We have read and understood BMJ policy on declaration of interests and have no relevant interests to declare.

Provenance and peer review: Not commissioned; externally peer reviewed.

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## Key messages

Both patients and clinicians are immersed in rhetoric emphasising the potential benefits of and urgency of access to new medicines

Policy makers are under increasing pressure to approve and fund medicines with poor quality evidence on safety, efficacy, and cost effectiveness

Alternative approaches are needed to meet the desire for quicker access and protect the interests of current and future patients as well as the broader community

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