Navjoyt Ladher
BMJ Analysis Editor

17th June 2017

Dear Navjoyt Ladher,

Please find attached the revised version of our article BMJ.2016.036035, now entitled Demands for access to new therapies: are there alternatives to accelerated access? We thank the reviewers and editors for their comments and our responses to these are outlined below.

We look forward to hearing from you in due course.

Sincerely,

Miss Jessica Pace (on behalf of Mr Narcyz Ghinea, Prof. Ian Kerridge and Dr Wendy Lipworth)
Centre for Values, Ethics and the Law in Medicine (VELiM)
Medical Foundation Building (K25)
University of Sydney NSW Australia 2006
Editors Comments:

1) Editors thought your paper covered an important and interesting clinical topic. The comments here are intended to strengthen your argument, pull out what is new and original, and broaden the appeal to our international readership. We thank the editors and reviewers for their insight and believe that our paper has been considerably strengthened as a result of this feedback.

2) The key comments from editors were around what is new and original in your article? We felt that these issues have been discussed previously, and though you make lots of good points and touch upon good research, we would want any Analysis article we publish to offer fresh insights and present compelling solutions. We would suggest only resubmitting if this is possible.

We agree that the potential dangers of accelerated access have been discussed previously and that the previous version of our article did not differentiate itself clearly enough from these other accounts. Our revised paper now offers new insights and adds to existing research and commentaries by:
1. linking the material more explicitly to the most recent international policy debates and trends
2. elucidating the values underlying the current discourse in order to identify alternatives to accelerated access.

To reflect the fact that we have changed the emphasis of the article, we have changed the title to: **Demands for access to new therapies: are there alternatives to accelerated access?**

3) We typically look for Analysis articles to present a compelling argument. We couldn't discern a specific argument other than a general tone of 'stop the rhetoric on miracle cures and overcautious slow regulators.' Any revised article would need to present a clear line of argument.

We have clarified our argument in the revised paper. As in the previous version, we first describe the powerful rhetoric on miracle cures and overcautious regulators, the resulting trends towards accelerated access, and the risks that these schemes raise. However, rather than simply railing against this rhetoric (as others before us have done), we have taken a different approach. We now systematically consider a number of practical ways of countering the rhetoric and also argue that there are alternative ways of responding to the values and concerns that underpin this rhetoric.

4) To make this a more international article it would be useful to give a global perspective and discuss the situation in the developing world, and in countries outside of the UK/US/AUS.

We have included examples from a wider range of countries (including access to therapies during the recent West African Ebola Virus epidemic) in the revised article in order to give a more global perspective.
5) Does this only apply to cancer drugs? We didn't see how this was specific only in that area. Perhaps you could be clearer about this
This issue is not unique to cancer medicines but arises in relation to new medicines for a range of conditions. We have removed the word “cancer” from the title and included both cancer and non-cancer-related examples throughout the revised paper.

6) It may be helpful to include the counterpoint - why do others argue for accelerated access and how are those concerns outweighed by the ones you present here?
We have provided more detail on the arguments for accelerated access. We also emphasise that while we are sympathetic to such arguments, we believe that other options (such as publically-funded clinical trials) are a more suitable response to the values which underlie these.

7) We note that in some sections of the paper, there is a conflation between access and approval. Please try to be clear and consistent about which you mean
We apologise for this confusion. In most cases, both regulatory approval and some form of subsidy are needed in order for patients to access new therapies. Thus, initiatives which provide accelerated access can involve either regulatory or reimbursement procedures. In the revised paper, we have clarified when we are referring to access in general (through both regulatory approval and subsidisation) and when we are focusing on either regulatory or reimbursement processes specifically.

8) If current strategies aren't working, what are the alternatives? You discuss rhetoric and expectation setting in the general media - is there a way to manage this?
In the revised manuscript we more clearly articulate ways in which a more balanced discourse could be encouraged, including: ensuring that press releases of research groups are factual, extending/enforcing regulations prohibiting the promotion of off-label uses of medications by pharmaceutical companies and encouraging media outlets to report on both positive and negative trial outcomes (through the introduction of media standards for the reporting of clinical trial results and the provision of alternative messages. However, we do not believe it is possible to completely prevent access to biased or incorrect information about new therapies. As such, we believe it is vital to identify the values and concerns that underpin the discourse, and determine policy approaches other than accelerated access to address these.

Reviewer Comments:
Reviewer 1:
Comments:
The processes behind access to new drugs is getting more and more complicated. As the authors point out, many countries now have institutions like PBS, NICE etc. It is probable that there has been a shift in the power balance between payers and drug industry. With increased professionalism among payers, substantial discounts are usually achieved in negotiations, as exemplified with NICE. However, negotiations take time and that’s when
"extracurricular" activities play a role. And we all know the "usual suspects"- drug industry, doctors (sometimes on the payroll of drug companies), patient organisations, politicians and media.

There is abundant, but unsystematic, evidence that this really does make a difference. The present paper is a readable narrative, but hardly adds new knowledge. It offers, in my opinion, naive solutions like "be alert to the discourse in which policymakers, clinicians and patients are all embedded...". In a time of limitless access to information, I suspect it is simply impossible to stem the tide of biased and incorrect information. I think the most important solution is that institutions like NICE are doing a good job and is respected, by patients and clinicians alike.

As I have already said, the present paper is worthy of reading, but I am inclined to say that it does not merit publication in the BMJ, as it offers essentially no new knowledge and no innovative thoughts on how to solve the problem.

In the revised paper we have provided more concrete solutions than “being alert to the discourse in which policymakers, clinicians and patients are all embedded”. First, we offer more detailed strategies for balancing the discourse, including ensuring that press releases of research groups are factual rather than rhetorical, extending/enforcing regulations prohibiting the promotion of off-label uses of medications by pharmaceutical companies and encouraging media outlets to report on both positive and negative trial outcomes (through the introduction of media standards for the reporting of clinical trial results and the provision of alternative messages). However, we agree that it is virtually impossible to prevent access to biased or incorrect information on new therapies. We believe, therefore that the best approach is to develop alternative policy approaches that take account of the values and concerns that underpin demands for accelerated access.

Reviewer 2:
This is a very well written paper, timely addressing an important and complex issue, and which surely deserves publication in the BMJ.

Thank you for this feedback.

A few issues should be further considered/adjusted before publication:
a) I fully agree that “when a medicine has not been registered and/or subsidised, this may not be a sign that the regulatory system is cumbersome or unfair but, rather, that that medicine has yet to be shown that it is safe, effective and/or cost-effective”. Nonetheless, I would suggest to separately address the issues of “lack of registration” and “lack of subsidization”, since the latter may be driven by factors related to the price-setting mechanisms, which are more and more controversial, in particular for new cancer medicines. If a medicine is not registered, there are doubts on its efficacy or safety. The non- subsidization, conversely, may be related to the financial constraints created by (not always clearly justified) high prices.

Thank you for suggesting this. We have articulated the different reasons for lack of registration and lack of subsidy of a medicine in the revised paper.
In this respect, I also suggest to quickly mention the current debate on the lack of transparency of cancer mechanisms. See for instance “The Price of Drugs for Chronic Myeloid Leukemia (CML); A Reflection of the Unsustainable Prices of Cancer Drugs: From the Perspective of a Large Group of CML Experts. Blood 2013; doi:10.1182/blood-2013-03-490003”; “Makers of anticancer drugs are “profiteering,” say 100 specialists from around the world. BMJ 2013;346:f2810 doi: 10.1136/bmj.f2810”; “In Support of a Patient-Driven Initiative and Petition to Lower the High Price of Cancer Drugs. Mayo Clinic Proceedings. August 2015 Volume 90, Issue 8, Pages 996–1000”.

Thank you for bringing this to our attention; however, we were unable include this in the revised paper due to space constraints.

b) From the point of view of individual patients, especially if facing a deadly condition, what counts is “efficacy and safety”, while “cost-effectiveness” is relevant at societal level. In addition, it is fully understandable that terminally ill patients with no alternative than palliative cares may be determined to accept the risk of futile treatment (“better a try than nothing”) and thus self-expose to possible additional harm. We have witnessed such a situation during the recent Ebola outbreak in West Africa, when in addition the first ones to benefit from “accelerated access “ where expatriate humanitarian workers from the US and Europe. I would suggest that the paper explicit acknowledges that the attitude of these patients is fully understandable (vulnerability), which makes the regulators’ responsibility to protect even greater.

Thank you for raising this- we have included more detail on the arguments in favour of accelerated access and the difficult position in which patients with few treatment options find themselves.

c) The paper might look more balanced if some positive examples of accelerated access were also quoted. This would not weaken the overall message that “easing” accelerated access is dangerous, and that the decision to grant accelerated access should be based on a solid risk:benefit evaluation and not on emotional drivers.

Thank you for this suggestion- we have now included a range of medications that were granted accelerated approval which was subsequently converted to regular approval and have since become part of standard practice as positive examples of accelerated access.

d) Reference 2 may be inappropriate to be quoted as negative example, because despite the title, the paper is quite detailed on the safety problems of idelalisib.

We have removed this reference.

e) I wonder (optional requirement) if it might be worthwhile to mention the current concerns about the attitude of the new US Administration vis-à-vis the US FDA (see https://www.statnews.com/2017/03/01/fda-trump-approval-process/ and others)

We now describe and reference the Trump administration’s attitude to the FDA and its drug deregulation agenda.

We have included a discussion of access to therapeutics during the 2014 Ebola Virus epidemic in West Africa in the revised paper.