Pablo Fernandez and **Philippa Taylor** assess the risks with early medicines ahead of full clinical trials

TO FAST TRACK OR NOT TO FAST TRACK?

key points

- There have been mixed reactions to the 'easy access to medicines' scheme. Fast-tracking ZMapp to treat Ebola appears to be a success story.
- Clinical research is highly regulated for good reasons. While costly and time consuming, it ensures protection against drug disasters.
- It's possible to over-estimate the likelihood of benefit based on early trials. Fast-tracking could lead to reduction of people willing to take part in double blind and placebo-controlled trials.
- Doctors can be pressurised by patients and families and may feel they are forced to act against their better judgement.

'Towards the end [Dad] was about ready to try anything. …There must be nothing more maddening than dying of a disease when there is a great clinical trial going on that suggests had you developed the disease a year later, you'd be saved.'

'There's a reason for pharmaceutical regulation: drugs can be unexpectedly dangerous. I'm concerned that desperate patients will be harmed as much as helped.'

These were two reactions to news about the 'early access to medicines scheme'[1] which gives patients with life-threatening or seriously debilitating conditions access to medicines that do not yet have a marketing authorisation. Since its introduction in April, Lord Saatchi has submitted a draft bill to the House of Lords, aiming to allow the use of innovative new treatments for cancer and other diseases.[2] It has Government support but is opposed by the BMA, Medical Defence Union and Academy of Medical Royal Colleges, among others.[3]

This debate reflects an increasing struggle between those who support the identification and use of effective and safe therapies through the standard, thorough but lengthy regulatory processes, and others who advocate greater access to promising therapies that are still undergoing efficacy and safety testing.

The recent Ebola outbreak has put a spotlight on the research efforts needed to combat global health threats and emergencies. The novel treatment, ZMapp, has been fast-tracked and appears – so far – to have been relatively successful in the few cases where it has been used.

A report on initiatives to try untested treatments on Ebola patients suggests legal changes are unnecessary.[4] 'Everyone has gone beyond their comfort zone', noted the chief investigator, showing the unease of administering untested drugs in a non-controlled, non-randomised way. However, results are reviewed carefully for risk-benefit, and strict stopping rules apply if the treatments do not drastically reduce mortality. This is a far cry from the very open criteria in the proposed legislation.

UK clinical research is highly regulated; patients' rights and interests are well protected. The increased oversight of drug development is designed to protect the public and ensure all human research is carried out in the best interests of the subjects.

However, whilst being rigorous, drug development is costly and time consuming. Current procedures decrease the risk of drug-related disasters but correspondingly increase costs and delays, thus delaying public benefits from potentially effective drugs.[5]

This is the drive behind the Saatchi Bill. However, its premise – to allow access to medicines before they have passed all standard regulatory processes and trials – raises practical and ethical questions.

Efforts to fulfil desperate hopes of extending life are understandable, particularly if the patient takes full responsibility for the consequences and no one else is harmed. However, using investigational drugs outside of clinical trials is not straightforward.

1. Drugs in the early phase of development may not only lack efficacy but may be more risky than preliminary data shows

It is estimated that only 5% of cancer drugs undergoing human testing are eventually approved for human use. Safety problems, lack of efficacy or economic unviability mean many studies fail before phase III testing (after promising earlier tests).[6] The Motor Neurone Disease Association (MNDA) claims only one drug for MND has ever been found to be efficacious in a phase III trial, although dozens more have appeared promising at phase II.[7]

2. Overestimate of benefit from phase I trials

Positive results from early tests can cause patients and investigators to overestimate the likelihood of benefit, and to forget these are experimental, tests, not

therapies. Media coverage claiming greater efficacy of investigational drugs, unsupported by research, can incite premature expectations and raise false hopes.

3. Clinical trials may take longer if patients who could participate are also given the option to have an untested or partially tested drug outside of a study context

If patients with an incurable disorder are offered a new (potential) treatment, they may not want to volunteer to take part in a double-blind, placebo-controlled trial where they might be given the placebo. For a low prevalence disease it could possibly even remove entirely the population of patients available to take part in phase II / III trials.[8]

4. Unbiased and meaningful data outside clinical trials can be difficult to gather, particularly information on efficacy

The rigorous process of protocol-driven data collection, verification and analysis required for clinical trials allows patient and treatment data to be interpreted with a high degree of confidence. This degree of standardisation and control is extremely unlikely in normal day-to-day clinical practice. Allowing access to a drug that has not passed all regulatory controls would likely adversely affect clinical data collection and thus ultimately delay approval and broad availability.

5. Balancing benefit and risk to commercial interests

Reduced trial recruitment and possible adverse reactions before safety trials are completed are a risk to companies. Conversely, advanced exposure to, and use of, new treatments can boost their marketing. Media and public exposure can provide a competitive and economic advantage for companies not just from the publicity generated but also from public pressure on regulatory bodies. This happened after NICE's 2006 decision to refuse funding of Herceptin in some forms of breast cancer, on the basis of low cost-effectiveness. The ensuing public outcry eventually resulted funding being granted.[9][10]

6. Dilemmas for doctors

Doctors can, under pressure from patients or families, be persuaded to provide a new treatment against their better judgment. They may feel they cannot refuse to offer investigational treatments as they could be seen to be removing hope from the patient or lacking compassion.

7. The rights of terminally ill patients to be treated with investigational drugs

The question of personal autonomy and individual rights is at issue here. Demand for access to investigational drugs centres on the right to forgo participation in clinical studies and regulatory protection and to take personal responsibility for the risks entailed.

Ethicist Edmund Pellegrino comments that the principle of autonomy has become absolutised in medicine and in the controversy over access to investigational drugs as well. He believes limits must be put on personal autonomy if it impacts others, for example, if a patient asks for a treatment that the doctor feels is not safe or effective and thus not in the patient's best interests.[11]

9. Will pressure to approve drugs prematurely progressively weaken the authority of regulators?

Granting rights based on personal autonomy may, in the long-term, lead to other 'rights' claims for access to other medicines, substances, artificial devices, or for self-administration, without a doctor's supervision or help. The drafting of the Saatchi Bill would prevent this for now.[12]

10. Informed consent

Informed consent, which can be difficult enough when a body of evidence has accumulated following clinical trials, becomes much more difficult when there is little evidence to support the effectiveness, safety and risk-benefit profile of the innovation.[13]

11. Providing hope

Understandably, seriously ill patients may reach out in desperation for anything that might help, without fully considering the consequences. However, while there is a danger that patients will turn to unproven remedies to restore hope, there is also a benefit to maintaining hope, which may serve partly to justify early investigational drug treatment, regardless of the chances that it will or will not work. Maintaining hope may improve the quality of life for the patient. And of course the drugs may work.

Clearly there are challenging questions here for regulation. Do concerns about the time and costs of the current system of regulation justify exposing patients to the risks of experimental interventions? How would evidence about the safety and efficacy of experimental, innovative, interventions be generated and collected? Under what conditions should evidence generated outside of a clinical trial be considered persuasive?

At the moment, using innovative treatments is a bureaucratic process and there probably should be a cultural shift towards more openness towards, and flexibility with, innovative treatments. The rapid use of the putative Ebola treatment is a good illustration of the fact that, given the political will combined with obvious public need, current legislation already has mechanisms that allow the development and use of innovative treatments. But it remains a rare example.

Research subjects, especially the seriously or terminally ill, are vulnerable and open to manipulation and abuse by the strong, including powerful academic, commercial and government agencies. There are no easy answers, but it is essential to try to achieve a balance between encouraging innovation and drug development while protecting patients.

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The recent Ebola outbreak has put a spotlight on the research efforts needed to combat global health threats and emergencies

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