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# Dilemmas in the Compassionate Supply of Investigational Cancer Drugs

Lewis J R R, Lipworth W, Doran E, Kerridge I. (2014)

**Abstract**

In Australia, patients who want to access medicines that are not yet approved have only two options: to enrol in a clinical trial if they are eligible, or obtain their medicine through 'compassionate supply', which is provided at the discretion of the manufacturer. In this article, we explore ethical issues associated with the provision of oncology medicines that are still in development, either prior to regulatory approval or government reimbursement.

**Keywords:** ethics; evidence-based medicine; health services accessibility; oncology

## Introduction

The possibility of developing cancer is a terrifying prospect for most people. It is unsurprising, therefore, that media reports relating to "breakthroughs" in the fight against the disease invariably capture the attention of the Australian public.

Stories of promising early clinical trial data presented in the media—as well as at conferences, in medical journals, and via the Internet—may also prompt interest from patients, their relatives and their doctors to gain access to new agents without the need to wait years for their regulatory approval.

Patients desiring access to medicines that are not yet approved generally have only two options: to enroll in a clinical trial if they are eligible (although this does not, of course, guarantee allocation to the new experimental treatment) or to ask the manufacturer to supply the medicine on "compassionate" grounds. The recent story of Nick Auden illustrates what happens when both of these options fail.

Nick Auden was an Australian patient and young father, who died in 2013 from advanced metastatic melanoma. He and his family attempted, unsuccessfully, to gain

access to two 'promising' new therapies currently under development— nivolumab (Bristol-Myers-Squibb) and lambrolizumab (Merck). While not approved by any international regulatory bodies, these two drugs had shown promise in phase I clinical trials, and at the time of Auden's approach to the two companies patients were being enrolled into phase II and III studies.

Advanced metastatic melanoma has a very poor prognosis, with an overall 5 year survival being 10-20%.(1) Conventional therapies such as surgery, radiotherapy, cytokines and established chemotherapeutic agents (such as dacarbazine, temozolamide, paclitaxel, cisplatin) offer little more than short-term palliative benefits for many patients. For this reason, enormous excitement has surrounded the emergence of newer targeted therapies (vemurafenib and ipilimumab) as early studies have suggested a clinical benefit with relative increases in average patient survival of 63% and 36% respectively.(2) (3)

However, because neither nivolumab or lambrolizumab were approved by the Therapeutic Goods Administration (TGA), and because he was not eligible to participate in phase II or III studies, Auden, his family and other high profile advocates pleaded for "compassionate access" from the companies developing these two medicines. The two companies, however, refused his requests, despite his case gaining international media coverage and a petition signed by many thousands of supporters.

The public disquiet surrounding this case, and many others like it, illustrate a number of ethical, legal, commercial and socio-political challenges associated with compassionate access to cancer medicines, particularly those still in clinical development. In this article we describe features of compassionate access processes in Australia, highlight their limitations, and suggest the kinds of changes that might be required to ensure more appropriate and equitable access to prescription medicines.

**Compassionate access to cancer medicines in Australia**

The most common mechanism for patients to access currently unapproved or approved but unfunded treatments is through patient access programs (PAPs)—also referred to as "compassionate use", "named patient" or "expanded access" programs. These programs, run by pharmaceutical companies, make drugs available (often, but not always, for free(4)) to patients within a structured company-administrated framework. Inclusion criteria are usually similar to, but less rigorous than, those of a clinical trial, and tend to be closely aligned to the indication being sought by the company for their new product.

Companies usually decide to institute PAPs following the emergence of phase III clinical trial data (i.e. data on efficacy and safety in patients with the relevant indication), and after an assessment of whether existing data is likely to support the eventual commercial launch of the new drug. In Australia, the ability to prescribe non-approved treatments is legislated for via the Australian Therapeutics Good

Administration Category A Special Access Scheme. This provides clinicians with the authority to prescribe non-approved treatments in the setting of a life-threatening condition.

Outside of formal patient access programs, patients can approach companies with individual requests for supply of a desired medicine. They can also purchase the medicine themselves, either locally if it is available, or from another country where the treatment has regulatory approval. Companies may or may not help patients afford these medicines, which are often expensive, through various kinds of co-payment or cost-sharing arrangements. Some hospitals also have high cost drug and therapeutics committees, which may agree to supply cancer medicines that are not approved by the TGA and/or not funded on the Pharmaceutical Benefits Scheme

**Companies' obligations**

As is evident in Nick Auden's case, companies are under no obligation to respond positively to requests for compassionate access. This is despite attempts made overseas to change this situation. In 2007, a group in the United States called the Abigail Alliance argued that both the United States Food and Drugs Administration (FDA) and pharmaceutical companies, had an obligation to provide early access to life-saving medicines.(5)

The Abigail Alliance claimed, on libertarian grounds, that if a terminally ill patient had a fundamental right to refuse life-sustaining treatment, knowing that they would die as a consequence of that choice (a statute ruling from previous US cases), a corollary had to be that terminally ill patients should have the right to access any treatment that may extend or improve the quality of their lives, including those still in development. In rejecting this proposal, the FDA countered that such access would undermine the entire clinical research process and thus have a 'devastating' impact on the interest of future patients.(6) Following the failure of the Abigail Alliance's case, at the current time, patients like Nick Auden have no option but to continue to lobby for compassionate access to medicines—leaving pharmaceutical companies to make their own decisions about whether or not they are able to help.

At present, each pharmaceutical company independently determines when to allow compassionate access to its products, who should receive such access, and for how long. As Auden's and other previous cases that led to the Abigail Alliance's actions have illustrated, decisions relating to *ad hoc* requests can be highly controversial, leaving some patients feeling that they have been abandoned for unjustifiable reasons. This, in turn, raises the question of how decisions about compassionate supply should be made and how compassionate access programs should be designed and overseen.

**Ethical considerations and tensions in the provision of compassionate access**

There are a number of tensions inherent in the provision of compassionate access to cancer medicines, resulting from a complex interplay among medical need, evidence,

ethics, medical law and commercial interest.

The first of these is the tension between providing benefit to patients without causing harm to them, to those supporting them, to the health system, or to the research enterprise. Although robust clinical research and regulatory processes take time and delay access to medicines, they have evolved for good reason and history has demonstrated that significant harms may arise where medications are inadequately researched or regulated—such as occurred with rofecoxib(7) for arthritis and thalidomide for "morning sickness."(8) Notwithstanding that 'risk/benefit' considerations may be considerably different for patients with immanently life-threatening illnesses, as compared to patients with, say, morning sickness or arthritis, potential harms still need to be considered.(9) In this regard it is noteworthy that several cancer and HIV medicines that have been the source of initial excitement have subsequently failed to live up to their promise—even for people in desperate situations. These include, for example, cytokines for renal carcinoma(10), anti-angiogenic therapies for breast cancer(11) and some earlier anti-retroviral drugs used in the treatment of AIDS.(12) In the context of life-threatening illness, we also need to bear in mind that effective palliation may be foregone if patients are led to believe that an expensive new treatment is their "only hope". This lost opportunity is a real harm that needs to be factored into any risk—benefit calculation.

Second, because resources are limited (even for companies, as will be discussed later) decisions have to be made about who should be privileged in terms of compassionate access. This inevitably creates a tension between allocating resources efficiently, so that the greatest amount of good is done for the greatest number of patients, and allocating resources in such a way that no particular individual or group is disadvantaged.(4)

Third, as was evident in the Abigail Alliance debate, there is a tension between clinical care, which focuses on the needs of current patients, and research, which is primarily concerned about future and, ultimately, many more patients. If enough patients receive supply of a medication outside of the clinical trial setting, then opportunities are lost to gather crucial data on safety and efficacy. Trials might also be impacted if compassionate access makes it difficult for manufacturers to supply enough medicines needed for research.

Finally, there are tensions between the needs of patients (both current and future) and the need for pharmaceutical companies to ensure early and maximal commercial returns. Pharmaceutical companies are businesses, and compassionate supply of their medicines may or may not be aligned with their longer-term commercial interests. On the one hand, as critics of industry have argued, companies may use compassionate access schemes as marketing tools designed to familiarize prescribers with their products, to create demand among patients and consumer for access and continued supply of these medicines, and to generate support from patients and clinicians for submissions to regulatory and funding bodies.(13) On the other hand, compassionate supply may work against the commercial interests of

companies, costing them money and diminishing community advocacy for third party (government or insurance company) funding as a means to access, thus reducing long-term revenues for manufacturers.

So, with these tensions in mind, what might be a scientifically, ethically, politically and commercially sound approach to early access to potentially life-saving medicines?

**The future of compassionate access programs**

The first thing for those considering compassionate supply or designing compassionate access programs is to acknowledge there is no simple solution to any of the tensions described above, and it is therefore unlikely that a satisfactory "one size fits all" process will ever be defined. Indeed, as described above, numerous models exist for patient access programs and there is significant heterogeneity between these.

In all cases, therefore, engagement between companies and other stakeholders who may be impacted, such as clinicians, patients and regulators should occur to ensure that values are made explicit, that all interests are considered, and that trade-offs are acknowledged and managed. In technically complicated and value-laden processes such as these, it may be important to establish an appropriate forum that brings together representatives of industry, consumers, government, health providers, insurers, physicians, researchers and ethicists to develop a framework for patient access programs and, where resources are available, to review and advise on specific programs. While it is beyond the scope of this article to consider the details of how such a forum should be established and run, it could draw upon frameworks for policymaking such as "accountability for reasonableness"(14) as this emphasizes inclusive, transparent, accountable processes rather than on pre-refined rules of allocation.

Second, properly informed consent should always be obtained—particularly when the treatment has not yet been approved by a regulatory agency. Patients requesting compassionate access are highly vulnerable and may feel a genuine sense of desperation, but they still need to understand the risks of bypassing research and regulatory processes, and the decision has to be theirs and not their family's or their doctor's.

Once access has been granted and consent obtained, patients need to be carefully monitored for adverse events. In this regard it is noteworthy that, while, as discussed above, some PAPs require approval by health authorities prior to opening within hospitals under their jurisdiction, these programs rarely go through a human research ethics committee (HREC) review process. Indeed, data collection is often kept to a minimum in order to avoid the need for such review. The explicit justification for this is that the need for review may delay patient access to, and clinician experience of, a new product. Implicitly, reluctance to collect data and submit it for review may be in conflict with the commercial interests of a company

wishing to launch a new product as quickly as possible. Whatever the reason for bypassing review, the absence of sufficient oversight by HRECs may place patients at greater risk than those enrolled in clinical trials if a treatment is very early in its development and also limit the extent to which PAPs can be used as alternative sources of data about safety and efficacy. Because of this it is important that appropriate safeguards are in place to protect the interests of the most vulnerable of patients.

In terms of forward planning, it is important for any company to consider the possibility that they might never achieve either regulatory approval or reimbursement, and to ask themselves what this would mean for the future of patients enrolled in a PAP. One option would be to simply apply a 'rule' that the PAP runs for a limited time, as is the case with Patient Familiarization Processes (PFPs). Under the rules of Medicines Australia Code of Conduct, PFPs may run for only 6 months. However, while the application of such a rule to PAPs provides transparency, clarity and consistency, it may not adequately account the many complex factors that underpin decisions to provide compassionate access.

A different approach, however, could take the form of single arm phase IV studies. These would have the benefit of generating useful additional evidence relating to safety, quality of life or other response-related endpoints. They may also help to generate evidence for outcomes that are difficult to demonstrate through randomized controlled trials due, for example, to confounding caused by crossover or post-study exposure to study treatments.(15). Indeed, compared to evidence generated within 'artificial' parameters of an RCT such activity may also be more reflective of the clinical effectiveness of a new treatment within a local and, because of less stringent inclusion criteria, a more diverse patient population. Such studies would, however, be reliant upon good biobank and patient registry infrastructure and would need to be managed very carefully so as not to compete with patient recruitment to clinical trials.

One other issue that needs to be considered is that pharmaceutical companies are only one "player" in this complex field. While the focus of our discussion has been on medicines that have not yet received regulatory approval, compassionate access programs exist in part because governments and/or private insurers may choose not to fund even those medicines that have been shown to be safe and effective (but may not be cost effective)—such as trastuzumab (Herceptin) for metastatic breast cancer. This raises a whole suite of issues about the organization and priorities of the public and private health systems that are beyond the scope of this article. But it is important to bear in mind that ensuring access to life-saving medicines is a shared responsibility that falls to many different stakeholders, each of whom is driven by a complex set of moral and socio-political concerns.

**Conclusion**

Despite some media reports to the contrary, decisions about compassionate supply of cancer medicines that are still to be approved is not a simple matter of helping, or

not helping, an individual in need. Rather, they involve highly complex decisions that raise many ethical, regulatory, commercial, scientific and clinical tensions, all of which need to be considered and balanced.

Importantly, the potential risk that PAPs may undermine or circumvent carefully structured processes for drug approval needs to be managed. This is because history provides us with a number of examples of drugs that initially appeared promising, but which were later found to be unsafe or of less clinical value than initially believed. In the context of cancer and other life-threatening illnesses where patients may be desperate for help and clinicians may feel enormous pressure to use whatever experimental treatments are available, it cannot be forgotten that appropriate palliative care may a more suitable option for some patients than access to treatments that may well prove to be ineffective and/or unsafe. For these reasons, the interests of both present and future patients need to be carefully considered, with decisions made in ways that are systematic, transparent, accountable, explicit about values, respectful of patient autonomy, and inclusive of all stakeholder perspectives.

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