# Experimental Drugs & Compassionate Use

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## Introduction

Controversies exist over the 'compassionate use' of experimental drugs. Several cases exist of desperately ill patients who believe that a drug that has not been approved for use by the Food and Drug Administration (FDA) in the USA will help them. And so patients and families in North America have applied pressure via social media to drug companies to give them access to experimental treatments.

New cancer drugs such as *keytruda* being manufactured by Merck, for example, are reportedly yielding encouraging results in harnessing the body's immune system to attack cancer cells.. Johnson & Johnson's experimental treatment for multiple myeloma, *daratumumab*, is in late-stage clinical trials and is also generating excitement.

Hence, in the USA, a growing number of patients with terminal illnesses have sought the right to obtain drugs that are still in the 'testing' phase of clinical trials, but which show promise for treating their diseases. This has prompted a debate over whether pharmaceutical companies should allow critically ill patients to have access to drugs that have not yet been approved.

Drug companies have been granting emergency access to their unapproved drugs since the AIDS epidemic of the 1980s, when the Food and Drug Administration of the USA set up a process to help desperate patients get experimental treatments. In 2014, the Agency approved 1,873 requests to grant what it calls 'expanded access', and this was an 85% increase over those granted in 2010, when it approved only a little over 1,000 (1,014) requests. However, saying 'yes' is not so simple, as drug manufacturers often have a very limited supply of such treatments, leading to anguished decisions over who should be given the products. The undercurrent issue also is that the unproven drugs might not work, or could even cause harm.

And so pharmaceutical companies are often reluctant to give patients with terminal illnesses promising drugs that are still being tested, fearing that it would interfere with clinical trials or that there is not enough of the treatment available, as it was with the issue in the Ebola vaccine matter during last year. The issue has raised questions about fairness and equal access to care, and more than a dozen states in the USA have proposed legislation to assist in the process.

## Clinical Trials

Before they become available on the market – experimental drugs are required to go through three phases of clinical testing. In phase 1 clinical trials – the drugs are tested for the acute, dose-related toxicities of new pharmacological products. In phase 2 clinical trials – the drug is tested for its safety and its dose efficacy ( its ability to produce the treatment effect at different doses). Phase 3 involves a much larger group of patients – evaluating safety, efficacy, and side-effects. Once the drug passes all these 3 phases – then it is approved and registered for general use in the marketplace.

Phase 1 testing normally involves testing for pharmacological effects in a small number of healthy persons. In phase 2 clinical trials, however, where it is evaluated for its effect or efficacy as well as safety, the drug has to be tested in the population of patients who have the particular disease it is meant to treat. For drugs that might benefit terminally ill patients such as those with end-stage cancer – the matter therefore involves a lot of ethical considerations.

**Ethical Issue – Fair Selection of research participants**

How will the research participants be selected?

One of the seven (7) criteria that research ethics committees/IRBs should use to determine whether a proposed research is ethical – is the fair selection of the research participants for the research endeavour. Important here are inclusion criteria and exclusion criteria.

For a very promising cancer drug – will there be a fair chance of access to the experimental drug? Phase 3 Clinical trials involve a process of randomization – and in this case very sick patients would be randomized to either arm of the clinical trial – some to get the experimental drug, and others to get what is customarily the known standard treatment for that particular illness. For a clinical trial – a state of equipoise should exist, meaning that the researchers and the general medical community would be uncertain whether this new experimental drug will be more beneficial or less beneficial than what is the standard therapy. Hence the need to compare them.

However, if based on its evaluation during the animal model stages of testing, and the results from phase 1&2 testing there is much promise that the experimental may in fact be of significant benefit to terminally ill patients, then all such patients would want to be in the experimental drug treatment arm of the research and not in the comparative standard treatment arm of the research.

Hence against this background involving terminally ill patients , urgent need, and the matter of treatment efficacy, the of randomization of very sick patients, fair chance and equality of access are critical ethical considerations.

**Ethical Issue – the Utility of scarce resources**

An experimental drug is a scarce resource. It takes millions of US dollars to take it through the various stages of animal testing, then phases 1, 2, and 3 of clinical trials. Therefore the manufacturers would not have produced any large quantity of the drug being tested, invariably producing just the amounts needed for the clinical trial.

This therefore creates a 'hope gap' between the very sick participants who are seeking some benefit, and the reality that there will not be enough experimental drug available to benefit them all. Within this milieu, in the interest of altruism or beneficence, should the manufacturer produce larger quantities of the experimental drug than what would be required for the clinical trial? Where large numbers of cancer patients are seeking to benefit – how much would be sufficient?

What will happen to those patients at the end-point of the clinical trial – if the experimental drug in fact provides therapeutic benefit? Will they lose access to the drug? Will they be able to financially afford the drug that would then be placed on the market? These are all ethical issues!

**Ethical Issues – matters of patient autonomy, informed consent, and appreciating relative risk**

Over the past decade or so, in our Caribbean countries, patients have been increasingly given the right to make decisions about themselves, as the body is theirs and so they have the right to be the final arbiter of what is done to it. Once all elements of the informed consent process have been accomplished, then the final decision is theirs. In this special case however, the terminally ill patients may be too sick or may not have the background or the ability to fully understand the risks associated with an experimental drug. Research on the matter has shown that the odds of a new experimental drug working ranges from 10 – 33%. Patients' expectations will be much higher!

These patients may be desperate as they have exhausted all therapeutic options, and so their perceptions of the balance between possible harms and potential benefits may be distorted. In this context, the patient is severely ill and more than likely does not wish to die, and so that person may undertake more risk than the average, reasonable person who is healthy is likely to undertake, given the same circumstance of enrolling in a clinical trial. This matter therefore is also a very important ethical concern.

**Ethical Issue – financial ability, country of citizenship, and the matter of access**

Clinical research always has to be judged and evaluated against the background of the local context in which it occurs. In this case – the drug being tested is expensive, and its use within the research setting as well as subsequently in the initial marketing phase of the drug, will very likely not be covered under health insurance policies and plans. The matter of the research participant's ability to pay for or purchase the drug is therefore another ethical issue.

Further, in enrolling research participants into a study – should researchers seek to ascertain their country of citizenship beforehand – particularly where the experimental drug is in very short supply? For the very sick patients, who are competing for access to this potentially beneficial experimental drug, should it matter whether they are registered citizens of the country or illegal aliens? In other words, should legal, registered members of a society have better access to such medication than illegal residents? These are all ethical issues to ponder!

**Conclusion**

In clinical care, we are more focussed on benefitting the current individual patient rather than on future patients or persons who will also need health care. However, if we take a "bird's eye view" of this particular dilemma before us involving terminally ill patients' access to experimental treatments, it may not be in the best interest of these very sick patients to gain access to treatments that may either be ineffective or at most provide only a 33% chance of benefit, and further could worsen their clinical state. The time and resources involved in granting access to such drugs could delay efforts to get them approved for a much wider population of needy patients, particularly at smaller pharmaceutical companies. For example, in the Ebola epidemic of last year, the FDA allowed ZMapp to be used on a handful of patients, but the company quickly exhausted it limited supply.

And so – if one uses a utilitarian view which seeks to maximize benefit for the greatest number of persons – one would opine that granting increased access to some terminally ill patients would divert resources from clinical trials and thereby delay the research process that could lead to approval and more speedy access by a greater number of patients as it would come on the market much sooner. Others however have critiqued that such an approach would be 'playing God', as some would get but not all can get!

If however we approach the matter using the ethical theories of deontology and the ethics of care, we might come to a different opinion. Perhaps even more important, we should note that sometimes, as in last year's Ebola virus epidemic, the allocation of experimental drugs can affect whole populations as well as a country's foreign policy. Navigating these ethically thorny issues is a job that will require not only medical knowledge but tact and much political skill!

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References:

- I. Cook.  Bioethicist to head compassionate use panel. Bioedge: May 9, 2015.
- Thomas, Katie.  J&J creates bioethics panel on trial drugs.  New York Times; May 7, 2015. https://www.pharmacist.com/jj-creates-bioethics-panel-trial-drugs. http://www.nytimes.com/2015/05/07/business/company-creates-bioethics-panel-on-trial-drugs.html?ref=health&_r=0