

Ethical Concerns for Global Cancer Research

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ABSTRACT

Cancer research seeks to improve quality of life and add new and better modalities for treatment to increase survival. Accompanying such research, however, should be specific ethical considerations as cancer patients may be rendered vulnerable by their particular diagnosis. Chief among these are possible conflicts of interest, especially when the researcher is the attending doctor for the cancer patient, achieving informed consent and research involving children with cancer.

As researchers in lower and middle-income countries (LMICs) often lack the financial and sometimes technical resources to conduct much cancer research, they often must collaborate with researchers and sponsors from the richer countries in the global north. Many ethical issues may arise in these collaborations, however, as LMICs have relatively more illiterate and historically more disempowered people, with a different ethical framework for healthcare decision-making.

The new paradigm for anticancer drug development involves the development of agents that specifically target a critical pathway within cancer cells. However, research with molecularly targeted agents includes the ethical consideration of *more than minimal risk*, and so while competent adults may volunteer for such research studies, it is ethically debated whether parents may give permission for their children to participate in them.

Another ethical requirement to be met in cancer research is that of the dissemination of the findings, whether positive or negative. To do otherwise is to waste the human and financial resources that went into the research endeavour, as well as commit a '*moral wrong*' to the participants who sacrificed for the research.

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INTRODUCTION

Research in cancer to find better modalities for treatment and improved quality of life is crucial, and will continue to be crucial in the foreseeable future in order to improve survival while decreasing the burden of disease and treatment-related morbidity in persons afflicted with cancer. Consequently, cancer research has sought to assess survival, compare survival through different modalities of treatment, as well as develop new forms of treatment for this much feared disease.

We have seen much progress in the development of cancer therapeutics through multi-agent clinical research trials. Further, new classes of therapies are also emerging, especially molecularly targeted therapies. Despite all this, however, the complexity of designing such research for adults and children afflicted with cancer, plus challenges posed in obtaining informed consent from adults and assent from children to participate in research continually pose challenges for oncology researchers, Research Ethics Committees/ The Institutional Review Board (IRBs), patients, parents and the affected children themselves.

There has also been the potential conflict of interest that is inherent in the conducting of clinical trials. Researchers may gain promotion or generally advance in the academic world through the publications of their results regarding new scientific studies. This begs the question of whether the research participant was offered entry into the research study because participation was in their best interests or for the researcher's best interests.

Further, was the researcher paid by a sponsor to conduct the trial? If so, does the level of payment increase as the number of research participants they enter increases? If a research participant departs the trial prior to its completion for any reason, does the researcher suffer financially, or academically? (1)

Would these considerations be incentives for the researcher to seek to keep the patient in the trial? Has the patient being informed about any of these potential conflicts? Even if the patient has been so informed, how does it affect his or her subsequent relationship with the researcher, particularly if the researcher is his or her attending physician?

In light of all these questions, it is therefore, important that all persons understand the ethical challenges involved in cancer research, so that it may occur within a sound ethical and regulatory framework.

An assymetry of resources

When we conceptualize research for cancer, do we conceive of research participants as individual entities, or rather as constituents of a group that have certain features in common? The primary role of research ethics is to protect the participants in research from harm, but how we devise and go about seeking to protect them depends on how we perceive them (2). This perception may vary from location to location, and between countries of the north and countries of the global south lower and middle-income countries (LMICs).

A wide gulf exists between countries of the global north and LMICs in the resources available to research cancer. Researchers in LMICs often lack the financial and sometimes technical resources to conduct much of this research, and so to achieve career advancement or progress in the field, they often must collaborate with researchers and sponsors from the richer countries in the global north. Consequently, global cancer research is often conducted as an international collaborative effort.

In such circumstances, however, many challenges exist. Lower and middle-income countries have relatively more illiterate and historically more disempowered people than do countries of the global north. Further, in LMICs, the framework for decision-making in healthcare often does not revolve around personal autonomy and notions of liberalism, but

rather is located within the ethical concepts of communitarianism, or hybrids of communitarianism and liberalism (3). So, in LMICs, the influence and opinions of family members, friends and other members of the local community often carry greater weight in personal decision-making than they do in countries of the global north. There is thus a greater sense of *solidarity* within the ethics of care.

Consequently, in global cancer research, many ethical issues arise that may not be present in national or local cancer research. These include how to achieve the requisite enrolment due to varying educational levels in potential research participants across different locations, wide disparities in their socio-economic status and in their cultural belief-systems regarding cancer and the causes of cancer, as well as in the asymmetry of power wielded by researchers of the global north (who have greater access to resources for cancer research) and researchers in LMICs.

Conflicts of interest

For physician-researchers, the potential for conflict between the *ethical physician* and the *clinical researcher* exists. The physician-researcher has an obligation of healthcare in the best interest of the patient, but also has an obligation to the process of research, with the desire for a favourable outcome. The international ethics guidelines for research with human participants require that researchers provide patients with all the relevant information they require to make an informed decision (4). The information is important as it will affect their willingness to enter into, or continue to participate in a clinical trial.

Whilst there may be a legitimate concern that detailed information about a cancer research clinical trial may confuse rather than enlighten patients and may add an additional emotional burden, the optimal choice for disease management can only be made when all relevant information regarding possible options have been provided to, and considered by the

patient and their loved ones. When patients are entered into research, an important consideration is the matter of risks and potential benefits. To whom do the possible benefits accrue – to the enrolled patient, or to generalizable knowledge to benefit other patients? When afflicted with cancer, patients invariably are seeking to personally benefit from any choice they make. However, when enrolled in clinical trials, they may or may not personally benefit, particularly if they are randomized to the arm where a placebo is being used, or where the experimental therapeutic agent does not prove beneficial.

What therefore, should the researcher tell the patient in this regard? Further, if the primary end-point of a research project could be overall survival, or the determination of progression-free survival, should this distinction be made clear to the prospective research participant? (1). Progression-free survival refers to the time from the initiation of treatment until the 1st evidence of progression of the disease. To the patient, overall survival can be quite clearly described and defined, but progression-free survival is a more difficult concept.

The matter of *therapeutic misconception* may also arise here. Where the clinical researcher is also the patient's treating physician, the patient may feel that when enrolled into research by the physician, that the physician-researcher has their best interest at heart and they will therefore get some therapeutic benefit from whatever intervention is being offered by the physician in the research project. This issue becomes even more pronounced when the research is being conducted in LMICs, where the level of education is significantly less than that existing in the more developed countries, and where physician paternalism is historically entrenched with no paradigm shift to patient autonomy as the locus for decision-making, as has occurred in most countries of the north (5).

The clinician-researcher is ethically obligated to make clear to the patient that the endeavour being proposed is not for their individual treatment, but actually research! Further, that having been provided the details that he or she has the option not to participate (6).

Informed consent

This ethical requirement for research stipulates that potential research participants who have the capacity to make decisions for themselves should be given sufficient information and time to make a considered determination about their desire to volunteer (7). However, in oncology research studies, the information to be conveyed is often very complex. Diagnosis with a potentially fatal disease such as cancer, might dispose all persons diagnosed with cancer to be classified as being *vulnerable*. This is because such persons possess one of the five criteria for vulnerability, namely, a reduced capacity to provide truly ‘informed’ consent (2). In other words, their ability to decide autonomously about participation in research may be compromised by their specific diagnosis. Consequently, vulnerable persons require special protections revolving around the consenting process and how to preserve voluntariness and autonomy (8), and so cancer researchers have the responsibility to be particularly sensitive to the special nature of these persons.

While all children are classified as vulnerable, in the case of children who have cancer, they may be perceived as being even more vulnerable. Most children do not develop a cognitive ability that approaches an adult’s ability to give appropriate informed consent until they are somewhere in the middle of their teenage years (1). So, in order to overcome these competence and capacity issues when wishing to enrol minors in cancer research, the same information that would be provided to adults in seeking informed consent is provided to their parents, while developmentally appropriate information is given to the child. Age seven years is often used as a rough guideline for when researchers should begin to explain to children what will be done to them and to obtain their agreement or *assent* for research.

Another ethical concern is whether there should be limits to parents’ ability to give permission for a child to participate in research where there are no direct potential benefits to

the child from the research. Further, parents are usually under considerable stress at the time of diagnosis or relapse of a child with cancer (1). This stress may interfere with their ability to comprehend and retain the information given to them as they normally would, even if the parents are otherwise completely competent. This situation may therefore, raise issues about whether any consent for research they may give on behalf of their child under the circumstances would be truly *informed*.

Molecularly targeted therapies

The new paradigm for anticancer drug development has moved away from identification of generally cytotoxic agents to the development of agents that specifically target a critical pathway within cancer cells (9). Inherent in this approach to drug development is the concept that different tumours are likely to have different critical pathways and that treatment may eventually be tailored to a specific tumour type. So, for instance, it is reasonable to expect that, at some point, agents could be developed that target paediatric tumours without an analogous target in adult tumours (1). Thus, there might be situations in which an anticancer drug could first be given to children, with no prior exposure in adults.

However, the development of molecularly targeted agents invariably includes assessment of the effect of the drug on the target. This brings into sharp focus the ethical consideration of *more than minimal risk* and the non-therapeutic components included in therapeutic research trials, such as tumour biopsies. While competent adults may volunteer for such research studies, it is ethically debated whether parents may give permission for their children to participate in them. Two court cases in the United States of America have ruled that, in otherwise healthy children, it is unacceptable for parents to provide consent for minors to participate in greater than minimal risk research, where there will be no possible direct therapeutic benefit for them (1).

Research outcomes and publications

Where research is conducted on an experimental drug, what will happen to the research patients at the end-point of the research, if the drug proves beneficial? Will they lose access to the drug? Will they be able to financially afford the drug that would then be placed on the market? In the initial marketing phase, the drug is unlikely to be covered under health insurance policies or plans. The ethical issue here speaks to those who suffered the burdens of research being able to share in the benefits of the research (10).

Another ethical requirement to be met in research is that of the dissemination of the findings, whether positive or negative. Respect for persons and their time, as well as international research ethics standards require that research participants be provided a summary of the outcomes of the research in which they participated (4). This ethical obligation derives from the reality that the research could not have proceeded without their volunteerism and participation and so respect for persons requires their being given a summary of the outcome for which they sacrificed their time and effort.

Further, research of the cancer clinical trials literature has revealed that there is a strong bias towards the publication of only positive results and that 75% of industry-sponsored studies had reached a positive conclusion (11). Also, that access to peer-reviewed, negative clinical trial results have contracted dramatically (12). Yet there is a clear ethical requirement for the rapid dissemination of clinical trials outcomes, particularly when toxicity results inherent in trials are not available through other means. The ethical dictate therefore, is that the results of all research should be disseminated, as knowledge may be gained whether the outcome is negative or positive. To do otherwise is to waste the human and financial resources that went into the research endeavour, as well as commit a '*moral wrong*' to the participants who sacrificed for the research (13).

CONCLUSIONS

Researchers should declare any conflicts of interest to their superiors, to the reviewing body of the research protocol and to potential research participants. They should also act in a manner that is above reproach.

Where physicians wish to enrol their patients into a research study, to avoid any element of coercion to participate, the objectives of the study and the invitation to the patient to participate in the research should be provided by a third party not directly involved in that patient's healthcare.

All cancer research should meet the seven requirements for the ethical conduct of research. The research must be valuable and there should be a clear scientific objective, a valid and practically feasible methodology, sufficient sample size (power) to test the objective, an acceptable plan for data analysis and the research should be able to be implemented.

There should be a fair selection of research participants, and there should be a favourable risk/benefit ratio. The ethical principles of non-maleficence and justice dictate that persons who are already burdened should not be selected for research if they will not have access to any of the benefits that may accrue from the research. Further, persons should be protected from bearing a disproportionate amount of the burdens or risks of the research.

The informed consent process should not be flawed and all efforts should be made to ensure the welfare of all the research participants. Researchers should respect their dignity, integrity, and humanity, as well as their fundamental rights and freedoms. Confidentiality of information about the research participant should be effectively maintained, and the participant's health and safety should be monitored throughout the duration of the research, with treatment provided for any untoward event or severe adverse reactions.

There should be an independent evaluation of the proposed research by a Research Ethics Committee or IRB beforehand, and Research Ethics Committees should have the power to require changes to improve research proposals, and to prevent unacceptable research from proceeding.

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