Article

Ethical Issues in Research With Vulnerable Populations

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Introduction

In this paper we define people who are at particular risk of exploitation by research activity, because of their personal, cultural or social circumstances, as a vulnerable population. Close examination of the historical precursors to the development of bioethics, at an interdisciplinary and at an international level, reveals that the burdens of experimentation have traditionally rested on those least able to defend themselves. Beneath such seminal events as the Nazi Camp experiments in Germany, the Tuskegee experiment in the United States of America, and the National Women's carcinoma in situ experiment in New Zealand are people who were already disempowered – vulnerable populations.

An understanding of the experiments which involved vulnerable populations gives insight into the primary principles currently employed in any ethical analysis of research. The application of these ethical principles, first codified in the 1947 Nuremberg Code, raises profound questions about the nature and practice of research. For example, the application of the principles of informed and voluntary consent of research participants and respect for patient autonomy is reflected in complex questions such as: What constitutes research? How can the rights of research participants be adequately maintained? Is it ethical to exclude vulnerable populations from research with or without their consent? What specific safeguards are required for potentially vulnerable populations? And, what is the role of the ethics committee or Institutional Review Board in monitoring such research?

This paper will address some of these ethical questions by focusing on research involving vulnerable populations, including research where there is the compassionate supply of drugs and research on palliative care populations. The term 'compassionate supply' is used to cover the full spectrum of situations where a drug is provided free of charge by drug companies for a fixed period in return for participation in a trial. The boundaries become blurred between genuine compassionate supply, and efforts to expand the market share of the drug. In the experience of the downward trajectory of terminal illness, the palliative care patient is especially vulnerable. Clinical research which endeavours to overcome barriers in the effective management of pain and other distressing symptoms may in fact compound the vulnerability of palliative care patients.

The international setting

A study of how a movement originated gives insight into its current shape. Historical events which are so central in the development of bioethics to an international level include the Nuremberg Trial of 23 leading Nazi physicians in 1947; the Tuskegee experiment 1932-1972, and the National Women's experiment 1966-1987.

The Nuremberg Code of Ethics, resulting from the trial of Nazi physicians, is regarded as the prototype of ethical codes. This ten-point statement outlined the basic principles that satisfy the moral, clinical, and legal concepts in biomedical research. The first two are often considered to be the most important: the voluntary consent of the patient is absolutely essential; and the experiment should yield fruitful results for the good of society which are unobtainable by other means. In focusing on informed consent, the Allied judges highlight the importance of mutual trust between researcher and participant and the protection of research participants.

'Tuskegee' was a major American illustration of unethical research. Men were promised free medical treatment, food, and free burials. The study, which began in 1932, sought to determine the untreated consequences of a disease not confined to this group. Although it was a proven drug by 1945, and although it could have cured their disease, the men were systematically deprived of penicillin. They were never told the true nature of their illness, nor fully informed of the nature of the study, that is, that they were **not** being treated.

Similarly, the so-called 'Unfortunate Experiment' at National Women's Hospital in Auckland sought to examine the untreated consequences of carcinoma in situ. Women were **not** told the true nature of their illness, nor were they informed that they were not being treated. The women were also unaware that standard treatment for precancerous carcinoma in situ was being withheld from them despite international concern. The revelation of this abuse led to the 1988 Cartwright Report.

The development of bioethics was, in part, a response to the new technologies of medicine, but equally, its evolution can be seen as the response of a culture sensitive to certain ethical dimensions, particularly to the rights of the individual and the potential abuse of these rights by powerful institutions. To label the abuse of the Nazi camps, the Tuskegee experiment, or the experiment at National Women's, as historical aberrations immediately isolates unethical research, and the deeper concerns of humanity and bioethics are overlooked. Once confined to special categories, important lessons are either not learnt or their application to current ethical issues in research is disregarded. Given that scientific data is multifaceted in meaning, Nazi Germany, Tuskegee and National Women's teach about the culture in which research takes place, and about how powerful prejudices can affect the presuppositions and outcomes of research, particularly for the vulnerable who are least able to protect themselves. The legacy of Nazi Germany, Tuskegee and National Women's was that the wider community began to demand that scientific progress did not compromise the integrity of the person. Beneath historical principles such as respect for patient autonomy, informed consent, non-maleficence, and beneficence is also the reminder that research which respects the autonomy and rights of patients is essentially collegial and interdisciplinary. While this is not, in itself, a guarantee of accountability and

protection for research participants, it does provide the climate where it can more easily occur.

The Cartwright Report

The parallels between Tuskegee and the research at National Women's are obvious. Just as the revelation of the abuse of research subjects at Tuskegee marked the start of the role of bioethics in United States policy-making, notably, in establishment of The National Commission for the Protection of Human Subjects, the major catalyst in the review of the ethics committees' role and structure in New Zealand was the 1988 Cartwright Inquiry. The Inquiry led to a major shake-up of the ethical review system, requiring the re-styled ethics committees to be independent of the institutions they reviewed. Other key recommendations of the inquiry have only recently been implemented, including the setting up of the Health and Disability Commissioner's Office, National Advisory Service and a Code of Consumers' Rights.

The boundary between reviewing research and ensuring adequate safeguards for vulnerable populations provides an ongoing challenge for ethics committees and IRBs. Following the Cartwright Report, the mandate for committees has been expanded so that the clinical aspects of innovative procedures, both therapeutic and diagnostic, are adequately considered. Innovative procedures are defined as:

> ...those procedures which are new to a particular provider setting in New Zealand or which are being used for a new purpose (e.g. bone marrow transplantation used in the treatment of breast cancer)... innovative procedures in disability services will also include any treatment or intervention which uses pain or deprivation of basic food or drink as a means to change behaviours. (Ministry of Health National Standard for ethics committees, 1996)

The rationale for the inclusion of innovative procedures reflects a key debate of the Cartwright Inquiry, namely, whether the failure to provide generally accepted treatment to the women could be considered research, particularly given the weakness of the scientific methodology. The introduction of innovative procedures not only widens the ambit of clinical review, but also, where these procedures are introduced by a clinician, highlights an inherent conflict between the role of clinician and researcher. Within this conflict the potential for harm and coercion to vulnerable populations is considerable. The rapid advance of medical technology can result in new procedures being introduced without adequate assessment of the ethical implications of their introduction. As Henry Beecher implied in 1966, research could be judged to be unethical not by its methodology or its results, but at its very inception.

Cultural Influences on Research

A further outcome of the Cartwright Report has been greater awareness of the needs of specific cultural groups, primarily the indigenous Maori people of New Zealand/Aotearoa who have been historically disadvantaged in access to healthcare. The health status of Maori remains relatively poor. For instance, in 1988, Maori women had a cervical cancer rate that was three times the Pakeha (white) rate.

The concept of biculturalism is distinctive to New Zealand. It is based on the signing of an agreement (the Treaty of Waitangi) between the Crown and Tangata Whenua (Maori) in 1840. In order to address the imbalance in health status that exists between Tangata Whenua and other New Zealanders, ethics committees require researchers to incorporate the principles of equity and partnership which are implicit in the Treaty. Health and disability research, and innovative procedures, must be undertaken in a culturally sensitive manner in full discussion and partnership with research participants.

The cultural impact on New Zealand's framework for addressing moral issues in health research is significant. Ethics committees have been required to increase their Maori membership. When reviewing health research, the question is asked, what consultation has there been with the Maori community? And, in terms of reciprocity, what benefit is the research to the particular community which is being researched? For Maori, the concept of *tino rangatiratanga* is an expression of self-governance and control of resources. The scope of the ethical principle of respect for autonomy is extended to a collective sense of autonomy. In practice, ethical review of research requires the informed consent process to operate at two levels, a community's consent for the project to proceed, and, only then, the voluntary consent of individuals to participate.

The cultural values and needs of Maori in New Zealand/Aotearoa has changed the shape of health research in recent years. Research in Maori communities can highlight strong philosophical and cultural differences. It is essential, however, that the relationships between these communities and researchers continue to evolve. These issues are further highlighted in a consideration of research that involves the compassionate supply of drugs.

Compassionate supply of drugs

The term 'compassionate supply' can mean the one-off free supply of a drug to a research participant but also a drug provided to patients by drug companies for a fixed period in return for participation in a trial for the specific drug. The boundaries become blurred between genuine compassionate supply, and efforts of drug companies to expand the market share prior to obtaining a subsidy on the pharmaceutical schedule. A major objection to clinical trials submitted for ethical review at the stage of post-marketing surveillance is that these 'trials' cannot truly be described as research at all. They carry little scientific value and are unlikely to be designed as comparative studies, comparing 'best conventional treatment' with the new treatment.

To what extent should ethics committees insist on a scientifically valid protocol at this latter stage of introduction of a new drug? The free supply of drugs for a clinical trial or post-marketing surveillance (dubiously described as research) may provide an opportunity for potential participants to benefit from a drug to which they would not otherwise have access. While an ethics committee's prime concern is to protect all health and disability research participants from harm, protection from harm must also be balanced with the possible benefit of participation in the research. Elks argues that the right to participate in research and enjoy its benefits is sometimes overlooked by institutional review boards (ethics committees).

There is a growing awareness among consumer groups that participation in research can give access to restricted treatments and new drugs. It is easy to understand how individuals faced with a grim prognosis, such as AIDS, would opt for the hope of a new drug rather than 'doing nothing'. In the study of Cassileth *et al*, (1982) 52% of respondents saw participation in

medical research as a way 'to help to get the best medical care'. If nothing else, there can be a perceived benefit through participation in research.

The supply of new drugs takes an interesting twist when clinician-researchers endeavour to obtain resources and medicines for the patients in their care through the research itself. There is an increasing awareness by researchers of the responsibilities for after-care of participants in clinical research, including the continued supply of the trial drug if it has proved to be beneficial. Consent by patients in clinical research may only be partially voluntary where it is given within the context of illness or the doctor-patient relationship. The vulnerability for the individual in this context is increased when their expectations of receiving a new drug or treatment are not realised. To raise false hopes through research is unethical.

Research and Palliative Care

Historically, there has been a degree of antipathy towards research in palliative care, primarily because the field was seen as an alternative to mainstream medicine at its inception. Now there is greater recognition of the need for research if palliative care is to develop. Research which improves the quality of life is becoming as important as research for the cure of the disease.

The palliative care patient frequently exhibits severe psychosocial distress and physical symptoms from terminal illness. Often the family or caregiver also shows evidence of distress and emotional and physical fatigue. In an analysis of 55 articles, Kristjanson et al (1994) identified the following characteristics of palliative care populations: patients are highly vulnerable because of their pain and other symptoms; they may not feel free to decline participation because of their continuing need for care from healthcare professionals who are also clinical investigators; patients may not feel free to withdraw from study due to the downward trajectory of illness and changes in their mental state; and, patients may not be able to give informed consent due to cognitive, emotional and physical limitations.

The fact that palliative care patients experience cognitive impairment due to the progression of their disease highlights the necessity of obtaining informed consent from the patient before any change in mental status occurs. Informed consent cannot be obtained once evidence of cognitive impairment occurs, neither can it be obtained from a healthcare proxy. Minogue *et al* (1995) consider that the recruitment of terminally ill patients as subjects in human experimentation exploits their vulnerability in a morally objectionable way.

They suggest two options: first, recruit only those patients who desire to contribute to medical knowledge, rather than to gain access to experimental treatment. Second, provide prospective subjects with the choice either to participate in a standard double-blind study or to receive the experimental treatment. If patients opt for treatment rather than the closed experiment then, Minogue *et al* argue, they have not been genuinely voluntary participants.

The worry is that subjects participate to gain access to otherwise non-available experimental medication, and not from a voluntary choice to participate in research. If in that case there is a slowing of research, that is unfortunate, but research progress at the price of autonomy violation is too steep a price. The voluntariness of participation and the possibility of coercion or lack of freedom to withdraw from a study are further ethical concerns for palliative care populations. A distinction may be drawn between the factors that influence a patient who has an ongoing care and treatment relationship with the researcher, and participants who are truly healthy volunteers and do not have the same ties or potential for exploitation. There is an inherent conflict between the role of clinician and researcher, particularly where there is a group of 'captive' individuals. Conflict between clinical and research roles can also be recollected in inter-professional difficulties and impact adversely on communication between researchers and clinicians.

The risks to vulnerable populations must be balanced with a consideration of possible benefits of research for them and for society. A vulnerable patient or individual may wish to give to others and help to influence healthcare practice. The effective clinical management of pain and the control of difficult symptoms, such as delirium, can often be improved only with the cooperation of the palliative care patient. Indeed, some would consider it unethical to exclude people who are terminally ill from research, labelling such exclusion a form of paternalism. Without controlled clinical trials and research it is not possible to state what is better care. The status quo trivialises care of the dying, a fact which may amplify their vulnerability. Research of palliative care populations rightly belongs on a continuum of good care alongside the adequate relief of pain, psychosocial and spiritual distress. Undue harm to patients can be reduced by careful attention to limiting discomfort such as unnecessary tests, prolonged interviews, and overly invasive research.

Conclusion

This paper has focused on the ethical issues of research with vulnerable populations. While the international codes provide a clear framework and guiding principles for the ethical review of research, the lesson of history reminds the researcher and ethics committee member alike that principles require careful application, particularly in research with groups of individuals who have additional layers of vulnerability. While recognising considerable advances in the application of ethical principles to research practice, the challenge for ethics committees is to be in touch with the multifaceted needs of all who may be disadvantaged by the research process or disadvantaged by a lack of research. In palliative care and with access to new drugs, research must be shaped by the cultural and social needs of vulnerable populations. Individuals who are disadvantaged by their personal, social or physical circumstances are at risk from any form of scientific zeal that overlooks their real needs.

The authors wish to acknowledge the contributions to this paper by Jocelyn Keith, and Regina Peretini [Ngati Kahungungu], Both are former members of the Wellington Ethics Committee.

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A full list of citations for this article is held at the Bioethics Centre