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Protection of Health Research Participants in the United States: a review of two cases

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Abstract

Two research-related deaths and controversies in the United States during recent years have raised public concern over the safety of research participants. This paper explores the reasons why, in two studies, there was a failure of ethical oversight. The issues exposed by these failures have international relevance as they could potentially occur anywhere where human health research is carried out. Five factors that contributed to these failures are highlighted:

1. *failure to support and resource research ethics committees;*
2. *failure of the research oversight process to adequately assess the risks and benefits of research, while giving undue emphasis to informed consent;*
3. *conflicts of interest arising from financial relationships and research ethics committee membership;*
4. *lack of consistent oversight of privately funded research; and*
5. *incompetent or intentional failure to adhere by ethical guidelines. There is considerably headway to be made in the United States, as in other countries, in the fostering and maintenance of robust systems of human research oversight.*

Key Words
United States, research ethics committees, health research participants, Jesse Gelsinger, Ellen Roche.

Introduction

The protection of participants who volunteer to participate in research is essential to the ethical conduct of research on humans. Events in recent years in the United States have caused considerable concern over the safety of some health research and the measures in place to protect participants. This paper will consider two studies in the United States where unacceptable harm occurred to the participants and, in both instances, resulted in the death of the volunteer participant. The first case involved Jesse Gelsinger, a relatively healthy research participant, who died in September 1999 in a gene transfer trial at the University of Pennsylvania. The second case is that of Ellen Roche, a healthy volunteer and employee, who died in an asthma study at Johns Hopkins Asthma and Allergy Center in June 2001. These studies have resulted in considerable public outcry and dramatic consequences to the researchers and institutions concerned, by way of a temporary ban on federal research funding in the Roche case, cessation of human research at the institute in the Gelsinger case, and in both cases, litigation brought by the families.

For over thirty years research in the United States has had extensive federal policies and regulatory oversight, yet ethical crises continue to occur. The purpose of this paper is to consider the two studies referred to above and to explore the reasons why, in these particular instances, the system of oversight of human research failed to protect the very people it is designed to protect. Although there were tragic outcomes in both cases, they were not isolated instances of ethical violations. The Office of Human Research Protection (OHRP) has reported suspensions of federally funded research at other prominent institutions and has focussed attention on the safety of participants in health research, particularly healthy volunteers (Steinbrook, 2002, Table 1).[1] The issues exposed by these failures have international relevance as they potentially could occur anywhere where human research is carried out.

The health care setting in which research is carried out in the United States is complex. For the purposes of this paper it is not possible to consider all aspects of the of the existing ethical review system, rather, the paper will provide a brief overview of research oversight and the role of the institutional review boards (IRBs – research ethics committees) in this process. The paper concludes by highlighting a number of factors that may have contributed to the failure of oversight.

Jesse Gelsinger

The death of an 18-year-old, relatively healthy research participant in a gene transfer trial in September 1999, and the subsequent investigation, revealed what Walters has described as 'fundamental flaws in the oversight system and have led to an agonizing reappraisal of clinical research involving human gene transfer' (Walters, In press for 2004, p.7).[2] Jesse Gelsinger had a mild form of ornithine transcarbamylase (OTC) deficiency, a single gene disorder that causes the build up of excessive levels of ammonia in the liver. At the University of Pennsylvania's Institute for Human Gene Therapy (IHGT) Gelsinger was injected with experimental high doses of an adenoviral vector containing a gene to correct the genetic defect. He was the eighteenth participant in the trial. He died four days later from what was probably an immune reaction to the viral vector. This was the first death directly attributed to gene transfer research. A subsequent investigation by the Federal Drug Administration (FDA) resulted in the suspension of all trials at the IHGT and it no longer conducts clinical trials. A wrongful death lawsuit filed by Gelsinger's family was later settled.[3]

A range of concerns arose from the conduct of the research and not all allegations were resolved. In general terms, the allegations included: the high level of Jesse's ammonia at the time he was infused with the vector and gene that was beyond the permissible level in the protocol; the researchers continued to increase the dose despite signs of toxicity in other participants; failure of the researchers to notify the FDA of adverse events in several prior patients and animals; and changing the original consent form which stated that monkeys had died from the treatment while the final version did not mention that. Jesse's father claimed that the principal investigator led his son to believe that his participation in the trial would be clinically beneficial as the most recent participant had a 50% increase in her ability to excrete ammonia (Gelsinger, 2000, p.13). This was despite the fact that it was a Phase 1 trial where no benefit was envisaged.

It was also later revealed that a conflict of interest existed which was not disclosed to participants. A funding arrangement had been entered into by IHGT, the University of Pennsylvania and Genovo, a company founded by the director of IHGT. The Director of IHGT was identified as having a conflict of interest because he owned stock in Genovo. Both he and the former dean of Pennsylvania's medical school had patents on some aspects of the procedures (Nelson and Weiss, 2000). Genovo provided funding for IHGT's research in exchange for the exclusive right to license patents resulting from the research. The funding arrangement provided approximately $4.7 million per year to IHGT and was approved by the University of Pennsylvania's Conflict of Interest Standing Committee (Walters, In press for 2004, p.8).

Perhaps the single most troubling aspect of this research was the failure to have a cohesive system of oversight in place at all. When the protocol for this study was first submitted for review, the Recombinant DNA Advisory Committee (RAC) of the National Institutes of Health was responsible for public oversight of human gene transfer research. In 1996, RAC's role was weakened and authority to further consider the protocol and monitor adverse events was handed over to the FDA. The significance of this change of oversight mechanism was that RAC required public disclosure, whereas the FDA did not, suiting more commercially minded researchers who seek more confidential, and therefore less transparent, regulation (Anon, 2000). A number of questions remain unanswered over the breakdown in reporting of the serious

adverse events in this trial. The death of Jesse Gelsinger led to the discovery by the National Institutes of Health (NIH) of many hundreds of unreported adverse events among volunteers enrolled in gene transfer experiments (Shalala, 2000). More recently, RAC's national oversight role in gene transfer research has been restored.

Ellen Roche

In June 2001, Ellen Roche, a 24-year-old healthy volunteer, died as a result of participating in an asthma study. Her death led to four separate reviews of clinical research at Johns Hopkins University (Steinbrook, 2002). An investigation by the federal Office for Human Research Protections (OHRP) reviewed the system of protecting research participants at Johns Hopkins medical institutions and, on the grounds of widespread deficiencies, suspended all federally supported research projects at Johns Hopkins and several affiliated institutions (Office for Human Research Protections, 2001).

Ellen Roche worked as a laboratory technician at the Johns Hopkins Bayview Medical Center in Baltimore, Maryland. She volunteered as a research participant in a baseline physiological test, which induced asthmatic reactions in people without asthma to determine how bronchiolar reflexes differ between two populations. Ellen Roche was recruited as the third participant in the second phase of the study and was administered hexamethonium, a ganglion blocker, which was expected to derail the protective mechanism of lung relaxation induced by deep breathing. After the inhalation she developed a cough and her condition worsened over the next week until she was put on a ventilator. She died within a month of entering the experiment .

Hexamethonium was used as an intravenous antihypertensive agent in the 1940s and 1950s but was later withdrawn by the FDA in 1972 after it was found to be ineffective (Steinbrook, 2002). In the 1950s there were medical journal reports of pulmonary toxic effects of inhaling hexamethonium (Josefson, 2001), and the drug never received FDA approval for administration via inhalation (Office for Human Research Protections, 2001). In the various reviews that were carried out following Ellen Roche's death the principal investigator was criticized on a number of grounds, including the failure to report the cough symptoms of the first participant promptly, not delaying the exposure of the next participant until the symptoms in the first participant had reduced, and not searching more comprehensively for previous reports of the toxic effects of inhaling hexamethonium. None of these risks, or potential for a fatal outcome, were mentioned in the consent form. Hexamethonium was referred to as a 'medication' and the consent form did not mention the fact that hexamethonium used by inhalation was experimental and not approved by the FDA (Office for Human Research Protections, 2001). An external investigation committee also criticised the Asthma and Allergy Center for 'a culture of possible coercion' with regard to the solicitation and recruitment of volunteers for its studies (Cassel *et al.*, 2001). A disturbing factor in Ellen Roche's death is that because she was a healthy volunteer she had nothing to gain by participating in the study (aside from any altruistic motive), other than a nominal fee of $365, yet clearly the research had severe consequences. (Similarly Jesse Gelsinger's condition was controlled through medication and the decision was made to include people like him with a mild form of the disease, rather than seriously ill newborn children.)

It was not simply the principal investigator, however, who was the focus of attention of the various investigations carried out, but also the effectiveness of the IRB, sponsors, and institutions where the research was conducted. In reaching its decision to suspend federally supported research, the OHRP was highly critical of the two IRBs at the medical school for their failure to properly review research (Office for Human Research Protections, 2001). Most protocols were neither individually presented nor discussed at convened meetings of IRBs. Minutes did not exist for a large number of meetings and often there was no documentation of the basis for requiring changes to research or discussion of unresolved concerns following reviews by the IRB subcommittee. The OHRP was particularly concerned that protocols were, by and large, reviewed by subcommittees of the IRBs which in its view 'does not represent substantive and meaningful IRB review'. Despite an initially defensive response to the criticisms, Johns Hopkins submitted a corrective plan and the ban on federal funding was lifted with a number of restrictions imposed. Ongoing changes have included a substantial increase of resources: a budget increase from $1million to $2 million per annum for IRBs, training for investigators, an increase in the number of IRBs from two to six, standardising procedures for literature reviews, and the reporting of adverse events to the IRBs.

The suspension of federal funding of research for unethical conduct at what is arguably the most prestigious medical

institution in the United States was significant. At the time of the suspension of clinical research at Johns Hopkins there were approximately 2500 active protocols. In 2001, about 50,000 people participated in research studies at Johns Hopkins, an institution ranked at or near the top in terms of federal research support (Steinbrook, 2002).

Individuals, Institutions or Systems – where do the problems lie?

The suspension of clinical research at Johns Hopkins was described by Caplan as 'a symptom of a much deeper disease in the collapse of adequate protections for those involved in research at every American medical center, clinic, testing facility and hospital. And if a culprit is to be singled out, it is that disease, not one institution' (Caplan, 2001). In recent years there has been a groundswell of national reports and recommendations calling for education and reform in an effort to increase accountability in human research protection (Holt, 2002; Institute of Medicine, 2002; National Bioethics Advisory Commission, 2001; Office of Inspector General DHHS, 1998).

Medical research was conducted for many decades in the United States without regulatory oversight. In the early 1950s nearly all participants in Phase 1 clinical trials, the first and riskiest phase of human research studies, were prisoners. As late as 1969 eighty-five percent of new medications were still tested on prisoners. As part of a set of initiatives to address human protection in research the Belmont Report articulated the ethical principles of respect for persons, beneficence and justice (Belmont Report, 1979). Federal regulations, known collectively as the 'Common Rule', require an IRB to ensure that risks and benefits are appropriately balanced, fairly distributed and informed consent is obtained from participants, as embodied in the Belmont Report.[4] The Common Rule requires that any research facility receiving federal funds submit a Federal Wide Assurance (FWA) to the department or agency from which the funding is sought. The FWA is a contract in which the research facility promises to abide by the Common Rule for federally funded research that involves human subjects. There is no such requirement for privately funded research, although some institutions elect to include privately funded research under their FWA. The implications of this voluntary election for the IRB has been described as 'profound' (Cohen, 2002, p.313). An IRB has no authority to regulate research in an organization that does not have a federal assurance or that has not extended its assurance to privately funded research (Cohen, 2002). It is this assurance scheme that has given the OHRP the leverage to hold non-compliant research organizations accountable.

The failure of the current system in its endeavour to provide human subject protection, particularly in terms of the oversight provided by IRBs, may be linked to a number of factors. First, as the volume of research involving human participants in recent years has grown exponentially, so too has the workload of the IRBs, and much research has become over-demanding in its complexity. The IRBs, in turn, are ill-equipped to effectively monitor all research and respond to the complex and ever-changing research environment (Institute of Medicine, 2002, p.5). While it may be too simplistic to lay the blame of the protection system wholly with the IRBs, the strongest criticisms in the Roche case were directed at the poor review of research protocols and the lack of support for the one IRB committee dealing with an unreasonable workload (Cassel *et al.*, 2001).

Second, ensuring informed consent from research participants is not a substitute for critical scrutiny of the risks and benefits of the research and an assessment of whether the research is sufficiently safe for the participation of volunteers. This is particularly so of high risk, early phase, clinical trials. A recurring theme to emerge from the reports of the crises referred to in this paper, is the failure of researchers to adequately inform participants of the risks, and in turn, the IRBs not drawing sufficient attention to these aspects. Commenting on the inadequacies in the current system of protections for research participants the retiring Secretary of Health and Human Services said: 'Full disclosure is a necessary precondition to free choice' (Shalala, 2000). While informed consent is important, it does not address the substantive question of whether a study should be conducted on humans at all. For example, the OHRP report on the Roche case endorsed the finding of an internal investigation that: 'An adequate evidence base did not exist for the IRBs to be confident that inhaled hexamethonium was safe for use in research subjects'. So too, ethical review of the study in the Gelsinger case has also been criticised. Originally the protocol proposed that participants in the trial should be newborns who could not consent but had an otherwise lethal form of the disease. Later this was changed to older participants who could consent but who had a mild form of the disease. Savulescu has argued that this trial illustrates

the increasing and mistaken tendency of ethics committees to give too much weight to consent and to fail to give sufficient attention to protecting participants from harm as, 'Jesse had something to lose while seriously affected newborns did not' (Savulescu, 2001). Indeed, an effective informed consent process is meaningful only if a thorough assessment of the risks and benefits is undertaken to ensure an acceptable level of safety for participants.

Third, conflicts of interest are another source of pressure on the system of protection and are revealed as either financial conflict between the researcher and private industry, or conflict of the reviewers and the IRB members themselves with the research. The sharp increase in privately funded research has resulted in conflicts arising from the researchers' and/or the institutions' relationships with industry, so that there is a blurring of the boundaries between academic interests and commerce (Angell, 2000). Academic medical institutions are becoming increasingly beholden to industry and must themselves justify conflict of interest policies to individual researchers when the institutions have extensive ties. As there is a strong incentive for universities to seek funding from private research companies, there is a potential conflict of interest from the affiliation because medical entrpreneurialism is not only a goal of individual researchers, but also of the universities themselves (Edgar and Rothman, 1995). The Gelsinger study is a case in point, where not only the researchers but the research institute and the university had a financial interest in the outcome of the research. Discussion has centred around either prohibiting conflicts of interest entirely or managing conflicts in what is regarded as an unavoidable part of the research process (Goldner, 2000).

Conflicts of interest can also permeate the regulatory structure itself. The independence of the IRBs from the researchers and their institutions is not always clear. Although IRB members are supposedly required to disclose any conflict of interest in the review of any study, there is no way to ensure that the research facility or individual researchers are not operating under such conflicts (Alvino, 2003). IRB membership often comprises of a majority of members who are employed by the institution from which the research emanates. In the wider investigation prompted by the Roche case the OHRP found instances in which IRB members inappropriately participated in the initial and continuing review of protocols for which they had a conflicting interest (Cassel *et al.*, 2001).

Furthermore, there is a public perception of the lack of independence of IRBs. This point is exemplified in a recent decision of the Maryland Court of Appeals, *Grimes v Kennedy Institute Inc.*[5] Parents of minor children were permitted to bring a negligence action against the Kennedy Institute, a research institute affiliated with Johns Hopkins University, for lead related injuries allegedly suffered by their children participating in a study concerned with lead abatement in housing. Despite only being concerned with the preliminary issue of whether the litigation could proceed, the Court made a sweeping condemnation of all IRBs, which were described as '... primarily, in-house organs'. The court said:[6]

> In our view they [IRBs] are not designed, generally, to be sufficiently objective in the sense that they are as sufficiently concerned with the ethicality of experiments they review as they are with the success of the experiments.

While it is not possible to assess any impropriety on the part of the IRB, the Court clearly expressed a lack of confidence in the IRB's ability to be objective and independent of the institution and the researchers concerned. In August 2001, the National Bioethics Advisory Commission published its report on human subjects protection (National Bioethics Advisory Commission, 2001). The Commission recommended that at least twenty-five percent of IRB members should be unaffiliated with the institution and represent the perspectives of participants. Despite its criticism, the Commission sought to help and strengthen the current system and not to recommend its demise. It argued for greater education, accreditation and oversight of IRBs.

Fourth, since many studies are privately funded at institutions where there is no federally funded research subject to the requirements of the Common Rule, there is no reliable way to determine the amount of research that is ongoing at any given time or to ensure the capture of research that ought to be the subject of ethical review. A phenomenon that has arisen in the United States is the growth of commercial IRBs which may be subject to criticisms of bias and the potential for conflicts of interest. In addition, research conducted outside of academic institutions (for example, innovative procedures conducted in some in vitro fertilisation clinics) may not be captured by the existing ethical review framework. A major weakness in the current system is the lack of uniformity in

the regulatory structure surrounding research. A key recommendation in a recent report of the Institute of Medicine (IOM) is to extend federal oversight to include every research project that involves human participants, regardless of funding source or research setting (Institute of Medicine, 2002).

Fifth, even if the system of ethical review were perfect, problems would still occasionally arise from incompetent or intentional failure to adhere to ethical guidelines by researchers in the zealous pursuit of their research. The Roche case is an example where the researchers disregarded existing scientific knowledge and ethical safeguards designed to protect vulnerable research participants like Ellen Roche. The influence of an organisation's culture is perhaps a more subtle barrier to effectively providing safeguards. Pellegrino argues that there is a collective responsibility and accountability on the part of the entire scientific community when serious misconduct occurs (Pellegrino, 1992). The external review committee commenting on the institutional culture surrounding the asthma study said that: 'Our interviews suggest that many people at Hopkins believe that oversight and regulatory processes are a barrier to research and are to be reduced to the minimum rather than their serving as an important safeguard' (Cassel *et al.*, 2001). The IOM report recommended that establishing the appropriate culture in institutions will require sustained efforts to educate researchers, research administrators, IRB members, and participants about research ethics and participant protection (Institute of Medicine, 2002).

Conclusion

Despite the United States' long history of federal policies for the protection of participants in human research, ethical disasters continue to take place. The events described in this paper are yet another wake-up call for the research community and those involved in its oversight. Both cases discussed in this paper represent relatively clear-cut instances of the failure of ethical oversight and are indicative of the lack of a cohesive framework under which the IRBs are operating.

In a health research environment as complex and intense as that in the United States, any system is bound to suffer occasional failures. However, the frequency of recent failures might suggest that the system of oversight needs more thorough overhaul. Steps are being actively taken to remedy some of the problems identified, in an effort to ensure that similar disasters are less likely to occur in the future.

The growing number of academic institutions that have a financial relationship with the private sector in carrying out research amplifies the issue of conflict of interest for researchers, institutions and IRBs, and emphasises the need for transparent independence of IRBs. Ideally, there needs to be one system of ethical oversight. It is an anomaly that, currently, there is no guarantee that privately funded research is captured by the ethical review system.

In any research environment where human lives are at stake, it is essential that there is a high level of critical self-awareness on the part of researchers, and a research culture that fosters ethical literacy. The fostering and maintenance of such a research culture is no small matter, and clearly the research community in the United States, as in other countries, has considerable headway to make.

Acknowledgements

We acknowledge helpful comments on an earlier draft by Dr LeRoy Walters, Joseph P. Kennedy, Sr, Professor of Christian Ethics, Kennedy Institute of Ethics, Georgetown University, Washington DC, USA.

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Notes

1 The Office of Human Research Protections reported suspensions of federally supported research at the following institutions: Duke University Medical Center (1999); University of Illinois, Chicago (1999);Virginia Commonwealth University (2000); University of Oklahoma Health Services Center (2001); and Johns Hopkins University Medical Institutions (2001).

2 Walters prefers to use the terminology 'human gene transfer research' rather than human gene therapy in light of meagre results of this research to date and the danger of seeming to over-promise benefits to the participants in the early clinical trials.

3 Arthur Caplan, PhD, Director of the Center for Bioethics at the University of Pennsylvania was initially named in the lawsuit for his role in giving expert advice to the researchers. This was possibly the first time a bioethicist has been directly sued in this context.

4 45 Code of Federal Regulations (CFA) 46 Subpart A.

5 *Grimes v Kennedy Krieger Institute Inc;* 782 A.2d 870 (Md.2001)

6 Ibid at 817.

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