RESEARCH ETHICS

Canaries in the mines: children, risk, non-therapeutic research, and justice

M Spriggs

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The Kennedy Krieger lead paint study received a lot of attention after a US Court of Appeals ruled that a parent cannot consent to the participation of a child in non-therapeutic research. The ruling has raised fears that, if it goes unchallenged, valuable research might not proceed and ultimately all children would be harmed. The author discusses significant aspects of the study that have been neglected, and argues that the study was unethical because it involved injustice and its design meant that the study lacked importance and value. Issues of benefit, risk, and consent are vital, but it is sometimes a mistake to consider these issues before settling questions about justice and the importance and value of a research project. The author concludes by offering a strategy for researchers and reviewers of research to appreciate, in a vivid way, the implications of research participation.

In a landmark case in human experimentation, a United States Court of Appeals condemned what it called a ''non-therapeutic research programme'' using children. The court ruled that in the state of Maryland a parent cannot consent to the participation of a child in ''non-therapeutic'' research. The case is being heralded as ''one of the most significant cases of the decade''[1] because it involves issues that have been virtually unanalysed by the courts, such as children's participation in research, proxy consent, and the duties of medical researchers towards their subjects.[2 3] In this paper I examine and expand on some of the issues raised by the court, but my main focus is on aspects of the study that have so far received little attention.[4–9] I argue that the question of whether the research was ''therapeutic'' or ''non-therapeutic'' is a red herring; and, based on the documents available, I argue that the lead paint study lacked importance and value. In the course of my argument I will examine research involving cost-benefit analysis, the design of the research, and study aims. Finally, I will outline a strategy that may be of use in helping identify when something is amiss with a research proposal and will prompt us to examine the issues more closely.

Correspondence to:
M Spriggs, Ethics Unit, Murdoch Children's Research Institute, RCH, Flemington Road, Parkville, Victoria, 3052, Australia, University of Melbourne and Centre for Human Bioethics, Monash University; merle.spriggs@mcri.edu.au

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THE LEAD PAINT STUDY

During the 1990s, US researchers from the prestigious Kennedy Krieger research institute carried out an environmental study to evaluate different methods of lead reduction in Baltimore's low income housing district, where lead poisoning in children is a problem.[10]

In order to test their interventions, the presence of small children in the houses was required. The Kennedy Krieger researchers encouraged, and in one case required landlords to rent premises to families with young children. Children living in study houses were also encouraged to continue living in the houses.[11] The repair and maintenance costs ranged from US$1650 up to US$6000–$7000 for the more comprehensive level.[12] Full lead abatement cost US$20 000 per house.[13] Some of the landlords who were required to employ only partial treatments to their properties were publicly funded.[14] The federal Environmental Protection Agency and the Department of Housing and Urban Development provided funds amounting to ''more than US$1 million''.[15]

The levels of lead that accumulated in the children's blood determined the success of the various methods.[16] Exposure to lead, however, has a detrimental affect on the health and cognitive development of young children.

Mothers of two of the children have filed lawsuits complaining that they were not fully informed of the risks and hazards involved in the study, and were not warned promptly of the high levels of lead in their homes and in their children's blood—information that would bear on their willingness to continue in the study.[17] In his judgment, the judge argued that the children were used as ''measuring tools'': ''the researchers intended that the children be the canaries in the mines, but never clearly told the parents''.[18]

The Maryland Court made a distinction between therapeutic and non-therapeutic research and claimed that direct benefit is unlikely for subjects of non-therapeutic research because it ''is designed to achieve beneficial results for the public at large (or, under some circumstances, for profit)''.[19] The court maintained that the lead paint study was a non-therapeutic research programme and ruled that a parent ''cannot consent'' to the participation of a child in ''non-therapeutic research or studies in which there is any risk of injury or damage to the health of the subject''.[20]

The court concluded that the lead paint study was ''inappropriate''[21] and the Johns Hopkins Institutional Review Board (IRB) ''abdicated [its] responsibility'' to protect subjects. Finally, the court likened the study to the infamous Tuskegee experiment in which syphilis in black men was untreated and allowed to progress in

order to study the natural course of the disease.[22] The case has now been sent back to the trial court.

REACTION TO THE COURT'S RULING

There has been a strong reaction to the court's ruling, in addition to the interest generated by the study itself. The public health and research community and some bioethicists have reacted with alarm to the ruling that children should not be included in trials that do not have a therapeutic benefit and which include risk.[4 13] They fear that if unchallenged, the judgment will stop valuable research and may ''do immeasurable harm to all children''.[7 24] According to one bioethicist, ''[T]he court didn't quite get how research works''.

The reactions to this ruling are understandable because it comes at a time when researchers are being encouraged to include more children in research. Historically, children have been disadvantaged by a lack of data about children—that is, a lack of information on which to base paediatric drug doses and a lack of information about environmental risks.[13 25 26] It is puzzling that the court is emphasising a distinction that has been previously rejected as unhelpful. The distinction between therapeutic and non-therapeutic research was deemed ''illogical'' by the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (1975–1978).[27] It was also one of the issues at the heart of the debate over changes to the World Medical Association's Declaration of Helsinki, and was dropped from the revised Declaration in 2000. I spell out the problems with the distinction below.

Another commentator, Glantz, argues that it would be ''unfortunate and shortsighted'' to characterise this case as an example of ''an overly zealous court's intruding into the prerogatives of the research community''. Like Glantz, I think that we would do well to examine and try to understand the ''legitimate'' ethical issues that ''so concerned'' the court.[28]

REACTIONS TO THE LEAD PAINT STUDY

In order to understand the issues fully, it is worth looking at the discussion that the study has generated, keeping in mind that it is based on the evidence and documents that have been made available. Although a full presentation of the facts is yet to take place and no facts have been proven, it is instructive to look at the discussion to date. I will then look at some issues that have been neglected. I begin by outlining and evaluating arguments in support of the lead paint study.

In defence of the lead paint study

The main defenders of the study are the researchers, the Kennedy Krieger Institute, the Johns Hopkins IRB, and the director of the Alliance to End Childhood Lead Poisoning. With regard to the commentators who analysed the study at length, one defends the study,[6] whereas the others are generally critical of it.[3–5 7–9]

The children benefited

The main argument in defence of the study is that the children benefited from their participation. Kennedy Krieger's Chief Executive argued that the study ''improved the lives of most participants''. If they hadn't moved into the research homes they might have ended up in other contaminated homes that were receiving no treatments: ''It's not that we intercepted people who were on their way to some treasure trove of lead-safe houses in Baltimore and directed them to houses with lead paint''.[29]

According to Don Ryan, Executive Director of the Alliance to End Childhood Lead Poisoning: ''this research made homes safer, not only for the children in Baltimore but for hundreds of thousands of others across the nation''. The study provided treatments that exceeded state and local requirements, making them safer than some neighbouring homes.[30] Ryan argues that children will be harmed if the research is stopped, and equates criticism of the study with acceptance of the situation where lead poisoning occurs: ''the outrage of childhood lead poisoning is blasé acceptance that five million American preschool children—primarily low income children—still live in homes with significant lead hazards''.[30]

In response to this argument, it could be true that some subjects are better off and that their homes received treatments that exceeded requirements, but ''better off'' is not necessarily a benefit.[31] Also, it is a mistake to assume that criticism of the study amounts to toleration of the lead hazard. We can criticise the study and still want something to be done about lead paint poisoning. To view this study as the only way for lead hazards to be addressed seems not only short sighted but bizarre.

No risk

The ''crucial question'' for the IRB that reviewed the study was whether ''continued exposure'' should be considered a risk of the study or part of the condition being studied. The IRB concluded that the study interventions posed no risk to the subjects and that the ''risk of lead exposure'' is not a ''risk of the study'', because that is a risk that is ''intrinsic to living in old housing in Baltimore''. All families involved in the study lived in or came from homes that contained lead paint hazards and were already ''at risk''. The study interventions, according to the IRB, consisted of blood tests and lead reduction methods, and these ''did not result in risk to subjects''.[32]

This argument that the study involved no risk is controversial. It is based on the question of ''whether a parent's decision to move a child into a home that underwent the experimental lead abatement procedure should be considered a study intervention or an inclusion criterion for defining a child's condition''. According to Nelson, this is ''the central point in dispute''.[8] The idea that the risk of lead exposure is not a risk of the study is also undermined when the line between a disease and the impact of social inequalities on health is ''blurred''.[33]

Researchers' motivations were good

There is a view that the motivations of the researchers determine the ethical acceptability of their research. According to a spokeman for the Alliance to End Childhood Lead Poisoning, the Kennedy Krieger Institute and its researchers are ''unlikely'' suspects for the crimes with which the lead paint study has been compared. Kennedy Krieger is a treatment centre for children with disabilities, and it ''pioneered the study of lead hazards, an overwhelming health problem for children in low income housing''.[34] From this view, the researchers should not be criticised, because they are the same researchers who discovered that traditional clean up methods such as blow torching actually increased lead exposure.[35]

This is not a satisfactory defence of the study. First, it is highly controversial to argue that a person's motivations are a good enough reason to justify an action or research as ethical. Secondly, it is not appropriate to gauge a person's motivations by looking to their past actions rather than to the details of the situation or action being assessed.

The research had scientific merit

According to one commentator, it is ''clear'' that the research ''had scientific merit'', because results of the lead paint study and other studies conducted by the principal investigators helped ''provide the basis for federal health based standards and prohibitions on unsafe practices''.[36]

Arguments about scientific merit are bolstered by the fact that knowledge about what were valid abatement procedures was uncertain. Ericka Grimes was living in one of the houses that had a complete clean up before the study.[37] The other child whose mother was suing Kennedy Krieger was in a house that received the middle level of repair and maintenance, and had a lower blood lead level than Ericka Grimes.

The argument that the study has scientific merit does not mean that the study will be worthwhile. It is not clear that we should judge the value of a study on assessments of the use to which the results may be put. The study may provide a basis for health standards, but the value of the study depends on adequate standards being set, and it is reasonable to argue that the standards from past studies were not adequate. Additionally, the idea that uncertainty about the abatement procedures is an indication of clinical equipoise and scientific merit is reasonable, but it should also be noted that this uncertainty undermines the arguments put forward about benefit to subjects.

A ''study of nature'', not a Tuskegee experiment

According to one commentator, the lead paint study was a ''study of nature''.[38] In other words, the study can be justified because researchers were merely passive observers of a process which they were powerless to change.[39]

The court compared the lead paint study to the infamous Tuskegee experiment, but that comparison was rejected by Mark Farfel who directed the study: ''Society was already doing a Tuskegee experiment…Very little if anything was happening to remove lead while children were being poisoned''. Farfel claims he and his colleagues were trying to do something about the problem.[15] The question of whether the study can be justified as a ''study of nature'' will be addressed in the discussion that follows.

Arguments against the study

We have seen that the arguments defending the study are not convincing. In mounting an argument that the review of the study and the scope of the review were not adequate, I begin by listing three reasonably uncontroversial arguments put forward by the appeals court judge.

- The children were harmed. Some otherwise healthy children ended up with increased lead paint levels. Risks were foreseeable and well known.[40]
- The study was not in the best interests of the children subjects. It is ''not in the best interest of any healthy child'' to be ''intentionally'' put in a situation ''where his or her health may be impaired''.[41]
- Ethics boards ''are primarily in house organs'', more concerned with the success of experiments than with the ethics of the experiments they review.[42]

I will not examine the issue of parental authority to consent to non-therapeutic research. Instead, in what follows, I reject the distinction between therapeutic and non-therapeutic research and take the view that if research is ethically acceptable, parental authority can be respected. Then in the remainder of this section, before focusing on issues that have received little attention, I expand on two arguments: (1) that the risks were unreasonable, and (2) that there was an increased potential for exploitation. First, I explain the reasons for disposing of the distinction between therapeutic and non-therapeutic research.

Disposing of the distinction between therapeutic and non-therapeutic research

I noted earlier that the distinction between therapeutic research and non-therapeutic research has been discredited. As we will see, there is no good reason to revive the distinction.

Research described as therapeutic is sometimes confused with treatment and thought to pose ''fewer problems than research described as non-therapeutic''.[43] Treatment is the utilization of knowledge whereas research creates knowledge.[44 45] Although therapeutic research may have a therapeutic intention, it also has a research intention. And because it is research, the therapeutic intention is modified by the aim of advancing knowledge.

Sometimes it is thought that research described as therapeutic confers benefit, and research termed non-therapeutic confers none. Nevertheless, children can be less protected in so called therapeutic research than in non-therapeutic research.[46] The risk of harm in some therapeutic research can be considerable—for example, unexpected side effects of new treatments, whereas the risk in non-therapeutic research can be negligible. Examples of beneficial non-therapeutic research in children include phase II vaccine trials when there is evidence in adults of the vaccine ''preventing or slowing the progression of an infectious disease'',[47] and also vaccine trials for diseases that do not occur in adults or which manifest differently in children.[47] An example of non-therapeutic research involving no additional risk or discomfort for individual children is the taking of extra blood during diagnostic or treatment procedures for ''legitimate research purposes''. Such research may benefit children as a whole.[48]

As we can see, research is not meaningfully divided into therapeutic and non-therapeutic because it is not clear whether these labels should apply to a project as a whole, or just to individual subjects. Some studies benefit some subjects but not others—for example, controls might not benefit, but some of the children and children as a whole might benefit.[49] Concern about whether research is therapeutic or non-therapeutic distracts us from other important issues. In the lead paint study it detracts from questions of whether the project had value, the role of cost benefit analyses, and the role of researchers and ethics committees.

Consent and unreasonable risk

There were problems with the parents' consent in the lead paint study. According to the judge, parents were not properly informed and were ''improperly enticed'' with trinkets, food stamps, money, and other items.[50] The court noted that ''the consent document did not contain information that the 'reasonable parent' would want to know''.[51] There was no information about the primary aim of the study and no information about the importance of lead levels in the blood, and nothing about the risks of inadequate lead abatement. The ''ultimate'' aim, according to the court, was about the commercial feasibility of abating lead dust within the constraint of blood lead content deemed hazardous to the health of children.[52] It is not clear that the ''constraint'' posed by the children's health had the same priority as ''commercial feasibility''.

The consent form suggested that the study had many benefits: ''…your house is going to have special repairs done in order to reduce exposure to lead in paint and dust…We are also doing free blood lead testing of children…The dust, soil, water, and blood samples would be tested for lead at the Kennedy Krieger Institute at no charge to you…Any information you provide would be considered confidential and will not be shared with landlords or anyone else without your expressed permission…We may not be able to include all families that sign up for the study or to test as frequently as planned due to limited funds''.[53]

The implication is that the free testing of dust, soil, water, and blood is something beneficial—an extravagance

almost—that these people are not entitled to, but will receive. There is even some suggestion that test results are something that the families would not want landlords to know and that researchers are protecting them by not divulging this information. The reference to a limit on the number of families reinforces the idea that the study is offering some kind of undeserved benefit. From this excerpt we can see how vulnerable people could be led to think that study participation is to their advantage. Under ''purpose of study'', parents were informed that: ''The repairs are not intended, or expected, to completely remove exposure to lead''. The implication is that repairs are not needed. It would not be unreasonable for a parent to assume when a researcher tells them that ''repairs are not intended, or expected, to completely remove exposure to lead'', that exposure to lead is not a problem; that it poses no danger.

Finally, a ''reasonable parent'' would not intentionally expose a child to environmental lead without making every effort to reduce or eliminate that exposure.[54] If parents knew of and understood the risks they may not have agreed to their child's involvement in the first place, or to their continued involvement.

It is important to note that resolving the consent issues will not resolve all of the problems with this study. Properly informed, some families may still choose to enter the trial, and the idea that some families may be better off is credible. The economic situation of some families might rule out other options.[55] Also, it would be wrong to view a parent's decision to enter the trial as necessarily aberrant. People take risks and make tradeoffs all the time in matters that affect their health and the health of their family.

Increased potential for exploitation

The lead paint study shows us that appeals to ''best interests'' are open to various interpretations, and the idea of ''minimal risk'', which has a relativistic interpretation, can pave the way for exploitation to occur.

Exploitation is consistent with freedom to choose, and in a society that is ''free but unequal'',[56] exploitation may be ''mutually advantageous and consensual''.[57] Because of the situation a person is in, it may be in their interest to accept an offer even though it is a situation they would prefer not to be in.[56]

The argument that the families benefited because they were not worse off can be compared with the arguments used in the infamous, widely discussed mother-child HIV transmission prevention trials in developing countries. These trials involved the problematic idea of a local standard of care.[9 58 59] In these circumstances, where poverty can make unethical research seem like an attractive proposition, the consent of research subjects becomes meaningless.

A point of comparison in the lead paint study is the idea of minimal risk: that which is ordinarily encountered in daily life. This idea is referred to in both US and Australian research regulations and has a relativistic interpretation. It suggests that risky research is less ethically problematic among people who are already disadvantaged. The relativistic interpretation of minimal risk could allow children living in hazardous environments or who face danger on a daily basis to be the subject of high risk studies.

ISSUES THAT HAVE RECEIVED LITTLE ATTENTION

Some issues have received little attention in previous discussions of the lead paint study. Issues such as justice, the role of cost benefit analyses in research, and the roles of researchers and ethics committees have been largely ignored. Although questions about risk, potential benefits, and consent are certainly important, they tend to overshadow everything else.

Instead of condemning the lead paint study as non-therapeutic or not beneficial, I am going to look at the question of whether the research was valuable—in the sense that potential benefits have some likelihood of being realised.

Was the study important and valuable?

Part of the justification for research is its importance and its value.[60] As well as asking if the resources used and the risks to subjects can be justified by potential benefits, we need to consider the likelihood of the benefit. Reducing lead exposure in children is certainly desirable, but there is no indication that the lead paint study was going to achieve this.

We have to ask if the knowledge gained from the study was really going to help the children of Baltimore. Knowing how to get rid of lead or reducing exposure was not as much of a problem as getting someone to pay for it. The reluctance of landlords to pay for lead reduction methods, and the lack of regulation to make them do anything about the problem, seem to be the major constraints. Nothing in the research suggests that the study would lead to the enforcement of more lead reduction. Rents may well rise with a reduction in the lead hazard. It might not be the participants and low income families who benefit from the study.

Johns Hopkins' University issued a press release defending the study as ''beneficial to all participants'' and claiming that the research ''would result in knowledge allowing advocacy for programs addressing lead hazards''. This is described as a ''potential benefit''.[61] But, in the same statement, reference is made to the ''history'' of government ''tolerance of an identified poison''.[61] This suggests that the potential benefit is unlikely to materialise without political pressure. Potential benefits of research usually depend on the success of what is being studied, but in this instance, potential benefit refers to an outcome that is quite independent of the effectiveness of the lead reduction methods being studied. It depends on an extra intervention that is not part of the research project. As such, this kind of potential benefit is not a sufficient or legitimate justification for research. This is a crucial point. A framework of risks and benefits is inadequate for the review of research when the potential benefits can only be realised by overcoming additional obstacles outside the study.

Research aimed at saving money

Another issue not addressed is the ethics of research aimed at saving money. Some people might think that research involving cost benefit analyses is not ''real'' health research. Nevertheless, with a limited health budget, there is a legitimate role for this kind of research. One justification is that it could attract funds or ''enable funds to be released from elsewhere in the health service''.[62]

In terms of the lead paint study, we are entitled to ask if profit for landlords was the primary aim and whether the funds provided should have been used in this way. Other uses for the funds include:

- direct funding of lead reduction
- educating families about the risks of lead exposure, ways to avoid lead exposure, and the need to check blood lead levels
- research into causes of increased lead absorption.

These possibilities seem more appropriate and more directly beneficial to the children exposed to lead hazards. Other approaches do exist. Since 1971, property owners in at least one other US state have been required to permanently control lead based paint hazards in housing in which a child under the age of six resides.[63 64]

Cost benefit analyses raise important questions about the design and the review of research. These questions include the following.

- What is the role of cost benefit analysis in health research—both in individual studies and in general?
- Who does cost benefit research help? Does it help patients/subjects, profits, or both patients and profits?
- How does the answer to the above question affect the ethical justification of research?

It is instructive to compare the lead paint study with a cost benefit analysis of drugs. Consider the situation where an existing drug developed by one company is put to a different use and tested against the standard drug treatment developed by another company. The objective of this kind of study is to show that the drug's efficacy is not inferior to the existing treatment. Rather than benefiting patients, the primary aim is to gain a share of the market. If there are potential benefits for patients we might not be too concerned, but it is not clear that we can justify exposing patients to risk for the financial gain of drug companies, landlords, and so on.

Have the researchers and the ethics review committees become accomplices in the problem?

Defenders of the study could argue that, even if the child subjects did not truly benefit from being in the study, their participation can be justified on the grounds that it did not bring additional risks. They could compare it to a situation of someone with a life threatening medical condition, with no effective available treatment. In these circumstances, a risk that would be considered unacceptable under less serious circumstances may be judged acceptable. This is the justification for expanded access to some experimental drugs such as new AIDS treatments.[65 66] I argue that there is a difference between justifying greater risk because of medical or biological considerations and justifying risk because of a person's social conditions.

In an analysis of experiments in which researchers claim they were only watching the inevitable, David Rothman claims that ''poverty, ignorance, filth'' and other ''miseries'' are ''not in any way comparable to the inevitable course of a mysterious disease'', and that ''Tuskegee and the Willowbrook experiments offer both practical and principled support for maintaining as rigid and principled a distinction between social deprivation and biological conditions as possible''.[67] Rothman's claim that there is an ''essential difference'' between taking advantage of social and biological conditions suggests that even if some children in the lead paint study were better off because they ended up in homes that were safer, there may still be something wrong with the study.

Rothman claims, in terms of Tuskegee and Willowbrook, that predictions of continued social deprivation tend to become self-fulfilling. Researchers ''may develop such an immense stake in their projects'' that they will intervene in ways which maintain the conditions for the experiment. They may manipulate the consent of subjects in ways, such as by keeping them ignorant of potential risks.[68] We saw that the parents whose children took part in the lead paint study were kept in ignorance of study aims and potential risks. Rothman concludes that ''social deprivation ought not to become the occasion for conducting a seemingly 'natural experiment''' because in taking advantage of the social predicament of subjects, researchers can end up being ''accomplices'' rather than ''passive observers'' to a problem.[68] It could be argued that the Kennedy Krieger researchers and the ethics review board became accomplices to the problem of lead poisoning in children.

CONCLUDING REMARKS

It is reasonable to argue that the researchers who designed and conducted the lead paint study involving a cost benefit analysis, and the ethics review board that approved the study, became accomplices to the predicament of the subjects. Cost benefit analyses are not value free assessments,[69] and the dominant value in the lead paint study seems to be it is not acceptable for landlords to lose out financially but it is acceptable for children in low income neighbourhoods to face the continuing risk of lead poisoning. This becomes an endorsement of the status quo which allows lead poisoning in children to continue.

We can criticise this study without condemning so called non-therapeutic research or restricting valuable paediatric research. The challenge is to discern and articulate the injustice that occurred and to find strategies to prevent it.

OUTLINE OF A STRATEGY TO PREVENT INJUSTICE IN RESEARCH

In Australia, researchers are commonly required to sign a statement that they have read and will observe the principles set out in the NH&MRC 1999 *National Statement on Ethical Conduct in Research Involving Humans*.[70] I propose an additional statement to be signed by researchers and by the members of ethics committees reviewing research, based on a recommendation by Pappworth in his 1967 book *Human Guinea Pigs*.

> No experiment should be contemplated, proposed or undertaken which, if he were in circumstances identical to those of the intended subjects, the experimenter would even hesitate to submit himself, or members of his own family, or anybody for whom he had any respect or affection.[71]

My proposal is that researchers and reviewers should be expected to contemplate and sign a statement that says: ''I would not hesitate to submit myself, or members of my own family, or anybody for whom I have any respect or affection, if in circumstances identical to those of the intended subjects''.

The aim is for researchers and reviewers of research to appreciate, in a vivid way, the implications of research participation. My proposal should prompt researchers to go beyond their own personal point of view, and give equal consideration to the interests of others. If we accept that ethics are in some sense universal,[72] understanding gained by rehearsing the facts in this kind of impartial, non-evasive way is a basis for ethical research.[73]

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