RESEARCH ETHICS

Legitimate requests and indecent proposals: matters of justice in the ethical assessment of phase I trials involving competent patients

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J Med Ethics 2005;31:205–208. doi: 10.1136/jme.2003.006684

The death of Jesse Gelsinger in 1999 during a gene therapy trial raised many questions about the ethical review of medical research. Here, the author argues that the principle of justice is interpreted too narrowly and receives insufficient emphasis and that what we permit in terms of bodily invasion affects the value we place on individuals. Medical research is a societally supported activity. As such, the author contends that justice requires that invasive medical research demonstrates sufficiently compelling societal benefit. Many consider this societal benefit to be self evident. However, medical research is a complex activity; it yields new treatments but also creates financial rewards and affects health resource allocation. As research evolves into a multibillion pound, multinational enterprise, justice requires a much broader analysis of societal benefit. Without such evaluation we risk undermining the value of bodily integrity and of research participants.

In September 1999, Jesse Gelsinger, an 18 year old student with a mild genetic disorder, died four days after taking part in a phase I gene therapy trial. His death was attributed to an atypical reaction to the experimental agent. In the subsequent Senate hearing established in response to Jesse's death¹ it transpired that information about deaths from liver injury in earlier animal studies had been withdrawn from the patient information sheets.¹ According to Jesse's father, Jesse had understood that the gene therapy worked.¹ In fact none of the preceding patients had shown significant gene delivery.¹ Disturbingly and unknown to Jesse or his family,¹ the principal investigator held \$13 million in equity in Genovo, the biotechnology firm supplying the viral vector used in the trial. The host institution also had a substantial financial interest in the research.²

Present day ethical codes concerning research in humans have been highly influenced by the 1979 Belmont Report,³ which recommended that research should be examined in terms of three basic ethical principles: respect for persons, beneficence, and justice. In this paper I will argue that in current ethical practice the principle of justice is interpreted too narrowly and accorded insufficient status. Instead, it appears

that respect for persons, interpreted as the principle of informed consent, has become the overarching principle in research ethics.⁴ Thus, closer inspection of the research ethics committees in the UK⁵ or institutional review boards⁶ in the USA suggests that their main role has, in fact, been to ensure the validity of the consent process. Within the Belmont report the principle of beneficence is interpreted as an obligation to show concern for the wellbeing of the research participant: to minimise harm and maximise benefit.³ This interpretation acts as a constraint on autonomy by setting limits on what harms can be consented to. Both on paper and in practice, the principle of justice simply requires that the benefits and burdens of research are distributed fairly. Thus specific social groups should not be excluded from the potential benefits of research trials because they are difficult to recruit, and specific groups should not be "overused" simply because the individuals are easy to recruit.

My contention is that the implications of justice are in fact far broader than present practice suggests. While justice may require a fair distribution of benefits and burdens, this is a consequence of a broader requirement that justice requires a society to treat its citizens with equal concern⁷ and how a society values individuals is clearly relevant to this. Thus while consent is essential, it is nonetheless inadequate if the researcher's original request undermines the value of individuals within society. I will use the terms "decent" and "legitimate" to describe how what is requested of would-be research participants reflects and affects the value of individual lives. I will argue that the legitimacy and decency of such requests are matters of justice not beneficence. I will examine the morally relevant aspects of research participation and the principles of autonomy and beneficence. I will argue that justice rather than beneficence constrains autonomy in terms of the harms and risks that are acceptable, and requires that the research in question demonstrate compelling societal interest. While some may view the societal interest in medical research as self evident, I will suggest that medical research is a complex social activity with many interests, not all of which necessarily concur with societal benefit.

In making this argument, I will examine the ethical assessment of phase I trials involving competent adult patients (as opposed to healthy volunteers). Non-therapeutic research

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Received 10 October 2003
In revised form
19 January 2004
Accepted for publication
5 February 2004

in children and incompetent adults raises additional ethical issues, which are beyond the scope of this paper.

WHAT DOES RESEARCH PARTICIPATION ENTAIL?

Phase I trials are proof of principle or dose finding studies aimed at finding the most appropriate treatment dose for subsequent trials of efficacy. The Royal College of Physicians states that phase I trials are generally non-therapeutic.⁸ Consequently, most are performed in healthy volunteers. Phase I trials involving patients (as opposed to healthy volunteers) usually involve interventions, which carry the risk of more than trivial harm (for example, trials of anti-cancer agents) and are often restricted to patients with terminal disease. Additionally, the chance of meaningful clinical benefit is, at best, remote. Although some of the risks are predictable (for example, nausea and vomiting with an anti-cancer agent), others, like Jesse Gelsinger's fatal inflammatory reaction, are not. This is inevitable given that the whole reason for research in humans is that we do not know what the response will be.

We value bodily integrity highly and disvalue harmful bodily invasion. At one level this reflects the value we place on autonomy—control of bodily integrity is a basic expression of an individual's control over how her life should go. But bodily integrity and avoidance of physical harm also have an intrinsic value; the wellbeing of our physical self is an integral part of our wellbeing as persons. Thus, we would be loathe to amputate a man's finger for no good reason other than curiosity. The degree of harmful physical invasion that society permits to some extent reflects the value it places on bodily integrity. Consent might render the amputation morally permissible but would certainly not make it a moral requirement. I shall argue that the social context of the harmful physical invasion is crucial to the relative weight given to autonomy and intrinsic value in determining moral permissibility.

The following example may help illustrate how the social context of an action affects its moral standing. If a man chose not to give a lift to a hitchhiker solely because the hitchhiker was overweight we might consider his decision unkind or narrow-minded but would not necessarily claim that he had done the portly hitchhiker an injustice. If, however, a taxi driver were to choose not to stop because the person hailing was overweight we would be more inclined to say that such behaviour was unjust. If it were the socially accepted norm for taxi drivers in general to refuse overweight passengers, few would argue that such behaviour was not simply rude or unkind but an unacceptable injustice. Furthermore, if such behaviour were the socially accepted norm, it would not only reflect unjust valuation of fellow humans but would also serve to condone and perpetuate such injustice.

Medical research is a societal activity justified by the societal belief in medical progress. It receives public support both directly (through taxation and charitable donations) and indirectly (through its high social status). Those undertaking medical research are from one perspective societal agents. In phase I trials, patients are participating in societally sponsored, potential harmful, physically invasive procedures. We live in a society that values bodily integrity highly and permits few types of harmful bodily invasion.⁹ What a researcher can and cannot do, and can and cannot ask, is determined by values implicit in the researcher-researcher participant interaction. These values reflect and perpetuate societally accepted norms and are therefore matters of justice not beneficence. When an individual agrees to be a research participant this is not simply a private decision between consenting, competent adults. Drawing an analogy (albeit an extreme one) with consensual mutilation, such activity between *private*, competent individuals for no

good reason other than personal pleasure might be morally permissible in that the arguments for personal autonomy probably outweigh the potential effect on how we as a society value bodily integrity and avoidance of physical harm. However, the case would be less strong for societally *condoned* consensual mutilation (for example, televised mutilation). I contend that societally *sponsored* consensual mutilation would be morally unacceptable because it would undermine unacceptably the intrinsic value we give to bodily integrity. Similarly the societally sponsored nature of medical research means that we do an injustice to research participants and to the community as a whole if we permit invasive medical research without good reason, irrespective of consent.

MEDICAL RESEARCH AND THE LEGITIMATE REQUEST

Medical research is a social activity whose principle justification is medical progress for which the assumed beneficiary is society. The generally held view is that medical progress is a societal necessity and this progress necessarily requires research, including experimentation on humans. But is medical progress really necessary? Given that human societies have existed for several millennia and that organised medical research is a relatively recent phenomenon, Han Jonas must be right when he contends that medical progress is not a necessity in the sense that society would not collapse in its absence.¹⁰ Nonetheless it is also true that we have come to expect not only that healthcare is provided as a social good, but also that as a society we should constantly strive for improvements in healthcare. We value healthcare out of proportion to the good (in terms of life and wellbeing) that it actually delivers. Healthcare in modern society has become an essential communal need and therefore a necessary social good.¹¹ The currency of healthcare is relief of suffering, freedom from disease, and prolongation of life. What we want in the arena of medicine (a cure for cancer, prevention of Alzheimer's disease) readily becomes converted to what we need, because it shares this common currency. Thus medical progress and medical research become a social need.

From one viewpoint, medical research is increasingly a commercial activity, the aim of which is to create new markets, maximise profits, and satisfy shareholders

It follows that medical research provides a sufficiently compelling reason for experimentation on humans only in as much as it equates with healthcare needs. However, medical research is a complex activity. From one viewpoint it is a human endeavour motivated by compassion for human suffering whose outcome is improved treatments for human diseases. Research is also the pursuit of knowledge for personal curiosity, career advancement, and prestige. A third interpretation, and one which is increasingly relevant in today's market society, is that medical research is a commercial activity, the aim of which is to create new markets, maximise profits, and satisfy shareholders. There is clearly some truth in all these viewpoints. What then is their relevance to the status of medical research as a social good provided that at least one of the outcomes is medical progress? Anne Sommerville's hypothetical example is medical research into the injuries caused by projectile weapons during combat sponsored by the munitions industry. One of the outcomes of such research might be improved medical care of the injured, but the primary purpose of the research would be to aid in the design of new weapons that could kill and maim more efficiently.¹² Does the possibility that some good may come out of the research outweigh the

undesirable outcomes so as to make a sufficiently compelling reason for human experimentation? Thus, just because a research project has one good motivation and outcome does not obviate the need to analyse all the outcomes and motivations of research in determining what requests we can legitimately make.

To legitimately claim to be a societal benefit, the outcomes of research must concur with what we as a society understand as benefits. Science and medical research are not value free. If, as is the case, medical research is increasingly funded by the pharmaceutical industry and biotechnology investors, then this will inevitably influence the questions asked and the solutions found. One recent market analyst predicted that gene therapy sales would be in the order of \$5 billion by 2008.¹³ It would be naïve to suppose the prospect of this size of financial market would not affect the allocation of resources (funding and researchers) in research. In research, as elsewhere, money follows money. The best and the brightest researchers are more likely to move into research areas with greater funding. Bright researchers combined with greater funding are more likely to achieve academic success and so attract more funding, both public and commercial. Similarly, institutional and cultural factors may favour certain research areas or research approaches over others, independent of clinical need or clinical efficacy. Research in one area diverts funding and manpower from other areas—healthcare provision relies on finite resources. Research policy today has implications for future healthcare spending and therefore for distributive justice. In today's culture of evidence based medicine, research policy can determine whether a treatment practice progresses or stagnates. But the values that determine research policy do not necessarily equate with the values of society. Which is more valuable—an expensive gene therapy based treatment for cystic fibrosis or improved antibiotic and physiotherapy regimens? What if the latter brings significant improvements for cystic fibrosis sufferers within one or two years while the gene therapy route offers the possibility of greater improvements but not for another 15 or 20 years? What if gene therapy research diverts funding and manpower from research into existing, cheaper therapeutic approaches?

Judging the value of the many outcomes of research is complex and requires a much better understanding of the relation between research and healthcare and of the many factors that influence decision making at all levels of research. For example: how does the type of research done affect our perceptions of disease and the direction of medical progress? How does the source of funding and financial interests of researchers affect the type of research that is done? Justice requires that we develop the tools needed to make these evaluations.

MEDICAL RESEARCH AND INDECENT PROPOSALS

In the preceding section I have defined the legitimate request for bodily invasion as one that carries a sufficiently compelling reason. In this section I contend that in the context of medical research, justice also requires that the proposal is decent. Thus, even in the face of compelling societal interest, justice limits in terms of harms, what requests a researcher can make, and who the researcher can ask to participate. Asking an individual to participate in research is a request for assistance. In requesting assistance we place the person asked in the position of having to agree or refuse to assist; we shift some of the responsibility for the outcome onto the person asked. Furthermore, societal requests, such as requesting patients to participate in research, reflect how we as a society value individuals and what we consider to be fair and reasonable burdens. An off-duty fire fighter might choose to go into a burning house

without protective equipment to rescue a trapped child but it would be unfair for the public to expect or ask off-duty fire fighters to risk their lives in this way.

How the decent or fair proposal is interpreted in terms of actual limits set in non-therapeutic research is beyond the scope of this article. However, the limits that are set will reflect and reinforce the value we place on the lives of others and bodily integrity. One academic's response to the Jesse Gelsinger case is that the intervention should not have been tried in a relatively healthy young adult but instead should have been tried in neonates with the more serious form of the disease who would "be likely to die anyway".¹⁴ Although this was not the conclusion of the Senate Committee examining the Gelsinger case, it does seem to have been an implicit notion in much of the literature surrounding the case. Thus, the fact that Jesse was a healthy, active adolescent is often referred to, implying that these features were relevant to the moral acceptability of the trial. Similarly, phase I trials of anti-cancer drugs are usually restricted to patients with terminal disease. Is it fair to ask the dying to assist the (future) dying? Is it possible to adopt such a policy and deny the accusation that such a policy carries the implicit assumption that the lives of the dying are less valuable and therefore more expendable than those of the healthy? There may be some merit in the argument that if there are only enough medical resources to save one life then it would be reasonable to save the life of a young, fit adult rather than a patient with only a few months left to live. But it does not follow that research which is unethical in a fit young adult is suddenly ethical because the patient is dying. The dying have as much right not to be harmed or used as the healthy. This is not simply a version of the acts and omissions doctrine. The allocation of scarce resources in healthcare is concerned with saving actual lives. Research is concerned with saving future lives. There are many future lives that could be saved and research will never save them all. Therefore no specific research project is absolutely necessary. Hence we all have an equal right not to be harmed or used in research.

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The counter argument is that such trials carry the risk of more than trivial harm and healthy volunteers or those with non-terminal disease have nothing to gain, whereas there may be a small (albeit remote) chance of benefit for the terminally ill. However, the chance of benefit is small, and any benefit will not be a cure but a temporary reduction of symptoms or a short prolongation of life. Although some with terminal disease might consider a remote chance of a small benefit worthwhile, it seems untenable to claim that this remote benefit renders the research ethical in the terminally ill while it remains unethical in the healthy. A second defence is that such trials are necessary for future drug development and healthy individuals would be extremely unlikely to volunteer for such trials (even though they stand a far greater chance of benefiting from future drug developments than the currently terminally ill). But is it fair to rely on the terminally ill? Although patients are also motivated by an element of altruism, the evidence suggests that terminally ill patients participate in research primarily out of desperation and a mistaken belief of likely meaningful benefit.^{15 16} In determining what constitutes a decent proposal in medical research we must be aware of the possibility of underlying societal prejudice and injustice and that the limits we set may reinforce and perpetuate those prejudices.

AUTONOMY AND BENEFICENCE

Traditionally it has been beneficence rather than justice that has limited autonomy in decisions regarding participation in invasive, non-therapeutic research. Given the pre-eminence of autonomy in much modern ethical thinking, the principle of beneficence makes for a rather awkward bedfellow. Beneficence suggests that we need to protect the would-be research participant from unwise decisions. Autonomy requires that the conditions of adequate information, comprehension, and voluntariness are met. Proponents of beneficence might argue that most research participants lack the training to fully appreciate the potential hazards of a research trial or that the unequal power relationship between researcher and participant inevitably limits voluntariness. Beneficence then becomes a paternalistic safety net necessitated by the impossibility of achieving true autonomy in this context. In the preceding sections I have tried to show that it is the requirements of justice rather than beneficence that limit autonomy. Thus, even if would-be participants did fulfil the requirements for autonomy, justice would still limit what they could give consent to.

How do we square this with the increasingly vocal patient groups who see research participation as a benefit and even argue for a right to participate in clinical research?¹⁷ Patient advocates argue that respect for persons means allowing patients to decide what does or does not constitute an acceptable risk. Certainly, in the context of medical treatment, the generally accepted view is that respect for personal autonomy means that competent patients have the right to refuse medical treatment for any reason or no reason. However, understood in these terms, personal autonomy as an absolute right of veto to bodily invasion is arguably better interpreted as a respect for bodily integrity. Accepting the intrinsic value of bodily integrity and the avoidance of physical harm, I contend that although consensual harmful bodily invasion may be morally permissible in some situations, there is no actual right to such invasion. Justice limits what we can ask of and do to research participants and as such does not conflict with a right to bodily integrity.

CONCLUSION

Participation in non-therapeutic research is a distinct form of assistance, involving physical invasion for the benefit of society. Medical research is an activity that finds its support and justification from society. As such, those involved in the research enterprise are in one sense public servants. It is this social context of medical research that underpins the importance of justice in determining ethical permissibility. I have tried to show that the moral legitimacy of medical research requires the demonstration of sufficiently compelling societal benefit and that fair limits are set on what we can ask of others. Arguably, these requirements are consistent with the principle of beneficence. However, accepting that these are matters of justice rather than beneficence recognises the societal context of medical research, the societal obligations of researchers, and that the limits set

reflect and affect the value society places on research participants. Justice therefore requires that those involved in the research enterprise examine their actions in the context of much broader societal obligations. Today, the value of research is largely determined by the scientific community and commercial investors. I have tried to show that judging the value of the many outcomes of research is complex and a far broader analysis of benefit is required. Delineating, comparing, and measuring the different outcomes of research is essential but beyond the scope of this paper. Furthermore, at present we lack many of the tools needed to make such analyses. However, without an honest evaluation of what we accept as societal interest in the context of research on humans, we devalue the meaning of societal interest and risk undermining the value of those who participate in research and the value of bodily integrity. The death of Jesse Gelsinger may have been a totally unexpected and unpredictable tragedy; however, the possibility remains that those involved lost sight of the true values at stake.

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