RESEARCH ETHICS

Challenge studies of human volunteers: ethical issues

T Hope, J McMillan

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See end of article for authors' affiliations

Correspondence to: Tony Hope, Ethox Centre, University of Oxford, Oxford, UK; tony.hope@ethox.ox.ac.uk

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There is a long history of medical research that involves intentionally infecting healthy people in order to study diseases and their treatments. Such research—what might be called ''human challenge studies''—are an important strand of much current research—for example, in the development of vaccinations. The many international and national guidelines about the proper conduct of medical research do not specifically address human challenge studies. In this paper we review the guidelines on the risk of harm that healthy volunteers may be exposed to in the course of medical research. We examine the ethical arguments that are implicit or explicit in these guidelines. We then ask whether there is reason for limiting such studies on grounds independent of risk of harm. We conclude that the major ethical concern with challenge studies is that of risk of harm and that the fact that a study is a challenge study is not a wrong in itself.

There is a long history in medical research of intentionally infecting healthy people in order to study disease. The somewhat romanticised story of Edward Jenner has fired the imaginations of generations of young people. On 14th May 1796, Jenner inserted the pus from a cowpox sore into cuts on the arm of a healthy boy, James Phipps. Six weeks later Jenner inoculated Phipps with the pus from a smallpox sore. Phipps did not suffer smallpox: the idea of vaccination, so the story goes, had been born. Healthy people have been infected not only to study prophylaxis but also to study the causes of disease, as in the famous case of the work of Walter Reed and the Yellow Fever Commission. A major purpose of that research was to investigate the theory that mosquitoes spread the disease. Volunteers were warned of the possibility of death from yellow fever, and were each paid a $100 gold piece.[1] For many years the Medical Research Council (MRC) common cold unit infected healthy volunteers with common cold viruses (rhinovirus) in order to study both the natural history of the disease and the effectiveness of potential treatments, such as antiviral agents.

Human challenge studies are an important strand of much current research, particularly in the development of vaccinations. Research into malarial vaccines is a good example, where the detailed study of both the clinical and immune responses of healthy volunteers to inoculation with candidate vaccines, followed by challenge with the infective organism, is proving an important approach to developing what is hoped will be an effective vaccine. Other examples include challenge with influenza A virus to assess both vaccines and antiviral drugs, challenge with cholera bacilli to evaluate novel vaccines, and challenge studies with pneumococcus to assess correlates of protection against nasopharyngeal colonisation.

ETHICAL REGULATION OF MEDICAL RESEARCH: HISTORICAL PERSPECTIVE

There are historical reasons why medical research is more tightly regulated than most other human activities and why its regulation differs from that of normal clinical practice.

It was the appalling experiments conducted by some doctors under the Nazi regime that led to the first internationally agreed guidelines on research involving people, the Nuremberg Code (1946). This consisted of ten principles and these were interpreted by the World Medical Association in their Declaration of Helsinki, first published in 1964 and last updated in 2000.[2] The declaration provides an internationally agreed ethical framework for the conduct of medical research involving humans. It is the basis for the various more detailed national and international guidelines that have been developed.[3–7]

The values incorporated into the various guidelines can be justified by a number of different traditions in moral and political philosophy. Most guidelines emphasise respect for the autonomy of the potential participants, the risk of harm, and the value and quality of the research. Two related aspects that run through all guidelines are worthy of note: first, that there are strict limits to the risk of harm that participants in research can be subjected to, even if they are adult, fully competent, and voluntarily agree to take those risks; second, that in weighing up the potential good that the research might bring to people in the future against the potential harm to participants, concern about the welfare of participants is given very much greater weight. Because of the origins in the Nuremberg code, the central concern of research guidelines is to ensure that the interests of society, or the enthusiasm of the researcher, do not override the interests of the individual participants.

Little explicit attention has been paid to human challenge studies in the many national and international guidelines for medical research. What we will explore in this paper is the question of whether such studies raise ethical concerns that require special consideration. The central concern with regard to microbial challenge studies is the fact that they involve infecting a healthy person with a disease such as malaria. There are two major ethical issues, we believe, that this raises: the question of the risk of harm to the research participant, and the question of whether infecting a healthy person is a wrong over and above the risk of harm that it entails. We will not consider issues such as the general standards of information provision, the scientific quality of the research, or the use of inducements, because there seems no reason to suppose that challenge studies are special in these regards. Our conclusion will be that human challenge studies should fall within the same guidelines as other areas of medical research with regard to the core ethical principles. Because such studies are likely to raise more concerns among the public than most other types of medical research, however, it would be wise to develop specific, although brief, guidelines for microbial challenge studies in order to lessen any risk of a negative public reaction that would jeopardise the carrying out of valuable research.

DEGREE OF RISK TO WHICH COMPETENT ADULTS MAY CONSENT: THE LEGAL POSITION

The degree of risk of harm, to which competent adults may legally expose themselves, is uncertain. The original meaning of mayhem (which is cognate with the word maim) was ''the crime of violently inflicting a bodily injury upon a person so as to make him less able to defend himself or annoy his adversary''.[8] Inflicting such bodily injury was a crime, in medieval England, even if the victim gave consent for the bodily injury, or indeed, even if he requested it. The original grounds for this may have been that it deprived the king of a potential soldier. In modern common law it remains the case that inflicting injury on another, with valid consent, may be a crime: the state protects people even from themselves.

Normal surgical operations, where they are therapeutic, are of course lawful. A problem arises where surgery is not therapeutic but where the patient has given valid consent for the surgery. It would be unlawful for a surgeon to mutilate a patient at the patient's request when there is no therapeutic justification. The sting in the tail of this principle is what counts as ''therapeutic justification''. In the late 1990s a Scottish doctor amputated healthy limbs from two patients. The patients were reported to be suffering from Body Dysmorphic Disorder and desperately wanted the limbs to be removed. Two and a half years after the operation, one of the patients is reported as saying that ''[b]y taking that leg away, that surgeon has made me complete...I have happiness and contentment and life is much more settled''. (Source for the information about these patients was BBC website news, 6 Feb 2000; the information has since been removed). No legal action was taken against the surgeon.

It would be unlawful to remove vital organs for donation where this would result in the death of the donor. Even if—for example, a parent wanted to donate her heart for transplant to her child, with her resulting death, it would be a crime (murder or manslaughter) for the surgeon to carry out this request. What is less clear is whether it would be lawful for a surgeon to remove both kidneys for transplant (again—for example, where a parent requested it) even though the parent could remain alive on dialysis. Such an operation by a surgeon might well be found to be unlawful. Thus, although a patient's valid consent (in the case of a competent patient) is, generally, a necessary condition for surgery to be lawful, it is not a sufficient condition. The question arises: to what extent is it lawful to proceed with surgery where valid consent has been given but where the surgery is not in the patient's best interests. One judge has said, extrajudicially, that he would: ''…be surprised if a surgeon were successfully sued for trespass to the person or convicted of causing bodily harm to one of full age and intelligence who freely consented to act as donor *always provided that the operation did not present unreasonable risk to the donor's life or health* ''.[9] (our italics)

The legal position with regard to non-therapeutic medical research and risk of harm is not clear. Researchers, and research ethics committees, will need therefore to turn to various ethics guidelines. Several such guidelines articulate a more restrictive approach with regard to the degree of risk of harm to which competent research participants can expose themselves than has emerged from common law. It seems likely that courts would take seriously such guidelines. In considering the legal position of microbial challenge studies, therefore, it is crucial to examine the key research guidelines.

GUIDELINES ON RISK OF HARM IN THE CONTEXT OF MEDICAL RESEARCH

The Declaration of Helsinki states: ''Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others'' (WMA,[2] principle I.5).

Several guidelines, including the above statement, suggest that the degree of risk of harm that is acceptable depends, at least to some extent, on the potential value of the research: that more risk is acceptable if the research is likely to lead to great benefit than for less beneficial research. Thus the International Committee on Harmonisation states: ''…foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject *and society*''.[10] (our italics) The World Health Organisation states: ''risks to the research participants should be weighed against the benefits to both the participants and to the 'concerned community'''.[11]

The General Medical Council (UK) guidelines for doctors state: ''...in non-therapeutic research, you must keep the foreseeable risks to participants as low as possible and the potential benefits from the development of treatments and furthering of knowledge must far outweigh any such risks''.[12]

This guidance, in addition to stating that there is to some extent a balance between risk of harm to the participants and the expected value of the research, makes the important additional point that the risks should be kept as low as is possible. In other words, even if the risks of harm were within acceptable limits, and, of course, the participant had given valid consent to take part, the research may be in breach of the guidelines if it could have been carried out more safely.

Some guidelines make clear distinctions between therapeutic and non-therapeutic research and between patients as participants and healthy volunteers. We will consider only the case of healthy volunteers since these are the usual participants in challenge studies. In the case of healthy volunteers, what degree of risk of harm, according to the guidelines, is it acceptable for fully informed healthy adult volunteers to take? The Royal College of Physicians (RCP) guidelines have been the most explicit on this point, and these guidelines introduced a concept that is often used in this context, that of minimal risk of harm, or minimal harm. The second edition of these guidelines (1990) made an important distinction between two senses of minimal harm.[13 14] On the one hand harm can be minimal in the sense that although quite likely, or even certain, it is not very great. The headache that can follow a lumbar puncture might be an example of minimal harm in this sense. The second sense of minimal harm is where there is a very low chance of serious harm. The second edition of the RCP guidelines states in the context of minimal risk:

> The second [sense] is where there is a very remote chance of serious injury or death. We regard this second risk to the healthy volunteer as comparable—for example, to that of flying as passenger in a scheduled aircraft.

The guidelines go on to state:

> 11.14 There are some situations, such as the treatment of serious disease, where it is ethical for research studies to involve more than minimal risk. *These would never involve healthy volunteers* (our italics).

In the third edition of the guidelines the Royal College no longer refers to airplane flights and elaborates the meaning of minimal risk in the following way[15]:

> 7.2 Minimal risk could include everyday risks such as travelling on public transport or a private car (the latter

> having considerably higher risk) but would not include travel by pedal or motorcycle; ...Minimal risk is where the chance of serious injury or death is very remote and may be ignored. ...Attempts have been made to quantify minimal risk as a risk of death of <1 per million or of major adverse effect of <10 per million, and low risk as 1 to 100 per million for death and 10 to 1000 per million for major adverse event.

The guidelines go on to state:

> 7.3 Benefit may be weighed against risk in two different ways. First and most obviously, the patient may benefit. This is typified in a therapeutic trial where at least one of the treatments offered may be beneficial to the patient. ...Second, society rather than the individual may benefit. In such situations, *however large the benefit, to expose a participant to anything more than minimal risk* needs very careful consideration and *would rarely be ethical* (our italics).

Although the Royal College has tried to grapple explicitly with the question of how much risk of serious harm a healthy volunteer can be exposed to, the guidance is not very satisfactory. It suggests quite rightly that, in the context of volunteer studies or indeed any other medical research with healthy volunteers, a judgment has to be made as to what that risk is. It is not clear, however, what degree is acceptable, other than that the risk has to be very low. The guidance uses two strategies. One is to give a figure, and specifically state that minimal risk is a risk of death of less than one in a million. It is notable, however, that the guidelines do not clearly endorse this view; they simply note that this figure has been put forward (no reference is given). The other is to relate the risk to aspects of normal life. These guidelines seem to be saying that the risk of death should not be as great as would be incurred by riding a bicycle.

One problem with this statement is that it is not clear what this risk is: do the guidelines mean the risk in riding a bicycle on a regular basis throughout one's life, or the risk incurred on a short journey (and, if so, how short) or some intermediate risk. These risks are clearly very different. Furthermore if the benefit from the exercise of cycling is taken into account, some estimates suggest that, overall, cycling leads to a gain in life years.[16]

The guidelines are remarkable in drawing the line such that the risk that a participant can take in helping with medical research must be less than a risk that many of us take in normal life.

Evans and Evans consider the idea of minimal risk at some length.[17] They do not offer guidelines but their book represents one of the most detailed discussions of this issue. They consider two interpretations of minimal risk. They write: ''When research is avowedly non-therapeutic, we could say that the risks are minimal if the research procedures involve no foreseeable harms which are either more likely, or more severe, than those which one could meet in everyday life. It is accepted that daily living involves a certain amount of risk, after all.'' (Evans, *et al,*[17] p 66)

This appears to be a promising approach. Although it provides no absolute precision, it suggests there is no reason why a potential participant (if competent and fully informed) should be stopped from taking the kind of level of risk that we take in our daily lives. Evans and Evans, however, go on to reject this interpretation on the grounds that different people take different levels of risk in their daily lives and that therefore this criterion does not present us with a single standard. These authors consider another standard, but unfortunately this is only meaningful in the context of patients as participants in research and gives no guidance in the case of healthy volunteers.

We believe that Evans and Evans may have been too hasty in their rejection of the ''everyday life'' standard for minimal harm. Any standard is likely to provide only an imprecise moral yardstick and given the need for defining a standard of minimal risk some degree of imprecision can be tolerated. The thought behind Evans and Evans's (rejected) view of minimal risk is that research which is no more harmful than activities that an individual takes part in during everyday life is not harming that individual in a way that he would not have been harmed had he not taken part in the research. In other words a research participant is not worse off by taking part in the research than he would have been if he got on with his life in other ways. Although this everyday life standard is vague it does provide a meaningful rule of thumb for identifying when a research project is too dangerous.

The fact that different people accept different levels of risk in their everyday lives may be a strength and not a weakness of this approach. Consider research aimed at examining the physiological responses of high levels of physical exertion in tropical conditions. The risk may be much higher than risks that most of us take in our lives, but may be comparable with that of an athlete who competes in the tropics. If such an athlete wants to take part in the research because it fits in with the training that he wants to do, it seems excessively paternalistic to say that he cannot take part on the grounds that the risk is more than most people take.

Although our view is that competent adults should generally be able to take risks in participating in medical research that are comparable with the risks they take in other areas of life this is clearly not the view endorsed by research guidelines. The position taken by guidelines can be summarised as three points:

1. Even though the volunteer is fully informed, competent, and not coerced, and gives consent to the research, the research could breach guidelines on the grounds that the risk of harm is too great.
2. The degree of harm that such a participant can be exposed to is greater, the more valuable the research. The significance of this, however, is not clear since the guidelines suggest that however valuable the research, the degree of harm can be no greater than ''minimal''.
3. Minimal risk is a lower level of risk than people can lawfully be helped to take in many areas of life. In so far as guidelines attempt to specify a level it seems to be set at a level taken by somewhat risk averse people in their normal lives.

RISK OF HARM: THE ETHICAL CONSIDERATIONS

Having discussed the legal position and the relevant research guidelines we will now turn specifically to the ethical considerations. After all, both the law and guidelines are presumably based on ethical considerations, albeit distorted by history and public policy. Furthermore the guidelines leave researchers and research ethics committees leeway for their own ethical considerations. The question we first want to consider is: why should risk of harm be more carefully controlled and more restrictive, in the context of adult competent volunteers for medical research, compared with other areas of our lives. We do not restrict or disallow people to sell skis, motorbikes or hang gliders, although these expose purchasers to moderate risk. Why should the control of medical research be more restrictive?

Evans and Evans write:[17]

> Whilst there are many contexts in which autonomous adults can choose to undertake more-than-minimal risks (sport is an obvious example), clinical research ought perhaps not to be among them. The main reason for thinking this is that we should distinguish between the degree of risk someone might privately undergo in an activity of his choice, and the degree of risk it is appropriate for a professional or other public figure to invite a patient to contemplate.

What reasons could be given in support of this statement? One reason is that patients may be vulnerable to acceptance of taking part in research because of their illness and their reliance on doctors for health care. When research is conducted on patients they are likely to be in a vulnerable situation and there is a danger they will agree to risky research because they are in a therapeutic relationship, and assume they will be asked only to do things that are consistent with their best interests. But this is not relevant to research with healthy volunteers such as challenge studies. When research is conducted on healthy volunteers it is less likely that there will be a therapeutic expectation and the volunteers are more likely to be able to make an informed choice about whether to accept risks that are greater than minimal. This provides an argument for why healthy volunteers should be allowed to take risks commensurate with risks taken in other areas of life. Although we find this a powerful argument it is not essential for the key question that we wish to investigate: are microbial challenge trials more morally problematic than other forms of research conducted on healthy volunteers.

A second possible reason in support of Evans and Evans's statement is that public figures or professionals may, in inviting people to take part, exert excessive coercion because potential participants may feel they ought to respond to such figures of respect and authority. Not only does this sound excessively paternalistic, however, it is unlikely that such a degree of coercion is as great as that exerted by advertisements for motorbikes, skiing holidays etc. A third possible reason is that there is something wrong in public figures or professionals inviting a person to take a risk with themselves in a way that it is not wrong for a motorbike salesman to do so. The idea here may be that we expect higher standards from professionals or other public figures.

One interpretation of this point is as follows: that in inviting a person to take part in slightly risky research, one is doing something slightly immoral. This degree of immorality is acceptable in a motorbike salesman but not in a professional person or public figure. Such an argument, however, begs the point at issue. The question that we are considering is: given that medical research can be of great benefit to people in the future, when is it immoral to enable someone to take part. In other words the issue is about what degree of harm is morally acceptable. We must therefore give an answer to this question before we can decide whether the public figure has done anything immoral in inviting the person to take part.

There is, however, another possible interpretation of why a professional person or public figure should not invite people to take a risk with themselves when it would be acceptable for other people to do so. And this brings us to what we believe is the only sound argument for greater restriction in terms of degree of risk that it is permissible for people to take in the context of medical research compared with other aspects of life.

If significant numbers of people were to die as a result of taking part in medical research, then this would be likely to have the effect of bringing such research into disrepute (even though all those who died knew the risks and gave valid consent). The result of this would be to reduce the amount of research that could take place because of a public reaction against such research. The fact that doctors are involved in designing the research may lead to a reaction against not only medical research but against medicine more generally. If doctors are involved in exposing people to risks of harm within the context of medical research, both the public, and those who are unfortunately harmed, might see this as very different from the involvement of a maker of hang glider equipment.

Medical research may be seen by the public as so closely related to medical practice, and doctors' roles as researcher and therapist so closely allied, that medical research does need to be more carefully regulated with regard to risk of harm than many other activities. One has only to think of Alder Hey to realise how careful health professionals need to be in ensuring that they carry out their work, including research work, in a way that the public can understand and accept.*

This argument only has force in those situations where significant harm to research participants will lead to a public reaction against medical research or medical practice, more generally. On the view that we are taking, research participants might be exposed to more than minimal risk of harm if, first, they give valid informed consent; second, the potential benefit of the research is large and, third, there is unlikely to be a public reaction against research as a result of harm to participants. The following situation might be an example of such research. Suppose that terrorists had at their disposal a biological agent for which there is no antidote. A well designed research project aimed at finding an effective antidote is proposed that places participants at considerably greater risks than ''minimal harm'', although risks that are within what is accepted in other walks of life. There is, let us suppose, no way in which the research can be carried out more safely. If fully informed competent adults were willing to volunteer for such research and such research was necessary to prevent a large number of deaths then, in our view, it would be morally justified.

We conclude there is one good reason why risk of harm from medical research needs to be more carefully regulated than most other areas of risk taking. This argument is pragmatic rather than based on principle. That is, it is based on a belief that the public will react in a certain way—and that the good that results from medical research may be jeopardised if there are not stringent safeguards to protect participants from harm. It is not, however, an argument that the public are right to react in that way.

We will now return to the specific issue of challenge studies. Whatever our views about the level of risk of harm that is appropriate for medical research in general, it is clear that challenge studies will need to be undertaken within the general regulatory framework of medical research—part of which we have outlined above. A key question for any such study is whether it poses more than minimal risk—and this will need to be judged by both researcher and ethics committee with the help of the guidelines (which, as we have seen are imprecise) and what is generally accepted in other areas of medical research. Even challenge studies that involve inoculation with a serious disease such as malaria can be undertaken in ways that involve less risk of harm than

*Alder Hey is a children's hospital in Liverpool, England. There was a public outcry leading to an official inquiry when the media reported that following postmortem examinations, organs were retained for research purposes without specific consent from parents.

many other types of medical research. In the case of malaria, strains can be used that have been carefully developed so that they are highly sensitive to antimalarials. This, coupled with very careful monitoring of participants during the experimental period, can keep risks very low.

Are there legitimate ethical concerns with challenge studies over and above the issue of harm?

IS GIVING A HEALTHY PERSON AN ILLNESS A WRONG IN ITSELF?

Concerns about challenge studies may derive from the fact that they involve giving healthy people a disease. Doctors should be curing diseases not giving them. There is a long and important history in moral philosophy that the morality of an action is not determined only by the consequences, or foreseen consequences of that action. Indeed, the idea that it is only the consequences that are of key importance (consequentialism) is a relatively modern one. Some moral traditions—for example, consider that actively killing someone may be wrong, even if the overall consequences of so doing are better than the consequences of not killing. This view is incorporated into English law and is relevant in medicine. Injecting a terminally ill patient with high doses of painkiller with the intention of controlling the pain, but foreseeing that this will shorten the patient's life, is not generally illegal. Injecting the person with potassium chloride with the intention of killing (even though this is done to prevent further suffering and at the request of the competent patient) is illegal, and indeed potentially murder. Thus, two acts with the same foreseen consequences may be viewed quite differently, both legally and morally, depending on the intention behind the act. It is tempting, on consequentialist grounds, to say that intention, in and of itself, does not make a moral difference, but this thought subjects the consequentialist to the following well known hypothetical case. For an interesting discussion of this case see chapter three of Kagan.[18]

Suppose five people will die from various organ failures unless they receive a compatible organ through transplantation. (This example presumes that such surgery is better developed than at present.) You are a surgeon about to carry out an operation for a completely curable condition, appendicitis—for example, on one person who is compatible with these five people. If your patient were killed, his organs could be used to save all five people: a kidney to this one; a liver to that, lungs and heart distributed between the sick people etc. If you do not kill the patient with appendicitis, five people will die. If you painlessly kill the one person on the operating table the other five will live. The consequentialist can simply bite the bullet here and say that the right thing to do is to increase the anaesthesia so that the person on the operating table dies. Most people, however, think that in such a case the intention to kill makes a significant moral difference. It is the fact that we would deliberately act so as to bring about harm (in this case death) to an individual that makes this act morally repugnant.

Now, imagine two research studies in medicine. The first involves deliberately infecting a healthy person as is done in some challenge studies such as in malaria vaccine research; the second involves a moderately invasive investigation—for example, lumbar puncture. For the sake of argument assume that both have exactly the same profile of risks. Both are within limits of minimal harm accepted in carrying out medical research. Both are carried out on fully informed healthy volunteers. Is there a sustainable moral objection to the first study, but not to the second, on the grounds that the act of infecting a healthy person is a wrong in itself over and above the foreseeable risks of harm? Such an argument would have to depend on claiming that the intention to give someone a disease is in itself a wrong beyond the risk of harm.

To pursue this line of argument requires an account to be given of why it is wrong to give someone a disease. Of course there are good reasons why it is normally wrong to give someone a disease. It is tempting, however, to think that these reasons are only the harms that accrue to people from disease and that there is no wrong over and above these harms. So, in the case of the two types of research outlined above, if the risks of harm are the same, a moral difference cannot be founded on the fact that one involves harms through disease and the other involves identical harms as unintended but recognised unwanted effects of the experimental intervention.

Perhaps the argument can be slightly adapted to focus on the distinction between intention and foresight. Philosophers have produced a number of thought experiments to tease out the implications of this distinction in addition to the surgical case outlined above.[19–21]

One involves a runaway trolley (railway carriage) that will kill five people who are on the track unless a railway worker switches the points to divert it down another track. Unfortunately there is one person on the second track who will be killed if the points are switched. It is an open question whether the points should be switched but most people consider that switching the points so that one person, rather than five, dies is the right thing to do. The problem is that this looks, on the face of it, very similar to the predicament faced by the surgeon in the previous case. In both cases if the person acts five people will live at the expense of another person dying. Those who want to say that the railway worker should switch the points but that the surgeon should not kill the one patient need to produce an explanation for what is different between the two cases. One standard view of this difference is that although the railway worker foresees that by saving the lives of the five people one person will die, he does not intend the death. It is because switching the points is the only means available to save the lives of the five that the railway worker takes this person's life. So we might say that the railway worker could foresee but did not intend the death of the person on the second line. In the case of the surgeon, the death of the patient is intended and not merely foreseen.

Applying this line of thought to the two types of research, we might say that any harm resulting from the research involving lumbar puncture is foreseen but not intended. On the other hand, harm resulting from deliberately infecting an individual with a disease cannot plausibly be described as unintended.

The problem with this approach is that the justification for switching the points (that it is the only means available of saving the five lives) might also apply to the surgeon. The surgeon might say that if it were possible to save the lives of the five without killing the patient with appendicitis—for example, because all the organs could regenerate then she would do this. The death of her patient is, on this view, foreseen but not intended. Likewise with deliberate exposure to a disease; if there were less harmful means of bringing about the testing of the putative vaccine they would be adopted: the risk of harm resulting from infecting the research participants is foreseen but not intended.

While the attempt to base the intention/foresight distinction on the significance of ''the only means available'' appears doomed it might be possible to defend the distinction by pointing to the causal closeness of the actions to the death of a person. Whatever the surgeon intends, there does seem to be a much closer causal connection between what the surgeon does and the death of the patient, than in the case of the railway worker who switches the points. This is what

Frances Kamm has in mind with her ''Principle of Permissible Harm''. She writes[22]:

> It is permissible to cause harm to some in the course of achieving the greater good of saving a greater number of others from comparable harm, if events which produce the greater good are not more intimately causally related to the production of harm than they are to the production of the greater good...

She intends this principle to help us distinguish between permissible and impermissible actions leading to the death of at least one person. It might be objected that it is a misappropriation of this principle to use it in contexts where the harm caused falls short of death. If such principles, however, are successful in giving an account of which acts of killing are justified, and which are not, they are likely to be relevant to similar distinctions for other actions that cause harm. Kamm's principle might, therefore, give an account of why it makes a moral difference that a person is deliberately infected with a disease over and above the risk of harm.

Kamm's principle can be illustrated by thinking about the surgeon and runaway trolley cases again. The surgeon's act of killing the patient while on the operating table is more intimately causally related to the death of the patient than it is to the saving of the five in need of organs. In the runaway trolley case the act of redirecting the trolley is no more intimately causally related to the death of the one person on the track than it is to the saving of the five on the track.

How does this apply to challenge studies that involve deliberately infecting a person with an illness? It looks like the causal directness of infecting somebody with a disease will be morally worse on this account than an equivalent harm that is brought about indirectly. In other words, the harm that may result from an illness caused by an act of deliberate infection is more directly causally related to what the researcher does than the harm that results as a side effect from a procedure such as lumbar puncture. If we think that the Principle of Permissible Harm is true and think it can be applied to harms in research, then it looks as though there is a reason for believing that deliberate infection with a disease is morally different from, and more problematic than, many other interventions with similar risks of harm used in medical research.

There are, however, two counterarguments to this position. The first questions whether the intimacy of causal connectedness does matter morally. The second questions whether the harm resulting from illness following deliberate infection is more closely connected, from a causal point of view, to the researcher's acts than the harm resulting as a known side effect of a procedure such as lumbar puncture.

With regard to the moral significance of the intimacy of causal connectedness, it is, in general, true that the more intimate the causal connection between the act and the harm, the more likely it is that the harm will occur. It may be the probability of the harm occurring that drives our intuitions about when it is right to act, rather than the intimacy of the causal relationship as such. Our intuitions about the runaway trolley case may be led by the possibility that after the points have been switched the person on the second track is saved. This may seem intuitively more likely than that of a patient whose vital organs were surgically removed and could thereby live. Although it is written into the examples that the death of the one person is certain (if the five are saved), it might be that our intuitions are being led by the lack of certainty that real world instances of this would bring. If it is the perceived difference in probability of a bad outcome that leads our intuitions in such cases then it is not the intimacy of the causal connectedness that makes the moral difference. For more on this point see Rakowski.[21]

With this discussion of the various thought experiments in mind, we will now return to a consideration of microbial challenge studies. When a medical researcher gives a disease to a research participant one might argue that this is against the longstanding principles of the proper relationship between doctor and patient. But the reality of the research situation might militate against this view. Consider the care with which the research is carried out. In a typical example, the parasite that the mosquito is infected with is genetically developed to be highly sensitive to chloroquine. The research participant is seen every day and carefully assessed for clinical signs of the disease and, if there are any, is immediately treated with the drug that is highly effective. Blood tests that can detect infection before it is clinically manifest are carried out on a regular basis. Participants are given a mobile phone and a contact number that is available 24 hours a day for the period during which they could become ill, so they can receive medical assessment if there are grounds for concern. All these procedures are of course important in ensuring that the risk of harm is very low and within the limits of other types of medical research that are considered to have acceptable risk. But they are also relevant to the question of whether any harm that results is more closely connected to the researcher's acts than harm that results from a procedure such as lumbar puncture. Given that the infection is carefully developed to be highly sensitive to treatment, and the care taken to detect any problems, any harm that did result could be seen as a rare side effect of the procedures. The probability of harm and the procedures carried out as part of the experiment are not significantly different from the probability of untoward effects in other kinds of research.

VIRTUE THEORY

There is one other ethical approach that might at first sight provide reasons for distinguishing morally between research studies that involve microbial challenge and those that do not when both carry the same risks of harm. This is the approach of virtue ethics. It might be argued that a virtuous doctor, or a virtuous medical researcher, would not give a healthy volunteer a disease even if the risks of harm to that volunteer were no greater than would be permissible in other types of medical research. This argument would depend on the idea that giving a disease is contrary to the characteristics of a virtuous doctor. The problem with this approach is that there is no clear tradition that tells us what the characteristic of a virtuous doctor would be in this situation. The virtuous doctor/scientist would try and help mankind by finding ways of curing or preventing disease. The question then arises as to how the virtuous doctor/scientist should carry out the necessary research. The questions addressed in this paper would become issues that the virtuous doctor/scientist would have to consider. What risk of harm to the research participant is acceptable? If the research requires microbial challenge is this a wrong over and above the risk of harm? In other words the virtuous doctor/scientist will have to consider exactly the questions and arguments that we have discussed above and come to a reasonable conclusion. We cannot find any arguments to the effect that giving a microbial challenge is a wrong in itself based on the concept of virtue that is independent of the considerations we have discussed above.

CONCLUSION

Our conclusion is that the central ethical issue with regard to challenge studies lies in the risk of harm to the participants. We do not believe that the fact of its being a challenge study is a wrong in itself. If we are right, and there is nothing

special about challenge studies in principle, what might account for the common intuition that there is something different and worrying about medical research being carried out that involves infecting healthy people with a pathogenic organism. We think our intuitions can be accounted for in terms that we have discussed. First, that many diseases cause very considerable harm to people both in terms of discomfort and risk of long term serious harm. We associate the term disease with such fears of harm. We have argued, however, that this does not provide grounds against challenge studies if, in fact, the risk of harm is no different from what is acceptable in other types of research study. Second, medicine is paradigmatically about curing disease, and therefore the carrying out of medical research that specifically involves giving disease to healthy people seems to go against the fundamental goals of medicine. But this argument fails to take into account the purpose of the challenge study. The overall purpose is not to give healthy people disease but—for example, to devise an effective vaccine to prevent disease. The aims of the research are in line with the goals of medicine, not against them.

There is one important implication of the power of these intuitive, if mistaken, responses. We have argued that the risk of harm in medical research needs to be more carefully regulated than in most walks of life in order to prevent public reaction from unduly restricting research, and therefore the good that comes from it. We believe this is especially so in the case of microbial challenge studies. The idea of giving a healthy person a disease is so alien to the public's expectations of medicine and medical research that it is vital to conduct such studies within a well considered and transparent set of guidelines and regulatory processes.

Authors' affiliations
T Hope, Ethox Centre, University of Oxford, Oxford, UK
J McMillan, Department of History and Philosophy of Science, University of Cambridge, Cambridge, UK

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ECHO

New guidelines may be impossible to implement

Please visit the *Journal of Medical Ethics* website [www.jmedethics.com]for a link to the full text of this article.

New guidelines from the Joint Specialty Committee for Genitourinary Medicine of the Royal College of Physicians on chaperoning patients in clinics for genitourinary medicine may have far reaching implications in terms of cost and staffing levels and may be impossible to implement, at least in their current form.

The guidelines were issued in response to guidance from the General Medical Council on doctors performing intimate examinations. The guidelines are more concerned with the comfort and protection of patients, although they are also intended to defend doctors against wrongful accusations. The Royal College of Nursing has produced similar guidance for nurses.

The chaperone should ideally be a healthcare professional, and his or her name should be recorded in the medical notes; family, friends, and partners should only in exceptions be the chaperone in a genitourinary medicine setting as their use would have implications on confidentiality. A patient's refusal of a chaperone may result in deferral of an examination, especially in the case of male doctors and female patients.

The impact of introducing these guidelines needs to be assessed with regard to numbers of patients accepting a chaperone, cost, and staffing implications, and acceptability to patients. They should be modified as appropriate.

▲ *Sexually Transmitted Infections* 2003;**79**:422–423.