

The **ethics of medical research on humans**

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An introduction to the ethical issues

Introduction

It must be the dream of any ill person to be cured effectively and immediately, with no side effects. Every doctor's dream must be to provide such a precise service. It might happen sometimes, but the reality is rarely so satisfactory. Even when 'miracle cures' like penicillin are discovered, the appearance of absolute cure with no side effects turns out to be different from the actual experience, sometimes long after the medicine has been discovered. However, it is just as well that throughout the history of medicine, some doctors have never accepted the idea that complete cures are a delusion and stopped looking for them. For if research is not undertaken, medicine would not progress in the remarkable ways that it has. There may not be many complete cures, but there are treatments for numerous conditions that previously would have killed or disabled for life. It has also been established that some treatments are useless or even harmful. The ultimate goal of medical research must be to find complete cures; the more prosaic actual achievements do, nevertheless, help a great deal.

To improve medical care as much as we can, if not to perfect it, means that we have to accept the need for research. Some argue that the real art of medical care is to prevent people falling ill in the first place. Prevention is better than cure, particularly if it does not involve taking drugs. Even to establish what constitutes healthy living requires research, however. In any case, prevention is helpful to those who have not yet succumbed to the effects of unhealthy living, but for those for whom it is too late, treatment is needed. Also, there are many causes of conditions which, not being understood, or being understood but not being controllable, cannot be avoided or changed. Research into causes is needed, and so is research into treatment of the conditions as they present themselves. Whatever the condition or its cause, medical research is needed. What is more, that research is almost always going to take the form of steps on the way to complete cures, rather than reaching the goal in one go. Giant leaps in understanding and treatment are not, by their very nature, planned, as the story of penicillin's discovery demonstrates. Meanwhile, the pedestrian plodding of routine research has to

go on. Over time it can show startlingly good results, such as the hard-won 50% improvement in the treatment of childhood leukaemia.

The recognition of the need for careful research, and participation in it, requires sacrifices on the part both of patients and of doctors. Doctors have to recognize that what knowledge they have had imparted to them is not complete, and that there is always more to learn and pass on within their discipline. To learn, doctors have to be ready to question their established practices and beliefs, and to recognize the possibility of really different ways of treating diseases. To pass on research results, doctors have to be able to communicate with their peers. Research means detailed and disciplined work. Research projects have to be planned and carried out, and their results disseminated. Patients, who would far rather not be treated as guinea pigs, have to be encouraged to want to help. Doctors may risk losing patients to colleagues who do not ask them to take part in research programmes. Doctors who do undertake research need to remember that even in the midst of a research project their patients still require their best interests to be served, and that those interests come before the successful completion of a project, should there be a conflict. Enthusiasm for reaching the goals of research should not make doctors view their patient participants merely as 'good clinical material'.

Patients have to recognize that if medical care is to continue to improve then they must play their part too, and allow their treatments to be offered as part of research programmes, if that is the best way to ensure continuing improvement. If research is well designed then their treatment should not be inferior, but they may have to accept that a computer, not a doctor, will allocate the treatment they receive, so that the doctor's bias is factored out and the results of the research are more reliable. Patients have to understand that, if their doctor says that she does not know which is the best treatment for their condition, but that they can participate in a trial to help find out, she is being a better doctor than the one who wrongly claims absolute knowledge, despite the (false) security conveyed by the second sort of doctor. If the doctor then goes on to suggest that her patients participate in a trial to help discover which treatment is best, the patients have to believe that their doctor has not suddenly transformed from a genial do-gooder to a sinister researcher in a white coat who from now on will not consider them as human beings. That is a big step for many people, who shudder at the thought of human subject research. The staff member at King's College, London, who used to serve our lunch when I was running courses called 'The ethics of research on humans', said as much. 'I saw the posters for your course,' she told me. 'It looks *horrible*.'

Such gut reactions are probably typical. They reflect the perception that being a good and caring doctor and being a good researcher simultaneously is not possible. They also indicate a lack of understanding of the need for

medical research to underpin good doctoring. But the King's College staff member could be the next patient in hospital eligible for enrolment in a research project. If her autonomy is to be respected, she is going to need to be fairly persuaded that the research is worth doing, and can be done in an ethical way.

This book is not written for the staff member, but the concerns that lie behind her shudder are where the ethics of research on humans are located. So although some might argue that medical research needs no justification, I would like to consider first of all the reasons why medical research has to be undertaken, and then go on to the question of how it can be done ethically.

What is the value of research?

Those who support the need for research argue that no new treatment should be offered outside the context of a controlled trial, so that the treatment's effectiveness and efficacy can be measured *ab initio*, not only for the sake of the patient receiving it but also for future patients. This view entails that patients should by custom and practice also be experimental subjects. Few would rather be a guinea pig than the recipient of tried and tested treatment, but the proponents of clinical trials point out that even an established treatment which is given outside the context of a trial is more often than not untested and unproven. Hence patients receiving it are, *de facto* if not *de jure*, guinea pigs in a uncontrolled trial whose outcomes are not being measured consistently.

Baum (1986) explained that the surgeon who carries out mastectomy for early breast cancer for 10 years and then switches to lumpectomy for the next 10 years, because custom and practice have changed, is in fact conducting a research project involving 'haphazard allocation'. The surgeon's patients are not receiving the best known treatment, they are receiving the treatment that she thinks is best on the basis of unreliable data. Because the surgeon is acting solely in what she believes to be the best interests of her patients, and her intentions towards them are unmixed with the desire to gain knowledge which will not be of direct benefit to them, the ethics of her behaviour have not, in the past, been openly questioned.

On the other hand, the surgeon might undertake a properly designed controlled trial, in which half her patients were chosen randomly (a technical word which means that patients' treatment is determined by the equivalent of tossing a coin rather than anyone's deliberate choice) to receive mastectomy and half to receive lumpectomy. If she then compared the treatment outcomes for each group, she would produce objectively convincing evidence for which of the two treatments is the better, instead of continuing in uncertainty or, worse still, thinking she knew which was better when she did not.

Whilst few would deny the need to demonstrate greater certainty than subjective observation allows, the attitude of the surgeon to the individual patients in the trial might nevertheless then be open to rebuke, because arguably she is not doing her best for each one, but treating each as a means to her own end: that of answering the question of whether mastectomy or lumpectomy is the better treatment for early breast cancer. However, Baum would argue that in fact the surgeon *is* doing the best for each of her patients because she is offering a 50% chance of receiving the best treatment, *whichever it is*. Since she does not know for certain which is better, it would be wrong for her to offer treatment in any other way than randomly (understood in its technical sense). If she switched to lumpectomy, without finding out for certain whether it was the better treatment, she might be exposing her patients to unknown risks and uncertain benefits. Hence, for the surgeon, putting her patients into such a trial means they are better off than if she offered just one of the two treatments.

The treatment for childhood leukaemia and the side effects of diethylstilboesterol are examples of why research is so important. For some decades in the UK, research into treatments for childhood leukaemia has been organized nationally, so that most children presenting with leukaemia will (with their parents' consent) be randomly allocated either the latest proven treatment or the latest novel and experimental treatment. As a result of this collaborative and carefully orchestrated activity, treatment for leukaemia has moved from being mostly unsuccessful to being 50% successful, in that mortality from the condition has dropped from 100% to 50%. The story of treatment development for leukaemia is an astounding success, from the point of view of its consequences. It has not been the result of some single, radical discovery like that of penicillin, which brought about a complete shift in the paradigm of treatment of those diseases which antibiotics can cure. Rather, it took, and continues to take, painstakingly small steps that have inched forward over years. Had such careful research not been conducted, successful treatments for leukaemia may have been developed, but, as Baum would argue, the discoveries would have been haphazard, subject to chance, and unlikely to have been received into the generality of practice so readily, since their efficacy would not be proven in the eyes of others.

Diethylstilboesterol was first synthesized in 1938 and administered to several million pregnant women to prevent spontaneous abortion and premature delivery (Dodds et al., 1938). Much later, in the 1970s, a group of doctors noticed a connection between the mother's exposure to the drug and the likelihood of her child, if female, contracting vaginal cancer (Noller and Fish, 1974). Now there are indications that the cancer risk is not so great as the 1970s observations indicated (Hatch et al., 1998). If the drug had been introduced by means of a properly conducted randomized controlled trial, with follow up of the patients in the trial, the questions about cancer would

have been discovered by the 1940s or 1950s at the latest. Because the drug was administered in an uncontrolled fashion, risks were only noticed much later on by chance observation and linking of factors in the women concerned, and even then they were not properly quantified.

What are the limitations of research?

Black warns against a ‘total surrender to the scepticism that is theoretically demanded by the scientist’ (1998). Some aspects of medicine are inappropriate for the researcher to question. Black argues that although there is a growing minority of situations in which scientific medicine ‘makes all the difference between a cure and a disaster . . . we should keep in mind that they are still, however important, only a small part of the whole province of medicine, and that we have a “duty of care” as well as a “duty of cure”’. He quotes Robert Platt:

However far the science of medicine and of surgery advances, the art of medicine will remain: the art of first identifying the patient’s problem (which is something more than merely diagnosing his disease) and the art of applying the science to the need of the individual patient. (Platt, 1972, p. 27)

Imagine a patient who presents his medical problem to his doctor, and asks her to do what is best for him. This doctor is persuaded of the reliability and desirability of randomized controlled trials. Armed with data, she explains the treatment options for her patient’s condition, their probable success rate and the statistical likelihood of unwanted side effects. However, the patient, instead of considering in a scientific way the relative merits of the options in front of him, repeats his question, asking the doctor to do what *she* believes is best for him. The patient trusts in and wants his doctor’s feelings and intuitions about himself in particular, not numbers and risk percentages for people who are like but not him. The doctor, unless she has trained herself to be mechanical in her response to her patients, is unlikely not to have such feelings and intuitions. Now the proponent of the randomized controlled trial will argue that unless knowledge is generated from the controlled situation of a trial, it is unreliable and should be ignored. This view underestimates what Black would call the ability and tendency of clinicians to work on a balance of probabilities, to which I would add their capacity for responding in detail to precisely what is in front of them. There are all sorts of differences between patients that may have important implications for the kinds of treatments they should receive. These differences may or may not be commensurable. The controlled trial may be capable of counting them in, or it may need to factor them out by means, *inter alia*, of randomization and sample size. Other kinds of research methods may be employed to measure

the less quantifiable aspects of the medical encounter, and these will be discussed elsewhere. But the fact remains that nothing can replicate precisely *this* encounter. Hence, the doctor in the example *should* bring her intelligence, intuition and experience to the particular patient in front of her.

It would be reasonable to combine both the science of medicine and the art of it as ‘interwoven activities’ (Black, 1998). Doctors need to know what research has discovered and then apply it to individual cases as they think fit, trusting in their intuitive responses, but also testing them against good empirical data to ensure they have not wandered off track in any way. Good doctors would be expected to know the relevant data gathered from well-designed, reliable research, and also to respond fully to the individual patients in front of them.

Of course, if doctors are to use data which are reliable, the research which generates them needs to be scientifically sound. There are a number of problems with this, and numerous possible solutions, because different research questions need appropriate methods for answering them. Finding out whether a particular drug lowers patients’ blood pressure will require one kind of method; finding out how the drug affects patients’ quality of life will require another. Debates persist over the extent to which different research designs are capable of producing reliable answers. Some designs rely heavily on subjective interpretation, for example. This sort of method is regarded with suspicion by many doctors. The issue is significant because the purpose of research is to produce data that are widely accepted. If a doctor goes to the trouble of conducting a research project whose results are disregarded because nobody thinks the study was properly designed, her endeavour, and all the resources it used, is wasted.

What is the right way to treat human research participants?

Dealing with such scientifically thorny questions as what constitutes reliable evidence would be difficult enough if the research subjects were, say, plants. But they are human beings, often patients, who must be treated with due respect. I have already moved away from the theoretically simple perspective of Baum and others, in which, provided there is genuine uncertainty about different treatments, the most appropriate treatment for a patient would be that which was allocated to him within a clinical trial. For, if doctors’ proper care of their patients consists of more than a machine-like response to symptoms, then more will be required of them than just to be in a state of uncertainty about treatments before routinely offering them as part of a randomized controlled trial. Their duty of care includes taking into account each individual patient, towards whom, as I have suggested, doctors will have quite specific responses, inappropriate to blind allocation of treatment. It is

the suggestion that the controlled trial removes this latter aspect of the doctor's duty of care that gives people in general a feeling of discomfort about, or even fear of, the notion of being research participants or of doctors being researchers, using their patients as their guinea pigs. It can be argued that by comparison with what is on offer outside the context of a clinical trial, being a participant in a trial is by far the preferable option (Chalmers, 1994). But that does not make the fact of becoming a statistic rather than being recognized as an individual any more desirable.

The problem is made more acute by the observation that the scientific validity of the trial, that is, its capacity to yield reliable results, *depends* upon a mechanical method of allocating treatments. In recognition of precisely this natural tendency of doctors to have specific responses to individual patients, the process of random allocation of treatments within trials has been made 'doctor-proof'. It used to be the case that doctors participating in research would be given a series of sealed envelopes, and asked to open them in turn as each patient presented for treatment within the trial. The envelopes would contain instructions as to which treatment should be offered, and the envelopes were randomized. Doctors would, notoriously, open the next envelope for the next patient, decide that it was not the best treatment for this patient, and keep on opening envelopes until the treatment instructions inside accorded with their idea of what this particular patient needed. Most randomized controlled trials now use a computer to allocate treatment, and participating doctors will be required to telephone a study centre as each patient in the trial presents, to be told by a computer which is the treatment to be allocated. For one of the purposes of random allocation is to erase all possibility of the results of the research being arrived at by virtue of a doctor's bias. But which patient is going to be happy for a computer to 'choose' his treatment rather than a doctor? A qualitative study of parents of children in the national extra corporeal membrane oxygenation (ECMO) study found this attitude amongst parents interviewed:

They [the parents] said they could not understand how a decision could be based on only a name, but also had problems when they considered the possibility that the computer had the information about their daughter's case. To them, she clearly needed treatment other than the conventional care she was receiving and with her details to hand it was incomprehensible that she was not given ECMO. They felt the computer had made the wrong decision. (Snowdon *et al.*, 1997)

It could be argued that the patients' feelings about how treatments are allocated in a trial can be set aside if the doctors are satisfied that the method works in the best interests of their patients. If a doctor is for any reason unhappy for her patient to be randomly allocated a treatment then the patient should not be invited to enter the trial. Hence, the problems with blind allocation might only be found within patient perceptions and not in

reality. The problem would therefore be solved by better communication with patients. That doctors are clear in their own minds about when patients are eligible for either treatment and therefore for the trial is belied by the envelope problem. However, this too may be an issue to do with doctors' misperceptions in that they too may believe wrongly in the efficacy of a particular treatment, or its benefit for a particular patient.

These observations hang upon certain assumptions about the objective reality of treatment success and the part that attitudes and beliefs of both doctors and patients have to play in the healing process. Randomized controlled trials have been useful because they can factor out both doctors' and patients' attitudes and beliefs. Because of random allocation, it does not matter whether the patient or the doctor believes the treatment will work. It will work objectively, or not at all. The question then remains whether successful medicine is dependent only on objective factors, or whether beliefs play their part as well, or, even, whether the willingness to accept objective factors depends upon prior beliefs. For example, is it necessary that a patient should have faith in his doctor for the doctor to be able to help him at all? At a minimum level the answer must be yes, because why otherwise would her patient seek and then act upon her advice? Suppose, then, that research was able to establish objectively that some medicines were better than others, but that in the process of establishing that fact – in the process of research – patients lost their faith in the medical profession because of the constant use of computers to allocate treatment?

Arguably, then, there is a dilemma: while the results of research are needed because they should form part of any good doctor's decision-making process, the means by which that information is obtained presents ethical problems. Although it is possible to show that the treatments offered within a controlled trial are the best available, what is lost is the individualized care, which was described earlier as an essential complement to the scientifically supported knowledge of appropriate treatments.

How can research participants' views be respected?

The case is made more complicated if it is considered that the ideal, individualized encounter between patients and doctors ought to include due consideration, not only of each patient's clinical condition, but also of his own thoughts, feelings, concerns and beliefs about both the condition and the proposed treatment. Random treatment allocation ensures that patient bias as well as doctor bias is factored out as a cause of the results of the research, since by the same 'coin-tossing' chance the patient's views on which is the treatment of choice are discounted.

Perhaps, however, instead of complicating the matter further, the intro-

duction of the wishes and needs of individual patients is a way out of this *impasse* between the scientific need to generate unbiased data, and the doctor's duty to respond sensitively to each individual. Suppose that patients actively wish to participate in research? Provided that their wish is based upon adequate information and is freely made, it could be argued that doctors then have no right to override them. The matter becomes one of patients' right to self-determination; doctors need only ensure that the patients have sufficient information and then leave them to make their own decisions. If the problem of the ethical acceptability of research is shifted on to the shoulders of the research subject, I have, arguably, retained the individually tailored response, since it is precisely an individual choice whether or not to take part.

However, by suggesting that the ethical question is answered by passing it on to the patient, the issue has been fudged. All the patient is agreeing to is treatment allocation by chance, which, after all, is all that the doctor was accepting. The individual choice of a particular treatment is still not being made. Moreover, there is always the danger that patients will agree, not because they think it is the right choice, but because their doctor has asked them, and they believe their doctor has their best interests at heart. The extent to which the patients' consent could be called an *informed* choice is, therefore, brought into question. Again, we are faced with the possibility that conducting research on humans is unethical, this time on the grounds that the right of individuals to self-determination is not being honoured. Arguably, then, research has not only brought into question the doctor's duty of care, but also the validity of patient consent.

Three areas of ethical concern in research: science, best interests and autonomy

In the foregoing discussion of the sorts of moral concerns that issue from research on humans, three broad areas have been looked at. The first is in the realm of what is necessary or valuable research, in terms both of its goals and of whether its methods will achieve the goals reliably. The second area concerns the doctor's moral obligation to do the best for her patients, understanding that to be not merely producing a textbook response but tailoring treatments to particular individuals. The third area lies in the realm of considering the wishes and needs of patients and potential research participants, who have rationality to be respected and benefits to gain or lose by virtue of their participation in research, about which only they may know.

These are the three areas on which the ethics of a research project will hinge. Therefore, if we want to be able to tell whether any given research project is ethical or not, we need to be able to analyse it by reference to these

concerns. In order to do that rigorously, we have to understand why these are the relevant areas of concern, so that we can have confidence in our conclusions. For the same reason, we also need to know how to conduct the analysis.

The three areas of concern about research on humans relate to three important moral theories. The concern with the scientific validity of a research project is related to morality which is teleological (from the Greek *telos*, meaning 'end, purpose'). That is to say, it is predicated on the notion that an action is justified by its results. The second concern, which is about the duty to care for a research subject's welfare, is related to one kind of deontological moral theory (from the Greek *deon -ontos*, meaning 'to be necessary'), which states that the moral agent owes people duties. The third area, concerned with the research subject's autonomy, is related to another kind of deontological theory, which states that the moral agent must respect people's right to self-determination.

Now some would propose that only one of these theories is necessary to make moral decisions. It could be argued, for example, that all that is necessary to decide whether an action is morally right is that its consequences maximize happiness. Or one might decide that all that is needed is to obey some sound principles of duty. Or one might think that, as long as my actions accord with the wishes of those most affected by those actions, then they are morally acceptable. But we have already discovered that the moral questions which arise in the context of research call upon all three of these theories. This means that they all have to be taken seriously, and we have to be able to make them work in combination, or know what to do if they come into conflict.

I therefore propose to investigate each of the moral approaches in turn as they have been described by different moral philosophers. We will find that if we try to make any one of them a comprehensive moral ideal, it will fall short. Taken in combination with the two others, however, a more robust way of making moral decisions emerges. But in so doing, it is necessary to distil from each approach that in it which is useful for the purpose of analysing the ethics of research on humans. I have given my distillation of the three approaches titles which are borrowed from Ronald Dworkin (1977, pp. 168–77), who used them in respect of political philosophy. The titles were successfully adapted to moral philosophy and medical ethics by Sophie Botros, who also applied them to the ethics of research on humans (Botros, 1992).

- (i) **The goal-based approach, also known as consequentialism.** Moral theories which work from this perspective judge an action's moral worth by its predicted or actual outcome. The goal at which the action is aimed provides the moral determinant for the action itself. No consideration is given to the question of whether the contents of the action are morally right. Absolute consequentialism is inappropriate for ethical research, but concern with the validity and importance of the research

question, that is, its goals, is appropriate. I will call this part of the ethical enquiry *goal-based morality*.

- (ii) **The duty-based deontological approach.** Moral theories based on notions of duty proffer rules of conduct related not to the goals at which actions are directed, but to the nature of the actions themselves. An example of such rules is the Ten Commandments (Exodus 20.1ff). The moral justification for people's actions is determined by the extent to which they adhere to the rules. Duty-based deontological theories have weaknesses, but they provide a counter-balance to goal-based arguments that can sometimes be compelling. In considering the ethics of research, the duty-based issues arise in relation to the way the research is conducted, rather than what it is trying to achieve. Rules such as not harming the research participant will apply. These sorts of considerations can be called *duty-based morality*.
- (iii) **Right-based deontological moral thinking.** There are many theories of rights, and the language of rights has become common in medical ethics as a counterbalance to overly paternalistic notions of the doctor's duty. For our purposes, the right with which those who conduct research on humans should be concerned is the right to self-determination, or autonomy. Its practical application is to ensure that research participants' consent is sought and their confidentiality respected. This approach can be called *right-based morality*.

This series of moral approaches will provide three distinct perspectives from which to consider the ethics of research, which we will need to be able to combine, for, in practice, every research project will need to be investigated in the light of all three. The combination should produce a systematic approach to deciding what makes research ethical. It should also produce conflict, in that it is not always possible to give equal weight to all three. What to decide in those circumstances is the principal challenge of the ethics of medical research on humans, and forms the basis for the idea that some research is simply unethical. Separating out the different parts of the ethical assessment should make it easier to establish which moral concerns need to take precedence in individual research proposals.

Identifying these moral perspectives, and showing how to use them in the context of research, will hopefully be of assistance in your own moral thinking about research. The issue to be addressed is, ultimately, whether any research project is ethical or not. But if it is to be addressed in a sound and reasonable way, then a prior question has to be answered, which is: What must I take into account if I am to come to a proper decision about whether this research is ethical? This book should provide you with the answers to the latter question, so that you can answer the former yourself.