Informed consent in medical research

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Abstract – That people should only be enrolled in medical research if they have given free and informed consent is now an unquestioned principle of research ethics. It is however a recent innovation. Prior to the prominence given to consent to participation in research in the condemnation of German doctors arraigned at Nuremberg in 1945, informed consent had appeared in American litigation, but only as an issue in clinical malpractice suits. Informed consent as an ethical requirement in medical research had arisen in some earlier European contexts. Despite the Nuremberg judgement, informed consent by participants in research was not widely recognised as ethically mandatory until the early 1970s. This delay seems to have been due in part to scepticism about the practicability of truly informed consent, but medical paternalism and the circumstances surrounding military research during the Cold War period may have contributed.

Key words: CPD, consent, ethics, Nuremberg Code, research

The world changes, and each succeeding generation believes itself the custodian of ultimate moral truths that predecessors failed to grasp through perversity or ignorance. Yet to treat as eternal verities customs and values that are no more than creatures of fashion or consequences of accident displays a lack of historical humility. The ideal of British virtue would be very different today if Constantine had lost the battle of the Milvian Bridge, Vienna had fallen to the Turks or Hitler had won the Second World War. Such things may be divinely ordained but, on the other hand, they may not. Whigs and Americans may believe in the inevitability of moral progress, but the quizzing glass of European history can reveal one generation's 'progress' as another's 'decadence'. Moreover, the history of ideas, like that of wars and politics, is written by the victors; it is only when the vanquished have been dragged from the field that we can be sure which side was in the right.

The principle that human subjects of medical experiments should be required to give informed consent is now firmly established in medical ethics. This is a recent development and there are researchers now living who carried out some of their work in an earlier and less explicit ethical framework. Should they be condemned for not recognising a need for informed consent from their subjects? A first step in answering this question is to characterise the earlier framework.

Informed consent in the literature

This review, necessarily selective and restricted to published sources, is primarily concerned with ill people but does not systematically distinguish between research on patients and on healthy volunteers. The distinction is made much of by some ethicists, partly because treatments can rarely follow the rigidly predefined protocols of research and partly, perhaps, to make permissible the therapeutic deceptions and half-truths sometimes needed in the compassionate practice of medicine. The distinction is also important to pharmaceutical companies who offer only expenses to patient-volunteers in drug trials but have to give worthwhile recompense to healthy subject volunteers. However, the border between treatment and experiment is not always distinct, and the essential distinction determining whether any special qualities of a doctor-patient relationship can be invoked does not depend merely on the health of the participants, but also on whether the experimental intervention is one from which the unhealthy participant might personally and directly benefit. Some of the experiments on hospital patients summarised by Pappworth in his book *Human guinea pigs*[1] were only remotely connected with their illnesses.

Faden and Beauchamp[2] comment that, although

Key Points

- **An ethical need for informed consent from participants in medical research was recognised in the 19th century**
- **The Nuremberg Code stipulated the need for such consent in 1945**
- **For more than 25 years this stipulation was largely ignored in the UK and the USA**
- **Reasons included scepticism and fear that it would inhibit research**
- **The Medical Research Council and the Royal College of Physicians were instrumental in establishing informed consent as mandatory in medical research**

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consent to treatment has been an ethical and legal issue from the 19th century, largely in the context of allegations of malpractice, informed consent in medical research became an issue in the USA only following the Second World War. This was partly because little non-therapeutic research took place earlier and partly following the revulsion at the experiments performed by Nazi doctors on residents of concentration camps.

Early references to informed consent

There were earlier references to the issue in Europe. In 1891, the Prussian Minister of the Interior issued a directive to all prisons that tuberculin for the treatment of tuberculosis must not be used against a patient's will. In 1898, Dr Albert Neisser was fined by the Royal Disciplinary Court of Prussia for not seeking patients' consent for his experimental studies of 'vaccination' for syphilis. This led to a directive from the Minister for Religious, Educational and Medical Affairs to all hospitals and clinics that medical interventions other than for diagnosis, healing and immunisation were excluded in all circumstances if the participant had not given his or her 'unambiguous consent' after a 'proper explanation of the possible negative consequences' of the interventions[3].

In responding to a specific enquiry in 1907, William Osler endorsed the necessity of informed consent in medical research (he had expressed a similar view in the USA nine years earlier). He asserted that to experiment upon man with possible ill-result was:

> *always immoral without a definite specific statement from the individual himself, with a full knowledge of the circumstances*[4].

The Health Department Regulations of the German Reich 1931 stated that both human experimentation and the use of novel treatment required consent 'in a clear and undebatable manner'[5]. This regulation was not repealed under the Third Reich, but the concept of 'human' became ideologically restricted.

Following the Nuremberg trial of 23 doctors accused of improper experiments on human subjects, a 10-point code was drawn up by the American judges presiding over the military tribunal. The first principle stated:

> *The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. The latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment. The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs, or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity*[6].

Although much cited in the last 30 years, the Nuremberg Code seems to have had little influence at the time. Joseph Gardella, Assistant Dean of the Harvard Medical School, is quoted as rejecting in 1961 the applicability of the Nuremberg Code to medical research in the USA:

> *The Nuremberg Code was conceived in reference to Nazi atrocities and was written for the specific purpose of preventing brutal excesses from being committed or excused in the name of science. {It} is not necessarily pertinent to or adequate for the conduct of medical research in the United States*[7].

Professor Paul Beeson (of Yale and the University of Oxford) noted in 1964:

> *I think we must read the Nuremberg Code in reference to the conditions under which it was written. This is a wonderful document to say why the war crimes were atrocities, but it is not a very good guide to clinical investigation which is done with high motives*[8].

Beecher noted in 1966:

> *A far more dependable safeguard than consent is the presence of a truly responsible investigator*[9].

Certainly, it seems from the many experiments quoted by Pappworth[1], and apparently carried out without informed consent, that investigators in the USA and Britain did not see the principles of the Nuremberg Code as applying to them.

None the less, following the publication of the Nuremberg Code, the American Medical Association defined three principles for human experiments[10]:

1. The voluntary consent of the person on whom the experiment is to be performed must be obtained.
2. The danger of each experiment must be previously investigated by animal experimentation.
3. The experiment must be performed under proper medical protection and management.

It has been suggested – with some credibility – that these principles were defined at the behest of Dr Ivy, chief prosecution witness at Nuremberg, who had claimed that they were already in virtual existence as a basis for ethical research in the USA before the time of the trials. This was necessary to rebut the Nazi doctors' defence claim that they had done nothing that was not common practice in the USA. (The emphasis was on practice in the USA, as the other victorious powers, the UK and France, who had acted as prosecutors in the earlier Nuremberg trials of war criminals, did not take part in the Nuremberg trial of doctors.)

Experimental medicine post-war

Some indication of the attitude of practitioners of experimental medicine to informed consent in the UK in the immediate post-war period is revealed in RA McCance's President's Address

to the Royal Society of Medicine Section of Experimental Medicine and Therapeutics in 1950[11]. He comments that, although 'patients provide the problems', 'it is often much more satisfactory to work on normal men and women'. While:

no experiments can be carried out on a healthy colleague without his co-operation and consent … many experiments, even quite elaborate ones, can be made on patients, within the therapeutic routine of the hospital so to speak, without anyone thinking anything of it.

However:

if the experiment is more elaborate and demands considerable co-operation, the investigator may feel it desirable to ask the patient for his 'permission'.

The inverted commas around 'permission' are McCance's. Later we read:

the investigator can only tell the patient in very general terms what his experiment will involve, explain the nature of the risks and ask for his co-operation.

No doubt ...

– McCance stated –

the practice differs from one hospital to another, but the principles just outlined about 'permission' seem to hold generally throughout this country.

The whole atmosphere of trust would be destroyed if patients had to be asked to fill in a printed form of consent for experiment as they are as a rule for an operation.

The Medical Research Council Memorandum

The first essay at a formal statement on medical research ethics in the UK appears to be a memorandum by the Medical Research Council (MRC) in 1953[12]. This has a virtue in focusing not on such egregious examples as presented at Nuremberg but on the realities of well-intentioned research in a civilised society. It drew attention, for example, to the 'apprehension' that a patient may feel in response to novelty in medical care. It required that the justification for the use of a new procedure on a patient has 'in his case … been made amply clear to him'. The document goes on to comment that:

to obtain the consent of the patient to a proposed investigation is not in itself enough.

The investigator must take personal responsibility since the technicalities of the proposed investigation may be such that the participant may not fully understand them. The memorandum called for the practice and attitude of investigators to be 'irreproachable'. It also called for critical discussion by informed investigators in each field to:

form a body of opinion of what is necessary, desirable and justifiable to guide investigators in their field.

The memorandum enjoined editors and editorial boards to ensure that anything they published should satisfy appropriate requirements, and to report this to be the case so that the reader would be left in no doubt. Finally, the MRC declared its belief that no single body, including itself, could be competent to provide detailed guidance, given the high degree of specialisation in clinical research, but acknowledged a responsibility to ensure that the practice of all the workers it supported should be unexceptionable.

This memorandum was circulated to medical members of staff, research workers in receipt of MRC support, deans of medical faculties, secretaries of medical societies and editors of relevant journals. Although annotated as 'strictly private', the memorandum seems to have become more widely known, being cited by Beecher in 1959[13] and 1966[14].

The principle of ethical standard setting by peer review was endorsed in the MRC memorandum, but it expressed scepticism about the practicability of a single ethical authority. It seems that there was no other ethical authority to look to for guidance, despite awakening concern over ethical aspects of research being carried out in British hospitals. In 1955, there was a parliamentary question about an experiment comparing the effects of two different preparations of penicillin on babies carried out in Bristol without parental consent being sought. In response, the Minister of Health (Iain Macleod) conceded that:

where a clinician intended to undertake an investigation which was so unusual and novel as to amount to an experiment, he would be wise to seek consent from parents or patient

– but it was not the Minister's duty to lay down what ethical and medical principles should govern the conduct of professional men in the work they undertook in hospital[15].

Following this parliamentary interchange, an editorial in the *British Medical Journal*[16] drew attention to the dangers to 'the traditional mores' of the medical profession of too strong an 'influence of the laboratory' leading to doctors looking upon patients as 'experimental material'. It seems that some guidance was also issued by the British government. In 1962, in a written reply to a parliamentary question about the conditions under which medical experiments were carried out, and to what extent they were carried out without consent, the Minister of Health (Enoch Powell) stated that guidance on the subject had been given to all hospital authorities in January 1959[17]. He thought there was no reason to suppose that the guidance was not generally observed.

In 1962, an issue of the journal *Twentieth Century*, dedicated to the NHS, contained an article by MH Pappworth listing some reported experiments that the author thought probably unethical[18]. This provoked widespread comment in the national press. The *British Medical Journal*[19] commented that:

general exhortation, letters in the press, and questions in Parliament seem to have had little restraining effect on those who cannot always understand the difference between guinea-pigs and human beings ...

The same issue of the journal printed a provisional English draft of what was to become the Helsinki Declaration; this included a requirement of informed consent[20].

Clear and authoritative guidance on ethical standards in medical research entered the public domain in the UK in 1964.

The MRC included a section on responsibility in investigations on humans in its 1962–63 report[21]. This quoted extensively from the 1953 memorandum, but distinguished between procedures contributing to the benefit of the individual and those not of direct benefit to the individual. In the first case, the normal requirements and responsibilities of the doctor-patient relationship apply:

> *That it is both considerate and prudent to obtain the patient's agreement before using a novel procedure is no more than a requirement of good medical practice.*

There were also comments on the use of controls, emphasising that:

> *in general, the patients participating in (controlled trials) should be told frankly that two different procedures are being assessed and their co-operation invited.*

Certain exceptions were conceded, but the ethical issues raised were of such gravity that the Council concluded that controlled clinical trials should always be planned and supervised by a group of investigators and never by an individual alone.

The report dealt with 'procedures not of direct benefit to the individual' as a separate category. With regard to such procedures, the Council commented that participants must be volunteers 'in the full sense of the word'. True consent must be explicitly obtained and has to be:

> *consent freely given with proper understanding of the nature and consequences of what is proposed.*

The problem of undue influence is recognised, with mention of the specific instances of patient with doctor and student with teacher. The Council expressly rejected on legal grounds the possible utilitarian argument that the benefit of mankind from research could override the rights of an individual to be protected from harm. This repudiates implications in both the Nuremberg Code and the Helsinki Declaration that some kind of moral equation might link benefit to mankind with disbenefits to individuals taking part in experiments. In its concluding paragraph, the Council expressed the view that the head of a department where investigations on humans take place has an:

> *inescapable responsibility for ensuring that practice by those under his direction is irreproachable.*

Again, the MRC emphasised the duty of editors to ensure that only those reports of research specifying that appropriate procedures have been followed should be published.

These MRC recommendations on the ethical aspects of human research were reproduced in both the *British Medical Journal*[22] and the *Lancet*[23] of 18 July 1964. The *British Medical Journal* noted it as:

> *a statement on investigations in human beings which is intended to serve as a guide to medical men engaged in this kind of work.*

– 'men', it is assumed, was intended to include women.

The Helsinki Declaration

Also in 1964, the first full English language version of the World Medical Association (WMA) Helsinki Declaration appeared, and was published alongside the MRC report in the *British Medical Journal*[24]. The WMA differs from the MRC in implicitly endorsing the moral relevance of a possible trade-off between risks to the participant and 'benefits to the subject or to others'. The Declaration emphasised the need for informed and explicit consent from healthy volunteers and also 'if … consistent with patient psychology' from patients taking part in research. Later revisions of the Helsinki Declaration have included a requirement for independent research ethics committees but this was not in the 1964 version.

The Royal College of Physicians Report

In 1967, the Royal College of Physicians (RCP) published the report of a committee on the supervision of the ethics of clinical investigations in institutions[25]. The report concluded that:

> *the competent authority {has} a responsibility to ensure that all clinical investigations carried out in its hospital or institution are ethical and conducted with the optimum technical skill and precautions for safety.*

This responsibility could be discharged by each institution requiring a group of doctors, including those experienced in clinical investigation, to 'satisfy itself of the ethics of all proposed investigations'. This conclusion and recommendation were endorsed in May 1968 by the Ministry of Health in a circular letter[26], which included a copy of the College report, to regional hospital boards, hospital management committees and boards of governors. A further report from the RCP committee in May 1973[27] was prompted by a request from the Chief Medical Officer for advice, *inter alia*, on:

> *the inadvisability or otherwise of giving all patients in a controlled trial a frank explanation of the experiment or to obtain their consent* {sic}.

In response, the report distinguished research not expected, or not intended, to benefit the individual from that intended to benefit the patient. In the latter case, although consent should ordinarily be sought, ethics committees might decide, using 'particular care', that in certain circumstances it would be inappropriate or even inhumane to require consent. In non-beneficial research, however:

> *a full explanation of the proposed procedure should be given, and the patient must feel completely free to decline to participate or to withdraw at any stage.*

The recommendations of this report were endorsed by the Department of Health and Social Security in June 1975, and circulated with a copy of the report to regional health authorities, area health authorities and boards of governors[28].

Doubts about informed consent

As already observed, the requirement for informed consent embodied in the Nuremberg Code was not immediately and

universally accepted by medical researchers. The literature suggests that there were three reasons for the belief expressed by American researchers that the Code did not apply to them:

1 *That no researcher in America would expose people to the severity of hazard or discomfort involved in the concentration camp experiments that were the subject of the Nuremberg Code.*

Such faith proved misplaced, as revealed by the notorious scandals of the Tuskegee study (in which black people with syphilis were left untreated and uninformed of their disease) and the Jewish Chronic Disease Hospital (where live cancer cells were injected into elderly indigent patients)[29].

2 *That truly informed consent may never be achievable.*

This was made explicit by Beecher[14] and echoed by Ingelfinger[30]. While facts and probabilities can be communicated, the meaning of those facts and probabilities will usually differ for a researcher and for a potential participant. The latter's best interests were better invested in the judgement and benevolence of the medical researcher.

3 *That a requirement for consent might impede or even totally prevent research.*

Gardella[7] expressed doubts about the practicality of informed consent:

> *The quality of the subject's consent depends … on an interpretation … of a factual situation which will frequently be complex … Moreover, being asked to sign a somewhat formal paper is likely to provoke inquiry in the subject {ie patient} who can but wonder at the need for so much protocol.*

Further examples can be found in the panel discussion at Yale[8] in which contributors clearly feared that truly informed consent would result in nobody being prepared to take part in research.

This objection becomes an objection only if linked to a belief in the necessity for research, and has the implication that actual or potential harm to a few experimental subjects might claim lower moral precedence than the potential benefits to a larger number of people. The argument that, at least in some circumstances, the latter may carry more weight than the former is often referred to as 'utilitarian'. In rejecting the argument, the MRC was in a tradition identifiable at least as far back as Claude Bernard in 1856:

> *The principle of medical morality consists, then, in never performing on man an experiment which could be harmful to him in any degree whatsoever, though the results may be of great interest to science, that is, of benefit to save the health of others*[19].

War is a circumstance in which people are encouraged and expected to sacrifice themselves to the common good and where such sacrifice is not necessarily voluntary. During the Second World War, in recognition perhaps of the sacrifice demanded of conscripted combatants, some conscientious objectors were subjects in experiments aimed at identifying minimal intakes of vitamins. One participant was brought to the brink of death from scurvy[31]. It is doubtful if such experiments would be regarded as ethical in peacetime, but the implication that some things otherwise proscribed are permissible in wartime has particular significance for the interpretation of the moral climate of research during the period 1945–89. One conclusion to the Report of the President's Advisory Committee[7] was that issues of consent had normally been observed by American medical researchers prior to 1944, but from then until 1974 a need for consent by experimental subjects was not generally acknowledged. Common usage prior to 1944 is in fact unclear, but it seems that some American authorities who had spoken out strongly against unethical aspects of research prior to 1944 were less enthusiastic about the need or validity of informed consent during the later period. Part of the debate was connected, directly or indirectly, with research funded from military budgets. The American nation still regarded itself as involved in a war, albeit a cold one, so it would not be surprising if some medical researchers considered that wartime ethics should prevail.

The MRC and RCP reports in the UK were perhaps conceived in a climate perceived as peaceful and, in contrast to the USA, military research had a much smaller budget and was almost exclusively carried out in armed services establishments. It is not clear whether the authorities of these establishments received copies of the reports, or would have recognised them as relevant.

Beecher[9] and Ingelfinger[30] had a point in implying that simply listing the 'facts' about an intervention may inform but fail to illuminate. Before the advent of research ethics committees, procedures for achieving informed consent were necessarily unvalidated and largely *ad hoc*. Now they are less *ad hoc* but little better validated. The RCP *Guidelines on the practice of ethics committees in medical research*[32], published in 1984, set out in some detail the procedures to be adopted in search of 'true' and 'informed' consent. There has been no shortage subsequently of additional advice[33,34]. None the less, whatever the formal procedures adopted, doubts often remain about the true comprehension of the participant. For this reason, the conscientious researcher does not seek participants for a study in which he or she would not be prepared to be a subject.

Comment

In a succinct overview of the problem of retrospective moral judgment, the President's Advisory Committee on human radiation experiments carried out in the USA during the Cold War period had first to decide whether, in the pluralistic society of the USA, there was sufficient consensus on moral values to make judgement possible[35]. The same issue arises for the UK. There is obvious and essential merit in a society agreeing an explicit system of values from which ethical implications can be logically derived and embodied in laws and behaviour. Not having a written constitution, the UK's system of values has to be deduced from its history and customs. In broad terms, the system aims at:

> *the freedom of individuals to pursue their own good in their own way so long as they do not attempt to deprive others of their freedom or impair their efforts to obtain it*[36].

There are theocratic minorities in the UK that do not respect this principle, but they have not as yet achieved ascendancy. Mutual respect between individuals is complemented by the lives of citizens being accorded a substantial and equal value in the institutions of the State. It is this ideology that underlies the conventional principles of medical ethics, benevolence, non-maleficence, equity and respect for autonomy. The reciprocity of respect links rights with duties, so that any subsystem of values or ethics subscribed to by professions or social groups that enjoy the privileges of citizenship in the UK must be compatible with and, if the issue arises, subordinate to, national values.

Despite this moral framework, which most British citizens would have accepted from a much earlier period, it is clear that informed consent was not generally acknowledged as an obligation in medical research in the UK until around 1970. We may deplore, but cannot ignore, the evidence that previous to that time indigents and black people in the USA, and non-private patients in the early NHS, were regarded by some investigators as legitimate experimental material whose consent was not an issue. It seems indeed that such people were regarded as to some extent under an obligation to contribute to research in return for free medical care. In addition, there was, and still is, uncertainty over the circumstances in which the potential benefits of research to many people might outweigh inconvenience and risk to a few.

A chief value of the study of history, as sages have averred, is to prevent a nation from repeating its mistakes. It also provides useful insight into the depravities of human nature, among which hypocrisy is always prominent. To understand why what was done in the past may not be acceptable now can be an aid to good behaviour. History may reveal past wrongs deserving present redress, but humility warns that few of us are intelligent enough, and never virtuous enough, to judge the past any more wisely than we shall be judged by our successors.

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