Chapter 22. The Ethics of Research on Humans in the United Kingdom 1939-1989
Dr Alasdair Maclean

22.1. Introduction

22.1.1 The Need for and Nature of Human Research

For Claude Bernard, "an experiment is… just an observation induced with some object or other" [1]. When the experiment is on a human being it involves the researcher influencing the subject's body or environment in a controlled way and observing the effect of the intervention [2]. The justification for research is that we lack the knowledge to be able to predict, with confidence, the outcome of the intervention. Thus, experimentation springs from uncertainty and the experiment is designed to eliminate uncertainty. Although any intervention may be seen as an experiment, treating each one as an isolated experiment results in an uncontrolled and uncoordinated increase in knowledge. This in turn places greater risks on society as a whole because both the harmful and therapeutic consequences – especially those that do not result each time an intervention is made – are less readily linked to the intervention. This kind of ad hoc research risks tragedies; such as the cases of blindness in premature babies resulting from supplemental oxygen therapy that occurred between 1942 and 1952 [3].

By conducting co-ordinated research on a number of persons the effect on each of those individuals can be added together to allow us to predict more readily the effect of the intervention on others. The knowledge gleaned from the experiments on these small groups is then applied for the benefit of everyone. It is because we use this group for the benefit of others that experimentation on humans is particularly problematic. As Charles Fried noted:

"The most crucial ethical issue in human experimentation [is] the extent to which the interests of an individual may be compromised for the benefit of a larger group." [4]

22.1.2. Aims, Objectives, Scope and Sources

The aim of this chapter is to consider the ethics and practice of non-therapeutic research using healthy human volunteers. The ethical principles and practice of therapeutic research will be drawn on. This is relevant because much of the non-therapeutic research was done, or supervised by, doctors who were also involved in therapeutic research. Also, the distinction between therapeutic and non-therapeutic is not always clear and, although ethical distinctions between the two types of research are justifiable, those distinctions provide insights into the basis of the ethical principles applied to non-therapeutic research.

The study is primarily concerned with the United Kingdom (UK), however, because the UK does not exist in a vacuum, the ethical codes and practices from other countries will be considered where relevant. The main period of interest is from 1939-1989 with a particular focus on 1940-1960. The period leading up to 1939 will also be briefly discussed as it will help to set the scene and may explain the prevailing attitudes and practices existing at the start of the study period.

The objectives are to consider the emergence, meaning, and development of eight themes that pervade the ethics of human research. The relationship – and its variation throughout the period - between the principles expressed in the various codes or guidelines and actual practice will also be examined. The themes considered are:

1. The meaning of a 'volunteer', with particular reference to the possibility of undue influence and the implication of a pre-existing relationship between the researcher and the subject:
2. The meaning and implications of consent:
3. The provision of study information:
4. The concepts of harm and risk:
5. The use and acceptability of payments and inducements:
6. The issue of compensating persons injured as a result of the research:
The development and function of ethics committees

The requirement of prior research before beginning research on humans.

Most of the commentaries and codes produced relate to medical research. When human experimentation is referred to it is usually in this context. The sources used in this study, therefore, are taken from this field. In addition to the codes and guidelines, the writings of commentators, both current and contemporary to the period of interest, will be considered. As a guide to practice the British Medical Journal (BMJ) between 1939-1989 was surveyed for commentary on human research. Finally, research publications in the Lancet were sampled. All research papers published in the Lancet in 1940, 1950, 1960, 1970 and 1980 were analysed in attempt to glean information about the changing mores of ethics in practice.¹

This is not intended to be a comprehensive or definitive analysis. Instead, it is hoped simply to provide an overview of the development and application of ethical principles.

22.1.3. Key Terms

It may be worthwhile to begin with a consideration of some of the less intuitive core terms used in the various codes and guidelines.

Therapeutic and Non-therapeutic Research

While all experimentation aims to increase our knowledge and so is of benefit to society as a whole, in some cases the experimenter may also hope to benefit the subject. This type of research, which includes research into the diagnosis, prevention and treatment of disease, is called ‘therapeutic’ research.² Those experiments that are not intended to directly benefit the subject, are called ‘non-therapeutic’.³ For example, experiments on healthy volunteers to investigate the efficacy of treatment for nerve gas poisoning are non-therapeutic. Although the volunteers may benefit in the future from such research (should they become victims of a nerve gas attack), at the time of the experiment participation does not provide a benefit to the volunteer. In this sense, ‘benefit’ refers to the effect of the experimental intervention and is not concerned with any other gain, such as financial reward or the altruistic benefit of ‘having done one’s bit’.

Consent

At the heart of the concept of consent is an agreement. But, consent in this context is more than a simple agreement. Gillon defines consent as:

“A voluntary, uncoerced decision, made by a sufficiently competent or autonomous person on the basis of adequate information and deliberation, to accept rather than reject some proposed course of action that will affect him or her.” [5]

More recently the phrase ‘informed consent’ has been used. This phrase is capable of many interpretations but there are broadly two ways in which it is used. First is the legal doctrine of informed consent which refers to the idea of determining the amount of disclosure by reference to a ‘reasonable’ patient. Since the concern here is with the ethics of human experimentation this sense of consent will not be discussed in any more detail. The other use of informed consent is the tautological ethical use of the phrase popularized by American bioethicists. Beauchamp and Childress define informed consent as:

“An individual’s autonomous authorization of a medical intervention or of participation in research.” [6]
In this context, autonomy means the individual’s freely willed decision based on sufficient information to allow the opportunity to make a rational or reasoned decision.

For consent to grant the investigator permission to use the individual for experimentation, three preconditions must be satisfied. These are:

1. Competence: the subject must be capable of understanding all aspects of the decision. He must also be able to make the decision and, for all practical purposes, must be capable of communicating his decision.

2. Knowledge: the subject must have sufficient information about the proposed intervention in order to make a reasoned decision whether or not to participate. Some would also argue that not only must the subject possess the information, he must understand it. [7]

3. Voluntary: the decision must be the result of a freely made action of the subjects will. It must be made in the absence of undue influence, coercion and deception.

_Undue Influence_

This refers to the excessive use of ‘power’ to overcome the subject’s will. In such a state, the subject is no longer able to make an autonomous decision and any consent would be invalid. The influence that a person has derives from their social position, their relationship with the subject and the degree of persuasion they are prepared to use. While some use of persuasion is acceptable, there is a point at which the individual is no longer capable of saying “no”. It is not possible to say with any precision where this point lies but the law expects the subject to have a reasonable amount of resistance to persuasion.

There are certain situations where the possibility of undue influence is particularly strong. These include where the experimenter is also the subject’s doctor, where the experimenter exists in a hierarchically superior position within a particular institution such as the armed forces, or where the subject is particular vulnerable e.g. where the subject is in prison.

_Coercion_

Coercion is a relatively straightforward form of ‘undue influence’. It is the use of force or the threat of harm in order to influence the subject’s decision. Harm is not restricted to physical injury but includes the loss of any pre-existing right or entitlement. _Coercion_ should be distinguished from an _inducement_, which is the offer of something to which the subject had no prior right or expectation. For example, consider a prisoner serving a ten-year sentence. If he were offered the chance of early release for participating in an experiment this would be an _inducement_. On the other hand, imagine that this same prisoner is up for parole. It would be _coercive_ if the experimenter suggested that his parole hearing would go badly unless he agreed to take part in the experiment. Whether an inducement is morally wrong is a contentious issue and may vary with the circumstances: offering £1000 to a millionaire for his co-operation in an experiment may be seen as unproblematic whereas, offering £1000 to an asylum seeker with a family and no income may be seen as wrong. However, it is debatable whether it is the inducement itself, or the circumstances that make the inducement so powerful, that is wrong.

_Risk_

Risk may be viewed either objectively or subjectively. The objective view of risk is the probability or chance that a particular adverse or detrimental event will occur. Some definitions include the magnitude of the harm as a component. Thus, risk may also be seen as probability x magnitude of harm [8]. Because harm affects each of us differently - the loss of a finger may be worse for a concert pianist than for a footballer – some argue that risk should be seen subjectively, by focusing on the person at risk. The subjective view, which allows for personal and cultural bias [9], highlights how the type and extent of the harm affects the particular individual.
Harm

Jay Katz describes three broad types of harm [10]:

1. Interference with self-determination and privacy: this includes experimenting without the subject’s awareness or agreement and not respecting the subject’s right to control personal information.
2. Psychological injury or detrimental change; for example, the psychological changes risked by experiments with psychoactive drugs (for example, LSD) are a type of harm [11].
3. Physical injury: this includes any unwanted touching, except perhaps those that occur as an unavoidable part of day-to-day life.

Another interpretation is Joel Feinberg’s suggestion that harm occurs when a person’s interests suffer a setback [12].

The Distinction Between Codes and Guidelines

A Code is a set of moral, professional or legal principles. Guidelines offer advice on the policy and implementation of the codes. Codes are generally more directive and more authoritative than guidelines. Because of this, they are usually written in more general terms. Guidelines, which offer more practical advice on how to implement the more general codes, tend to be more specific. Here, guidelines are treated as interpretative documents that allow greater leeway than do the more directive codes.

22.1.4. A Brief Sketch Charting the History of Human Research

Although the foundations of modern science were not laid until the fifteenth and sixteenth centuries [13], “experimentation on humans is as old as that of medicine itself” [14]. Celsus noted [15], with marked disapproval, that Alexandrian physicians – in the third century B.C. – practised vivisection on condemned criminals. Following the fall of the Roman Empire, Arab physicians carried out many experiments testing the effects of drugs on man. Avicenna, for example, counselled that experiments must be done on man because animal testing proved nothing about the drug’s effect on humans [16]. In 1537, driven by a shortage of oil, Ambroise Paré was forced to experiment in the treatment of the gunshot wounds of injured soldiers [17]. In the seventeenth century, experiments were done with blood transfusion [18], and in the eighteenth century, trials with smallpox variolation and cowpox inoculations were performed on humans to try and prevent infection with smallpox [19].

In the nineteenth century, much of the research was performed on the experimenter himself [20]. This practice of self-experimentation became an important ethical principle in determining which experiments could justifiably be performed on others. Despite this increase in self-experimentation, experimentation on others continued. Of note were the syphilization experiments performed, first in France, then other European countries and latterly in Britain. Despite the fact that syphilization had been condemned some 14 years earlier in France, the Norwegian physician, Boeck, was invited to London in 1865 where he began a trial of syphilization with predictably little success [21].

Advances in the second half of the nineteenth century and the early twentieth century, fuelled the growth of medicine as a science. Microbiology, X-rays and the development of diagnostic equipment such as thermometers and sphygmomanometers, opened a whole new world of human research [22]. Furthermore, the doctors who embraced the merger of science with

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4 Vivisection is literally the dissection of an animal while still alive. It is sometimes used to mean any sort of experiment on an animal. Here, it is used in its literal sense.
5 Syphilis is a venereal disease that, because it was untreatable, threatened to ravage mid-nineteenth century society. In an attempt to control the spread of the disease physicians experimented with syphilization, which was based on the theories of inoculation and variolation, the techniques used to prevent smallpox.
6 A sphygmomanometer is a machine for measuring blood pressure that utilises an inflatable cuff placed on the arm and linked to a barometer.
medicine noticed just how irrational prescribing habits had become and realised the need for research to rationalise and improve the safety of drug therapy. ‘Clinical science’ initially expanded in the laboratory setting and the classic treatise, *Introduction to the Study of Experimental Medicine*, written by the French physician and scientist Claude Bernard was published in 1865. Clinicians were initially reluctant, but, with Germany leading the way, they eventually embraced this new science [23]. France and the United States were not far behind. However, despite the foundation of the Medical Research Committee in 1913 [24], Britain, with its tradition of gentleman physicians [25] lagged behind [26].

Spurred on by the successes of the discovery and experimentation with insulin and the development of chemotherapy, research on humans continued to increase. Since 1935, when the landmark paper demonstrating the effectiveness of Prontosil in the treatment of streptococcal infections in mice was published, Bull notes that we “have possibly seen more clinical trials than occurred in the whole of previous medical history” [27]. This increase in human experimentation, coupled with the institutionalisation of research, the increasingly close relationship between science and the state and the use of public funds increased public awareness and the need for accountability [28]. Other important developments that increased public scrutiny of research practices include the increasing focus on human rights that followed the Second World War, the emergence and development of bioethics as an academic discipline [29], and the formation of specific pressure groups such as the Patients Association.

22.2 The Development of Codes and Guidelines

22.2.1. Introduction

Before continuing, it is worth noting that much of the attention during 1939-1989 was focused on research using patients. Early documents issued by the World Medical Association (WMA) and the Royal College of Physicians (RCP) were produced by physicians for physicians, so it was natural for them to concentrate on the use of patients rather than healthy volunteers. Following the Nuremberg Code, the first guidelines that considered healthy volunteers were those produced by the Association of the British Pharmaceutical Industry (ABPI) in 1970 considering the use, initially, of staff volunteers. However, it was not until the RCP issued their guidelines in 1986 that the issues concerning healthy volunteers received more sophisticated attention. This focus on patients was partly down to the autonomy/paternalism debate that occupied much of the early discussions.

For healthy volunteers the need for consent, at least post-Nuremberg, was never in doubt. However, the notion of consent in the early post World War Two period was underdeveloped with information disclosure being seen as more relevant to co-operation than consent. Following the death of a healthy volunteer in 1985, attention was diverted to that group of research subjects. Triggered by this event, the 1986 RCP guidelines and the Medicines Commission Advice were produced allowing some of the arguments developed in relation to patients to be applied to healthy volunteers. The discussion (and the Figures which appear later) should be read with this in mind.

22.2.2 The Development of Codes

*The Hippocratic Oath and the Declaration of Geneva* [30]

Prior to the Nuremberg Code 1947, there were no international or UK codes or guidelines regulating the ethical conduct of researchers experimenting on humans. However, this does

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7 The Medical Research Committee became the Medical Research Council (MRC) in 1919.
8 In 1830, English law was interpreted as prohibiting experimentation without consent: See: Howard-Jones, N. “Human Experimentation in Historical and Ethical Perspectives”. *Social Science and Medicine*, 1982; 16: 1429-1448, 1430 citing Willock, J.W. *The Laws Relating to the Medical profession with an Account of the Rise and Progress of its Various Orders*, 1830, London: J. & W.T. Clarke, 109-110. See also, the earlier English case in which the use of an experimental device was unlawful unless the patient had given consent: *Slater v Baker and Stapleton* (1767) 95 ER 860.
not mean that the experimenters operated in an ethical void. Investigators who were also doctors had a long tradition of professional ethics guiding them. Personal codes were also formulated. The English physician Thomas Percival, in his book *Medical Ethics* (published in 1803), suggested that a doctor should consult his peers before beginning novel treatment [31]. And the American physician, William Beaumont, formulated a code in 1833 that required both a well-designed trial and the subject’s voluntary consent. It also required the study to be stopped if it causes the subject to become distressed [32]. Interestingly, Beaumont himself may have paid less than strict attention to his code, which he formulated to justify his experiments on the unfortunate Alexis St. Martin whose partly healed gunshot wound allowed direct observation of his stomach. Beaumont paid St. Martin to allow him to conduct experiments on his stomach but the unhappy St. Martin ran away on several occasions! [33]

For the most part, physicians who undertook human experimentation were guided by personal values or general codes. The dominant ethics of western medicine originated in Greek and Roman medicine [34]. A code of ethics persisting to this day is the Hippocratic Oath and, regardless of its contested origins, the Oath remains influential. It was restated in modernised form in the WMA’s Declaration of Geneva in 1948 [35]. Both of these Codes are advisory rather than legally binding. As with all guidelines, any deviation in practice might require justification, although with bodies such as the General Medical Council (GMC) producing more specific guidance, the influence of these codes is perhaps less direct today than it was fifty years ago.

The Hippocratic Oath primarily guides medical care and is silent on experimentation. However, one section may be relevant:

> "I will follow that system of regimen which according to my ability and judgment, I consider for the benefit of my patients, and abstain from whatever is [to their harm or injustice] deleterious and mischievous." 9

This obligation appears to rule out all non-therapeutic experiments performed by doctors, but, if read literally, it applies only to the doctor’s patients. Where the subject is not one of the doctor’s patients the Oath is arguably not relevant. Regardless of the scope of the Oath, it does not refer to the idea of consent and the doctor’s ethical practice stands or falls on the basis of providing a benefit and avoiding harm.

In the Declaration of Geneva, which again is a general ethical code silent on the issue of experimentation, the doctor must swear that: "the health of my patient will be my first consideration" and that he "shall act only in the patient’s interest…" Although the code envisages research – it states that the doctor must "use great caution in divulging discoveries or new techniques or treatment through non-professional channels" – it again is of greatest relevance to the use of patients rather than healthy volunteers. Perhaps the phrase most relevant to non-therapeutic research is the pledge that: "I will not use my medical knowledge contrary to the laws of humanity". This, however, is a non-specific statement that begs the question as to what are the ‘laws of humanity’. Again, there is no reference to consent or any of the other themes under consideration.

*The Prussian Code* 10

Although of no direct relevance to practice in the UK, the Prussian Code of 1900 may have been indirectly influential through Sir William Osler (see below) and is, therefore, worth mentioning. The Code, issued by the Prussian minister for religious, educational, and medical affairs, was the Prussian parliament’s response to the "critical public discussion and political debate on the Neisser case" [36]. Albert Neisser injected cell-free serum taken from patients suffering from syphilis into prostitutes without disclosing what he was doing or asking for their consent. The press exposed the cases when some of the women developed syphilis. A government report was commissioned, which concluded that both information about the

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9 Hippocratic Oath as translated by Francis Adams. The section in brackets is from the 1996 translation by Heinrich von Staden.

10 Sometimes called the Berlin Code.
intervention and consent were prerequisites to experimentation [37]. This short Code requires that, following "a proper explanation of the possible negative consequences of the intervention" [38], the subject must have given "unambiguous consent" [39]. The Code is basic and is predicated entirely on the idea of the individual's right to self-determination. The importance of the scientific discovery is irrelevant, as is the degree of potential harm that the subject might be exposed to.

The Nuremberg Code

The Nuremberg Code, primarily authored by the prosecution's expert witness Andrew Ivy [40], was laid down by the US judges at the war crimes trial of Nazi physicians. The motivation for the Nuremberg Code is admirably summed up by George Annas who stated:

"The Nazi experiments involved systematic and barbarous interventions in which death was the planned endpoint. The subjects of these experiments were concentration camp prisoners, mostly Jews, Gypsies and Slavs. The judges at Nuremberg viewed human experimentation as suspect, and the Nuremberg Code itself resulted from horrendous non-therapeutic, non-consensual prison research." [41]

For the Allies, the pre-trial desire was to distance medical research in general from the Nazi experiments. The International Scientific Committee secretly met some four months before the trial. Hazelgrove notes that:

"It was an explicit objective of the Committee that 'normal' research with human beings should be protected against Nazi taint when the activities of the Nazi doctors became public knowledge." [42]

Before detailing the ten-point code: the judges summed up their opinion as to the acceptability of human experimentation. They stated:

"The great weight of the evidence before us is to the effect that certain types of medical experiments on human beings, when kept within reasonably well-defined bounds, conform to the ethics of the medical profession generally. The protagonists of the practice of human experimentation justify their views on the basis that such experiments yield results for the good of society that are unprocurable by other methods or means of study. All agree, however, that certain basic principles must be observed in order to satisfy moral, ethical, and legal concepts." [43]

The Nuremberg Code, which makes "voluntary consent … absolutely essential", is a valid and current statement of public international law [44]. As Annas notes:

"The Nuremberg Code, despite its inherent limitations, remains the most authoritative legal and ethical document governing international research standards..." [45]

Arnold and Sprumont note that there has been a tendency for doctors to treat the Code as a non-binding set of ethical principles, which allows doctors to retain "control over human experimentation" [46]. That the Code might be legally persuasive, if not binding, is evidenced by the recent US case in which the Maryland Court of Appeals relied on the Nuremberg Code to declare unlawful non-therapeutic research on children that might be harmful [47]. The Code has no direct legal effect in the UK and there has been no comparable legal case to determine its legal status. Predictions as to whether the courts would rely on the Code would be speculative.

The Declaration of Helsinki

The Declaration of Helsinki was adopted by the WMA in 1964, although discussions had been ongoing for a number of years and, in 1954, the Resolution on Human Experimentation

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required the researcher to explain to subjects the nature, purpose and risks of participation. Then, in 1962 a draft code was published in the BMJ [48]. The BMJ introduced the draft code and noted that:

"It will eventually be prefaced by a general statement on the essential part played by research in medicine. But, as the subject has recently received a lot of attention in the press in this and in other countries, it is thought desirable that the medical profession in Britain should be made aware of what progress has been made in this admittedly difficult subject."

The anonymous leading article in the same issue of the BMJ implied that it was this public concern with some of the research practices of the time that motivated the WMA to produce the Declaration [49].

The introduction to the 1964 Declaration begins by reminding the doctor of his duty to the health of his patient. It then declares:

"Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, The World Medical Association has prepared the following recommendations as a guide to each doctor in clinical research."

The implication is that the WMA were concerned by public criticism and wished to pre-empt a possibly more restrictive approach by the various national governments. Thus, their motivation was, by condemning the worst excesses of human experimentation, to provide permissive guidance. If a court case ensued then, in the absence of other guidance the courts would have nowhere to turn except the restrictive Nuremberg Code. As, Annas suggests:

"The Declaration’s goal is to replace the human rights-based agenda of the Nuremberg Code with a more lenient medical ethics that permits paternalism." [50]

The Basic Principles established by the 1964 Declaration required the research to be well designed and justified by either existing knowledge or prior animal or laboratory experiment. The expected benefits of the research must justify the risk and the experimenters should be suitably qualified. A distinction was made between therapeutic and non-therapeutic research. As with the 1954 Resolution, the subject was to be informed of the "nature, the purpose and the risk" of the research, which may not be undertaken without his "free consent". The Declaration, unlike the Nuremberg Code, envisaged that research on children and incompetent adults might be permissible.

For the period we are considering here, the Declaration has consistently been promoted as a guide. In 1964 the Declaration stated:

"It must be stressed that the standards as drafted are only a guide... Doctors are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries."

Although the Declaration may be the "most influential" of all the codes of research ethics [51], it still remains simply a guide rather than a legal requirement. Breach of the code, however, may have professional implications for the researcher.

The Declaration has undergone a number of changes since its inception (1975; 1983; 1989; 1996; 2000) and those changes and their implications will be discussed when considering how the eight themes have been handled by the Codes and Guidelines.

The United Nation's International Covenant on Civil and Political Rights

While this Covenant, adopted in 1966, is not specific to human research it does include a short statement that is relevant. Article 7 states:
"No one shall be subjected to torture or to cruel, inhuman or degrading treatment or punishment. In particular, no one shall be subjected without his free consent to medical or scientific experiment."

Like the Nuremberg Code, the Covenant makes voluntary consent an absolute requirement. The Covenant has no direct legal effect in the UK but may have importance politically and in international law.

22.2.3. The Development of Guidelines

*The Richtlinien (Guidelines) of the Reichsgesundheitsamt (Reich’s Health Department)* [52]

The German Minister for the Interior issued these regulations in 1931. Although there is controversy as to whether they had legal force in Nazi Germany, the guidelines did constitute the prevailing ethical standard and were cited as such during the Nuremberg trial [53]. They had no legal status in the UK. In relation to non-therapeutic human research they required: prior animal or laboratory studies; an acceptable level of risk in relation to the expected benefit; the provision of "relevant information" and consent of either the subject or his legal guardian. "Exploitation of social hardship" and experimentation on the dying were prohibited. Whether or not these regulations had legal or only ethical force is moot, but whichever position is true the fact of the Nazi experiments demonstrates the futility of codes and guidelines if they are not enforced.

*Medical Research Council (MRC) Guidelines*

In 1953 the MRC circulated a statement on human experimentation to its staff [54], MRC grant recipients, medical school deans, medical societies secretaries and editors of scientific journals. The statement recognised the limitations of a patient’s consent resulting from the relationship of trust between the doctor and his patient. It placed responsibility for deciding whether to include a patient in a study firmly in the hands of the individual researcher. It further stated that, because of the complexity and diversity of human experimentation, a single set of guidelines would not be possible. Since it was only the specialist researcher who could pass judgement in their own field, the MRC called for the various medical societies to produce guidelines relevant to their own particular field.

In their Annual Report for 1962-1963, the MRC published their response to a renewed request for guidance [55]. Like the subsequent Declaration of Helsinki, the MRC drew a distinction between therapeutic and non-therapeutic research. Therapeutic research fell "within the ambit of patient-care... governed by the ordinary rules of professional conduct in medicine". Non-therapeutic research, however, required an explicit "true consent" because the individual’s rights may not be infringed for the public good [56]. This consent, which should be evidenced by a third party, must be "freely given with proper understanding of the nature and consequences of what is proposed". The guidelines also required that "particular care" be taken when the existence of a "special relationship" between the investigator and subject raises the question of "undue influence". This advice remained unchanged until the MRC produced new guidelines in 1992 [57].

*The BMA motion on “Experimental Research on Human Beings”* [58]

This motion was debated and carried at the Annual Representative Meeting in 1963. As with the MRC guidance and the declaration of Helsinki, this motion came at a time when human research was under public, political and media scrutiny. Pappworth had published an article in the *Twentieth Century* entitled “Human Guinea Pigs: A warning”. A leading article in the BMJ reported that this had provoked widespread debate in the press [59]. And, as the anonymous author noted:

"There has for some time been public uneasiness about investigations carried out in hospitals which have not always been obviously in the interest of the subject." [60]
The motion required "prior investigation" and, for non-therapeutic research, a "free and valid consent" based on a "full explanation". The motion also stated that:

"The patient must never take second place to a research project nor should he be given any such impression." [61]

Like all professional guidance these were not legally binding although it may be taken into account by a court of law [62]. The GMC may also consider such guidance were a doctor to be charged with serious (or gross) professional misconduct.

The Guidelines Issued by the RCP

1. Concerning Ethics Committees

The initial RCP report was published in 1967 [63]. The Committee that produced the Report was established in 1966 following a letter from a number of College Fellows. The letter noted the increasing "disquiet" within the profession, the public concern – prompting the formation of the Patient's Association – and the moves in the US to institute independent ethical review. The Report distinguished therapeutic and non-therapeutic research and suggested that therapeutic research was a part of the doctor's duty and "seldom poses serious ethical problems" [64]. The Committee stated that the Declaration of Helsinki and the MRC guidelines "define the ethical situation", but they "only provide general guidance, and their application to specific problems must often remain a matter of opinion". Noting the generally high standard of ethical conduct, the need to avoid unnecessary interference and to allay public concern, the Committee declined to lay down formal rules but recommended that human experimentation should be subjected to prior peer review [65]. Commenting on the 1967 Report, Hazelgrove noted that it followed so closely on the heels of the publication of Pappworth's book (Human Guinea Pigs) that it seemed "like a white-washing exercise" [66].

In 1971, the Committee carried out a questionnaire survey to consider the effect of their recommendations [67]. This was followed by a request for further guidance from Sir George Godber, the Chief Medical Officer, perhaps motivated by pressure from the Patient's Association [68]. The RCP published more detailed guidelines in 1973 [69].

The guidelines were further expanded in 1984 [70]. While the original 1967 Report consisted of just four conclusions and recommendations, the guidelines in 1984 now covered more than 19 different issues including consent, the problems of vulnerable subjects, compensation and payment of subjects. An updated and expanded second edition of the guidelines was published in 1990 [71].

All three recommendations were advisory in nature rather than being either professionally or legally binding. As Neuberger notes about 1990 guidelines, these were unenforceable unless the Institution or Health Authority chose to specifically implement them [72]. The guidelines (1973) did, however, have the support of the Department of Health and Social Security (DHSS), which "advised Health Authorities on their implementation" [73].

2. Research on Healthy Volunteers:

At the request of the Medicines Commission, the RCP set up a working party in 1984 to consider research on healthy volunteers. The initiative was motivated partly by the concern over growing commercial interest in human research. In the introduction to the Report, the working party states:

Hazelgrove's statement is based on a letter to the BMJ in which Pappworth described the report as a "white-washing, worthless document"; Pappworth M.H. "Experiments on Man", British Medical Journal, 1967; iii: 616.
"We accept and emphasise the need for research on healthy volunteers, but we are concerned about their health, their safety and their rights." [74]

The report *Research on Healthy Volunteers* was published in 1986 [75]. It covered a wide range of issues including: consent, confidentiality, the use of vulnerable groups, the necessary protections to safeguard volunteers, the role of ethics committees, payment and compensation.

*Medicines Commission Advice to Health Ministers on Healthy Volunteer Studies* [76]

Although this advice is not a set of guidelines, it is worth briefly mentioning them at this juncture. The advice – to be read in conjunction with the RCP report - was formulated in 1987 for the benefit of and at the request of the Minister for Health. The Commission noted that, unlike clinical trials on patients, the Medicines Act 1968 did not cover drug research on healthy volunteers. Such trials, however, should not be prohibited nor brought under "statutory control" [77]. It was recommended that self-regulation should be strengthened through voluntary registration on a central list. This list would maintain a register including details of compliance with recognised guidelines. It also recommended that annual returns should be made giving details of the studies carried out. Studies should be submitted to ethics committees for prior approval and consent was an absolute pre-requisite, thus excluding the mentally handicapped, children and prisoners. Steps should be taken to avoid "undue influence", payment was acceptable providing it would not "encourage people to take part... against their better judgement" and compensation should be available without the need to show fault [78].

*Guidelines Issued by the Council for International Organizations of Medical Sciences (CIOMS) and the World Health Organization (WHO)*

CIOMS and WHO first issued joint guidelines for human research in 1982 [79]. The aim of the guidelines is to indicate how the Helsinki principles can be applied in practice. The guidelines are advisory only and possess no legal force. It is, therefore, unfortunate that they stated that "Helsinki II" had "superseded" both the 1964 Declaration and the Nuremberg Code. The Declaration of Helsinki, not being a legal document, has no effect on the Nuremberg Code, which remains valid, at least as a document of international law. The guidelines, which were updated in 1992 [80], are of most relevance to research in developing countries.

*Guidelines Issued by the ABPI*

In 1970, the ABPI established a committee to consider the issue of experiments on volunteers who were also members of staff [81]. The report was particularly concerned with ensuring that the member of staff was a true volunteer. Thus, "there should be no shadow of a suggestion that he is required or expected to participate as part of his duties" [82]. To this end, subjects should be recruited by general notice rather than a direct request. The Committee suggested that companies should honour a "moral" obligation to compensate an injured subject irrespective of legal liability. The Committee also considered a number of safeguards: the volunteer should be fit to take part and this might require a prior clinical examination; a medically qualified person should supervise the research; and "habitual volunteering" should be avoided.

The Guidelines were updated in 1984 and again in 1990 [83]. While the earlier guidelines were intended to cover staff volunteers, it was noted in the 1990 version that they had also been applied to research with non-staff volunteers. The 1990 guidelines reflected this by simply referring to "non-patient human volunteers". The 1990 guidelines specifically excluded prisoners and the mentally handicapped from being volunteers. Pregnant women, children and the elderly were also considered to be vulnerable groups who, while not completely excluded, should not normally be used. Payment was acceptable, but only that which was reasonable in relation to inconvenience and discomfort. The study should be well designed.
and preceded by animal experimentation. An independent ethics committee should approve the study and informed consent should be evidenced in writing.

22.3 The Eight Themes as Reflected Through the Codes and Guidelines

22.3.1. The meaning of a ‘volunteer’.

Pre-1939. No directly relevant codes or guidelines were published at the time; however, given some international movement of doctors it is worthwhile considering three early sources that may have influenced practice.

1. William Beaumont’s code contained no mention of a ‘volunteer’, ‘undue influence’, ‘special relationship’ or ‘vulnerability’ of the subject. At best the codes conception is the fairly simple idea of a subject who has given a ‘voluntary consent’.

2. The 1900 Prussian Code is particularly relevant since Sir William Osler was in Berlin and in contact with Virchow during the period culminating in the publication of the code. Osler later became a Professor of Medicine in Oxford and was closely involved with the MRC. He was also a "friend, admirer, and enthusiastic supporter" of Walter Fletcher [84], Secretary to the MRC between 1914 and 1933 [85]. Although the term ‘volunteer’ is not used, the code does prohibit research on minors and adults incapable of consenting. Consent is also a requirement. The conception of a volunteer is basic but there is some idea that certain vulnerable groups are not capable of volunteering.

3. The 1931 Richtlinien (Guidelines) of the Reichsgesundheitsamt (Reichs) Health Department. The guidelines do not use the term ‘volunteer’, but the concept of ‘undue influence’ is recognised. Point 8 of the circular states:

   "Exploitation of social hardship in order to undertake innovative therapy is incompatible with the principles of medical ethics."

1947. The Nuremberg Code speaks of a "voluntary consent". This requires the ability:

   "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."

Although there is no specific mention of vulnerable groups or relationships, the code requires that:

   "The human subject should be at liberty to bring the experiment to an end."

1962. The Helsinki Draft Code [86], which underwent radical change before publication, made a number of references to vulnerable groups, dependent relationships and the possibility of coercion or undue influence.

   "No doctor should lightly experiment on a human being when the subject is in a dependent relationship to the investigator, such as a medical student to his teacher, a patient to his doctor, a technician in a laboratory to the head of his department."

   "Prisoners of war… should never be used as subjects of experiment"

   "Civilians detained in any place as a result of military invasion or occupation, or for administrative or political reasons, should never be used for human experiment."

   "Persons retained in prisons, penitentiaries or reformatories – being “captive groups” – should not be used as subjects of experiment…"
1962/3  MRC guidelines:

"Particular care is necessary when the volunteer stands in special relationship to the investigator as in the case of a patient to his doctor, or a student to his teacher."

1964.  The Declaration of Helsinki dropped all of the references to specific groups of vulnerable individuals contained in the draft code, but retained the general principle.

"The investigator must respect the right of each individual to safeguard his personal integrity, especially if the subject is in a dependent relationship to the investigator."

1970.  The ABPI guidelines were specifically aimed at avoiding the exploitation of staff members.

"In the case of a staff employee there should be no shadow of a suggestion that he is required or expected to participate as part of his duties. He must agree of his own free will to undertake the enterprise for which he is volunteering."


"Freedom to refuse to participate or to withdraw at any stage is particularly important where the subject is in a dependent relationship to the investigator."

1975.  The Amended Declaration of Helsinki (essentially unchanged by the 1983 and 1989 amendments) suggested a possible safeguard:

"When obtaining informed consent… the doctor should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a doctor who is not engaged in the investigation and who is completely independent of this official relationship."

1984.  The RCP guidelines, while accepting that patients are vulnerable decided that they were still capable of being 'volunteers'. However:

"Subjects other than patients may also be in a potentially dependent relationship with investigators. Recruiting such subjects, e.g. students, junior medical staff, nurses, employees of pharmaceutical or other industry and members of the armed forces requires special care."

And:

"The quality of the consent of candidate subjects who are junior or subordinate members of a hierarchically-structured group requires careful consideration, as willingness to volunteer may be unduly influenced by the expectation, whether justified or not, of adventitious benefits (reproduced from the CIOMS/WHO guidelines)."

1986.  These RCP guidelines, which focused particularly on healthy volunteers, explored the issues in slightly more depth:

"Recruitment of healthy volunteers for research projects may involve conscious or subconscious pressures… Financial incentives in particular may over-persuade individuals, including students, who have low incomes… There should, therefore, be no coercion, overt or covert, of anyone to volunteer for research, whether the pressure be financial, for academic or employment advantage, for job security, or for other reasons."
"We do not consider it to be inherently unethical to carry out research on prisoners... Particular care needs to be taken to avoid coercion in any form including any impression that inducements such as a reduction of sentence or pardon or other favours could be given. Nevertheless we appreciate that there is no precise point where recompense becomes an inducement."

"Students are... particularly vulnerable to academic, personal and financial pressures... It is normally undesirable to recruit students who are in close contact with the investigator e.g. in his class... [as they] are, or may feel, vulnerable to pressure from someone in a position to influence their careers."

"The junior colleague is in a vulnerable position, on the one hand because of over-enthusiasm, and on the other because any lack of eagerness to participate might be thought to prejudice his future career."

"Volunteers in the armed or other Services might also be subject to coercion and this again should be guarded against. There may, however, be good reason for recruiting healthy volunteers in the armed forces, e.g. in experiments designed to help servicemen in action."

22.3.2. The meaning and implications of 'consent"

**Pre-1939.** Beaumont’s Code, the Berlin Code of 1900 and the 1931 German Richtlinien all required the subject’s consent before experimentation was permitted. The Berlin Code, for example stated:

"All... [research] interventions... are excluded under all circumstances, if... the human subject has not given his unambiguous consent."

**1947.** The Nuremberg Code stated:

"The voluntary consent of the human subject is absolutely essential. This means that the person involved should have... sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding an enlightened decision."

**1962.** The Helsinki Draft Code allowed the subject to "have complete freedom to decide whether or not to take part".

**1962/3.** The MRC guidelines noted that "Assumed consent... is valueless" and that a third party should witness consent because:

"Written consent unaccompanied by other evidence that an explanation has been given, understood and accepted is of little value."

**1964.** The Declaration of Helsinki made inroads into the absolute requirement of consent, as it allowed proxy consent:

"Clinical research on a human being cannot be undertaken without his free consent after he has been informed; if he is legally incompetent, the consent of the legal guardian should be procured."

"Consent should, as a rule, be obtained in writing. However, the responsibility for clinical research always remains with the research worker; it never falls on the subject even after his consent is obtained." 12

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12 This latter statement is interesting because it suggests that the investigator remains responsible for any harm, whether or not it was as a result of negligence, caused by the experiment. In other areas consent may be seen as a mechanism for transferring responsibility for non-negligent outcome.
1970. The ABPI guidelines require that consent should be ‘knowledgeable’ and in writing:

"The Committee recommends that in all cases there should be a simple form of written contract recording the volunteer’s willingness to undergo the desired administration, his understanding of the purpose of the trial and any known risks attached."

1973. The RCP guidelines suggested that, excluding "trivial procedures", explanation of the procedure should be given in the "presence of a witness" and:

"The agreement of the subject… should be recorded with the signatures of the person who gave the explanation and of the witness."

1975. The amended Declaration of Helsinki (essentially unchanged by the 1983 and 1989 amendments) reiterated that consent does not shift the burden of responsibility and stated:

"The doctor should… obtain the subject’s freely given [adequately] informed consent, preferably in writing."

1984. The RCP guidelines noted that "consent is central to the ethical conduct of clinical investigation". "Trivial" procedures only required a verbal consent, but:

"More substantial procedures should be the subject of an explanatory document… The subject may study this and then sign a paper that states that the document has been studied and discussed with the investigator and that the subject agrees to participate."

1986. The RCP guidelines stated:

"By implication a volunteer taking part in an activity has given consent, but before agreeing to participate in a research project it is important that the volunteer should be properly informed and have given valid consent."

"It is usual and desirable, except in trivial cases, that a consent form be signed by the volunteer, and the investigator should state that he has explained the nature of the investigation to the volunteer."

22.3.3. The provision of study information

Pre-1939. While the Berlin Code 1900 required: ‘a proper explanation of the possible negative consequences of the intervention’, the 1931 German Richtlinien refers simply to the need for ‘Relevant information’.

1947. The Nuremberg Code was far more explicit:

"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 and person which may possibly come from his participation in the experiment."

1962/3. The MRC guidelines advised that the investigator should disclose "the nature and consequences of what is proposed".

1964. The Declaration of Helsinki required that:

"The nature, purpose and the risk of clinical research must be explained to the subject by the doctor."
1973. The RCP guidelines, without explaining exactly what this entailed, demanded that:

"Wherever the research investigation is not expected or is not intended to benefit the individual, a full explanation of the proposed procedure should be given."

1975. The Amended Declaration of Helsinki (essentially unchanged by the 1983 and 1989 amendments) resembled the Nuremberg Code in requiring that:

"In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail."

1984. The updated RCP guidelines suggested that, for non-trivial procedures the information should be provided in writing:

"Setting out the purpose of the investigations, the procedures, the risks, the benefits, a statement that the subject will be free to withdraw at any time without giving a reason and without in any way impairing his/her management or incurring displeasure, and an invitation to ask questions."

1986. The RCP guidelines provided a far more detailed explanation of what was required:

"The investigator’s obligation… is to explain in understandable terms the nature and purpose of the study and to provide sufficient information and advice on possible risks… so as to give meaning to the volunteer’s right to self determination."

"An investigator should give full details in writing to a healthy volunteer explaining the nature, object and duration of a study. The volunteer should be informed of any risk, and told what the study will involve, e.g. the number of blood tests or injections, and whether there are any restrictions on, e.g. driving or drinking alcohol."

"[The volunteer] should also be told whether any intended procedures will be associated with discomfort."

"The healthy volunteer will also need to know what his position is in the event of an accident, injury or the development of ill health as a result of having taken part in the research project."

22.3.4. The concepts of harm and risk

Pre-1939. Beaumont’s Code simply required that: "The experiment is to be discontinued when it causes distress to the subject" while the 1931 German Richtlinien suggested a risk-benefit analysis.

1947. The Nuremberg Code also required a risk-benefit analysis in that:

"The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment."

Furthermore, where possible, harm should be avoided:

"The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury."
"No experiment should be conducted where there is an a priori reason to believe that death or disabling injury will occur; except perhaps, in those experiments where the experimental physicians also serve as subjects."  

"Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death."

"The scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of good faith, superior skill and careful judgment required of him, that a continuation of the experiment is likely to result in injury, disability, or death to the subject."

1954. The WMA Resolution on Human Experimentation also required a risk-benefit analysis:

"Every clinical research project should be preceded by careful assessment of inherent risks in comparison to foreseeable benefits to the subject or to others."

1962. The Helsinki Draft Code suggested a risk-benefit analysis and followed the Nuremberg Code in maintaining that: "any scientifically or medically qualified person associated with... [the study] should be free to discontinue the experiment if in his or their judgement it may, if continued, be harmful to the subject".

1962/3. The MRC guidelines simply pointed out that:

"The individual has rights that the law protects and nobody can infringe those rights for the public good."

1964. The Declaration of Helsinki required a risk-benefit analysis and stated that:

"Clinical research cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject."

And, as with the Nuremberg Code:

"The investigator... should discontinue the research if in his or their judgement, it may, if continued, be harmful to the individual."

1975. The amended Declaration of Helsinki (essentially unchanged by the 1983 and 1989 amendments) reiterated the need for a risk-benefit analysis and stated that:

"Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject."

"Doctors should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Doctors should cease any investigation if the hazards are found to outweigh the potential benefits."

"The investigator... should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual."

"In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject."

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13 This latter statement is interesting, because there has been a long standing historical tendency to assume a study is ethically acceptable if the investigator is either willing to undergo it himself or would be willing for his wife or children to be subjects (see later).
1984. The RCP guidelines simply demanded that: "Subjects... will be exposed to a minimum of risk and inconvenience".

1986. The RCP guidelines placed an absolute – although imprecisely defined – limit on the degree of risk or harm that a subject may be allowed to face:

"A risk greater than minimal is not acceptable in a healthy volunteer study."

"We... use the term 'minimal risk' to cover two types of situation. The first is where there is a small chance of a recognised reaction which is itself trivial, e.g. a headache or feeling of lethargy. The second is where there is a very remote chance of a serious disability or death. We regard this second risk to the healthy volunteer as comparable, for example, to that of flying as a passenger in a scheduled aircraft."

"Both we and the [British Psychological Society] believe that experiments that cause more than minimal anxiety, distress, lowering of self-esteem or long term harm should be avoided."

22.3.5. The use and acceptability of payments and inducements:

Pre-1939. No guidance about the acceptability of payments existed in the early codes although William Beaumont did pay his subject Alexis St. Martin.

1947-1964. Both the Nuremberg Code (1947) and the Declaration of Helsinki (1964) are silent on the issue.

1970. The ABPI guidelines suggested that:

"The payment of a reward in cash or kind would tend to establish the voluntary character of the service." The amount should be reasonably related to the effort and discomfort anticipated."

1984. The RCP guidelines argued that:

"There is a tradition that healthy volunteer subjects should engage in research for purely idealistic or educational motives. Today healthy volunteer subjects cannot always be expected to participate in research without reward."

"Ethics Committees should be informed of all proposed payments and should be satisfied that they are reasonable and not so large as to induce subjects to take risks primarily for reward."

"Reimbursement of subject’ expenses, e.g. journeys, is plainly desirable and should not be overlooked."

1986. The RCP guidelines counselled that "financial reward[s]" should not be advertised and:

"There should be no financial inducement or any coercion that might persuade a volunteer to take part in a study against his better judgement."

"Any payment to a healthy volunteer should be for expenses, time, inconvenience or discomfort, and never for risk. Increased payments may be reasonable for procedures requiring extra care or involving more discomfort."

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The context of this statement, coming shortly after the Committee expressed concern over the coercive potential of the investigator also being the subject’s employer or superior, implies that the Committee believed that a ‘reward’ would go some way to negating the appearance of exploitation.
22.3.6. The issue of compensating persons injured as a result of the experiment:

Pre-1970. No guidance about compensation existed in either the Nuremberg Code or the Declaration of Helsinki.

1970. The ABPI guidelines noted that compensation available to an injured subject was available through legal claims in negligence or “assault”, which would require him to: “establish the responsibility of the manufacturer”. The Committee felt this was inadequate and recommended that:

“A manufacturer should accept a moral liability to compensate in any case where injury to or deterioration in health or well-being, actual or prospective, or any harmful susceptibility or toxicity can fairly be ascribed to the administration, irrespective of the legal position. This acceptance of responsibility should extend to dependants.”

1982. Although the declaration of Helsinki made no provisions for compensation, the CIOMS/WHO guidelines, which were an attempt to apply the Declaration to developing countries states:

“Any volunteer subjects… who may suffer injury as a result of their participation are entitled to such financial or other assistance as would compensate them fully for any temporary or permanent disability. In the case of death, the dependants should be eligible for appropriate … compensation.”

“Experimental subjects should not, in giving their consent to participation, be required to waive their rights to compensation in the case of an accident; nor should they be required to show negligence or lack of a reasonable degree of skill on the part of the investigator.”

1984. The RCP guidelines noted that the injured subject was only "entitled" to compensation if he could show that the researcher had been negligent. Because of the inherent uncertainty of research work harm may occur “despite the highest care”. If this were the case:

"[The] only... means by which a participant or his dependant might receive some compensation would be by seeking an ex gratia payment from the sponsor of the research or the authority employing the researcher. This situation is clearly unsatisfactory... There remains the lacuna of the injury occurring in the absence of fault."

"The major issues of liability will have to await solution on a national basis and there is nothing that individual Ethics Committees can do about them. Responsible research organisations and the DHSS have stated that they may offer ex gratia payments to volunteers who are injured as a result of participation in a clinical investigation."

1986. The RCP again noted that: "The volunteer has no legal redress if he is unable to show negligence". They recommended that:

"The sponsor... should agree to pay compensation for injury, accident, ill health or death caused by participation in a research study without regard to proof of negligence and without delay. Provision for arbitration of disagreement should be included".

One of the major difficulties in making compensation claims for these types of injury lies in proving that the intervention was the cause of the injury. To alleviate this, the RCP suggested that:

15 The essential proposition is for 'no-fault' compensation. But this is only a moral obligation.
"Where there is any doubt about causation the benefit of the doubt should be given to the volunteer."

Further, the RCP suggested that the sponsor should also compensate a volunteer injured as a result of the study through the negligence of someone whom the sponsor is not responsible for. For example, imagine a research study that uses a warming device such as an electric blanket. If the electric blanket was faulty and burned the volunteer he would ordinarily have to sue the manufacturer of the blanket rather than the research sponsor. Under the RCP guidelines, the research sponsor would compensate the volunteer without him having to go to court or show that the blanket was faulty.

22.3.7. The development and function of ethics committees

Pre-1939. Although the Berlin Code of 1900 did not require an ethics committee, it did require senior supervision:

"[Research] interventions… are to be only performed by the medical director…[of the institution] or with his special authorization."

The 1931 German Richtlinien contained a similar condition.

1962/3. While not actually recommending an ethics committee, the MRC did make three relevant suggestions. First, for therapeutic research on patients, the doctor should consult with colleagues if he is in any doubt about the value of the procedure. Second, controlled clinical trials should be undertaken and supervised by a team rather than by individuals. Third, the head of department "has an inescapable responsibility for ensuring that practice by those under his direction is irreproachable".

1967. The RCP perhaps produced the first UK guidelines to recommend a formal ethics committee, although it decided not to formulate "precise rules" because it would be best left to the individual institutions. Notably, there was no provision for lay membership:

"The competent authority… has a responsibility to ensure that all clinical investigations carried out within its… institution are ethical and conducted with the optimum technical skill and precautions for safety. This responsibility would be discharged if in medical institutions… it were ensured that all projects were approved by a group of doctors including those experienced in clinical investigations. This group should satisfy itself of the ethics of all proposed investigations. In non-medical institutions… the supervisory group should always include at least one medically qualified person with experience in clinical investigation."

1973. Following the results of their questionnaire survey, the RCP suggested that all clinical research should be submitted to an ethical committee and:

"To function efficiently ethical committees should be small and they must not be so constituted as to cause an unreasonable hindrance to the advancement of medical knowledge. The medical members should be experienced clinicians with a knowledge of clinical research… and in addition there should be a lay member. By layman we mean an individual who is not associated with the profession in any paramedical activity, i.e. a biochemist or psychologist would not be considered as a layman for this purpose."

1975. The amended Declaration of Helsinki (essentially unchanged by the 1983 amendments) required that there should be a formal protocol and that the committee should be independent:

"The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be
transmitted to a specially appointed independent committee for consideration, comment and guidance."

1984. The RCP noted that:

"The objectives [of Ethics Committees] are to facilitate medical research in the interest of society, to protect subjects of research from possible harm, to preserve their rights, and to provide reassurance to the public that this is being done."

As such, "optional submission [of human research projects]… cannot be justified" and the Committee should consider that:

"The objectives of research are directed to a justifiable advancement… the required information cannot be obtained from animal models… the responsible investigator is appropriately qualified… and commands [suitable] facilities to ensure… the safety of the subjects; adequate preliminary literature research and experimental studies have been undertaken to define, as far as is practicable, the risks inherent in participation; every effort will be made to inform prospective subjects of the objectives and consequences of their involvement."

"Membership should… [include] a general practitioner… a nurse…[and] one, or perhaps better, two [lay] persons not trained in or practising any medical or paramedical discipline."

The RCP also noted that "Ethics Committees have no direct sanctions", and suggested:

"In the event of their discovering that their advice is unheeded or that clinical investigations are being conducted without reference to them, then they should report the facts to the body that set them up."

1986. The RCP again emphasised that "all research… on healthy volunteers" should be submitted to the ethics committee, which should:

"Satisfy itself that studies are scientifically sound because this is an essential ingredient of ethical research. It should also ensure that volunteers are fully aware of the details, implications and possible risks of the study and are able to give a valid consent. The Committee should also satisfy itself that there is adequate provision for compensation… The Committee should be made aware of payments made not only to healthy volunteers, but also to the investigator, his staff or department."

22.3.8. The requirement of prior research before beginning experiments on humans.

Pre-1939. The 1931 German Richtlinien stated:

"Innovative therapy may be carried out only if it has been tested in advance in animal trials (where these are possible)."

1947. Similarly, the Nuremberg Code required that:

"The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study."

1954. Likewise, the WMA Resolution on Human Experimentation stated:

"Clinical research… should be based on laboratory and animal experiments or other scientifically established facts."
This provision was restated in the original and amended versions of the Declaration of Helsinki, although the 1975 declaration referred to "a thorough knowledge of scientific literature' rather than 'scientifically established facts''.

1986. The RCP also required that:

"Before new chemical entries are administered to healthy volunteers, they are first examined by pharmacological and toxicological studies in animals."

"In studies of established drugs, the drug will have been tested in animals and already administered to many patients. With many such drugs the risk may be regarded as minimal, provided that the proper procedures and adequate safeguards are followed."

"Ethics Committees should be satisfied that there has been adequate evaluation of background pharmacological, toxicological data, etc., in all drug studies, particularly in the case of new chemical entities or combinations."

22.4. The Ethics of Human Research in Practice

22.4.1. Historical Introduction: Ethical principles in practice up to 1939

Prior to and up to the middle of the twentieth century, the ethics of experimentation on humans was largely a matter for the individual investigator [87]. The early history was, with notable exceptions, mostly of therapeutic research [88], and it was not until the advances in microbiology in the second half of the nineteenth century, that non-therapeutic research took off [89]. While consent was a legal requirement, and had been noted by the courts in the late eighteenth century to be the usual practice of surgeons [90], it was often not obtained prior to experimentation. Even where it was claimed that consent had been obtained, it was perhaps closer to acquiescence, lack of objection or submission than a true consent. The Russian physician, Vikenty Veressayev, published an account of numerous unethical experiments conducted throughout the nineteenth century [91]. In many of these cases consent was not possible or not sought. For example, a German physician in 1885 inoculated the eyes of dying infants with gonorrhoea [92]. In other cases, the physician claimed to have the consent of his subject, but they were often children or other vulnerable individuals [93].

The history of human experimentation is one highlighted by the exploitation of vulnerable, disadvantaged groups [94]. Prisoners – especially the condemned, the dying [95], slaves (latterly racial minorities) [96], orphans, prostitutes and "charity cases" were commonly used subjects. In 1879 for example, Armauer Hansen inoculated the eye of an institutionalised woman with leprosy.16 This was done after the distressed woman was "calmed down by the superintendent of the hospital" without disclosure of the purpose of his action and without consent. In the criminal prosecution that followed, Hansen was removed from his clinical position but allowed to continue as Chief Medical Officer for Leprosy [97]. Similar use of vulnerable subjects may be found in the UK [98]. In 1721, for example, smallpox inoculation was tested on six prisoners and five orphans before the Princess of Wales was happy to allow her own children to be inoculated [99].

In the latter half of the nineteenth century, criticism of this use of humans for experimentation was growing. The anti-vivisection movement was particularly vocal in this respect [100], but concern also came from within the medical profession. In 1898 William Osler, for example, criticised Sanarelli’s experiments with yellow fever on patients without their knowledge or consent. He stated:

"Even granting that every dose of medicine we give is an experiment, to deliberately utilize a human being for the purpose of experiment without the sanction of the individual is... criminal." [101]

16 Hansen was a Norwegian physician.
It was just two years later, in 1900, that Walter Reed drew up the first ‘contract’ for an "understanding" consent to be signed by volunteers before they were accepted as subjects for his yellow fever experiments [102]. Then, in 1908, Sir William Osler reiterated his views before the Royal Commission on vivisection stating that consent in the "full knowledge of the circumstance" is essential [103].

While the abuses of human subjects are perhaps not as "rare" as William Bean suggested [104], most experimenters did operate with a personal code of ethics. In 1865, Claude Bernard stated:

"May we make experiments on men condemned to death or vivisect them? Instances have been cited... in which men have permitted themselves to perform dangerous operations on condemned criminals, granting them pardon in exchange. Modern ideas of morals condemn such actions; I completely agree with these ideas... A helminthologist had a condemned woman without her knowledge swallow larvae of intestinal worms, so as to see whether the worms developed in the intestines after her death. Others have made analogous experiments on patients with phthisis doomed to an early death; some men have made experiments on themselves. As experiments of this kind are of great interest to science and can be conclusive only on man, they seem to be wholly permissible when they involve no suffering or harm to the subject of the experiment." [105]

For Bernard, the main moral principle was to avoid harm rather than any need to gain the subject’s consent. One way in which the idea of avoiding significant harm was put into practice was through self-experimentation. If an experimenter was happy to use himself, his wife or his children as subjects then it was acceptable to perform the experiments on others. Other ethical principles important at the turn of the century included, prior animal experimentation, and – for non-therapeutic research – the limited consent of the subject [106].

To conclude this section it seems that professional ethical values at the turn of the century, persisting up until the middle of the twentieth century, were more codes of etiquette than consistent ethical principles. The human subjects of research were "hostage to the conscience of the individual physician" [107]. A survey of the BMJ revealed little concern with the ethics of experimentation that persisted largely until the mid 1950s. Although human experimentation was written about, the concerns were largely financial and administrative, reflecting the struggle between clinicians and clinical scientists that dominated the years between the two world wars [108]. Comments in the BMJ in 1930 were limited to statements such as:

"The conflicting claims of the individual patient and of experimental medicine are, of course, obvious; no clinical experiment can be pushed to its logical conclusion like a laboratory experiment." [109]

Implementation of the eight ethical themes in practice will now be considered. Discussion of the themes prior to the mid 1950s is hampered by a lack of contemporary comment on the issues. For example, in 1943, Walshe was able to discuss what was required of a good researcher without seeing the need to refer to ethics [110]. It is also interesting to note that following Kenneth Mellanby’s account of the Nuremberg trials only two letters were published in response (see below), which perhaps confirms other commentator’s views that the events at Nuremberg – and hence the Nuremberg Code – were not seen as relevant to research practice in general [111].

22.4.2. The meaning of a 'volunteer'

Pre-1939. The possibility of undue influence invalidating the voluntary nature of a subject’s participation in research was not a major concern prior to the twentieth century. In 1777 John Aiken wrote that hospital patients were the most suitable for research because: of their illness, their consequent obligation to society and the hierarchical power structure of hospitals [112]. By focusing on patients’ suitability because of their vulnerability, Aiken demonstrates
an approach to the research ethics that is entirely disparate to current thinking. However, not everyone was completely insensitive to the issue and Bazin notes that, as early as 1852, Napoleon’s chief surgeon

"Had already claimed that it was forbidden to test new drugs on servicemen in military hospitals because these persons had no right to refuse the treatments." [113]

That this view was not consistently held may be seen by the example in 1918, when Turkish prisoners of war in Egypt were used as subjects of a dietary experiment on protein loss [114].

1939-1947. In 1940, the Lancet published reports of 43 non-therapeutic studies. In only 3 (7%) of these was the subject described as a volunteer. In 2 studies staff members were used as subjects and in 1 study the subjects were students. In one study, the ‘volunteers’ were new Naval recruits aged between 15 and 17 [115]. Although the study was not particularly risky, it may be reasonable to question whether young recruits arriving at their first training ship should really be considered ‘volunteers’. Along similar lines, Hazelgrove notes that during the war, Witts thought that volunteers for infection transmission experiments: "were to be obtained from service personnel serving long sentences in detention barracks" [116]. Also illuminating was the short interchange that took place in the BMJ shortly after the Nuremberg Trials. Discussing the victims of Nazi experimenters, Kenneth Mellanby stated:

"The victims of the experiments were not the willing co-operators who have taken part as volunteers in so many experiments in this country." [117]

In response, Dr Louise Fraser wrote:

"The so-called “voluntary” medical experiments on conscientious objectors, prisoners in jails, and so forth are not ethical. The practice differs in degree, but not in principle, from the German prison-camp experiments." [118]

Three such conscientious objectors who acted as volunteers replied:

"We were under no sort of external compulsion to participate; nor, having started, were we compelled to continue any longer than we thought fit." [119]

The fact that so many individuals were making huge sacrifices by fighting to defend the nation and its values during the Second World War may have blurred the edges as to what was acceptable. The desire to “do one’s bit”, and possibly the awareness that being a conscientious objector carried a degree of stigma, may have had a significant influence on the “volunteer’s” willingness to participate [120]. In the context of the war, this was left largely unquestioned. Kenneth Mellanby, who performed much research using conscientious objectors during the Second World War, wrote the following instructive passage:

"When a regular soldier volunteers to take part in an experiment he nearly always does so either because the sergeant-major says “I want three volunteers... Jones, Smith and Robinson report, etc.,” or else he thinks that by being a volunteer he will get a cushy job for a time, and perhaps some extra leave as well... Furthermore, once he has “volunteered” he is expected to continue with the experiment until he is dismissed... It must be borne in mind that the [conscientious objector] volunteers had come entirely of their own free will – they had not been drafted or compelled to take part in the experiments. Had they not volunteered they would have been in other work... Furthermore, there was no way in which we could hold a man to the job if he found the conditions intolerable, and so any volunteer could have left whenever he so wished." [121]

A statement later in his book confirms the range of freedom within which an individual may still be thought of as a volunteer. He suggested:
"There is one circumstance which might make pacifist the most likely and most easily available volunteers in peace-time, however, and that is the continuation of conscription." [122]

This statement implies that providing there is some choice a subject may still be considered a volunteer, even if the only other option is unacceptable to the subject's conscience. To some extent, perhaps, the definition of a volunteer has been dependent on the social conditions of the time. A final point worth noting here is that, during the war, the Home Office refused to consider a War Office proposal that anti-malarial drugs should be tested on criminals in British prisons [123].

1947-1964. In 1950 the Lancet published reports of 49 non-therapeutic experiments. In 9 (18%) of these the subject was referred to as a “volunteer”. None included members of staff but 2 used students. In 1960 the term ‘volunteer’ was used to describe the subjects in only 6 (7%) of 91 non-therapeutic experiments. 7 of the experiments used staff members as subjects, while students or members of the armed forces were used in 8. In one of the studies, the way the term ‘volunteer’ is used implies that it was simply the alternative category to ‘patient’ rather than carrying any information about the extent of the subject’s freely willed participation [124].

The use of junior staff members was not seen as problematic. In 1997 Malcolm Watson recalled being a junior doctor in the 1950s when he “volunteered” to be a research subject:

"My cooperation was voluntary: I wanted that job, but I was a captive subject and my consent was implied." [125]

Similarly, the eagerness of patients to please their doctors by agreeing to non-therapeutic research was noted by Ann Dally in an interview with Jenny Hazelgrove. To the medical students at the time, this use of patients was regarded "as a joke rather than as a problem" [126].

In 1951 the President of the Royal Society's section on experimental medicine, R. A. McCance, noted, without any apparent awareness of the potential for abuse, that:

"I have never had much difficulty in obtaining the co-operation of normal subjects. It is always a great help to have made the same experiment on oneself first."

Despite a relative insensitivity to the issue, some were more thoughtful. In 1952, Richard Doll, an eminent scientist, noted the ethical importance of age and “voluntary status” and criticised a research report that had described as volunteers, subjects believed to be infants [127]. And, in a leading article in 1955 an anonymous author noted the vulnerability of someone in a dependent relationship [128].

1964-1975. In 1970, the Lancet published reports of 129 non-therapeutic studies. In 18 (14%) the subjects were referred to as volunteers. In 6 studies the subjects were staff members and in 4 they were either students or members of the armed forces. The use of the term ‘volunteer’ to mean a ‘non-patient’ persisted [129].

During this period there appears to be greater attention paid to the problems of ‘volunteers’ in dependent relationships. For example, Professor Witts stated that it was generally accepted in the UK that no experiments should be performed on prisoners [130]. Similarly, Campbell noted the danger of undue influence. He argued:

"We know the phrase "Dr So-and-so is wonderful – I would do anything for him". We must beware this "slippery slope" where infectious enthusiasm, charismatic salesmanship, or gentle persuasion descends to coercion and intimidation, no matter how subtle." [131]

Louis Lasagna explored the use of potentially vulnerable groups as subjects. He noted the debate over whether prisoners should or should not be used, which is problematic because of
the potential for exploitation and lack of true voluntariness. However, he also noted that some commentators were arguing that outlawing the use of prisoners as subjects would be to their detriment. The research gave the prisoners something to do, raised their standing in the prison community and helped them to "maintain, or develop a sense of personal value". Furthermore, he suggested that while undue influence was more acute in such a captive group, it was not an insurmountable problem if sufficient care was taken [132].

Focusing on students and patients, Talcott Parsons suggested that:

"Neither patients nor students are wholly free to refuse reasonable requests to serve as research subjects. They tend to retain a "Formal right" to refuse, but seldom exercise that right in normal circumstances. Scarcity factors also play a part, as in shortages of hospital beds or places in the "better" colleges." [133]

Interestingly, one of the more vocal and influential critics of unethical experiments considered that medical students and medical staff, because of their training and ability to understand the consequences, might be the least objectionable subjects. However, he acknowledged the coercive danger of a dependent relationship [134], and later suggested that any use of deception negates the subject's volunteer status [135].

**1975-1989.** In 1976, in an article in Scientific American, Bernard Barber noted that there had been a sea change:

"People who define themselves as being unequal, underprivileged or exploited are demanding better treatment and better protection… This moral revolution of rising value-expectations has combined with revolution in medicine to focus attention on the ethics of experimentation with human subjects." [136]

In 1978, Lebacqz and Levine noted that there was academic debate as to whether the "subtle or indirect "constraints" or "coercions"… [that exist] when prospective subjects are highly dependent, impoverished or needy", are sufficient to invalidate consent. They drew a distinction between "coercion", which always invalidates consent, and "enticement", which may invalidate consent depending on how it affects the subject's "rational grounds for choice" [137].

In 1980 the Lancet published reports of 116 non-therapeutic studies. Of these, 19 (16%) described their subjects as volunteers. In 2 studies the subjects were staff members and in a further 2, the subjects were students or members of the armed forces.

In 1981, the Ethical Committee of University College Hospital (UCH) in London reported on their experiences. Although they recognised the debate about the suitability of using patients as volunteers for non-therapeutic research they felt that, despite their special position, patients were still capable of being volunteers [138]. Then, in 1983, confirming Pappworth's argument, the Cancer Research Working Party in Breast Conservation opined that withholding or distorting "material" facts left the subject "involuntarily ignorant" [139]. They also counselled against too easily accepting the patient's compliance because it may be more indicative of the patient's desire to please than a truly voluntary decision [140].

**22.4.3. The meaning and implications of "consent":**

**Pre-1939.** There are many examples of early experiments where consent was either not sought or was more akin to a submissive and ignorant acquiescence than to consent as we currently understand it. A notable exception was Walter Reed's yellow fever experiments (see above). His ideas of consent were reflected by Sir William Osler who believed, at least for non-therapeutic experiments, that consent in the "full knowledge of the circumstance" was essential [141]. Others, such as Claude Bernard, made the avoidance of harm their main ethical principle [142]. In 1930, Sir Thomas Lewis required both the subject's willing co-operation, which perhaps falls short of a 'real' or 'true' consent, and an absence of harm. He stated:
"Interference giving rise to temporary discomfort, the patient willingly co-operating, may be permissible; interference calculated to bring risk, however slight, to a patient's health must remain unjustifiable."

That practice fell short of this on many occasions is well documented and some examples have been discussed earlier.

1939-1947. In 1940, of the 43 non-therapeutic and 48 therapeutic studies reported in the *Lancet*, none mentioned whether the subject had given their consent. While this does not mean that consent was not obtained, it perhaps suggests that it was not seen as a particular issue. Instead of discussing "consent", the reports usually thanked other medical colleagues for allowing access to their patients [144]. During this period, the BMJ does not contain a single reference to the issue of consent.

In *Human Guinea Pigs*, Mellanby described his experience with conscientious objectors who volunteered for experiments instead of active service during the Second World War. The implication that runs through his book is that the volunteers willingly co-operated. The closest he came to discussing an express, as opposed to the implied consent of co-operation was when he stated:

"At the outset I imagined that it would be a necessary safeguard for each man to sign some sort of detailed contract, setting forth his duties and the risks he was taking, in order to cover me in an emergency and to have something to which to hold a recalcitrant subject if he proved non-co-operative." [145]

This is a particularly formalistic approach to consent that views it as a means of protecting the investigator from legal redress rather than protecting the subject from an infringement of his rights.

1947-1964. In 1950, the *Lancet* published reports of 72 therapeutic and 49 non-therapeutic studies. None of these reports mentioned that consent had been obtained. Similarly, in 1960 consent was not referred to in any of the 77 therapeutic or 91 non-therapeutic studies. In 1951, McCance suggested that for non-therapeutic experiments on 'healthy colleagues' consent was necessary. However, for research using patients, the requirement was not so stringent "unless requiring considerable co-operation" [146]. Then, in 1953, Michael Shimkin referred to the Nuremberg code and suggested that a voluntary consent was one of "two primary principles" of human experimentation [147].

In the BMJ of this period, consent was unmentioned until 1955. In discussing non-therapeutic research, the anonymous author stated:

"The main requirement is a full explanation to patient or parent before permission is obtained." [148]

The author then goes on to refer to Shimkin's article in *Science*, which emphasised the Nuremberg Code's requirement of voluntary consent. It is worth noting, that this article was published following a parliamentary discussion on the issue. The BMJ reported that Mr Swingler MP asked the Minister for Health, on the 7th of February, whether human experimentation in hospitals should be restricted to volunteers. The Minister replied that such research should only take place with the consent of the patient or parent. He also stated that he had no reason to believe that this was not the usual practice [149]. Further parliamentary questions followed, in both 1955 and 1958 [150], with MPs criticising reported experiments. The Minister for Health, while acknowledging that consent should be sought, defended the research by emphasising the harmless nature of the studies [151].

At an international conference on medical ethics in 1955, M. Pasteur Vallery-Radot is reported as stating that one of the principles of clinical research is that the researcher must obtain the subject's free and "enlightened" consent [152].
Much of the discussion during this period centred on research using patients, with physician commentators reflecting the dominant paternalism of the time. Both Professor Witts [153], and later, the influential Sir Austin Bradford Hill argued that patient consent was not always necessary [154]. Sir Austin Bradford Hill’s article sparked, what Hazelgrove describes as "a furious debate… between representatives of the medical profession and sections of the public" [155]. Helen Hodgson, the Chairman of the Patient’s Association was particularly critical of Sir Austin Bradford Hill’s views on consent [156]. It should, however, be noted that while Sir Austin Bradford Hill questioned the need for consent in some therapeutic research studies, he did accept it was necessary for non-therapeutic research [157].

What little discussion there is from non-medical commentators suggests that they placed a greater emphasis on consent than did the researchers. For example, a few years before Sir Austin Bradford Hill’s controversial article, the American theologian, J.J. Lynch, emphasised the "primary importance" of informed consent, which should, as a general rule be explicit. He also pointed out that while consent was necessary, it was insufficient to justify experimentation [158].

1964-1975. During the period following the Declaration of Helsinki, the issue of consent, although by no means universal, appears to be more at the forefront of researchers mind. Of the 129 non-therapeutic experiments reported in the *Lancet* in 1970, 10 (8%) of them made some reference to the notion that the subjects (or their parents) had given their consent. The same was true in 6 (9%) of the 64 therapeutic studies.

In 1966, Thurston noted the need for "full and free consent" [159]. However, later that year – and reminiscent of Sir Austin Bradford Hill, Atkins stated that, while it may be desirable so as to ensure cooperation:

"At a meeting of the Medical Research Council… it was decided that there was no obligation on the part of the investigator to inform a patient that he was participating in a trial." [160]

In Human Guinea Pigs, Pappworth’s critique of human experimentation, he affirmed the Nuremberg Code’s requirement of consent [161]. He stated that consent is of "vital importance" but noted that:

"In many cases where apparently consent is asked and obtained there is so little candour toward the subject that, although in the event consent is given, the subject really has no proper idea of what he has consented to." [162]

As an illustration, he recounted a conversation he had with a London cardiologist in which the cardiologist offered the opinion that consent to "a few small blood samples" would be a valid consent to obtaining blood samples directly from the patient’s heart by means of a technique called cardiac catheterisation.

In 1969, Freund noted both the limitations and the benefits of requiring consent. He stated:

"The concept of consent has been much derided as unrealistic and artificial, and of course it embraces a range of responses that differ in their degree of autonomy and understanding. The psychological constraints or compulsions that operate on a seriously ill patient are different from those that affect a person attracted to an experiment through an advertisement. Nevertheless a requirement of "voluntary, informed consent" does have values beyond the symbolic one of respect for individual autonomy and personality. It is far from the be-all and end-all of legal and ethical safeguards, but it is a valuable ultimate check." [163]

In 1971, the Under Secretary for Health distinguished therapeutic research, in which consent was good practice but ultimately up to the individual doctor’s judgement, from non-therapeutic research in which free consent was the "guiding principle" [164].
Reflecting a somewhat ambivalent approach to the idea of consent, Eilenberg, in 1973, paternalistically suggested:

"[Obtaining] the patient's consent to all experimental procedures has to be balanced by the distress that may result." [165]

As part of the same discussion, Williams raised doubts about both the possibility and value of consent that have been echoed several times since. He argued:

"Much has been made of "informed consent" but when the subject is uneducated this ritual is a deception to both patient and doctor and provides no real safeguard." [166]

1975-1989. In 1975, sociological research in the US suggested that experimenters tended to respect the "form but not the spirit" of the requirement for voluntary consent with subjects signing consent forms without even being aware they were enrolling in a research study [167]. This failure to engage with consent perhaps reflected the view that subjects were unable to understand the information, making the whole process an exercise of "jumping through hoops" to satisfy formal requirements. A study performed in 1975 sought to demonstrate this. Introducing the study, Garnham stated:

"It is on … [consent] that most of the ethical codes falter, and they fail because they use such terms as 'true', 'informed' or 'understanding' to qualify the word consent, resulting in internationally accepted codes which are more honoured by breaches than by adherence to the concept they seek to convey." [168]

The results of the study suggested that the volunteer's understanding was generally poor. Even in subjects who worked in scientifically related disciplines, understanding was only partial [169]. Garnham concluded that "informed consent is extraordinarily difficult to achieve… [and] a practical impossibility in medically naive subjects" [170]. However, he still maintained that a "full explanation" should be given to the subject, although he did not explain why this should be so [171].

In 1980, the *Lancet* published reports of 116 non-therapeutic experiments and 96 therapeutic trials. Some reference to the subject's consent was made in 22 (19%) of the non-therapeutic studies and in 40 (42%) of the therapeutic ones. This shows a marked increase from studies reported ten years previously. Also of note is that the phrase "informed consent" was being used more frequently. However, consent was not seen as a universal requirement in practice and, in one notable study the investigators appeared to have no problem with taking samples of brain matter from patients with dementia for entirely non-therapeutic purposes [172]. Despite the increased focus on consent, the Cancer Research Campaign Working Party in Breast Cancer Conservation was still able to note, in 1983, that:

"The issue of informed consent, particularly as it relates to controlled clinical trials, has not attracted much attention in British medical practice." [173]

In 1979, members of the Harrow District Ethical Committee stated that, in their view, a written consent might make the patient believe he had signed away his right to withdraw. As such, they did not insist on a written consent but did require consent to be obtained in the presence of a witness who was present to ensure that the researcher followed the proper procedure [174]. Then, in 1981, the University College Hospital Ethical Committee also stated that written consent was not always required but researchers had to explain how they would obtain consent [175].

In 1985, Arpaillange et al. criticised the formalistic approach to consent as a legal requirement that impeded research. Instead, consent should be seen as an ethical law [176]. Similarly, the GP philosopher, Ranaan Gillon argued that doctors should respect the research subject's autonomy [177]. However, in 1986, Jonathon Glover suggested that, unless the study carried "unacceptable" risks for the subject, the benefit to future individuals might outweigh the harm of not obtaining the patient’s informed consent [178].
In 1989, Baum et al. noted that there had been "an enormous shift" away from the beneficent nature of the doctor-patient relationship towards a more autonomy-based model. However, they counselled that:

"Autonomy… is not the only ethical imperative… perhaps an exaggerated regard for this single principle will put at risk… the practice of scientific medicine." [179]

Throughout the period covered, most of the problems with consent per se arise in relation to the use of patients – whether for therapeutic or non-therapeutic research - rather than with healthy volunteers. As Gillon observed:

"Healthy volunteer studies are the most obvious examples of non-therapeutic medical research in which, for example, the effects of medications on normally healthy people are tested. No one has any difficulty in recognising why… explicit consent from subjects of such research is required." [180]

However, a bare consent may be insufficient to satisfy the researcher's obligations. There is also the more contentious issue of how much information is required.

22.4.4. The provision of study information:

Pre-1939. There is little information about the standards of disclosure. The issue is not mentioned in the BMJ between 1930 and 1939 and Massey notes that "informed consent" had not yet been "invented" [181]. We do know that Sir William Osler knew Walter Reed whose yellow fever experiments required volunteers to sign a document stating:

"That he consents to submit himself to experiments for the purpose of determining the methods of transmission of yellow fever… The undersigned understands perfectly well that in the case of the development of yellow fever in him, that he endangers his life but it being entirely impossible for him to avoid the infection during the stay in this island, he prefers to take the chance contracting it intentionally in the belief that he will receive from said Commission the greatest care and the most skilful medical service." [182]

Osler himself required that for a valid consent a "full knowledge of the circumstance" is essential [183]. But there are also many instances in practice where information was withheld or distorted [184].

1939-1947. That information disclosure was not seen as a particular issue is demonstrated by the complete failure of any study reported in the Lancet in 1940 to mention either consent or disclosure.

Describing his wartime experiments with conscientious objectors, Mellanby wrote:

"One thing only was essential in the managing of the volunteers in these experiments, and that was to be willing to take the trouble to explain in detail just what was the purpose of anything we asked them to do. I always made a practice of holding periodical meetings which they all attended, and where I gave a progress report and answered the questions which they had to ask." [185]

However, this information was disclosed, not to enable understanding for consent, but to encourage co-operation with the study protocols. Mellanby also considered the need for a written document for the volunteer to sign "setting forth his duties and the risks he was taking" but it is unclear whether he went through with this and its purpose was to protect himself rather than the volunteer [186]. Hazelgrove questions how well informed some of Mellanby’s volunteers actually were. One conscientious objector recalled that "nothing was explained to us in detail". Another wrote to his parents and, because he was only 17, asked for permission to enrol in malaria experiments. He assured his parents the experiments were "quite safe" [187].
1947-1964. In the *Lancet* in 1950, of the 72 therapeutic experiments, 2 (3%) reported providing their subjects with some degree of information. None of the 49 non-therapeutic experiments did so. In 1960 the situation was very similar, with 3 of 77 therapeutic studies providing some information, but none of the 91 studies recorded that information was given to subjects.

The anonymous author of leading article in the BMJ in 1955 displayed a not uncommonly held ambivalent attitude to information disclosure. While discussing experiments on children, he stated:

"Of course every safeguard is introduced. Parents... are informed with the greatest scrupulousness of the nature of the experiment, of its object, of the risks entailed... but however careful and conscientious the explanation... there is a limit to the layman’s understanding of it." [188]

Mr Swingler MP raised the issue in Parliament that year and argued that consent should be based on knowledge of the nature of experiments, including the risk, benefits and possible injury that may result [189]. The Minister for Health, however, was keen not to dictate such requirements to clinicians. The rest of the discussion in the BMJ for that period was centred on the need to gain the consent of all patients entered into controlled trials.

While not particularly explicit, Shimkin argued that the subject must "understand... the procedure" [190]. However, Katz recalls some experiments he was involved with in the 1950s. He stated:

"It did not occur to us to wonder whether we were obligated to disclose to our subjects our concerns about the detrimental impact that our experiments might have on them, or whether, in light of our concerns, we should have proceeded with our investigations." [191]

Like the anonymous author in the BMJ (see above), McCance noted the problem of disclosure to a lay person. He stated:

"It is often difficult for an investigator to explain the nature and object of his work to a non-scientific colleague and generally quite impossible to a patient. 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."

He suggested that these principles appear to hold throughout the country, but he then emphasised the primary role trust played, which explained why permission was not always necessary for “common place” procedures [192].

1964-1975. By 1970, a few more investigators felt that information disclosure was sufficiently important to be recorded in the study report. In the *Lancet*, 4 (6%) of 64 therapeutic studies and 5 (4%) of 129 non-therapeutic studies reported that some information was given to subjects. The researchers that reported giving information tended to describe it as being of the “nature” of the study. In only one study was it specifically reported that the “hazards” of the experiment were disclosed [193].

In a 1964 article in the BMJ, Mitchell stated that parents of prospective child subjects should understand simply the “nature” of the experiment [194]. Little discussion of the issue takes place through the remainder of the 1960s. In 1971, the Minister for Health responded to a question by stating that the professional bodies had given guidance that required proper understanding of the nature and consequences of the intervention [195]. Later that year at the BMA Annual Conference, Dr Addison, the Secretary of the Medical Defence Union (MDU) stated that a “true” consent required an explanation of the nature and purpose of the procedure [196]. However, in 1973, Professor Witts reiterated the researcher’s standard response to the question of information disclosure. He stated:
"Practically all codes demand the "informed consent" of the subject but many experiments are difficult to explain to people without medical knowledge." [197]

Similarly, Campbell argued that:

"We must admit that truly informed consent is always impossible in theory and is very difficult to achieve in practice."

However, he then demonstrated a rare attention to the process of achieving sufficient understanding in the subject. He argued that an "acceptable" level may be reached if the information is brief, is in lay terms, is repeated and the subject is given the opportunity for questions [198]. He also suggested that neither deceit nor subterfuge should be tolerated and a written explanation of the project should be provided [199].

Pappworth noted that the two types of information most likely to be withheld were "that the procedure is experimental and its consequences are unpredictable" [200]. As far as non-therapeutic experiments on healthy volunteers is concerned the fact that it is experimental will almost certainly be known. Information about the consequences, however, is applicable to both types of experiment and is an important element of rational decision-making.

Other commentators argued that "informed consent" might be an inadequate safeguard because of the ease with which a "persuasive" researcher can get around its requirements. This, Edsall suggested, may be a more important issue than trying to define exactly what "informed consent" means [201].

1975-1989. In the studies reported in the *Lancet* during 1980, there is an increased use of the term "informed consent" implying that researchers are getting more sensitive to the issues of information disclosure. Whether this is an ethical or simply a procedural sensitivity is, however, impossible to say. In addition to the notable increase in explicit consents disclosure was specifically referred to in 6 (6%) of 96 therapeutic studies and 8 (7%) of 116 non-therapeutic studies.

In 1979, the Harrow District Ethical Committee reported that the consent forms for approved studies contained six items of information: the purpose of the research; the procedures involved; the risks; the benefits; a statement that the subject was free to withdraw; and an invitation to ask questions [202]. This appears to be a fairly comprehensive requirement, but not all studies at this stage were submitted to ethics committees, and this particular committee also allowed that consent was unnecessary for minor procedures. It is of interest to note that, in 1981, consent issues formed one of the two most frequent problems with research proposals [203].

As with the earlier period, it is noticeable that disclosure was viewed as most problematic when patients rather than healthy volunteers are involved. This was especially so for therapeutic research [204]. While some focused on the problems of comprehension and unnecessary anxiety caused by "full" disclosure and suggested instead that disclosure need only be adequate (see above), others maintained the need for "full" disclosure [205]. There was also, towards the end of this period, an attempt to incorporate the ethical requirements of informed consent within a medical model [206].

22.4.5. The concepts of "harm" and "risk"

Pre-1939. For the early researcher, not causing harm was the primary concern. Thus, Claude Bernard stated:

"Christian morals forbid only one thing, doing ill to one's neighbor. So, among the experiments that may be tried on man, those that can only harm are forbidden." [207]

This concept of harm, however, had nothing to do with a breach of bodily integrity or infringement of rights in general. Bernard's opinion concerning the type of experiments that
may be performed on the dying (see earlier) suggest that his concept was limited to one of suffering or permanent injury. Bernard expressed the rule as an absolute, however, a clue that some minimal amount of harm might have been considered acceptable may perhaps be abstracted from the other prevalent rule that an experiment was permissible providing the experimenter was prepared to subject himself or his children to it. However, it is apparent that there have been many notable occasions when those rules appear to have been flouted (see above). Often the subjects in these experiments were criminals, slaves, the poor, or the “immoral”. It may be that, rather than the principles being forgotten in the quest for knowledge, the investigator felt that they simply did not apply to those classes of humans.

In the 1930s Sir Thomas Lewis was quite clear as to what ought to be considered acceptable. He stated:

"Interference giving rise to temporary discomfort, the patient willingly co-operating, may be permissible; interference calculated to bring risk, however slight, to a patient's health must remain unjustifiable." [208]

This view, however, may be less helpful than it appears because all interventions carry some risk of harm and his view, if strictly applied, would rule out all experimentation.

1939-1947. These years, which were mostly spent at war, are atypical in that, given the risks young conscripts faced, it may have seemed reasonable to be less concerned if subjects were willing to face more significant risk [209]. As an anonymous author noted, both research worker and other volunteers subjected themselves "with a personal devotion, a courage, and a sacrifice" to distressing, painful and dangerous research [210]. Mellanby, for example, thought nothing of subjecting volunteers to deliberate infection with scabies and, more seriously, malaria. At one point he noted quite cheerfully:

"A substantial proportion developed clinical malaria and were unpleasantly ill, but they put up with this in a most praiseworthy manner." [211]

Grimley Evans and Beck note that:

"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. 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." [212]

Whether wartime affects the protection we offer to prospective research subjects is an important question. After all, if some can be conscripted to face huge risks during active service, why should other not be 'conscripted' into research studies and face equivalent risks? The question was considered by the WMA in 1957. The Association produced a code governing Medical Ethics in Wartime [213]. It stated that: "Human experimentation in time of war is governed by the same code as in times of peace". Furthermore, it was considered unethical for doctors to: "weaken the physical or mental strength of a human being without therapeutic justification".

1947-1964. Commenting on dangerous experiments and noting the distinction between war and peace, Professor Witts stated:

"The plain fact is that few researchers would willingly inoculate themselves with jaundice, and it is an absolute rule of clinical research that one should never do to others what one would not do to oneself. Once break this rule and one is on the slippery slope that led so many Nazis to the abyss. Moreover, it is a moot point
whether a healthy citizen is within his legal rights in volunteering for a dangerous experiment… [which] are rarely wise in peacetime." [214]

Despite this admonition, subjects were harmed and placed at risk of greater harm in some experiments. In one study investigating the connection between malnourishment and liver damage African infants were subjected to liver biopsy, which is hardly a risk free procedure [215].

For McCance, who acknowledged that all experimentation carries some risk, the crucial issue for the experimenter was whether he retains some control over the risk. Thus, he argued, he would not inject 'icterogenic serum'\(^{17}\) because once injected the outcome was beyond the investigator’s control [216].

In 1955, an anonymous author pointed out one of the reasons why public and political concern about human experimentation was increasing. He stated:

"The conditions under which such experiments can be justified – are ethical – are not necessarily easy to determine. What to the doctor may be a seemingly harmless procedure may to the onlooker… be something to be challenged in the name of ethics or morality." [217]

This same author insightfully exposed the illogical position, that an experiment was ethically acceptable if the researcher was also prepared to be a subject. He stated:

"A doctor voluntarily contracting a tropical disease to discover some link in the chain of causation is one thing; to subject a lay person – even a volunteer – to a similar experience is another, especially if the lay person is in a subordinate position." [218]

In 1960 Lynch described what he believed was the prevailing view:

"At the present time it seems safe to say that a subject may for the benefit of others authorize and submit to any experimental procedure which will not seriously and permanently impair his functional integrity or cause a grave risk to his life." [219]

1964-1975. During this period, clinical researchers still preached the doctrine of using one’s own family as subjects as a measure of ethical acceptability. For example, in discussing experiments on children, Mitchell - although aware of the danger posed by the ‘zealot’ - fell back on the well-worn principle (reiterated by Sir Hedley Atkins in 1972 as a fundamental rule applicable to all research) [220]:

"When deciding whether an experiment is justifiable, the old question: “would you subject your own child to this?” is still a good yardstick for most moderately minded people." [221]

Pappworth also relied on this principle. He stated:

"No experiment should be contemplated, proposed or undertaken to which, if he were in circumstances identical to those of the intended subjects, the experimenter would even hesitate to submit himself or members of his own family." [222]

However, he also noted that the subject might see certain events as seriously harmful or painful, while the "hardened" experimenter may see the same event as nothing out of the ordinary [223]. This different approach to harm may lead to very different ethical judgements about an experiment. Unfortunately, this implies that the principle may be less useful than if the experimenter was as sensitive to harm as the inexperienced subject.

\(^{17}\) Icterogenic means, “to cause jaundice”.

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1975-1989. Much of the discussion of risk and harm focused on children. In 1980, the Working Party on the Ethics of Research in Children stated that the acceptability of research involving children was premised on, amongst other things, the “degree of benefit… assessed in relation to the risk of disturbance, discomfort, or pain”. Acceptable risk was categorised under three headings. Negligible risk was defined as being lower than the risks run as part of everyday life. Minimal risk was: "risk questionably greater than negligible risk"; an example would be an additional venepuncture. 18 "More than minimal risk" was left undefined but an example given was of a kidney biopsy taken during a therapeutically necessary abdominal operation [224]. This approach to risk was criticised by an editorial in the *Journal of Medical Ethics*, which pointed out that defining risks by reference to everyday life allowed risks that many would regard as "substantial" to be classed as negligible [225].

In 1982, Pochin noted that people often approached risk subjectively and that what might appear to be a reasonable risk/benefit ratio to a researcher may not appear so reasonable to a lay person. Also, the perception of risk may be affected by whether the risk is accepted voluntarily or imposed [226].

22.4.6. The use and acceptability of payments and inducements

**Pre-1939.** The use of payments prior to 1939 appears to have been acceptable if not desirable. Walter Reed paid his yellow fever volunteers $100 for participating. To Spanish immigrants in Cuba this amount of money may have been more of an inducement than fair recompense. Lederer comments that, this offer was so appealing that some immigrants not chosen apparently “almost wept” [227]. Lederer also notes that in the US during the early part of the twentieth century, financial recompense for participating in research was looked on favourably [228].

**1939-1947.** Bryer notes that the MRC Committee on Tuberculosis in War-time:

"Advocated the introduction of allowances for tuberculous patients and their families to ensure the voluntary co-operation of the workers in the radiography schemes."

[229]

Similarly, Mellanby was keen to ensure that his volunteers were paid, although he noted that they still ended up worse off than if they had joined the army [230].

**1948-1964.** For the BMJ during this period, the question of financial recompense or other inducements was effectively a non-issue. The only mention was in relation to a report of the use of convicts as research subjects in the US and South Africa. The report notes, without comment, that one of the ethical safeguards to ensure the convicts were true volunteers was to avoid offering any direct incentives [231].

Also during this period, McCance - the President of the experimental medicine section of the Royal Society of Medicine - stated that he was not in favour of "hiring" subjects [232].

**1964-1975.** For Pappworth, "rewards" were not seen as problematic. His way of avoiding exploitation was to completely exclude certain groups, such as prisoners, from participation. In fact, he argued that offering "proper terms of compensation" to prisoners would be essential if any sort of case were to be made in favour of using prisoners. For Pappworth, where an experiment was inherently ethical, "reward" was not an issue [233]. The issue of providing suitable recompense was not raised in the BMJ during this period. Talcott Parsons simply noted that research subjects get rewards other than monetary, and that payment may or may not be made. When payment was made, he suggested it was not viewed as "matching the economic value of the contribution" but rather was "thought of as an "honorarium" [234].

As with the question of whether research subjects should be paid, the problem of avoiding overly persuasive inducements was not discussed in the BMJ during this period.

18 A venepuncture is a blood sample taken from a vein, as opposed to blood taken from e.g. a heel or thumb prick.
1975-1989. During this period, the issue of payment to research subjects was more openly discussed. In 1978, Vere considered the argument against offering financial inducements. Giving short shrift to the argument that any payment is unethical, he stated:

"The inducement argument is practical nonsense. If no payment or present is offered, very few people value the well being of others sufficiently to volunteer. If large payments, enough to 'be an inducement', are offered people would volunteer and the inducement would be wrong. But, if small payments or presents are offered, just enough to compensate for inconvenience, not large enough to 'be an inducement', these are right in most people's eyes." [235]

In 1979, the Harrow District Ethical Committee reported on its practices. Without explaining why, the report stated that, while meeting out of pocket expenses may be acceptable, actual payment was not. The implication here is that a commercial level of payment would be too great an inducement, but it would be unfair to expect subjects to pay for the privilege [236]. On the other hand, the UCH Ethical Committee did not make this distinction and simply noted that they had agreed to allow both patients and healthy volunteers to receive payments [237].

An anonymous author in the BMJ in 1985 noted that early drug trials more commonly involved paid volunteers. The author stated that the subjects are often:

"Vulnerable individuals… who are primarily participating for money." [238]

He did not condemn this practice but argued that these "special people" deserve "special consideration" if they were harmed by the experiment and he called for a very close scrutiny of this commercial activity by ethics committees.

Some commentators, however, were more explicit about the potential for financial rewards to be problematic. Robbins, for example, stated:

"Sometimes subjects in trials are rewarded for their participation… On the face of it, this practice seems distasteful and coercive. If done solely to entice subjects to participate, it probably is ethically suspect. On the other hand, an argument could be made that participation does inconvenience the individual and may, indeed, cost something. It would seem reasonable to pay for inconvenience and/or costs such as those for transportation." [239]

22.4.7. Compensating persons injured as a result of the experiment

Pre-1939. The issue of compensation was not much discussed. Legal redress has, in recent history, always been a possibility and ex gratia payments have been made in individual cases. Walter Reed, for example, offered those volunteers who actually contracted yellow fever an additional $100, which, in the event of the subject's death would be paid to a person designated by the volunteer [240].

1939-1947. Again, the issue of compensation for injuries was not really addressed.

1947-1964. During this period, the main focus lay with the ethical issues of study design and recruitment rather than with the problem of how to manage adverse consequences. The issue of compensation was not raised at all in the BMJ. However, Irving Ladimer considered the issue from an American perspective. He stated that the traditional way of dealing with the issue was to "assume that some liability or malpractice policy is the answer". He criticised this approach because:

"The pay-off generally depends on proof of fault, whereas the likelihood of harm comes not so much from negligence… but from the inherent nature of research. Chance factors, unknown elements, unanticipated actions and reactions and idiosyncratic responses are all too familiar gremlins." [241]
For Ladimer, the cost of harm should not be borne by the subject but should be considered as part of the costs of the research project, to be assumed as an administrative charge, by the sponsor.

1964-1975. The issue of compensation was not discussed in the BMJ during this period. A 1968 WHO technical report noted:

"There has been a failure to consider the needs of human subjects who are injured in the course of an ethically irreproachable human experiment. There is need for some process, such as an insurance system, that will pay for medical care, where necessary, and provide appropriate compensation when research subjects sustain injury or death during an investigation, regardless of possible negligence… The cost of this protection should be considered part of the basic cost of the conduct of clinical investigation." [242]

Ladimer suggested that providing compensation was the social responsibility of the research sponsor. Without such "common sense" compensation:

"There can be no proper expectation that volunteers… will long engage in research projects. As more is advertised and known about experimental medicine… the pressures for protection of this kind will mount. It is preferable to prepare in advance, in a climate of scientific and public accord, rather than to react to another “thalidomide” incident." [243]

1975-1989. In 1978, the Pearson Commission, which looked at the issue of civil liability and compensation, recommended that:

"Any volunteer for medical research or clinical trials who suffers severe damage as a result should have a cause of action on the basis of strict liability, against the authority to whom he has consented to make himself available." [244]

In 1980, the Ciba Foundation noted that the only means of compensation for a research subject was either a legal claim in negligence or an ex gratia payment from the research sponsor. This, it believed, was "clearly unsatisfactory". The Foundation considered three possible bases for compensation: negligence; strict liability; and no-fault compensation. It preferred the third option since it was non-adversarial and administratively efficient. The Foundation also noted the difficulty of proving that the injury was caused by the experiment. Its solution was to suggest that "unexpected events not readily explained" could be "attributed" to the experiment [245].

Shortly after this, in 1981, the UCH Ethical Committee stated that:

"In the case of healthy volunteers sponsored by a pharmaceutical company we require a contract accepting strict liability."

In the case of other research sponsors, compensation was dependent on ex gratia payments. The Committee also noted that it did not require researchers to inform subjects that there was no formal system for compensation [246].

In 1983, Diamond noted that:

"It is becoming common practice for ethical committees to expect assurances that patients participating in clinical trials will be appropriately compensated… should they be adversely affected by reason of their involvement in the trial." [247]

In 1985, following the death of a healthy volunteer medical student, an anonymous author argued that ex gratia payments are too uncertain to be acceptable and compensation should

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19 The Ciba Foundation is not the Novartis Foundation.
be legally enforced [248]. And, in 1990, Marshall and Moodie suggested that volunteers should be made aware of the arrangements for compensation [249].

The issue of compensation for studies other than those sponsored by a pharmaceutical company remained unresolved at the beginning of the 1990s, with legal redress being the only option in many cases [250].

**22.4.8. The development and function of ethics committees**

**Pre-1964.** During this period there were no formal ethical committees. Protection of research subjects was generally at the mercy of the ethical values of individual researchers. In 1951, for example, Sir Cecil Wakely stated:

"It is important to remember that ultimately all depends on the doctor. He must always remember that the patient is human." [251]

The presumed safeguard of individual responsibility and the high moral values of the medical profession prompted the Minister for Health in 1955 to reject calls for formal regulation. Medical ethics were best left to the profession and only the clinician in charge could really say what was right and what safeguards were required [252]. Calls for Government regulation were again rejected in 1958 when the Minister for Health stated:

"Investigations of this kind involve medical and ethical problems which are not susceptible of control by regulations." [253]

However, in 1962, an anonymous author noted 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." [254]

At this point in time, the WMA were in the process of producing the Declaration of Helsinki. Even though this would not be as restrictive as a supervisory ethics committee, advent of the code still drew fierce criticism from such notables as Sir Austin Bradford Hill [255]. However, not all researchers were against the idea of independent advice or supervision. Shimkin, for example, suggested that:

"Research on human beings is too hazardous and implies too many responsibilities to be undertaken by lone investigators. It should be a group effort supported by a proper consultative body." [256]

Pappworth, also, believed that safeguards were necessary if the public were to continue supporting clinical research. He did not, however, specify what form those safeguards should take [257].

**1964-1975.** In 1967, Pappworth noted that while most doctors were generally supportive of ethical codes as guidance for human research, a number of doctors remained sceptical. Although he recognised the value of codes, Pappworth suggested that they were still no substitute for individual conscience and since:

"No appeal to conscience will be effective with anybody who lacks a conscience… I have reluctantly come to the conclusion that the voluntary system of safeguarding patient’s rights has failed and new legislative procedures are absolutely necessary." [258]

Pappworth’s solution was to recommend a "consultation committee" with statutory authority. The members of this committee should include doctors, one of whom should not be engaged in any research and a lay member (preferably a lawyer). These committees would be immediately responsible to the GMC [259]. This, however, was not universally a popular
The anonymous author of a leading article in the BMJ, for example, argued that discussion with colleagues was just as useful and the "consultation committees" would be superfluous [260]. His belief was that individual conscience was the ultimate safeguard, although medical journals could bolster this by refusing to publish unethical work.

In March 1970, the RCP sent out a questionnaire to all hospitals to discover how far ethical committees now supervised research [261]. Only 55% of the 309 non-teaching hospitals replied, but 86% of the 37 teaching hospitals responded. Of the 32 teaching hospitals that replied, 30 (94%) had a functioning ethics committee. The figure was lower in non-teaching hospitals with 74% (125 of 169) confirming an active ethics committee. Of all the ethics committees, it was compulsory in 74% for research proposals to be reviewed by the committee. Only 6 of the 30 teaching hospital committees had a lay member. Lay members were even more rare in non-teaching hospitals. The survey also showed that the size of the committees varied from having only 1 or 2 members up to an unwieldy 65 members. Despite the number of ethical committees in existence, none of the studies reported in the Lancet in 1970 stated that they had ethical committee approval.

In 1971, 4 years after the RCP report, the BMJ's legal correspondent wrote that: "many hospitals now have ethical committees which enforce the WMA code of ethics" [262]. Also in 1971, the Under Secretary of State for Health noted that nearly all of the teaching hospitals had ethics committees [263]. By 1972, he stated that all teaching hospitals and more than 70% of other hospital authorities had ethics committees and a fifth of these committees had lay members [264]. By 1973 commentators were arguing that ethics committees ought to be "independent and authoritative" [265], and comprise lay and nursing views as well as medical [266].

In 1974, Campbell noted the lack of consistency between different ethical committees. He argued that it was a priority to establish "more effective ethical committees" since "medical ethics has now become too complex to be left to doctors alone" [267].

1975-1989. By 1980, 39 of the 212 studies reported in the Lancet specifically stated that they had ethical committee approval.

In 1981, a review of Scottish ethics committees revealed that the number of members varied from 1 to an unwieldy 73 and only 3 of the 34 that replied had lay members. 16 of the 34 saw their role as advisory rather than supervisory and 13 had not met at all in the previous year. Only 6 committees had formal procedures for monitoring the research once it was underway. The authors concluded that:

"In their present form research ethical committees do not satisfy fully the interests of the public or the research worker. There is inadequate representation of lay interests at all levels, and with most committees maintaining strict confidentiality over their proceedings there is little scope for public accountability." [268]

In a questionnaire survey looking at the attitudes of 58 members of ethics committees, Allen and Waters found that 67% felt that the system of review could be improved and 47% thought that this should include some system for monitoring work in progress. Non-medical members were far more strongly in favour of monitoring research. 33% of respondents thought that ethical committee decisions should be seen as advisory rather than mandatory. In their discussion of the survey the authors instructively commented:

"Ethical Committees are still a relatively unknown quantity and it appears that in the 15 years or so since ethical review... has been widely undertaken in Britain, little has been done to allow any problems to be brought into the open for discussion either by the medical profession as a whole, or by the general public, with the result that sometimes even research workers are unaware of the requirements of the ethical committee within their own health districts." [269]

A 1983 survey conducted by the Institute of Medical Ethics also revealed marked variability in the size of the committee with 8% still having no lay membership. 12% of the committees
were aware of research conducted in their institution that had not been approved by the ethics committee [270]. As a result of his survey Nicholson concluded that ethics committees were unsure of their role and were inconsistent in their practices. McNeill notes that ethics committees were still being criticised for the poor quality of their work at the end of the 1980s [271]. Finally, a survey in the early 1990s revealed that membership was still overly medical with insufficient lay representation. Ethnic minorities were particularly under-represented. Members were also often untrained, uninformed and isolated from members of other ethics committees. The survey also found that ethics committees were under-staffed and overburdened with paperwork [272]. Neuberger concluded that legislation was badly needed because ethics committees had failed to follow earlier guidelines and lacked any real power to deal with unethical research.

22.4.9. The requirement of prior research.

The requirement of prior research, either animal or laboratory, has been a long standing principle of research ethics. In the 14th Century, for example "Bernard de Gordon, suggested a hierarchy of drug testing: from birds, to brute animals, to "those in the hospital", to the "lesser brethren", and then on to others" [273]. Similarly, Claude Bernard stated in 1865:

"If it is immoral, then, to make experiment on man when it is dangerous to him, even though the result may be useful to others, it is essentially moral to make experiments on an animal, even though painful and dangerous to him, if they may be useful to man." [274]

Although a strong antivivisection movement grew in the second part of the nineteenth century, researchers continued to require prior animal experimentation. In England, the Research Defence Society was founded specifically to defend the use of animals for prior experimentation. And William Osler defined ethical experimentation on humans by consent and prior animal experimentation [275].

In 1932, Gunn noted that drug research had lagged behind other forms of human experiment and he explained this as the result of the paucity of good animal models [276]. Then, in 1948, Professor Witts, also indirectly, indicated the requirement for prior animal experimentation. He stated:

"The only justification for experiments on patients is that the information cannot be obtained from animals and that it is likely to be of benefit to the patient and his fellow sufferers." [277]

Lynch reiterated the principle in 1960. He stated:

"Implicit in this concession [to allow human experimentation] is the supposition that the procedure has been adequately tested short of human experimentation." [278]

Similarly, Pappworth made prior animal experimentation one of his six cardinal principles of human experimentation [279]. The only justifiable exception to this principle was where there was no suitable animal model. However, it should be obvious from earlier discussion that what is stated in principle was not always observed in practice.
22.5 Summary figures

The development and application of codes/guidelines relating to the ethics of human experimentation in the UK between 1939 and 1989, discussed in the preceding sections are summarised in figures. The figures are intended to be a handy pictorial guide to the main topics discussed under each of the eight themes.

Figure 22.1. The Volunteer

Figure 22.2. Consent
Figure 22.3. Information

Figure 22.4. Harm and Risk
Figure 22.5. Payments and inducements

Figure 22.6. Compensation
Figure 22.7. Ethics committees

Figure 22.8. Prior research
22.6 Conclusions

Prior to the Second World War there were no specific national or international codes or guidelines directed at UK practice. Ethical judgements were largely left in the hands of the individual researcher. In 1947, the Nuremberg Code, which made consent an absolute requirement, was formulated. However, it appears that most researchers felt that this Code was inapplicable to them and it had little if any impact on practice [280]. In the second half of the 1950s public, media and political scrutiny of research activity increased culminating in the MRC recommendations and the Declaration of Helsinki as the medical profession sought to put its house in order before it was taken out of their hands. With Pappworth’s publications in the UK (and Beecher’s in the US) [281], the emergence of bioethics as a discipline and the creation of interest groups such as the Patient’s Association, debate continued. This debate led to the requirement for ethics committees [282]; initially the protective peer review suggested by the RCP and then more independent ethics committees with nurses and lay persons included as members. Although important advances were made during this period ethics committees were insular, inefficient, inconsistent and idiosyncratic in both membership and practice. This was still the case some 5 years after our period ends [283].

The writings of eminent scientists, such as Claude Bernard and Sir Thomas Lewis suggest that the primary concern of researchers before the 1930s was to avoid causing suffering or harm. Sir William Osler was more prepared to accept that the subject might be harmed provided he had given his consent and it was largely accepted that, for research involving volunteers, consent was required. The situation was murkier when using patients, even where the research was fundamentally non-therapeutic. At this juncture, consent was largely viewed as simply an agreement by the subject to allow the intervention. Information disclosure was seen as necessary only when the subject’s co-operation was required and a ‘volunteer’ was often meant to refer to a ‘non-patient’. Despite the Nuremberg Code, information disclosure was not seen as a priority until the mid seventies and even then, it was subject to fierce criticism and some resistance as researchers argued that it was a futile – possibly dangerous – exercise since the subjects were unable to understand the disclosure.

The issue of undue influence began to be raised around the end of the nineteenth century. However, during the Wars it seemed less important and conscientious objectors were used as subjects without question. Indeed, they were applauded for their sacrifice. The circumstances of war may also have affected the researcher’s (and the volunteer’s) attitude to acceptable risk/harm. The issue again became important in the mid 1960s, coinciding with the MRC guidelines and the Declaration of Helsinki, as researchers and commentators became more sensitive to the subversive pressures exerted on potential volunteers. In the 1970s, attention was turned once more to the issues of payment and compensation. There was widespread acceptance that subjects should not be left out of pocket but should not be ‘induced’ to participate by overly large rewards. There was also heavy criticism of the lack of formal arrangements for compensation. Leaving it to the subject to claim in negligence was seen as undesirable and the debate culminated in the RCP recommending, in 1986, that subjects should be compensated by the research sponsor irrespective of negligence.

As can be seen, this period saw the introduction of important and influential codes and guidelines. These Codes have been both reactive, reflecting prevalent ethical concerns, and pro-active. Noticeably, the most influential of these documents were those formulated by the profession itself. By the end of the 1980s the regulation of human experimentation, although far improved from that in place in 1939, still had a long way to go. In particular the structure and functioning of ethics committees was hugely inconsistent and they lacked any real power to enforce their requirements. Despite that, this period saw a marked shift in attitude towards an approach that attempted to balance respect for individual autonomy and protect the vulnerable while not stifling research. This is a difficult equilibrium to achieve which is unlikely to satisfy everyone. Nor will it always be able to prevent exploitative or dangerous research. It is, however, far better than the ‘leave it to the individual researcher’s conscience’ approach prevalent in the past.
87. Howard-Jones, N. "Human Experimentation in Historical and Ethical Perspectives". Social Science and Medicine, 1982; 16: 1429-1444, 1442.
90. Slater v Baker and Stapleton (1767) 95 ER 860.
255. See: Bradford Hill, A. "Medical Ethics and Controlled Trials", *British Medical Journal*, 1963; i: 1043-1049. See also the subsequent correspondence.