

# ETHICAL ISSUES IN THE DEVELOPMENT OF MEDICINAL PRODUCTS

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*This article considers some of the ethical issues facing those involved in the development of medicinal products for human use*

The primary objectives of all health care interventions are to prevent, cure or alleviate disease. Such objectives may or may not be achieved with the use of medicinal products, but the development of medicines for human use does invoke a wide scope of ethical issues that must be borne in mind alongside the basic scientific considerations.

The importance of ethical issues, particularly in the research carried out during the development of new health care products, has increased significantly over the past 15 to 20 years with the greater knowledge and more complex techniques developed, especially in cell biology. The range of tissues now available for experimental techniques for the development of new drugs has increased greatly. Such developments have also thrown into sharp relief the use of animals in medical research, which has always been a highly contentious issue for many people. This article focuses on the toxicological and clinical aspects of the drug development process, and the ethical considerations that must be taken into account at all times.

It must be stressed at the outset that there are no definitive "rights" and "wrongs" in the determination of ethical issues: what one person may consider to be an ethically acceptable experimental technique might be viewed as totally inappropriate by another person. Each person will be guided by his or her own individual morals, and their social, religious and cultural environment. The brief consideration in this article of the ethical issues that can arise in the development of medicinal products is provided with the objective of stimulating discussion on these sometimes sensitive issues.

## HISTORICAL PERSPECTIVES

The standards applied to research on human subjects have varied enormously over the course of the past 100 years. It should be remembered that the pharmacological revolution that resulted in the development of vast numbers of new therapeutic agents really only began during the early 1950s. However, research of varying kinds had been conducted for many years before that.

Perhaps the worst examples of ethical standards applied to such "research" occurred during the 1939–45 war. At that time, investigations carried out under the guise of "medical research" were performed by physicians working for the Nazi adminis-

tration on members of their own population and on those from countries that had been occupied by the Germans. Pseudo-scientific experiments were carried out on identical twins, on the mentally subnormal, on prisoners of war and on concentration camp inmates, all of whom were among the most vulnerable members of society at the time for differing reasons.

Some of those who were involved in these experiments were brought to justice during the Nuremberg medical trials, which brought to light for the first time the horrendous experiments that had been carried out on unwilling and uninformed individuals. Besides the prosecutions that were brought, one major outcome of the trials was the Nuremberg Code, published in 1947, which highlighted the principle and need for informed consent for any participant in a medical experiment.

Much of the impetus for the legislation that controls the development of medicinal products arose from the problems of the use of thalidomide in the early 1960s. The legislation has confirmed the importance of scientifically sound studies into the effects of any medicinal products given to people of all age groups. Society has demanded that the medicines that it uses are of a high quality, are safe and are clinically effective. The ethical basis for clinical research is founded upon the Declaration of Helsinki.

## THE WMA DECLARATION OF HELSINKI

The World Medical Association (WMA) Declaration of Helsinki was originally developed at the 18th (WMA) Helsinki conference in June 1964. The declaration has gone through a number of revisions, most recently at the WMA meeting in Scotland in October 2000. It is based upon and developed from the ethical principles in the Nuremberg Code, but it is not a legally binding document. It does stress, however, that the role of a physician takes precedence over that of the investigator in a clinical trial.

In its introduction the declaration makes the point that "medical progress is based on research which ultimately must rest in part on experimentation involving human subjects". It stresses the primacy of the well-being of the individual subject over

the interests of science and society in general. It also recognises that most procedures that are carried out within medical practice, be they prophylaxis, diagnosis, or therapy, involve an element of both benefit and risk. It is important to ensure that the degree of risk incurred is proportionate to the level of benefit expected.

The section of the declaration covering "Basic principles for all medical research," stresses that any subjects involved in medical research must be volunteers and must be fully informed about the reasons for the research, its potential outcomes and any personal or other benefits that may accrue to them as participants. It also addresses the issues concerning the participation of potentially vulnerable members of society. These may include people who are legally incompetent, who are physically or mentally incapable of giving consent or who may be under the age of legal majority. One further important point raised by the declaration concerns the use of placebo in medical research. This is especially important since no patient involved in a trial should be adversely affected by their participation and the potential use of a placebo may prevent that person receiving the appropriate medical treatment for the condition that is being assessed.

## PROTECTING THE VULNERABLE

One of the most important aspects of the Declaration of Helsinki is the fact that it is intended to protect the most vulnerable people in society. Mention has already been made of the unethical use made of those who were most vulnerable during the 1939–45 war. Such occurrences have unfortunately been repeated (on a smaller scale) since that time in other conflicts and parts of the world. One of the groups who are most vulnerable to unethical research are children, for whom appropriate medicines have been produced only infrequently. The issue of promoting better medicines for children and the ethical issues that that raises will be discussed later.

Besides children, there are a number of other potentially vulnerable groups of individuals. These groups have been highlighted by a 1995 World Health Organization guideline on the conduct of clinical trials. Vulnerability may be the result of the status of an individual within a hierarchical society or group, through being placed in a situation where they are not fully aware what is being asked of them as potential participants in clinical research or due to financial vul-

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nerability as a result of the payments that are often offered in clinical trials.

Those who may be at particular risk from undue pressure from senior members of a hierarchy to participate in a trial include:

- Undergraduate students in any health care profession, but especially those in medicine, nursing and pharmacy
- Personnel working in a hospital or health care environment or those working in a laboratory in a non-clinical setting
- Employees within the pharmaceutical industry
- Serving members of the armed forces

Those of the last above-mentioned groups may face a special problem since they are expected to obey orders without question. For enlisted members of the armed forces, failure to do so can result in a charge of insubordination, which is a punishable offence.

Another vulnerable group is those who may have an incurable disease who may be (unethically) persuaded to take part in trials. Such patients may believe they have been enrolled in a trial for a product that might reverse their terminal illness; equally they may feel that, since they have an incurable illness, there would be no sense in not participating in something because they have nothing else to lose. Such patients should obviously not be placed in that difficult situation in the first place.

Financial and social vulnerability are also potential problems. Some people may be more susceptible to persuasion to take part in clinical research because of their place of residence or social and financial situation. Examples might include residents of nursing or care homes, and especially those who have little or no contact with relatives or other members of the community outside their local environment. Prisoners, refugees or others who are socially vulnerable may also feel it necessary to agree with "suggestions" for participation in such research.

The issue of payment for participation in clinical studies has long been subject to debate. Financial inducements will clearly be a great attraction to those on low incomes or who are unemployed, either with a view to taking part in a trial themselves or enrolling other members of their families (eg, their children). When any application is made to an ethics committee to carry out a clinical study using volunteers, the way in which participants are recruited into the trial will be carefully scrutinised to ensure that there has been no undue or inappropriate pressure exerted on those who have agreed to take part.

#### RESEARCH ON PRE-NATAL TISSUE

Many of the most contentious issues in research ethics have arisen within the past 10 to 15 years following the introduction of new techniques that have allowed research on embryonic and fetal tissue. To understand the origin of such tissue, a brief summary of the fertilisation and gestation

period is given.

**The origin of fetal tissue** Fertilisation takes place when a sperm penetrates the outer layers of the ovum and stimulates the maturation of the female egg. From the period of fertilisation to eight weeks' gestation, the fertilised tissue is referred to as an embryo. From eight weeks to birth, the tissue is referred to as a fetus.

It is important to recognise that fertilisation is a continuous process rather than an event that occurs at a specific time since fertilisation is only completed between 26 to 30 hours after the initial ovum penetration by the sperm. The fertilised ovum is referred to as a zygote, whose formation marks the beginning of the development of the embryo. It should also be noted that, although the combination of genes from the ovum and sperm is complete at fertilisation, the zygote can still split into two or more separate entities up to two weeks after fertilisation has occurred, producing twins or higher multiple births.

Cell division begins almost immediately after completion of fertilisation, producing a number of undifferentiated cells called blastomeres. The removal of any of these undifferentiated cells can take place without threatening the development of a complete individual. By the third day after fertilisation, a small sphere of approximately 16 cells has been formed, which remains unattached within the uterus for a further one to two days. It is therefore at about six days after fertilisation that this bundle of cells, probably now numbering 50 or 60, becomes implanted within the wall of the uterus. This process takes a further 12 to 14 days to complete, at the end of which time a primitive placental circulation has been established. The primitive streak, which marks the appearance of the early nervous system within the embryo, develops at about 15 to 16 days after fertilisation. It is the generation of this tissue that has formed the basis of the 14-day post-fertilisation limit in legislation in many countries beyond which research may not be conducted on the embryo.

At the time of implantation into the wall of the uterus, the fertilised ovum is described as a blastocyst. The blastocyst has been formed approximately five or six days after fertilisation but, in consideration of ethical issues, its importance lies in it being one source of stem cells. The importance of stem cells, particularly in the research into new drugs, is in their potential to develop into almost any other cell type in the human body, including those of the blood, heart, or brain. They are described as "pluripotent".

**Use of the embryo or fetus** Much of the debate about the ethical issues surrounding the use of embryos and fetuses has arisen because of the introduction of *in vitro* fertilisation (IVF) techniques. This process invariably produces a number of "spare" embryos.

The main arguments about the use of embryos for research purposes focus on the

stage in its maturation at which it is perceived to be a non-person or a person. At one end of the spectrum exists the belief that, at the time of fertilisation, another person has been created who has the full rights of a healthy and normally living individual. At the other end of the argument, the embryo is regarded as having no status as a person until such time as there is some brain function. This emphasises the importance of the development of the primitive streak described above.

To further complicate the argument, there also exists considerable debate as to the stage at which the central nervous system development becomes meaningful. Should it be at the time the embryo is able to feel pleasure or pain? Should it be at some stage at which the embryo responds to external stimuli? Some people believe that this takes place only much later during the development of the fetus, sometimes as late as 28 weeks of gestation.

There is also the "slippery slope" argument, which provides an intermediate view that neither an embryo nor a fetus is a "full" person but has the potential for becoming so. In effect there exists a continual process of increased potential for the fetus to become a person, with a corresponding increasing significance and importance attached to that tissue during the period of gestation.

As mentioned above, most tissue is derived from IVF procedures. At the time of such IVF procedures, usually far greater numbers of embryos are generated than are likely to be used. The remainder are often kept in cold storage until such time as the donor parents determine that they should no longer be kept or further attempts at implantation are tried. Once there has been a successful pregnancy from IVF, the donor parents are often unconcerned about the fate of the other potential embryos held in storage. What needs to be borne in mind by those who might consider their use unethical is that the further development of this embryonic tissue can only occur if implantation takes place. Their availability outside the body therefore presents an ideal opportunity for various techniques to be assessed — providing the embryos are less than 14 days old, which the bulk of those that have been stored following IVF generation usually are.

**Stem cell research** As previously described, the group of cells formed after fertilisation but before implantation is termed the blastocyst. The implantation of the blastocyst into the wall of the uterus marks the beginning of the development of the embryo and fetus. The further successful development of the embryo is very much dependent upon the activity of the stem cells. Their pluripotent properties render them potentially extremely valuable in the treatment of degenerative diseases and has led to their being cultured *in vitro*. Stem cells can potentially produce nerve cells that might be used for the treatment of Parkinson's disease, pancreatic cells for the treat-

ment of diabetes and regenerated heart tissue for the treatment of ischaemic heart disease. It has also been suggested that they could be used to generate new bone marrow, lung, kidney, muscle, skin, and retinal tissue. Their potential is therefore enormous.

Most currently available stem cells have been derived from human embryos and in particular from those unused in IVF clinics. An alternative method of preparation has been to use cloning techniques that generate a cell line from which the human embryonic stem cells can be cultured. However, their use has caused considerable controversy in many countries. The ethical issues that concern the use of stem cells derive from both their origin in human embryos and, equally importantly, their ability to create and form almost any other type of cell that is found in human tissues.

#### RESEARCH IN CHILDREN

There exists a difficult balance to be struck between almost everyone's concern at seeing a child who is ill and the fact that, to be able to provide an adequate range of treatments for that child, research must be carried out in children. Traditionally, a medicinal product for an adult has been given to a child at a reduced dose, but often without any clinical research during the product's development into its effects on the younger age group. The reasons why medicines have not routinely been developed for children at the same time as those for adults are varied. First, there is a much wider spectrum of disease and illness in adults than in children with many adult illnesses, for example, rheumatoid arthritis, hypertension and renal disease occurring relatively rarely in those under 16 years of age.

Secondly, children are not a homogeneous group: the effects of a medicinal product on a child of two years of age can be significantly different from those produced in a child of 12 years of age. As a consequence, the conduct of clinical trials in those under 16 years presents major difficulties and can sometimes significantly delay the introduction of a new medicinal product to the market.

Finally, parents or carers are often understandably reluctant to allow their child to participate in clinical trials, significantly reducing the numbers of subjects available to be enrolled in such studies.

Many of the specific ethical issues facing researchers carrying out clinical trials with children have been addressed by Directive 2001/20/EC on "... the implementation of good clinical practice (GCP) in the conduct of clinical trials on medicinal products for human use". This legislation was adopted in May 2001 and aspects of the performance of clinical trials in minors are covered in Article 4 of the directive.

All individuals taking part in a clinical study, whether they are adults or children or both, can only take part when they have freely given their agreement to do so. It must be fully explained to any participant

why the clinical trial is taking place, what is hoped to be achieved by the trial and what the role of the participants will be in the trial (eg, will blood samples be required, will it be necessary to take tablets or capsules, or will they be required to undergo regular medical examinations during the trial?). How long the trial will last, the fact that they can withdraw from the trial at any time without penalty, and any arrangements for remuneration for their participation in the trial must also be explained.

Clearly, there are difficulties in obtaining this informed consent from children under the age of eight years. However, it is vital that as much information as possible is given to children who have some degree of understanding of what they are being asked to participate in, communicated ideally to the child by somebody with expertise in doing so. If the child is unwilling to take part in the trial, that decision must be respected. A request to withdraw from the trial by the child must equally be respected and acted upon.

For those children under the age of consent, it is a requirement for the child's parent or legal representative to provide the written informed consent for that child's participation in the trial. The amount of information given to the parent or legal representative should be consistent with that that would be given to any adults who would themselves be participating in the trial.

Society's concern for the welfare of children is also reflected in the directive's requirement that a trial can only be carried out in children if it is for the benefit of the child and if it is to confirm experimental data previously generated in clinical trials carried out on those who have been able to give their informed consent. Unlike in some trials conducted in adults, it is also necessary for the child to be suffering from the clinical condition that is being treated during the trial. Additionally, the trial can only be performed if it can only be carried out in children. All trials should be designed to ensure that minimum pain, discomfort, fear and other foreseeable risks are experienced during their conduct. It is vital that the level of risk and that any distress caused to the child is monitored constantly throughout the trial.

The European Commission and European regulatory authorities have for some time been concerned about the lack of availability of medicines specifically for the treatment of childhood diseases, and early in 2002 suggested a strategy to try to rectify this situation. It is therefore likely that the number of clinical trials carried out in those under the age of 16 years will increase significantly over the next five to 10 years. Everyone involved in such research needs to be aware of the significant ethical issues and standards under which such trials should be conducted.