**Lecture 6 Dr. Haider Raheem**

**Ethical Issues Related to**

**Clinical Pharmacy Research**

**Research ethics and clinical trials in therapeutic research**

All medicines employed in pharmacy are subjected to two linked phases of activity: discovery and validation. Some botanical species like the opium poppy were discovered by chance to have medicinal value some 2000 or more years ago and validated by simple trial and error. The vast majority of the more potent and selective drugs used in the UK today have been subjected to systematic processes of discovery, evaluation, testing and approval. Since the introduction of voluntary assessment by the Committee on Safety of Drugs in the UK in 1964, formal regulatory approval of all medicines has become rigorous and mandatory.

Formal validation involves testing both in animals and in humans. In the first instance, there is a requirement for testing in animals for evidence of potential activity, mode of action, metabolic route and toxicity. Once empirical safety and activity are confirmed, subsequent testing in human beings is undertaken to determine basic pharmacokinetics, pharmacodynamics, and to evaluate effectiveness and freedom from adverse effects. All human beings and non-human animals have interests, for instance in not being harmed, and this is at the heart of ethical considerations.

Clinical trials in human beings have two main functions:

* to demonstrate efficacy
* to identify possible adverse (side) effects.

Early forerunners of today’s clinical evaluation procedures are James Lind’s demonstration of the ability of citrus fruit juice to prevent scurvy, a disease common among sailors on long voyages (*A Treatise on Scurvy*, 1754) and William Withering’s studies with foxglove preparations to treat dropsy, oedema caused by congestive heart failure (*An Account of* *the Foxglove and some of its Medical Uses*, 1785). By modern standards, these studies would be considered to be rather crude and it is unlikely that much thought was given to matters of patient autonomy. But the real precursor of the modern comparative clinical trial procedure is probably the Medical Research Council’s evaluation of streptomycin in the treatment of tuberculosis, reported in the *British Medical* *Journal* in 1948. The so-called gold standard of contemporary clinical trials is the double-blind placebo-controlled study, where neither patient nor practitioner knows who receives an experimental treatment or who receives a control (an established comparator or placebo).

Clinical trials are undertaken on a phased basis, with increasing numbers:

* phase I: small-scale study in healthy volunteers (about 20–80) to assess pharmacokinetics, safe or tolerable dosage and route of administration
* phase II: patients (100–300) suffering from relevant disease to provide evidence of effective dosage, and safety
* phase III: patients (1000–3000) to establish formal safety, effectiveness and comparability
* phase IV: postmarketing studies in patients to identify low-level adverse effects (unlimited > 3000).

Although very many clinical trials and experimental studies are largely unproblematic, they are not always routine matters and risk free. In March 2006, eight young, healthy male volunteers participated in a phase I study involving an experimental T cell agonist TGN1412 in London. All six of those who received the active drug rather than placebo rapidly developed severe widespread functional failure in what appears to have been a cytokine storm. This is an exaggerated response that occurs when the normal reaction of T cell stimulation of cytokines becomes uncontrolled. The incident provoked many questions about the nature of this particular study (ethical and technical), and the controls, prestudy assessment and recruitment policy.

**Ethical issues**

Various aspects of randomised clinical trials have an ethical dimension. In participating in clinical trials, both healthy volunteers and patients are entitled not to be harmed and for respect to be shown for their autonomy. A duty of care to prevent harm is generally taken care of by (a) ensuring the adequacy of pretrial safety data and (b) by appropriate supervision and monitoring during and if necessary, following the trial. The most important issues concern personal autonomy and consent. This means being sure that the patient:

* is fully aware of the main aspects of the study, including an assessment of possible personal benefits or risks
* has a clear understanding that they may receive an inactive placebo
* does not feel obliged to participate for any reason and knows that he or she may withdraw at any stage without being penalised.

In other words, the patient’s or volunteer’s consent must be truly informed and voluntary. In philosophical terms this means *express consent*, as opposed to *tacit*, implied or supposed consent. Intervention without express consent is an assault. Additionally, patients are entitled to expect that their personal details will remain confidential unless anonymised or express approval and reason for disclosure is given.

A pivotal aspect of non-open, comparative clinical studies is that treatment is allocated not by a practitioner exercising judgement and knowledge of an individual patient but by following a randomization schedule. Studies are ‘blinded’ to eliminate the risk (as far as is possible) of bias that could call into question the reliability of a study and its conclusions. It is only because there is genuine doubt about the efficacy or adverse profile of a potential but unproven treatment that a study involving a control group and randomisation may be justified.

The term ‘equipoise’ is sometimes used to indicate the balance of knowledge prior to a clinical trial study. It means that there must be indisputable uncertainty concerning what is the best or optimum treatment. At the same time, physicians have an express obligation to benefit their patient’s illness or disease. Randomisation with or without blinding prevents a practitioner from exercising personal judgement with respect to a patient’s medication. Hence there is a tension between therapeutic obligation to an individual patient and therapeutic research that tends to be overlooked or glossed over when patients are entered into clinical trials.

**Legal considerations**

The World Medical Association in its Declaration of Helsinki has made influential policy statements: Ethical Principles for Medical Research Involving Human Subjects (adopted June 1964, amended 1983, 1989, 1996, 2000, 2002 and 2004).

The Medicines for Human Use (Clinical Trials Regulations) 2004 (Statutory Instrument 2004 No. 1031) covers requirements for informed consent of potential clinical trial participants and incorporates the provisions of the European Clinical Trials Directive (EC2001/20) into UK law. Paragraph 3(1) of Part 1 of Schedule 1 to the UK Regulations defines informed consent for capable adults:

A (capable) person gives informed consent to take part in a clinical trial only if his decision:

(a) is given freely after that person is informed of the nature, significance, implications and risks of the trial; and

(b) either

(i) is evidenced in writing, dated and signed, or otherwise marked, by that person so as to indicate his consent, or

(ii) if the person is unable to sign or to mark a document so as to indicate consent, is given orally in the presence of at least one witness and recorded in writing.

The regulations define an incapable adult as an adult unable by virtue of physical or mental capacity to give informed consent.

Provision is also made in the 2004 Clinical Trials Regulations for minors who are defined in the regulations as being under the age of 16 years. Consent must be given on behalf of a minor prior to inclusion in a trial by a parent or person with parental responsibility.

**Use of animals in research**

Thousands of animals, including rodents, rabbits, guinea pigs, some monkeys and higher apes are used in the assessment of the mode of action and toxicity of new chemical entities with potential to become medicinal substances. Over 2.85 million procedures with animals were undertaken in Britain in 2004 – an increase of approximately 63,000 above 2003.

**Ethical issues**

Significant reports on animals in research were published by a parliamentary select committee on Animals in Scientific Procedures (July 2002), and by the Nuffield Council on Bioethics (2005). There are two main points of criticism of the use of animals for drug testing.

1. The use of animals for such purposes is morally wrong – in particular, it is speciesist (the lives of animals are considered to be of less value than those of human beings). In other words, because animal lives are less valued, they can be treated as a means to human ends, even where this involves causing pain or distress.

2. Using animals to try to predict the behaviour of drugs in human beings is scientifically invalid. It relies on a mistaken analogy between the biological systems of animals and humans – there are similarities but often there are crucial differences. Even if some biochemical or enzyme systems are common to both humans and some other animal species, those systems operate within the holistic context of the individual species. Hence the pharmacological and toxicological behaviour of the drug may be species dependent.

The two criticisms can be made independently or in conjunction: the use of animals in research is morally indefensible and/or intellectually unsupportable, or as a fallback position if one fails.

**Legal considerations**

The use of animals in research in the UK is controlled within The Animals (Scientific Procedures) Act 1986. All relevant procedures, premises and personnel are subject to licensing within the Act, and the Home Office operates an inspectorate to ensure compliance. The Act covers all live (non-human) vertebrates at various stages of development, but also the common octopus from the time when capable of independent feeding. Under the Protection of Animals Act 1911 (1912 in Scotland), it is an offence to cause unnecessary suffering to any domestic or captive animal. The Royal Society publishes a useful summary, *The Use of Animals in Research: A Guide for Scientists* (2004; [www.royalsoc.ac.uk](http://www.royalsoc.ac.uk)).

**The Declaration of Helsinki**

**A. Introduction**

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data. The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.

2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.

3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician’s knowledge and conscience are dedicated to the fulfillment of this duty.

4. The Declaration of Geneva of the World Medical Association binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act only in the patient’s interest when providing medical care.”

5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation

in research.

6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.

7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

8. In medical practice and in medical research, most interventions involve risks and burdens.

9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.

10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this declaration.

**B. Basic principles for all medical research**

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.

12. Medical research involving human subjects must conform to generally accepted scientific principles, [and] be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.

14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.

15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards, but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.

16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.

17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.

18. Every medical research study involving human subjects must be preceded by careful assessment of the predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.

19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.

20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.

21. Medical research involving human subjects may only be conducted if the importance of the objectives outweighs the inherent risks and burdens to the research subjects.

22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.

23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of the personal information and to minimize the impact of the study on their physical, mental and social integrity.

24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject’s freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.

26. When seeking informed consent for participation in a research study, the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.

27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.

28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative.

29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.

30. Authors, editors and publishers all have ethical obligations with regard to the publication of the result of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

**C. Additional principles for medical research combined with medical care**

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has a good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:

The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or

Where for compelling and scientifically sound methodological reason the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.

34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient’s decision to withdraw from the study must never interfere with the patient-physician relationship.

35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician’s judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the

29th WMA General Assembly, Tokyo, Japan, October 1975

35th WMA General Assembly, Venice, Italy, October 1983

41st WMA General Assembly, Hong Kong, September 1989

48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996

52nd WMA General Assembly, Edinburgh, Scotland, October 2000

53rd WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)

55th WMA General Assembly, Tokyo 2004 (Note of Clarification on paragraph 30 added)

59th WMA General Assembly, Seoul, October 2008