

# **INTRODUCTION TO THE WORK OF RESEARCH ETHICS COMMITTEES IN THE UNITED KINGDOM**



**What is involved in being on a  
Research Ethics Committee**

**3rd Edition**

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## FOREWORD



The need for a booklet for new or would-be members of research ethics committees was concluded at a meeting of members of clinical pharmacology units at Sopwell House Hotel, St Albans, in November 1995.

This was put together following discussion at working parties and Sopwell House meetings. I would like to thank participants who have helped, but particularly Frank Wells, Richard Tiner, Kathy Doyle, Tony Birmingham, Laurie Prescott and Adrian Holden.

The predecessor of this booklet was devoted to Phase 1 Studies, but as all phases must be considered in a like manner since the transposition into British Law of the European Union Clinical Trials Directive, this booklet has been widened in its scope.

To keep it up-to-date and relevant, there are many website references. The main text of this booklet, along with a list of appendices and referenced websites, will be posted on the ABPI website ([www.abpi.org.uk](http://www.abpi.org.uk)).

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# GLOSSARY OF USEFUL TERMS

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**Absorption** The process of drug uptake by the body from a given site of administration.

**Acute** Short, sharp and quickly over.

**Acute toxicity study** A study in which animals are given a single large dose of drug and observed over a period of time for any ill effects.

**Adverse effect** Unwanted effect of a drug, which is either most usually dose dependent (type A) or unusually non dose dependent and unpredictable (type B).

**Agonist** A foreign substance that acts at a cell receptor site to produce the same effect as the normal body's chemical messenger.

**Amendment** A change made to the terms of the REC application, the protocol or any other supporting documentation after the study has started.

**Antagonist** A drug that counteracts or neutralises the action of another drug or normal chemical messenger or receptor of the body.

**Antidote** A substance which can reverse the toxic effects of a drug or poison.

**Apoptosis** Programmed cell death necessary to make way for new cells (e.g. turn over of skin cells).

**Appeal** Following the issue of an unfavourable opinion, the submission of the application essentially without revision to another REC for a second ethical opinion.

**Appointing Authority** A body responsible under GAfREC for the establishment and support of a REC.

**Approval conditions** Conditions to be observed by the applicant in the conduct of the research. Approval conditions are issued by the REC with the final letter confirming a favourable ethical opinion. (Note : approval conditions are distinct from the further information or clarification requested from the applicant when issuing a provisional opinion.)

**Atrophy** Wasting and loss of substance due to cell disuse and degeneration.

**Authorised REC** A REC established under GAfREC but not recognised by UKECA. An authorised REC may review all applications except those concerning

CTIMPs and multi-site research in two or more domains.

**Autopsy** Postmortem pathological examination.

**Battery** is any act which causes physical contact with a person, without his/her consent.

**Benign** Mild form of a disease or a tumour that neither spreads locally nor to a distant site.

**Bioavailability** The fraction of the administered dose which is absorbed and which enters the systemic circulation unchanged. Drugs can be 100% absorbed from the gut, but they must then pass through the liver before being released into the general circulation. During this 'first pass' through the liver drugs may be extensively metabolised and in many cases this reduces the bioavailability considerably. Thus the bioavailability of a drug can be reduced by poor absorption and/or extensive 'first pass' metabolism in the liver.

**Biotechnology** The application of the biological sciences, especially genetics, to technological or industrial uses.

**Blinding** Blinding is the process which prevents the research subject and/or the researcher from knowing the identity of different treatments in a trial.

**Bradycardia** Slow heart rate.

**Carcinogen** A compound which can cause cancer in animals and man; Carcinogens can be divided into

- a) genotoxic, which cause tumours by damaging the genetic material in cells
- b) non genotoxic, which causes tumours by affecting cell division but not by direct damage to genetic material.

**Chief Investigator (CI)** The Investigator with overall responsibility for the research. In a multi-site study, the CI has co-ordinating responsibility for research at all sites. All applications for ethical review should be submitted by the CI.

**Chronic** Lasting for a long time.

**Clearance** A measure of the effectiveness of an organ of elimination in the removal of a drug from the blood. It is defined as the volume of blood completely cleared of a drug during passage through the organ.

**Clinical trial** A formal research study in subjects to find out whether a new way of treating a disease is better, worse or the same as accepted present therapy or an inactive treatment (placebo).

**Clinical trial of a medicinal product** A trial designed to support a medicinal claim.

**Cmax** The maximum or peak concentration that a drug attains in the blood.

**Control group** A group of patients or healthy volunteers in a study who receive a standard treatment or placebo for the purposes of comparison with a 'test' treatment. The standard treatment may be the best medical treatment that would normally be given to a patient. When there is no standard treatment, the control group may receive either no treatment or a placebo (dummy treatment).

**Controlled trial** A clinical trial in which an experimental treatment is compared with a standard treatment or placebo.

**Correlation coefficient** This measures how closely data points are scattered round a regression line. The closer this value is to '1' the better the correlation.

**Crossover trial** A clinical trial in which all patients receive two or more treatments at different times in sequence. For example, in a two-part design, halfway through the study, one group is switched from the control treatment to the experimental treatment, and the other is switched from the experimental treatment to the control.

**Cultured cell lines** A population of disaggregated tissue cells, maintained and propagated, *in vitro* (outside the body, in the laboratory).

**Data Protection Act** Legislation to give individuals the right of control of information that is held about them.

**Deoxyribonucleic acid** A very long molecule that contains the complete genetic code for the automatic construction of an organism.

**Diastolic pressure** Pressure in the arterial system when the heart is relaxing and filling with blood.

**Domain** The area covered by a SHA (England), a Health Board (Scotland), a regional office of the NHS Wales Department or the whole of Northern Ireland.

**Dose comparison trial** A clinical trial in which the effects of different doses of the same drug are compared.

**Double-blind** In a 'double-blind' trial, neither the patient nor the researcher knows who is receiving the active and control treatments.

## Drug administration abbreviations

*od* once a day

*om* each morning

*on* at night

*bd* twice a day

*tds* three times a day

*qds* four times a day.

## Drug administration routes

*bolus* a fairly rapid intravenous injection

*dietary* drug mixed with the food

*epidural injection* into space between the dura mater (outermost lining of brain and spinal cord) and bony canal

*gavage* given by tube directly into the stomach

*infusion* intravenous injection of drug lasting many minutes

*inhalation(ih)* inhaled into the lungs via the mouth or nose

*intraarterial* injected into an artery

*intraarticular* injected into a joint

*intradermal(id)* injected just under the surface of the skin

*intramuscular(im)* injected into a muscle

*intranasal(in)* instilled in the nostrils

*intraoperative(ip)* injected into abdominal cavity

*intrathecal* injection within the subarachnoid space (surrounding brain and spinal cord)

*intravenous(iv)* injected into a vein

*oral(po)* by mouth

*pr* per rectum

*pv* per vagina

*subcutaneous(sc)* injection between skin and muscle

*sl* sub lingual

*tds* transdermal drug delivery system

**Drug disposition** The processes of drug absorption, distribution, metabolism and excretion.

**Electrolytes** The inorganic components of the blood or tissues (e.g. sodium or chloride ions). They carry either positive or negative charges and have an

important role in conduction of electrical impulses in nerves and muscle.

**Eligibility criteria** 'Inclusion criteria' are conditions which must be met to join a trial or study. Some are obvious, such as age, or specific diseases; others, such as blood test results require laboratory investigation. 'Exclusion criteria' are conditions that would disqualify a subject from the study. These may include taking drugs other than the drug being studied, or certain diseases. Often patients are excluded for safety reasons, because doctors know that the new drug may cause undesirable effects in people with a certain illness or blood test result.

**Enzyme** A protein which catalyses a specific chemical reaction.

**Excretion balance study** A study to examine by what routes the drug is eliminated by the body, and to determine the extent of removal by each route.

**Excipients** Those components of a formulation of a drug which do not contribute to its pharmacological activity. Lactose is an example.

**Exclusion criteria** These are safety conditions that would disqualify a subject from a study. These may include subjects taking certain drugs, having certain diseases or having certain laboratory results.

**Fast track drug development** This is the process of accelerating the new product pipeline, to counter the effects of patent expiration and external pricing pressures.

**Genetics** The branch of biology concerned with the structure, location, abnormalities and effects of genes.

**Genomics** is the study of the whole genetic make up of an organism.

**Genotype** The total genetic information contained in a cell.

**Half life** The time taken for drug concentrations to fall to half of their original value, once absorption and distribution is complete.

**Histology** The study of the microscopic structure of the tissues of the body.

**Human pharmacology studies** (Phase 1) are those studies carried out in the early phase of drug development on healthy volunteers or non therapeutic research carried out on patients.

**Hyperplasia** An increase in the number of cells in a tissue or an organ, causing an increase in the size of the part.

**Hypertrophy** An increase in the size of a tissue or organ caused by enlargement of the individual cells.

**Inflammation** A type of response to tissue injury typified by increased blood supply to the affected area and white blood cells entering this area (usually accompanied by redness, swelling and pain).

**Informed consent** Consent from a patient or volunteer to participate in a study following a full written or verbal explanation, which includes the risks and benefits of taking part.

**Investigator's research brochure** A compilation of the clinical and non-clinical data on the investigational product(s) which is relevant to their study in human subjects.

**Investigational medicinal product** A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorisation but used or assembled in a way different from the authorised form, or when used for an unauthorised indication, or to gain further information about the authorised form.

**In vitro** Occurring in the laboratory rather than in the body.

**In vivo** Occurring naturally within the body.

**Latent** Present but not manifest.

**Lead site** In the case of a multi-site study, the site for which the Chief Investigator is also the Principle Investigator.

**Ligand** A molecule that binds to another molecule e.g. an antigen binding to an antibody, a hormone or neurotransmitter binding to a receptor.

**Local collaborator** A person undertaking certain types of straightforward research procedure, not requiring the appointment of a Principle Investigator and a site-specific assessment.

**Main REC** In the case of multi-site studies, the REC undertaking the ethical review of the application. The main REC may be a LREC or MREC.

**Malignant** A term usually applied to invasive cancer and tumours or to unusually severe forms of a disease.

**Mean** of a set of measurements is their numerical average. It is obtained by adding all the values and dividing by the number of measurements.

**Median** is the value that splits a distribution of values exactly in half.

**Meta-analysis** tries to bring together an accumulation of information from a variety of published sources, relating to a similar hypothesis.

**Metabolism** The breakdown of a drug or any other molecule by the body.

**Metastasis** The spread of a cancer from its original site to another place in the body.

**Minor amendment** An amendment not requiring review by a REC.

**Mode** Measures the peak of a frequency distribution (i.e. the most commonly occurring value).

**Modified amendment** Following the issue of an unfavourable opinion on a substantial amendment, the re-submission of the amendment in modified form.

**Mutagen** A compound which has potential to alter DNA and thus cause genetic damage.

**Necrosis** Cell death.

**Neoplasia** The process of tumour production.

**Open study** A study in which both the subject and the researcher know what treatment is being administered.

**Oncogenicity** Potential of a substance to cause tumours.

**Organogenesis** The first three months of pregnancy during which time the organs of the foetus form.

**P value** The statistical probability that a difference at least as large as that seen in the data would occur by chance.

**Pharmacodynamics** The study of the effects of the drug on the body and the mechanisms by which it acts (what the drug does to the patient).

**Pharmacogenetics** The branch of biology that looks at how an individual's genes affect the way that they react to a particular drug.

**Pharmacokinetics** The study of the time course of the concentrations of drugs and their metabolites in the different compartments of the body. Drug concentrations depend on the processes of absorption, tissue distribution, metabolism and excretion (what the patient does to the drug).

**Phenotype** Any identifiable structure or function of an organism.

**Placebo** A preparation that may look and taste exactly like a test drug, but which contains no active substance (a 'dummy drug').

**Placebo effect** A therapeutic action brought about by a dummy drug.

**Principle Investigator (PI)** The investigator for the research site where the study involves specified

procedures requiring site-specific assessment. There should be one PI for each research site. In the case of a single-site study, the CI and the PI will normally be the same person.

**Protein binding** This is the ability of proteins to bind to drugs, with the effect of modifying therapeutic action. This can result in a low initial response and prolonging of effect.

**Protocol** A document which gives the background, scientific rationale to and detailed plan for the design, conduct and analysis of a study.

**Provisional opinion** A decision reached by a REC on an application, subject to the receipt of further information or clarification from the applicant. The statutory sixty day time period is suspended until the information is received.

**QT interval** A segment of the electrocardiogram at which some anti-arrhythmics produce their therapeutic benefit but which can be affected by a low potassium or other drugs, possibly producing a lethal arrhythmia (torsade de pointes).

**Radiolabelling** The technique of incorporating an isotope emitting radiation into a molecule present in the body of man or an animal. The radio labelled drug is thereby "tagged" and it can be imaged in different organs and its metabolic fate can be more easily determined.

**Randomisation** The process of selecting by chance the treatment a subject will receive in a trial.

**Receptor** A region in, or on the surface of a cell which interacts with a drug or specific chemical messenger. The effects on the cell can be inhibitory or stimulatory. Many pharmaceuticals are designed to mimic natural messengers: if they stimulate a process in the cell they are called agonists (or stimulants), if they inhibit, they are called antagonists (or blockers).

**Recovery group** A group which is treated with drug and left for a period without treatment to assess reversibility of any drug-induced changes.

**Referee** A person who gives expert advice to a REC on an application or any related matter.

**Regression line** This is the line that best fits a scatter of plots on a graph.

**Rescue medication** Treatment given to relieve a problem, brought about by the research.

**Research site** The organization responsible for hosting the research at a particular locality.

**Reversible change** Any change which disappears without trace once treatment has been stopped.

**Ribonucleic acid** The molecule that carries coded instructions for the synthesis of specific proteins from amino acids.

**Run in** Period in a trial where no test drugs are administered.

**Sensitisation** An enhanced (toxic) effect of a drug, caused by an immunological response arising from previous exposure. This type of response is often manifest as 'allergy'.

**Side-effect** Unintended adverse effect from a drug or other treatment.

**Single blind** In a 'single blind' trial the subject does not know what treatments they are receiving, but the researcher does.

**Standard deviation** A measure of the scatter of data points around the mean value.

**Stopping rules** The conditions laid down in the protocol for a research subject to be withdrawn from a study or a research project to be ended.

**Substantial amendment** Under the Directive and the Regulations, an amendment to a CTIMP that must be notified to both the ethics committee and the competent authority; it requires a favourable opinion from the main REC and it must not have objection from MHRA before it can be implemented. In the case of non-CTIMPs, a substantial amendment always requires the issue of a favourable opinion from the main REC.

**Surrogate marker** Indirect measure of a biological effect.

**Systolic pressure** Arterial blood pressure during maximum contraction of the heart.

**Tachycardia** Fast heart rate.

**Test group** A group of subjects in a study who receive the new treatment (other groups may receive other treatments including a placebo and may be called the 'control group').

**Therapeutic index** The ratio of the effective to toxic dose of a drug. A safe drug has a large therapeutic index.

**Tort** A breach of duty, other than a breach of contract, for which the offender will be subject to legal remedy, *in the civil courts*.

**Unblinding procedures** Revealing the details of the randomisation process, in relation to a research subject or subjects.

**Validation** An administrative check carried out by a REC Administrator to verify that an application is complete and may be accepted for review. Decisions on validation should be made within 5 days of receipt.

**Variance** The average of the squared deviations from the mean value. It represents the scatter, or dispersion of values about a central, mean value.

**Vehicle** The substance in which the active drug is dissolved or suspended.

**Vital signs** Indications that a person is still alive, such as breathing, heart beat or pupillary reaction.

**Volume of distribution** A measure of the tissue distribution of drug. It can be thought of as the volume into which the dose of a drug must be diluted to give the observed concentration in the blood or plasma. A drug with a large volume of distribution is extensively taken up into the tissues and the concentration in the blood is low. Conversely a drug with a small volume of distribution has a limited distribution to the tissues but the concentration in the blood is high.

**Washout** Period in a trial either during which excluded medication is discontinued, prior to administration of test drugs or between two arms of a cross over trial.



# ABBREVIATIONS

<b>ABPI</b>	Association of the British Pharmaceutical Industry.	<b>MCA</b>	Medicines Control Agency – the predecessor of MHRA.
<b>ADME</b>	Absorption, distribution, metabolism and excretion (of a substance).	<b>MHRA</b>	Medicines and Healthcare products Regulatory Agency.
<b>ADR</b>	Adverse drug reaction.	<b>MNLD</b>	Maximum non lethal dose – the maximum dose that can be administered without killing animals.
<b>ARSAC</b>	Administration of Radioactive Substances Advisory Committee.	<b>MRD</b>	Maximum repeatable dose – daily dose that can be administered to animals for extended periods without causing significant overt symptoms.
<b>AUC</b>	Area under the plasma-time curve: a measure of total exposure to drug.	<b>MREC</b>	Multi-centre Research Ethics Committee.
<b>CAS</b>	Central Allocation System – the booking system administered by COREC for applications to be reviewed by recognised RECs. Bookings of applications relating to a CTIMP or a multi-site study in two or more domains must be made through CAS. Multi-site studies in a single domain will normally be submitted direct to LRECs, but may be allocated through CAS.	<b>MTD</b>	Maximum tolerated dose.
<b>COREC</b>	Central Office for Research Ethics Committees.	<b>NEL</b>	No effect level – dose level at which a specific effect does not occur (NB different effects can have different NELs).
<b>CRF</b>	Clinical research form.	<b>NHS</b>	National Health Service.
<b>CRO</b>	Contract Research Organisation (usually a company to which a pharmaceutical company might ‘contract out’ a clinical trial).	<b>NOEL</b>	No observable effect level – level at which no effects are seen.
<b>CTA</b>	Clinical Trial Authorisation, the authorisation issued by the MHRA in the case of a CTIMP. No CTIMP can commence in the UK without the issue of both a CTA and a favourable ethical opinion. Applications to the MHRA and the REC may be made in parallel.	<b>pH</b>	A measure of acidity or alkalinity of a solution – pH 1 is very acidic, pH 7 is neutral, pH 14 is very alkaline.
<b>CTIMP</b>	Clinical trial of an investigational medicinal product.	<b>PIAG</b>	Patient Information Advisory Group.
<b>DNA</b>	Deoxyribonucleic acid.	<b>REC</b>	Research Ethics Committee.
<b>ECG</b>	Electrocardiogram.	<b>RDSU</b>	Research and Development Support Unit.
<b>EMA</b>	European Medicines Evaluation Agency	<b>RNA</b>	Ribonucleic acid.
<b>FDA</b>	Food and Drug Administration.	<b>SAE</b>	Serious Adverse Event.
<b>GAfREC</b>	Governance arrangements for research ethics committees.	<b>SHA</b>	Strategic Health Authority.
<b>GCP</b>	Good Clinical Practice.	<b>SOPs</b>	Standard Operating Procedures.
<b>GMC</b>	General Medical Council.	<b>SSA</b>	Site-specific assessment, an assessment of the suitability of the investigator, site and facilities made for any study with a Principle Investigator at each research site. The application for SSA should be made by the Principle Investigator using Part C of the application form. In the case of a multi-site study, the outcome of the SSA should be notified to the main REC within 25 days.
<b>GMP</b>	Good Manufacturing Practice	<b>SSAR</b>	Suspected Serious Adverse Reaction.
<b>ICH</b>	International Conference on Harmonisation.	<b>SUSAR</b>	Suspected Unexpected Serious Adverse Reaction.
<b>IMP</b>	Investigational medicinal product.	<b>UKCC</b>	United Kingdom Central Council (for Nursing, Midwifery and Healthvisiting).
<b>LREC</b>	Local Research Ethics Committee.	<b>UKCRC</b>	United Kingdom Clinical Research Collaboration.
		<b>UKECA</b>	United Kingdom Ethics Committee Authority.



# ABOUT RESEARCH ETHICS COMMITTEES



## Introduction

When you became interested in joining a Research Ethics Committee (REC), you may only have had a vague idea about what would be involved. This booklet is intended to help you broaden that understanding to make it easier for you to decide whether or not this is something with which you wish to be associated.

If you have become a committee member, already, you will, most likely, have been presented with very comprehensive documentation to help you with the task. Just to know what is written here will hopefully give you a good start.

In the past some special committees considered applications, usually from pharmaceutical companies, to carry out research in the development of new drugs or devices, but that has now all changed.

At the beginning of March 2004, the Central Office of Research Ethics Committees (COREC) introduced standard operating procedures (SOPs) for research ethics committees in order to comply with the European Union Clinical Trials Directive. Whilst that Directive only applied to clinical trials with investigational medicinal products, the new procedures applied to all research in the United Kingdom which involved human subjects in health and social care. These SOPs were revised in October 2004 (Website 1).

The composition of a committee will be dealt with in a later section, but the reasons for the variety of people chosen is to give the committee the necessary expertise in a balanced way.

The committee is very important, as it represents the interests of the research subject volunteers and individual researchers, and it is powerful because it could stop, by its decisions, the development of potentially important products or have an impact on policies of organisations and governments. For this reason its membership must be well defined and its members well trained.

It will take some time to appreciate the full implications of the committee's function. This is to be expected. If you are appointed to be a committee member, you will be expected to take part in some formal training and this training will be on-going.

A Manual for Research Ethics Committees was originally compiled and edited by Claire Foster. It is an invaluable source of reference if and when you need to search more deeply into topics. This manual was revised by Sue Eckstein and the 6th edition is published by Cambridge University Press.

Resulting from an accumulation of regulatory failures of the medical profession and research failures and scandals, the government brought in measures to prevent a repetition. This was in the form of clinical and research governance.

In 2001, the Department of Health published a Research Governance Framework for Health and Social Care and Governance Arrangements for NHS Research Ethics Committees (GfREC). Further revisions have recently been published (April 2005) following the EU Directive's transposition into UK law. The current versions of these publications can be found on Websites 2 and 3 respectively.

The framework was to cover all research on human subjects in health and social care. At present much of social care research is considered by National Health Service Research Ethics Committees (NHS RECs), but in the future, following consultation an implementation plan has been formulated so that this could be separately considered. (Website 4).

The Central Office of Research Ethics Committees (COREC) was set up by the Minister of Health in 1997, to manage health related research. It changed its role in 2004 in order that the provisions in the EU Directive could be met.

On April 1st 2005, COREC, which was part of the Research and Development Directorate, of the Department of Health, became part of the National Patient Safety Agency, under the chairmanship of Lord Hunt.

Major requirements that the EU Directive 2001/20/EC (Appendix 1) set for ethical review are

- To deliver a decision on a valid application within 60 days
- One decision to be valid for the whole of the UK
- Restriction to one written request for clarification or further information to applicants (clock stops whilst waiting response).

A summary of the New Operational Procedures for NHS RECs – Guidance for applicants to Research Ethics Committees – is given in Appendix 2.

The Directive brought about the creation of the United Kingdom Ethics Committee Authority (UKECA) which consists of the Ministers of State for Health or their nominees for the four nations of the UK. Only UKECA-recognised RECs could review research that involved Clinical Trials of Investigational Medicinal Products (CTIMPs). Non-recognised but authorised RECS would be able to look at all other health and social care related research involving human subjects.

In due course, UKECA will inspect RECs. REC appraisal by COREC commenced in 2005.

COREC was involved with the development of past versions and is involved with future versions of the Research Governance Framework and Governance Arrangements for Research Ethics Committees.

Some disquiet has arisen in sections of the research community and as a result in November 2004 an ad hoc advisory group was set up by Lord Warner, Minister of State for Health. The remit of this committee was to review the systems that support NHS RECs in England and to make recommendations for further steps to improve their operations, building on changes that are already underway. This group will report to the Minister, later in 2005.

The main funding bodies, academic medicine, the NHS, regulatory bodies, representatives for industry and patients have come together in a new partnership called the UK Clinical Research Collaboration (UKCRC). The partnership's aim is to establish the UK as a world leader in clinical research, realising the clinical research position offered by the NHS.

## What is research ethics?

One dictionary definition of ethics is 'that branch of philosophy which studies the principles of right and wrong in human conduct' and the definition of research is 'a systematic search for facts'. Research Ethics is thus the systematic search for facts governed by the principles of right and wrong in human conduct.

It is worth briefly going over the history of the origin of research ethics. Following the Second World War (1939-45) Nazi doctors were brought to trial at Nuremberg for carrying out unethical medical research projects in their prison camps. From these trials arose the Nuremberg Code. The World Medical Association drew up a code of research ethics in 1947 and this evolved as the Declaration of Helsinki in 1964. This Declaration has been revised on a number of occasions since then. The latest version has proved

to be controversial in certain quarters, largely over the question of testing against a placebo.

The current version was published by the World Medical Association (WMA), in Edinburgh in October 2000 and this and the previous version are reproduced in Appendix 1a and 1b. Attempts are in progress to resolve the controversy mentioned above and arrive at a near worldwide acceptance. After amendments have been made to the Declaration of Helsinki, the General Assembly of the World Medical Association is the only body with authority to adopt these changes. The changes of October 2000 would have been considered by the 53rd Assembly meeting in October 2001, but this meeting had to be cancelled. Because of this, the WMA published a clarification note with this full text:

"The WMA is concerned that paragraph 29 of the revised Declaration of Helsinki (October 2000) has led to diverse interpretations and possible confusion. It hereby affirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:

- Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method, or
- Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm."

A further clarification note was issued concerning paragraph 30 and reads

"The WMA hereby reaffirms its position that it is necessary during the study planning process to identify post-trial access by study participants to prophylactic, diagnostic and therapeutic procedures identified as beneficial in the study or access to other appropriate care. Post-trial access arrangements or other care must be described in the study protocol so the ethical review committee may consider such arrangements during its review".

All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review."

It must be noted that it is the provisions in the 1996 version of the Declaration of Helsinki that is referred to in the Medicines for Human Use (Clinical Trials) Regulations 2004 (Website 6), which lay down the UK law.

In the mid 1960s Henry Beecher in the USA and Maurice Pappworth in Britain drew attention to the amount of dubious medical research being carried out without the knowledge and consent of the research subject. Since then, the Royal College of Physicians of London, The Department of Health and the Association of the British Pharmaceutical Industry (ABPI) have published reports and issued guidelines, as have many other professional bodies.

In the United Kingdom, Research Ethics Committees were first set up nearly 33 years ago and they functioned on an informal basis for the regulation of research carried out in NHS hospitals, university departments and the pharmaceutical industry.

However, in recent years the Department of Health has realised the importance of the timely review of good research as a cornerstone of good health care and it has produced the framework and arrangements previously referred to and has facilitated the training of committee members.

The European Union Clinical Trials Directive (Appendix 1) was passed by the Council of Ministers and the European Parliament in December 2000 and published in May 2001. It was transposed into UK law as a Statutory Instrument as the Medicines for Human Use (Clinical Trials) Regulations on May 1st 2004. This has resulted in changes to research ethics committees and the way that they work. One major change was that

Human Pharmacology Studies (Phase I) in the UK are now subject to the scrutiny of both the ethics committees and the regulatory authority, the Medicines and Healthcare products Regulatory Agency (MHRA).

Most Phase I Research Ethics Committees are either Multi centre or Local Research Ethics Committees which have Clinical Pharmacology Units in their 'territory' or special private committees originally set up by the Pharmaceutical Companies or contract research organisations (CROs) themselves.

These latter committees, unless authorised, will be unable to review clinical trials, under the Regulations, from 1st May 2005.

### Critical pathway of drug development

At this point, it would be of interest to consider the process of drug development. From the original idea to the marketing of a drug, a period of up to 12 years might elapse and during this time the company might invest £500-600 million in this venture. Increasingly, however, some drugs may be developed on a 'fast track' basis. Many thousands of compounds are often discarded in the quest for the successful one.

An aid to understanding this process is given in Figure 1

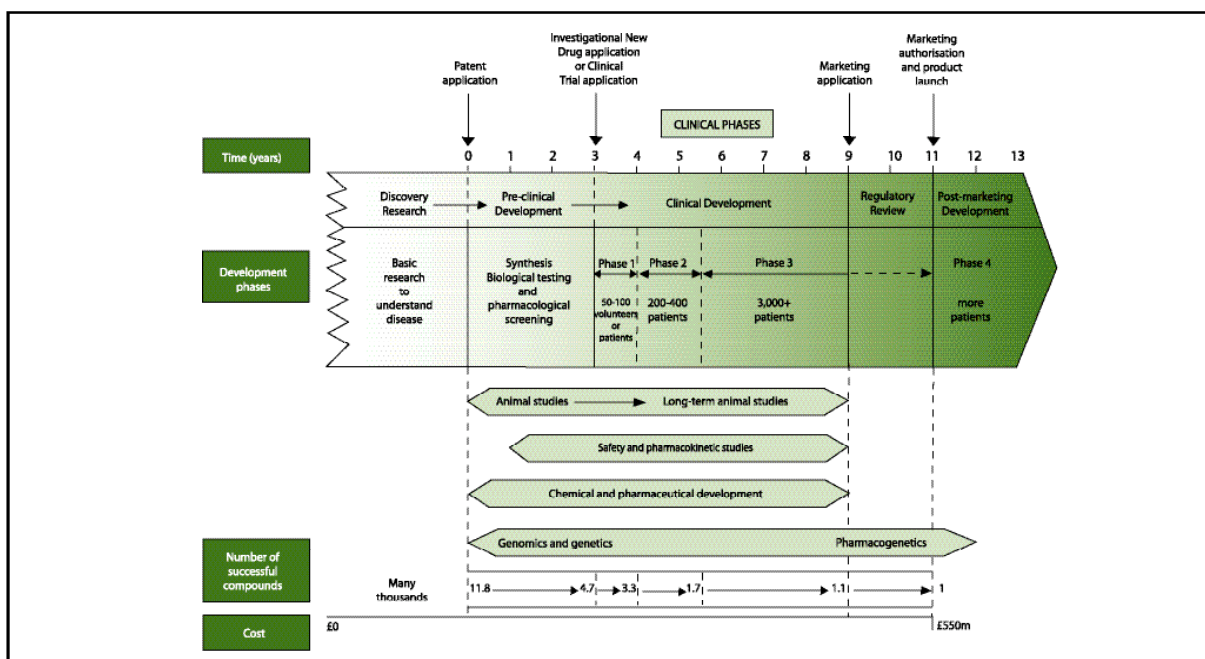


Figure 1. Diagram to illustrate the complex issues and stages in the discovery and development of a new medicine. It shows the timescale, regulatory landmarks, phases of drug development, attrition rates (fallout of potential drugs with the passage of time) and cost.

Clinical trials are used to study new ways to prevent, diagnose or treat diseases. Generally they are designed to evaluate new drugs or drug combinations, but they could involve the use of new devices, radiation or surgical treatments.

Early studies of new drugs are performed in laboratory animals or cultured cell lines. Increasingly, human tissues are becoming important in drug development. The tissue comes from surgery, biopsies, autopsies, childbirth(placenta) and transplantation. Consent from the patient or a surviving relative is required and approval is required from an REC. Tissues should be anonymised but may be coded by the suppliers for age, sex, major diseases, recent treatments and cause of death. After division into components the tissues can be processed for DNA, RNA, cell lines, proteins, preparations of membranes and microsomes and culture of primary cells.

With regard to consent, storage etc., what must be done is laid down in the Human Tissue Act 2004 (see later section).

The use of foetal tissue for these purposes is governed by strict legislation and a code of practice (Research) for such use has been issued by the Human Fertilisation and Embryology Authority (Website 5).

Beyond this stage clinical trials are conducted in four main stages or phases.

Phase I trials test the treatment in a small number of people (usually 20-50 healthy volunteers per study) to define pharmacology but not long-term safety, and to find a likely effective dose (Human Pharmacology).

Phase II trials test the treatment in a few hundred patients to see if it is active against the disease in the short term. If the treatment is not effective or there is unexpected toxicity, no more trials will take place. This phase is divided into two parts a) for healthy volunteers and non therapeutic research in patients and b) early therapeutic trials (Therapeutic/Exploratory).

Phase III trials test the treatment on several hundred or several thousand patients, often at many different clinics or hospitals in many different countries. These trials usually compare the new treatment either with a treatment already in use, a placebo (dummy treatment) or occasionally with no treatment (Therapeutic Confirmatory).

Phase IV studies involve post-marketing development (Therapeutic Use).

These phases are illustrative and Phases I and IIa are experimental medicine and moving towards a 'proof of concept' or 'proof of principle'.

The results of the trials are sent to the national drug licensing body, the Medicines and Healthcare

products Regulatory Agency (MHRA) or to the European Medicines Evaluation Agency (EMA). If an Agency agrees that the new treatment is efficacious, safe and of good quality, it is licensed for marketing.

Most medicines which were in general use when the Medicines Act came into force have now been evaluated, but some established treatments have never been properly assessed and some now looked at critically have been found to be of doubtful or no benefit.

In the mid 1990s, if a company wished to carry out research in many locations, they had to apply to many Local Research Ethics Committees (LRECs). These committees could alter the submitted protocols and often delayed or refused approval.

Multi-centre Research Ethics Committees (MRECs) were set up in 1997 to simplify review of studies which were to take place in five or more centres. The European Clinical Trials Directive changes this definition to apply to two or more centres. Single-centre research will, generally, still be considered only by LRECs (see below).

### Research Ethics Committee Applications

All clinical trials involving human subjects and the testing of investigational medicinal products (IMPs) require approval from a UKECA recognised REC.

Any recognised MREC or LREC can consider multi-site research and their decisions will be nationally binding.

Single-site research can be considered by a recognised or authorised LREC, in the domain or the neighbouring domain in which the research chief investigator is professionally based.

A domain is an area covered by a Strategic Health Authority (England), a Health Board (Scotland), a regional office of the NHS in Wales or the whole of Northern Ireland.

Other multi-site research if it is to be carried out in two or more domains can apply to COREC central allocations system (CAS) to request allocation to a recognised REC. For multi-site research to be carried out in a single domain, application can be made to CAS or direct to an LREC (usually in the domain of the Chief Investigator).

Non NHS research not involving IMPs can be reviewed by committees at their discretion, on a voluntary basis. As mentioned elsewhere, social care research may ultimately be reviewed outside the NHS REC system. Special arrangements will eventually be

required to review student research. A working group chaired by Professor Len Doyal produced a draft proposal. (Website 7).

### ***Site Specific Assessment.***

Because CTIMP research applications are decided nationally, there is a need for Site Specific Assessment (SSA). This usually is carried out by the LREC for the geographical area (see Section 4 in the SOPs). The SSA of the research goes on in parallel with the review of the main REC. This process is also time limited to 25 days, within the same 60 days allowed to the REC.

### ***Multi-site Studies with no Local Investigators.***

These studies do not involve clinical interventions or other significant research procedures. The main REC considers these applications, but there is no need to inform LRECs or to apply for SSAs.

Main RECs as well as considering applications must consider substantial amendments. Ninety per cent of amendments are substantial and have to be reported to the REC and the MHRA. The REC have to respond within 35 days, but the MHRA need not respond unless the amendment is relevant to them. Objection to an amendment by the MHRA is not time-limited.

Sponsors have to keep a log of all non-substantial amendments.

## **Research and Development Committee Approval**

This is carried out at Trust level and is quite distinct from the Site Specific Assessment. This committee has knowledge of all research carried out in the Trust. It identifies the resources that are needed in personnel and equipment, ensuring that resources are not diverted away from patient care.

In March 2005, the NHS R&D Forum launched an on-line NHS R&D application form. This will dovetail with the NHS REC application, allowing cross-pollination with the NHS REC application. This has allowed Part D of the NHS REC application form to be withdrawn.

## **What is Good Research?**

A committee is looking for research which is safe and sound, and which does not infringe the dignity and confidentiality of the research subject.

The principles of good ethical research are enshrined in the World Medical Association's Declaration of Helsinki.

A Research Ethics Committee ensures that:

1. there is a well written protocol that clearly sets out the problem. This should show that the question is reasonable to ask and can be answered by the study and there is no other way to do it
2. the project must not put the research subject or the researcher to any significant danger. Previous work should not demonstrate a significant risk of adverse events
3. data collection respects the confidentiality of the individual
4. the investigators, their staff and facilities are suitable
5. the study subject has a clear explanation of the trial verbally, accompanied by a written description in language that he/she can understand. The risks and benefits must be pointed out
6. in virtually all cases, the subjects should give their consent in writing and there must be an opportunity for the subject not to take part or to withdraw from the study at any time without any detriment
7. with permission the study subject's general practitioner is informed and given the chance to object to a subject being included in a trial.

A useful checklist for committee members is given in Appendix 4.

## **European Perspective**

The European Directive on Clinical trials was passed by the Council of Ministers and the European Parliament in December 2000. Member States were required to transpose it into national legislation at the 1st May 2004.

The European Union intended to publish nine sets of guidance notes for clarification. To date it has published five, which can be accessed from their website. The last four were published in April 2005 as a Directive (2005/28/EC), to limit the scope of Nation States to use local interpretation This Directive covers GCP, GMP and inspections (Website 8 and 9).

Hitherto, clinical trials involving medicines, with a view to licensing, have to be carried out according to the internationally recognised Good Clinical Practice Guidelines of the International Conference on Harmonisation (Website 10).

National standards must reach, at least, to those of these Directives but in some aspects some Nation States will exceed them.

Since the enactment of the European Directive in the UK, as The Medicines for Human Use (Clinical trials) Regulations 2004 (The Regulations), the considerable responsibility of the Sponsor, Chief Investigator and others has been defined. These can be found within the regulations, the standard operating procedures and within the Research Governance Framework.

## Databases.

There are two databases maintained for clinical trial research in the EU and these are maintained by the European Medicines Evaluation Authority (EMA).

The databases are the European Clinical Trials Database (EudraCT) and EudraVigilance.

EudraCT entry is created when the sponsor received a CTA from the MHRA. It can be accessed only by the EMA and the Competent Authorities (in UK, the MHRA).

EudraVigilance contains all the SUSARs and has a similar availability.

The world's major drug companies are under pressure to publish all their clinical trial data, including that containing negative results. Results of all industry-sponsored clinical trials on marketed medicines, will now be disclosed via free, publicly accessible databases (Website 11). Also details of all clinical trials to determine a medicine's therapeutic benefit will be publicly registered at initiation so patients and clinicians will be able to enroll. The scheme will take effect during 2005. Such a registry maintained by the National Library of Medicine in the US is already in place and can be used for this purpose, regardless of where the trial is conducted. (Website 12). Further information is available from the ABPI website.

## The Law Relating to Consent and Confidentiality.

These are very important areas for committee members to consider.

Much of the law is derived from that relating to treatment and patient consultations. Acts which are lawful are not necessarily ethical, but those which are ethical are usually lawful.

The EU Clinical Trials Directive contains articles on consent generally and the consent of children and incompetent adults in particular.

Two chapters from the Manual for Research and Ethics Committees (6th edition, 2002) edited by Sue Eckstein, from The Centre of Medical Law and Ethics, King's College, London and published by Cambridge

University Press are reproduced in Appendices 5 and 6, with kind permission of the authors.

Where changes have been made to the law since these chapters were written, these are included as compiler's notes.

## Genetic Testing.

In early Phase studies it is increasingly likely that blood will be taken from volunteers for genetic testing. This is so that companies can know the genetic characteristics of those who are in early stage trials. This could offer explanations as to why individuals respond to drugs in different ways. Panels of healthy volunteers could be used in drug development and eventually the knowledge gained could help to tailor drugs to particular individuals to get the maximum response with minimal side effects.

The Department of Health set up an Advisory Committee on Genetic Testing and this committee reported in October 1998 and passed on its guidance in the form of a 'Points to Consider' document, the following month. (Appendix 7).

Comparisons between patients using their responses to drugs and differences in genetic patterns are likely, eventually to lead to important genetic discoveries.

- For these studies to take place subjects should give separate informed consent after a period of reflection
- Samples for genetic studies should be kept separately and clearly marked that they are for that purpose
- In samples that can be identified by the decoding process, the subject should be able to request and be assured that their particular sample has been destroyed
- No data should be passed on to others
- The research subject should be clearly told if there will be any feedback of results to themselves. This would be highly unlikely and if it was then there would possibly need to be the help of counsellors for them and their families.

## The Licensing System for medicines in the United Kingdom.

Medicines to be marketed must have a Product Licence. The Licensing Authority is the Secretary of State, who acts on the advice of the Medicines and Healthcare products Regulatory Agency (MHRA).

A medicinal product is any substance which is manufactured, sold, supplied, imported or exported wholly or mainly in either or both of the following ways:

- a) for administration to one or more human beings or animals for medicinal or investigational purposes
- b) as an ingredient in an article or substance for such administration, when the ingredient is used in a pharmacy, or a hospital, or in a business where herbal remedies are sold by retail, or by a practitioner, that is, a doctor, dentist or veterinarian.

This could include, for example, some shampoos and food substances.

For a clinical trial to be conducted as well as obtaining a favourable opinion from a REC, a Clinical Trial Authorisation has to be obtained from the MHRA by the sponsor. The application for this can be made in parallel with that to a REC.

Unless the trial involves genetic and somatic cell therapy or medicinal products containing genetically modified organisms, the authority has to either issue a written authorisation or a notice refusing authorisation within 30 days. In addition to the above, the MHRA can accept the request subject to the conditions specified in the notice. The sponsor may respond within 14 days, or such extended period as the MHRA allows by sending an amended request for consideration. The MHRA has 60 days in total to respond to include that amended request. The MHRA set itself a target of fourteen days for the review of Phase I studies, with a maximum of twenty-one days.

Failure to respond by the MHRA within the statutory timetable is treated as an authorisation.

Regulations 19 and 20 of The Medicines for Human Use (Clinical Trials) Regulations 2004 should be consulted when trials involve medicinal products for gene therapy etc. and medicinal products with special characteristics. (Website 6).

A summary of the Regulations is given in Appendix 8.

The MHRA has responsibility for good manufacturing practice. Manufacturing sites must have available an approved scientist known as the Qualified Person. The MHRA have the power to send in teams of inspectors who like the Inland Revenue and Customs and Excise can visit without notice. They have the authority to initiate changes and even close a site down.

Licensed medicines used in clinical trials will be subject to prescription charges.

The MHRA charges fees for CTAs of between £600-2000. Amendment applications will be charged at £100. RECs do not charge their applicants.

## How your Committee will operate.

The regulations by which your committee will operate are laid down in the SOPs for RECS in the UK published by COREC. These SOPs will eventually be issued as a new version of Governance Arrangements for Research Ethics Committees (GAFREC)

Members are recruited by public advertisement and appointed by the delegated authority of the Ministers of State.

A typical Research Ethics Committee meets once per month and the meetings last for 1-3 hours. A committee usually has 12-18 members. The chairman, vice-chairman and alternate vice-chairman are appointed as such by the accountable Authority. One third of the members should be lay persons and half of those should have no connection with health and social care – these possibly could include a lawyer and a minister of religion. Members with a health and social care connection might include two nurses, four doctors, a biological scientist, a clinical pharmacologist and someone with a knowledge of statistics. Both sexes, a range of ages and ethnic minorities should be represented. The tenure of appointment will be 3-5 years, renewable for a further term. Phased retirement of members allows new people to contribute. In addition, the committee must appoint a mentor.

Sometimes a particular problem in a protocol cannot be answered by those on a committee. In this case, expert outside opinion should be sought. This may particularly arise in “first into man” studies, where independent toxicological advice may be required and also in research involving children.

Some committees have an expertise in research involving prisoners. Undergraduate student research produces its own challenges, with regard to non-complex applications, often batched together to meet term and end of the year deadlines. Separate arrangements for these students will eventually have to be made.

The quorum necessary to hold a legitimate meeting is seven members and it must include the chairman, vice-chairman or an alternate vice-chairman, one lay member and one expert member.

The committee considers protocols which have been submitted by the applicant in good time to be looked at before the meeting. Details are submitted on a special application form. The use of such an application form helps to describe the protocol in a way that all the committee understands and makes it easier to ensure that all necessary aspects are covered. Committees often interview the researcher, to discuss and clarify the research proposal, but the deliberations of the committee must take place



independently without the presence of any interested party or company representative.

Decisions are generally arrived at by consensus, but in some committees a specified majority would allow a research project to be approved. In these cases the reasons for the minority view must be recorded in the committee records. In some committees, the decision to approve a protocol must be unanimous.

It is important that committees consider properly presented applications as soon as possible and that the decisions are passed on quickly. The strict timetable from the Regulations is referred to in the section on Research Ethics Committee Applications.

If a sponsor seeks to request an amendment, the committee has 35 days to send back a decision. Substantial amendments will normally be considered by a subcommittee of the REC, but not by a member acting alone.

When a trial is completed, the sponsor must notify the competent authority and the research ethics committee, within 90 days. Premature closing of a trial requires notification giving reasons, within 15 days.

The time limits described above comply with both the governance arrangements for NHS RECs and the European Union Clinical Trials Directive.

For regulatory reasons, investigators need to know if committees are quorate and which members were present at meetings when particular protocols were discussed.

The number of protocols to be considered will be limited to allow time for a full discussion. An administrator will be responsible for the administration and accurate records must be kept of the proceedings. Members are reimbursed for all their expenses, but only under rare circumstances do they get a fee or honorarium.

Applicants should refer protocol amendments back to the committee and also inform them of findings which might have altered the decision if that information had been available when the application had first been made.

It is the duty of the applicant to report all significant adverse reactions to the main REC within 15 days of the chief investigator becoming aware.

The European Directive establishes the Research Ethics Committee as a legal entity; in the event of a research subject suing, the individual members would be sued. In practice it is more likely that they will sue the drug company as the more likely prospect for compensation. (see below). Members should be appropriately indemnified.

You will find it helpful to look at the Governance Arrangements for NHS Research Ethics Committees published by the Department of Health, referred to previously as well as the SOPs. The composition of committees, at present, as described in GAFREC 1, are at variance with the Clinical Trials Regulations, but with the GAFREC revision, in progress, they will become concordant.

Sometimes it is difficult to decide if what is proposed is research or audit. Some guidance is given in Appendix 9, reproduced with the kind permission of the United Bristol Healthcare Trust, Clinical Audit Central Office.

## Safety of Clinical Trials.

When clinical trials are being carried out using investigational medicinal products, sponsors must send COREC issued forms to main RECs within three days, when serious unexpected adverse reactions (SUSARs) occur.

The main REC is not required to review these expedited SUSARs, but they must be reviewed at least every three months by the chairman and an expert member.

Primary responsibility for safety rests with the sponsor. The MHRA has the main regulatory responsibility and will keep the REC informed about safety issues.

For other research all serious adverse events must be reported to the REC within 15 days, using a separate form issued by COREC.

## Indemnity and Compensation in Medical Research.

Indemnity is defined as the promise of full reimbursement in respect of any potential liability and compensation is defined as recompense for loss or damage. The former will be used in relation to the researcher or research ethics committees and the latter, the researched subject.

### Indemnity.

Volunteers agree to participate in studies on the understanding that there is only minimal risk but from time to time things do go wrong.

There are various ways that indemnity can be provided for researchers and committees.

Guidelines have been issued by the ABPI, the Royal College of Physicians and the International

Conference on Harmonisation. Providers of this indemnity are referred to in the remainder of this section.

The ABPI is a trade organisation which was formed in 1930. It now represents more than 100 companies which produce more than 90 per cent of the medicines supplied to the NHS. The ABPI Code of Practice for the Pharmaceutical Industry has been regularly revised since its inception in 1958 and was drawn up in consultation with the British Medical Association, the Royal Pharmaceutical Society of Great Britain and the Medicines Control Agency of the Department of Health.

It is a condition of membership of the ABPI to abide by the Code in both the spirit and the letter. Companies which are not members of the Association may agree to abide by the Code and accept the jurisdiction of the Prescription Medicines Code of Practice Authority. Thus the Code is accepted by virtually all the pharmaceutical companies operating in the United Kingdom.

Some companies contract out their 'Phase I' and other studies to other independent research companies. These are known as Contract Research Organisations (CROs) and they have the opportunity of affiliate membership of the ABPI.

The ABPI Indemnity Agreement gives standard terms for indemnity, but investigators/NHS Trusts must be aware that

- a) it is their responsibility to ensure that the contract with the drug company is correctly worded
- b) the company will not indemnify them in respect of negligence or deviations from the protocol by the researcher
- c) the company may be based in a country which is beyond the jurisdiction of a British Court.

General Practitioners and private doctors are only covered by their Defence Organisations for damages arising from negligence.

Members of Research Ethics Committees might be sued for their part in approving research and they should seek indemnity from their appointing bodies, e.g. Health Authorities or the Secretary of State

## Compensation.

In many ways, it seems unfair that if a subject is harmed by research that he should go through the stressful and protracted course of taking his claim to law.

National Health Service Trusts which employ staff on contracts or honorary contracts are liable for their negligence. To lessen the effect of claims, groups of Trusts have come together to contribute a pool of money to pay damages or out of Court settlements.

Trusts will require that research is approved by Research Ethics Committees, any drugs used have product licences or the appropriate MHRA certificate and that all sponsors provide standard indemnity.

Trusts can make ex gratia payments to persons injured by research, without negligence having to be proved. Since the issue of HSG(96)48 by the Department of Health, Trusts can make such payments up to £50,000. This figure was decided on almost 10 years ago and is due to be reviewed.

Research outside the NHS (e.g performed by universities and pharmaceutical companies) should be covered by the insurance of the 'parent bodies'.

The possibility of an NHS Trust making an ex gratia payment has been mentioned above. Also mentioned was the position of the ABPI members. Their guidelines seek to minimise the problems of subjects who suffer an adverse event caused by participation in a trial. The ABPI guidelines insist that subjects should be compensated on a 'no fault' basis, i.e that the subject whose problem was caused by his participation in a trial should be compensated automatically without him having the added burden of proving negligence. The considerations can be complex such as what happens when a subject suffers from being in a placebo (dummy tablet) group or during a wash-out period. It must be noted that continued administration of a product to a patient beyond the trial period becomes the doctor's responsibility, and he should notify the employer and his Defence Organisation, to that effect. Please see Appendix 10, for ABPI guidelines.

## Research on Healthy Volunteers and Non Therapeutic Research.

Phase I studies can never be in the interests of the research subject, whether they be healthy volunteers or patients taking part in non therapeutic research.

The London Royal College of Physicians set up a committee for the Medicines Commission because of the increasing volume of research being carried out

on healthy volunteers. They were partly worried by the possibility that drug companies might think that the more of this more risky work they carried out, the more likely they were to obtain a Clinical Trial Certificate or it would ease their way to getting a Clinical Trial Exemption, in the days when the MHRA was called the Medicines Control Agency.

Sections of the Third Edition of the Royal College of Physicians Guidelines on the practice of Ethics Committees in Medical Research involving Human Subjects on Research relevant to Healthy Volunteers are reproduced with their kind permission, in Appendix 11. This deals with part of the sections on Responsibilities in Law (3), Recruitment (7) and Compensation (9).

### Recruitment of Research Subjects.

This can be done by word of mouth, notices, newspapers, television, radio and websites. This material should be reviewed by RECs. The offers should be open and there should be full disclosures of risks. Payments should be made for loss of earnings, provision of childcare etc. in all post Phase I studies. In addition to the aforementioned situations with Phase I studies, payment can be made for discomfort and inconvenience, but not for risk and should not be seen as an inducement.

Advertising should not be aimed at the disadvantaged or the vulnerable.

Minority groups should be recruited into research projects, because this is their right and because to exclude them could invalidate or limit the value of the research as the results would not be generalisable to a nation's population, as a whole.

The ABPI guidelines on Advertising for Subjects for Clinical Trials is reproduced in Appendix 12.

A small number of volunteers (1 per cent) are taking part in several clinical trials at the same time or in quick succession, putting their own safety at risk and compromising the results of these safety studies. Two schemes have been proposed whereby volunteers could be screened for overvolunteering. One involves the use of a photo identification card and is described at [www.ahppi.org.uk](http://www.ahppi.org.uk) and the other the use of a national insurance or passport number and with identification and password can be accessed through [www.TOPS.org.uk](http://www.TOPS.org.uk). Volunteers could be checked against these web-based databases, to see whether they were still, or had recently been, taking part in other Phase I studies. There is evidence that systems can detect overvolunteering and knowledge of their existence could be acting as a deterrent. Effectiveness

would be increased if these systems could be combined.

### Recent Legislation (See Website 6).

#### Human Rights Act 1998.

This incorporates the European Convention of Human Rights into United Kingdom law. Like Common Law it provides for judgements on the balance between the rights of the individual and the legitimate needs of society.

With regard to research, Article 2: Right to life and Article 3: Prohibition of torture and inhuman and degrading treatment could be invoked, in the latter case if experimental medical treatment was carried out without consent. Article 8: Right to Respect for Private and Family Life may be invoked over matters of disclosure of medical records, failure to obtain informed consent and confidentiality issues.

#### The Data Protection Acts 1984 & 1998.

The later act incorporates the European Directive. It deals with the following concepts:

- Fair processing – which means that an individual has a right to know which organisations hold data about them, why, to whom it could be made available and to give them the opportunity to check the data for errors
- When the data are collected, the collector should seek permission from the subject
- The law recognises that in research the information may be used in an unforeseen way
- Special exemption is given for research work that is not used as a basis for a decision affecting the individual and where it is unlikely to lead to substantial damage or distress. Anonymised data is excluded from the Act, but the process of anonymising data is covered by the Act.

#### Health and Social Care Act 2001.

The important issue in this Act concerns confidentiality and new powers given to the Secretary of State for Health. See *compiler's note in Appendix 6*.

## Medicines for Human Use (Clinical Trials) Regulations 2004.

These regulations transpose into UK law the European Union Clinical Trials Directive 2001/20/EC. This is secondary legislation. The contents of the Regulations will be embodied in the Research Governance Framework for Health and Social Care, the Governance Arrangements for Research Ethics Committees and the Standing Operating Procedures published by COREC.

These Regulations clarify the situation regarding clinical trials, impose strict time limits over the considerations by RECs and the MHRA, introduce an enforceable legal basis and change the law on consent for incapacitated adults.

A description of the Regulations published by the MHRA are given in Appendix 8 and the full text of the Regulations can be found on the HMSO website.

The regulation that deals with consent in medical emergency research is in the process of consultation before amendment, because currently it is unworkable. This consultation is being carried out by the MHRA, who will issue a MLX.

## Human Tissue Act 2004.

This has had a complicated passage on its journey through Parliament. In its original form, it would have imposed impossible conditions which could impact on the training of medical personnel. Explanatory Notes are available on the HMSO website (Website 13).

## Mental Capacity Act 2005.

This Bill also had a complicated passage through Parliament. It was enacted by cross party agreement before the pre-election dissolution.

It covers issues of consent both in respect of treatment and some aspects of research. It deals with Persons Who Lack Capacity. That is a person who, at the time, is unable to make a decision for himself in relation to the matter because of an impairment of, or a disturbance in the functioning of, the mind or brain. Account must be taken of advance decisions made by persons, over the age of 18 and with capacity at the time.

Section 30 of this Bill excludes research carried out under The Medicines for Human Use (Clinical Trials) Regulations 2004.

## Toxicology.

Toxicology is defined as the study of the harmful actions of drugs and chemicals. Before a substance can be administered to man, its potential for causing injurious effects needs to be investigated.

The purpose of toxicity testing is to detect harmful effects in vivo and in vitro, to identify the circumstances of occurrence, relationship with dose and duration of exposure, species differences in susceptibility, the pattern of effect and to suggest possible mechanisms. It is hoped to be able to predict what harmful effect could occur in man, under what circumstances and how important and severe, reversible, recoverable and treatable they may be.

Toxicity can be an acute, chronic, latent or delayed disorder of function or structure in any body system or tissue.

There are two types of toxicity, known as Type A and Type B. Type A is common, predictable and dose related, being due to excess therapeutic or pharmacological action or target organ toxicity (e.g. that seen with Digoxin). Type B is unpredictable (idiosyncratic) and is not dose related.

Toxicity can affect a target organ by local or systemic action. It can have an effect on fertility and the foetus. It can have an effect on the genes and chromosomes and it can result in the production of tumours. It can affect the immune system by sensitisation or its depression.

Pharmacodynamics, "safety pharmacology" and pharmacokinetics must be considered in the assessment of toxicity. In man, there may rarely be information from occupational exposure or from clinical trials and post marketing surveillance. There may have been exposure in veterinary medicine or analogous or similar substances may have been studied previously. The pharmaceutical company should have a database of published and unpublished literature.

In animal studies, single doses are tested to look for acute toxicity, usually in two species (one in rodent and one in non-rodent), and if possible, blood concentrations of the drug are measured. Multiple doses are then studied over periods of several weeks and then for longer periods in the later stages of drug development. During toxicity studies, fertility and effects on the foetus, genes and chromosomes are usually examined. The potential of the drug to cause tumours in animals may also need to be assessed in long term studies.

The testing of potential new therapeutic agents in man is outlined in the section on Drug Development.

In the case of drugs which might be administered to children, toxicity studies are carried out in animals during their growing stages. Anti-cancer drugs are too toxic to be given to healthy volunteers and studies are usually carried out directly in patients, at an early stage.

In interpreting toxicity test data, consideration should be given to the effects seen as well as those not seen. In this latter case, committee members need to know if these effects have been sought. They need to know what tests have been done and the extent of the exposure to the drug, bearing in mind its absorption, body distribution, metabolism and excretion. If problems arise in animal toxicity testing, it is important to determine the mechanisms likely to occur in man. This may help to clarify whether there is risk of similar effects and whether they are acceptable in healthy volunteers. Such information may also indicate increased risks in patients with particular diseases.

## Statistics

Statistics is defined as a mathematical methodology for the analysis and interpretation of data from observations. By a characteristic inductive process, these methods lead to precise statements in probability terms about the degree of uncertainty attaching to the conclusions drawn.

Statistics is an important and complex branch of specialised mathematics. Terms such as *correlation coefficient*, *mean*, *median*, *mode* and *p value* are used and are defined in the Glossary.

You may hear of tests of significance described as being parametric and non-parametric and of specific tests such as the *Student t test* and *chi squared test*. These tests are well described in textbooks of statistics.

# REFERENCED WEBSITES



*Please note because of the changing nature of websites, in some cases, only the 'root section' of the web address is listed. With any website difficulty return to the 'root' or use a search engine.*

1. Standard Operating Procedures for Research Ethics Committees.  
[www.corec.org.uk](http://www.corec.org.uk)
2. Research Governance Framework for Health and Social Care.  
[www.dh.gov.uk/research/rd3/nhsrandd/researchgovernance/govhome.htm](http://www.dh.gov.uk/research/rd3/nhsrandd/researchgovernance/govhome.htm)
3. Governance arrangements for NHS Research Ethics Committees.  
[www.dh.gov.uk/research/documents/gafrec.doc](http://www.dh.gov.uk/research/documents/gafrec.doc)
4. Research in Social Care  
[www.dh.gov.uk/assetRoot/04/10/48/89/04104889.doc](http://www.dh.gov.uk/assetRoot/04/10/48/89/04104889.doc)
5. Code of Practice issued by Human Fertilisation and Embryology Authority. Part 11 deals with Research. [www.hfea.gov.uk](http://www.hfea.gov.uk)
6. Acts of Parliament. Go to [www.legislation.hmsso.gov.uk/acts.htm](http://www.legislation.hmsso.gov.uk/acts.htm) and select by year
  - i. Human Rights Act (1998)
  - ii. Data Protection Act (1998)
  - iii. Health and Social Care Act (2001)
  - iv. Medicines for Human Use (Clinical Trials) Regulations (2004)
  - v. Human Tissue Act (2004)
  - vi. Mental Capacity Bill (2005)
7. The Ethical Governance and Regulation of Student Projects. A Draft Proposal.  
[www.orecni.org.uk/display/ethical\\_review\\_of\\_student\\_re](http://www.orecni.org.uk/display/ethical_review_of_student_re)
8. EU Directive 1-5 Guidance Notes  
<http://pharmacos.eudra.org>
9. EU Directive on GCP, GMP and Inspections. 2005/28/EC. <http://pharmacos.eudra.org>
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## SUGGESTED FURTHER READING



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A Manual for Research Ethics Committees. (6th edition, 2002). Written and Compiled by Sue Eckstein. Cambridge University Press.

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Royal College of Physicians London(1986). Research on Healthy Volunteers. A Working Party Report.

Royal College of Physicians London(1990). Research Involving Patients. A Working Party Report.

Royal College of Physicians London(1996). Guidelines on the Practice of Medical Research Involving Human Subjects.

Statistics: a Gentle Introduction. Coolidge FL. Sage Publications. 2000

Human Genetics BMA. Oxford University Press (1998).

### Useful websites

ABPI website for access to this booklet and its updates and other ABPI publications. [www.abpi.org.uk](http://www.abpi.org.uk)

Many useful website references can be found at the end of the Research Governance Framework document. (See website address above).

UK Clinical Research Collaboration [www.ukcrc.org](http://www.ukcrc.org)

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