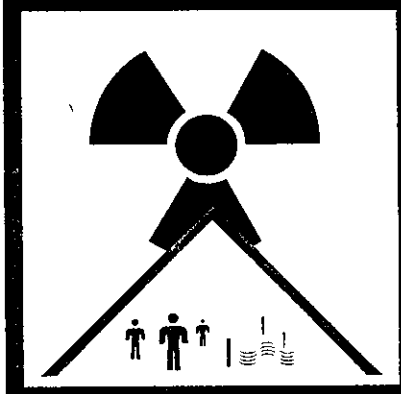
RADIATION PROTECTION 99



Guidance on medical exposures in medical and biomedical research

European Commission

European

This document has been prepared for use within the Commission. It does not necessarily represent the Commission's official position.

A great deal of additional information on the European Union is available on the Internet.
It can be accessed through the Europa server (http://europa.eu.int).

Cataloguing data can be found at the end of this publication.

Luxembourg: Office for Official Publications of the European Communities, 1998

ISBN 92-828-4391-2

Printed in Belgium

Contents

1. FOREWORD

(1) A comprehensive culture of radiation protection and safety in medicine has been progressively developing throughout the European Union with regard to the medical use of ionising radiation and has been integrated into the various branches of diagnosis and treatment.

(2) The European Commission has contributed to this evolution with the establishment of legal requirements to be implemented by Member States for the radiation protection of persons undergoing medical examinations or treatment.

(3) The establishment of the Directive 84/466/EURATOM laying down basic measures for the radiation protection of persons undergoing medical examination or treatment, the so called 'Patient Directive' (PAD) was one of the milestones of these European initiatives.

(4) Since 1984, the use of ionising radiation in medical practice has continued to develop, the number of installations to increase and the applications to diversify with an increase in collective radiation doses. This, together with the scientific and technical progress, urged the European Commission to revise Directive 84/466/EURATOM. The revision broadens the scope of the directive to include, among others, medical and biomedical research programmes. The revised Medical Exposure Directive (MED) 97/43/EURATOM was approved by the Council on 30th June 1997.

(5) In this context, medical and biomedical research includes all situations where radiation is given to healthy volunteers or additional radiation is given to patients over and above that required for their clinical management.

(6) Those who voluntarily accept to undergo an experimental diagnostic or therapeutic exposure to ionising radiation can be considered in three groups. Firstly they may be patients who may benefit from the procedure. Secondly patients may agree to take part in such procedures when they will receive no direct benefit themselves, and thirdly there are healthy volunteers.

(7) Such medical and biomedical research includes medical trials using x-ray procedures including CT, new radiopharmaceuticals, or new or modified radiodiagnostic or radiotherapeutic equipment or procedures. Physiological studies within these categories are also included. While the risks and benefits from radiation must be considered, so must any other risks or benefits arising from the procedure.

(8) It is the aim of the European Commission to bring together the existing guidance on clinical biomedical research. For this reason the Commission consulted the group of health experts established by Article 31 of the Euratom Treaty.

(9) The present guidance was approved by the group of Article 31 experts during its session of 8 and 9 June 1998 taking into account comments made at the international workshop on the implementation of the MED in Madrid on 27 April 1998.

(10) This guidance is addressed to prescribers and practitioners, to nurses, to medical physicists and other professional staff who are involved in medical and biomedical research. It is also addressed to research ethics committees and competent authority.

(11) The document is structured as follows: the introduction sets out the background against which research is conducted. The chapter 'Ethical aspects' gives general guidance on how to conduct biomedical research using ionising radiation with particular attention for research on children, mentally ill, unconscious subjects and pregnant and breastfeeding women. The risk assessment chapter which follows, gives a flavour of how to design the research taking account of dose related risks for different categories of individuals. Finally, a list of definitions and reference documents to this guide is presented.

(12) This document will be made available in all official languages of the European Union.

Suzanne FRIGREN
Director Nuclear Safety and Civil Protection

2. INTRODUCTION

(13) The Declaration of Helsinki (He96) sets out the basic principles for those undertaking biomedical research. In addition it provides guidance on research where patients may benefit and also research involving volunteers.

(14) An expert Committee of the World Health Organisation (WHO77) has published a report "Use of ionising radiation and radionuclides on human beings for medical research, training, and non-medical purposes". It deals with radiation to which people are exposed during the course of medical research, medical teaching, and in various procedures not directly related to their health needs.

(15) ICRP has published a report (ICRP 62) "Radiological Protection in Biomedical Research". This covers ethical aspects of research involving ionising radiation, the risks involved and how to assess them, research design and project evaluation.

3. ETHICAL ASPECTS

(16) The purpose of medical and biomedical research must be to improve diagnostic, and therapeutic procedures, and the understanding of the aetiology and pathogenesis of diseases, disorders or conditions affecting human beings.

(17) Such research must conform to generally accepted scientific principles and must be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

(18) However in the treatment of sick patients the physician must be allowed to use a new diagnostic or therapeutic measure if in his or her judgement it offers hope of saving life, re-establishing health, or alleviating suffering.

(19) For all irradiation of human beings there must be a net benefit. For patients the benefit to the individual from diagnostic or therapeutic procedures must exceed the potential detriment. In the case of medical and biomedical research the benefit to society, by the increase of knowledge, must outweigh the potential harm to the individual. Such research should only be carried out on a voluntary basis as set out in the Declaration of Helsinki (He96).

(20) Research volunteers can be divided into different categories. The first includes those patients whose diagnosis or treatment may benefit from the research. In such cases levels of dose or activity should be planned on an individual basis by the practitioner and/or prescriber (MED). Secondly there are patients who agree to take part in diagnostic procedures which will not benefit them directly and thirdly healthy volunteers, both of whom should be subject to a dose constraint.

(21) Where the potential subject is able to consent he/she must be adequately informed of aims, methods, benefits, and potential hazards of the study and any discomfort it will entail. Where the subject is not able to consent, the representative, authority, person or

body provided for by law to authorise a medical intervention should be given the same information. Such information should be sufficient to enable consent to be based on appreciation and understanding of the relevant facts. The legislation regarding consent varies in Member States.

(22) Refusal to take part in the research should never prejudice the patient's management.

(23) The principal investigator is responsible for ensuring that the individual or the representative, authority, person or body mentioned in paragraph 21 is informed that the individual is at liberty to abstain from the study and that consent may be withdrawn freely at any time without giving a reason.

(24) No one should be subject to biomedical research without them or their representative giving free and informed consent, which should be given in writing, and after sufficient time to consider the information (at least 1 day) and to ask questions about it. The written information provided and the consent form should be as non-technical as possible and understandable to the subject or their representative.

(25) Medical and biomedical research involving ionising radiation should only be undertaken by practitioners after approval by ethics committees and/or competent authority (GEC 97). Approval should only be given when the hazards involved are judged to be predictable. If the hazards are found to outweigh potential benefits the investigation should cease immediately. In interventional radiology and radiotherapy the possibility of unintended deterministic effects must be taken into account and measures taken to avoid such effects. In other exposures deterministic effects are unlikely.

(26) Medical research in radiotherapy on patients should only be performed if in the judgement of the practitioner and the prescriber that is the best method of treatment for these particular patients.

(27) Personal data relating to research subjects should be kept securely to ensure confidentiality.

(28) To ensure an impartial and independent view of the need for any medical and biomedical research, and the balance between likely benefits and risks, all proposals should be vetted by an ethics committee and/or competent authority composed of persons not engaged in the project and who are independent of the investigators. Some of these persons should be external to the organisation conducting the research. The ethics committee and/or competent authority should consider the proposal, and where necessary comment on it and give guidance to the research team. Where members of the ethics committee and/or competent authority lack the technical expertise necessary to assess a project properly, an appropriate external expert should be asked to advise.

(29) Competent authorities in each member state must set up ethics committees and/or competent authority in accordance with national procedures to assess such research involving humans. Authorisation in accordance with national legislation and approval from the ethics committee and/or competent authority must both be obtained prior to starting the research.

(30) The ethics committee and/or competent authority should be particularly careful in examining procedures for obtaining consent where the subject may be in a dependent relationship to the investigator or if there is any question of consent being given under duress or after payment. The principal investigator must make any such relationship clear. In such circumstances, the research/ethics committee and/or competent authority may recommend that a medical practitioner who is not involved with the investigation should seek consent.

(31) Because of the possibility of genetic effects of irradiation, and because of the long latent period associated with somatic effects, subjects should where possible be over the age of 50. It should also be noted that in the case of terminally ill patients long term risks of radiation are minimal.

(32) The number of individuals participating in a research project should be restricted to the minimum necessary to acquire the appropriate information with sufficient accuracy.

(33) The administered activity or individual radiation exposure should be the minimum consistent with obtaining adequate information. Alternative techniques not involving ionising radiation must always be considered.

(34) Pregnant women should not be asked to take part in any research projects involving irradiation to their unborn child, unless the pregnancy itself is essential to the research or therapeutic research may be life saving for the mother. Where there is or may be excretion in the milk, breastfeeding women should not be involved in research using radiopharmaceuticals except where problems concerning breastfeeding are being examined and where there are no alternative techniques. In both situations the proposed benefit must substantially exceed the possible detriment to the child.

(35) As consent must be given freely with proper understanding of the nature and consequences of what is proposed, research involving children or those who are mentally ill or defective should be avoided. Furthermore unconscious patients cannot consent. In all such circumstances those responsible for the individuals might be able to agree to their participation, in accordance with national legislation. It is particularly important that the risks must be sufficiently small that proposed benefit to such patients in general or individually must substantially exceed the risk. This applies especially to children where radiation risk factors may be 2 to 3 times higher than in adults.

(36) Investigators should seek relevant information on previous radiation doses in order to identify individuals who repeatedly take part in research projects which expose them to risks including those of ionising radiation exposures. The pre-existing and proposed risks should both be explained.

(37) Before the investigator performs examinations involving ionising radiation, in order to find out if a volunteer meets the inclusion criteria, he/she should seek to obtain previous diagnostic information or medial records relevant to the planned examination.

(38) The medical practitioner must keep a confidential list of subjects involved in each research project so that any queries about radiation dose to individuals can be resolved.

4. RISK ASSESSMENT

General

(39) Risks of medical and biomedical research can be categorised into those due to the radiation, and other hazards, for example complications associated with interventional procedures in interventional radiology, and the pharmacological action of drugs or their side effects.

(40) Reliable assessments of the likely doses to be delivered in medical and biomedical research must be made. The absorbed dose or mean absorbed dose to specific organs and the effective dose should be assessed. The effective dose can be used as an overall indicator of the likely radiation detriment to an average individual in the population and as a comparator of the radiation risk with other research projects. The effective dose from diagnostic procedures can be substantial, for example from computed tomography or extended fluoroscopy, and must be properly evaluated.

(41) For radiotherapy procedures and for prolonged interventional radiology where deterministic effects may occur, doses to the most heavily irradiated tissues outside the treatment (target) volume should also be estimated, since effective dose is an inappropriate quantity for assessing the risk of deterministic effects. Furthermore such radiation may subsequently cause cancer induction. The services of a medical physics expert should be sought for calculation of the dose.

(42) Internal dosimetry is necessary when using radiopharmaceuticals. For some radiopharmaceuticals there are established biokinetic models and published data enabling mean organ doses and effective doses to be derived from knowledge of the administered activity (ICR 53 & ICR 62). However disturbed organ function in disease must be taken into account. For new radiopharmaceuticals, dosimetry may be based on animal experiments but should be tested in pilot research on humans (also subject to requirements of paragraph 28) before any extensive investigation is planned. Even when using radioactive substances in tracer amounts the absorbed dose should still be assessed. Dosimetry calculation should always be performed and taken into account so that risks are known and not unduly dismissed.

Research Design

(43) During the design stage justification for the use of ionising radiation must be made by the research team under the guidance of the principal investigator. This team should comprise those with the appropriate academic education, clinical and research experience, and knowledge of radiation safety. Clinical responsibility for the subjects, and methods and procedures consistent with good medical practice must be ensured.

(44) Every project should be preceeded by an assessment of predictable risks compared with the foreseeable benefits for the subject or to others. Concern for the interest of the subject must always prevail over the interests of science and society.

(45) All equipment and procedures used for medical and biomedical research projects should be subject to rigorous quality assurance requirements.

Project evaluation

(46) The aims, outline methods, justification, optimisation, and detailed plans should be evaluated by the ethics committee and/or competent authority before a project is started.

(47) All medical and biomedical research should be published to ensure that information is disseminated widely. This is particularly true for research involving exposure to ionising radiation in order to prevent the unnecessary irradiation of further volunteers as part of similar studies. Studies with a negative outcome should also be published if possible. Publication must preserve the accuracy of the results, and research which does not fulfil the guidelines set out in the declaration of Helsinki (He96) should not be carried out nor accepted for publication. Anonymity of research subjects must be preserved.

Risk Categorisation (Based on ICR62)

(48) To assist those planning research, and also research/ethics committees and/or competent authority, categorisation of projects depending upon the radiation dose to be received by each subject is useful. This is given in table 1.

(49) Category I: Effective doses less than 0.1 mSv (adults)
This category involves a risk (total detriment from the radiation exposure) for normal subjects of the order of one in a million or less. This level of risk is considered to be trivial; the level of benefit needed as the basis for approval for such investigations will be minor and would include those investigations expected "only to increase knowledge".

(50) Category IIa: Effective dose range 0.1-1 mSv (adults)
This category involves risks of the order of one in a hundred thousand. In order to justify such risks the benefit of a research project should probably be related to "increases in knowledge leading to health benefit".

(51) Category IIb: Effective dose range 1-10 mSv (adults)
This category involves risks to the irradiated individual of the order of one in ten thousand. The degree of benefit to society from studies in this category should be "moderate"; the benefit would be expected to be "aimed directly at the diagnosis, cure or prevention of disease".

(52) Category III: Effective doses greater than 10 mSv (adults)
Here the risks to the irradiated individual are estimated at greater than one in a thousand. This is a moderate risk for a single exposure but might be considered as verging on the unacceptable for continued or repeated exposure. To justify investigations in this category the benefit would have to be "substantial and usually directly related to the saving of life or the prevention or mitigation of serious disease". Doses should be kept below the threshold for deterministic effects unless these are necessary for the therapeutic effect.

(53) Table 1 applies to adults under 50 years of age. For each of the above categories the dose figures could be increased by a factor of 5 to 10 for people aged 50 years or over. In the unlikely event of approval being granted for research on children, the corresponding dose figures should probably be reduced by a factor of 2 or 3.

Table 1 Categories of levels of benefit and corresponding levels of risk for healthy adults under 50yrs

(based on ICR62)

Level of social benefit	Risk level corresponding to the benefit	Risk category (total risk - see text)		Corresponding effective dose range (adults) (mSv)[b]
Minor	Trivial	Category I	~ 10^{-6} or less	< 0.1
Intermediate to moderate	Minor to intermediate	Category II		
		IIa	~ 10^{-5}	0.1 - 1
		IIb	~ 10^{-4}	1 - 10
Substantial	Moderate	Category III	~ 10^{-3} or more	> 10[a]

[a] To be kept below deterministic thresholds except for therapeutic experiments.

[b] These figures can be increased by a factor of 5-10 for those over 50 years.

In the case of children they should be reduced by a factor of 2 or 3.

DEFINITIONS (FROM MED)

(54) **Clinical Responsibility**: responsibility regarding individual medical exposures attributed to a practitioner notably: justification; optimisation; clinical evaluation of the outcome; co-operation with other specialists and staff as appropriate regarding practical aspects; obtaining information, if appropriate, on previous examinations; providing existing radiological information and/or records to other practitioners and/or prescribers, as required; giving information on the risk of ionising radiation to patients and other individuals involved as appropriate.

(55) **Medical Physics Expert**: an expert in radiation physics or radiation technology applied to exposures within the scope of this Directive, whose training and competence to act is recognised by the competent authorities; and who, as appropriate, acts or gives advice on patient dosimetry, on the development and use of complex techniques and equipment, on optimisation, on quality assurance including quality control, and on other matters relating to radiation protection concerning exposure within the scope of the MED.

(56) **Practitioner**: a physician, dentist or other health professional, who is entitled to take clinical responsibility for an individual medical exposure in accordance with national requirements.

(57) **Prescriber**: a physician, dentist or other health professional, who is entitled to refer individuals for medical exposure to a practitioner, in accordance with national requirements.

(58) **Dose Constraint:** a restriction on the prospective doses to individuals which may result from a defined source, for use at the planning stage in radiation protection whenever optimisation is involved.

REFERENCES

GEC 97 Guidelines and Recommendations for European Ethics Committees. Leuven: European Forum for Good Clinical Practice, 1997.

HE 96 Recommendations Guiding Medical Doctor in Biomedical Research Involving Human Subjects. Adopted by the Eighteenth World Medical Assembly, Helsinki, Finland 1964; and revised by the 48th World Medical Assembly, South Africa, October 1996

ICR 53 Radiation dose from radiopharmaceuticals. ICRP Publication 53. Annals of ICRP. Oxford: Permagon Press, 1987.

ICR 62 Radiological Protection in Biomedical Research. ICRP Publication 62. Annals of ICRP. Oxford: Permagon Press, 1992.

MED Council Directive 97/43/Euratom of 30 June 1997 on health protection of individuals against the dangers of ionising radiation in relation to medical exposures
O.J. L-180, 22-27, 1997

PAD Council Directive 84/466/Euratom of 3 September 1984 laying down basic measures for radiation protection of persons undergoing medical examination or treatment
O.J. L-265, 1-3, 1984

WHO77 WHO. Use of ionising radiation and radionuclides on human beings for medical research, training and non medical purposes. Technical report series 611. Geneva : World Health Organisation, 1977.

ABSTRACT

The Medical Exposures Directive (97/43/Euratom) broadens the scope of medical exposures, among others, to medical and biomedical research programmes. It includes all situations where radiation is given to healthy volunteers or additional radiation is given to patients over and above that required for their clinical management. When research is conducted it must be conform to a number of ethical criteria which are listed in the guide. Risk assessment is important for research design and project evaluation and the guide provides with a risk categorisation in relation to dose and age of the volunteer.