

Notes for Guidance on the Clinical Administration of Radiopharmaceuticals and Use of Sealed Radioactive Sources

**Administration of Radioactive Substances
Advisory Committee**

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Preface

These Notes for Guidance have been prepared by the Administration of Radioactive Substances Advisory Committee and its Working Parties.

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Introduction

- 1** The guidance given in these Notes is not mandatory and does not have the force of statutory regulations: nevertheless, it is based on national and international recommendations and represents the advice of the Administration of Radioactive Substances Advisory Committee (ARSAC). These Notes can be considered to be a guide to good clinical practice in the UK for nuclear medicine.
- 2** Other guidance on the protection of the patient in investigations involving radiopharmaceuticals has been issued by the International Commission on Radiological Protection (ICRP)^{1,2}. Further guidance is issued by the European Commission. In the case of research projects involving volunteers, attention is drawn to the guidance published by the Medical Research Council³ and a World Health Organization (WHO) expert committee⁴.
- 3** The Notes include a number of changes from the previous revision. These include:
 - (a) a revised summary of the legislation most relevant to nuclear medicine practice;
 - (b) advice regarding variations and extensions to existing research certificates;
 - (c) advice regarding renewal of diagnostic and therapy certificates;
 - (d) revised sections on children and young people, conception, pregnancy and breast feeding, and thyroid blocking;
 - (e) revised guidance on training and experience requirements for certificate holders, including advice for those who wish to provide PET services;
 - (f) advice on training and experience requirements for those working under the written directions of a certificate holder;
 - (g) revised effective dose values utilising data from the ICRP;
 - (h) a new appendix on communication of risk.

Future Revision and Updates

- 4** It is intended that the ARSAC will review these Notes at such periods as may be appropriate. In addition, some detailed updating will be provided through a newsletter published on the ARSAC website – www.arsac.org.uk. The major professional bodies will be notified of these newsletters so that they can bring them to the attention of their fellows and members.

Section 1

The Medicines Regulations, Order and Amendment Regulations (with respect to Radioactive Substances)

Introduction

- 1.1** These Notes provide general guidance for use by medical and dental practitioners concerned with the administration of radiopharmaceuticals to and the use of sealed radioactive sources with human beings. A description of the Regulations and Order specific to these practices is given in this section.
- 1.2** A summary of additional associated statutory requirements in relation to the medical use of ionising radiations (including radioactive substances) is given in Appendix V. Particular attention is drawn to the Ionising Radiation (Medical Exposure) Regulations 2000⁵ and the relationship between that legislation and the Regulations addressed in that section.
- 1.3** Although Regulations refer to radioactive medicinal products, practitioners may find this term unhelpful. Therefore in these Notes the term ‘radiopharmaceuticals’ is often used.
- 1.4** Three sets of legislation have been made under the Medicines Act 1968⁶ and the European Communities Act 1972⁷ to establish a licensing system for the use of radiopharmaceuticals and sealed radioactive substances. These are the Medicines (Administration of Radioactive Substances) Regulations 1978⁸, the Medicines (Radioactive Substances) Order 1978⁹ and the Medicines (Administration of Radioactive Substances) Amendment Regulations 1995¹⁰. This legislation has been introduced to comply with the requirements of Article 5(a) of the European Council Directive 76/579/Euratom and its later revisions, 80/836/Euratom, 84/467/Euratom and 96/29/Euratom, on basic safety standards for health and protection against the dangers of ionising radiation¹¹⁻¹⁴.
- 1.5** The Regulations, Order and Amendment Regulations apply to:
- (a) unsealed radioactive substances when administered to a human being, including labelled drugs for metabolic studies;
 - (b) radioactive substances induced within the body as the primary purpose of the irradiation, but not to those which arise as a byproduct of treatment; at present the former applies only to *in vivo* neutron activation analysis;
 - (c) solid radioactive sources, including radioactive substances in the form of insoluble compounds, ceramics or metal foils or wires, introduced into the body or body cavities or applied to the surface of the body, but not to teletherapy sources nor to nuclear powered cardiac pacemakers nor to apparatus for the production of X-rays.
- 1.6** The Health Ministers are responsible for administering and enforcing these regulations through the Medicines and Healthcare Products Regulatory Agency (MHRA) in Great Britain and the Department of Health, Social Services and Public Safety in Northern Ireland (DHSSPS(NI)). Any NHS authority or hospital which has reason to believe that radioactive substances are being administered other than in accordance with these Regulations should report its concern to the MHRA or the DHSSPS(NI).
- 1.7** Details of the legislation are provided below.

The Medicines (Administration of Radioactive Substances) Regulations 1978 (the MARS Regulations 1978)⁸

1.8 The MARS Regulations 1978 provide for a system of prior authorisation which provides protection of the patient or volunteer during the clinical or research use of radioactive substances and, indirectly, protection of the staff who are involved. The Regulations were made under Section 60 of the Medicines Act 1968 and Section 2(2) of the European Communities Act 1972. They implement part of Council Directive 76/579/Euratom and its later revisions (see paragraph 1.4). Irrespective of the degree of danger involved to the subject, they prohibit the administration to human beings of radioactive medicinal products except by a doctor or dentist holding a certificate issued by the Health Ministers or by a person acting under the directions of such a doctor or dentist. Breach of this obligation is a criminal offence by virtue of Section 67(2) of the 1968 Act.

Summary of the MARS Regulations 1978

1.9 Regulation 1 contains essential definitions, which include those listed below.

- (a) 'Radioactive medicinal product' is defined for the purpose of these Regulations as a medicinal product which contains or which generates a radioactive substance and which is, contains or generates that substance, in order, when administered to a human being, to utilise the radiation emitted therefrom. Medicinal products containing only naturally occurring radionuclides in normal concentrations, whose radioactivity is not relevant to the medicinal process, eg naturally occurring potassium, do not require certification.
- (b) 'Medicinal product', 'purpose' and 'radioactive substance' are also defined for the purpose of the Regulations in Regulation 1. The definition of radioactive substance is taken verbatim from Council Directive 80/836/Euratom. The term has not been more closely defined, eg by reference to a specified level of activity or concentration of particular radionuclides, because it is recognised that the effect of radioactive substances once administered varies according to the way they are metabolised and concentrated in the body, sometimes over a long time. Thus the chemical form and circumstances of the administration and the sex and age group of the persons to whom they are administered have to be taken into account, as do the radiation protection measures required. Advice on whether particular radioactive substances and the circumstances of their administration fall within the scope of the Regulations can be obtained through the ARSAC Support Unit. 'Purpose' has a specific meaning within the Regulations and is defined as diagnosis, treatment or research.
- (c) Other expressions used in the Regulations and Order have the same meaning as in the Medicines Act 1968, and, in particular, 'doctor' has the meaning given to it in Section 132(1) of the Act, ie a fully registered person within the meaning of the Medical Act 1956.
- (d) 'Administer' has the meaning given to it in Section 130(9) of the Medicines Act 1968, ie 'administer ... whether orally, by injection or by introduction into the body in any other way, or by external application, whether by direct contact with the body or not. Any reference ... to administering a substance or article is a reference to administering it either in its existing state or after it has been dissolved or dispersed in or diluted or mixed with, some other substances used as a vehicle.'

1.10 Regulation 2 contains the substance of the Regulations: it makes plain that only doctors or dentists or persons acting in accordance with their directions may administer radioactive medicinal products and that they may do so only if they hold a certificate issued by the Health Ministers. The certificate may specify the particular description or classes of radioactive medicinal products which may be administered by the holder and the purposes for which the administration is authorised.

- 1.11** Regulation 3 describes the Administration of Radioactive Substances Advisory Committee (ARSAC) under the chairmanship of a medical practitioner and with a majority of medical practitioners as members. All members have wide and recent experience relevant to the main function of this Committee, which is to advise the Health Ministers on matters relevant to the granting of certificates. Members include clinical radiologists, clinical oncologists, nuclear medicine physicians, physicists, radiopharmacists, radiographers and technologists. The Committee regulates its own proceedings with a secretariat provided by the Health Protection Agency.
- 1.12** Regulation 4 sets out the information which may be specified on the certificate, the information to be provided in making application for a certificate and the conditions under which Health Ministers may grant a certificate.
- 1.13** Regulation 5 concerns the duration of (up to five years) and conditions for the renewal of a certificate.
- 1.14** Regulation 6 specifies the grounds and ways in which the Health Ministers may suspend, revoke or vary a certificate.
- 1.15** Regulation 7 lays down the procedure to be followed if the Health Ministers propose to refuse to grant or renew a certificate or to suspend, revoke or vary it, including the opportunity for hearings or representations.

The Medicines (Radioactive Substances) Order 1978⁹

- 1.16** This Order brings within the terms of the Regulations the following items as if they were medicinal products:
- (a) certain radioactive appliances and applicators which are not medicinal products, but are used for medicinal purposes;
 - (b) apparatus to generate neutrons for *in vivo* neutron activation analysis;
 - (c) radioactive substances or articles (not including teletherapy apparatus) when used for research purposes where there is no direct benefit to the person to whom they are administered.
- 1.17** It does so by extending the scope of Section 60 of the Medicines Act 1968 to articles and substances specified in the Schedule to the Order. Therefore, the MARS Regulations also apply to brachytherapy (implants, intracavitary or surface applicators) with sealed and other solid sources and *in vivo* neutron activation analysis. But the Regulations do not apply to the irradiation of persons by ionising radiations from X-ray and teletherapy machines.

The Medicines (Administration of Radioactive Substances) Amendment Regulations 1995¹⁰

- 1.18** These Regulations amend the MARS Regulations 1978 and make various administrative changes including provision for:
- (a) directions and notices to be given in writing;
 - (b) the granting to those who already hold certificates of further certificates for particular descriptions or classes of radioactive substances;
 - (c) the granting to those who already hold certificates of further certificates for particular patients;
 - (d) the functions of the Health Ministers under the MARS Regulations 1978 to be performed by any one of them or by any two or more of them acting jointly.

Section 2

Certificates

Who Should and Who Need Not Apply

- 2.1** Any doctor or dentist wishing to administer radioactive medicinal products to persons on a regular basis may apply for a certificate; however, applicants should be normally of specialist status and involved in the justification of procedures and development of appropriate clinical protocols. It is expected that the use of radioactive medicinal products is a significant part of their clinical practice.
- 2.2** Separate certificates will be issued only in special circumstances to doctors or dentists at other grades who can demonstrate the appropriate training and experience.
- 2.3** Doctors or dentists only requesting that radioactive medicinal products be administered to their patients, those who only provide reporting or clinical evaluations of procedures, those who follow routine established diagnostic protocols or those who use radioactive medicinal products as a minor part of their practice would not normally need to apply for a certificate. The MARS Regulations 1978⁸ allow such persons to act under the directions of a certificate holder. It is a requirement of the Amendment Regulations 1995¹⁰, however, that such directions are in writing. The employer should ensure that procedures are established to enable persons administering radioactive medicinal products under the direction of a practitioner to ascertain that the latter holds an appropriate certificate.
- 2.4** Such persons may continue to administer radioactive medicinal products during periods when the said certificate holder is temporarily absent, on leave, etc. This applies also to a doctor employed to maintain the service under a locum arrangement. In these circumstances, it is not expected that there will be a requirement to make changes to the services provided or the protocols used.
- 2.5** In the case, however, of long absences, or of the appointment being vacated, where it is reasonably foreseeable that there will be a requirement to change the way the service is delivered or the protocols used, the employer must make alternative arrangements to permit radioactive medicinal products to be administered by or under the direction of a certificate holder. This could include the transfer of responsibilities to another certificate holder already in post within the employing authority. Alternatively, a longer term locum appointment could be made or an honorary contract offered to an established certificate holder at another hospital. In these cases, the external certificate holder or locum doctor should apply for a certificate of his/her own for the employer's site. If no such person is available, radioactive medicinal products must not be administered.
- 2.6** Doctors or dentists who habitually work under the direction of a certificate holder should review whether they also need a certificate or whether they can continue to work under the certificate held by another practitioner. If, for example, such individuals begin to work independently and wish to develop their own specific protocols they must then apply for a certificate in their own right.
- 2.7** Under the MARS Regulations 1978, no limit is placed on the number of doctors or dentists that can hold certificates for any individual site. However, there is little value in having large numbers of such practitioners holding certificates covering the same procedures, if such procedures are conducted under agreed protocols. This may lead to confusion over which practitioner is responsible under the MARS Regulations for each procedure. In practice, two clinicians holding certificates for the same procedures should be sufficient to provide a continuous service under all eventualities, eg long-term absence of one

certificate holder. It must be made clear in the department protocols which practitioner is responsible for each individual procedure undertaken.

- 2.8** Applicants must include information about the equipment, facilities and scientific support available to him or her. Such information can be supplied either by the applicant or by the senior scientist responsible for the facilities available to the applicant.
- 2.9** The Department of Health may make further enquiries about training or such facilities if this seems necessary. If an application is referred back to the applicant for additional information it cannot be considered further until an appropriate reply is received.

Issuing Authority and Validity

- 2.10** Certificates authorising the administration of radioactive medicinal products will be granted in accordance with the MARS Regulations 1978 by the Health Ministers advised by the ARSAC. A certificate will be specific to the purpose, the site and the practitioner.
- 2.11** The purpose for which each class or description of radioactive medicinal products specified in a certificate may be administered is defined as diagnosis, treatment or research. Issues relevant to each of these purposes are discussed in Sections 3, 4 and 5 of this document.
- 2.12** If a practitioner, having a certificate to administer a particular radioactive medicinal product for a specific purpose, ie diagnosis, treatment or research, wishes to administer it for another purpose, he or she must apply for another certificate.
- 2.13** A certificate may be suspended, revoked or varied by the Health Ministers as set out in Regulation 6.
- 2.14** A certificate will normally be valid for five years in the case of diagnosis or treatment: for research applications, the normal period of validity is two years. If the research takes longer than the two year period then the certificate holder should write to the ARSAC Support Unit for an extension of the certificate (paragraph 2.37).
- 2.15** The original certificate will be issued to the applicant. Two copies of the certificate will be supplied to the employer concerned, who should provide a copy to the Radiation Protection Adviser (RPA). A further copy is retained by the Department of Health.

Requirements for Initial Applications for Diagnosis or Treatment

- 2.16** The information required to support an initial application for a certificate is outlined in Regulation 4. The application must contain the following particulars:
- (a) the name, address, qualifications and relevant experience of the applicant and the post or position which the applicant holds or is to hold and the premises in which he or she proposes to administer the radioactive medicinal products specified in the application;
 - (b) the particular descriptions or classes of radioactive medicinal products the applicant proposes to administer or to have administered and the purpose for which they are to be administered;
 - (c) information as to the equipment, facilities and staff available to the applicant for the proposed administration of radioactive medicinal products;
 - (d) such other information as the Health Ministers may reasonably require.

NB Under Regulation 4(2)(b)(iv) an applicant for a certificate may be required to furnish such other information as the Health Ministers may require in order to assist the ARSAC when deciding upon the advice to be offered.

- 2.17** The certificate will be granted to the practitioner who is clinically responsible for the administration of the medicinal product. The information that will usually be required is specified in the Application Form (Full Form). Applications should be signed by the applicant and Part C of the Form should be signed by the scientists with responsibility for local scientific support, radiation protection and provision of radioactive medicinal products. In some circumstances some of these functions may be provided by the applicant. The applicant must list and provide details of the radioactive medicinal products for which he/she wishes to receive a certificate and the purpose or purposes for which the radioactive medicinal products are to be administered. Information about intended administered activity and resulting dose should be included. Alternatively, the applicant may request particular procedures by reference to the serial numbers given in Appendix I, Parts A–D, in these Notes. In this case, it is assumed that the administered activities will be those in Appendix I, where given. Applications should be submitted to:

**ARSAC Support Unit
Radiation Protection Division
Centre for Radiation, Chemical and Environmental Hazards
Health Protection Agency
Chilton Didcot Oxon OX11 0RQ**

- 2.18** Applications for diagnostic procedures can be made by referencing individual procedures listed in Appendix I, Parts A and B, by providing detailed information about procedures required that are not included in Appendix I, Parts A or B, or by reference to functional groups (see Appendix I, Part E) or any combination of these. When using the functional group facility, it is not necessary to list the individual procedures, or their serial numbers. If, however, the applicant wishes to use a procedure included within Appendix I, Part A, but at a higher activity, detailed information is required.
- 2.19** Applications for therapy procedures can be made by referencing individual procedures listed in Appendix I, Parts C and D, or by providing detailed information about procedures required that are not included in Appendix I, Parts C and D. There are no functional groups for therapy procedures.
- 2.20** Application forms are available from the ARSAC Support Unit or can be downloaded from the ARSAC website, www.arsac.org.uk, or via links on the websites of the Department of Health and the Health Protection Agency. All applications must be submitted as hard copy and require written signatures of the applicant and others. The application forms include sections on training and experience and this information should be included with each application. Failure to do so may lead to delays in processing applications as previous information is often archived and retrieval may take some time.
- 2.21** In order to allow sufficient time for the processing of applications and issue of certificates, applications should be submitted well in advance of the date by which authorisation is required (but see paragraphs 2.40–2.42 on urgent applications). In general, certificates are issued within six weeks of receipt of a complete application. Applications which require additional information or clarification can take longer. Incomplete applications will be returned to the applicant with a request for provision of the missing information before consideration by the ARSAC. A flow diagram indicating how initial applications are processed is provided in Appendix VI.
- 2.22** Advice specific to research applications is given in Section 5. In addition, the application forms contain guidance notes to help the applicant to supply the information required. Common areas where further information is required include training and experience of first-time applicants (see Appendix IV), absence of dosimetry information for procedures not included in Appendix I, Part A, and an incomplete or inappropriately completed Part C of the Application Form.

Qualifications and Experience of the Practitioner

- 2.23** The degree of special training required by a practitioner in the clinical aspects of work with radioactive substances and in radiation protection will vary with the nature of the work to be undertaken.
- 2.24** Nuclear medicine consultants, clinical oncologists and many clinical radiologists who already undertake regular clinical work with radioactive substances will be proficient in their use. Other doctors and dentists may not have received comprehensive training and experience in the appropriate diagnostic or therapeutic procedures and radiation protection necessary to hold a certificate. To assist those who wish to apply for a certificate to administer radioactive substances, a core curriculum for nuclear medicine has been developed. This is included at Appendix IV, Part A.
- 2.25** This curriculum is intended as a guide for those who wish to carry out procedures using radioactive substances, whether as part of another specialty or in the provision of a specialist service. Those doctors or dentists who apply for ARSAC certificates are asked to provide details of their training and experience, and this will be assessed against the curriculum included at Appendix IV, Part A. To hold a certificate and to be competent to assume the responsibilities of a certificate holder, it is essential to receive both theoretical and practical training in the use of the radioactive substances concerned.
- 2.26** Appendix IV, Part B, provides additional information for applicants who wish to undertake diagnostic or research studies with positron emission tomography (PET). This training and experience will be additional to that identified in the core curriculum.
- 2.27** Appendix IV, Part C, provides information on training and experience required when new techniques are introduced. Appendix IV, Part D, provides guidance on the relationship between the certificate holder and others who effectively work under his/her written directions and models for training of such staff, eg surgeons undertaking sentinel lymph node probe studies.

Qualifications and Experience of Supporting Staff

- 2.28** Practitioners will normally be expected to collaborate with physicists and (if appropriate) radiopharmacists, and have available technical staff with appropriate training and experience, who may or may not be under their direct control. Such staff will assist the practitioner:
- (a) with the procedures (including calibration and assessment of technical performance of equipment);
 - (b) in the evaluation of the procedures for the performance of tests (including estimation of tissue dose);
 - (c) to account for the radioactive material;
 - (d) with the radiation protection of staff (including monitoring of staff and decontamination, as necessary);
 - (e) with the radiation protection of patients;
 - (f) with the radiopharmaceutical formulation of the medicinal products.
- 2.29** Regulations require that employers must ensure that those treating patients by radiotherapy or administering radioactive medicinal products have access to the services of one or more appropriately qualified and experienced physicists. An appropriate standard for this responsibility is at least six years' experience in the relevant branch of medical physics and national assessment for competence by two members of the National Panel of Assessors¹⁶.

2.30 The degree of access will depend upon the scope of the nuclear medicine service offered. Departments offering a comprehensive service including imaging, non-imaging and non-standardised therapy procedures using unsealed sources would normally have access to a minimum of one whole time equivalent physicist with experience as specified above. Radiotherapy departments would expect similar staffing levels. Other scientific staff would be expected to be available also.

Supporting Services

2.31 Whether or not under the direct control of the applicant, the adequacy of supporting services will depend upon the nature and complexity of the work involved^{17,18}. Factors to be considered will include the suitability of:

- (a) equipment to undertake the procedure involved;
- (b) working areas and related laboratory equipment;
- (c) trained staff for the supervision, treatment and nursing of subjects to whom the radioactive medicinal product is administered.

2.32 Much of this information is requested in Part C of the Application Form. In cases where radiopharmaceuticals are supplied from an off-site radiopharmacy, the local scientists responsible for the provision of radioactive medicinal products at both sites should sign Section 6 of the Form. Applications for certificates for the use of sealed and unsealed sources may require signatures of two people, depending upon the experience of the scientists.

Renewal, Extension and Variation of Certificates

2.33 A certificate for diagnosis or treatment may be renewed in accordance with Regulation 5. Reminders to renew such certificates are automatically sent to certificate holders. However, it should be noted that it is the responsibility of the practitioner to hold a current valid certificate.

2.34 Applications for renewal of certificates for diagnosis and treatment should be made on the Renewal Form. At this time, up-to-date information regarding the applicant's continuing involvement in the procedures requested, supporting staff and available facilities is required. Maintenance of competence is a clinical governance issue and an essential part of modern clinical practice and applicants may be asked to demonstrate this competence. Certificate holders are expected to show evidence of continuing medical education associated with the nuclear medicine procedures they undertake as part of the appraisal and revalidation processes and to reference this at the time of applying for the renewal of their certificate. Advice regarding continuing training of support staff is given in Appendix IV, Part C.

2.35 Renewal of certificates provides an opportunity to remove any procedures that are no longer required. Requests for additional procedures should not be included on the Renewal Form.

2.36 Applications for additional procedures for diagnosis or treatment can be added within the duration of an existing certificate. These should be made as and when required and submitted on the Additions Form or the Functional Group Application Form. Further information concerning the latter is given in Appendix I, Part E. Where applications are made for a certificate to include procedures that are considerably different from those already held, then further evidence of appropriate training and experience may be requested.

2.37 Research certificates are valid for two years only and as they are project specific there is no formal renewal process. Reminders therefore are not issued for renewal of research certificates. A research certificate can be extended if the subject numbers in the original application have not been met or if

some of the originally specified investigations for individual subjects will fall outside the duration of the certificate. Such a request should be submitted by letter, containing all relevant information, rather than by a new application form. This should be sent to the ARSAC Support Unit. If approved, a new certificate will be issued.

- 2.38** Occasionally, the original parameters associated with a research study may change after a certificate has been granted. Examples include small changes in administered activity or chemical form, age range of subjects or subject numbers. Where the material change to the original application is minor, an application for variation of a certificate can be made by letter. This should include a full justification for the variation. In most circumstances an acknowledgement can be issued and a new certificate will not be necessary.

Changes of Premises or Appointment

- 2.39** All certificates relate to the appointment and facilities quoted in the application, and the ARSAC should be informed promptly of any material change in these circumstances since the certificate may need to be varied. If in exceptional circumstances, for clinical reasons, a certificate holder wishes to administer the radiopharmaceuticals concerned in premises not quoted in his/her application, he/she is not precluded from doing so under the MARS Regulations. However, prior to doing so he/she should notify the Radiation Protection Adviser and ensure that the conditions and supporting staff and facilities are adequate for the work to be carried out safely, and that other legislation is satisfied. If such administrations are to be a regular practice, the practitioner should provide the ARSAC and Radiation Protection Adviser with details of the new premises, supporting staff and facilities and a new certificate may be issued.

Urgent Applications – Particular Patient Requests

- 2.40** In cases where the certificate held by a clinician or doctor is not appropriate for an administration he/she wishes urgently to undertake, an application on behalf of a particular patient may, to save time, be submitted by fax (01235 834925) using the Particular Patient Request Form. Advice about such applications, and other matters, can be sought from the ARSAC Support Unit by telephoning (01235 832421/834925) or by writing.
- 2.41** Where such procedures are to be undertaken more than very occasionally, the certificate holder should apply for an addition to his/her diagnostic or therapy certificate.
- 2.42** Clinicians or doctors who do not hold a certificate cannot apply for one using the Particular Patient Request Form. In cases of extreme urgency they must seek the direction of, or refer the patient to, a certificate holder. The ARSAC Support Unit may be able to help such clinicians or doctors to locate an appropriate certificate holder and advise on special circumstances when a standard referral to another site is not appropriate.

Representations

- 2.43** The Health Ministers, if they intend to refuse to grant or renew or to suspend, revoke or vary a certificate, will notify the applicant and give him/her an opportunity to appear before a person appointed by them or, if he/she prefers it, to make representations in writing.
- 2.44** Notification of a proposal to refuse to grant or renew a certificate or of a proposal to suspend, revoke or vary a certificate will be accompanied by an explanation of the reasons.

- 2.45** A period of not less than 28 days will be specified, within which an applicant must give notice that he/she wishes to make representations in writing or to appear before a person appointed by the appropriate Health Minister. The Health Minister will consult the professional organisations mainly concerned, before selecting the person to be appointed.
- 2.46** If the ARSAC proposes to advise the Health Ministers against the authorisation of an applicant to administer a radioactive medicinal product which is the subject of a marketing authorisation, on the grounds that it is unsafe, the ARSAC shall so advise the licensing authority. It will then be for that authority to decide whether or not the marketing authorisation for the product concerned should be suspended, varied or revoked. If the licensing authority proposes to vary or revoke the marketing authorisation the licensee will be notified and may then apply for a hearing or make representations in writing in accordance with Sections 28 and 29 and Schedule 2 of the Medicines Act 1968 as appropriate.

Section 3

Diagnosis

Data

- 3.1** The advice of the ARSAC regarding certain well-established radiopharmaceuticals for diagnostic purposes is contained in Appendix I, Parts A and B. The basis of the data and their use are explained in the introductory notes to that appendix.

Activity Administered

- 3.2** In relation to diagnostic procedures, the practitioner should note the diagnostic reference level for each adult investigation as listed in Appendix I, or as specified in correspondence concerning the application. It is important that the activity for each exposure is optimised such that appropriate diagnostic information is obtained with the lowest practicable dose to the patient. This is the principle underlying optimisation.
- 3.3** All procedures should be undertaken in accordance with departmental written protocols.
- 3.4** In certain circumstances, eg individuals significantly below 70 kg in weight, it may be possible to reduce the activity administered.
- 3.5** It is recognised that clinical reasons, eg patients who are very much overweight, may in some cases make greater activities necessary (see Appendix I, paragraph 10). The guiding principle, however, remains that for the investigation of any subject, the activity administered should be the minimum consistent with acquiring adequate information from the investigation concerned.
- 3.6** Where activity is increased on the basis of an individual patient's weight, it is not necessary to inform the ARSAC. If such increased activities are used infrequently, they should be justified and recorded by the ARSAC certificate holder. The requirement for this should be included in written procedures.
- 3.7** Where this becomes a regular process, but is still assessed for each individual patient, a basis for the increase in activity can be established and should be included in local protocols. This can then be applied by staff other than the certificate holder but the requirement to record the activity and the reason for the increase remains.
- 3.8** If a practitioner believes that within the context of local circumstances (eg all patients for bone scans at the centre have confirmed cancer), all patients will require a standard activity for a particular procedure higher than that stated in Appendix I, then a separate application should be made to the ARSAC, giving the justification for the increased activity. If agreed, this should be included within written protocols. The radiation dose estimates given in column 7 of Appendix I, Parts A and B, give the data (see ICRP Publication 80¹⁹) which are currently accepted within the meaning of the MARS Regulations 1978.

General Techniques for Dose Reduction

- 3.9** A number of simple techniques can be used to reduce radiation dose. For example, many radionuclides are excreted by the kidneys. Bladder doses can be minimised by drinking plenty of fluid and frequent bladder emptying.

- 3.10** In some cases, if the patient is healthy and cooperative, activity might be reduced and scan times increased. Examples might include scaphoid imaging or lung scans for pregnant women. In all cases, however, it is important that the diagnostic information produced is not compromised by reduction in activity.
- 3.11** Where two imaging investigations exist that give equivalent information and both are available to the patient within the timeframe of their clinical management, then on radiation protection grounds the procedure resulting in the lowest dose should be selected.
- 3.12** Advice on the use of thyroid blocking agents is given in Section 8.

Females and Males – Conception, Pregnancy and Breastfeeding

- 3.13** Special consideration should be given to investigations involving either sexually active males who may father children or females of childbearing potential. Further details on conception, pregnancy and breast feeding are given in Section 7.

Children and Young Persons

- 3.14** Special consideration should be given to investigations on children and young persons. Details concerning administered activities, practical aspects and radiation protection are given in Section 6.

Section 4

Treatment

General

- 4.1** It is recognised that the therapeutic use of radioactive medicinal products requires recent training and facilities specific to the therapy because of the radiation protection implications. Diagnostic radionuclide studies are a prerequisite for the safe administration of most therapeutic radiopharmaceuticals. Applications should include details of existing diagnostic radioisotope facilities as well as those for therapy where relevant or provide written protocols for patient selection if these facilities are not available.
- 4.2** Certification for therapy purposes will be granted only if the applicant can demonstrate recent training, competence and significant experience in the use of therapeutic radiopharmaceuticals and/or sealed radioactive sources for which approval is sought. This is reflected in the training requirements outlined in Section 2 and detailed in Appendix IV, Part A.
- 4.3** Evidence must be provided of facilities and supporting staff appropriate to the administered activity of the radiopharmaceutical. Designated in-patient accommodation, which for some treatments will include en-suite facilities, may be required. In many cases, it may be appropriate to restrict therapeutic procedures to specialist centres. The administration of some therapeutic radiopharmaceuticals may require access to additional medical expertise, eg in rheumatological or haematological applications. The applicant should provide evidence of multidisciplinary collaboration in these cases.
- 4.4** Certificates for treatment purposes are normally issued only for radionuclide therapy products with Marketing Authorisation or for those products in which efficacy is proven. Such certificates are valid for five years. Other applications will be considered on a research basis and a research protocol should be submitted with the application. If applicants are in doubt about the appropriate procedure then they should contact the ARSAC Support Unit. If the proposed study forms part of a clinical trial, authorisation from the MHRA may be required under the Medicines for Human Use (Clinical Trials) Regulations 2004²⁰. Guidance on the type of studies that will need authorisation, and information on how to apply, are available on the MHRA website (<http://medicines.mhra.gov.uk>). NHS R&D offices will be able to assist with the application.
- 4.5** It is recognised that the total activity administered for the purpose of treatment must be a matter of clinical judgement by the responsible certificate holder. This includes treatment with sealed sources, as described in the Schedule to the Medicines (Radioactive Substances) Order 1978, that are used in contact with the surface of the body, or inserted into the body or body cavities.
- 4.6** The advice of the ARSAC regarding certain well-established radioactive medicinal products for treatment purposes is contained in Appendix I, Parts C and D. Changes in relation to certificates for treatment will be posted on the website, www.arsac.org.uk.

Section 5

Research

Requirements for Research Certificates

- 5.1** As a guiding principle, an ARSAC research certificate must be obtained for all research projects which result in radiation exposure to subjects additional to that involved in their routine diagnostic or therapeutic management. A certificate must be obtained or a variation approved for each project.
- 5.2** More precisely, subject to paragraph 5.3 below, research in the context of the MARS Regulations 1978⁸ and the Medicines for Human Use (Clinical Trials) Regulations 2004²⁰ includes investigations or treatments which fall into one or more of the following categories:
- (a) all clinical trials as defined in Part 1, Regulation 2, of the latter Regulations where a clinical trial authorisation has been granted or is to be obtained;
 - (b) the administration of radioactive medicinal products where the study does not come within the scope of the Regulations;
 - (c) additional radiation exposure above that incurred in the routine management of the patient – the definition of routine management in diagnosis, continuing assessment or therapy should be established by the ARSAC certificate holder, with regard to the referring clinician, and written down in the appropriate protocol.

If in doubt, the applicant should contact the ARSAC Support Unit.

- 5.3** Research using new or unestablished procedures intended to benefit a single patient will be considered under the heading of diagnosis or treatment; the practitioner in charge must hold an appropriate certificate for diagnosis or treatment covering the radioactive medicinal product in question.
- 5.4** The Medical Exposure Directive 97/43/Euratom²¹, implemented in May 2000, addresses the exposure of individuals as part of biomedical and medical research. The principles of justification and optimisation are applied to research and the Directive differentiates between those individuals where there is no direct medical benefit (often referred to as healthy volunteers or controls) and patients who may be expected to receive a diagnostic or therapeutic benefit from the research. Dose constraints are required for the former, while target levels of dose are to be established for the latter.

Activity Administered

- 5.5** The activity administered to individuals should be the minimum consistent with obtaining adequate information, especially for administrations to volunteers who are not expected to benefit directly. Research involving high radiation doses may be approved if specific justification is provided. The justification must apply to the individual recipient as well as to the population as a whole. All unnecessary administrations should be avoided.
- 5.6** The ARSAC expects that when an application relating to a research project is submitted, estimates of effective dose will be based on the best information available at the time. Where such estimates are not possible from similar existing human studies, data from animal dosimetry studies, or where practicable from human studies involving extremely low radiation doses, should be submitted as part of the

application. Once the work has been carried out more accurate information on dosimetry may be forthcoming. In order to help the ARSAC in its task of reviewing future applications, such information should be made available to it as soon as possible.

Other Exposures

- 5.7** The WHO⁴ and the ICRP²² recognise the possibility that research projects might be proposed in which the effective whole body dose from all medical exposures to ionising radiation would exceed 50 mSv. The ARSAC will only very exceptionally advise in favour of an application involving this level of radiation dose.

Selection of Subjects for Research Projects

- 5.8** When selecting subjects for a research study involving radioactive medicinal products, the following general considerations should be taken into account:
- (a) age;
 - (b) numbers;
 - (c) multiple studies;
 - (d) multicentre studies;
 - (e) females;
 - (f) workers occupationally exposed to ionising radiation;
 - (g) classified radiation workers;
 - (h) staff.

Age

- 5.9** Consideration must be given to the age of the subjects proposed for investigation. In particular, persons under 18 years of age should not be involved except where problems specific to their age groups are under investigation. Special justification would be required for the inclusion of children and young persons in research studies. Whenever possible, healthy volunteers should be aged over 50 years¹⁷. If the study requires patients below the age of 50 years then explicit justification for the age range required should be included within the application. For studies in patients over 50 years then an upper age limit need not be stated for the purposes of the application for certification.

Numbers

- 5.10** The numbers of individuals participating in a research project should be restricted to the minimum necessary to obtain the information required. The applicant should be able to justify the sample size (number of patients/volunteers) which is being requested. Where relevant, consideration should be given to the statistical power of the study design to ensure that the number of subjects is appropriate to the hypothesis under test. Further detail is provided in Appendix III.
- 5.11** This is in keeping with ICRP Publication 62² which states that all research involving human subjects must be carefully planned so as to gain the maximum medical or scientific knowledge with the minimum risk and inconvenience to the subject. This planning must encompass a statistical overview to ensure the utilisation of the minimum exposure to radiation by the smallest number of subjects needed to achieve the desired result.
- 5.12** Applicants are recommended to seek appropriate statistical advice on the planning of research studies. Further information is also given in Appendix III.

Multiple studies

- 5.13** Consideration should be given to the risks to an individual who is involved in several research investigations. It is unacceptable that an individual should repeatedly take part in research projects leading to substantial cumulated radiation dosage. This is particularly relevant for normal healthy volunteers who should not normally be exposed such that an annual dose constraint of 10 mSv from all research exposures is exceeded (including those from non-nuclear medicine procedures).
- 5.14** It is the responsibility of the certificate holder to keep a list of the names of the subjects involved in each research project. This applies both for patient subjects and for control volunteers. Records should be kept for periods consistent with those given in Health Service Circular 1999/053²³.
- 5.15** Investigators should always review the previous radiation exposure of the proposed participants. In the case of patients where there is potential benefit to those individuals, previous exposures as part of diagnosis or treatment do not need to be discussed when obtaining consent. In the case of normal healthy volunteers, previous exposures as part of diagnosis or treatment should not be included as part of the proposed annual dose constraint of 10 mSv. They should, however, be discussed with the volunteer as part of the process of obtaining informed consent.

Multicentre studies

- 5.16** In the case of multicentre trials the total numbers of subjects in the trial should be stated in addition to the number of studies to be undertaken at the site for which the application is made. This is required so that the statistical power of the study as a whole can be assessed. The applicant should provide information regarding the processes in place to ensure consistency of data across centres.

Females

- 5.17** The possibility of early pregnancy should always be borne in mind in connection with the use of females of childbearing potential as subjects.
- 5.18** Pregnant females and females who are breast feeding must not be involved in any project, except where problems related to their condition are under investigation and alternative techniques that do not involve ionising radiation have been considered and rejected.
- 5.19** Further information is given in Section 7.

Workers occupationally exposed to ionising radiation

- 5.20** When workers who are occupationally exposed to ionising radiation are asked to volunteer, the researcher must ensure that as volunteers they are aware of the additional risk arising from their exposure from radiation at work.

Classified radiation workers

- 5.21** Radiation workers who are classified under the Ionising Radiations Regulations 1999²⁴ should not normally be accepted as volunteers in a research project.

Staff

- 5.22** Staff who are employed within the department of the researcher should not normally be accepted as volunteers in a research project. Inclusion of staff can suggest inappropriate coercion.

Ethical Approval

5.23 Every clinical research investigation involving the use of radioactive medicinal products should be checked and approved by a local research approval body as required by the research governance framework for the NHS. ARSAC applications should usually be made at the same time as protocols are submitted to the local research approval body. The ARSAC application should be accompanied by a one-page summary of the submission to the approval body. The summary should indicate the aims of the study and the need for the radionuclide procedures. In all instances, ultimate approval for the project as a whole will lie with the approval body, which should ensure that the applicant holds all the necessary authorisations.

5.24 The following points should be noted.

- (a) Approval by a multicentre research ethics committee does not remove the need for submission to a local research approval body. However, where research is to be conducted at more than one centre, this fact should be noted on each separate ARSAC application for authorisation. This will help to eliminate unnecessary duplication when research applications are assessed.
- (b) The fact that an ARSAC certificate has been granted (or that a clinical trial certificate or a Marketing Authorisation has been granted by the licensing authority on the recommendation of the MHRA) in no way absolves the practitioner from the need to seek approval from the appropriate local research approval body.

Further information may be obtained from the Central Office for Research Ethics Committees at www.corec.org.uk.

Section 6

Investigations in Children and Young Persons

Children and Young Persons – Principles

- 6.1** Prior to embarking on a radionuclide procedure in children, the three questions given below should be particularly considered.
- (a) Is this the most appropriate investigation to answer the clinical problem? Where appropriate and practical, an investigation that does not involve radiation should be employed.
 - (b) Is the procedure, and the resulting radiation dose, clinically justified?
 - (c) Are the facilities within the nuclear medicine department appropriate for children or should the child be referred to a specialist centre?
- 6.2** In diagnostic investigations in children²⁵, particular care must be exercised to ensure that the most appropriate investigation is chosen to answer the clinical problems. When considering the choice of investigation, factors which should be considered are risk/benefit ratios, economic cost, invasiveness and radiation dose. The radiation dose from radionuclide studies, when used in the appropriate clinical situation, is justifiable assuming the information gained cannot be obtained using diagnostic procedures with either a lower or no radiation exposure and/or a less invasive procedure. Where appropriate and practical, an investigation which does not involve ionising radiation should be chosen in a given clinical situation, assuming access to such procedures is available within a timeframe appropriate to the clinical management of the patient.

Scheduling the Procedure

- 6.3** Procedures involving children always take longer than the equivalent adult procedure. Children tend to be less predictable and more varied in their responses than adults. It is advisable to schedule at least 50% extra time for paediatric procedures.
- 6.4** All staff involved in paediatric procedures should be familiar with local arrangements. Delay in carrying out parts of the procedure can often lead to the child being less cooperative. This can lead to an increase in the time taken for the procedure or in some cases the procedure may not be successful.

Scanning Children

- 6.5** Where scintigraphy is deemed necessary for the clinical management of the child, it must be properly planned²⁶. The parent/guardian of the child should be fully informed about the procedure in advance of the imaging appointment. Leaflets providing full information on the particular examination should be given to the parent/guardian at the time of the appointment. On the day of the examination the entire procedure should be explained to the child and accompanying adult. This could be done when a local anaesthetic cream is applied, especially as the cream takes upwards of 45 minutes to have the desired effect.

Activity Administered

- 6.6** The activity administered should be the minimum consistent with obtaining a diagnostic result. As this is the same principle which is applied to adults, the normal activity administered to adults should be used as a baseline for the calculation of activity to be administered to children weighing less than 70 kg. Advice has been provided by the Paediatric Task Group European Association Nuclear Medicine Members²⁷. This is presented in Table 6.1. For children or young persons, body weight should always be measured. The adult administered activity should then be scaled down as shown in Table 6.1. This will produce image quality and imaging time comparable with that expected for adults as it will give a count density consistent with that of an adult patient. The effective dose, however, is higher.

Table 6.1 Scaling of adult administered activity for children or young persons by body weight

Weight (kg)	Fraction of adult administered activity	Weight (kg)	Fraction of adult administered activity	Weight (kg)	Fraction of adult administered activity
3	0.10	22	0.50	42	0.78
4	0.14	24	0.53	44	0.80
6	0.19	26	0.56	46	0.82
8	0.23	28	0.58	48	0.85
10	0.27	30	0.62	50	0.88
12	0.32	32	0.65	52–54	0.90
14	0.36	34	0.68	56–58	0.92
16	0.40	36	0.71	60–62	0.96
18	0.44	38	0.73	64–66	0.98
20	0.46	40	0.76	68	0.99

- 6.7** As a general guide, activities less than 10% of the value of the equivalent adult activity should not be administered. For most purposes this simple approach will be adequate. For a number of procedures however, if adequate image quality is to be achieved, the administered activity should be not less than that set out in Table 6.2.

Environment/Specific Needs/Injection Process

- 6.8** Nuclear medicine departments designed for adults often provide a poor environment for children. Successful nuclear medicine procedures for children require some simple modifications to the environment and normal procedures. Comprehensive practical information can be found on the European Association of Nuclear Medicine website under each specific examination (www.EANM.org) and in other publications.

Imaging Technique

- 6.9** There should be specific protocols in place for imaging children in nuclear medicine departments. These should include the choice of collimator, imaging parameters and views for the various examinations. For example, in bone scintigraphy, it is essential that the limbs should be imaged separately from the torso unless a whole body scan protocol is used. In this case, specific localised views of the knees and any abnormal focal areas are essential.

Table 6.2 Recommended minimum administered activity for children

Radiopharmaceutical	Investigation	Minimum activity (MBq)
⁶⁷ Ga-Ga ³⁺	Tumour imaging	10
⁶⁷ Ga-Ga ³⁺	Infection/inflammation imaging	10
^{99m} Tc DTPA	Renal imaging	20
^{99m} Tc DMSA	Renal imaging	15
^{99m} Tc MAG3	Renal imaging	15
^{99m} Tc-pertechnetate	Cystography	20
^{99m} Tc-phosphonates and phosphates	Bone imaging	40
^{99m} Tc-colloid	Liver/spleen imaging	15
^{99m} Tc-colloid	Bone marrow imaging	20
^{99m} Tc denatured erythrocytes	Spleen imaging	20
^{99m} Tc normal erythrocytes	Cardiac blood pool imaging	80
^{99m} Tc human albumin	Cardiac blood pool imaging	80
^{99m} Tc-pertechnetate	Cardiac first pass imaging	80
^{99m} Tc human albumin macroaggregates or microspheres	Lung perfusion imaging	10
^{99m} Tc-pertechnetate	Ectopic gastric mucosa (Meckel's)	20
^{99m} Tc-colloid	Gastric reflux imaging	10
^{99m} Tc exametazine	Cerebral blood flow imaging	100
^{99m} Tc exametazine labelled leucocytes	Infection/inflammation imaging	40
^{99m} Tc-iminodiacetates	Functional biliary system imaging	20
^{99m} Tc-pertechnetate	Thyroid imaging	10
¹²³ I o-iodohippurate	Renal imaging	10
¹²³ I-iodide	Thyroid imaging	3
¹²³ I MIBG	Neuroectodermal tumour imaging	70
¹³¹ I MIBG	Neuroectodermal tumour imaging	35

Note

Myocardial studies for children are not routinely undertaken at most centres and advice concerning these is not included in the table above. As a general guide, if sestamibi or tetrofosmin is used, a minimum activity of 50 MBq is suggested.

Sedation

- 6.10** A cooperative child will not normally require sedation or general anaesthetic²⁸. Sedation may be required for long examinations when movement should not occur. This applies especially to SPECT studies (rCBF / bone / MIBG) and pin-hole views of the hips in the young child.
- 6.11** Sedation or general anaesthetic may, in some cases, be considered necessary, but this should be based on an individual assessment. Children in pain require analgesia and, if this is adequate, sedation may not be required.
- 6.12** Sedation if given must be effective and safe. In 2003 the Royal College of Radiologists produced useful guidance on this subject²⁹. Before sedating the child, consideration should be given to the effect that sedation may have on function. This is especially important for rCBF studies.

Radiation Protection

- 6.13** When a radiopharmaceutical is administered that is excreted by the kidneys, simple protective measures such as encouraging a high fluid intake, active bladder emptying or frequent nappy changing will enhance the process of elimination of the radionuclide and reduce gonadal and bladder doses. There are some circumstances where the appropriate choice of radiopharmaceutical can result in a major reduction in radiation dose, eg where possible ^{99m}Tc exametazime should be used in preference to ^{111}In for labelled leucocyte scanning in acute infection.
- 6.14** Where appropriate, thyroid blocking agents should be administered. Further information is provided in Section 8.

Section 7

Conception, Pregnancy and Breast Feeding

Advice to Females

- 7.1** When it is necessary to administer radioactive substances to a female of childbearing potential, the radiation exposure should be the minimum consistent with achieving the desired clinical information, whether or not the female is known to be pregnant. Alternative techniques which do not involve ionising radiation should be especially considered. Such consideration is particularly important when use of radionuclides having long half-lives is contemplated.
- 7.2** If the possibility of pregnancy cannot be excluded, the patient should be asked whether her menstrual period is overdue. Low dose procedures can continue to be undertaken, provided that the period is not overdue. For higher dose procedures resulting in fetal doses of some tens of milligray and particularly those for therapeutic purposes or those which involve higher doses to the uterus, confirmation of pregnancy or otherwise is recommended.
- 7.3** Only such investigations which are imperative should be conducted during pregnancy. Investigations carried out on pregnant females result in radiation doses to both the mother and the fetus. Any female of childbearing potential undergoing procedures involving radioactive medicinal products should therefore be asked whether she is or might be pregnant. A policy should be established on the age range of females involved (eg 12 to 55 years) and followed unless there are known exceptional circumstances applying to an individual patient.
- 7.4** Where a patient is probably or definitely pregnant, the justification for the procedure should be considered by the ARSAC certificate holder following consultation with the clinician responsible for the patient. It should be noted that a procedure of clinical benefit to the expectant mother may be of indirect benefit to the unborn child.
- 7.5** If it is decided that the procedure should be undertaken, special attention should be given to the optimisation of the exposure, taking into account the exposure of the expectant mother and the unborn child. The principle adopted here is that the absorbed dose to a fetus should not exceed 1 mGy. Any reduction in administered activity must not impact on the likelihood of achieving a diagnostic outcome.
- 7.6** Estimates of dose to the uterus are included in column 8 of Appendix I, Parts A and B, to help assess any risk. No component of dose from cross-placental transfer of radiopharmaceuticals is included in these values. These dose estimates refer to early pregnancy, before organogenesis has proceeded far enough for there to be concentrations of radioactivity in particular fetal organs. The choice of a cut-off level of dose in deciding whether possible fetal irradiation needs to be considered in requesting or performing an investigation is an individual one, but a dose to the fetus greater than 1 mGy requires particular justification. A dose up to 1 mGy corresponds to a level of risk comparable to that due to variations in natural background radiation. The available evidence³⁰ suggests that the risk of an adverse effect (eg childhood cancer) from a dose of 1 mGy is about 1 in 20,000.
- 7.7** Specific instructions must be given to the mother of an infant in order to minimise irradiation to the latter.

Advice to Males

- 7.8** There is no evidence that pre-conceptual irradiation of males can cause any abnormality in their offspring^{31,32}. The ARSAC does not consider that males who have received routine diagnostic administrations of radiopharmaceuticals need be given any advice concerning avoidance of conception.
- 7.9** The administration of therapeutic doses of ionic forms of longer-lived radionuclides is, however, a possible source of concern because of the appearance of larger quantities of such radionuclides in ejaculate and in sperm. It may be prudent, therefore, to advise sexually active males who have received therapeutic level administrations of ¹³¹I-iodide, ³²P-phosphate or ⁸⁹Sr-chloride to avoid fathering children for a period of four months. The period of four months is suggested as it is greater than the life of a sperm cell^{33,34}.

Advice to Females of Childbearing Potential after Administration of Long-lived Radionuclides

- 7.10** In some circumstances it will be necessary to advise females not to become pregnant for a period following the administration of long-lived radiopharmaceuticals.
- 7.11** The female patient should be advised to avoid pregnancy for a period following therapy administration as given in Table 7.1.

Table 7.1

Nuclide and form	For treatment of	All activities up to (MBq)	Avoid pregnancy (months)
³² P-phosphate	Polycythaemia and related disorders	200	3
⁸⁹ Sr-chloride	Bone metastases	150	24
⁹⁰ Y-colloid	Arthritic joints	400	0
⁹⁰ Y-colloid	Malignancy	4000	1
¹³¹ I-iodide	Thyrotoxicosis/non-toxic goitre	800	6 (at least)
¹³¹ I-iodide	Carcinoma thyroid	6000	6 (at least)
¹³¹ I MIBG	Phaeochromocytoma	7500	3
¹⁵³ Sm-colloid	Bone metastases	2600	1
¹⁶⁹ Er-colloid	Arthritic joints	400	0

Note

The administration of activities smaller than those indicated in column 3 does not imply that the advisory period specified in column 4 may be reduced.

- 7.12** No such advice is necessary for any diagnostic procedure using radiopharmaceuticals with a physical half-life of less than seven days. Attention must, however, be paid to the potential fetal dose following maternal administration of radiopharmaceuticals with long effective half-lives, such as proteins labelled with ¹²⁵I or ¹³¹I.
- 7.13** The fetal thyroid gland is known to concentrate radioiodine avidly during the second and third trimesters of pregnancy; during this period the quantity of radioactivity within the mother should not exceed 0.1 MBq of ¹²⁵I or 0.03 MBq of ¹³¹I. Consideration of the listed diagnostic serials 53b3 (4 MBq ¹²⁵I fibrinogen) and 53b4iii (0.2 MBq ¹²⁵I human albumin) has shown that these will decrease to below

0.1 MBq in 22 days and 15 days, respectively: it is not, therefore, necessary to issue any warning to delay pregnancy following these procedures.

7.14 Of the diagnostic investigations listed in Appendix I, Part A, only the following two give cause for advice to delay pregnancy:

53c7 ^{131}I MIBG: tumour imaging – pregnancy should be avoided for two months;

53c6ii ^{131}I -iodide: thyroid metastases imaging – any quantity of ^{131}I greater than 30 MBq should be considered as a ‘therapy’ administration for radiation protection purposes; advice on pregnancy should be as for treatment of thyrotoxicosis (see Table 7.1).

Diagnostic Administrations to Those Who Are Breast Feeding

7.15 Where the mother is breast feeding, specific written instructions must be given and these instructions should be recorded in the patient’s medical records.

7.16 Before administering a radiopharmaceutical to a female who is breast feeding, wet-nursing or donating milk to a milk bank (where this practice is considered safe and effective), consideration should be given as to whether:

- (a) the test could reasonably be delayed until after she has ceased breast feeding;
- (b) the most appropriate choice of radiopharmaceutical has been made, bearing in mind the secretion of activity in breast milk.

It is particularly important that appropriate quality control measurements be made on the radiopharmaceutical because the presence of radionuclide impurities or of free ions, such as pertechnetate, iodide, or In^{3+} , will incur additional radiation dose to the infant.

7.17 Information on secretion of radioactivity into human breast milk is limited, and for most radiopharmaceuticals the advice given here is based on small numbers of measurements. Practitioners are encouraged to send the results of any further measurements on breast milk samples to the ARSAC Secretariat.

7.18 Precautions should be taken to minimise the radiation dose to the infant (and to ensure that the dose is below 1 mSv). Specific advice should be given as follows.

- (a) At least one feed may be ‘banked’ in advance of the test in accordance with local practice, by expressing milk and storing it in a refrigerator or freezer. Appropriate advice and facilities should be available.
- (b) The baby should be fed naturally just before the test.
- (c) Three to four hours after the test the mother should express her breast milk as completely as possible. This milk should not be used. The baby may be fed at this time with a previously ‘banked’ feed.
- (d) Breast feeding should not resume until after a total period of interruption as given in Table 7.2, or as calculated from measured samples. During the period of interruption, milk should be regularly expressed as fully as possible and discarded.
- (e) It should be explained that if this advice is followed, the radiation dose to the infant from breast feeding should be less than half of the annual natural background dose, and within the range of geographical variations in natural background, within the UK.

Table 7.2

Radiopharmaceutical	Activity administered to mother (MBq)	Feeding interruption time* (hours)
³² P-phosphate	Any	STOP
⁵¹ Cr EDTA	3	0
⁶⁷ Ga-Ga ³⁺	Any	STOP
^{81m} Kr gas	6000	0
^{99m} Tc-pertechnetate	80	24
^{99m} Tc-pertechnetate	800	48
^{99m} Tc macroaggregates	80	12
^{99m} Tc macroaggregates + ^{99m} Tc technegas	100 + 20	14
^{99m} Tc microspheres	100	18
^{99m} Tc normal erythrocytes [†]	800	18
^{99m} Tc DTPA	800	0
^{99m} Tc DMSA	80	0
^{99m} Tc-iminodiacetates	150	0
^{99m} Tc exametazime	500	0
^{99m} Tc MAG3	200	0
^{99m} Tc sestamibi	1000	0
^{99m} Tc-colloid	80	0
^{99m} Tc phosphate compounds	600	0
¹¹¹ In leucocytes	10 [‡]	0
¹²³ I-iodide	20	27
¹²³ I MIBG	400	21
¹²⁵ I human albumin	Any	STOP
¹³¹ I-iodide	Any	STOP
²⁰¹ Tl-Tl ⁺	80	0

* Feeding may be restarted immediately after the stated time has elapsed since administration of the radionuclide. The interruption time advised is based such that the dose to the infant should be less than 1 mSv. In many cases this time is ZERO, ie no interruption of feeding is strictly necessary.

The principle of 'as low as reasonably practicable' (ALARP), however, indicates that it is usually appropriate to discard one feed. For some radiopharmaceuticals the necessary 'interruption time' would be so long that the mother should be advised to STOP feeding altogether. Breast feeding can be undertaken following subsequent pregnancies. These figures do not apply during the period of early lactation when colostrum is being secreted. During that period feeding should be interrupted until measurements on milk samples prove that it is safe to recommence.

[†] For labelled normal erythrocytes the figures will be sensitive to changes in the labelling efficiency, which can vary substantially.

[‡] It is recommended that the activity of ¹¹¹In leucocytes administered to a nursing mother should not exceed 10 MBq (see paragraph 7.21).

[§] ¹²³I should not be administered to breast feeding females unless it is pure (containing no ¹²⁴I or ¹²⁵I).

7.19 The effect of other radiopharmaceuticals may be estimated by measuring the radioactive concentration in a sample (or in successive samples) of the breast milk and predicting the dose to the infant either by using the method which assumes exponential clearance³⁵ or by using the expressed milk model³⁶. It is important to note that the expressed milk model is not applicable to situations where activity is still being taken up by the breast after the first expression of milk.

7.20 When it is known that the radioactive concentration in breast milk is declining (either by reference to the literature or by means of successive measurements on samples) then one of the following formulae may be used to convert a measured radioactive concentration in a milk sample into an estimate of the activity which will be excreted subsequent to the expression of that sample. The figures have been derived from the worst cases^{35,36} assuming an average volume of feed of 140 ml and a mean time between feeds of four hours:

$$\text{for } ^{99m}\text{Tc radiopharmaceuticals} \quad E = 150 \times C$$

$$\text{for } ^{111}\text{In leucocytes} \quad E = 7000 \times C$$

where E MBq is the total activity estimated to be excreted subsequent to the sample and C MBq ml⁻¹ is the radioactive concentration in the sample.

7.21 The effective dose to the infant H_{inf} (mSv) resulting from ingesting E MBq may be estimated as:

$$H_{\text{inf}} = I_{\text{inf}} \times E$$

where I_{inf} (mSv MBq⁻¹) is the ingestion dose coefficient for an infant for the relevant radionuclide.

7.22 The annual dose to the infant from breast milk should be less than 1 mSv.

7.23 Age-specific ingestion dose coefficients are given in ICRP Publication 72³⁷. For ^{99m}Tc the values are 0.21 and 0.13 mSv MBq⁻¹ at the ages of three months (approximately 6 kg body weight) and one year (approximately 10 kg body weight), respectively. These correspond to maximum intakes of 5 and 7.7 MBq, respectively.

7.24 The possibility of the infant receiving external radiation dose from close contact with the mother has been investigated and advice is given in the Medical and Dental Guidance Notes¹⁷. Precautions are recommended when patients have been administered more than: 10 MBq of ¹¹¹In-labelled white blood cells; 30 MBq of ¹³¹I; 120 MBq of ¹¹¹In-octreotide; 150 MBq of ²⁰¹Tl-chloride; 200 MBq of ⁶⁷Ga-citrate; or 800 MBq of ^{99m}Tc myocardial perfusion agent. Precautions may also be necessary after administration of positron emitting radionuclides.

Section 8

Thyroid Blocking

Use of Blocking Agents

- 8.1** Blocking the uptake of radionuclides by the thyroid is used to reduce radiation dose³⁸. Of the radionuclides commonly used in nuclear medicine, only technetium and iodine are concentrated by the thyroid.

Technetium-99m

- 8.2** It is considered unnecessary to use blocking agents to reduce the radiation dose to the thyroid following administration of radiopharmaceuticals containing ^{99m}Tc.

Radioiodines

- 8.3** When ¹²³I, ¹²⁵I or ¹³¹I are administered as iodide, iodine-labelled compounds (such as iodinated albumin which metabolise to iodide in the body) or iodine-labelled compounds that contain iodide as a radiochemical impurity, a substantial part of the effective dose stems from thyroid irradiation. This is not the case with compounds such as o-iodohippurate where the labelled compound is stable and excreted unchanged.

- 8.4** Blocking will reduce the absorbed dose to the thyroid when radioiodine is administered as MIBG, albumin or as other labelled compounds. It should be performed if the absorbed dose to the unblocked thyroid will be greater than 50 mGy. Assuming full metabolism of the labelled compound and uptake of 25% of the released radioiodine by the thyroid, guidance values for the body burdens of radioiodine which will give this dose are:

¹²³I 15 MBq

¹²⁴I 0.2 MBq

¹²⁵I 0.2 MBq

¹³¹I 0.1 MBq

- 8.5** Before administering a radioiodinated compound which is metabolised to iodide or which contains radioiodine impurities, consideration should be given to blocking the thyroid if the administered activity will be greater than these values. Blocking should be continued until the estimated activity of radioiodine in the body has fallen to these levels.

Blocking Agent Equivalents

- 8.6** Various formulations of iodide and iodate are available for oral and intravenous administration. The iodine contents of the blocking agents are:

60 mg potassium iodide contains 45 mg iodine

85 mg potassium iodate contains 50 mg iodine

1 ml of Aqueous Iodine Oral Solution BP (Lugol's Iodine) contains 130 mg iodine

- 8.7** In individuals sensitive to iodine (or those with diseases such as dermatitis herpetiformis or hypocomplementaemic vasculitis), thyroid blockade can be carried out with potassium perchlorate (200 mg adult dose) given one hour prior to the procedure and repeated at eight hourly intervals till the estimated radioiodine levels have fallen to the levels shown above. Sodium perchlorate injection (2 ml vials containing 200 mg for intravenous use) is also available.

Blocking Protocols

- 8.8** An oral dose equivalent to approximately 100 mg iodine will reduce thyroid uptake to less than 1% of normal. This should be administered the day before the investigation and then daily until the estimated activity of radioiodine in the body has fallen to the level shown above, eg for ^{123}I MIBG and ^{131}I MIBG, blocking should be continued for one and five days, respectively.
- 8.9** Where individuals have forgotten to take their thyroid blockade medication then the dose should be given to them at least one hour prior to the procedure. Use of potassium iodide two hours after exposure to ^{131}I still offers a 'protective effect' of 80%.
- 8.10** When thyroid blocking agents are administered to children, consideration should be given to reducing the dosage. This should be broadly consistent with Department of Health advice given in relation to the use of thyroid blocking in the event of a nuclear accident³⁹, ie
- | | |
|--------------------------------|-------------------|
| children of 3 to 12 years | 50% of adult dose |
| children of 1 month to 3 years | 25% of adult dose |
- 8.11** In children, the dosage of potassium perchlorate required is 10 mg kg^{-1} . The maximum total dosage should be 500 mg and the minimum total dosage is 50 mg. Potassium perchlorate comes in 200 mg capsules and these should be opened and the contents either placed on a sugar lump (or similar) or dissolved in a flavoured drink. The second can be given on the same evening between 6 and 10 pm. If the thyroid gland is seen at the time of scanning the following day, then the child should be given another (third) dose of potassium perchlorate.

Appendix I

Routine Procedures, Activities and Doses

Introduction

- 1 The data provided have been prepared with the advice of the ARSAC for the convenience of the applicant in making an application for a certificate (see Section 2) and thereafter of the ARSAC in considering routine applications on which it has to advise the Health Ministers. The appendix is arranged in five parts, as follows:

- Part A Diagnostic investigations – adult patients
- Part B Diagnostic investigations – PET
- Part C Therapeutic procedures with unsealed sources
- Part D Therapeutic procedures with sealed sources
- Part E Functional groups

- 2 The nature and the diagnostic reference level of particular radiopharmaceuticals, which the ARSAC advises may be administered under specified conditions, have been listed in Parts A and B. This information refers only to certain established diagnostic procedures. Similar information relating to therapeutic procedures is given in Parts C and D. The appendix is intended to be neither exhaustive nor exclusive. The omission of a particular radiopharmaceutical from the following parts does not imply that it is in any way unsatisfactory. Products may be omitted if, for example, they are not in general use, they are very new or the technique requires especially high standards of skill and facilities.
- 3 Where several different chemical forms and/or investigations are shown in the appendix against the same radionuclide, applicants should ensure that they clearly identify those for which they are seeking authorisation. It will simplify the administration of the Regulations if applicants refer to appropriate procedures by serial number (see Parts A–D) or functional groups (Part E) wherever possible.
- 4 Where an application is made in respect of radiopharmaceuticals or sealed radioactive sources not listed in Appendix I, estimates of dosimetry should be provided for the administered activity proposed. In such cases subsequent correspondence may set out the recommendation of the ARSAC as to the maximum activity per procedure and any other relevant advice. When considering such applications, the ARSAC, unless informed to the contrary, will give its advice on the assumption that the subjects have not recently been exposed to other procedures involving radioactive medicinal products.

Toxicological and pharmaceutical safety

- 5 It should be noted that this appendix includes certain products which do not have Marketing Authorisations. The fact that the radiological hazard to the patient from a particular product is considered acceptable subject to the clinical judgement of the practitioner, and that its use is within the competence and facilities of the certificate holders, in no way absolves practitioners from responsibility for all aspects of the safety, quality and efficacy of such products. This also applies to the use of licensed products outwith the terms of their Marketing Authorisation and pharmaceutical safety.

Numbering system

6 The serial numbering system used in the appendix is as follows:

Parts A and B	Atomic number/letter [*] /Arabic number [†] /Roman number [‡]
Part C	OC/Arabic number
Part D	OT/Arabic number

Notes to Parts A and B

Chemical form – column 3

7 In the case of licensed medicinal products, attention should be paid to the manufacturer's data sheet. Minor variations between the data sheet and these Notes for Guidance will normally be within the clinical judgement of the practitioner; major differences should be referred to the ARSAC. Major differences of this type may also be advised to the Medicines and Healthcare Products Regulatory Agency.

Diagnostic reference levels – column 6

8 The Medical Exposure Directive 97/43/Euratom²¹ requires Member States to promote the establishment and use of diagnostic reference levels (DRLs) for diagnostic purposes. The Ionising Radiation (Medical Exposure) Regulations 2000⁵ define DRLs as: 'dose levels in medical radiodiagnostic practices or, in the case of radioactive medicinal products, levels of activity, for typical examinations for groups of standard sized patients or standard phantoms for broadly defined types of equipment'.

9 The ARSAC recommended DRLs satisfy this definition. These levels are expected not to be exceeded for standard procedures when good and normal practice regarding diagnostic and technical performance is applied. Administrations above these levels would only be considered as good practice in particular circumstances (see paragraph 10).

10 For diagnostic and research purposes, the activities recommended for procedures listed in Parts A and B apply to the use of radiopharmaceuticals in patients who are themselves expected to benefit from the procedures and refer to a single administration. The activities are to be regarded as guidelines and should be exceeded only in individual patients in whom particular clinical circumstances make it necessary, eg patients who are very much overweight or in severe bone pain. In many cases, it will be possible to administer activities less than those recommended. This is encouraged. Sensitive equipment should be used whenever possible in order to keep administered activities as low as reasonably practicable⁵ while achieving the desired clinical information.

11 Where applications are made for procedures by reference to functional groups or specific serial numbers, then the activities administered to patients should be those quoted in the guidance or lower.

12 Persistent administration of activities larger than those contained in Parts A and B without prior approval, could lead the ARSAC to advise the Health Ministers to suspend, vary or revoke the certificate as appropriate. The ARSAC is prepared to consider an application to increase the recommended levels in particular cases provided adequate scientific and clinical justification is given. Further advice concerning increased activities for individual patients is given in Section 3, paragraphs 3.2 to 3.8.

* The letter is used to differentiate between the various radioisotopes of the same element, eg 53a = ¹²³I, 53b = ¹²⁵I. In some cases, more than one letter may be used to denote the same radioisotope, eg ^{99m}Tc is denoted by 43a and 43w.

† To differentiate between chemical forms.

‡ To specify the investigation.

- 13** Applications can be made for use of activities greater than those quoted in this appendix, particularly for research purposes. Such requests would need to be supported by an adequate justification.
- 14** The activity administered must be recorded in the patient's medical or departmental records.

Effective dose – column 7

- 15** Most of the available knowledge on radiation hazards relates to whole body irradiation. When radiopharmaceuticals are administered, different organs receive widely different absorbed radiation doses. In order to lay down recommended annual limits of intake for occupationally exposed workers, an effective dose is defined which represents the total radiation dose to a number of organs weighted according to a risk estimate for each organ concerned. The effective dose is thus the whole body dose which would produce the same risk as a non-uniformly distributed absorbed dose. Although the concept of effective whole body dose is only intended for occupational risks, it provides a useful index when used in connection with radiopharmaceuticals.
- 16** The effective doses given in Parts A and B have been calculated using estimated organ absorbed doses and the above weighting factors. It is requested that estimates of dose included in Part B of the Application Form should be calculated in accordance with the methodology described in ICRP Publication 80¹⁹.
- 17** The figures in column 7 are based on clinically normal subjects and may vary considerably in pathological states. Caution should therefore be exercised in conditions where the abnormal retention of the radionuclide can result in a substantially higher absorbed radiation dose.
- 18** The figures given in column 7 are for the effective dose that could be expected to result from an administration of the diagnostic reference level shown in column 6. They are the best currently available estimates for the effective dose (mostly derived from the work of the ICRP¹⁹).
- 19** Those applying for authorisation for tests which are not included in the appendix should include references to professional literature in which estimates of the effective dose have been made or arrange for such estimates to be supplied with the application using the weighting factors and methods recommended in ICRP Publication 60⁴⁰.
- 20** Appendix II gives further information on calculating doses.

Estimated dose to the uterus – column 8

- 21** Estimates of dose to the uterus as a guide to dose to the fetus are provided to help clinicians decide whether investigation should proceed if pregnancy is known or suspected. Figures are derived from the literature, mostly from that stemming from the efforts of a committee of the ICRP¹⁹. It should be noted that these figures do not include a component of dose from the cross-placental transfer of radioactive medicinal products.

Part A: Diagnostic Procedures – Adult Patients

Radioactive medicinal product			Investigation	Route of administration	Diagnostic reference level (MBq)	Effective dose (mSv)	Dose to the uterus (mGy)	Functional Group
Serial	Radionuclide	Chemical form						
1	2	3	4	5	6	7	8	
6a50	¹⁴ C	Urea	H Pylori detection	Oral	0.2	0.02	0.02	24: NI Gastrointestinal
24a1i	⁵¹ Cr	Normal erythrocytes	Red cell volume	IV	0.8	0.3	0.07	22: NI Haematology
24a1ii	⁵¹ Cr	Normal erythrocytes	Red cell survival	IV	2	0.6	0.2	22: NI Haematology
24a1iii	⁵¹ Cr	Normal erythrocytes	Sites of sequestration	IV	4	1	0.4	22: NI Haematology
24a1iv	⁵¹ Cr	Normal erythrocytes	GI blood loss	IV	4	1	0.4	24: NI Gastrointestinal
24a4	⁵¹ Cr	EDTA	GFR measurement	IV	3	0.006	0.008	25: NI Genito-Urinary
27a1	⁵⁷ Co	Cyanocobalamin	GI absorption	Oral	0.04	0.1	0.05	22: NI Haematology
31a1i	⁶⁷ Ga	Ga ³⁺	Tumour imaging	IV	150	15	12	14: I Tumour
31a1ii	⁶⁷ Ga	Ga ³⁺	Infection/inflammation imaging	IV	150	15	12	9: I Infection/Inflammation
34a3	⁷⁵ Se	23-Seleno-25-homo-tauro-cholate (SeHCAT)	Bile salt absorption	Oral	0.4	0.3	0.3	20: NI Absorption
36a1	^{81m} Kr	Gas	Lung ventilation imaging	Inhalation	6000	0.2	<0.001	3: I Lung
43a1i	^{99m} Tc	Pertechnetate	Thyroid uptake	IV	40	0.5	0.3	23: NI Endocrine
43a1ii	^{99m} Tc	Pertechnetate	Thyroid imaging	IV	80	1	0.6	11: I Endocrine
43a1iii	^{99m} Tc	Pertechnetate	Salivary gland imaging	IV	80	1	0.6	6: I Gastrointestinal
43a1iv	^{99m} Tc	Pertechnetate	Ectopic gastric mucosa imaging (Meckel's)	IV	400	5	3	6: I Gastrointestinal
43a1xii	^{99m} Tc	Pertechnetate	Micturating cystogram	IB	25	0.3	0.2	8: I Genito-Urinary
43a1xvi	^{99m} Tc	Pertechnetate	First pass blood flow imaging	IV	800	10	6	1: I Cardiac
43a2vii	^{99m} Tc	Human albumin	Cardiac blood pool imaging	IV	800	5	4	1: I Cardiac
43a2viii	^{99m} Tc	Human albumin	Peripheral vascular imaging	IV	800	5	4	2: I Vascular

Part A: Diagnostic Procedures – Adult Patients (continued)

Radioactive medicinal product			Investigation	Route of administration	Diagnostic reference level (MBq)	Effective dose (mSv)	Dose to the uterus (mGy)	Functional Group
Serial	Radionuclide	Chemical form						
1	2	3	4	5	6	7	8	
43a3i	^{99m} Tc	Human albumin macroaggregates or microspheres	Lung perfusion imaging	IV	100 200 SPECT	1 2	0.3 0.6	3: I Lung
43a3ii	^{99m} Tc	Human albumin macroaggregates or microspheres	Lung perfusion imaging with venography	IV	160	2	0.4	3: I Lung
43a4ii	^{99m} Tc	Phosphonates and phosphates	Bone imaging	IV	600 800 SPECT	3 5	4 5	5: I Bone/Joint
43a5i	^{99m} Tc	DTPA	Renal imaging/renography	IV	300	2	2	8: I Genito-Urinary
43a5ii	^{99m} Tc	DTPA	Brain imaging (static)	IV	500 800 SPECT	3 5	4 6	4: I Brain
43a5iii	^{99m} Tc	DTPA	First pass blood flow studies	IV	800	5	6	4: I Brain
43a5xi	^{99m} Tc	DTPA	GFR measurements	IV	10	0.06	0.06	25: NI Genito-Urinary
43a5xix	^{99m} Tc	DTPA	Lung ventilation imaging	Aerosol inhalation	80	0.4	0.5	3: I Lung
43a6i	^{99m} Tc	DMSA(V)	Tumour imaging	IV	400	3	2	14: I Tumour
43a6iii	^{99m} Tc	DMSA(III)	Renal imaging	IV	80	0.7	0.4	8: I Genito-Urinary
43a7i	^{99m} Tc	Colloid	Liver imaging	IV	80 200 SPECT	0.8 2.0	0.2 0.5	7: I Hepatobiliary
43a7ii	^{99m} Tc	Colloid	Bone marrow imaging	IV	400	4	0.8	5: I Bone/Joint
43a7iv	^{99m} Tc	Colloid	GI bleeding	IV	400	4	0.8	6: I Gastrointestinal
43a7v	^{99m} Tc	Colloid	Oesophageal transit and reflux	Oral	40	0.9	0.5	6: I Gastrointestinal
43a7vi	^{99m} Tc	Colloid	Lacrimal drainage	Eye drops	4 (each eye)	0.04	<0.01	13: I Lacrimal
43a7xi	^{99m} Tc	Colloid	Sentinel node (breast) imaging*	Interstitial/ peri-tumoural	20	0.05	0.004	15: I Sentinel Node
43a7xii	^{99m} Tc	Colloid	Sentinel node (breast) probe studies*	Interstitial/ peri-tumoural	20	0.05	0.004	28: NI Sentinel Node

Part A: Diagnostic Procedures – Adult Patients (continued)

Radioactive medicinal product				Route of administration	Diagnostic reference level (MBq)	Effective dose (mSv)	Dose to the uterus (mGy)	Functional Group	
Serial	Radionuclide	Chemical form	Investigation						
1	2	3	4	5	6	7	8		
43a7xiii	^{99m} Tc	Colloid	Sentinel node (melanoma) imaging*	Interstitial/peri-tumoural	20	0.05	0.004	15: I	Sentinel Node
43a7xvii	^{99m} Tc	Colloid	Lymph node (lymphoedema) imaging [†]	Interstitial	20	0.05	0.004	2: I	Vascular
43a8	^{99m} Tc	Iminodiacetates	Functional biliary system imaging	IV	150	2	2	7: I	Hepatobiliary
43a9	^{99m} Tc	Denatured erythrocytes	Spleen imaging	IV	100	2	0.2	10: I	Haematology
43a10iii	^{99m} Tc	Normal erythrocytes	GI bleeding	IV	400	3	2	6: I	Gastrointestinal
43a10iv	^{99m} Tc	Normal erythrocytes	Cardiac blood pool imaging	IV	800	6	3	1: I	Cardiac
43a10v	^{99m} Tc	Normal erythrocytes	Peripheral vascular imaging	IV	800	6	3	2: I	Vascular
43a11i	^{99m} Tc	Non-absorbable compounds	Gastric emptying	Oral	12	0.3	0.2	6: I	Gastrointestinal
43a11ii	^{99m} Tc	Non-absorbable compounds	Oesophageal transit and reflux	Oral	40	0.9	0.5	6: I	Gastrointestinal
43a13i	^{99m} Tc	MAG3	Renal imaging/renography	IV	100	0.7	1	8: I	Genito-Urinary
43a13ii	^{99m} Tc	MAG3	First pass blood flow imaging	IV	200	1	2	8: I	Genito-Urinary
43a14	^{99m} Tc	Exametazime labelled leucocytes	Infection/inflammation imaging	IV	200	2	0.7	9: I	Infection/Inflammation
43a15i	^{99m} Tc	Sestamibi	Parathyroid imaging	IV	900	8	7	11: I	Endocrine
43a15iv	^{99m} Tc	Sestamibi	Non-specific tumour imaging	IV	900	8	7	14: I	Tumour
43a15v	^{99m} Tc	Sestamibi	Thyroid tumour imaging	IV	900	8	7	11: I	Endocrine
43a15vi	^{99m} Tc	Sestamibi	Breast imaging	IV	900	8	7	14: I	Tumour
43a15vii	^{99m} Tc	Sestamibi	Myocardial imaging	IV	300 [†] 800 [†] SPECT	3 8	2 6	1: I	Cardiac

Part A: Diagnostic Procedures – Adult Patients (continued)

Radioactive medicinal product			Investigation	Route of administration	Diagnostic reference level (MBq)	Effective dose (mSv)	Dose to the uterus (mGy)	Functional Group
Serial	Radionuclide	Chemical form						
1	2	3	4	5	6	7	8	
43a17	^{99m} Tc	Exametazime	Cerebral blood flow imaging (SPECT)	IV	500	5	4	4: I Brain
43a18	^{99m} Tc	Sulesomab	Infection/inflammation imaging	IV	750	6	4	9: I Infection/Inflammation
43a55	^{99m} Tc	Technegas	Lung ventilation imaging	Inhalation	40	0.6	0.07	3: I Lung
43a61	^{99m} Tc	Arcitumomab (CEA scan)	Tumour imaging	IV	750	7	4	14: I Tumour
43w46iv	^{99m} Tc	Tetrofosmin	Parathyroid imaging	IV	900	7	7	11: I Endocrine
43w46v	^{99m} Tc	Tetrofosmin	Myocardial imaging	IV	300 [†] 800 [†] SPECT	2 6	2 6	1: I Cardiac
43w49	^{99m} Tc	ECD	Brain imaging	IV	500	5	4	4: I Brain
43w77	^{99m} Tc	Depreotide	Lung tumour imaging	IV	600	6	5	14: I Tumour
49a1vii	¹¹¹ In	DTPA	GI transit	Oral	10	3	2	6: I Gastrointestinal
49a1ix	¹¹¹ In	DTPA	Cisternography	Intra-cisternal	30	2	0.9	4: I Brain
49a3	¹¹¹ In	Leucocytes	Infection/inflammation imaging	IV	20	9	3	9: I Infection/Inflammation
49a5ii	¹¹¹ In	Platelets	Thrombus imaging	IV	20	8	2	10: I Haematology
49a6	¹¹¹ In	Non-absorbable compounds	GI transit	Oral	12	4	2	6: I Gastrointestinal
49a61i	¹¹¹ In	Pentetreotide	Somatostatin receptor imaging	IV	110 220 SPECT	6 12	4 9	14: I Tumour
53a1i	¹²³ I	Iodide	Thyroid uptake	Oral or IV	2	0.4	0.03	23: NI Endocrine
53a1ii	¹²³ I	Iodide	Thyroid imaging	Oral or IV	20	4	0.3	11: I Endocrine
53a1iii	¹²³ I	Iodide	Thyroid metastases imaging (after ablation)	Oral or IV	400	5	6	14: I Tumour
53a5iii	¹²³ I	MIBG	Neuroectodermal tumour imaging	IV	400	5 [§]	4	14: I Tumour

Part A: Diagnostic Procedures – Adult Patients (continued)

Radioactive medicinal product			Investigation	Route of administration	Diagnostic reference level (MBq)	Effective dose (mSv)	Dose to the uterus (mGy)	Functional Group
Serial	Radionuclide	Chemical form						
1	2	3	4	5	6	7	8	
53a71i	¹²³ I	loflupane	Movement disorder imaging	IV	185	4.4	3	4: I Brain
53b4iii	¹²⁵ I	Human albumin	Plasma volume	IV	0.2	0.06 [§]	0.04	22: NI Haematology
53c6i	¹³¹ I	Iodide	Thyroid uptake	Oral	0.2	6	0.01	23: NI Endocrine
53c6ii	¹³¹ I	Iodide	Thyroid metastases imaging (after ablation)	Oral or IV	400 [¶]	24	22	14: I Tumour
53c7	¹³¹ I	MIBG	Neuroectodermal tumour imaging	IV	20	3 [§]	2	14: I Tumour
54a2	¹³³ Xe	Gas	Lung ventilation studies	Inhalation	400 [∇]	0.4	0.3	3: I Lung
81a1i	²⁰¹ Tl	Tl ⁺	Non-specific tumour imaging	IV	150	26	8	14: I Tumour
81a1ii	²⁰¹ Tl	Tl ⁺	Thyroid tumour imaging	IV	150	26	8	14: I Tumour
81a1iv	²⁰¹ Tl	Tl ⁺	Myocardial imaging	IV	80	14	4	1: I Cardiac
81a1vi	²⁰¹ Tl	Tl ⁺	Parathyroid imaging	IV	80	14	4	11: I Endocrine
81a1vii	²⁰¹ Tl	Tl ⁺	Myocardial (re-injection technique) imaging	IV	120	21	6	1: I Cardiac

* The activity may be raised to 40 MBq if probe studies, with or without imaging, are to be undertaken on the day following administration.

† Activity per limb.

‡ For combined rest–exercise protocols carried out on a single day the total activity administered should not exceed 800 MBq for planar imaging. For rest–exercise protocols with SPECT, activity administered should not exceed 1600 MBq. Two-day protocols are recommended on the basis of superior image quality, but it is recognised that these may not be practicable.

§ With the thyroid blocked.

¶ Activities of ¹³¹I greater than 30 MBq should be considered as therapy administration for radiation protection purposes.

∇ Assumed to be diluted in 10 litres and rebreathed for 5 minutes. The effective dose is determined by the radioactive concentration (MBq per litre).

Part B: Diagnostic Procedures – Positron Emission Tomography

Radioactive medicinal product							
Serial	Radio-nuclide	Chemical form	Investigation	Route of administration	Diagnostic reference level (MBq)	Effective dose (mSv)	Dose to the uterus (mGy)
1	2	3	4	5	6	7	8
9a21i	¹⁸ F	FDG	Tumour imaging	IV	400	8	8
9a21iii	¹⁸ F	FDG	Brain imaging	IV	250	5	5
9a21iv	¹⁸ F	FDG	Infection/inflammation	IV	400	8	8
9a21v	¹⁸ F	FDG	Differential diagnosis of dementia	IV	250	5	5
9a21vi	¹⁸ F	FDG	Focal epilepsy	IV	250	5	5
9a21vii (was 9a22ii)	¹⁸ F	FDG	Myocardial imaging	IV	400	8	8
9a23i	¹⁸ F	Fluoride	Bone imaging	IV	250	6	5

Part C: Therapeutic Procedures with Unsealed Sources

Radioactive medicinal product				
Serial	Radionuclide	Chemical form	For treatment of	Route of administration
1	2	3	4	5
OC2	¹³¹ I	Iodide	Thyrotoxicosis	IV or oral
OC3	¹³¹ I	Iodide	Non-toxic goitre	IV or oral
OC4	¹³¹ I	Iodide	Carcinoma of thyroid	IV or oral
OC5	³² P	Phosphate	Polycythemia vera and related disorders	IV or oral
OC6	⁹⁰ Y	Colloidal silicate in aqueous solution Colloidal citrate in aqueous solution	Arthritic conditions	Intra-articular
OC7	⁹⁰ Y	Colloidal silicate in aqueous solution	Malignant disease	Intracavitary
OC8	¹⁶⁹ Er	Colloid	Arthritic conditions	Intra-articular
OC9	⁸⁹ Sr	Chloride	Bone metastases	IV
OC10	¹³¹ I	MIBG	Malignant disease	IV
OC38	¹⁵³ Sm	EDTMP	Bone metastases	IV
OC39	¹⁸⁶ Re	HEDP	Bone metastases	IV
OC53	⁹⁰ Y	Ibritumomab tiuxetan (Zevalin)	Non-Hodgkins lymphoma	IV

Note

The activity per administration is a matter for clinical judgement; caution is advised in treatments for non-malignant disease especially in young patients.

Part D: Therapeutic Procedures with Sealed Sources

Solid radioactive source			
Serial	Radionuclide	Physical form	For treatment of
1	2	3	
OT21	⁹⁰ Y	Rods	Malignant disease
OT23	¹³⁷ Cs	Appliances	Malignant disease
OT24	⁹⁰ Sr	Appliances	Eye diseases
OT25	¹⁹² Ir	Wire/appliances	Malignant disease
OT26	¹⁹⁸ Au	Grains	Malignant disease
OT26	¹⁹⁸ Au	Grains	Malignant disease
OT29	¹²⁵ I	Seeds	Malignant disease
OT30	¹⁰⁶ Ru	Eye plaques	Eye diseases
OT37	¹⁰³ Pd	Seeds	Malignant disease

Note

The target volume dose and dose rate are a matter for clinical judgement.

Part E: Functional Groups

- 1** The radioactive medicinal products in this appendix have been organised into ‘functional groups’, relevant to patient pathology and physiology. These groups apply only to the diagnostic procedures included in Appendix I, Part A, of these Notes. In the previous Notes for Guidance issued in December 1998 this facility was available also for therapy procedures. Following review of its value, this facility has now been withdrawn.
- 2** These groups are designed to enable applicants to apply for those procedures regularly used as part of their practice by simply requesting a functional group or groups by name. By doing so, the applicant will receive automatic updates to his/her certificate when new procedures are adopted within the functional group(s) requested. This facility will remove the necessity for certificate holders to apply for additional procedures when they become routine or are granted Marketing Authorisations.
- 3** Current certificate holders are encouraged to apply to the ARSAC Support Unit requesting this facility, using the Functional Group Application Form. Applications can be made independently of any request for changes to a diagnostic or therapy certificate and will only result in changes to current certificates if the previously issued schedule does not include all the procedures listed in the requested group.
- 4** In some cases, certificate holders may be asked for further information regarding their training and experience before this facility is granted.
- 5** It is assumed that certificate holders that have been granted the functional group facility will, as required by clinical governance, ensure that they have sufficient skill to undertake any new procedure added to the schedule to their certificates as part of the process. In some cases it will be necessary for other staff working under the written directions of the certificate holder to acquire additional competence also. A number of procedures falling into this category have been highlighted in Appendix I, Part A.
- 6** Other investigations outside the functional group can still be requested by reference to individual serial numbers. Similarly, procedures not included within the appendix can be requested using the Additions Form. ARSAC certificates will continue to list all serials individually.

ARSAC Functional Classification

Imaging groups

Group 1 I – Cardiac

43a1xvi	^{99m} Tc	Pertechnetate	First pass blood flow imaging
43a2vii	^{99m} Tc	Human albumin	Cardiac blood pool imaging
43a10iv	^{99m} Tc	Normal erythrocytes	Cardiac blood pool imaging
43a15vii	^{99m} Tc	Sestamibi	Myocardial imaging
43w46v	^{99m} Tc	Tetrofosmin	Myocardial imaging
81a1iv	²⁰¹ Tl	Tl ⁺	Myocardial imaging
81a1vii	²⁰¹ Tl	Tl ⁺	Myocardial (re-injection technique) imaging

Group 2 I – Vascular

43a2viii	^{99m} Tc	Human albumin	Peripheral vascular imaging
43a7xvii	^{99m} Tc	Colloid	Lymph node (lymphoedema) imaging
43a10v	^{99m} Tc	Normal erythrocytes	Peripheral vascular imaging

Group 3 I – Lung

36a1	^{81m} Kr	Gas	Lung ventilation imaging
43a3i	^{99m} Tc	Human albumin macroaggregates or microspheres	Lung perfusion imaging
43a3ii	^{99m} Tc	Human albumin macroaggregates or microspheres	Lung perfusion imaging
43a5xix	^{99m} Tc	DTPA	Lung ventilation imaging
43a55	^{99m} Tc	Technegas	Lung ventilation imaging
54a2	¹³³ Xe	Gas	Lung ventilation studies

Group 4 I – Brain

43a5ii	^{99m} Tc	DTPA	Brain imaging (static)
43a5iii	^{99m} Tc	DTPA	First pass blood flow studies
43a17	^{99m} Tc	Exametazime	Cerebral blood flow imaging (SPECT)
43w49	^{99m} Tc	ECD	Brain imaging
49a1ix	¹¹¹ In	DTPA	Cisternography
53a71i	¹²³ I	Ioflupane	Movement disorder imaging

Group 5 I – Bone/Joint

43a4ii	^{99m} Tc	Phosphonates and phosphates	Bone imaging
43a7ii	^{99m} Tc	Colloid	Bone marrow imaging

Group 6 I – Gastrointestinal

43a1iii	^{99m} Tc	Pertechnetate	Stomach and salivary gland imaging
43a1iv	^{99m} Tc	Pertechnetate	Ectopic gastric mucosa imaging (Meckel's)
43a7iv	^{99m} Tc	Colloid	GI bleeding
43a7v	^{99m} Tc	Colloid	Oesophageal transit and reflux
43a10iii	^{99m} Tc	Normal erythrocytes	GI bleeding
43a11i	^{99m} Tc	Non-absorbable compounds	Gastric emptying
43a11ii	^{99m} Tc	Non-absorbable compounds	Oesophageal transit and reflux
49a1vii	¹¹¹ In	DTPA	GI transit
49a6	¹¹¹ In	Non-absorbable compounds	GI transit

Imaging groups (continued)

Group 7 I – Hepatobiliary

43a7i	^{99m} Tc	Colloid	Liver imaging
43a8	^{99m} Tc	Iminodiacetates	Functional biliary system

Group 8 I – Genito-Urinary

43a1xii	^{99m} Tc	Pertechnetate	Micturating cystogram
43a5i	^{99m} Tc	DTPA	Renal imaging/renography
43a6iii	^{99m} Tc	DMSA(III)	Renal imaging
43a13i	^{99m} Tc	MAG3	Renal imaging/renography
43a13ii	^{99m} Tc	MAG3	First pass blood flow imaging

Group 9 I – Infection/Inflammation

31a1ii	⁶⁷ Ga	Ga ³⁺	Infection/inflammation imaging
43a14	^{99m} Tc	Exametazime labelled leucocytes	Infection/inflammation imaging
43a18	^{99m} Tc	Sulesomab	Infection/inflammation imaging
49a3	¹¹¹ In	Leucocytes	Infection/inflammation imaging

Group 10 I – Haematology

43a9	^{99m} Tc	Denatured erythrocytes	Spleen imaging
49a5ii	¹¹¹ In	Platelets	Thrombus imaging

Group 11 I – Endocrine

43a1ii	^{99m} Tc	Pertechnetate	Thyroid imaging
43a15i	^{99m} Tc	Sestamibi	Parathyroid imaging
43w46iv	^{99m} Tc	Tetrofosmin	Parathyroid imaging
53a1ii	¹²³ I	Iodide	Thyroid imaging
81a1vi	²⁰¹ Tl	Tl ⁺	Parathyroid imaging

Group 13 I – Lacrimal

43a7vi	^{99m} Tc	Colloid	Lacrimal drainage
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Group 14 I – Tumour

31a1i	⁶⁷ Ga	Ga ³⁺	Tumour imaging
43a 6i	^{99m} Tc	DMSA(V)	Tumour imaging
43a15iv	^{99m} Tc	Sestamibi	Non-specific tumour imaging
43a15v	^{99m} Tc	Sestamibi	Thyroid tumour imaging
43a15vi	^{99m} Tc	Sestamibi	Breast imaging
43a61	^{99m} Tc	Arcitumomab (CEA scan)	Tumour imaging
43w77	^{99m} Tc	Depreotide	Lung tumour imaging
49a61i	¹¹¹ In	Pentetreotide	Somatostatin receptor imaging
53a1iii	¹²³ I	Iodide	Thyroid metastases imaging (after ablation)
53a5iii	¹²³ I	MIBG	Neuroectodermal tumour imaging
53c6ii	¹³¹ I	Iodide	Thyroid metastases imaging (after ablation)
53c7	¹³¹ I	MIBG	Neuroectodermal tumour imaging
81a1i	²⁰¹ Tl	Tl ⁺	Non-specific tumour imaging
81a1ii	²⁰¹ Tl	Tl ⁺	Thyroid tumour imaging

Group 15 I – Sentinel Node

43a7xi	^{99m} Tc	Colloid	Sentinel node (breast) imaging
43a7xiii	^{99m} Tc	Colloid	Sentinel node (melanoma) imaging

ARSAC Functional Classification (continued)

Non-imaging groups

Group 20 NI – Absorption

34a3	⁷⁵ Se	23-Seleno-25-homo-tauro-cholate (SeHCAT)	Bile salt absorption
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Group 22 NI – Haematology

24a1i	⁵¹ Cr	Normal erythrocytes	Red cell volume
24a1ii	⁵¹ Cr	Normal erythrocytes	Red cell survival
24a1iii	⁵¹ Cr	Normal erythrocytes	Sites of sequestration
27a1	⁵⁷ Co	Cyanocobalamin	GI absorption
53b4iii	¹²⁵ I	Human albumin	Plasma volume

Group 23 NI – Endocrine

43a1i	^{99m} Tc	Pertechnetate	Thyroid uptake
53a1i	¹²³ I	Iodide	Thyroid uptake
53c6i	¹³¹ I	Iodide	Thyroid uptake

Group 24 NI – Gastrointestinal

6a50	¹⁴ C	Urea	H Pylori detection
24a1iv	⁵¹ Cr	Normal erythrocytes	GI blood loss

Group 25 NI – Genito-Urinary

24a4	⁵¹ Cr	EDTA	GFR measurement
43a5xi	^{99m} Tc	DTPA	GFR measurement

Group 28 NI – Sentinel Node

43a7xii	^{99m} Tc	Colloid	Sentinel node (breast) probe studies
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Appendix II

Calculating the Radiation Dose

- 1 The radiation dose received from internal radionuclides may be estimated using a method developed by the Medical Internal Radiation Dose (MIRD) Committee of the Society of Nuclear Medicine⁴¹. In this scheme organs which accumulate radioactivity are considered as source organs and organs which are irradiated are target organs. The dose to a target organ from activity in a particular source organ is calculated as the product of two quantities:

$$D = \tilde{A} \times S \quad (1)$$

- 2 Here \tilde{A} is the cumulated activity (or area under the activity–time curve) in the source organ, with units of, for example, Bq s or MBq h. Since one becquerel is one disintegration per second, the unit of Bq s is simply one disintegration and, with this unit, \tilde{A} may be interpreted as the total number of disintegrations taking place in the source organ. The term S is the S-factor which is the absorbed dose in the target organ per unit cumulated activity in the source organ, with units of, for example, $\mu\text{Gy} (\text{Bq s})^{-1}$ or $\mu\text{Gy} (\text{MBq h})^{-1}$. The term \tilde{A} must be estimated from biokinetic data concerning the particular radio-pharmaceutical and the expected physiological response to its administration, whereas the S-factors represent physical relationships which have been tabulated for each radionuclide and standardised pairs of source and target organs.

S-factors

- 3 For each radionuclide it is necessary to consider the contribution to each S-factor from each type of emission: beta, gamma, X-ray, etc. Beta particles are assumed to be completely absorbed in the source organ and therefore only contribute to the radiation dose when source and target are identical. For gamma rays and X-rays the contribution to the S-factor depends on the energy of the radiation, the size and shape of the source and target organs, the distance between them and the nature of the intervening tissues. The MIRD Committee has calculated values of the S-factor for many radionuclides and for various source and target organs using a mathematical model of a standard adult phantom and a Monte-Carlo computer simulation⁴². Values of S-factors for adults and children are included in software (the MIRDOSE program), which can be obtained from the Oak Ridge Institute for Science Education⁴³.

Cumulated Activity

- 4 If a graph of activity in a given source organ is plotted as a function of time, then the area under this curve is the cumulated activity, \tilde{A} , typically in units of MBq h.
- 5 Sometimes the activity–time curve in a source organ comprises a rapid initial rise to a peak uptake value, followed by a slow decay as an inverse exponential. In such a case the cumulated activity may be estimated as the area under the exponential.

$$\tilde{A} = A_0 \times F_s \times 1.44 \times t_{1/2}(\text{eff}) \quad (2)$$

where A_0 is the activity administered, F_s is the fraction of this activity which localises in the source organ, and $t_{1/2}(\text{eff})$ is the effective half-life taking account of both biological elimination and physical decay.

$$1/t_{1/2}(\text{eff}) = 1/t_{1/2}(\text{biol}) + 1/t_{1/2}(\text{phys}) \quad (3)$$

- 6 In general, the activity–time curve will not be a sharp rise followed by a simple inverse exponential decay, but it may be approximated by a sum of a few exponentials so that the cumulated activity is given by a sum of several terms similar to equation 2, each with a different biological half-life. The actual values must be determined from theoretical models, animal data or human measurements. However, variations in physiological function, particularly in diseased patients, may lead to large variations in these parameters so that estimates of cumulated activity are always subject to uncertainty.

Absorbed Dose

- 7 The dose, D_{st} , absorbed in a particular target organ arising from activity in a given source is calculated as

$$D_{st} = \tilde{A}_s \times S_{st} \quad (4)$$

where \tilde{A}_s is the cumulated activity in the source organ and S_{st} is the S-factor for the radionuclide for this source–target pair. The total absorbed dose to the target organ, D_t , is obtained by adding up the doses due to all possible source organs.

$$D_t = \sum \tilde{A}_s \times S_{st} \quad (5)$$

Equivalent Dose

- 8 The emissions from almost all radionuclides used in medicine (beta particles and gamma rays) have a radiation weighting factor of one, so the equivalent dose to the target organ (measured in Sv) is usually numerically equal to the absorbed dose (measured in Gy).

Effective Dose

- 9 The effective dose, D_{eff} , to the patient is calculated as a weighted sum of the doses to all target organs.

$$D_{eff} = \sum w_t \times D_t \quad (6)$$

where the tissue weighting factor w_t allows for the different risk factors associated with each target organ. The ICRP has recommended the use of the tissue weighting factors tabulated below⁴⁰.

Tissue weighting factors

Organ/tissue	Weighting factor (w_T)
Gonads	0.20
Red bone marrow	0.12
Colon	0.12
Lungs	0.12
Stomach	0.12
Bladder	0.05
Breast	0.05
Liver	0.05
Oesophagus	0.05
Thyroid	0.05
Skin	0.01
Bone surfaces	0.01
Remainder	0.05
TOTAL	1.00

- 10 For all commonly used radiopharmaceuticals the above calculations have been completed using available biological data and results have been compiled by the ICRP¹⁹. In new situations it is possible to draw upon analogies to the published data, or to carry out a new calculation using the MIRDOSE scheme as a basis.
- 11 The MIRDOSE software⁴³ can be very helpful in carrying out these calculations. It requires the user to provide input data in the form of residence times for the radionuclide in each source organ. The residence time is the cumulated activity divided by the activity administered to the patient.
- 12 The uncertainties in estimation of biokinetic and physical data indicate an inaccuracy of at least 10% (probably much worse).

Dose to Children

- 13 Doses to children can be calculated using S-factors determined for an appropriately sized anatomical phantom. ICRP Publication 80¹⁹ gives results for one year, five year, ten year and fifteen year old phantoms as well as adults. Alternatively, since dose is approximately proportional to administered activity divided by organ mass, as a simple rule of thumb it may be assumed that the radiation dose to a child will be roughly the same as that to an adult if the administered activity is scaled down in proportion to body weight. However, this is only valid if the biological handling is the same as for an adult and if organ weight is proportional to body weight.

Appendix III

Sample Size and Power Calculations

- 1 Hypothesis testing is the process of deciding statistically whether the findings of an investigation reflect chance or real effects at a given level of probability⁴⁴. As a result of the probabilistic nature of the process, decision errors in hypothesis testing cannot be completely eliminated. Two types of error may commonly occur, as listed below.
 - (a) Type I errors occur when it is concluded that a real effect exists (the result is significant at a given probability level) when, in fact, it does not exist.
 - (b) Type II errors occur when it is concluded that there is no effect (the result is not significant) when, in fact, a real effect exists.
- 2 The probability (α) of a Type I error is obtained directly from the statistical results – for example, a result quoted with a probability value of $p = 0.05$ means that there is less than a 5% chance of making a Type I error. However, the probability (β) of a Type II error depends on a variety of factors, the most important of which is sample size.
- 3 In the design of a research study consideration should be given to the Type II error. This is done by calculating the statistical power ($1 - \beta$) of the study. Statistical power is an important concept in the interpretation of negative results. Only if the research design has sufficient power can the investigator be confident that any real effects, if they exist, will be detectable. Thus, if the statistical power is 0.95, for a given effect size, its existence will be correctly detected 95 times out of 100. A power of 0.8 or above is desirable.
- 4 A relevant factor in determining the sample size needed to yield a given level of statistical power is the least non-negligible difference, ie the smallest difference between treatment/patient groups, etc, which would be scientifically or practically meaningful. For example, in a clinical trial to assess the cardiotoxic effects of a drug, the main outcome of which is the change in ejection fraction as measured by MUGA scan, a difference of 5% might be the least non-negligible difference. This is a subjective decision on the part of the investigator. The value represents the smallest difference between groups which the study is designed to detect with the specified power. If the standard deviation of the difference in paired ejection fraction measurements is estimated to be 10% then a sample size of 26 would be required to detect a difference in ejection fraction of 5% with a power of 0.8. A larger sample would be required to detect the same difference with a higher statistical power. Formulae exist for the calculation of sample sizes for comparing two or more groups which are necessary to ensure a power ($1 - \beta$) of detecting the least non-negligible difference (δ), and the reader is referred to a number of texts on statistical methods^{45–48} for a more thorough analysis.
- 5 There may be instances where, for example, owing to the rarity of a particular disease, patient recruitment is likely to be limited and the sample size will therefore be small. In such cases, the investigator should determine the power of the study to detect the least non-negligible difference when the maximum available sample size is employed. If an appropriate power cannot be obtained with the number of patients expected, consideration should be given to abandoning the trial or conducting a multicentre study.

- 6** Some studies are designed to estimate effects rather than test hypotheses about the size of effects. In these cases the estimates are also subject to the play of chance. The study estimate may be too big or too small. Key estimates should therefore be reported with 95% confidence intervals, the size of which also depends most importantly on the sample size. When studies are designed to estimate effects, therefore, the sample sizes should be chosen to yield confidence intervals which are small enough to make the estimates useful. The texts referenced above give appropriate formulae.
- 7** Applicants are recommended to seek appropriate statistical advice on the planning of research studies.

Appendix IV

Training and Experience

Introduction

- 1 A number of training programmes, recognised by the Royal Colleges, are now in place for doctors wishing to specialise in the clinical use of radioactive substances.
- 2 Doctors who, for the first time, wish to apply for a diagnostic certificate to enable them to provide a comprehensive nuclear medicine imaging service should have satisfactorily completed the Royal College of Physicians Nuclear Medicine Training Programme or the Royal College of Radiologists Radionuclide Radiology Sub-specialty Programme.
- 3 Those doctors who wish to apply for a certificate to provide therapy services should have completed the RCP Programme or the RCR Clinical Oncology Specialist Training Programme or equivalent.
- 4 To assist others who have not undertaken any of these structured training programmes, and who wish to apply for a certificate to administer radioactive substances, a core curriculum has been developed against which applications for certification will be assessed. In principle, all applicants should be able to demonstrate equivalent training, experience and competence pertaining to the procedures they wish to undertake, regardless of the way this training and experience was acquired. It should be noted that the theoretical training within this core curriculum does not address the comprehensive medical knowledge necessary for the management of patients.

Scope of the Service

- 5 The scope of the service will dictate the extent of the training and experience required before a certificate can be issued. In general, the scope will fall into one of four general categories, for which appropriate training can be identified, as follows.

Full nuclear medicine service

The curriculum outlined below would be that required for those wishing to provide a full nuclear medicine service. Holders of a CCST in Nuclear Medicine would normally expect to receive a certificate including the majority of serials included in Appendix I, Parts A and C.

Diagnostic imaging service

Sections A.1.7, A.1.8, A.2.8, A.3.4 and A.5.2 can be omitted from the full curriculum. Those who have successfully completed training in radionuclide radiology would normally expect to get certification for all those serials listed within the functional imaging groups for which training is included in the RCR Radionuclide Radiology Training Programme.

Diagnostic non-imaging service

Sections A.1.7, A.1.8, A.2.3, A.2.4, A.2.5, A.2.7, A.2.8, A.3.2, A.3.4, A.4.3 and A.5.2 can be omitted from the full curriculum.

Therapy service

Sections A.2.3, A.2.4, A.2.5, A.2.7, A.3.2 and A.4.3 can be omitted from the full curriculum.

Part A: Core Curriculum for Those Using Radioactive Substances

Requirements for theoretical training

- 1 The theoretical training particularly emphasises aspects related to radiation safety, an understanding of the principles of radiation detection as these affect the quality of the data, and interpretation of data. It is intended to provide sufficient detail so that the certificate holder has an appreciation of all aspects which are involved in nuclear medicine, but cannot provide the same depth of understanding that other professionals within the specialty will bring to the subject, eg radiopharmacists and physicists.
- 2 The time taken to cover the areas indicated below will vary depending on the scope of the service to be offered.

A.1 Fundamental physics of radionuclides

A.1.1 Atomic structure

Mass, atomic and neutron number
Energy levels – nuclear and electronic

A.1.2 Radioactivity

Radionuclides
Units of radioactivity
Specific activity
Physical half-life
Decay constant
Count statistics

A.1.3 Radioactive decay

Mechanism of alpha, beta and gamma emission
Electron capture and X-ray emission
Isomeric transition, internal conversion
Auger electrons

A.1.4 Properties of radiation

Excitation and ionisation
Attenuation of X-rays and gamma rays
Scattering and absorption

A.1.5 Radionuclide production

Production methods
Isotope generators
Cyclotron and nuclear reactors

A.1.6 Radiation hazards and dosimetry

Biological effects of radiation
Risks/benefits of radiation
Cellular radiobiology
Biological and effective half-lives
Absorbed dose, dose equivalent, effective dose and their units
MIRD

A.1.7 Radiobiology aspects for therapy

Uptake ratios
Cell cycles
Cell kill
Total lethal dose

Radiosensitisation
Tissue homogeneity

A.1.8 Dosimetry for therapy

Dose rate
Fractionation
Microdosimetry – residence and clearance
Mass estimations

A.2 Principles of radiation detection, instrumentation and equipment

A.2.1 Detection of radiation

Scintillators, photographic emulsion, solid state detectors
Collimators
Multichannel analysers and pulse height analysers

A.2.2 Detection systems – general

Isotope assay calibrator
Contamination monitors
Personal dosimeters and dose rate meters
Sample counters, including counting geometry
External probes

A.2.3 Detection systems – gamma camera

Gamma camera detector and associated equipment
Construction, function of main components
Care of scintillation crystal
Principles of collimation
Output signals – X and Y position, strobe
Interfacing to other equipment
Energy and linearity correction
Resolution, information density and noise
Anatomical markers
Principles of tomography
Whole body imaging
Photographic recording media
Processing and hard copy
Characteristic curves, optical density, contrast, fog saturation
Fault identification
Multi-image formatter

A.2.4 Associated electronic equipment

Photomultiplier tubes
Power supplies (high and low voltage)
Amplifiers
Multichannel analysers and pulse height analysers
Scalers, ratemeters – time constant and its effect
Cathode ray tubes – oscilloscopes, persistence monitors
Visual display units

A.2.5 Image formation and quality

Image quality 'v' radiation dose
Administered activity
Investigation time
Counting statistics, 'information density'
Choice of collimator (sensitivity/resolution)
Acquisition protocol for dynamic study (spatial/temporal resolution)

- A.2.6 Analysis of data**
 - Manipulation of data
 - Algorithms
 - Physiological basis of models
- A.2.7 Computing**
 - Hardware
 - Software
 - Region of interest
 - Image processing
 - Tomography
- A.2.8 Therapy equipment**
 - Design safety
- A.3 Calibration techniques**
 - A.3.1 Preparation of calibration sources and phantoms**
 - A.3.2 Quality assurance**
 - Pulse height and window selection
 - Uniformity of field
 - Linearity
 - Resolution – intrinsic and at depth, point and line spread functions
 - Count loss
 - Sensitivity
 - Collimator performance
 - Display performance
 - Image processing
 - A.3.3 Routine quality control checks**
 - A.3.4 Calibration of therapy sources**
- A.4 Radiopharmaceuticals**
 - A.4.1 Chemistry of relevant radiopharmaceuticals**
 - Principles of their localisation
 - A.4.2 Tracer principles and techniques**
 - Kinetics of radioactive tracers used in nuclear medicine
 - Use of principles of kinetics and modelling techniques applied to radionuclide investigations
 - Physiological principles of tracer techniques
 - Errors associated with the quantitative measurement
 - A.4.3 Preparation of radiopharmaceuticals**
 - Radiopharmacy, and working practices in respect of radiation safety and microbiological safety
 - Principles of labelling blood products
 - Individual dose preparation
 - Identification of prepared products
 - Quality control – radiochemical sterility, pyrogens
 - Documentation – packaging and transport of radiopharmaceuticals
 - Monitoring of work areas and waste disposal
 - Use of kits, dilution and transfer of activity
 - A.4.4 Safe handling and elution of generators**

A.5 Management and radiation protection of the patient

A.5.1 Patient selection

Disease process and other investigations relevant to the disease
Patient preparation and consent (as appropriate)
Drug interactions
Arrangements for radioactive patients in the hospital and home
Administration of radioactivity – techniques and procedures, apparatus
Preparation and disposal of syringes/needles
Documentation
Hygiene in relation to radioactivity
Reporting procedures (including accidents, adverse reactions, errors in preparation and administration)
Medico-legal responsibility
Special groups and contraindications:

- pregnancy
- breast feeding
- infants and children
- the seriously ill

A.5.2 Therapy aspects

Planning of investigations including the selection of appropriate tests and imaging techniques for the diagnosis of malignant disease
Consent for therapy administrations
Interaction with other pharmaceuticals and clinical investigations
Radiation safety issues both within the hospital and at home
Possible toxicity of the therapy both early and late
Follow up, assessment of efficacy and retreatment

A.6 Statutory and advisory publications and general radiation protection

A.6.1 Statutory and advisory aspects

National and international regulatory requirements relevant to the practice of nuclear medicine including:

- IRR99
- MARS legislation
- RSA 93
- IR(ME)R 2000
- Radioactive Material Transport Regulations and Orders

(see Section 1 and Appendix V)

National and international guidance on nuclear medicine including:

- ARSAC Notes for Guidance
- Medical and Dental Guidance Notes
- local rules and other guidance
- Marketing Authorisation mechanisms
- responsibility for radiation safety
- medico-legal responsibility
- routine inspection and testing of equipment
- notification of faults and DH hazard warnings

A.6.2 General radiation protection

Radiation protection, with particular emphasis on:

- storage and shielding, preparation, dispensing, administration of doses
- minimising radiation dose to staff, annual dose limits
- monitoring of working areas and persons
- decontamination procedures in dealing with spills
- waste disposal
- protection of the patient, their contacts and their comforters and carers

Requirements for practical experience

- 3** The amount of appropriately supervised practical experience needed for a certificate will vary and can be restricted to those procedures which are to be undertaken. The practical experience should not be limited to reporting alone. It should include vetting of requests, decisions on the most appropriate procedure, patient preparation, procedures for supplying the appropriate radiopharmaceutical, the procedure itself, post-procedure processing, etc.
- 4** As a guide, applicants should have experience of supervising and reporting procedures consistent with the curriculum of the European Nuclear Medicine Society and the JCHMT of the Royal College of Physicians, for the procedures which they wish to offer. Provision of a comprehensive service would require experience of approximately 3000 procedures. This level of experience will enable a certificate holder to justify, perform, and change and develop the protocols for those procedures included within the issued certificate.
- 5** If an applicant wishes to hold a certificate for a limited range of diagnostic procedures then the practical experience required will be consistent with that required for specialist training in nuclear medicine, but restricted to the limited range requested. It is not possible to specify a precise number of procedures to be undertaken as this will vary with the area of clinical investigation and the previous training and experience of the applicant. Nevertheless, the curriculum of the European Nuclear Medicine Society and the JCHMT of the Royal College of Physicians offer a useful guide.
- 6** For those wishing to hold a certificate for the purpose of treatment, the practical experience required will need to be broadly similar to that required for therapy aspects of specialist training in nuclear medicine for unsealed sources and the Fellowship of the Royal College of Radiologists (Faculty of Clinical Oncology) for sealed sources.

Part B: Additional Requirements for Those Using Positron Emission Tomography

- 7** Positron emission tomography (PET) has become an established diagnostic tool in the investigation of oncology patients. Its role in cardiac and neurological conditions is not as widespread. In recent years, PET CT has become the modality of choice in clinical settings.
- 8** Both PET and PET CT are developments within nuclear medicine and as such retain the essential quality of provision of functional rather than anatomical imaging. Specialists who wish to provide PET and PET CT services will require training and experience additional to that required for conventional nuclear medicine studies. Such specialists will need to hold an ARSAC certificate including PET serials and applicants for such certificates should already hold certificates for a comprehensive range of nuclear medicine imaging procedures.
- 9** Such certificates will not attest to the holder's knowledge, experience, competence and skill in relation to any use of CT as this is outside the scope of the MARS Regulations 1978. The use of CT in nuclear medicine procedures is of course subject to clinical governance considerations.
- 10** In order for an ARSAC certificate to be issued, applicants will need to demonstrate adequate theoretical training and supervised practical experience in PET. Tumour imaging with PET covers a wide range of malignancies with different uptake mechanisms and patterns of spread. Although most PET imaging for oncology is undertaken with FDG, the development and application of other radiopharmaceuticals is growing. Training and experience undertaken by nuclear medicine specialists will need to address these differences.
- 11** Since 2004, those undertaking structured training through the Royal Colleges for a nuclear medicine CCST will have been provided with sufficient theoretical knowledge and practical experience to satisfy this requirement and a certificate for PET procedures will be issued on completion of the training grade.
- 12** This does not currently apply to those who are undertaking radionuclide radiology training, where PET is not part of the curriculum. Similarly it will not be the case for others, including those who have undertaken CCST in nuclear medicine or radionuclide radiology training prior to 2004 and those who completed the training grades some time previously and have been providing conventional nuclear medicine services for some time. Before a certificate can be issued therefore, such nuclear medicine specialists may need to make special arrangements post qualification to reasonably satisfy the Health Ministers of their knowledge, experience, competence and skill in PET before a certificate can be issued.
- 13** Theoretical knowledge can be obtained through attendance at conferences and lectures as well as through keeping up to date with current literature. A number of courses are now available in Europe and North America and these will provide sufficient theoretical knowledge for the applicant, when considered in conjunction with an existing broad knowledge of nuclear medicine.
- 14** Practical experience may be more difficult to achieve and will need to be sufficient to cover a wide range of tumour types. Experience should be obtained through attendance at an established clinical PET centre. The applicant should be able to demonstrate active involvement in protocol development, participation in patient selection and procedure justification, participation in MDMs and, within the nuclear medicine facility, day-to-day running of the service and clinical evaluation. Such experience will prepare the applicant for patient management problems that may arise.
- 15** Consideration of experience abroad as well as of that of current PET practitioners in the UK suggests that applicants who wish to provide an FDG-based oncology service should be able to demonstrate active involvement in approximately 600 cases typically over a period of about three months. This

should be achieved in blocks rather than through sessional involvement and it is recommended that the blocks should be of no less than four weeks' duration. Experience gained in this way should ensure experience of a representative patient case-mix.

- 16** Arrangements of this type are not easy to achieve, particularly for nuclear medicine specialists already providing a comprehensive nuclear medicine service. However, it should be noted that the introduction of a comprehensive PET facility represents a significant resource commitment and such a service will need to demand at least one additional whole-time equivalent specialist's time. It should be noted that once the service is established, other specialists will be able to gain equivalent experience within their own centre.
- 17** It should be noted that those individuals who wish purely to provide clinical evaluations of PET images will not require an ARSAC certificate. They will still be required, under the Ionising Radiation (Medical Exposure) Regulations 2000 to have adequate training and experience, but this does not need to be as extensive as for those wishing to hold an ARSAC certificate. Training may still be required over and above that acquired as part of specialist registrar training, as this does not currently include PET. It is recommended that medical practitioners acting in this capacity should have experience of reporting 300 scans, achieved as part of an interactive programme rather than by reviewing a library of images and reports.

Part C: Requirements for Support Staff Resulting from the Introduction of New Techniques into the Nuclear Medicine Department

- 18** Under the MARS Regulations 1978, persons wishing to administer radioactive substances may do so only when a certificate has been issued by the Health Ministers (see Section 1). Before a certificate is issued, the Health Ministers need to be reasonably satisfied regarding the training and experience of the applicant and his/her support staff (see Section 2). It follows that when a certificate holder wishes to undertake new procedures, before a certificate can be extended, the applicant will need to satisfy the Health Ministers regarding any further training and experience that might be required, both for the applicant and for the support staff.
- 19** As nuclear medicine techniques and services develop, and new functions and processes are expected to be undertaken by staff within the nuclear medicine department, it is important that the certificate holder only delegates tasks associated with a procedure to those who have demonstrated competence through appropriate training and experience. This approach is consistent with advice issued by the GMC and with the requirements of IR(ME)R 2000. If the competence of others cannot be demonstrated, the nuclear medicine specialist cannot justify the procedure and it should not be undertaken.
- 20** Demonstration of initial competence can be provided through formal theoretical training, supervised practical experience and mentored practical experience. Theoretical understanding can be achieved through attending conferences and practical training can be provided through formal visits to other centres with experience of a new technique, often acquired by involvement in early research applications.
- 21** This competence must be maintained. Continuing competence can then be demonstrated through appraisal and similar mechanisms. The requirement for maintaining competence applies to all staff, some of whom will be within the direct line management control of the certificate holder and some of whom will not.
- 22** Previously, the training and competence of support staff has not been explicitly addressed in the application forms for additional procedures. Nevertheless, it has long been recognised that such training is an integral part of running a service under a clinical governance framework and development of such services needs full documentation of training and written protocols in advance of commencing new elements of the service. Persons who intend working under the written directions of the certificate holder will need also to be entitled to undertake these functions by their employer under the requirements of IR(ME)R 2000. Revised application forms for extension of the scope of a certificate will, in the future, expect the applicant to vouch for the additional training and experience required of all staff in support of the application.
- 23** In recent years suppliers have developed training for those departments that wish to introduce new radiopharmaceuticals into the UK, where the use of the radiopharmaceutical demands expertise and skills not usually available within an existing nuclear medicine service. Specific training has been developed for the labelling, administration and acquisition phases of a number of techniques and reference to this supplier training within an application will provide confidence in all aspects of the process and enable applications to be processed more quickly.
- 24** Alternative local methods of developing appropriate skills can always be used but recognised training schemes may be preferable as these provide evidence of competence that might be more easily transferable. Where local training is developed, this should be equivalent to existing formal schemes. Within any application to the ARSAC, greater detail will be required about local training schemes so that the Committee can satisfy itself as to the competence of all staff involved.

Part D: Requirements for Those Working under the Written Directions of a Certificate Holder, eg Sentinel Lymph Node Biopsy Procedures

- 25** Under the MARS Regulations 1978 and the Amendment Regulations 1995, a person may undertake elements of a procedure utilising radiopharmaceuticals under the written directions of a certificate holder. These directions should set out the radiopharmaceutical and activity to be used and the technique to be employed and can be considered as equivalent to written protocols as required by IR(ME)R 2000.
- 26** As nuclear medicine techniques and services develop, and are undertaken by staff and in locations that are not under the direct line management control of the nuclear medicine specialist, it is important that the certificate holder only delegates tasks associated with a procedure to those who have demonstrated competence through appropriate training and experience and can show that this competence has been maintained. This approach is consistent with advice issued by the GMC. If the competence of others cannot be demonstrated, the nuclear medicine specialist cannot justify the procedure and it should not be undertaken.
- 27** Development of such services needs full documentation of training and written protocols in advance of commencing the service. Persons who intend working under the written directions of the certificate holder will need also to be entitled to undertake these functions by their employer under the requirements of IR(ME)R 2000.
- 28** Demonstration of initial competence can be provided through formal theoretical training, supervised practical experience and mentored practical experience. Continuing competence can be demonstrated through appraisal and similar mechanisms
- 29** The approach proposed and developed by the Royal College of Surgeons (RCS) for training of qualified surgeons who wish to undertake sentinel lymph node (SLN) probe studies as part of the treatment of breast cancer provides a model for such training.
- 30** Following initial theoretical training, supervised practical training is provided by the RCS at the surgeon's hospital. The surgeon then continues to perform the procedure under an audited scheme to demonstrate competence. This includes imaging and histological assessment. After final assessment by the RCS, the surgeon is deemed competent to undertake the procedure as part of routine practice, as long as he or she maintains competence by undertaking approximately 25–30 SLN procedures per year.
- 31** For additional consultant surgeons and specialist registrars, training might be delivered under the direct supervision of a surgeon who has completed the RCS training programme. This would remove the need for axillary clearance, although it is expected that imaging will still be required in this training phase.
- 32** With a commitment to such an approach, the nuclear medicine specialist can be confident of the competence of the surgeon in this technique and can apply for an ARSAC certificate. Information regarding the training arrangements should be supplied to the ARSAC as part of the application and a certificate can be issued. This can be made available to enable the initial supervised training sessions to be undertaken at the certificate holder's site.
- 33** Alternative methods of developing appropriate skills can always be used to demonstrate competence has been achieved in order that an ARSAC certificate can be issued. Formal training schemes, however, are preferable as these provide clear evidence of competence. Where local training is developed, this should be equivalent to existing formal schemes. Within any application to the ARSAC, greater detail will be required about local training schemes so that the Committee can satisfy itself as to the competence of all staff involved.

Appendix V

Additional Acts and Regulations

- 1 This summary of legislative requirements additional to the Medicines Regulations, Order and Amendment Regulations (with respect to radioactive substances) is not exhaustive and direct reference to the underlying legislation and the relevant government departments and agencies is advisable. Ultimately, a definitive interpretation of the legislation is a matter for the Courts.

The Radioactive Substances Act 1993⁴⁹ (RSA 1993)

- 2 The main purpose of the Radioactive Substances Act is to control radioactive waste in order to provide radiation protection of members of the public. The Act provides for control on the use of radioactive materials which can give rise to waste, and in particular on the accumulation and disposal of radioactive waste itself.
- 3 The Environment Agency is responsible for administering and enforcing the Act in England and Wales. The Scottish Environment Protection Agency is responsible in Scotland, and the Environment and Heritage Service is the regulator in Northern Ireland. Before April 1, 1996, the regulatory bodies in these countries were, respectively, HM Inspectorate of Pollution, HM Industrial Pollution Inspectorate and the Alkali and Radiochemical Inspectorate.
- 4 The Act requires:
 - (a) users of radioactive materials and mobile radioactive apparatus to be registered;
 - (b) the accumulation and disposal of radioactive waste to be authorised.
- 5 Hospitals wishing to use radioactive materials or accumulate and dispose of radioactive waste need to apply, in advance, for registrations and authorisations. If applications are successful, certificates of registration and authorisation are granted by the appropriate agency. These will include limitations and conditions which provide the detailed controls required for the safe management of radioactive materials and waste. Conditions typically include: specification of the types and limits on the amounts of radioactive material which may be kept, and radioactive waste which may be accumulated; specification of the types and amounts of radioactive waste which may be disposed of by specified routes during a specified period; requirements to keep radioactive sources and waste securely, to prevent damage to sources and the spread of contamination; to notify the appropriate agency in case of loss or accident; and to keep detailed records. The conditions of registration and authorisation are legal requirements; failure to comply with them is an offence under the Act.
- 6 Hospitals will be required to have management systems capable of achieving compliance with authorisation and registration conditions. Access to advice from Radiation Protection Advisers (RPAs) or suitably qualified experts may be required.
- 7 Under RSA 1993 the appropriate agencies are required to recover their costs of regulation under the Act, including determining applications and ongoing inspection and enforcement. Applications for registration and authorisation must be submitted with a fee, and for premises where authorisations, and some registrations, are issued there is an ongoing annual subsistence fee. More detailed information is available from the appropriate agency offices.

- 8** Applications are processed within four months from the date of receipt of an application, unless a longer period has been agreed with the applicant. In more complex cases, the appropriate agency will agree upon a response period with the applicant. The appropriate agency will also attempt to determine applications on shorter timescales in cases of genuine need.
- 9** A number of Orders have been made under RSA 1993 providing for exemptions from registration and authorisation. There are 17 Exemption Orders currently in force, and many are conditional. The responsibility for making Exemption Orders lies with the Secretary of State for the Environment, Food and Rural Affairs in England and with the devolved administrations in Scotland, Wales and Northern Ireland.
- 10** The Exemption Order with most relevance to hospitals is SI 1990 No. 2512 Hospitals Exemption Order as amended by SI 1995 No. 2395 Hospitals (Amendment) Order. This Order exempts *small* hospitals, clinics, etc, from the need for registration and authorisation. Larger hospitals will need to apply for registration and authorisation if their holdings of radioactive material exceed the limits of the Order.

Registration for the keeping and use of radioactive material

- 11** Hospitals must apply for registration on the appropriate forms to their local appropriate agency office with the information required by the agency for each hospital where radioactive substances are used. This will include the following:
- (a) the address where radioactive material(s) will be kept or used plus the name and address of the person and organisation responsible (at law) for ensuring compliance with the Act – generally the chief executive of the hospital or health authority;
 - (b) the purpose for which the materials will be kept or used;
 - (c) a description of the radioactive material, eg names of radionuclides, whether sealed or unsealed sources;
 - (d) the maximum quantity and maximum radioactivity which will be present on the premises at any time and which will be used per week or per month. Allowance should be made in the above list for in-patients who are administered radioactive substances at another hospital;
 - (e) declaration of public access to information.
- 12** Provider units should name contact(s) at the hospital who are competent to supervise the keeping and use of radioactive materials and accumulation/disposal of radioactive waste. This person may well be a Radiation Protection Adviser (RPA) or Radiation Protection Supervisor (RPS) appointed under the Ionising Radiations Regulations 1999²⁴. His or her duties normally encompass control of use and disposal. Confirmation of such authority by the employer is desirable.
- 13** Provider units should send a revised application if the amount of radioactive material they use or hold is expected to rise above the maximum level previously registered or authorised for accumulation or disposal or if they wish to use new radionuclides. Fees are required for significant changes or major variations to registrations and authorisations. It is therefore prudent to consider carefully any likely future development or expansion in the use of radioactive materials, including research, when making an application or seeking a variation so as to avoid regular, and expensive, reapplications.

Authorisation for the accumulation and disposal of radioactive waste

- 14** Hospitals providing services must apply for authorisation if they accumulate and/or dispose of radioactive waste. They should apply on forms obtainable from the appropriate agency. A separate application is needed for each individual hospital on a separate site. The application will need to include

full details of the nature, types and activity of the waste, proposed disposal routes and radiological assessments of the impact of disposals.

- 15 Provider units should regularly review their current practices for disposal of radioactive waste. This should include a 'housekeeping' exercise to review the location of all radioactive sources held and, if necessary, to dispose correctly of those no longer required. In particular, they should be aware of disposal routes for the transfer of radioactive clinical waste off-site for incineration, ie to which incinerators the waste is sent, and these transfers must be covered in the authorisations.
- 16 It follows that any proposed permanent or contingency changes in the arrangements for incineration of clinical waste must be notified to the RPA at the earliest opportunity so that the suitability of the proposed change can be verified and the requisite modification to the Certificate of Authorisation (which may take several weeks or months) can be obtained from the appropriate agency before the change is implemented.

Multiple occupancy of a site

- 17 Where there is multiple occupancy of a single site (eg an NHS hospital trust and a university medical school on a hospital site) it can sometimes be difficult to decide who is the appropriate applicant for registrations and authorisations. The straightforward solution is for occupants to apply separately for registration of clearly defined premises, ie parts of the overall site. However, this may lead to difficulties where radioactive material frequently passes between the occupants, staff fulfil roles in both organisations or there is interaction in the use of facilities. The overriding requirement is for proper control. Exceptionally, when separate applications would present severe operational difficulties, the matter may be resolved by a single party (eg a hospital trust) agreeing to take full responsibility under the Act for the overall premises (ie the hospital site). Before issuing any registration or authorisation the appropriate agency will require to be satisfied that the applicant has effective management control which will enable it to comply with the limits and conditions of the registration or authorisation. Where a hospital trust proposes to take such a course of action it should recognise that it is assuming full legal responsibility for the actions of all persons on the site keeping and using radioactive materials and accumulating and disposing of radioactive waste.

Record keeping

- 18 Records of radionuclide stocks, and amounts of waste accumulated and disposed of, must be kept and made available on request to the appropriate agency. In addition, the appropriate agency will require an annual return of the radioactive waste disposed of, for inclusion in its Pollution Inventory.

The Medicines Act 1968⁶

- 19 Radiopharmaceuticals are relevant medicinal products and their sale, supply and manufacture are subject to the licensing provisions of the Medicines for Human Use (Marketing Authorisations etc) Regulations 1994⁵⁰ and the Medicines Act 1968. A radiopharmaceutical for human use placed on the market must have a Marketing Authorisation (formerly known as a Product Licence) unless the provisions of Schedule 1 to the Regulations apply. The applicable provisions include those in paragraph 5 of Schedule 1 to the Regulations which permit the preparation of a radiopharmaceutical if prepared at the time of administration, in accordance with the manufacturer's instructions, by the person by whom it is to be administered, from a kit (generator or precursor) which has a Marketing Authorisation.
- 20 When unlicensed radiopharmaceuticals are manufactured in a hospital, for supply to doctors or dentists for the purpose of administration to individual patients, under the provisions of paragraphs 1 and 2 of Schedule 1 to the Regulations, a Manufacturer's (Specials) Licence is required. Licence holders are

subject to periodic inspection by the Medicines Inspectorate of the Medicines and Healthcare Products Regulatory Agency or the Department of Health, Social Services and Public Safety in Northern Ireland. A person preparing radiopharmaceuticals in a hospital under the supervision of a pharmacist is exempt from the requirement to hold a Manufacturer's Licence under Section 10 of the Act.

The Ionising Radiations Regulations 1999²⁴ (IRR 1999) and the Ionising Radiations Regulations (Northern Ireland) 2000⁵¹ (IRR(NI) 2000)

- 21** The Ionising Radiations Regulations 1999 and the Ionising Radiations Regulations (Northern Ireland) 2000 were made under the Health and Safety at Work etc Act 1974⁵² and the Health and Safety at Work (Northern Ireland) Order 1978⁵³, respectively. They require employers to establish a framework for ensuring that exposure from ionising radiation resulting from work activities, whether man-made or natural radiation and from external radiation (eg an X-ray set) or internal radiation (eg inhalation of a radioactive substance), is kept as low as reasonably practicable and does not exceed the dose limits specified in the regulation. The Regulations are supported by an Approved Code of Practice ('Work with ionising radiations')⁵⁴.
- 22** These Regulations are enforced by the Health and Safety Executive (HSE) in Great Britain and by the Health and Safety Executive for Northern Ireland. HSE Guidance Note PM77⁵⁵ gives guidance on the fitness of equipment used for medical exposure to ionising radiation. This guidance is currently being reviewed.
- 23** The onus is placed on employers to ensure compliance with the Regulations. A breach of these Regulations is an offence under Section 33 of the Health and Safety at Work etc Act 1974 or Article 31 of the Health and Safety at Work (Northern Ireland) Order 1978. The Approved Code of Practice gives practical advice on how to comply with the Regulations. Employers may use alternative methods to those set out in the Code in order to comply with the law. However, the Code has a special legal status. If an employer is prosecuted for breach of health and safety law, and it is proved that the employer did not follow the relevant provisions of the Code, the employer will need to show that they have complied with the law in some other way or a court will find them at fault.

Some relevant Regulations

Regulation 13 – appointing Radiation Protection Advisers (RPAs)

- 24** Every employer who in the course of a trade, business or other undertaking carries out work with ionising radiation must appoint an RPA to advise them on compliance with the Regulations and other radiation protection matters. (There are certain exceptions to this set out in Schedule 1 of the regulations, although employers may still wish to consult an RPA, at least initially, for checking or reassurance purposes.) Paragraphs 216 to 231 of the Approved Code of Practice and Guidance that supports the Regulations gives information on choosing a suitable RPA. Further guidance on the qualifications, experience and qualities needed by an RPA are set out in the HSE Statement on Radiation Protection Advisers, which may be viewed at www.hse.gov.uk/hthdir/noframes/state.htm.
- 25** The duties under the Regulations remain with the employer. The RPA is there to provide advice on compliance with the Regulations. The employer is required to consult the RPA in the situations set out in the Regulations and the Approved Code of Practice. Beyond this, there are a range of matters where, depending on the experience of the employer, the expertise of the RPA may be necessary.

Regulation 32 – equipment used for medical exposure

- 26** Regulation 32(1) states that any equipment or apparatus which is used in connection with a medical exposure must be of such design and construction, and be so installed and maintained, as to be capable of restricting, so far as is reasonably practicable, the exposure to ionising radiation of any person who is

undergoing a medical exposure to the extent that this is compatible with the intended clinical purpose or research objective. Failure to do so might result in enforcement proceedings. Under Regulation 32(6) if the exposure of a patient to ionising radiation is much greater than intended as a result of equipment defect or malfunction, the employer must make an immediate investigation of the suspected incident and, unless that investigation shows beyond reasonable doubt that no such incident occurred, employers are required to notify the HSE or HSE for Northern Ireland, as appropriate.

The Ionising Radiation (Medical Exposure) Regulations 2000⁵ (IR(ME)R 2000) and the Ionising Radiation (Medical Exposure) Regulations (Northern Ireland) 2000⁵⁶

- 27** The Ionising Radiation (Medical Exposure) Regulations 2000 (IR(ME)R 2000) and the Ionising Radiation (Medical Exposure) Regulations (Northern Ireland) 2000 were made under Section 2(2) of the European Communities Act 1972 but are enforced as if they were made under Section 15 of the Health and Safety at Work etc 1974 and Article 17 of the Health and Safety at Work (Northern Ireland) Order 1978, as appropriate. They identify a number of duty holders with responsibilities associated with medical exposures, the required training for duty holders associated with justification and practical aspects of medical exposures, the keeping of relevant records and the availability of expert advice. They apply to all types of procedure resulting in medical exposure and, in contrast to the regulations they replace, include the use of ionising radiation in scientific research.
- 28** The Regulations are enforced by the appropriate authorities defined within Regulation 2. There is a requirement that exposures ‘much greater than intended’ are reported to the appropriate authority.

Summary of the Regulations

Regulation 2 – interpretation

- 29** ‘Appropriate authority’ is defined and reflects the role of the devolved administrations in health matters.
- 30** ‘Diagnostic reference levels’ are defined and these are intended as a tool to aid optimisation.
- 31** Four duty holders are identified – the ‘employer’, the ‘referrer’, the ‘practitioner’ and the ‘operator’. The definition of employer goes beyond the term as conventionally understood and should not be interpreted as within employment law. This has implications for individuals who are contracted to provide elements of a service. Under IR(ME)R 2000, these individuals are considered as operators and must be entitled to act as such and follow the procedures of the employer carrying out the medical exposures. A duty holder can be prosecuted for failing to comply with the appropriate provisions of the Regulations.

Regulation 4 – duties of the employer

- 32** The employer is responsible for providing a framework for medical exposures and does so by ensuring that written procedures and protocols are in place. Schedule 1 of the Regulations sets out a minimum of essential procedures.
- 33** In nuclear medicine, the employer will consult the doctor or dentist holding a certificate under the MARS Regulations 1978 in order to ensure that written procedures and protocols are in place. In many circumstances, detailed working procedures and clinical protocols will equate to the written directions required under the MARS Regulations.

Regulation 5 – duties of the referrer, practitioner and operator

- 34** The referrer is primarily responsible for supplying sufficient medical data on which the justification of a medical exposure can be based. The practitioner is responsible for justification of the medical exposure. The operator is responsible for the practical aspects of the medical exposure. Every medical exposure

involves a range of practical aspects and will involve a number of operators including doctors, medical physicists, medical physics technicians, nurses, radiographers and radiopharmacists. It is essential that the referrer, practitioner and operators are identified for each task associated with each individual medical exposure. This can be achieved through signatures and written procedures which define functions and roles.

Regulation 6 – justification

- 35 No medical exposure shall be carried out if it has not been justified. A range of requirements is identified and a facility is available for authorisation of an exposure by an operator against guidelines issued by the practitioner.

Regulation 7 – optimisation

- 36 Regulation 7 is intended to ensure that the radiation dose received from a medical exposure is as low as reasonably practicable consistent with the intended purpose. It requires, where appropriate, that certain information and instructions are given when radioactive medicinal products are administered.

Regulations 2, 4 and 11 – training

- 37 The Regulations require that practitioners and operators are adequately trained to undertake medical exposures. The employer is required to take steps to ensure compliance with training requirements including continuing training. Training records should be available for inspection by inspectors acting on behalf of the relevant appropriate authority. Further information is provided in Schedule 2 of the Regulations.

Regulation 9 – expert advice

- 38 Regulation 9 requires that a medical physics expert is available. The degree of availability will vary with the range and complexity of procedures undertaken. Where services include complex therapeutic and diagnostic procedures, it is expected that at least one such person will be available on a full-time basis.

Regulation 10 – equipment

- 39 An inventory should be available of any equipment that delivers ionising radiation or directly controls the extent of such an exposure.

The Radioactive Material (Road Transport) (Definition of Radioactive Material) Order 2002⁵⁷, the Radioactive Material (Road Transport) Regulations 2002⁵⁸, the Radioactive Substances (Carriage by Road) Regulations (Northern Ireland) 1983⁵⁹, and the Radioactive Substances (Carriage by Road) (Amendment) Regulations (Northern Ireland) 1986⁶⁰

- 40 When an NHS authority or hospital sends radioactive substances by road it becomes a consignor; if it uses its own vehicles and/or drivers it also acts as a carrier. In both sets of circumstances, management, in consultation with the RPA, should ensure compliance with the requirements of the Radioactive Material (Road Transport) Regulations 2002 (RAM Road Regulations), the Radioactive Substances (Carriage by Road) Regulations (Northern Ireland) 1983 and the Radioactive Substances (Carriage by Road) (Amendment) Regulations (Northern Ireland) 1986, as appropriate.
- 41 It should be understood that under these Regulations ‘transport’ has a wider than normal definition and includes the design, manufacture, maintenance and use of the package containing radioactive material, as well as the actual preparation, consigning, handling, carriage, storage in transit and receipt of each package. The Regulations are comprehensive and cover all aspects of ‘transport’ of radioactive material by road. Further guidance, if required, is available from the Radioactive Material Transport Division of the Department for Transport.

- 42** Also relevant to the transport of radioactive material by road are the Carriage of Dangerous Goods by Road (Driver Training) Regulations 1996⁶¹ and the Road Traffic (Training of Drivers of Vehicles Carrying Dangerous Goods) Regulations (Northern Ireland) 1992⁶². Regulation 3 requires drivers of vehicles carrying radioactive material, subject to certain exemptions, to have had adequate instruction and training to understand the nature of the danger, actions to take in an emergency and their responsibilities under the RAM Road Regulations. Records of that training must be kept and a copy given to the driver.
- 43** Under Regulation 4 any driver transporting a labelled package of radioactive material, in accordance with the provisions of the RAM Road Regulations, is required to obtain a Vocational Training Certificate under the terms of these Regulations. However, where a vehicle is carrying no more than ten non-fissile Type A packages and the sum of the transport index of those packages is not more than three then only the provisions of Regulation 3 apply.
- 44** As far as radioactive material is concerned, there are no exemptions based on the weight of the vehicle.
- 45** The Driver Training Regulations do not apply to the transport of excepted packages (Regulation 2(2)(c)).

Changes to Regulations

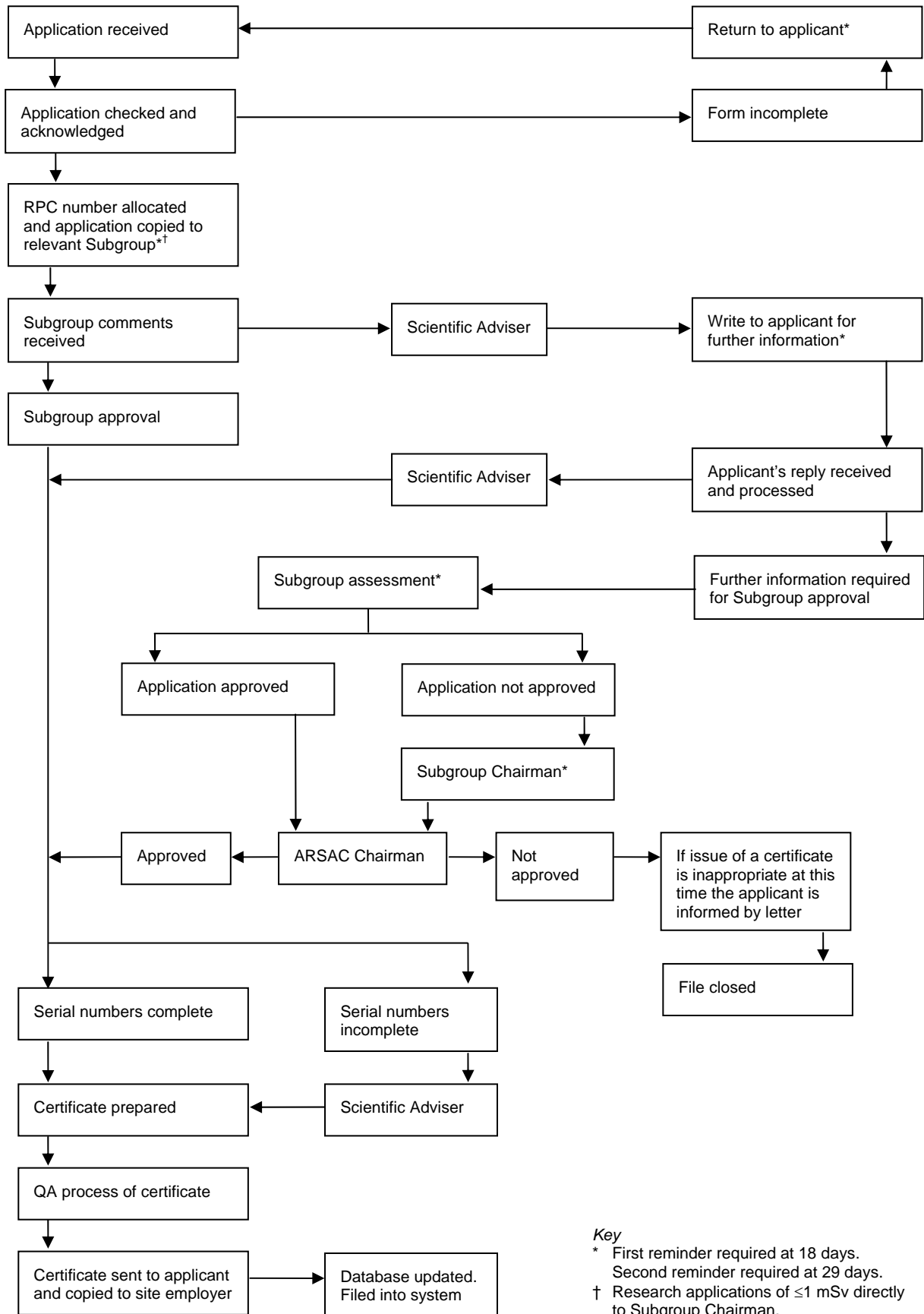
- 46** ARSAC certificate holders will be notified of changes to regulations and orders through the ARSAC Newsletter.

Appendix VI

Certification Process under the MARS Regulations 1978

- 1** The issuing of certificates under the MARS Regulations 1978 is carried out with input from the ARSAC members, the ARSAC Support Unit and the ARSAC Secretariat. The Committee's primary role is to advise the Health Ministers on the issuing of certificates.
- 2** The process varies with the type of certificate issued, but as an example, the process for new certificates is represented in the figure overleaf. This is the most involved process. Other applications for additional procedures, renewal of certificates, etc, eliminate some of these steps.
- 3** The ARSAC Support Unit processes in excess of 1300 applications per year. The Committee is divided into a number of subgroups. Each subgroup contains members from a range of specialties. All applications for certificates are dealt with by post and by e-mail, as appropriate. Committee members do not see applications from their own hospitals. Each phase of the process has a target period for completion and this is monitored. The overall performance is monitored quarterly and compared to performance specified by contract between the ARSAC Support Unit and the Department of Health.
- 4** Consistency of response is ensured by the involvement of the ARSAC Chairman in all applications where the Committee requests further information from the applicant. It should be noted, however, that certificates are issued by the Health Ministers and not by the Committee and that no application is seen by a single person only.

Current Certification Procedure – New Applications Diagnostic, Therapy (including Functional Groups) and Research



Appendix VII

Communicating Risk to Local Research Approval Bodies, Patients and Research Subjects

- 1 Knowledge and communication of risk to patients and others form an essential element of modern medical practice and, without it, informed consent cannot truly be obtained. This is particularly true in nuclear medicine and other disciplines where legislation requires that medical exposures are justified – which involves consideration of benefits, detriment efficacy and risk – and that written instructions to patients and others include the risks associated with ionising radiation.
- 2 While all aspects of life entail risk, effective communication is limited by confusion over the meaning of words and differing perceptions. Culture, age and gender all influence perception of risk. Other factors include whether individuals choose to expose themselves to the risk or the risk is a public or collective one. Involuntary risks are generally considered to be more dangerous than voluntary ones, eg exposure to pollution compared with participation in dangerous sports.

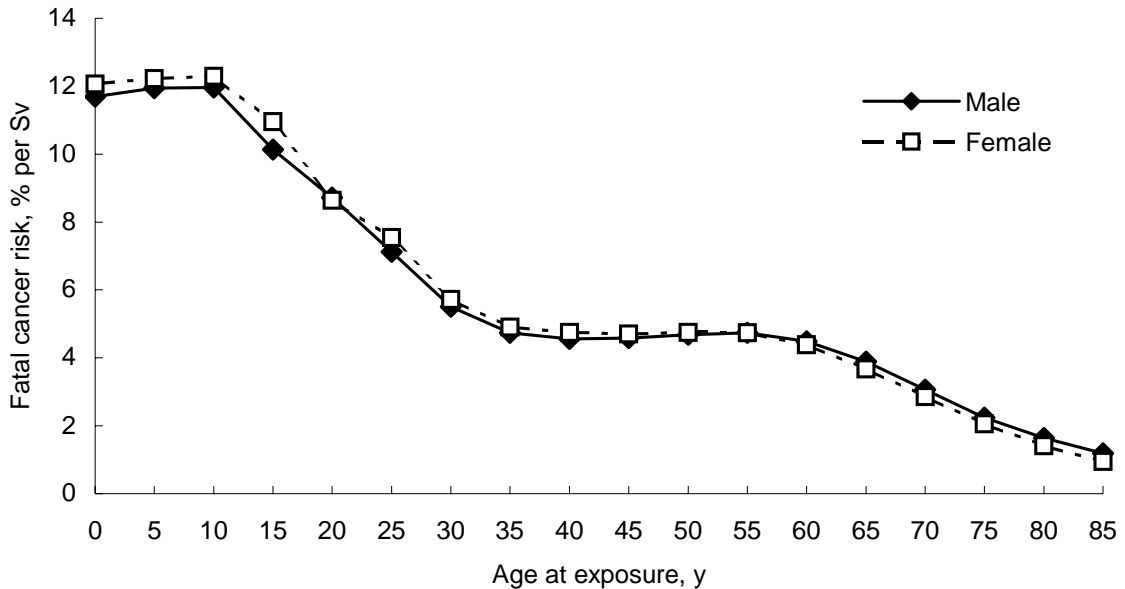
Communicating Risks to Local Research Approval Bodies

- 3 ICRP Publication 62 provides general guidelines for assessing research proposals (see Table 1). The risk is the total detriment from the exposure including fatal and non-fatal cancers and probability of hereditary disease. The detriment will change also with age. The detriment per unit dose for children is two to three times bigger than for young adults, while that for people over 50 years declines with age to one-fifth of that for young adults (see the figure overleaf).

Table 1 General guidelines for assessing research proposals

Level of risk	Total risk of detrimental radiation effect	Effective dose for adults (mSv)	Level of societal benefit needed
I Trivial	$\sim 10^{-6}$ or less	<0.1	Minor
IIa Minor	$\sim 10^{-5}$	0.1 to 1	Intermediate
IIb Intermediate	$\sim 10^{-4}$	1 to 10	Moderate
III Moderate	$\sim 10^{-3}$ or more	>10	Substantial

- 4 When assessing research applications, a local research approval body should satisfy itself that the extra clinical information to be gained from the study warrants the risk involved. Clearly this is only possible if the radiation doses involved are known.
- 5 When considering research proposals, the local research approval body should consider the risk associated with the study in relation to the risk associated with the disease to be studied. In some cases the risk associated with the research will reduce the risk of the disease and this should be taken into account also. This may make easier acceptance of quite small risks, such as research with risks at Levels I, IIa and IIb above.
- 6 Finally, the local research approval body should assess how the investigators intend to communicate the level of risk to subjects, depending on the level of risk. The approval body should ensure that a requirement is included within the protocol that risk information is provided in writing to volunteers at the time of obtaining consent.



Total fatal cancer risk for uniform whole body exposure as a function of age at exposure and sex

Communicating Risks to Patients and Research Subjects

- 7** Research has shown that patients, and by implication research subjects, extract the gist of information rather than making decisions on detail. The importance of emotions in assessing risks should not be underestimated and this frequently presents healthcare professionals with a problem. Presenting risks in a calm and caring manner is likely to have the most effective results.
- 8** Where ionising radiation is being used for diagnostic purposes, and the benefit is considered to significantly outweigh the detriment, the objective is often seen to be to allay the fear of the patient. Terms such as hazard, risk and safe are often used to convey the same impression. Understanding of these terms varies enormously. For example, the term 'safe' might convey at least six different meanings:
- no risk at all;
 - no evidence of risk;
 - no current evidence of risk, but risk cannot be excluded;
 - no need to worry about risk;
 - safe enough in the context of other common risks;
 - no hazard present.
- 9** In many cases, the use of the term 'safe' does not remove the difficulties associated with the term 'risk' as varying interpretations exist for both. In general, attempts to present risk in terms that imply acceptability are counterproductive.
- 10** Most research suggests that an open approach is beneficial in risk communication. This implies that the patient has an opportunity to contribute to the discussion. By contrast, a 'transparent approach' is one where the basis and the decision process is available for analysis but not open to input. The 'transparent approach' is less suitable in this context.

- 11** When communicating with patients, it is normal to discuss risk in terms of numbers. A number of techniques can be used to assist the process:
- (a) avoid using descriptive terms alone – low risk has different meanings to different people;
 - (b) use a consistent denominator – 10 in 1,000,000, 100 in 1,000,000;
 - (c) consider offering positive as well as negative outcomes – 97 out of 100 chance of success is more acceptable than 3 out of 100 chance of failure;
 - (d) use absolute numbers not relative risk – eg ‘three times as many’ can be easily misinterpreted;
 - (e) use visual aids – eg pie charts.
- 12** In some circumstances, and particularly when trivial levels of risk are involved, the use of absolute numbers is not practical. The difficulty of envisaging very small probabilities is well known. Patients often respond positively to comparisons of risk associated with everyday activities, when expressed within the same number base – see Table 2⁶².

Table 2 Examples of risks estimated to increase the annual chance of death by 1 in 1,000,000 (US statistics)

Activity	Cause of death
Smoking 1.4 cigarettes	Cancer, heart disease
Spending 1 hour in a coal mine	Black lung disease
Living 2 days in New York or Boston	Air pollution
Travelling 10 miles by bicycle	Accident
Flying 1,000 miles by jet	Accident
Living 2 months in Denver (rather than New York)	Cancer (cosmic radiation)
One chest X-ray in a good hospital	Cancer (from radiation)
Eating 40 tbs. of peanut butter	Liver cancer (aflatoxin B)
Drinking 30 12-oz cans of diet soda	Cancer (from saccharine)
Living 150 years within 20 miles of a nuclear power plant	Cancer (from radiation)

- 13** Alternatively, for a more direct comparison of radiation dose, the radiation dose from a range of nuclear medicine procedures (see Table 3) can be contrasted with the dose associated with background radiation (approximately 2.6 mSv per year) or flying at altitude across the Atlantic (approximately 0.035 mSv).

Table 3 Typical doses and risks from radionuclide studies

Study	Typical effective dose (mSv)	Increased annual chance of death
Lung ventilation (¹³³ Xe)	0.3	10 in 1,000,000
Lung perfusion (^{99m} Tc)	1	30 in 1,000,000
Kidney (^{99m} Tc)	1	30 in 1,000,000
Thyroid (^{99m} Tc)	1	30 in 1,000,000
Bone (^{99m} Tc)	4	120 in 1,000,000
Dynamic cardiac (^{99m} Tc)	6	180 in 1,000,000
PET head (¹⁸ F FDG)	5	150 in 1,000,000

- 14** It may also be helpful to place into context the radiation dose from diagnostic nuclear medicine procedures and those from other diagnostic imaging studies (see Table 4).

Table 4 Band classification of the typical effective doses of ionising radiation from common imaging procedures

Band	Typical effective dose (mSv)	Increased annual chance of death	Examples
0	0	Less than 1 in 1,000,000	US, MRI
I	<1	Up to 30 in 1,000,000	CXR, XR limb, MR pelvis
II*	1–5	30–150 in 1,000,000	IVU, XR lumbar spine, NM (eg skeletal scintigram), CT head and neck
III	5–10	150–300 in 1,000,000	CT chest or abdomen, NM (eg cardiac)
IV	>10	More than 300 in 1,000,000	Extensive CT studies, some NM studies (eg some PET)

* The average annual background dose in most parts of Europe falls in band II.

- 15** Care should be taken, however, that the risks from radiation exposures are not compared with practices that are unfamiliar or considered unacceptable. Comparing the risk associated with a paediatric procedure with that of smoking cigarettes or using internationally derived comparisons, such as drinking half a bottle of red wine per day, may give a false impression or trivialise the risk.
- 16** As the level of risk becomes greater, quoting risks in numerical terms may be helpful. At moderate levels of risk, it is likely that only in exceptional circumstances would a properly informed individual volunteer without a balancing individual benefit.

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