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

Administration of Radioactive Substances Advisory Committee

January 2016
Preface

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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)\textsuperscript{1,2,3}. Further guidance is issued by the European Commission and is available on its website. In the case of research projects involving volunteers, attention is drawn to guidance published by the Medical Research Council\textsuperscript{4} and a World Health Organization (WHO) expert committee\textsuperscript{5}.

3 The Notes include a number of changes from the previous revision. These include:

(a) advice regarding applying for research studies and ethical approval;
(b) advice regarding applications for therapy certificates;
(c) revised dosimetry information for commonly used radiopharmaceuticals based on recent ICRP publications;
(d) a revised summary of the legislation most relevant to nuclear medicine practice.

4 The advice on scaling of adult administered activity for children in Section 6 and breastfeeding interruption times in Section 7 have not been updated in this, December 2015, version. These sections will be addressed when further published data is available.

Future Revision and Updates

5 It is intended that ARSAC will review these Notes at such periods as may be appropriate. In addition, some detailed updating will be provided through additional guidance notes published on the website. Notification of changes or updates will be made using the email subscription newsletter.

6 This document is uncontrolled when printed. The most up-to-date version of the Notes will be published on the website. Printed copies are no longer available.
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 2000\(^7\) (including Amendment Regulations 2006\(^8\) and 2011\(^9\)) (IR(ME)R) 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. In these Notes the term ‘radiopharmaceuticals’ is often used.

1.4 Four sets of legislation have been made under the Medicines Act 1968\(^9\) and the European Communities Act 1972\(^10\) to establish a licensing system for the use of radiopharmaceuticals and sealed radioactive substances. These are the Medicines (Administration of Radioactive Substances) Regulations 1978\(^11\), the Medicines (Radioactive Substances) Order 1978\(^12\) and the Medicines (Administration of Radioactive Substances) Amendment Regulations 1995\(^13\) and 2006\(^14\). This legislation has been introduced to comply with the requirements of Article 5(a) of the European Council Directive 76/579/Euratom\(^15\) and its later revisions, 80/836/Euratom\(^16\), 84/467/Euratom\(^17\) and 96/29/Euratom\(^18\), on basic safety standards for health and protection against the dangers of ionising radiation. Following publication of European Council Directive 2013/59/Euratom\(^19\) on basic safety standards, UK regulations will be revised.

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 may need to report its concern to the MHRA or the DHSSPS(NI). Advice on reporting to these authorities is provided by the ARSAC Secretariat on a case-by-case basis.

1.7 Details of the legislation are provided below.


1.8 The Medicines (Administration of Radioactive Substances) Regulations 1978 (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 Medicines Act 1968.

**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, 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 96/29/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 Secretariat. ‘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 registered medical practitioner person within the meaning of the Interpretation Act 1978\(^{20}\) and the Medical Act 1983\(^{21}\).

(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 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 in accordance with the Code of Practice for Scientific Advisory Committees\(^{22}\), with a secretariat provided by Public Health England.

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 1978

1.16 The Medicines (Radioactive Substances) Order 1978\(^{12}\) 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 1978 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 1995

1.18 The Medicines (Administration of Radioactive Substances) Amendment Regulations 1995 amend the MARS Regulations 1978 and make various administrative changes including provision for:

(a) directions and notices to be given in writing;

(b) granting to those who already hold certificates of further certificates for particular descriptions or classes of radioactive substances;

(c) granting to those who already hold certificates of further certificates for particular patients;

(d) 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.

The Medicines (Administration of Radioactive Substances) Amendment Regulations 2006

1.19 The Medicines (Administration of Radioactive Substances) Amendment Regulations 2006 amend the MARS Regulations 1978 to provide that radioactive medicinal products may be administered by a person who is not a certificate holder in the absence of written directions, in specified circumstances, where the administration involves a medical exposure under IR(ME)R.

1.20 The Amendment Regulations 2006 make provision for persons who are operators under IR(ME)R to administer radioactive medicinal products. The operator must be acting in accordance with the relevant procedures and protocols under IR(ME)R. In addition, the operator must be acting under the authorisation of, or in accordance with guidelines issued by, a person who is a practitioner under IR(ME)R and also a certificate holder.
Section 2
Certificates

Who Should and Who Need Not Apply

2.1 Any doctor or dentist wishing to administer radiopharmaceuticals 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 radiopharmaceuticals 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 radiopharmaceuticals 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 radiopharmaceuticals as a minor part of their practice would not normally need to apply for a certificate. The MARS Regulations 1978\(^{11}\) allow such persons to act under the directions of a certificate holder. These directions must be made in writing\(^{19}\) except in specified circumstances, as detailed in the Amendment Regulations 2006\(^{14}\), where the administration involves a medical exposure under IR(ME)R. The employer should ensure that procedures are established to enable persons administering radiopharmaceuticals under the direction of a practitioner, to ascertain that the latter holds an appropriate certificate.

2.4 Such persons may continue to administer radiopharmaceuticals 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 radiopharmaceuticals 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 their own for the employer’s site. If no such person is available, radiopharmaceuticals 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 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, e.g. 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.

Issuing Authority and Validity

2.8 Certificates authorising the administration of radioactive medicinal products will be granted in accordance with the MARS Regulations 1978 by the health ministers advised by ARSAC. A certificate will be specific to the purpose, the site and the practitioner.

2.9 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, respectively, of these Notes.

2.10 If a practitioner, having a certificate to administer a particular radioactive medicinal product for a specific purpose, i.e. diagnosis, treatment or research, wishes to administer it for another purpose, they must apply for another certificate.

2.11 A certificate may be suspended, revoked or varied by the health ministers as set out in Regulation 6.

2.12 A certificate will normally be valid for five years.

2.13 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 medical physics expert (MPE). A further copy is retained by the Department of Health.

Requirements for Initial Applications for Diagnosis or Treatment

2.14 The information required to support an initial application for a certificate is outlined in Regulation 4. The application must contain the following particulars:

(a) 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 they propose to administer the radioactive medicinal products specified in the application;

(b) 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.
2.15 The certificate will be granted to the practitioner who is clinically responsible for the administration of the radioactive 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 MPE, the healthcare professional responsible locally for the provision of radioactive medicinal products, the scientist or other healthcare professional responsible for local scientific support and the radiation protection adviser (RPA).

2.16 The applicant must list and provide details of the radioactive medicinal products for which they wish 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 effective 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  
Centre for Radiation, Chemical and Environmental Hazards  
Public Health England  
Chilton, Didcot, Oxon OX11 0RQ

2.17 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 unnecessary 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.

2.18 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.

2.19 Application forms can be downloaded from the website, www.gov.uk/arsac. All applications must be submitted as hard copy by post and require original signatures of the applicant and supporting staff. The forms include sections on training and experience and this information should be completed in each application. Failure to do so may lead to delays in processing applications.

2.20 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 2.43 and 2.44 on urgent applications for particular patient requests). 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 ARSAC. A flow diagram indicating how initial applications are processed is provided in Appendix VI.

2.21 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.
for first-time applicants and additions applications (see Appendix IV); absence of dosimetry information for procedures not included in Appendix I, Part A; absence of information on multidisciplinary team involvement for complex or therapeutic procedures; incomplete information on supporting staff and an incomplete or inappropriately completed part C of the application form.

2.22 Advice specific to therapy applications can be found in Section 4.

2.23 Advice specific to research applications is given in Section 5.

2.24 Once an application has been submitted, further information about the equipment, facilities and scientific support available to the applicant can be supplied either by the applicant or by any of the part C signatories. Further enquiries about training or facilities may be made if necessary. If an application is referred back for additional information it cannot be considered further until an appropriate reply is received from the applicant or part C signatories as appropriate.

Qualifications and Experience of the Practitioner

2.25 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.

2.26 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 in Appendix IV, Part A.

2.27 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 in 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.

2.28 Appendix IV, Part B, provides additional information for applicants who wish to undertake diagnostic or research studies with positron emission tomography/computed tomography (PET/CT).

2.29 Appendix IV, Part C, provides information on training and experience required when new techniques are introduced and on the relationship between the certificate holder and others who work under the holder’s written directions.
Qualifications and Experience of Supporting Staff

2.30 Practitioners will normally be expected to collaborate with physicists and (if appropriate) radiopharmacists, and have available healthcare professionals (eg radiographers and technologists) with appropriate training and experience, who may or may not be under their direct control. Such staff will assist the practitioner:

(a) with undertaking clinical and non-clinical 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) with the radiation protection of patients;
(d) with the radiation protection of staff (including monitoring of staff and decontamination, as necessary);
(e) to account for the radioactive material;
(f) with the radiopharmaceutical formulation of the medicinal products.

2.31 Regulations require that employers must ensure that those treating patients by radiotherapy or administering radiopharmaceuticals have access to the services of one or more MPEs. An appropriate standard for this responsibility is at least six years’ experience in the relevant branch of medical physics and registration as a clinical scientist with the Health Care Professionals Council.23

2.32 The availability and proximity of the MPE should bear a direct relation to the radiation risk involved with the procedures listed in part B of the application. For example, an MPE for a diverse therapy service should be readily available and normally employed at the site listed in the application. An MPE for an application including low dose procedure(s) in a research laboratory could be offsite and at some distance from the site. The MPE should be satisfied with the local control arrangements for external sites.

Supporting Services

2.33 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.23 Factors to be considered 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.

2.34 Much of this information is requested in part C of the application form. In cases where radiopharmaceuticals are supplied from an offsite radiopharmacy only the local healthcare professional responsible for the delivery, receipt and safe storage of the radiopharmaceuticals should sign section C5 of the form to indicate that they are satisfied with the quality of the radiopharmaceuticals. Applications for certificates for the use of both sealed and unsealed...
sources may require signatures of two people, depending upon the experience of the healthcare professionals.

Renewal, Extension and Variation of Certificates

2.35 A certificate for diagnosis or treatment may be renewed in accordance with Regulation 5 of the MARS Regulations 1978 (as amended). 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.

2.36 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 undertake appropriate continuing medical education associated with the nuclear medicine procedures for which they are certified as part of the appraisal and revalidation processes and to confirm 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.

2.37 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.

2.38 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 should be included in the application.

2.39 Research certificates are valid for five years 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 recruitment is ongoing or if some of the originally specified investigations for individual subjects will fall outside the duration of the certificate. To request an extension to a research certificate, the certificate holder should write to the ARSAC Support Unit, detailing all the relevant information.

2.40 Further information about applying for a research certificate can be found in Section 5.

Changes of Premises or Appointment

2.41 All certificates relate to the appointment quoted in the application, and ARSAC should be informed promptly of any material change in these circumstances (e.g., retirement or change of post) as the certificate may need to be varied.

2.42 ARSAC should be notified of any changes to equipment and facilities. A single notification is appropriate where changes affect more than one certificate at a site.
Urgent Applications – Particular Patient Requests

2.43 In cases where the certificate held by a clinician or doctor is inappropriate for an administration they wish urgently to undertake, an application on behalf of a particular patient may, to save time, be submitted by fax or email to the ARSAC Support Unit using the particular patient request form. Advice about such applications, and other matters, can be sought from the ARSAC Support Unit.

2.44 Where such procedures are to be undertaken more than very occasionally, the certificate holder should apply for an addition to their diagnostic or therapy certificate.

2.45 Clinicians or doctors who do not hold a certificate cannot submit a particular patient request. 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 inappropriate.

Representations

2.46 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 them an opportunity to appear before a person appointed by the ministers or, if the applicant prefers, to make representations in writing.

2.47 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.

2.48 A period of not less than 28 days will be specified, within which an applicant must give notice that they wish 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.

2.49 If 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, 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

Routine Diagnostic Procedures

3.1 The advice of 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 I.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 unnecessary to inform 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 variation request should be made to ARSAC, giving the justification for the increased activity. If agreed, this should be included within written protocols.
3.9 The radiation dose estimates shown in Appendix I, Parts A and B, give the data which is currently accepted within the meaning of the MARS Regulations 1978\textsuperscript{11}.

**General Techniques for Dose Reduction**

3.10 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.

3.11 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.

3.12 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 lower dose should be selected.

3.13 Advice on the use of thyroid blocking agents is given in Section 8.

3.14 Software programs (eg resolution recovery) that improve image quality are now readily available. The use of such programs may allow for a reduction in the administered activity while maintaining the required levels of diagnostic information. Where available, such programs should be used and optimised in local protocols.

**Females and Males – Conception, Pregnancy and Breastfeeding**

3.15 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 breastfeeding are given in Section 7.

**Children and Young Persons**

3.16 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

Routine Therapeutic Procedures

4.1 The advice of ARSAC regarding certain well-established radioactive medicinal products for treatment purposes is contained in Appendix I, Parts C and D.

Applying for a Therapy Certificate

4.2 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.

4.3 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. The following information should also be provided:

(a) specific training and experience with the requested serial – this may take the form of teaching courses, clinical experience during training or experience gained under the mentorship of another ARSAC certificate holder either locally or at another site. The certificate holder’s name and location should be included as well as indicative numbers of cases and the applicant’s level of involvement;

(b) details of relevant multidisciplinary team meetings attended including details of start-up discussions for procedures new to the site;

(c) details of other medical and non-medical staff involved in treatment delivery for each serial;

(d) attendance at relevant training courses to include certificates and syllabus as appropriate.

4.4 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 applications, haematological applications or therapies requiring significant interventional radiological skills. The applicant should provide evidence of multidisciplinary collaboration in these cases.
4.5 Certificates for treatment purposes are normally issued only for radionuclide therapy products with marketing authorisation or for those products in which efficacy is proven. Other applications will be considered on a research basis and a research application should be submitted through the integrated research application system (IRAS) system. 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 2004. Guidance on the type of studies that will need authorisation, and information on how to apply, is available on the MHRA website, www.gov.uk/mhra. If applicants are in doubt about the appropriate procedure then they should contact the ARSAC Support Unit.

4.6 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.
Section 5

Research

Research Authorisations

5.1 As a guiding principle, ARSAC research authorisation must be obtained by the study sponsor for all research projects involving radiopharmaceuticals. A medical practitioner must apply for a research certificate at each site where the administrations and radiation exposure to subjects is additional to that involved in their routine diagnostic or therapeutic management.

5.2 More precisely, research in the context of the MARS Regulations 1978\(^{11}\) and the Medicines for Human Use (Clinical Trials) Regulations 2004 (as amended)\(^{24}\) 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 radiopharmaceuticals where the study does not come within the scope of the latter 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 for advice.

5.3 IR(ME)R 2000\(^{6}\) (as amended) addresses the exposure of individuals as part of biomedical and medical research. The principles of justification and optimisation are applied to research and IR(ME)R differentiates between those individuals where there is no direct medical benefit (eg healthy volunteers and some patients) 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.

Applying for a Research Certificate

5.4 The research application process is split into two parts – the study assessment and the individual certificate application, both of which require ARSAC authorisation.

5.5 A preliminary research assessment (PRA) form is automatically generated for new studies which involve the administration of radioactive medicinal products on the IRAS. The study sponsor should email the PRA form to the ARSAC Support Unit (to include any relevant patient information sheets or supplementary documentation), for all studies which include the administration of radioactive medicinal products to humans. Submissions to ARSAC should be made at the same time as ethical approval is sought. A study must receive confirmation of ARSAC approval prior to any individual certificates being issued.
5.6 An ARSAC certificate holder at a site wishing to administer radiopharmaceuticals in accordance with a specific research protocol involving additional radiation exposure above that incurred in the routine management of the patient at that site, should complete an application using parts A and C of the full ARSAC application form and the research certificate application (RCA) form from IRAS in lieu of part B. The certificate holder should indicate any changes in local practice from the study protocol electronically or by hand, eg difference in activity or number of standard of care administrations. This must be submitted in hard copy by post with original signatures to the ARSAC Support Unit.

5.7 ARSAC would not normally issue a certificate for a study to more than one medical practitioner at a site. In the case of studies which require different expertise (eg diagnostic and therapy serials) ARSAC will allow multiple medical practitioners to apply for the serials within the scope of their expertise.

5.8 Occasionally, the original parameters associated with a research study may change after a study has been approved. Examples include changes to the number of administrations, changes to the radiopharmaceuticals administered or changes to the study cohort. These changes constitute a substantial amendment to the study and must be made through IRAS. A summary of the amendment including a full justification for the variation should be submitted to ARSAC by letter or email when the amendment is submitted for ethical approval. In most circumstances an acknowledgement can be issued and a new certificate will not be necessary.

Activity Administered

5.9 The activity administered to individuals should be the minimum consistent with obtaining adequate information, especially for administrations to individuals 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.

5.10 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 ARSAC in its task of reviewing future applications, such information should be made available to it as soon as possible.

Selection of Subjects for Research Projects

5.11 When selecting subjects for a research study involving radiopharmaceuticals, the following general considerations should be taken into account:

(a) age;
(b) numbers;
(c) multiple studies;
(d) females;

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(e) workers occupationally exposed to ionising radiation;
(f) classified radiation workers;
(g) staff.

**Age**

5.12 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 group 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 years. If the study requires subjects below the age of 50 years then explicit justification for the age range required should be included within the application. For studies in subjects over 50 years then an upper age limit need not be stated for the purposes of the application for certification.

**Numbers**

5.13 The numbers of individuals participating in a research project should be restricted to the minimum necessary to obtain the information required. 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.

5.14 This is in keeping with ICRP Publication 103 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 use of the minimum exposure to radiation by the smallest number of subjects needed to achieve the desired result.

**Multiple studies**

5.15 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 where an annual dose constraint of 10 mSv from all research exposures (including those from non-nuclear medicine procedures) should be applied.

5.16 It is the responsibility of the investigator 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 the Department of Health publication, Records Management: NHS Code of Practice.

5.17 Investigators should always review the previous radiation exposure of the proposed participants. However, 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.

**Females**

5.18 The possibility of early pregnancy should always be borne in mind in connection with the use of females of childbearing potential as subjects.
5.19 Pregnant females and females who are breastfeeding 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.

5.20 Further information is given in Section 7.

**Workers occupationally exposed to ionising radiation**

5.21 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 to radiation at work.

**Classified radiation workers**

5.22 Radiation workers who are classified under the Ionising Radiations Regulations 1999 should not normally be accepted as volunteers in a research project.

**Staff**

5.23 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 coercion.

**Ethical Approval**

5.24 Every clinical research investigation involving the use of radiopharmaceuticals should be checked and approved by a research ethics committee as required by the research governance framework for the NHS. The sponsor should send the PRA form to the ARSAC Support Unit for study approval at the same time that the full application form is submitted to a research ethics committee through IRAS. In all instances, approval for the project as a whole will lie with the ethics committee.

5.25 The fact that an ARSAC certificate or approval for an amendment has been granted for a site (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 confirmation of approval from the appropriate research review bodies for that site.

5.26 Further information may be obtained through the Health Research Authority, www.hra.nhs.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 children, 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 response 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 in turn 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 a nuclear medicine procedure is deemed necessary for the clinical management of the child, it must be properly planned. 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 of the European Association of Nuclear Medicine (EANM). This is presented in Table 6.1. An update to this guidance was released in the form of a new paediatric dosage card in 2007 and further amended in 2014 to provide weight-independent scaling factors dependent on the class of investigation. This was supported by further guidance detailing scaling information for \(^{18}\)F-FDG PET imaging. ARSAC is of the view that this area requires further research as the new proposed method is complex and may not always result in adequate image quality.

6.7 It is recommended that for children or young persons, body weight should always be measured. With the exception of \(^{18}\)F-FDG, the adult administered activity should then be scaled down as shown in Table 6.1. This will produce an image quality and an imaging time comparable with that expected for adults by maintaining the same image count density. The resulting effective dose by weight when compared to an adult will be higher. For centres using \(^{18}\)F-FDG for paediatric patients, the most recent guidance from the EANM should be followed and the administered activity should be optimised locally based on equipment settings and clinical reporting preferences.

6.8 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.

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

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<th>Fraction of adult administered activity</th>
<th>Weight (kg)</th>
<th>Fraction of adult administered activity</th>
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<td>40</td>
<td>0.76</td>
<td>68</td>
<td>0.99</td>
</tr>
</tbody>
</table>
### Table 6.2 Recommended minimum administered activity for children

<table>
<thead>
<tr>
<th>Radiopharmaceutical</th>
<th>Investigation</th>
<th>Minimum activity (MBq)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{67}$Ga-citrate</td>
<td>Infection/inflammation imaging</td>
<td>10</td>
</tr>
<tr>
<td>$^{99m}$Tc-DTPA</td>
<td>Renal imaging</td>
<td>20</td>
</tr>
<tr>
<td>$^{99m}$Tc-DMSA(III)</td>
<td>Renal imaging</td>
<td>15</td>
</tr>
<tr>
<td>$^{99m}$Tc-MAG3</td>
<td>Renal imaging</td>
<td>15</td>
</tr>
<tr>
<td>$^{99m}$Tc-pertechnetate</td>
<td>Micturating cystogram</td>
<td>20</td>
</tr>
<tr>
<td>$^{99m}$Tc-phosphonates and phosphates</td>
<td>Bone imaging</td>
<td>40</td>
</tr>
<tr>
<td>$^{99m}$Tc-colloid</td>
<td>Liver/spleen imaging</td>
<td>15</td>
</tr>
<tr>
<td>$^{99m}$Tc-colloid</td>
<td>Bone marrow imaging</td>
<td>20</td>
</tr>
<tr>
<td>$^{99m}$Tc-denatured erythrocytes</td>
<td>Spleen imaging</td>
<td>20</td>
</tr>
<tr>
<td>$^{99m}$Tc-normal erythrocytes</td>
<td>Cardiac blood pool imaging</td>
<td>80</td>
</tr>
<tr>
<td>$^{99m}$Tc-pertechnetate</td>
<td>Cardiac first pass imaging</td>
<td>80</td>
</tr>
<tr>
<td>$^{99m}$Tc human albumin macroaggregates or microspheres</td>
<td>Lung perfusion imaging</td>
<td>10</td>
</tr>
<tr>
<td>$^{99m}$Tc-pertechnetate</td>
<td>Ectopic gastric mucosa imaging (Meckel’s)</td>
<td>20</td>
</tr>
<tr>
<td>$^{99m}$Tc-colloid</td>
<td>Gastric reflux imaging</td>
<td>10</td>
</tr>
<tr>
<td>$^{99m}$Tc exametazine</td>
<td>Cerebral blood flow imaging (CBF)</td>
<td>100</td>
</tr>
<tr>
<td>$^{99m}$Tc exametazine labelled leucocytes</td>
<td>Infection/inflammation imaging</td>
<td>40</td>
</tr>
<tr>
<td>$^{99m}$Tc-iminodiacetates</td>
<td>Functional biliary system imaging</td>
<td>20</td>
</tr>
<tr>
<td>$^{99m}$Tc-pertechnetate</td>
<td>Thyroid imaging</td>
<td>10</td>
</tr>
<tr>
<td>$^{123}$I-iodide</td>
<td>Thyroid imaging</td>
<td>3</td>
</tr>
<tr>
<td>$^{123}$I MIBG</td>
<td>Neuroectodermal tumour imaging</td>
<td>70</td>
</tr>
</tbody>
</table>

**Note**

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

---

**Environment, Specific Needs and Injection Process**

### 6.9 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 EANM website under each specific examination, [www.eanm.org](http://www.eanm.org).

**Imaging Technique**

### 6.10 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 a radioisotope bone scan, 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.
Sedation

6.11 A cooperative child will not normally require sedation or general anaesthetic. Sedation may be required for long examinations when movement should not occur. Before sedating the child, consideration should be given to the effect that sedation may have on function. This applies especially to SPECT studies, PET/CT and pinhole views of the hips in the young child.

6.12 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.

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 Breastfeeding

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 acquiring 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 the 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, in which the foetal dose is likely to be below 10 mGy, can continue to be undertaken, provided that the period is not overdue. For procedures resulting in higher foetal doses, exceeding 10 mGy, if pregnancy cannot be excluded then the procedure should only be undertaken during the first 10 days of the menstrual cycle.\textsuperscript{36}

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 foetus. Any female of childbearing potential undergoing procedures involving radiopharmaceuticals should therefore be asked whether she is or might be pregnant. A policy should be established on the age range of females involved (e.g. 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 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 foetus 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 Appendix I, Parts A and B, to help in assessing 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 foetal organs. The choice of a cut-off level of dose in deciding whether possible foetal irradiation needs to be considered in requesting or performing an investigation is an individual one, but a dose to the foetus 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 evidence suggests that the risk of an adverse effect (e.g., childhood cancer) from a dose of 1 mGy is about 1 in 17,000.

7.7 Further information regarding biological effects after prenatal irradiation has been published by the ICRP.

7.8 Specific instructions must be given to the mother of an infant in order to minimise irradiation to the latter.

Advice to Males

7.9 There is no evidence that pre-conceptual irradiation of males can cause any abnormality in their offspring. ARSAC does not consider that males who have received routine diagnostic administrations of radiopharmaceuticals need be given any advice concerning avoidance of conception.

7.10 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 $^{131}$I-iodide, $^{32}$P-phosphate or $^{89}$Sr-chloride to avoid fathering children for a period of four months. The period of four months is suggested as it is greater than the lifecycle of a sperm cell.

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

7.11 In some circumstances it will be necessary to advise females not to become pregnant for a period following the administration of long-lived radiopharmaceuticals.

7.12 The female patient should be advised to avoid pregnancy for a period following therapy administration as given in Table 7.1.

Table 7.1 Period following therapy administration for which female patients should be advised to avoid pregnancy

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

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.
7.13 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 foetal dose following maternal administration of radiopharmaceuticals with long effective half-lives, such as proteins labelled with $^{125}$I or $^{131}$I.

7.14 The foetal 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 $^{125}$I or 0.03 MBq of $^{131}$I. Consideration of the listed diagnostic serial 53b4iii (0.2 MBq $^{125}$I human albumin) has shown that this will decrease to below 0.1 MBq in 15 days: it is, therefore, unnecessary to issue any warning to delay pregnancy following this procedure.

7.15 Of the diagnostic investigations listed in Appendix I, Part A, only 53c6ii ($^{131}$I-iodide, thyroid metastases imaging) gives cause for advice to delay pregnancy. 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 Breastfeeding

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

7.17 Before administering a radiopharmaceutical to a female who is breastfeeding, 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 breastfeeding;

(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.

7.18 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.

7.19 Precautions should be taken to minimise the radiation dose to the infant (and to ensure that the effective 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) Breastfeeding 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 breastfeeding should be less than half of the annual natural background dose, and within the range of geographical variations in natural background, within the UK.

7.20 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 clearance or by using the expressed milk model. 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.

7.21 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 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 \( E \, \text{MBq} \) is the total activity estimated to be excreted subsequent to the sample and \( C \, \text{MBq ml}^{-1} \) is the radioactive concentration in the sample.

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

\[
H_{\text{inf}} = I_{\text{inf}} \times E
\]

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

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

7.24 Age-specific ingestion dose coefficients are given in ICRP Publication 72. For \(^{99m}\text{Tc}\) 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.

7.25 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 Notes. Precautions are recommended when patients have been administered more than 10 MBq of \(^{111}\text{In}\)-labelled white blood cells, 30 MBq of \(^{131}\text{I}\), 120 MBq of \(^{111}\text{In}\)-octreotide, 150 MBq of \(^{201}\text{Tl}\)-chloride, 200 MBq of \(^{67}\text{Ga}\)-citrate, or 800 MBq of \(^{99m}\text{Tc}\) myocardial perfusion agent. Precautions may also be necessary after administration of positron emitting radionuclides.
Table 7.2  Breastfeeding interruption times by radiopharmaceutical administered

<table>
<thead>
<tr>
<th>Radiopharmaceutical</th>
<th>Activity administered to mother (MBq)</th>
<th>Feeding interruption time[1] (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{32}$P-phosphate</td>
<td>Any</td>
<td>STOP</td>
</tr>
<tr>
<td>$^{51}$Cr EDTA</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>$^{67}$Ga-citrate</td>
<td>Any</td>
<td>STOP</td>
</tr>
<tr>
<td>$^{81m}$Kr gas</td>
<td>6000</td>
<td>0</td>
</tr>
<tr>
<td>$^{99m}$Tc-percotechnetate</td>
<td>80</td>
<td>24</td>
</tr>
<tr>
<td>$^{99m}$Tc-percotechnetate $^{99m}$Tc technegas</td>
<td>100 + 20</td>
<td>14</td>
</tr>
<tr>
<td>$^{99m}$Tc macroaggregates</td>
<td>80</td>
<td>12</td>
</tr>
<tr>
<td>$^{99m}$Tc macroaggregates $^{99m}$Tc technegas</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$^{99m}$Tc normal erythrocytes[2]</td>
<td>800</td>
<td>18</td>
</tr>
<tr>
<td>$^{99m}$Tc DTPA</td>
<td>800</td>
<td>0</td>
</tr>
<tr>
<td>$^{99m}$Tc DMSA</td>
<td>80</td>
<td>0</td>
</tr>
<tr>
<td>$^{99m}$Tc-iminodiacetates</td>
<td>150</td>
<td>0</td>
</tr>
<tr>
<td>$^{99m}$Tc exametazine</td>
<td>500</td>
<td>0</td>
</tr>
<tr>
<td>$^{99m}$Tc MAG3</td>
<td>200</td>
<td>0</td>
</tr>
<tr>
<td>$^{99m}$Tc sestamibi</td>
<td>1000</td>
<td>0</td>
</tr>
<tr>
<td>$^{99m}$Tc-colloid</td>
<td>80</td>
<td>0</td>
</tr>
<tr>
<td>$^{99m}$Tc phosphate compounds</td>
<td>600</td>
<td>0</td>
</tr>
<tr>
<td>$^{111}$In leucocytes</td>
<td>10[3]</td>
<td>0</td>
</tr>
<tr>
<td>$^{123}$I[4]-iodide</td>
<td>20</td>
<td>27</td>
</tr>
<tr>
<td>$^{123}$I[4] MIBG</td>
<td>400</td>
<td>21</td>
</tr>
<tr>
<td>$^{125}$I human albumin</td>
<td>Any</td>
<td>STOP</td>
</tr>
<tr>
<td>$^{131}$I-iodide</td>
<td>Any</td>
<td>STOP</td>
</tr>
<tr>
<td>$^{201}$TI-TI`</td>
<td>80</td>
<td>0</td>
</tr>
</tbody>
</table>

Notes

[1] Feeding may be restarted immediately after the stated time has elapsed since administration of the radionuclide. The interruption time advised is calculated 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. Breastfeeding 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.

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

[3] It is recommended that the activity of $^{111}$In leucocytes administered to a nursing mother should not exceed 10 MBq.

[4] $^{123}$I should not be administered to breastfeeding females unless it is pure (containing no $^{124}$I or $^{125}$I).
Section 8

Thyroid Blocking

Use of Blocking Agents

8.1 Blocking the uptake of radionuclides by the thyroid is used to reduce radiation dose\(^\text{43}\). 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 most radiopharmaceuticals containing \(^{99m}\text{Tc}\).

Radioiodine

8.3 When \(^{123}\text{I}\), \(^{125}\text{I}\) or \(^{131}\text{I}\) is administered as iodide, iodine-labelled compounds (such as iodoxal albumin which metabolises 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 irradiation of the thyroid.

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:

\[\begin{array}{c}
^{123}\text{I} & 15 \text{ MBq} \\
^{125}\text{I} & 0.2 \text{ MBq} \\
^{131}\text{I} & 0.1 \text{ MBq}
\end{array}\]

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
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 until the estimated radioiodine levels have fallen to the levels shown above. It should be noted that currently potassium perchlorate is not licensed in the UK. Sodium perchlorate (2 ml vials containing 200 mg for intravenous use) may also be 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 advice given in relation to the use of thyroid blocking in the event of a nuclear accident, ie

- children of 3 to 12 years: 50% of adult dose
- children of 1 month to 3 years: 25% of adult dose
- neonates (birth to under 1 month): 12.5% 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.
References

4. Medical Research Council (Great Britain) Responsibility in investigations on human participants and material and on personal information. London: MRC, 1992


Royal College of Radiologists. Safe Sedation, Analgesia and Anaesthesia within the Radiology Department. London: RCR, 2003, [www.rcr.ac.uk](http://www.rcr.ac.uk)


Health Protection Agency, Royal College of Radiologists, College of Radiographers. Protection of Pregnant Patients during Diagnostic Medical Exposures to Ionising Radiation. [Doc HPA, RCE-9, March 2009](http://www.rcr.ac.uk)


International Commission on Radiological Protection. Age-dependent Doses to the Members of the Public from Intake of Radionuclides Part 5, Complications of Ingestion and Inhalation Coefficients. ICRP Publication 72. *Ann ICRP*, 26, No. 1, 1996


Appendix I

Routine Procedures, Activities and Doses

Introduction

I.1 The data provided have been prepared with the advice of ARSAC for the convenience of the applicant in making an application for a certificate (see Section 2) and thereafter of 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

I.2 The nature and the diagnostic reference level of particular radiopharmaceuticals, which 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. 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.

I.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 MARS Regulations 1978 if applicants refer to appropriate procedures by serial number (see Parts A–D) or functional groups (Part E) wherever possible.

I.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 ARSAC as to the maximum activity per procedure and any other relevant advice. When considering such applications, 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 radiopharmaceuticals.

Toxicological and Pharmaceutical Safety

I.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 outside the terms of their marketing authorisation and pharmaceutical safety.

**Numbering System**

I.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**

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

**Diagnostic reference levels (DRLs)**

I.8 The Medical Exposure Directive 97/43/Euratom requires member states to promote the establishment and use of DRLs for diagnostic purposes. The Ionising Radiation (Medical Exposure) Regulations 2000 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’.

I.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 I.10).

I.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, e.g. patients who are very much overweight or unable to tolerate standard acquisition times. 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 practicable while acquiring the desired clinical information.

* The letter is used to differentiate between the various radioisotopes of the same element, e.g. 53a = $^{123}$I, 53b = $^{125}$I. In some cases, more than one letter may be used to denote the same radioisotope, e.g. $^{99m}$Tc is denoted by 43a and 43w.
† The Arabic number is used to differentiate between chemical forms.
‡ The Roman number is used to specify the investigation.
I.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.

I.12 Persistent administration of activities larger than those contained in Parts A and B without prior approval could lead ARSAC to advise the health ministers to suspend, vary or revoke the certificate as appropriate. 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 3.4 to 3.8.

I.13 Applications can be made for the 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.

I.14 The activity administered must be recorded in the patient’s medical or departmental records.

**Effective dose (ED)**

I.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.

I.16 The effective doses given in Parts A and B have been calculated using the methodology described in ICRP Publication 128\(^4\), using weighting factors from ICRP Publication 60\(^5\). Revised weighting factors have been published in ICRP Publication 103\(^6\), but have yet to be applied to the ICRP models.

I.17 The effective doses 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.

I.18 The effective dose listed in Parts A and B arises from the corresponding diagnostic reference level. Information on radiation doses to patients from radiopharmaceuticals is provided in ICRP Publication 53\(^7\) and its addendums\(^8\)-\(^11\) and summarised in ICRP Publication 128\(^7\). For those procedures not covered in ICRP publications, other published dosimetry estimates have been used\(^12\)-\(^16\).

I.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 by the ICRP.

I.20 Appendix II gives further information on calculating doses.
**Estimated dose to the uterus**

I.21 Estimates of the dose to the uterus as a guide to the dose to the foetus are provided to help clinicians decide whether an 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 ICRP\(^4\). It should be noted that these figures do not include a component of dose from the cross-placental transfer of radiopharmaceuticals.

**Training requirements**

I.22 Please refer to Appendix IV for details of training requirements relating to applications forserials in Parts A–E.
### Part A: Diagnostic Procedures – Adult Patients

<table>
<thead>
<tr>
<th>Serial</th>
<th>Radio- nuclide</th>
<th>Chemical form</th>
<th>Investigation</th>
<th>Route of admin</th>
<th>DRL (MBq)</th>
<th>ED (mSv)</th>
<th>Dose to uterus (mGy)</th>
<th>Functional group</th>
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### Part A: Diagnostic Procedures – Adult Patients (continued)

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<td>Thyroid metastases imaging (after ablation)</td>
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<td>2.6</td>
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<td>Human albumin</td>
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<td>Parathyroid imaging</td>
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<td>80</td>
<td>11.2</td>
<td>4.0</td>
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**Notes**

1. With the thyroid blocked.
2. The activity should be increased in order to give a retained activity of approximately 10 MBq at the time of surgery if probe studies, with or without imaging, are to be undertaken on the day following administration.
3. Effective dose based on 18 hours from injection to surgery.
4. 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.
5. Effective dose calculated without contribution from thyroid.
6. Activities of $^{131}$I greater than 30 MBq should be considered as therapy administration for radiation protection purposes.
### Part B: Diagnostic Procedures – Positron Emission Tomography

<table>
<thead>
<tr>
<th>Serial</th>
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<th>Chemical form</th>
<th>Investigation</th>
<th>Route of admin</th>
<th>DRL (MBq)</th>
<th>ED (mSv)</th>
<th>Dose to uterus (mGy)</th>
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<tbody>
<tr>
<td>9a21i</td>
<td>$^{18}$F</td>
<td>FDG</td>
<td>Whole body tumour imaging</td>
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<td>$^{18}$F</td>
<td>FDG</td>
<td>Brain tumour imaging</td>
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<td>250</td>
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<tr>
<td>9a21iv</td>
<td>$^{18}$F</td>
<td>FDG</td>
<td>Infection/inflammation</td>
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<td>FDG</td>
<td>Differential diagnosis of dementia</td>
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<td>4.5</td>
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<td>$^{18}$F</td>
<td>FDG</td>
<td>Focal epilepsy</td>
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<td>$^{18}$F</td>
<td>FDG</td>
<td>Myocardial imaging</td>
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<td>Fluoride</td>
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Part C: Therapeutic Procedures with Unsealed Sources

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<th>For treatment of</th>
<th>Route of admin</th>
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<td>OC2</td>
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<td>Iodide</td>
<td>Thyrotoxicosis</td>
<td>IV or oral</td>
</tr>
<tr>
<td>OC3</td>
<td>$^{131}$I</td>
<td>Iodide</td>
<td>Non-toxic goitre</td>
<td>IV or oral</td>
</tr>
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<td>OC4</td>
<td>$^{131}$I</td>
<td>Iodide</td>
<td>Carcinoma of thyroid</td>
<td>IV or oral</td>
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<tr>
<td>OC5</td>
<td>$^{32}$P</td>
<td>Phosphate</td>
<td>Polycythemia vera and related disorders</td>
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<tr>
<td>OC6</td>
<td>$^{90}$Y</td>
<td>Colloid</td>
<td>Arthritic conditions</td>
<td>Intra-articular</td>
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<tr>
<td>OC8</td>
<td>$^{166}$Er</td>
<td>Colloid</td>
<td>Arthritic conditions</td>
<td>Intra-articular</td>
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<tr>
<td>OC9</td>
<td>$^{89}$Sr</td>
<td>Chloride</td>
<td>Bone metastases</td>
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<td>OC10</td>
<td>$^{131}$I</td>
<td>MIBG</td>
<td>Malignant disease</td>
<td>IV</td>
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<tr>
<td>OC21</td>
<td>$^{186}$Re</td>
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<td>Arthritic conditions</td>
<td>Intra-articular</td>
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<tr>
<td>OC35</td>
<td>$^{90}$Y</td>
<td>Microspheres</td>
<td>Hepatic malignancy</td>
<td>Intra-arterial</td>
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<tr>
<td>OC38</td>
<td>$^{153}$Sm</td>
<td>EDTMP</td>
<td>Bone metastases</td>
<td>IV</td>
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<tr>
<td>OC39</td>
<td>$^{186}$Re</td>
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<td>Bone metastases</td>
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<tr>
<td>OC53</td>
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<td>Ibritumomab tiuxetan (Zevalin)</td>
<td>Non-Hodgkins lymphoma</td>
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<tr>
<td>OC54</td>
<td>$^{223}$Ra</td>
<td>Dichloride</td>
<td>Bone metastases in castration resistant prostate cancer</td>
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<tr>
<td>OC56</td>
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<td>DOTATATE</td>
<td>Neuroendocrine tumours</td>
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<tr>
<td>OC57</td>
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<td>DOTATATE</td>
<td>Neuroendocrine tumours</td>
<td>IV</td>
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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

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<tr>
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<td>Malignant disease</td>
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<td>OT23</td>
<td>$^{137}$Cs</td>
<td>Appliances</td>
<td>Malignant disease</td>
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<td>OT24</td>
<td>$^{90}$Sr</td>
<td>Appliances</td>
<td>Eye diseases</td>
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<tr>
<td>OT25</td>
<td>$^{192}$Ir</td>
<td>Wire/appliances</td>
<td>Malignant disease</td>
</tr>
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<td>OT29</td>
<td>$^{125}$I</td>
<td>Seeds</td>
<td>Malignant disease</td>
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<td>OT30</td>
<td>$^{106}$Ru</td>
<td>Eye plaques</td>
<td>Eye diseases</td>
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</table>

**Note**
The target volume dose and dose rate are a matter for clinical judgement.
Part E: Functional Groups

1.23 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.

1.24 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 their 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.

1.25 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.

1.26 In some cases, certificate holders may be asked for further information regarding their training and experience before this facility is granted.

1.27 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.

1.28 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.
### Imaging groups

#### Group 1 I – Cardiac

<table>
<thead>
<tr>
<th>Code</th>
<th>Isotope</th>
<th>Agent</th>
<th>Imaging Type</th>
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<tbody>
<tr>
<td>43a1xvi</td>
<td>$^{99m}$Tc</td>
<td>Pertechnetate</td>
<td>First pass blood flow imaging</td>
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<td>43a2vii</td>
<td>$^{99m}$Tc</td>
<td>Human albumin</td>
<td>Cardiac blood pool imaging</td>
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<td>43a10iv</td>
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<td>Normal erythrocytes</td>
<td>Cardiac blood pool imaging (MUGA)</td>
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<td>Sestamibi</td>
<td>Myocardial imaging</td>
</tr>
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<td>43w46v</td>
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<td>Tetrofosmin</td>
<td>Myocardial imaging</td>
</tr>
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<td>53a5iv</td>
<td>$^{123}$I</td>
<td>MIBG</td>
<td>Sympathetic innervation imaging of the heart</td>
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<tr>
<td>81a1iv</td>
<td>$^{201}$Tl</td>
<td>Thallous chloride</td>
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#### Group 2 I – Vascular

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<tr>
<td>43a7xvii</td>
<td>$^{99m}$Tc</td>
<td>Colloid</td>
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#### Group 3 I – Lung

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<td>Gas</td>
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<td>Human albumin macroaggregates or microspheres</td>
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<td>Human albumin macroaggregates or microspheres</td>
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#### Group 5 I – Bone/joint

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<td>Colloid</td>
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#### Group 6 I – Gastrointestinal

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<td>Salivary gland imaging</td>
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<td>Pertechnetate</td>
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<tr>
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<td>$^{99m}$Tc</td>
<td>Colloid</td>
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<td>Oesophageal transit and reflux</td>
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<td>43a10iii</td>
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<td>43a11i</td>
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<td>Non-absorbable compounds</td>
<td>Gastric emptying</td>
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### Imaging groups (continued)

#### Group 7 I – Hepatobiliary

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#### Group 8 I – Genito-urinary

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<td>Renal imaging/renography</td>
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#### Group 9 I – Infection/inflammation

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<td>Gallium citrate</td>
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#### Group 10 I – Haematology

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#### Group 11 I – Endocrine

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<tbody>
<tr>
<td>43a1ii</td>
<td>$^{99m}$Tc</td>
<td>Pertechnetate</td>
<td>Thyroid imaging</td>
</tr>
<tr>
<td>43a15i</td>
<td>$^{99m}$Tc</td>
<td>Sestamibi</td>
<td>Parathyroid imaging</td>
</tr>
<tr>
<td>53a1ii</td>
<td>$^{123}$I</td>
<td>Iodide</td>
<td>Thyroid imaging</td>
</tr>
<tr>
<td>81a1vi</td>
<td>$^{201}$Tl</td>
<td>Thallous chloride</td>
<td>Parathyroid imaging</td>
</tr>
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</table>

#### Group 13 I – Lacrimal

<table>
<thead>
<tr>
<th>Code</th>
<th>Radionuclide</th>
<th>Isotope</th>
<th>Imaging procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>43a7vi</td>
<td>$^{99m}$Tc</td>
<td>Colloid</td>
<td>Lacrimal drainage</td>
</tr>
</tbody>
</table>

#### Group 14 I – Tumour

<table>
<thead>
<tr>
<th>Code</th>
<th>Radionuclide</th>
<th>Isotope</th>
<th>Imaging procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>43a6i</td>
<td>$^{99m}$Tc</td>
<td>DMSA(V)</td>
<td>Tumour imaging</td>
</tr>
<tr>
<td>43a15iv</td>
<td>$^{99m}$Tc</td>
<td>Sestamibi</td>
<td>Non-specific tumour imaging</td>
</tr>
<tr>
<td>43a15vi</td>
<td>$^{99m}$Tc</td>
<td>Sestamibi</td>
<td>Breast imaging</td>
</tr>
<tr>
<td>49a6i</td>
<td>$^{111}$In</td>
<td>Pentetreotide</td>
<td>Somatostatin receptor imaging</td>
</tr>
<tr>
<td>53a1iii</td>
<td>$^{123}$I</td>
<td>Iodide</td>
<td>Thyroid metastases imaging (after ablation)</td>
</tr>
<tr>
<td>53a5iii</td>
<td>$^{123}$I</td>
<td>MIBG</td>
<td>Neuroectodermal tumour imaging</td>
</tr>
<tr>
<td>53c5ii</td>
<td>$^{131}$I</td>
<td>Iodide</td>
<td>Thyroid metastases imaging (after ablation)</td>
</tr>
</tbody>
</table>

#### Group 15 I – Sentinel node

<table>
<thead>
<tr>
<th>Code</th>
<th>Radionuclide</th>
<th>Isotope</th>
<th>Imaging procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>43a7xi</td>
<td>$^{99m}$Tc</td>
<td>Colloid</td>
<td>Sentinel node (breast) imaging</td>
</tr>
<tr>
<td>43a7xiii</td>
<td>$^{99m}$Tc</td>
<td>Colloid</td>
<td>Sentinel node (melanoma) imaging</td>
</tr>
</tbody>
</table>
### Non-imaging groups

#### Group 20 NI – Absorption

| 34a3 | $^{75}$Se | 23-seleno-25-homo-tauro-cholate (SeHCAT) | Bile salt absorption |

#### 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 |
| 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

| 6a1 | $^{14}$C | Glycocholic acid | Breath tests |
| 6a50 | $^{15}$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 |
References


15. NANOCOLL Summary of Product Characteristics

16. LeukoScan Summary of Product Characteristics
Appendix II

Calculating the Radiation Dose

II.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 Medicine\(^1\). 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:

\[
D = \bar{A} \times S
\]

(1)

II.2 Here \(\bar{A}\) 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. One becquerel is one disintegration per second, so the unit of Bq s is simply one disintegration and, with this unit, \(\bar{A}\) 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, \(\mu\)Gy (Bq s\(^{-1}\)) or \(\mu\)Gy (MBq h\(^{-1}\)). The term \(\bar{A}\) must be estimated from biokinetic data concerning the particular radiopharmaceutical 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

II.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 the 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 simulation\(^2\). 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 Education\(^3\).

Cumulated Activity

II.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, \(\bar{A}\), typically in units of MBq h.

II.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:

\[
\bar{A} = A_0 \times F_s \times 1.44 \times t_{(\text{eff})}
\]

(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:

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

II.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

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

$$D_{st} = \tilde{A}_s \times S_{st}$$  \hspace{1cm} (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 summing the doses due to all possible source organs:

$$D_t = \Sigma \tilde{A}_s \times S_{st}$$  \hspace{1cm} (5)

Equivalent Dose

II.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

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

$$D_{\text{eff}} = \Sigma w_t \times D_t$$  \hspace{1cm} (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 given in Table II.1.

II.10 For all commonly used radiopharmaceuticals the above calculations have been completed using available biological data and results have been compiled by the ICRP. In new situations it is possible to draw upon analogies to the published data, or to carry out a new calculation using the MIRD scheme as a basis.
Table II.1 Tissue weighting factors

<table>
<thead>
<tr>
<th>Organ/tissue</th>
<th>Weighting factor ($w_T$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gonads</td>
<td>0.20</td>
</tr>
<tr>
<td>Red bone marrow</td>
<td>0.12</td>
</tr>
<tr>
<td>Colon</td>
<td>0.12</td>
</tr>
<tr>
<td>Lungs</td>
<td>0.12</td>
</tr>
<tr>
<td>Stomach</td>
<td>0.12</td>
</tr>
<tr>
<td>Bladder</td>
<td>0.05</td>
</tr>
<tr>
<td>Breast</td>
<td>0.05</td>
</tr>
<tr>
<td>Liver</td>
<td>0.05</td>
</tr>
<tr>
<td>Oesophagus</td>
<td>0.05</td>
</tr>
<tr>
<td>Thyroid</td>
<td>0.05</td>
</tr>
<tr>
<td>Skin</td>
<td>0.01</td>
</tr>
<tr>
<td>Bone surfaces</td>
<td>0.01</td>
</tr>
<tr>
<td>Remainder</td>
<td>0.05</td>
</tr>
<tr>
<td>TOTAL</td>
<td>1.00</td>
</tr>
</tbody>
</table>

II.11 The MIRDOSE software\(^3\) 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.

II.12 The uncertainties in estimation of biokinetic and physical data indicate an inaccuracy of at least 10% (probably much worse).

Dose to Children

II.13 Doses to children can be calculated using $S$-factors determined for an appropriately sized anatomical phantom. ICRP publications give results for one, five, ten 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.

References

Appendix III

Sample Size and Power Calculations

III.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 probability\(^1\). 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 1 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.

III.2 The probability (\(\alpha\)) of a type 1 error is obtained directly from the statistical results, eg a result quoted with a probability value of \(p = 0.05\) means that there is less than a 5% chance of making a type 1 error. However, the probability (\(\beta\)) of a type II error depends on a variety of factors, the most important of which is sample size.

III.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.

III.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 or 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 (\(\delta\)), and the reader is referred to a number of texts on statistical methods\(^2\)\(^-\)\(^5\) for a more thorough analysis.

III.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.
III.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.

III.7 Applicants are recommended to seek appropriate statistical advice on the planning of research studies.

References

5. Lowe D. *Planning for Medical Research*. Wiltshire: Anthony Rowe, 1993
Appendix IV

Training and Experience

Introduction

IV.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.

IV.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 (RCP) Nuclear Medicine Training Programme or the Royal College of Radiologists (RCR) Radionuclide Radiology Subspecialty Training Programme.

IV.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.

IV.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

IV.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*

IV.6 The curriculum outlined in Table IV.1 would be that required for those wishing to provide a full nuclear medicine service. Holders of a CCT – certificate of completion of training – or CESR(CP) – certificate of eligibility for specialist registration (combined programme) – 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*

IV.7 Sections A.1.7, A.1.8, A.2.9, 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 Subspecialty Training Programme.
**Diagnostic non-imaging service**

**IV.8** Sections A.1.7, A.1.8, A.2.3, A.2.4, A.2.5, A.2.6, A.2.8, A.2.10, A.2.11, A.3.2, A.3.4, A.4.3 and A.5.2 can be omitted from the full curriculum.

**Therapy service**

**IV.9** Sections A.2.3, A.2.4, A.2.5, A.2.6, A.2.10, A.2.11, 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**

**IV.10** 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.

**IV.11** The time taken to cover the areas indicated in Table IV.1 will vary depending on the scope of the service to be offered.

**Requirements for practical experience**

**IV.12** 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.

**IV.13** As a guide, applicants should have experience of supervising and reporting procedures consistent with the curriculum of the European Board of Nuclear Medicine (EBNM) and the Joint Royal Colleges of Physicians Training Board (JRCPTB), 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.

**IV.14** 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 EBNM and the JRCPTB offer a useful guide.

**IV.15** 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.
### Table IV.1 Full nuclear medicine service curriculum

#### A.1 Fundamental physics of radionuclides

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<thead>
<tr>
<th>Section</th>
<th>Sub-section</th>
<th>Content</th>
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<tbody>
<tr>
<td>A.1.1</td>
<td>Atomic structure</td>
<td>Mass, atomic and neutron number, energy levels – nuclear and electronic</td>
</tr>
<tr>
<td>A.1.2</td>
<td>Radioactivity</td>
<td>Radionuclides, units of radioactivity, specific activity, physical half-life, decay constant, Poisson (count) statistics</td>
</tr>
<tr>
<td>A.1.3</td>
<td>Radioactive decay</td>
<td>Mechanism of alpha, beta and gamma emission, electron capture and X-ray emission, isomeric transition, internal conversion, Auger electrons, positron emission and annihilation</td>
</tr>
<tr>
<td>A.1.4</td>
<td>Properties of radiation</td>
<td>Excitation and ionisation, attenuation of X-rays and gamma rays, scattering and absorption, bremsstrahlung radiation</td>
</tr>
<tr>
<td>A.1.5</td>
<td>Radionuclide production</td>
<td>Production methods, isotope generators, cyclotron and nuclear reactors</td>
</tr>
<tr>
<td>A.1.6</td>
<td>Radiation hazards and dosimetry</td>
<td>Biological effects of radiation, risks and benefits of radiation, cellular radiobiology, biological and effective half-lives, absorbed dose, equivalent dose, effective dose and their units, application of MIRD concepts for calculating whole body, organ and tumour doses</td>
</tr>
<tr>
<td>A.1.7</td>
<td>Radiobiology aspects for therapy</td>
<td>Uptake ratios, cell cycles, cell kill, total lethal dose, radiosensitisation, tissue homogeneity</td>
</tr>
<tr>
<td>A.1.8</td>
<td>Dosimetry for therapy</td>
<td>Dose rate, fractionation, biological effective dose, dose volume histogram, tumour control probability, microdosimetry – residence and clearance, mass estimations</td>
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</table>

#### A.2 Principles of radiation detection, instrumentation and equipment

<table>
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<th>Section</th>
<th>Sub-section</th>
<th>Content</th>
</tr>
</thead>
<tbody>
<tr>
<td>A.2.1</td>
<td>Detection of radiation</td>
<td>Geiger-Müller detectors, proportional counters and ionisation chambers, scintillation and solid state detectors, spatial discrimination, collimators, basic design and function, energy discrimination, multichannel analysers and pulse height analysers, temporal discrimination, count-rate (dead-time) effects and corrections</td>
</tr>
</tbody>
</table>
Table IV.1  Full nuclear medicine service curriculum (continued)

| A.2.2 Detection systems – general | Radionuclide assay calibrators  
| | QA programmes and QC testing for radionuclide calibrators, and requirements for traceability  
| | Personal and Environmental contamination monitors  
| | Personal whole body and extremity dosimeters and dose rate meters  
| | Gamma sample counters; counting geometry and establishing protocols for counting  
| | External probe systems including intra-operative probes |
| A.2.3 Detection systems – gamma camera | Gamma camera detectors, camera systems and associated equipment  
| | Construction and function of main components  
| | Care of scintillation crystals  
| | Principles of collimation, and main designs  
| | Output signals – X and Y position signals, Z energy signal  
| | Digitisation of event data, formation of digital images and optimal selection of discrete matrices |
| | Spatial resolution, information density and noise  
| | Energy resolution  
| | Energy, linearity and uniformity (sensitivity) corrections  
| | Anatomical markers  
| | Static, dynamic, ECG-gated and scanned (whole body) imaging  
| | Planar quantification of radiopharmaceutical uptake, distribution and kinetics  
| | Image processing techniques, region of interest analysis and time–activity curve generation  
| | Techniques for background correction, motion correction, attenuation correction, scatter correction and partial volume correction  
| | QA programmes and QC testing for planar gamma camera imaging |
| A.2.4 Associated electronic equipment | Photomultiplier tubes and photodiodes  
| | Power supplies (high and low voltage) and amplifiers  
| | Analogue to digital conversion |
| A.2.5 Single photon emission computed tomography (SPECT) | Principles of single photon emission computed tomography  
| | Requirements for performing SPECT on a gamma camera system  
| | Centre of rotation correction  
| | Energy, linearity and uniformity (sensitivity) corrections  
| | SPECT/CT – appropriate CT protocols, registration and fusion of SPECT and CT data  
| | Reconstruction of projection datasets  
| | Filtered back projection and iterative reconstruction techniques  
| | Attenuation correction, scatter correction and partial volume correction  
| | Algorithms for reconstruction with resolution recovery  
| | SPECT quantification of radiopharmaceutical uptake, distribution and kinetics  
| | Acceptance testing, QA programmes and QC testing for SPECT and SPECT/CT systems |
| A.2.6 Image formation and quality | Image quality – noise, contrast resolution and spatial resolution  
| | Image artefacts  
| | Optimisation of image quality and radiation dose  
| | Optimisation of image display, including windowing, thresholding, saturation and the use of grayscale and colour lookup tables  
| | Acceptance testing, QA programmes and QC testing of display devices  
| | Administered activity and DRLs  
| | Investigation time  
| | Counting statistics and ‘information density’  
| | Choice of collimator (design and specifications – energy range, sensitivity and resolution)  
| | Acquisition protocols for dynamic study (spatial and temporal resolution)  
| | Acquisition protocols for SPECT (collimation, angular sampling, image matrix and projection time) |
| A.2.7 Analysis of data | Manipulation of data  
Image processing techniques, region of interest analysis and time–activity curve generation  
Correction techniques, background correction, decay correction and motion correction  
Quantification of uptake, retention, clearance and distribution  
Kinetic analysis, compartmental analysis and deconvolution  
Algorithms  
Physiological basis of models |
|---|---|
| A.2.8 Computing | Electronic image data storage, native and standard file formats (Interfile, DICOM)  
Structure of digital images and determination of image file sizes  
Anonymisation of image data  
Archiving of image data including RIS, PACS and VNA  
Major considerations regarding processing and review systems – hardware, performance and operating systems  
Image processing applications software  
Computing for tomography, requirements for data reconstruction and corrections  
Fusion, registration and visualisation of tomographic image datasets  
Acceptance testing and QA of processing and review systems |
| A.2.9 Therapy equipment | Design safety  
Control of administration including automated infusion devices  
Management of radioactive waste from administration and the patient |
| A.2.10 Positron emission tomography (required for PET certificates) | Principles of tomography  
Principles of positron emission tomography  
Design of PET/CT systems – PET detectors, detector block architecture and performance  
Time of flight (TOF)  
Noise equivalent count rate (NECR) and optimised data acquisition protocols  
PET image formation, sinograms and data blocks, from 2D to 3D geometries  
PET image reconstruction, FBP and iterative reconstruction techniques  
PET/CT – appropriate CT protocols, registration and fusion of PET and CT data  
Use of CT for attenuation correction and anatomical fusion, CT artefacts and use of CT contrast  
Reconstruction with CTAC and scatter correction  
Quantification – requirements for calibration of PET systems  
PET quantification of radiopharmaceutical uptake, distribution and kinetics and SUV analysis  
Acceptance testing, QA programmes and QC testing for PET/CT  
QA and standardisation of protocols for clinical trials imaging |
| A.2.11 Computed tomography (required for certificates including SPECT/CT or PET/CT) | Construction, function and operation of a contemporary multislice CT scanner  
CT image reconstruction, FBP and iterative reconstruction techniques  
Factors controlling CT image quality  
Factors controlling CT radiation dose to patients  
Optimising CT radiation dose to patients  
Dose metrics for CT – DAP, DLP, CT dose indices (CTDI), effective dose, local and national DRLS and dose investigation levels (DIL)  
Radiation safety in CT  
Acceptance testing, QA programmes and QC testing for CT |
| A.3 Calibration techniques |
| A.3.1 Preparation of calibration sources and phantoms | Preparing calibration sources and phantoms |
Table IV.1  Full nuclear medicine service curriculum (continued)

<table>
<thead>
<tr>
<th>Section</th>
<th>Description</th>
</tr>
</thead>
<tbody>
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<td>A.3.2</td>
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<tr>
<td>A.3.3</td>
<td>Routine quality control checks</td>
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<td>A.3.4</td>
<td>Calibration of therapy sources</td>
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<td>A.4</td>
<td>Radiopharmaceuticals</td>
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<td>A.4.1</td>
<td>Chemistry of relevant radiopharmaceuticals</td>
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<td>A.4.2</td>
<td>Tracer principles and techniques</td>
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<td>A.4.3</td>
<td>Preparation of radiopharmaceuticals</td>
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<td>Generators</td>
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<td>A.5</td>
<td>Management and radiation protection of the patient</td>
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<tr>
<td>A.5.1</td>
<td>Patient selection</td>
</tr>
</tbody>
</table>
Table IV.1 Full nuclear medicine service curriculum (continued)

A.5.2 Therapy aspects
Planning of investigations including the selection of appropriate tests and imaging techniques for the diagnosis of malignant disease
Formal consent for therapy administrations
Interaction with other pharmaceuticals, foods and clinical investigations
Criteria for discharge of the inpatient
Radiation safety issues in public areas, the workplace 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
Underpinning concepts of radiation protection:
- justification, optimisation and limitation
- application of the ALARP principle to practices
- UK regulatory framework for radiation protection
National and international regulatory requirements relevant to the practice of nuclear medicine including:
- role of the ICRP and its recommendations
- role of the IAEA
- the Ionising Radiations Regulations 1999 (IRR 1999) and Approved Code of Practice and Guidance L121 (ACOP) (HSE)
- the Medicines (Administration of Radioactive Substances) Regulations 1978 and ARSAC
- Environmental Permitting (England and Wales) Regulations 2010 (EPR 2010), permits and exemption orders, and the Radioactive Substances Act 1993 (RSA 1993)
- the Ionising Radiation (Medical Exposure) Regulations 2000 (IR(ME)R)
  (see Section 1 and Appendix V)
- road transport regulations
National and international guidance on nuclear medicine including:
- ARSAC Notes for Guidance
- Medical and Dental Guidance Notes (IPEM)
- local rules and other guidance
- professional body good practice guidelines
- marketing authorisation mechanisms
- responsibility for radiation safety
- medico-legal responsibility
- research governance; including requirements for ethical approval, sponsorship and trial management
- routine inspection and testing of equipment
- notification of faults and DH hazard warnings

A.6.2 General radiation protection
Regulatory duty holders and their training and responsibilities:
- role under IRR 1999 of the employer, radiation protection adviser (RPA), radiation protection supervisor (RPS) and radiation worker
- role under EPR 2010/RSA 1993 of the radioactive waste adviser (RWA) and competent person
- role under IR(ME)R of the employer, referrer, practitioner and operator
- IRR 1999 local rules, and designation of areas
- dose limits, dose constraints and classification of workers
- comforters and carers
- IR(ME)R employers procedures
Radiation protection, with particular emphasis on:
- shielding, preparation, dispensing and administration of doses
- minimising radiation dose to staff, including pregnant and breastfeeding staff
- prior risk assessment, restriction of exposure and dose monitoring
- use of time, distance and shielding to reduce radiation dose
- use of personal protective equipment to reduce exposure
- environmental contamination monitoring of working areas
- personal contamination monitoring of staff
- decontamination procedures in dealing with spills
- security, transportation and storage of radioactive substances
- storage and disposal of radioactive waste
- protection of the patient, their contacts and the wider public, and their comforters and carers
Part B: Additional Requirements for Those Using Positron Emission Tomography/Computed Tomography (PET/CT)

IV.16 Positron emission tomography/computed tomography (PET/CT) has become an established diagnostic tool in the investigation of oncology patients. Its role in cardiac and neurological conditions is not as widespread.

IV.17 PET/CT is a development within nuclear medicine, providing unique functional information coupled with correlative anatomical imaging. Specialists who wish to provide PET/CT services will require training and experience additional to that required for conventional nuclear medicine studies. Such specialists should already hold certificates for a comprehensive range of nuclear medicine procedures.

IV.18 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.

IV.19 In order for an ARSAC certificate to be issued, applicants will need to demonstrate adequate theoretical training and supervised practical experience in PET/CT. Tumour imaging with PET/CT covers a wide range of malignancies with different uptake mechanisms and patterns of spread. Although most PET/CT 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.

IV.20 Those undertaking structured training through the royal colleges for a nuclear medicine CCT or CESR(CP) will have been provided with sufficient theoretical knowledge and practical experience to satisfy this requirement and a certificate for routine diagnostic PET/CT procedures will be issued on completion of the training grade. This also applies to those who undertook radionuclide radiology subspecialty training according to the 2007 curriculum, and took the optional module in PET/CT, and those training according to the 2010 curriculum.

IV.21 The above arrangement does not apply to those who have undergone radionuclide radiology training according to earlier curricula, those who have undertaken a CCST in nuclear medicine prior to 2004, or 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/CT before a certificate can be issued.

IV.22 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 available in the UK, 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.

IV.23 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/CT centre. Mobile PET/CT facilities may contribute to the experience of an individual but are not sufficient to be recognised as the sole site of training. A period of training at an established fixed site PET/CT centre will also be required. The applicant should be able to demonstrate active involvement in protocol development, participation in patient
selection and procedure justification, participation in multidisciplinary team (MDT) meetings 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.

**IV.24** 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.

**IV.25** 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/CT 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 also be noted that once the service is established, other specialists will be able to gain equivalent experience within their own centre.

**IV.26** Applicants who wish to provide a more comprehensive PET/CT service, eg to include cardiac and neurological investigations, will need to demonstrate appropriate specialised training in relation to the serials requested.

**IV.27** ARSAC recognises that there are relatively low numbers of centres providing cardiac and neurological services across the UK. As a guide, an applicant would need to be working within a specialised unit with sufficient throughput of cases to maintain competency, be involved in an appropriate MDT, and have adequate back up if commencing a new service, eg second read from an established centre.

**IV.28** To assist applicants for neurological PET/CT serials, theoretical training should include knowledge, experience and certification relating to SPECT imaging of the brain, and a specific understanding of neurological PET/CT consistent with the RCP syllabus for nuclear medicine. Practical experience should include a visit to an established neurological PET/CT centre (two or three cases per week) for approximately four to six weeks to establish practical competence. There should be mentored review of approximately 50 cases (including library cases) for each indication.

**IV.29** To assist applicants for cardiac PET/CT serials, theoretical training should include knowledge, experience and certification relating to SPECT cardiac imaging, and a specific understanding of cardiac PET/CT consistent with the RCP syllabus for nuclear medicine. Practical experience should include a visit to an established cardiac PET/CT centre (approximately 20 cases per week) for approximately four weeks to establish practical competence. There should be mentored review of approximately 50 cases (including library cases) undertaken during the attachment.
Part C: Requirements for Supporting Staff Working under the Written Directions of a Certificate Holder

IV.30 When a certificate holder wishes to undertake new procedures, an additions application must be submitted to extend the scope of their current certificate. The applicant will need to provide specific information regarding training and experience relevant to the procedure, both for the applicant and for the supporting staff.

IV.31 As nuclear medicine techniques and services develop, new functions and processes are expected to be undertaken by staff within the nuclear medicine department and may be undertaken by staff in locations that are not under the direct line management control of the certificate holder. 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 General Medical Council\(^2\) and with the requirements of the Ionising Radiation (Medical Exposure) Regulations 2000\(^3\) (IR(ME)R). If the competence of others cannot be demonstrated, the certificate holder cannot justify the procedure and it should not be undertaken.

IV.32 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.

IV.33 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.

IV.34 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. Staff 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.

IV.35 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.

IV.36 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 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.
IV.37 Where formal training (or approved equivalent) has been undertaken, the certificate holder can be confident in the competence of the supporting staff.

References

Appendix V

Additional Acts and Regulations

V.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 1993 (RSA 1993) (as amended) and the Environmental Permitting Regulations 2010 (EPR 2010) (as amended)

V.2 The keeping and use of radioactive material and the accumulation and disposal of radioactive waste is covered by the Environmental Permitting Regulations 2010 in England and Wales, and the Radioactive Substances Act 1993 in Scotland and Northern Ireland. The legislation is intended to minimise the generation of radioactive waste in order to protect the public and the environment, and ensure that radioactive material is kept securely.

V.3 In England, the Environment Agency is responsible for enforcing EPR 2010. In Wales, EPR 2010 is enforced by Natural Resources Wales. In Scotland and Northern Ireland the Scottish Environmental Protection Agency (SEPA) and the Northern Ireland Environment Agency (NIEA) are responsible for enforcing the Radioactive Substances Act (RSA 1993).

V.4 Both EPR 2010 and RSA 1993 are permitting regimes. The scope and extent of the two sets of legislation, and the standards of environmental protection expected, are similar. Where the term ‘permit’ is used below this refers both to permits issued under EPR 2010 and registrations/authorisations issued under RSA 1993.

(a) RSA 1993 requires users of radioactive materials to have a certificate of registration from the relevant regulator, and an authorisation is needed to accumulate and dispose of radioactive waste;

(b) under EPR 2010, users must have a permit, which covers both the holding of radioactive material, and the accumulation and disposal of radioactive waste.

V.5 Permits impose conditions and limits on the holder. These include a requirement to use the best available techniques (BAT) or best practicable means (BPM) to minimise the activity and volume of radioactive waste generated. There are limits on the quantity of radioactive waste that can be accumulated, and the maximum accumulation time. Disposal routes, either by transfer or discharge to the environment, and quantities are controlled. Other conditions require that radioactive material and waste are kept securely, and records of holdings and disposals are maintained. There are numerical limits on the radioactive materials that can be kept.

V.6 Permits are issued to an organisation, such as a hospital trust, for its operation at a site or premises. Separate permits are issued for open and sealed sources. Government security directions means that information on sealed sources is regarded as ‘OFFICIAL–SENSITIVE’, previously termed ‘RESTRICTED’, and withheld from public registers.
V.7 Organisations must have a permit from the relevant regulator before starting work with radioactive material or generating radioactive waste. If a hospital wants to use a new radionuclide or increase holdings of radioactive materials or disposals of waste beyond the limits in existing permits, then an application for a variation has to be submitted to the regulator. A fee is charged, as the regulators are required by government to cover their costs; annual subsistence fees also apply. The regulators need time to assess applications, so permits can take up to four months before issue. (Permits in England are normally issued within three months of an application being submitted provided no further information is needed from the applicant.) More information can be found on the relevant websites, but hospitals are advised to consult their local regulator before submitting an application.

V.8 Permits and authorisations require holders to consult with suitable radioactive waste advisers (RWAs). It is likely that advice from an RWA will be required when an application is made for a new or varied permit. More information on the scheme for approving RWAs can be found on the SEPA website, www.sepa.org.uk.

V.9 Applications for permits and authorisations which include direct disposals to the environment, eg through the sewerage system, must submit an assessment of the radiological impact of these releases. The assessment must show that the radiation dose to members of the public from the annual releases is below 300 µSv. UK regulators have developed principles for calculating the radiation dose to different groups which are described in ‘Principles for the Assessment of Prospective Public Doses arising from Authorised Discharges of Radioactive Waste to the Environment’. There are a number of models which can be used to calculate radiation dose based on these principles and more information may be available on request from the relevant regulator. Regulators will make their own assessment of the radiological impact, and will also look at the impact of releases on wildlife at sensitive sites such as sites of special scientific interest (SSSIs).

V.10 Radionuclides discharged to the sewerage system in human excreta must be included in the permitted releases. Values for the proportion of the administered activity that should be assumed to be released to the sewerage system for routinely used radiopharmaceuticals are published on the Institute of Physics and Engineering in Medicine (IPEM) website in an advice note, www.ipem.ac.uk.

V.11 Hospitals must have suitable management arrangements, including sufficient, competent staff and resources, to ensure compliance with their permit or registration/authorisation. The roles and responsibilities of staff should be documented. More detailed guidance on compliance can be found on the regulators’ websites.

V.12 Where larger sealed sources are held, eg the high activity sealed sources (HASS sources) used in 192Ir brachytherapy, specific security measures are required. Counter terrorism security advisers (CTSAs) from the local police will visit the hospital to review the security measures and advise regulators on suitable requirements.

V.13 Regulators make periodic inspections of compliance, and can impose a range of sanctions, including prosecution in the most serious cases, where there has been non-compliance with the permit.

V.14 There are conditional exemptions from the requirement to have a permit where small quantities of radioactive material are used or waste disposed. In 2011, the exemptions were reviewed; the 18 exemption orders were replaced with a single exemption order in Scotland.
and Northern Ireland, and amendments to EPR 2010 in England and Wales. The effect of the exemptions made under the two legislative regimes is the same, and a single government guidance document is available. The regulators have also jointly produced detailed guidance on specific aspects of exemptions, which is available from www.gov.uk or www.sepa.org.uk. Most relevant to the healthcare sector are the exemptions that allow limited quantities of open source material, intended for medical or veterinary use, to be held without a permit or registration. Up to 10 GBq of $^{99m}$Tc, and 5 GBq of other radionuclides, in human excreta can be disposed to the sewerage system without a permit or authorisation. This means that nursing homes caring for patients who have had a nuclear medicine investigation at another institution do not require a permit or authorisation. Other exemptions cover small sealed sources and the disposal of very low level radioactive waste (VLLW).

V.15 Both RSA 1993 and EPR 2010 only apply to undertakings such as limited companies, hospital trusts and universities, and not to patients’ own homes.

V.16 In some cases there may be more than one organisation operating on the same site (eg a hospital trust and a university). Separate permits can be issued to the hospital and the university if both are carrying out work with radioactive substances. Each organisation is responsible for control of its activities and where interfaces arise, such as in the use of shared facilities, arrangements should be clearly specified in management documentation to ensure that all work with radioactive material and management of radioactive waste is adequately controlled.

The Medicines Act 1968

V.17 Radiopharmaceuticals are medicinal products and their sale, supply and manufacture are subject to the licensing provisions of the Medicines for Human Use (Marketing Authorisations etc) Regulations 1994 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.

V.18 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 1999 (IRR 1999) (as amended) and the Ionising Radiations Regulations (Northern Ireland) 2000 (IRR(NI) 2000) (as amended)

V.19 The Ionising Radiations Regulations 1999\(^7\) and the Ionising Radiations Regulations (Northern Ireland) 2000\(^8\) were made under the Health and Safety at Work etc Act 1974\(^9\) and the Health and Safety at Work (Northern Ireland) Order 1978\(^10\), 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’) (ACOP)\(^11\).

V.20 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 PM77\(^12\) gives guidance on the fitness of equipment used for medical exposure to ionising radiation.

V.21 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. ACOP gives practical advice on how to comply with the regulations. Employers may use alternative methods to those set out in ACOP in order to comply with the law. However, ACOP 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 ACOP, the employer will need to show that they have complied with the law in some other way or the courts will find them at fault.

Some relevant regulations

Regulation 13 – appointing radiation protection advisers (RPAs)

V.22 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 ACOP give 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/radiation/rpnews/statementrpa.htm.

V.23 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 ACOP. 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

V.24 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 2000 (as amended) and the Ionising Radiation (Medical Exposure) Regulations (Northern Ireland) 2000 (IR(ME)R 2000)

V.25 The Ionising Radiation (Medical Exposure) Regulations 2000\(^1\) and the Ionising Radiation (Medical Exposure) Regulations (Northern Ireland) 2000\(^2\) were made under Section 2(2) of the European Communities Act 1972\(^3\) 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, include the use of ionising radiation in biomedical research.

V.26 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

V.27 ‘Appropriate authority’ is defined and reflects the role of the devolved administrations in health matters.

V.28 ‘Diagnostic reference levels’ are defined and these are intended as a tool to aid optimisation.

V.29 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

V.30 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 to the regulations sets out a minimum of essential procedures.

V.31 In nuclear medicine, the employer will consult the doctor or dentist holding a certificate under the Medicines (Administration of Radioactive Substances) Regulations\(^4\) 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 1978.
**Regulation 5 – duties of the referrer, practitioner and operator**

V.32 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**

V.33 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**

V.34 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**

V.35 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 to the regulations.

**Regulation 9 – expert advice**

V.36 Regulation 9 requires that a medical physics expert is available. The degree of availability will vary with the range and complexity of procedures undertaken.

**Regulation 10 – equipment**

V.37 An inventory should be available of any equipment that delivers ionising radiation or directly controls the extent of such an exposure.

**References**

4. Department for Environment, Food and Rural Affairs. Guidance on the scope of and exemptions from the radioactive substances legislation in the UK; DEFRA, PB 13625; 2011

January 2016


The Ionising Radiation (Medical Exposure) Regulations (Northern Ireland) 2000 (SR 2000 No. 194). Belfast: HMSO

The European Communities Act 1972. London: HMSO

Appendix VI

Certification Process under the MARS Regulations 1978

VI.1 The issuing of certificates under the Medicines (Administration of Radioactive Substances) Regulations 1978 (SI 1978 No. 1006) 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.

VI.2 The process varies with the type of certificate issued, but as an example, the process for new certificates is represented in Figure VI.1. This is the most involved process. Other applications for additional procedures, renewal of certificates, etc. eliminate some of these steps.

VI.3 The ARSAC Support Unit processes in excess of 1500 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 email, 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.

VI.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. In most cases, advice to the health ministers to issue a certificate is not provided by a single member of the Committee. Exceptions include circumstances of urgent clinical need. Such authorisations are carried out under a strict procedure and involve a senior scientific member of the ARSAC Secretariat.
Figure VI.1 Current certification procedure – new applications (diagnostic, therapy – including functional groups – and research)

Application received

Application checked and acknowledged

RPC number allocated and application copied to relevant subgroup*†

Subgroup comments received

Subgroup approval

Scientific adviser

Application approved

Application not approved

Scientific adviser

Subgroup assessment*

Further information required for subgroup approval

Application approved

ARSAC Chairman

Not approved

If issue of a certificate is inappropriate at this time the applicant is informed by letter

Serial numbers complete

Serial numbers incomplete

Certificate prepared

QA process of certificate

Certificate sent to applicant and copied to site employer

Certificate prepared

Scientific adviser

Database updated. Filed into system

Key

* First reminder required at 18 days.
Second reminder required at 29 days.
† Research applications of ≤1 mSv directly to the subgroup chairman.
Appendix VII

Communicating Risk to Research Ethics Committees, Patients and Research Subjects

VII.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.

VII.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 the 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 to participation in dangerous sports.

Communicating Risks in Research Applications

VII.3 ICRP Publication 62\(^1\) provides general guidelines for assessing research proposals (see Table VII.1). The risk is the total detriment from the exposure including fatal and non-fatal cancers and probability of hereditary disease. The detriment also will change 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 Figure VII.1).

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

VII.4 When preparing research applications, consideration should be given to whether the extra clinical information to be gained from the study warrants the risk involved. For studies involving patients, the risks associated with the research should be related to the risk associated with their disease. 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 in Table VII.1.
VII.5 The investigators should consider how to communicate the level of risk to subjects, depending on the level of risk. Risk information should be provided to subjects in advance, e.g., in writing at the time of obtaining consent.

Communicating Risks to Patients and Research Subjects

VII.6 Research has shown that patients, and by implication research subjects, extract the gist of information rather than making decisions on the details. 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.

VII.7 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:

(a) no risk at all;
(b) no evidence of risk;
(c) no current evidence of risk, but risk cannot be excluded;
(d) no need to worry about risk;
(e) safe enough in the context of other common risks;
(f) no hazard present.

Figure VII.1: Lifetime cancer risk for uniform whole body exposure as a function of age at exposure and sex (adapted from Wall et al²)
VII.8 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.

VII.9 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 are available for analysis but not open to input. The ‘transparent approach’ is less suitable in this context.

VII.10 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 – a 97 out of 100 chance of success is more acceptable than a 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.

VII.11 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 VII.2.

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

<table>
<thead>
<tr>
<th>Activity</th>
<th>Cause of death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking 1.4 cigarettes</td>
<td>Cancer, heart disease</td>
</tr>
<tr>
<td>Spending 1 hour in a coal mine</td>
<td>Black lung disease</td>
</tr>
<tr>
<td>Living 2 days in New York or Boston</td>
<td>Air pollution</td>
</tr>
<tr>
<td>Travelling 10 miles by bicycle</td>
<td>Accident</td>
</tr>
<tr>
<td>Flying 1000 miles by jet</td>
<td>Accident</td>
</tr>
<tr>
<td>Living 2 months in Denver (rather than New York)</td>
<td>Cancer (cosmic radiation)</td>
</tr>
<tr>
<td>One chest X-ray in a good hospital</td>
<td>Cancer (from radiation)</td>
</tr>
<tr>
<td>Eating 40 lbs of peanut butter</td>
<td>Liver cancer (aflatoxin B)</td>
</tr>
<tr>
<td>Drinking 30 12-oz cans of diet soda</td>
<td>Cancer (from saccharine)</td>
</tr>
<tr>
<td>Living 150 years within 20 miles of a nuclear power plant</td>
<td>Cancer (from radiation)</td>
</tr>
</tbody>
</table>

VII.12 Alternatively, for a more direct comparison of radiation dose, the dose from a range of nuclear medicine procedures (see Table VII.3) can be contrasted with the average dose to which people are exposed in a year in the UK (approximately 2.7 mSv).

VII.13 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 VII.4).
Table VII.3  Typical doses and risks from radionuclide studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Typical effective dose (mSv)</th>
<th>Increased annual chance of death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney (99mTc)</td>
<td>1</td>
<td>30 in 1,000,000</td>
</tr>
<tr>
<td>Planar bone (99mTc)</td>
<td>3</td>
<td>90 in 1,000,000</td>
</tr>
<tr>
<td>Cardiac blood pool imaging (99mTc)</td>
<td>6</td>
<td>180 in 1,000,000</td>
</tr>
<tr>
<td>PET tumour (18F FDG)</td>
<td>8</td>
<td>240 in 1,000,000</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Band</th>
<th>Typical effective dose (mSv)</th>
<th>Increased annual chance of death</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>&lt;1 in 1,000,000</td>
<td>MRI, ultrasound</td>
</tr>
<tr>
<td>I</td>
<td>&lt;1</td>
<td>&lt;30 in 1,000,000</td>
<td>Chest or limb X-ray</td>
</tr>
<tr>
<td>II</td>
<td>1–5</td>
<td>30–150 in 1,000,000</td>
<td>Lumbar spine X-ray, CT head and neck, some nuclear medicine studies (eg bone scan)</td>
</tr>
<tr>
<td>III</td>
<td>5–10</td>
<td>150–300 in 1,000,000</td>
<td>CT chest or abdomen, some nuclear medicine studies (eg cardiac)</td>
</tr>
<tr>
<td>IV</td>
<td>&gt;10</td>
<td>&gt;300 in 1,000,000</td>
<td>Extensive CT studies, some nuclear medicine studies (eg pentetreotide and SPECT/CT), some PET/CT studies (eg FDG tumour)</td>
</tr>
</tbody>
</table>

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

VII.14 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 a day, may give a false impression or trivialise the risk.

VII.15 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.

References