



National Patient Safety Agency

National Research Ethics Service

Approval for research involving ionising radiation

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1. Purpose and scope

- 1.1 This document provides guidance to researchers, radiation experts, employers (including NHS Trusts) and Research Ethics Committees on procedures for planning, review and authorisation of all medical and biomedical research involving any use of ionising radiation.
- 1.2 The guidance reflects the need to comply with the following:
 - The Ionising Radiation (Medical Exposure) Regulations 2000 (“IRMER”) as amended by the Ionising Radiation (Medical Exposure) (Amendment) Regulations 2006
 - The Medicines for Human Use (Clinical Trials) Regulations 2004 (“Clinical Trials Regulations”)
 - The Medicines (Administration of Radioactive Substances) Regulations 1978 (“MARS”)
 - The Ionising Radiations Regulations 1999.
- 1.3 In particular, the guidance explains the requirement both for a favourable opinion from the main REC, including ethical consideration of radiation exposures, and local employers’ approval for these exposures under IRMER. These requirements apply equally to single- and multi-site studies. The guidance aims to harmonise these procedures, facilitate communication and consultation between those concerned and avoid unnecessary duplication of effort.
- 1.4 The guidance is designed to provide a general framework for compliance with IRMER in research. It does not prescribe or replace detailed procedures for local implementation by Trusts or other host organisations in fulfilment of their responsibilities as employers under IRMER.
- 1.5 The guidance has been developed in consultation between the following organisations:
 - Health Protection Agency, Medical Exposure Department (HPA-RPD-MED)
 - Administration of Radioactive Substances Advisory Committee (ARSAC)
 - British Institute of Radiology (BIR) – Radiation Protection Committee
 - Institute of Physics and Engineering in Medicine (IPEM) – Special Interest Groups for diagnostic radiology, radiation protection and nuclear medicine
 - Royal College of Radiologists
 - British Nuclear Medicine Society
 - College of Radiographers
 - NHS R&D Forum
 - National Research Ethics Service (NRES)
- 1.6 Members of the drafting group are listed at Appendix 1.
- 1.7 A glossary of terms used in this document is at Appendix 2.
- 1.8 Flowcharts summarising key procedures are at Appendix 4.

2. Application of IRMER to research

Scope of IRMER

- 2.1 The Ionising Radiation (Medical Exposure) Regulations 2000 (IRMER) govern the exposure to ionising radiation of patients or other persons voluntarily participating in medical or biomedical, diagnostic or therapeutic research programmes.
- 2.2 Procedures involving ionising radiation include:
- Diagnostic X-rays, CT scans or DXA scans
 - Radiotherapy (including brachytherapy and therapy using unsealed sources)
 - Radionuclide imaging (including diagnostic imaging and in vitro measurements).
- 2.3 Magnetic Resonance Imaging (MRI) or ultrasound investigations do not involve ionising radiation.
- 2.4 The research provisions of IRMER apply to any research exposure involving ionising radiation, not only to exposures that are additional to routine care.
- 2.5 *In this guidance, a “research exposure” is defined as any exposure required by the research protocol following initial consent from the participant. It includes all exposures carried out on the participant as determined by the protocol, including those which would otherwise be part of routine clinical care for patients treated outside the research setting.*
- 2.6 For example, in a comparative study of two radiotherapy schedules (conventional versus ultrafractionated), the control group might be receiving normal radiotherapy and additional diagnostic CT scans. However, all the exposures would be research exposures required by the protocol.
- 2.7 Research exposures include any exposure required by the screening procedures for the research. For example, where the protocol requires a diagnostic X-ray to confirm suitability for inclusion in the study, this would be a research exposure. Consent is required from potential participants to undergo screening procedures. Such procedures should not start until the research proposal has completed the approval process described in this guidance, including fulfilment of all requirements of IRMER relating to research exposures.
- 2.8 In some cases, the selection criteria may refer to exposures received outside the study but the study procedures themselves do not include any exposures. Such exposures may be considered normal clinical exposures rather than research exposures. This would apply where both the following criteria are met:

- The exposures are authorised and undertaken in the course of normal clinical management, not for research purposes; and
 - The decision to authorise the exposures is clearly separated from the decision to include the participant in the research and is not determined by the research protocol.
- 2.9 For example, an epidemiological study of the long-term effects of radiotherapy might require that the participant had received radiotherapy of a particular type or within a particular period prior to inclusion in the research. The radiotherapy would have needed to comply with the provisions of IRMER relating to clinical exposures. However, it is not a research exposure for the purpose of the study. Similarly, a study of acupuncture or psychosocial support for patients with breast cancer might refer to chemo-radiation treatment in the selection criteria and make use of clinical data, but the study itself would not involve radiation exposures.

Further advice

- 2.9 Where any doubt arises as to whether a procedure involves ionising radiation or is a research exposure for the purposes of IRMER, researchers are advised to seek early advice from a Medical Physics Expert (MPE) in their organisation or one of the host organisations for the research.

3. Statutory roles and responsibilities

Introduction

- 3.1 Where research involves ionising radiation, IRMER places specific responsibilities on:
- The NHS Trust, or other responsible employer at each research site, represented by its Chief Executive (paragraphs 3.5-3.6)
 - Researchers requesting examinations involving ionising radiation for the purposes of research (paragraphs 3.16-3.19)
 - Practitioners justifying and authorising individual research exposures (paragraphs 3.23-3.26)
 - Operators carrying out medical exposures for the purposes of research.
- 3.2 The detailed responsibilities of individual duty holders are not covered in this document. They must comply with their employer's procedures under IRMER.
- 3.3 Any research exposure must be approved by a research ethics committee (paragraphs 3.7-3.12).
- 3.4 IRMER does not mention the responsibilities of research sponsors (see paragraph 3.30).

Employers

3.5 For all medical exposures to ionising radiation, the employer must comply with the duties set out in Regulation 4 of IRMER. These include a requirement for written procedures to meet the statutory requirements listed in Schedule 1 of IRMER. In addition, in the case of research exposures there are specific requirements in Regulations 4(3)(d) and 7(4) for the procedures to provide that:

- Dose constraints are established for biomedical and medical research programmes where no direct medical benefit for the individual is expected from the exposure.
- These dose constraints are adhered to.
- Individual target levels of doses are planned by the Practitioner for patients who voluntarily undergo an experimental diagnostic or therapeutic practice from which the patients are expected to receive a diagnostic or therapeutic benefit.
- The individuals concerned participate voluntarily in the research programme.
- The individuals concerned are informed in advance about the risks of the exposure.

3.6 These requirements apply to all research studies where patients recruited receive any research exposures.

Research ethics committees

3.7 All research involving ionising radiation should be reviewed by a Research Ethics Committee (REC). Under IRMER, research exposures must be approved by one of the following:

- An ethics committee recognised under the Clinical Trials Regulations (as well as a number of NHS RECs this includes the Gene Therapy Advisory Committee, the Ministry of Defence Research Ethics Committee and independent ethics committees recognised for the review of Phase 1 trials in healthy volunteers)
- The ethics committee constituted under the Adults with Incapacity (Scotland) Act 2000 (currently this is the Scotland A REC)
- Any other committee established to advise on the ethics of research investigations into human beings and recognised for that purpose by the Secretary of State, Welsh or Scottish Ministers (in effect this means all NHS RECs and HSC RECs in Northern Ireland, including all “authorised” RECs).

Details of ethics committees are given on the NRES website at <http://www.nres.npsa.nhs.uk/contacts/>

- 3.8 In relation to medicinal trials, the Clinical Trials Regulations provide for a single ethical opinion on any trial by one committee (referred to in this guidance as the “main REC”). The policy of the UK health departments is that broadly speaking the same procedures should apply to all other health research undertaken within the NHS. Approval systems for research involving radiation therefore need to harmonise the single ethical opinion with the site-based procedures required for compliance with IRMER.
- 3.9 The main REC is the single committee responsible for giving an ethical opinion on the research and the suitability of sites, whether the research is a single- or multi-site study. The main REC issues a favourable or unfavourable opinion on an application within 60 calendar days of receiving a valid application from the Chief Investigator, allowing for the clock to stop once to request further information or clarification.
- 3.10 The main REC is responsible for review of all ethical issues in the research, taking account of potential variations in clinical practice at sites. The ethical review will consider the whole burden from the research exposures, giving particular consideration to exposures that would be additional to exposure received by participants as part of normal clinical care if they opted not to participate in research. The main REC will consider whether the research exposures are ethically acceptable, the risks and burdens involved in relation to the potential benefits, and the description of risk in the participant information sheet. Where there are differences between sites in radiation practice in clinical care, the main REC will need to consider whether this affects the ethical opinion.
- 3.11 A favourable ethical opinion does not replace the statutory requirement for exposures to be individually justified by Practitioners at each site under IRMER (see paragraph 3.23).
- 3.12 For all medicinal trials and some other types of research, the main REC must also ethically approve each site participating in the research. The local Principal Investigator (see paragraphs 3.16-3.20) applies for site-specific assessment (SSA) to a local REC or R&D office, which then advises the main REC on the general suitability of the site. Following SSA the main REC issues approval for each site. The SSA does not address issues of IRMER compliance at the site and does not replace the need to comply with the employer’s procedures under IRMER.

Chief Investigators

- 3.13 The Chief Investigator (CI) is the investigator with overall responsibility for the conduct of research. In a multi-site study the CI has the co-ordinating responsibility for the research at all sites.
- 3.14 The CI is responsible for submitting the ethics application to the main REC, together with all supporting documentation (including the protocol and participant information sheet). The application should be completed using the Integrated Research Application System (IRAS), which has been designed to facilitate the process described in this guidance. The protocol may have been written either by the CI or by the research sponsor, but the CI is responsible for its completeness and scientific accuracy. The CI is responsible for obtaining a favourable opinion for the whole study from the main REC, taking account of potential variations in practice at other sites.

- 3.15 The CI will usually also have the role of local Principal Investigator (PI) at his/her own site and this will be regarded as the *lead site* for the research. When acting as the local PI, the CI is obliged to comply with Trust policies and procedures at the site. Where the CI is not a PI at any site (for example, in a commercially sponsored clinical trial where a registered health professional employed by the sponsor is named as CI), one of the trial sites should be selected as the lead site for NHS research governance purposes.

Principal Investigators

- 3.16 The local Principal Investigator (PI) is the lead investigator responsible for the conduct of research at a particular site.
- 3.17 Where Site Specific Assessment (SSA) is required as part of the ethical review process, this will address the general suitability of the site and PI to undertake the research. It does not cover radiation protection issues and does not fulfil the employers' statutory responsibilities under IRMER.
- 3.18 Under the NHS Research Governance Framework the PI must apply to the R&D office for management permission to conduct the research. The PI will need to assure the R&D office that the conduct of the research complies with the Trust's local policies and procedures for the use of ionising radiation in research and meets the requirements of IRMER.
- 3.19 Applications for SSA and management permission are made using the Site-Specific Information Form in IRAS.
- 3.20 Trials to be undertaken on multiple sites have to meet the applicable requirements of IRMER at each site. The research sponsor must ensure that each local PI is aware of the need to comply with their employer's local policies and procedures for the use of ionising radiation in research prior to recruitment.

Investigators and other health professionals

- 3.21 Investigators and other registered health professionals (in particular, research nurses) will be involved in the recruitment and consent of potential study participants.
- 3.22 They must:
- Comply with the selection criteria for each study.
 - Be aware of and comply with local Trust policies and procedures for research, which may involve advanced communication of relevant information between themselves and the radiology or other department performing research procedures.
 - Support compliance with the Trust's legislative record keeping requirements.

- Ensure that patients are fully informed of the nature of the trial and that they are able to provide informed consent based upon the information provided in the participant information sheet.

Practitioners

- 3.23 Under IRMER all medical exposures must be justified by a “Practitioner”. The legislation requires the Practitioner to take particular care with the justification of research exposures where there may be no direct health benefit for the participants. Guidance for Practitioners at research sites is given in paragraphs 5.9-5.14.
- 3.24 The Practitioner will usually be a Clinical Radiologist, Clinical Oncologist, Cardiologist, Nuclear Medicine Specialist or other registered health professional with expertise in the relevant field. The Trust or other local employer is responsible for ensuring that a suitable registered health professional is entitled to act as a Practitioner for this purpose under IRMER. In a multi-site trial, a Practitioner must be appointed at each site. More than one Practitioner may be required at each site, depending on the modalities involved in the research.
- 3.25 Each Trust or other employer should have internal authorisation procedures in place to determine that all research exposures have been justified by a Practitioner and authorised either by the Practitioner or by an operator acting in accordance with guidelines issued by the Practitioner.
- 3.26 The Practitioner at the lead site (or another site) may also be asked to advise the Chief Investigator on the development of the protocol and fulfil the role of “lead Clinical Radiation Expert” in completing the REC application (see section 4). However, this role is distinct from the legal responsibilities of the Practitioner at his/her site under IRMER.

Medical Physics Experts

- 3.27 Under IRMER the employer is required to ensure that a Medical Physics Expert (MPE) is involved in all medical exposures, including research exposures. The role of the MPE at each site is to advise on optimisation, including patient dosimetry and quality assurance for these exposures. Guidance for MPEs at research sites is given in paragraphs 5.15-5.18.
- 3.28 The MPE will usually, but not always, be a member of the local Medical Physics department. An MPE may only be qualified to advise on one modality. Advice may need to be sought from more than one MPE.
- 3.29 The MPE at the lead site (or another site) may also be asked by the Chief Investigator to act as the “lead MPE” for the purposes of the REC application (see section 4). However, just as in 3.26, this role is distinct from the role of the MPE at his/her site under IRMER.

Sponsors

- 3.30 The role of the research sponsor is not referred to in IRMER. However, under the Clinical Trials Regulations and research governance systems within the NHS the sponsor has ultimate responsibility for the initiation, management

and financing of a study. For studies involving research exposures under IRMER, the sponsor will require assurance that employers hosting the study (whether NHS or non-NHS organisations) will comply with their IRMER responsibilities. This should be addressed in the terms of the agreements between the sponsor and the host organisations. Sponsors should also ensure that local PIs are aware of the need to follow local IRMER procedures.

ARSAC certificate holders

- 3.31 The administration of radioactive substances is governed by the Medicines (Administration of Radioactive Substances) Regulations 1978 (MARS) as well as by IRMER. Regulation 2 of MARS requires that any doctor or dentist wishing to administer radioactive medicinal products to humans should hold a certificate issued by Health Ministers. MARS also established the Administration of Radioactive Substances Advisory Committee (ARSAC) to advise Ministers on applications.
- 3.32 Where research involves the administration of radioactive substances, an ARSAC certificate must be held at each research site where administrations take place. The certificate is site, procedure and holder specific. A “research ARSAC certificate” will only be required if the research exposure is additional to those carried out by the certificate holder as part of normal clinical care.
- 3.33 The application form for a research ARSAC certificates can be electronically generated from the Site-Specific Information (SSI) Form for the site in the Integrated Research Application System (IRAS), drawing on the same information provided in the REC application.
- 3.34 Detailed guidance from ARSAC is available in the “Notes for Guidance on the Clinical Administration of Radiopharmaceuticals and Use of Sealed Radioactive Sources” (see www.arsac.org.uk).

Radiation Protection Advisers

- 3.35 The Ionising Radiations Regulations 1999 lay duties on employers to protect staff and other persons from ionising radiation. Where research involves a “new activity”, i.e. a novel form of ionising radiation not covered by existing authorisations and risk assessments, the employer must seek advice from a Radiation Protection Adviser (RPA) on compliance with the Regulations.

4. Protocol development and main REC application

Advice from lead experts

- 4.1 The system of single ethical review makes it essential that the protocol and main REC application are informed by a single source of expert advice, which should address the radiation issues in the study as a whole. Part B Section 3 of the application form in IRAS requires input from the following experts:
- A lead Clinical Radiation Expert (lead CRE), who assesses whether the protocol could involve additional radiation exposure at any site in the

study and advises the CI and the main REC on the suitability and ethical acceptability of additional exposures.

- A lead Medical Physics Expert (lead MPE), who performs a dose/risk assessment for all the radiation exposures proposed in the protocol.
- 4.2 The roles of these experts are non-statutory. They are however crucial to harmonising the ethical review of additional radiation exposures with local IRMER compliance at sites. Although the roles of lead experts are not formally governed by IRMER, they should take full account of IRMER in the advice they provide.
- 4.3 During the development of the study protocol the Chief Investigator should seek advice from the lead experts at the earliest possible stage.
- 4.4 Where the CI is also a local PI, he/she should also seek early advice on IRMER compliance from the R&D office and other departments involved in the study at the lead site (see paragraph 5.3).

Identifying a lead Clinical Radiation Expert

- 4.5 The lead CRE should be a registered health professional with clinical expertise in the modality (imaging/treatment method) involved in the study. Typically this might be a radiologist, a clinical oncologist (for radiotherapy) or a nuclear medicine specialist. Where more than one modality (or type of radiotherapy) is involved, it may be necessary for the lead CRE to seek input from other CREs. Where the study involves additional exposures requiring further assessment of suitability (see 4.16), the CRE should provide a combined assessment and name any other CREs who have contributed.
- 4.6 The CI will often wish to approach a colleague at the lead site to undertake the role of lead CRE. If a suitable individual is not available, it is acceptable for the role to be undertaken by a registered health professional at another research site or who is not involved at any site, provided they are suitably qualified to give expert advice. It is the responsibility of the CI to ensure that the person appointed has appropriate expertise.
- 4.7 It is not essential for the lead CRE to be independent of the research team.
- 4.8 It is not essential for the lead CRE to be employed by the NHS. The role may be undertaken by a suitably qualified registered health professional at a private hospital or independent sector treatment centre.
- 4.9 However, the lead CRE should always be professionally based in the United Kingdom, as the role requires expertise in the UK regulatory and clinical environment.

Identifying a lead Medical Physics Expert

- 4.10 The role of lead MPE should be undertaken by a Medical Physics Expert who is a registered health professional and has expertise relevant to the proposed procedures. MPEs are usually registered as clinical scientists by the Health Professions Council under the Health Professions Order 2001.

- 4.11 As with the lead CRE, the CI may wish to approach a colleague at the lead site to undertake the role of lead MPE. If a suitable individual is not available, it is acceptable for the role to be undertaken by a registered health professional at another research site or who is not involved at any site, provided they are suitably qualified. It is the responsibility of the CI to ensure that the person appointed has appropriate expertise. Where more than one modality is involved, it may be necessary for the lead MPE to seek input from other MPEs. The lead MPE should provide a combined assessment for the main REC, giving the names of any other MPEs who have contributed.
- 4.12 It is not essential for the lead MPE to be independent of the research team.
- 4.13 It is not essential for the lead MPE to be employed by the NHS. The role may be undertaken by a suitably qualified registered health professional working in the private sector.
- 4.14 However, the lead MPE should always be professionally based in the United Kingdom, as the role requires expertise in the UK regulatory and clinical environment.

Review by lead CRE

- 4.15 The Chief Investigator should submit a draft of the application form, study protocol and participant information sheet to the lead CRE(s) who will:
- Review the proposed exposures (as summarised in the list of clinical interventions in Part A of IRAS)
 - Assess whether the exposures in the protocol would exceed the exposures performed under existing clinical protocols as part of normal clinical management *at any site in the study*
 - Where additional exposures are involved, advise on their suitability to the objectives of the study and ethical acceptability.
- 4.16 The assessment of additional exposure by the lead CRE should demonstrate for the benefit of the main REC that the exposure(s) are necessary and that the potential benefits of exposure, whether benefits to the participant or to society, outweigh the potential harm from the radiation. Particular care should be taken in assessing research exposures where there may be no direct health benefit for the participants.
- 4.17 In undertaking the assessment, the lead CRE should consider:
- The specific objectives of the exposure and the characteristics of the research population
 - The potential diagnostic or therapeutic benefits, including direct benefits to the participant and the benefits to society
 - The detriment to participants that the exposure may cause
 - The availability of alternative techniques involving less, or no, exposure to ionising radiation
 - The possibility that participants will be participating in other trials involving additional radiation (see Question A17 in the IRAS application form, stating the exclusion criteria for the trial, and Question A32 on

involvement in other research).

- 4.18 The characteristics of the research population will include such factors as the age of the participants and their likely life expectancy.
- 4.19 The lead CRE should review the information sheet for participants and ensure that it contains accurate and appropriate advice on radiation exposure, in particular that:
- Where there is no direct benefit to the participant, this is made clear.
 - The risks are realistic and not over- or under-stated.
 - The information is comprehensible to participants.
 - It is sensitive to cohort prognosis by taking into account the population and illness under study.
 - 'Raw' numerical risks are not quoted without reference to reasonable comparators, and terminology is harmonised by reference to tables such as the HPA table in their patient information leaflet concerning x-rays, available at:
http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1194947388410
- 4.20 For multi-site trials, variations in normal practice around the UK will have a bearing on whether or not research exposures represent an *additional* radiation burden for participants. The lead CRE should take such variations into account. Where any additional exposure is involved in the study, the assessment should provide a quantitative estimate of the range of normal/additional exposures across the study sites. To achieve this, it may be helpful to consult Practitioners and Medical Physics Experts at other research sites. Where existing clinical guidelines have been used in reaching a judgement about normal/additional exposures, these should be referenced.
- 4.21 The lead CRE should copy the assessment to the lead MPE for the research. The REC application form should not be signed off by the lead CRE at this stage. Co-operation with the lead MPE during protocol development will ensure that any variability is taken into account by the lead MPE when drawing up radiation dose and risk information for consideration by the main REC.

Review by lead MPE

- 4.22 On receipt of the lead CRE's review the lead MPE(s) will perform a dose/risk assessment of the proposed investigations for inclusion in the application form in IRAS. The assessment should include all research exposures, including those that might be received as part of normal clinical care at some or all sites.
- 4.23 The lead MPE will calculate appropriate doses for the proposed examinations, estimating the Total Research Protocol Dose (see paragraph 4.26) and the element that is potentially additional to normal clinical exposure. The assessment should also include information about risks to facilitate the

REC's deliberations as follows:

- Risks should be quantified where possible, referencing risk co-efficients used (e.g. HPA, ICRP).
- The risk assessment should take into account the population being irradiated. Any adjustments made to these co-efficients (e.g. to take account of a paediatric cohort) must be clearly stated. Any risk model used should be referenced (e.g. BEIR VII).
- The clinical prognosis of the study cohort should be taken into account when assessing risk, either following a risk calculation that excluded prognosis to place the risk in context, or as part of the risk assessment model.
- A risk statement should be included that gives an appropriate risk comparator, i.e. compares a radiation risk with an activity that has an appropriately similar level of risk.

4.24 The lead MPE may also advise the CI on the explanation of risks in the participant information sheet, practical aspects of the examinations, additional statutory requirements and any resource/organisational issues at research sites. Part B Section 3 of the application form can be completed by the lead MPE at this point.

4.25 The dose assessment should facilitate local IRMER compliance at participating sites by:

- Setting a Total Research Protocol Dose (TRPD) for the whole study.
- Assessing additional radiation dose based upon the lead CRE's statement on normal/additional exposures.
- Using national Diagnostic Reference Levels (DRLs) for examination dose where available, or an estimated dose to a standard patient. Where estimated, the methodology must be stated.

4.26 Under IRMER, it is the role of the local MPE at each site to help establish the dose constraint or target dose level. However, the assessment by the lead MPE will facilitate this process by proposing for ethical approval an approximate total dose for an average patient for the whole study (TRPD), along with an order of magnitude risk from this dose. The TRPD will establish a level of exposure that is ethically acceptable while allowing for reasonable variation around this level.

4.27 It is therefore important for the lead MPE to take account of potential variations in dose arising from differences both in examination protocols and in what constitutes normal practice among participating UK sites, using DRLs where appropriate. This will ensure that the main REC is fully apprised of the potential additional radiation burden to participants and how it may vary from centre to centre. The lead MPE may wish to consult colleagues at other sites that will be taking part in the study.

4.28 Where the study involves changes to the standard therapeutic dose or the target volume to which the radiation is delivered, the lead CRE will advise on the expected therapeutic outcome compared to standard protocols. The lead

MPE can also provide relevant patient dosimetry advice and predictions of radiobiological effectiveness of all additional exposures associated with a patient treatment that does not follow standard protocols, even if the therapy dose itself does not change. The assessment should include consideration of doses as part of the treatment planning process (for instance an imaging modality such as PET CT for tumour delineation) or the verification process (such as Image Guided Radiotherapy).

- 4.29 The lead MPE's assessment should be copied to the lead CRE, who should check that his/her original advice remains valid in the light of the detailed dose and risk assessment. The lead CRE can then complete Part B Section 3 of the application form.
- 4.30 The lead CRE and lead MPE should sign the final version of the application form or give electronic authorisation in IRAS prior to submission of the application to the main REC.

Participant information sheet

- 4.31 The CI is responsible for submitting the participant information sheet to the main REC for ethical review. Advice should be sought from the lead CRE and lead MPE on the content of information sheets.
- 4.32 IRMER includes specific requirements for the provision of information. Regulation 7, paragraph (4) (b) requires that *"the individuals concerned are informed in advance about the risks of the exposure"*. This applies to all participants receiving radiation exposures in research, regardless of whether the exposures are additional to normal care. It is a statutory requirement that participants are informed of the risks arising from the procedures even if it is to inform them that the risks are the same as undergoing normal clinical treatment. Participants should therefore be informed of the whole burden, clarifying the element that is additional to normal care. The review of the participant information sheet by the lead CRE should ensure that appropriate information is provided (see paragraph 4.19).
- 4.33 Detailed guidance about provision of information is available from:
- Appendix VII of the ARSAC Notes for Guidance (see www.arsac.org.uk)
 - NRES guidance on information sheets and consent forms (see <http://www.nres.npsa.nhs.uk/applicants/guidance/>)
- 4.34 As a general rule, there should be a single generic Participant Information Sheet (PIS) for the research, approved by the main REC as part of the single ethical opinion. The generic PIS should normally be used at all sites with no changes other than to customise for local use, for example by using Trust headed paper and inserting local contact points. Such adjustments are considered "non-substantial" or "minor" amendments to the conduct of the research and do not require ethical approval.
- 4.35 Where the protocol allows for significant variation in radiation practice between sites, this may require changes to be made to local versions of the PIS, relating to the number or type of examinations, number of clinic visits, and the risks compared to normal clinical care.

- 4.36 Wherever possible, the need for such variation should be identified prior to the main REC application so that consideration can be given at the outset to the need for alternative wordings. Where local variations in the PIS are approved by the main REC, the local PI should then select the appropriate wording according to local clinical practice. Alternatively, the main REC may decide that a single form of words is appropriate.
- 4.37 If the need to vary the PIS emerges following issue of the favourable opinion, the CI should submit a Notice of Substantial Amendment to the main REC.

Submission of REC application

- 4.38 On the Project Filter page of IRAS the CI must indicate that the study involves ionising radiation. This generates Part B Section 3 of the form, which should be completed by the lead CRE and lead MPE and either signed or electronically authorised prior to submission. Detailed guidance on completion of each question is available on-line by clicking information buttons.

Approval from the environment agencies

- 4.39 If the study requires examinations or treatments using novel radiopharmaceuticals or much higher quantities than are routinely used, the CI and sponsor should note that there may also be statutory requirements to obtain approval from the relevant environment agencies for the UK countries concerned. This does not normally apply in the case of research trials but the possibility cannot be entirely excluded.
- 4.40 Where application has to be made to the environment agencies, the necessary approval may take several months. The costs incurred in preparing the application and the charges levied by the agencies would need to be met by the study funder.

5. IRMER compliance at research sites

- 5.1 The following guidance applies both to the lead site and other sites undertaking radiation exposures as part of the research.
- 5.2 Arrangements for ensuring IRMER compliance at NHS Trusts and other participating research sites will vary. The guidance is not intended to be prescriptive about detailed local procedures.

Preparations

- 5.3 The local Principal Investigator (PI) is advised to notify the relevant R&D office and the Radiology, Radiotherapy and/or Nuclear Medicine Departments at an early stage of plans to conduct research (or participate in a multi-site study) involving radiation exposures. Early discussion will give departments more time to prepare for the research. Advice can be given on local procedures for research governance and compliance with IRMER and other statutory requirements. Where the Chief Investigator is also a local PI,

preparations should include discussion with the R&D office as well as development of the protocol and main REC application (see paragraph 4.4).

ARSAC certificates

- 5.4 In the case of research involving administration of radioactive substances, preparatory work may include application for a research ARSAC certificate from the Department of Health in order to comply with MARS (see paragraphs 3.31-3.34).

R&D application

- 5.5 The local Principal Investigator (PI) at each site must seek management permission to conduct the research from the care organisation by applying to the relevant R&D office. For NHS sites, application should be made using the R&D application form and Site-Specific Information Form (SSI Form) in IRAS. Except in Northern Ireland, the R&D application may be made in parallel to the ethical review. (If a HSC Trust in Northern Ireland is the lead site, R&D approval must be sought before applying to the main REC.) The R&D review will include checks that the local conduct of the study is IRMER compliant.
- 5.6 The PI may be required to complete local paperwork in addition to the SSI Form as part of the internal discussion and authorisation process, so that the relevant departments are supplied with the necessary administrative information to enable them to assist with the study. NHS organisations should consider appointing a central point of contact for research involving ionising radiation.

Local IRMER compliance

- 5.7 The main REC application process generally ensures that any additional radiation exposure required by the protocol is appropriate to the objectives of the research and ethically acceptable. However, there is still a legal requirement for the employer to demonstrate compliance with IRMER for research, in particular that:
- Dose constraints are established and adhered to in studies where there is no health benefit to be expected from the exposure
 - Target dose levels are established where there is some expected health benefit for participants
 - Exposures are individually justified by a Practitioner
 - Individuals participate voluntarily
 - Participants are informed of the risks of exposure.
- 5.8 Departments undertaking research exposures should be aware that the referral is part of a research study and this should be clearly identified on the request card.

Justification by the Practitioner

- 5.9 The PI should identify a suitable individual within the care organisation who is entitled to act as the Practitioner for the site. The expertise required is analogous to that for the lead Clinical Radiation Expert (lead CRE) (see paragraph 4.5). The Practitioner should be a registered health professional

with clinical expertise in the modality involved. Where more than one modality is involved, it may be necessary to seek input from more than one Practitioner.

- 5.10 The Practitioner should review the protocol and main REC application and confirm in writing to the PI and the R&D office that:
- The site can adhere to the protocol.
 - Where local patients would receive additional exposure, this has been identified in the REC application and has been ethically approved by the main REC.
 - Any additional exposure is justified having regard to IRMER.
- 5.11 As with the justification of clinical exposures, the Practitioner must determine that there is sufficient net benefit to allow research exposures to go ahead. In arriving at that decision, he/she is required to consider:
- The specific objectives of the exposure and the characteristics of the individual
 - The potential diagnostic or therapeutic benefits, including direct benefits to the individual and the benefits to society
 - The individual detriment that the exposure may cause
 - The availability of alternative techniques involving less, or no, exposure to ionising radiation
 - The possibility that participants will be participating in other trials involving additional radiation (see Question A17 in the IRAS application form, stating the exclusion criteria for the trial, and Question A32 on involvement in other research).
- 5.12 The Practitioner is required by IRMER to pay special attention to research exposures that have no direct health benefit for participants.
- 5.13 The lead CRE for the research should already have considered these issues in relation to the project as a whole and given the main REC appropriate advice on the suitability of any exposures that would be additional to those undertaken in the course of normal clinical care. In most cases it is expected that the Practitioner will be able to justify the exposures having regard to the assessment by the lead CRE.
- 5.14 Where the Practitioner has concerns that additional exposures may not have been identified in the REC application, or are not justified, it may be helpful first to discuss the issues with the lead CRE and the CI. Amendments may need to be made to the protocol or the Participant Information Sheet, either generally or in relation to the local site, and submitted to the main REC for review. (If an amendment is required, the lead MPE and local MPE should also be consulted before submission in case they wish to suggest changes.) If the concerns cannot be resolved with the lead CRE and CI, or the main REC does not approve the amendments, the Practitioner may exceptionally need to advise the R&D office that the care organisation is unable to take part in the research.

Review by local MPE

- 5.15 The PI should contact the Radiology, Radiotherapy and/or Nuclear Medicine Departments as appropriate and provide a copy of the approved protocol, participant information sheet, supporting documentation from the Practitioner and the following information:
- examinations required
 - number and frequency
 - clinical conditions to be studied
 - age ranges of subjects
 - use of healthy volunteers
 - any other relevant information.
- 5.16 The local MPE should review the protocol and the REC application form and confirm to the PI that the protocol can be performed at the site within the estimated range of dose made by the lead Medical Physics Expert (lead MPE) for the research (see paragraphs 4.22-4.28). (The R&D office may also require written confirmation; local authorisation procedures should be followed.) A local dose constraint or target dose should be established under IRMER. This should be in line with the Total Research Protocol Dose estimated in the REC application (see 4.26). If the local MPE has concerns about the dose estimate it may be helpful to discuss the matter with the lead MPE initially. If the concerns cannot be resolved, the PI may need to refer the issue to the CI. If necessary, a Notice of Substantial Amendment can be submitted to the main REC to notify a variation in the dose estimate for the site and seek ethical approval.
- 5.17 The local MPE will also wish to check that the approved PIS accurately reflects the additional radiation and risk to which local patients will be exposed, and may wish to discuss this with the Practitioner. Any concern should be referred to the PI for discussion with the CI. This aspect of the PIS should not be amended locally without approval from the main REC. If necessary, a Notice of Substantial Amendment may be submitted with a site-specific variation to the information sheet.
- 5.18 In the case of research involving administration of radioactive substances, the local MPE will usually advise on whether a research ARSAC certificate is required (see paragraphs 3.31-3.34) and may assist with the application.

Novel uses of ionising radiation

- 5.19 If the research involves a novel use of ionising radiation (see paragraph 3.35), a Radiation Protection Adviser should be consulted about compliance with the Ionising Radiation Regulations 1999.

Costs

- 5.20 The PI and R&D office should liaise with relevant departments to agree on the costs of the procedures.

Extension to new sites or “subsidiary sites”

- 5.21 Where research is extended to a new site in the course of the study, the relevant Trust or other host organisation should follow the same process described above in order to meet its statutory obligations.
- 5.22 In some cases, a research site may arrange for another organisation to conduct part of the protocol on their behalf, for example because of a shortage of resources or because it is more convenient for a participant to attend a local facility. These organisations may be referred to as “subsidiary sites” and the organisation they are supporting as “main research sites”.
- 5.23 Any separate organisation (e.g. another Trust or a private scanner centre) responsible for conducting part of a research protocol should be regarded as a research site, even though it may not be recruiting participants or conducting the whole of the protocol. If the study is one requiring SSA (e.g. a medicinal trial or device investigation), the subsidiary site must be formally approved by the main REC to take part. However, where the procedures delegated to the site are within the normal clinical competence of the registered health professionals at the site, there is no need to make the normal application for SSA to the local REC or R&D office. The Chief Investigator should notify the main REC by letter. The main REC will normally confirm approval for the subsidiary site without requirement for SSA. (See paragraph 4.32 of the NRES SOPs, available at <http://www.nres.npsa.nhs.uk/news-and-publications/publications/standard-operating-procedures/>)
- 5.24 Where the research procedures delegated to a subsidiary site include the administration of ionising radiation, the employer and relevant health professionals at the subsidiary site are legally responsible for meeting their obligations under IRMER. It is recommended that the MPE and Practitioner at the main research site contact their opposite numbers at the subsidiary site to discuss any issues arising. Any potential for significant variation in radiological practice should be reported to the PI. Exceptionally, discussion may need to take place with the CI and lead MPE and CRE and a Notice of Substantial Amendment submitted to the main REC.

6. Further review and reporting during the study

Substantial amendments

- 6.1 A favourable opinion is required from the main REC before implementing any substantial amendment to an approved study, except where urgent safety measures are required. Detailed guidance is available on the NRES website at: <http://www.nres.npsa.nhs.uk/applicants/after-ethical-review/>
- 6.2 Where substantial amendments include significant changes to ionising radiation exposures (e.g. changes to the modality, dose, number of procedures or participant information, whether study-wide or site-specific), the same principles apply as for approval of the initial application. It is recommended that the following procedures are followed:

- The Chief Investigator should seek further expert advice from the Lead MPE and Lead CRE and enclose their assessments with the Notice of Substantial Amendment form submitted to the main REC.
- The Notice of Substantial Amendment form (with enclosures) should be forwarded to local Principal Investigators together with the favourable opinion letter from the main REC when available.
- The local Principal Investigator should notify the R&D office and seek further advice from the local MPE and Practitioner on the implications of the amendment for local authorisations.

Reporting serious breaches and serious adverse events

- 6.3 Serious breaches of the protocol or Good Clinical Practice, including those related to radiation exposures, should be reported to the main REC by the sponsor or Chief Investigator within 7 days of the matter coming to their attention (see paragraph 9.68 of the NRES SOPs). The R&D office for the site concerned should also be notified.
- 6.4 Serious adverse events, which are unexpected and could be related to the radiation exposures required by the research, should be reported to the main REC by the sponsor or Chief Investigator within 15 days of the event coming to their attention. The SAE report form published on the NRES website should be used (see <http://www.nres.npsa.nhs.uk/applicants/after-ethical-review/>). A copy of the report should be sent to the R&D office for the site concerned and the local MPE.

Enforcement

- 6.5 Responsibility for enforcement of IRMER lies with the inspectorates in each UK country. Any information relating to possible serious non-compliance with the provisions of IRMER should be sent to the relevant lead inspector (see contact points at Appendix 3).

7. Further advice

- 7.1 Further advice on the application of this guidance may be sought from the organisations and individuals represented on the drafting group as follows:

IRMER: researchirmeradvice@hpa.org.uk

Ethical review: queries@nres.npsa.nhs.uk

NHS R&D review: janet.messer@rdforum.vispa.com

HPSS R&D review:
(Northern Ireland) zoe.hunter@bch.n-i.nhs.uk

Clinical radiology: bob.bury@leedsth.nhs.uk
(including the role of the lead CRE and the Practitioner)

Medical physics:
(including the role of the MPE)

giles.morrison@sth.nhs.uk

andy.rogers@nuh.nhs.uk

peter.marsden@uclh.nhs.uk

Nuclear medicine and ARSAC:

thomas.nunan@gstt.nhs.uk

paul.hinton@royalsurrey.nhs.uk

Appendix 1 Members of the drafting group

Name	Post	Organisations represented
Dr. Bob Bury	Consultant Radiologist, Leeds Teaching Hospital	Royal College of Radiologists
Paul Hinton	Consultant Physicist, Medical Physics – Nuclear Medicine, Royal Surrey County Hospital, Guildford	Institute of Physics and Engineering in Medicine, Nuclear Medicine Special Interest Group
Zoe Hunter	Research Co-ordinator, Belfast City Hospital	Northern Ireland Research Governance Working Group Northern Ireland Research Management System User Group NI observer at NHS R&D Forum
Len Key	Co-ordinator, Newcastle and North Tyneside Research Ethics Committee 1	NRES
Joan Kirkbride	Acting Head of Operations (England), NRES	NRES
Dr. Peter Marsden	Head of the Radiation Protection Service, UCL Hospitals NHS Trust	Institute of Physics and Engineering in Medicine, Radiation Protection Special Interest Group
Dr. Janet Messer	Acting Director, NHS R&D Forum	NHS R&D Forum
Giles Morrison	Clinical Scientist, Head of Radiation Protection Services, Sheffield Teaching Hospitals NHS Foundation Trust	Institute of Physics and Engineering in Medicine, Diagnostic Radiology Special Interest Group
David Neal	Head of Policy and Deputy Director, NRES	NRES
Dr. Tom Nunan	Nuclear Medicine Consultant, St. Thomas's Hospital, London	Chairman, ARSAC
Dr. Dipak Patel	Research Manager, Sheffield Teaching Hospitals NHS Foundation Trust	NHS R&D Forum
Andy Rogers	Head of Radiation Physics, Nottingham University Hospitals NHS Trust	British Institute of Radiology Radiation Protection Committee
Kathlyn Slack	Senior Clinical Officer, Medical Exposure Department, HPA-RD	Initially DH, now Health Protection Agency and subsequently advising on behalf of DH

Appendix 2 Glossary

ARSAC	Administration of Radioactive Substances Advisory Committee
CI	Chief Investigator, the investigator with overall responsibility for the conduct of the research and for submission of the ethics application
CRE	Clinical Radiation Expert
IRAS	Integrated Research Application System (see https://www.myresearchproject.org.uk)
IRMER	Ionising Radiation (Medical Exposure) Regulations 2000
Main REC	The single Research Ethics Committee responsible for giving an ethical opinion on a new application to conduct research.
MARS	Medicines (Administration of Radioactive Substances) Regulations 1978
Modality	Imaging/treatment method
MPE	Medical Physics Expert
PI	Principal Investigator, the investigator responsible for the conduct of research at a local site
REC	Research Ethics Committee
SSA	Site-specific assessment undertaken for the purpose of the ethical review either by a local REC or NHS R&D office with responsibility for the site. Application for SSA is made using the Site-Specific Information Form in IRAS.
TRPD	Total Research Protocol Dose

Appendix 3 IRMER Inspectorate contacts for the UK

England

Rina Rabadia
IRMER Co-ordinator
Healthcare Commission
1st Floor, Finsbury Tower
103-105 Bunhill Row
London
EC1 8TG
Tel: 0207 9448 9393

The following dedicated email address may be used only for the notification of incidents resulting in a person receiving a radiation dose much greater than intended:

IRMER@healthcarecommission.org.uk

Northern Ireland

Inspectorate for the Ionising Radiation (Medical Exposure) Regulations
DHSSPS
Castle Buildings
Stormont
Belfast
Tel: 028 9052 0710
Email: glenda.mock@dhsspsni.gov.uk

Scotland

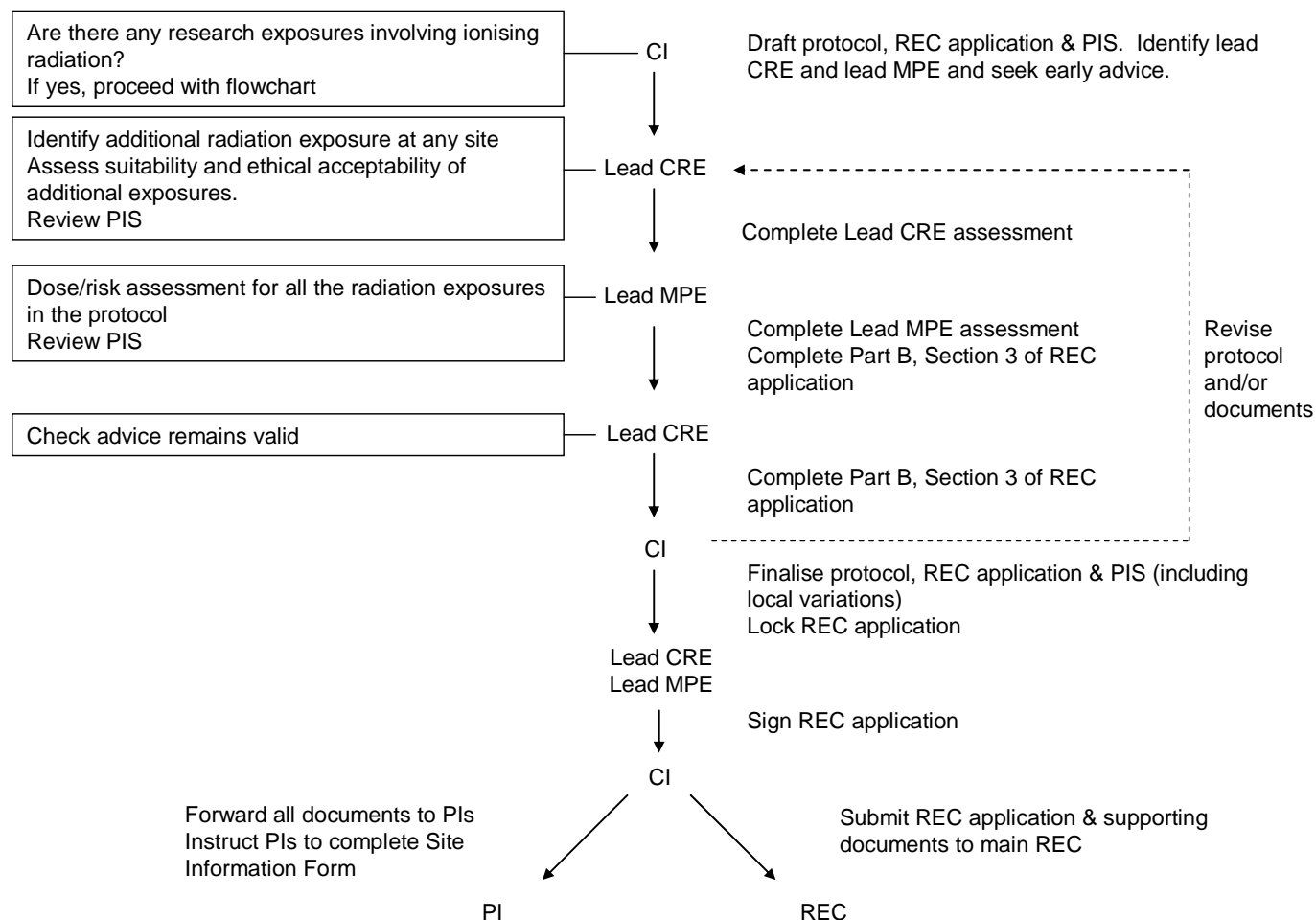
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Appendix 4 Flowcharts

Process for finalising protocol and obtaining favourable opinion from REC



Process for meeting local requirements and NHS permission

*Local processes for internal authorisation should be followed – contact the R&D office.
Consult local experts as early as possible.*

