

Medical Physics Expert (MPE) Review Procedure

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1 About this document

The MPE Review Procedure clarifies the information requirements for the MPE assessments. This document is maintained by the HRA Four Nations Radiation Assurance Working Party, and was initially produced by the Radiation Guardians Group, which assisted with the initial development of Radiation Assurance.

Feedback and/or suggestions for updates to the MPE Review Procedure should be sent to: radiation.assurance@hra.nhs.uk. Feedback received will be considered by the Four Nations Radiation Assurance Working Party.

Where this guidance differs for studies using Radiation Assurance, this is specified.

For studies not using Radiation Assurance: The MPE assessments should be provided in IRAS, however, some applicants may prefer the MPE to provide their review by email.

For Radiation Assurance studies only: The MPE assessment should be entered into section F2 of the Research Exposure Form. This will be later transferred into IRAS. This guidance should be used in conjunction with the Reviewer Handbook, which clarifies the logistics of the process rather than the contents of the review.

2 Generic Risk Statements

This section describes how the generic risk statements should be chosen for the assessment in IRAS and also to be used in the participant information sheet (PIS). It gives guidance on which situations will require more information in IRAS than that which is present in the generic risk statement on its own.

2.1 General procedure

2.1.1 Review the research exposures in the application and determine which category they fall into using the information in the [Generic ionising radiation risk statements](#) guidance. It should be noted that where the study includes different participant cohorts it may be necessary to choose different categories for the cohorts and you should follow this procedure accordingly for each category used.

For studies not using Radiation Assurance: please refer to the research exposures listed in Part A Question 19 in the IRAS application.

For Radiation Assurance studies only: please refer to the research exposures listed in section F1 of the Research Exposure Form.

2.1.2 No dose and risk assessment is required if either of the following apply:
a. The exposures are all unequivocally standard of care; or

- b. Participants have a poor prognosis, unless there is a possibility of deterministic effect such as skin erythema, and/or the study involves nuclear medicine exposures.

For studies not using Radiation Assurance: The Lead MPE should state estimated cohort survival in Question C1 of Part B Section 3 in IRAS.

For Radiation Assurance studies only: The Lead MPE should state estimated cohort survival in the first box of question C1 of section F2 in the Research Exposure Form.

2.1.3 If the exposures fall into any of the other categories, a dose and risk assessment is required as described in 2.2-2.4.

2.1.4 The Lead MPE for the study should liaise with any other MPEs required and combine all their responses into a single assessment.

For studies not using Radiation Assurance: The Lead MPE should list the names, job titles, employers and professional registration numbers of the other MPEs involved in Question C1 of Part B Section 3 in IRAS, and indicate whether any of these MPEs are named in the protocol.

For Radiation Assurance studies only: The Lead MPE should list the names, job titles, employers and professional registration numbers of the other MPEs involved in the first box of question C1 of section F2 in the Research Exposure Form, and indicate whether any of these MPEs are named in the protocol.

2.1.5 Use the appropriate IRAS statement and complete it if required (entries in red). Add a bespoke statement on deterministic risks where required. If mammography is involved, a specific risk of breast cancer will be required. If a bespoke statement is required, structure as follows:

- a. Present the total protocol dose i.e. the dose of all research exposures throughout the study period
- b. Express the protocol dose in terms of natural background radiation
- c. Indicate whether all/most/some of the protocol dose is additional to routine clinical care
- d. Identify the nature of the radiation risks (cancer, skin injury etc.)
- e. Present the risk of cancer induction expressed as xx %
- f. Present other risks as xx % if possible, or qualitatively if not.

For studies not using Radiation Assurance: enter the statement into Question C1 of Part B Section 3 in IRAS.

For Radiation Assurance studies only: enter the statement into the first box of question C1 in F2 of the Research Exposure Form

2.1.6 Where there is a difference in the maximum and median number of exposures this should be specifically commented on in the dose/risk assessment.

For studies not using Radiation Assurance: provide a comment if required in Question C1 of Part B Section 3 in IRAS.

For Radiation Assurance studies only: provide a comment if required in the first box of question C1 of F2 in the Research Exposure Form.

2.1.7 Some protocols indicate that additional research exposures might be required as a result of side effects of study treatment or for other clinical reasons. Whilst these may reasonably be expected as part of the study, in some instances it will not be possible to say how many exposures there will be, or what they might be.

For studies not using Radiation Assurance: provide a comment if required in Question C1 of Part B Section 3 in IRAS. There is no need to specify any further information about these exposures in Questions A1 or B1 in Part B Section 3, or in A19 of the IRAS form.

For Radiation Assurance studies only: provide a comment if required in the first box of question C1 of F2 in the Research Exposure Form. There is no need to specify any further information about these exposures in questions A1 or B1 of F2 in the Research Exposure Form.

2.1.8 Some protocols include research exposures for which there is no clear end date e.g. treatment is until disease progression, or follow-up is until death. The dose and risk calculated should indicate the expected dose and risk based on the latest likely end date of the exposures; in the previous two examples this would be based on expected time to disease progression or maximum life expectancy. A comment should be provided in the dose/risk assessment to reference the potential additional dose and risk if the expected end date of the exposures is exceeded.

For studies not using Radiation Assurance: provide a comment if required in Question C1 of Part B Section 3 in IRAS.

For Radiation Assurance studies only: provide a comment if required in the first box of question C1 of F2 in the Research Exposure Form.

2.1.9 If the study does not require a dose and risk assessment as per 2.1.2, the following should occur:

For studies not using Radiation Assurance: Question B1 of Part B Section 3 in IRAS should list the procedures and number of exposures but without doses, and no dose/risk assessment needs to be written in

Question C1 of Part B Section 3 in IRAS, only the generic risk statement.

For Radiation Assurance studies: Question B1 in F2 of the Research Exposure Form should list the procedures and number of exposures but without doses, and no dose/risk assessment needs to be written in the first box of question C1, only the generic risk statement.

2.1.10 The Lead MPE should work with any additional MPE reviewers and the Lead Clinical Radiation Expert (CRE) to assess the suitability of information about the risks of exposure to ionising radiation in the PIS.

For studies not using Radiation Assurance: It should be noted that where a statement is already provided in the PIS it does not have to be one of the generic risk statements to be considered suitable. Where the information about the risks of ionising radiation exposure is not suitable, the Lead MPE should ask the applicant to make changes accordingly in line with 2.1.11-2.1.14.

For Radiation Assurance studies only:

- a. The Lead MPE should indicate in the first check box of C1 in F2 whether the applicant has provided a risk statement in the PIS. Where no statement was provided the Lead MPE should follow 2.1.11-2.1.14.
- b. Where a statement has already been provided by the applicant the Lead MPE and Lead CRE should assess whether the statement is acceptable and indicate this in the second check box of C1 in F2. It should be noted that the statement does not have to be one of the generic risk statements to be considered suitable. Where the statement is deemed unacceptable, the Lead MPE should follow the instructions in 2.1.11-2.1.14.

2.1.11 Where required, copy the appropriate PIS statement to the MPE assessment and modify entries in red as appropriate. Add a bespoke statement on deterministic risks where required as per 2.1.12.

For studies not using Radiation Assurance: Copy the PIS statement into Question C1 of Part B Section 3 in IRAS.

For Radiation Assurance studies only: Copy the PIS statement into the second free text box of C1 in F2 of the Research Exposure Form.

2.1.12 If a bespoke statement is required in the PIS, it should be structured as follows:

- a. Identify the procedures that will expose participants to ionising radiation
- b. Indicate whether all/most/some of the procedures or total dose are additional to routine clinical care
- c. Describe the nature and magnitude of the radiation risks associated with participation in the study.

2.1.13 Any misleading wording in the PIS that needs to be removed should also be highlighted in the MPE assessment.

For studies not using Radiation Assurance: highlight wording for removal in Question C1 of Part B Section 3 in IRAS.

For Radiation Assurance studies only: highlight wording for removal in the second free text box of C1 in F2 of the Research Exposure Form.

2.1.14 The Lead MPE should not authorise the application form in IRAS until the final risk wording in the PIS has been agreed with the applicant.

2.1.15 The Lead MPE should enter their details into the “Details of Lead MPE” section:

For studies not using Radiation Assurance: enter these details into Question C3 in Part B Section 3 of IRAS.

For Radiation Assurance studies only: enter these details at the end of section C of F2 in the Research Exposure Form, including their HRA registered reviewer number.

2.2 Studies without radiotherapy

2.2.1 Calculate the total protocol dose (i.e. the dose of all research exposures throughout the study period) and estimate the risks as described in sections [3](#) and [4](#) of this document.

2.2.2 Estimate the number of years of average natural background radiation in the UK that the total dose is equivalent to, using a UK average of 2.3 mSv per year given in the Public Health England report [PHE-CRCE-026 \(2010\)](#).

2.2.3 Formulate an opinion as to whether all/most/some of the exposures/total radiation dose are additional to routine clinical care.

For studies not using Radiation Assurance: Use Part A Question 19 of IRAS to help you do this.

For studies using Radiation Assurance: Use section F1 of the Research Exposure Form to help you do this.

2.2.4 If the study lends itself to the use of generic statements, select the appropriate category, copy the appropriate IRAS statement to the dose/risk assessment and complete it (entries in red).

For studies not using Radiation Assurance: Add the statement into the dose/risk assessment box in Question C1 of Part B Section 3 in IRAS.

For studies using Radiation Assurance: Add the statement into the first dose/risk assessment box in C, section F2 of the Research Exposure Form.

Additionally, include a statement on deterministic risks where required. If mammography is involved, a specific risk of breast cancer will be required. If a bespoke statement is required, include it in your assessment, structured as follows:

- a. Present the total protocol dose i.e. the dose of all research exposures throughout the study period
- b. Express the protocol dose in terms of natural background radiation
- c. Indicate whether all/most/some of the protocol dose is additional to routine clinical care
- d. Identify the nature of the radiation risks (cancer, skin injury etc.)
- e. Present the risk of cancer induction expressed as xx %
- f. Present other risks as xx % if possible, or qualitatively if not.

2.2.5 Your assessment can also be used to highlight any misleading wording in the PIS that needs to be removed, in line with section 2.1 of this Procedure. In any case the MPE should not authorise the application form in IRAS until the final version of the PIS has been agreed.

2.3 Studies where radiotherapy is part of routine care and not the intervention under investigation

2.3.1 Calculate the doses and estimate risks as described in sections [3](#) and [4](#). When preparing the dose and risk assessment, consider the radiotherapy and all other exposures together. Use professional judgement to assess the risks from all other ionising radiation exposures with respect to the radiotherapy risk, being aware that the suggested radiotherapy related second cancer risk is NOT a lifetime risk.

2.3.2 Where the dose and risk assessment confirms that the radiation dose/risk is dominated by that from the radiotherapy, a generic statement may be used. Select statement 5 of the Generic ionising radiation risk statements.

For studies not using Radiation Assurance: Add the statement into the dose/risk assessment box in Question C1 of Part B Section 3 in IRAS.

For studies using Radiation Assurance: Add the statement into the first dose/risk assessment box in C, section F2 of the Research Exposure Form.

2.3.3 If the dose/risk is not dominated by that from the radiotherapy edit the generic statement to provide a bespoke statement about the dose and the risk.

For studies not using Radiation Assurance: Add the bespoke statement into the dose/risk assessment box in Question C1 of Part B Section 3 in IRAS.

For studies using Radiation Assurance: Add the bespoke statement into the first dose/risk assessment box in C, section F2 of the Research Exposure Form.

2.4 Studies where radiotherapy is the intervention under investigation

2.4.1 Calculate the doses and estimate risks as described in sections [3](#) and [4](#). When preparing the dose and risk assessment, consider the radiotherapy and all other exposures together. Use professional judgement to assess the risks from all other ionising radiation exposures with respect to the radiotherapy risk, being aware that the suggested radiotherapy related second cancer risk is NOT a lifetime risk.

2.4.2 Where the dose and risk assessment confirms that the radiation dose/risk is dominated by that from the radiotherapy, a generic statement may be used. Select statement 6 of the Generic ionising radiation risk statements.

For studies not using Radiation Assurance: Add the statement into the dose/risk assessment box in Question C1 of Part B Section 3 in IRAS.

For studies using Radiation Assurance: Add the statement into the first dose/risk assessment box in C, section F2 of the Research Exposure Form.

2.4.3 The bespoke statement section describing the differences between the intervention and routine care should mention variations in any of the components of the radiotherapy episode (as defined in section [3.7](#)).

2.4.4 For both the target and the organs at risk comment on any changes from standard of care in the dose and/or changes in the volume irradiated (e.g. whole organ versus partial organ).

3 Calculating Doses

This section describes how to assign typical doses for each research exposure in order to declare them in the MPE dose/risk assessment.

Where studies involve healthy volunteers, it must be clear what the total annual ionising radiation exposure is, and the ICRP 62 guidelines should be referenced as any dose should be related to societal benefit. Particular regard should be paid to any nuclear medicine exposures as this information will be used by ARSAC.

MPEs should use their judgement when calculating doses in line with national diagnostic reference levels (NDRLs).

For studies not using Radiation Assurance:

- For nuclear medicine procedures, ensure that each procedure has a separate entry in Question A1 of Part B Section 3 in IRAS for each radiopharmaceutical which can be used for that procedure.
- The total dose will need to be included in IRAS Part B Section 3 Questions A1 and B1 as appropriate for each procedure, and also for each participant/healthy volunteer group in IRAS Part B Section 3 Question A2.
- The Lead MPE is expected to ensure that the total protocol dose referenced in the MPE review is the correct sum of all the figures listed in IRAS Questions A and B of Part B Section 3.
- In all instances, published data should be used wherever possible to calculate doses of ionising radiation to participants.

For Radiation Assurance studies only:

- For nuclear medicine procedures, ensure that each procedure has a separate entry in question A1 in section F2 of the Research Exposure Form for each radiopharmaceutical which can be used for that procedure.
- The total dose will need to be included in questions A1 and B1 of section F2 of the Research Exposure Form as appropriate for each procedure, and also for each participant/healthy volunteer group in question A2 of section F2 of the Research Exposure Form.
- The Lead MPE is expected to ensure that the total protocol dose referenced in the MPE review is the correct sum of all the figures listed in questions A and B in section F2 of the Research Exposure Form.
- In all instances, published data should be used wherever possible to calculate doses of ionising radiation to participants. Where it is not possible to use published data, any unpublished data used to complete the review should be

forwarded to the HRA with the completed review for quality control purposes only.

3.1 Diagnostic and interventional radiology (excluding mammography and CT) in adults

3.1.1 Where available use typical effective doses (E-103) in mSv given in tables 11, 12 and 13 of report [HPA-CRCE-012 \(2010\)](#).

3.1.2 If the examination is not listed in HPA-CRCE-012, check whether it is listed in tables 8, 11, 14, 16 or 19 of report [HPA-CRCE-034 \(2012\)](#).

HPA-CRCE-034 gives values of dose-area product (DAP) and entrance skin dose (ESD), not effective dose. If these values are used they will need to be converted to effective dose in mSv. Use the conversion factors for E-103 given in tables 7 and 15 of report [HPA-CRCE-028 \(2011\)](#).

If conversion factors are unavailable in report HPA-CRCE-028, use values given in the appendix of report [NRPB-W4](#) (this only has conversion factors for E-60)

3.1.3 If the examination effective dose is not listed in any of these reports then professional judgement should be used to establish a typical dose. When making this judgment the following should be considered:

- a. Where possible use published dose data, otherwise use local data.
- b. Consider variation between sites. This is particularly important for interventional procedures where doses may vary by an order of magnitude due to variations in equipment type and protocol selection. You will probably have a view as to whether the dose data, particularly local data, is likely to be at the low or high end of national practice and could scale accordingly.

3.2 Diagnostic and interventional radiology imaging in children

3.2.1 There is a limited amount of published paediatric dose data covering a small range of examinations. Where available use values of effective dose (E-60) given in table 24 of report HPA-CRCE-028, or values of DAP and ESD given in tables 15, 16 and 19 of report HPA-CRCE-034 (2012). The latter will need to be converted to effective dose in mSv. Use the conversion factors for E-60 given in table 25 of report HPA-CRCE-028 where available. If the examination is not listed then professional judgement should be used to establish a typical dose, using local data where available.

3.3 Computed tomography

- 3.3.1 Use the mean effective dose E-103 of the national distribution from the 2011 survey published in Table 6 of Shrimpton PC, Jansen JTM, Harrison JD. *Updated estimates of typical effective doses for common CT examinations in the UK following the 2011 national review.* (Br J Radiol 2016; 89: 20150346.)
- 3.3.2 If the examination is not listed in this report then professional judgement should be used to establish a typical dose. This will include hybrid CT. Either the ImPACT or CT-Expo dose calculators could be used for adults and the CT-Expo dose calculator for children. Alternatively use the data in Shrimpton et al or Deak et al *Multisection CT protocols: sex- and age-specific conversion factors used to determine effective dose from dose-length product* (Radiol 2010; 257:158-166). Convert published or local dose length product (DLP) values to effective dose in mSv using the conversion factors (E-103) in Shrimpton et al (Table 6, 2011 survey) or in Deak et al.
- 3.3.3 If any hybrid nuclear medicine procedures may be performed (SPECT/CT, PET/CT) then the details of each hybrid procedure and the resulting radiation dose(s) should be detailed separately.

For studies not using Radiation Assurance: Detail the hybrid procedure in IRAS Part B Section 3 Question A1.

For Radiation Assurance studies only: Detail the hybrid procedure in question A1 of section F2 of the Research Exposure Form.

3.4 Mammography

- 3.4.1 Effective dose is not a suitable dose descriptor for mammography. Mean glandular dose to the breast in mGy should be used instead. A mean glandular dose of 1.6 mGy for medio-lateral oblique views and 1.4 mGy for cranial-caudal views, giving a total dose for standard two view mammography of 3.0 mGy, is recommended as indicated in Oduko J., Young K. (2016) *Patient Dose Survey of Mammography Systems in the UK in 2013–2015.* (In: Tingberg A., et al (eds) Breast Imaging. IWDM 2016. Lecture Notes in Computer Science, vol 9699. Springer, Cham). Dose estimates will need to be amended for magnification, stereotactic and tomosynthesis exposures.

3.5 Diagnostic nuclear medicine

- 3.5.1 For each procedure, use the effective dose for the radiopharmaceutical and the diagnostic reference level [standard administered activity] listed in the [ARSAC Notes for Guidance](#). Refer directly to the online document – it will be updated periodically and released as a softcopy pdf only.
- 3.5.2 Paediatric administrations should follow the recommendations given in the ARSAC Notes for Guidance. Data is listed for those radiopharmaceuticals considered by ARSAC to be in routine clinical use.

- 3.5.3 If the protocol for the procedure specified by the trial requires an administered activity that differs from the diagnostic reference level [standard administered activity] in the ARSAC guidance then calculate the effective dose (ED) for the specified activity by interpolation and state this ED and the specified activity in the entry for the radiopharmaceutical, and add a statement explaining the rationale for the trial-specific protocol in the text of the dose and risk assessment.
- 3.5.4 If the radiopharmaceutical does not appear in the Notes for Guidance state the effective dose (mSv/MBq) as cited in a published dosimetry assessment for the tracer, and make a statement explicitly referencing this ED and the cited publication in the text of the MPE dose and risk assessment.

For studies not using Radiation Assurance: Ensure that its full chemical name is stated in the table entry for the radiopharmaceutical in IRAS Part B Section 3 Question A1.

For Radiation Assurance studies only: Ensure that its full chemical name is stated in the table entry for the radiopharmaceutical in question A1 of section F2 of the Research Exposure Form.

- 3.5.5 If no published dosimetry assessment exists, then in line with the recommendations in the ARSAC Notes for Guidance, cite the most definitive dosimetry data currently available (where this may be obtained via personal communication); and where it may comprise pre-clinical data and/or preliminary human biodistribution data if no formal human dosimetry assessment has yet been performed. If the trial constitutes a 'first in human' study for the radiopharmaceutical under study this should be clearly stated. The applicant is encouraged to contact the ARSAC Secretariat here for specific advice, but pre-clinical data is typically required to support an estimate of the expected human dosimetry unless the effective dose is very low. ARSAC approval is normally granted for studies of this type with the expectation that data will be obtained that can be used to conduct a preliminary human dosimetric assessment and this used to support further study applications.
- 3.5.6 The maximum total effective dose per individual resulting from the sum of radiopharmaceutical/radionuclide administrations only should be entered into the Details of study participants section.

For studies not using Radiation Assurance: This is within Part B Section 3 Question A2.

For Radiation Assurance studies only: This is in question A2 of section F2 of the Research Exposure Form.

- 3.5.7 If any hybrid CT procedures may be performed (SPECT/CT, PET/CT) then the details of each hybrid procedure and the resulting radiation dose(s) should be detailed separately.

For studies not using Radiation Assurance: Detail the hybrid procedure in IRAS Part B Section 3 Question B1.

For Radiation Assurance studies only: Detail the hybrid procedure in question B1 of section F2 of the Research Exposure Form.

3.6 Molecular radiotherapy (radionuclide therapy)

- 3.6.1 There is great variability in the study design for research trials involving radionuclide therapy. It is not therefore possible to give prescriptive guidance, but the following advice highlights what should be presented within the MPE dose and risk assessment.
- 3.6.2 Note that any additional and associated diagnostic radionuclide imaging, CT imaging and other non-imaging radionuclide procedures specified by the study protocol should also be detailed alongside the therapeutic procedure(s), in accordance with the guidance provided elsewhere in this document. All investigations subject to IR(ME)R performed for the purpose of therapy, dosimetry and/or post-treatment assessment and monitoring are expected to be clearly listed, with a statement of the specific purpose for each.
- 3.6.3 The therapeutic radiopharmaceutical should be clearly detailed in a specific table entry.
- 3.6.4 This will include a statement of the therapeutic purpose, the radionuclide label, full details of the chemical form, the route of administration and number of administrations. The administered activity per administration and intended radiation dose prescription per administration should be specified, the full details of which should be contained within the text of the radiation dose and risk assessment.

For studies not using Radiation Assurance: the table entry is within IRAS Part B Section 3 Question A1.

For Radiation Assurance studies only: the table entry is in question A1 in section F2 of the Research Exposure Form.

- 3.6.5 The total radiation dose to the tumour, target organ or critical organ (as per the study protocol) resulting from the therapeutic radiopharmaceutical administration only should be entered within the “total dose or target tissue dose per individual” entry of the appropriate table. It is not appropriate to state an effective dose here.

For studies not using Radiation Assurance: The table for “total dose or target tissue dose per individual” is in Part B Section 3 Question A2.

For Radiation Assurance studies only: The table for “total dose or target tissue dose per individual” is in question A2 of section F2 in the Research Exposure Form.

3.6.6 If prospective 'tracer dose(s)' of the therapeutic radiopharmaceutical are to be used, or where imaging is to be performed by labelling the pharmaceutical with a different radionuclide for dosimetry purposes, then this should be included in a specific table entry, which should clearly define the purpose of the exposure.

For studies not using Radiation Assurance: the table entry is within IRAS Part B Section 3 Question A1.

For Radiation Assurance studies only: the table entry is in question A1 in section F2 of the Research Exposure Form.

3.6.7 The dose and risk assessment should re-state the name of the therapeutic radiopharmaceutical, together with its ARSAC procedure code if available (refer to the ARSAC Notes for Guidance).

For studies not using Radiation Assurance: the dose and risk assessment is within IRAS Part B Section 3 Question C1.

For Radiation Assurance studies only: the dose and risk assessment should be included in the first box of question C1 in section F2 of the Research Exposure Form.

3.6.8 If the trial features a novel radiopharmaceutical that does not appear in the Notes for Guidance, selected published references to its previous use in patients should be given (and soft copy of these should be supplied to the ARSAC). If the trial is a 'first-in-human' study for the radiopharmaceutical then summary pre-clinical biodistribution, organ dose and toxicity data should be detailed. Fuller data may be required for review by the ARSAC and should be available for submission if requested. The applicant is specifically encouraged to contact the ARSAC Secretariat for advice here.

3.6.9 There are many different methods for determining the administered activity of the therapeutic radiopharmaceutical, including, but not limited to:

- a. Standard activity
- b. Activity calculated per kg body weight
- c. Activity calculated using patient BSA
- d. Delivery of a specific absorbed radiation dose to tumour and/or target organs
- e. Delivery of a maximum absorbed radiation dose to one or more critical organs

3.6.10 The method specified by the study protocol for the therapeutic activity/dosing prescription should be clearly stated within the dose and risk assessment. The level of detail included in the dose assessment should be proportionate to the complexity of the methodology but should be sufficient to allow ARSAC to review this specific aspect of the study.

- 3.6.11 Where relevant, information should be included outlining the methodology to be used to calculate absorbed radiation doses e.g. retrospective organ and/or whole body retention data obtained by multiple time-point imaging, probe measurements and/or other biodistribution data. Where prospective 'tracer doses' or imaging studies are used, the details of this should be included in the dose assessment.
- 3.6.12 If the study design additionally follows a 'dose escalation' model, then this should be clearly stated in sufficient detail to allow the ARSAC to specifically review this aspect of the study. The dose assessment should include a detailed statement of the dose escalation and cohort model, with a clear account of the escalation steps to be followed and the dose and/or toxicity criteria to be used to reject further escalation.
- 3.6.13 If sequential gamma camera and/or PET imaging is required for dosimetry and/or post-treatment monitoring then the modality(ies) and protocol(s) should be clearly stated (SPECT, planar, whole body, mixed) and if hybrid CT imaging (for SPECT/CT, PET/CT) is required then the dose assessment should include an assessment of the expected resulting CT dose(s). This information should be supplied and included within the relevant parts of the assessment, in accordance with the guidance provided in this document.
- 3.6.14 The study protocol may also require the protocolled administration of concomitant medication administered to alter the biodistribution of the therapeutic radiopharmaceutical, and/or to provide a protective effect to critical organs (e.g. thyroid blocking, reno-protective amino acids). Similarly, the study protocol may also require the protocolled administration of one or more radiosensitising agent(s). If applicable, the purpose and prescription of the agents to be used should be clearly stated in sufficient detail to allow the ARSAC to specifically review this.
- 3.6.15 The radiation dose and risk assessment addressing the effective dose resulting from all purely diagnostic and dosimetric radiopharmaceutical administrations, and other ionising radiation exposures should be performed in accordance with the guidance elsewhere in this document. This aspect of the dose assessment should be separate from that of the radiation dose to the patient resulting from the administration of the therapeutic radiopharmaceutical.

3.7 Radiotherapy-related exposures (general guidance)

- 3.7.1 A radiotherapy MPE is expected to be involved in all studies where radiotherapy is indicated.
- 3.7.2 Diagnostic radiology and/or nuclear medicine MPE(s), as appropriate, should be involved in the MPE review process for a study where radiotherapy is the intervention under investigation.

- 3.7.3 It should not be assumed that as the radiotherapy prescription dose is high that all other ionising radiation exposures are negligible or insignificant. Whilst it is likely that the radiotherapy treatment dose will dominate the total radiation burden, statements about the relative contributions of radiotherapy treatment and other exposures can be justified only where dose data have been reviewed.
- 3.7.4 Radiotherapy can be considered as an episode of treatment which includes pre-treatment imaging, treatment and on-treatment imaging (concomitant/image guidance) and any imaging for radiotherapy treatment adaptation. It includes imaging which is used as part of the radiotherapy planning and treatment process e.g. PET or PET/CT (see [References, 6.1.1](#)). Dose estimates should be provided for all these radiotherapy related exposures, so that a full picture of the radiation burden is obtained.
- 3.7.5 This guidance assumes all non-radiotherapy exposures within the study (i.e. diagnostic, follow-up etc.) have been considered and assigned an effective dose or mean glandular dose, by an appropriate MPE.

3.8 Studies where the radiotherapy is part of routine care and not the intervention under investigation

- 3.8.1 In the dose and risk assessment state the radiotherapy treatment as one of the procedures with the expected standard radiotherapy prescription(s) given in Gy with the standard number of fractions for the treatment.

For studies not using Radiation Assurance: the dose and risk assessment is within IRAS Part B Section 3 Question C1.

For Radiation Assurance studies only: the dose and risk assessment should be included in the first box of question C1 in section F2 of the Research Exposure Form.

- 3.8.2 For studies using external beam radiotherapy, estimate the rest-of-body dose bath from leakage and scattered radiation as follows:
- Use an estimate of 0.1% of the prescription dose for combined leakage and scattered radiation contribution to distant organs - this will be of the order of tens of mGy. (See [6.1.1](#) for the reference and section [5.3](#) for comment)
 - State the rest-of-body estimate in mSv (weighting factors unnecessary) in the dose and risk assessment.
 - For brachytherapy the rest of body dose bath may be considered low enough not to be considered in the dose estimate.

3.9 Studies where radiotherapy is the intervention under investigation

- 3.9.1 Pre-treatment imaging:

- a. Determine the type and number of radiotherapy planning sessions e.g. CT, 4D CT, PET/CT.
- b. Include each type of planning session with a label of 'Pre-treatment imaging – [insert scan type]', number of scans and a dose estimate.

For studies not using Radiation Assurance: Include this in IRAS Part B Section 3 Question B1.

For Radiation Assurance studies only: Include this in question B1 of section F2 of the Research Exposure Form.

3.9.2 Radiotherapy treatment:

- a. Review the radiotherapy prescription(s). Enter the radiotherapy treatment as one procedure and state the radiotherapy dose prescription(s) in Gy with the number of fractions for each phase and/or trial arm of the study.

For studies not using Radiation Assurance: Include this in IRAS Part B Section 3 Question B1.

For Radiation Assurance studies only: Include this in question B1 of section F2 of the Research Exposure Form.

3.9.3 On-treatment imaging:

- a. Determine the type and number of radiotherapy on-treatment sessions.
- b. Multicentre radiotherapy trials often allow a range of on-treatment imaging technologies e.g. 2D/3D kV/MV.
- c. In addition, a radiotherapy trial may permit a range of verification protocols e.g. daily imaging with on-line correction or, imaging for the first three fractions then weekly for the treatment duration. These details should be stated in the protocol.
- d. If these are not well specified in the study protocol use the National Radiotherapy Implementation Report (see [6.1.3](#)) to guide a choice of a verification regime appropriate to the treatment site and the complexity of the radiotherapy, and hence obtain the number of imaging sessions.

For studies not using Radiation Assurance: Include this in IRAS Part B Section 3 Question B1.

For Radiation Assurance studies only: Include this in question B1 of section F2 of the Research Exposure Form.

3.9.4 Estimate doses from the radiotherapy treatment and imaging to one or two main organs at risk (see Appendix sections [5.1 - 5.3](#) for comment).

- a. The research ethics committee needs to understand how a new intervention compares to standard treatment. For radiotherapy studies providing information on the dose to the target and representative organs at risk is appropriate.
- b. Estimate the rest of body dose bath from leakage and scattered radiation where the radiotherapy is external beam. This dose can be

considered as the radiotherapy dose contribution to an appropriate distant radiosensitive organ.

- i. Use an estimate of 0.1% of the prescription dose for combined leakage and scattered radiation contribution to distant organs - this will be of the order of tens of mGy. (see [6.1.2](#))
 - ii. For brachytherapy the rest of body dose bath may be considered low enough not to be considered.
- c. State the chosen organs at risk and distant organ below the statement of the radiotherapy prescription(s) and give the estimated dose from the radiotherapy treatment.
 - d. For the same organs at risk and distant organ enter the estimated dose from the imaging.

For studies not using Radiation Assurance: Include this in the dose/risk assessment in IRAS Part B Section 3 Question C1.

For Radiation Assurance studies only: Include this in the dose/risk assessment in the first box of question C1 in section F2 of the Research Exposure Form.

4 Estimating the risk of cancer induction

4.1 Cancer risk from effective dose

- 4.1.1 The lifetime cancer risk associated with medical x-ray examinations has previously been estimated in HPA-CRCE-028, on the basis of the risk models described in ICRP Publication 103. Based on this work, it is recommended that the lifetime cancer risk for a standard adult cohort is taken as 5×10^{-5} per mSv. This figure is based on the gender-average of the whole-body data for 20-69 year olds, as presented in Table 29 of HPA-CRCE-028. This figure is comparable to the nominal risk coefficients presented in ICRP 103, which have historically been used for such calculation.
- 4.1.2 Although the above data is based on x-ray exposures, given the underlying uncertainty in the process of dose and risk estimation, it is judged reasonable to also apply this figure to diagnostic nuclear medicine exposures.
- 4.1.3 The data of HPA-CRCE-028 could be used to establish corrections to estimates of risk for body-part, age and gender although in most cases such corrections are deemed unnecessary in the context of ethical approval, given the underlying uncertainty in the whole process. However, modifiers for age may be appropriate for elderly study cohorts and necessary for paediatric study cohorts. Table 1 provides suitable risk modifiers to be used in these instances, based on Table 29 of HPA-CRCE-028.

Risk in relation to age (years)	Multiplication factor for risk
Any cohort involving children under 10	x 2.5
10-17	x 2
18 and over	x 1
50 and over	x 0.7
70 and over	x 0.3

Table 1. Age-dependent modifiers to the standard cancer risk coefficient of 5×10^{-5} per mSv.

- 4.1.4 Some study cohorts may include individuals with heightened radiosensitivity compared to the general population, e.g. due to genetic factors. It is recommended that the additional radiation-induced cancer risk to these individuals is estimated only when values for the additional risk are available and validated in the scientific literature.

4.2 Cancer risk from mean glandular dose to the breast

- 4.2.1 In mammography, only the breast is exposed to ionising radiation. It is therefore not appropriate to estimate effective dose and use the radiation-induced lifetime cancer risk coefficients above. Risk coefficients applicable to mean glandular dose should be used. Furthermore, these risk coefficients change by approximately a factor of 2 between each decade of age range.

Table 2, below, provides suitable risk coefficients. These use values taken from table 2 of report HPA-CRCE-028 (which uses the ICRP 103 excess absolute risk model), but these have been multiplied by 2 to correct to a DDREF of 1 as proposed by Warren et al *Radiation risk of breast screening in the UK with digital mammography* (Br J Radiol 2016; 89:1067). If risk coefficients are required for age ranges not given in Table 2, the values given in report HPA-CRCE-028 multiplied by 2 should be used.

Risk in relation to age (years)	Risk coefficient per mGy
40-49	1.7×10^{-5}
50-59	9.0×10^{-6}
60+	4.2×10^{-6}

Table 2. Radiation-induced lifetime cancer risk coefficients to be used with mean glandular dose to the breast.

4.3 Cancer risk from radiotherapy

4.3.1 Studies where radiotherapy is part of routine care and not the intervention under investigation

- a. Use the value of 5 excess cancers per 1000 adult patients treated at 15 years post radiotherapy (Berrington et al (6.1.4); also see 5.2 for comment) as the radiotherapy risk. Note this is NOT a lifetime risk.
- b. For studies involving paediatric patients, use professional judgement and the literature to assess the potential radiation related second cancer risk.

4.3.2 Studies where radiotherapy is the intervention under investigation

- a. Assigning the risk of cancer induction in radiotherapy patients is very difficult (see discussion in section 5.2). The following are some issues to consider and describe in the review as appropriate.
- b. Use the value of 5 excess cancers per 1000 adult patients treated at 15 years post radiotherapy (Berrington et al (6.1.4)) as the general risk from radiotherapy over a dose range of 30 to 60Gy for conventional treatments without dose escalation (pre-intensity modulated and image guided era), including brachytherapy.
- c. Consider the total target dose (dose required to achieve the therapeutic benefit). If this is >10Gy outside of this range the excess cancers per thousand patients at 15 years may increase/decrease by a small amount.
- d. Consider the total (treatment plus imaging) organ at risk doses and whether any changes from standard of care would be likely to change the risk of a second cancer.
- e. Consider the expected patient age range. If this is skewed towards younger or older patients groups then the excess cancers per 1000 adult patients over a short or longer time span may increase/decrease.
- f. Use professional judgement to assess the possibility of a meaningful change in the risk from the radiotherapy intervention from that for

standard of care. (Second cancer risk estimates have high uncertainties, 20% – 50%).

- g. For studies involving paediatric patients, use professional judgement and the literature to assess the potential radiation related second cancer risk.

4.4 Estimating any other radiation-induced risks

4.4.1 In the event of other types of radiation-induced risks being associated with exposures required by the study protocol, for example skin erythema, radiation experts should provide a statement on the nature of these risks and use their professional judgement to estimate their likely magnitude.

4.4.2 For radiation related heart disease after breast cancer radiotherapy, use Darby et al 2013 (see [6.1.5](#)).

5 Appendix 1: Rationale on Radiotherapy Guidance

5.1 Whole body dose estimates for radiotherapy treatments

Whilst radiotherapy is a high dose, high conformal treatment, both leakage radiation and internally scattered radiation contribute to a low dose bath over the whole body throughout the radiotherapy treatment.

Manufacturers are required to keep the leakage radiation levels low – less than 0.1% of the dose at the isocentre in the patient plane at 1m measured in a mini-phantom i.e. without a scattered radiation component. In practice values will be lower e.g. ~ 0.05% at 75cm – 100 cm from the isocentre.

For radiation review purposes using an estimate of both leakage and scattered radiation together is pragmatic. Guidance for this document was obtained from Stovall et al (see [6.1.2](#)). Figure 2 indicates a dose to organs 30 – 40 cm from the radiotherapy fields, of 0.1% of the isocentre dose. The radiotherapy prescription dose can be considered as the isocentre dose for this estimate.

5.2 Second cancer risk from radiotherapy

Although second cancer induction following radiotherapy is a known side effect of treatment it is very difficult to quantify. Epidemiological studies struggle with lack of high quality data, low sample sizes, confounding effects, high uncertainties and to distinguish the radiotherapy related component from other contributors such as chemotherapy, smoking and genetics. Report Number 170 (see [6.1.3](#)) from the National Council on Radiation Protection and Measurements surveyed the epidemiological data in detail for both second primary cancers and heart disease (from external beam radiotherapy only). Whilst this report is comprehensive, still it is difficult to derive cancer risk values analogous to those in sections [4.1](#) and [4.2](#) for radiation review purposes.

Some of the most robust evidence is via publications from the National Cancer Institute Radiation Epidemiology section. Berrington et al (see [6.1.4](#)) estimated that approximately 10% of a cohort of 650,000 adult cancer patients developed a second solid cancer. Around 8% of these second cancers were estimated to be related to radiotherapy, including brachytherapy (i.e. in < 1 in 100 patients is the second cancer attributable to the radiotherapy). This proportion, for a population incorporating 15 common cancer sites, was similar to previous estimates for breast and cervix cancer. From these data Berrington et al suggested a radiotherapy related excess of 5 cancers per 1000 patients treated at 15 years post radiotherapy. This value is similar to that suggested by Bremner et al (see [6.1.6](#)) post radiotherapy for prostate cancer (3 excess cancers per 1000 patients).

Evidence for the dose response relationships for individual organs is limited. A systematic review by Berrington et al (see [6.1.7](#)) supported a linear relationship up to

and beyond 60Gy (although thyroid was an exception). In addition they derived excess relative risk per Gy which were several fold less than those derived from low dose acute exposure data e.g. A-bomb survivors.

Based on these publications we have utilised a value of 5 excess cancers per 1000 patients at 15 years post-radiotherapy in this document as a comparator to the estimated risks from all non-radiotherapy exposures, and to assess novel radiotherapy interventions (including all on-treatment imaging) against the standard of care.

5.3 Selection of organs at risk for radiotherapy radiation review

Dose to target and organs at risk is appropriate for studies where radiotherapy is the intervention under investigation.

The purpose of the information is to allow the research ethics committee to understand the variation in dose between standard of care and the intervention under investigation via one or two representative radiosensitive organs. The purpose is not to create full description of the total radiation dose received by all radiosensitive organs in the body. Estimates of mean dose are sufficient even where the radiation dose varies widely over an organ.

Relevant organs at risk will be close to the target and likely to have dose constraints (maximum limits on the dose) for treatment planning set in the radiotherapy protocol.

One distant organ is included to provide context for on-going imaging e.g. progression monitoring or follow-up. This imaging is not necessarily restricted to the site of the radiotherapy treatment.

The table below is for indication only and is not exclusive or comprehensive. The requirements for each trial have to be considered on an individual basis.

Region of radiotherapy treatment	Proximal organs	Distant organs
Brain, head & neck	Parotids Thyroid	Stomach Bladder
Thorax	Lung Stomach Spinal cord Heart Oesophagus	Bladder
Breast	Contralateral breast Ipsilateral lung	Bladder

Region of radiotherapy treatment	Proximal organs	Distant organs
	Heart	
Abdomen	Stomach Kidneys	Bladder
Pelvis	Bladder Rectum Ovaries	Thyroid

6 Appendix 2: References

- 6.1.1 Radiotherapy Services in England 2012, Department of Health 2012.
- 6.1.2 Stovall M et al 'Dose reconstruction for therapeutic and diagnostic radiation exposures: Use in epidemiological studies', Radiation Research, 166, 141-157, 2006.
- 6.1.3 National Cancer Action Team, National Radiotherapy Implementation Group Report, Image Guided Radiotherapy (IGRT) Guidance for Implementation and Use, 2012.
- 6.1.4 Berrington et al 'Proportion of second cancers attributable to radiotherapy treatment in adults:a cohort study in the US SEER cancer registries'. Lancet Oncology, 12, 353-360, 2011.
- 6.1.5 Darby et al 'Risk of ischemic heart disease in women after radiotherapy for breast cancer' New England Journal of Medicine, 368(11), 987-998, 2013.
- 6.1.6 Bremner et al 'Second malignancies in prostate carcinoma patients after radiotherapy compared with surgery'. Cancer, 8, 398-406, 2000.
- 6.1.7 Berrington et al 'Second solid cancers after radiotherapy; a systematic review of the epidemiological studies of the radiation dose-response relationship'. International Journal of Radiation Oncology Biology Physics, 86(2), 2013.

7 Appendix 3: Guardians Group

This table gives the names of positions of the original MPE Guardians who developed this guidance. The Group was disbanded in 2016. As stated on the cover page of this document, it is maintained by the Radiation Assurance Four Nations Working Party.

MPE Guardian	Role / Job Title	Organisation
Elly Castellano	Radiology MPE / Senior Physicist	The Royal Marsden NHS Foundation Trust
Ellen Donovan	Radiotherapy MPE / NIHR Career Development Fellow	The Royal Marsden NHS Foundation Trust
Paul Hinton	Nuclear Medicine MPE / Head of Nuclear Medicine Physics	Royal Surrey County Hospital NHS Foundation Trust
Peter Marsden	Radiology MPE / Head of Medical Physics & Bioengineering	University College London Hospitals NHS Foundation Trust
Giles Morrison	Radiology MPE / Head of Radiology Physics	Sheffield Teaching Hospitals NHS Foundation Trust
Claire Skinner	Radiology MPE / Head of Radiological Physics and Radiation Safety	The Royal Free London NHS Foundation Trust
Wendy Waddington	Nuclear Medicine MPE / Head of Clinical Nuclear Medicine Physics	University College London Hospitals NHS Foundation Trust
Stuart Yates	Radiology MPE / Head of EARRPS	Cambridge University Hospitals NHS Foundation Trust