Clinical Radiation Expert (CRE) Review Procedure

Contents

1. About this guidance

The CRE Review Procedure clarifies the information requirements for the CRE assessments in IRAS. 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 CRE 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 going through Radiation Assurance, this is specified.

For studies not using Radiation Assurance:
The Lead CRE should review the number of ionising radiation procedures which are additional to standard of care; these are listed in Part A Question 19 of IRAS. If all

exposures will be conducted as standard of care at all participating sites, the Lead CRE should answer “no” to Question D1 of Part B Section 3 in IRAS; a written assessment will not be required. If any exposures may exceed those conducted as standard of care at any participating site, they should answer “yes” to Question D1 of Part B Section 3 in IRAS and use this guidance to complete their assessment. This should be provided in Question D2 of Part B Section 3 in IRAS, however, some applicants may prefer the CREs to provide their review by email and will transfer it to IRAS themselves.

For Radiation Assurance studies only:
CREs should use this guidance in all circumstances to complete the assessment in the research exposure form.

2. List of type and number of exposures

2.1 The CRE should include in the assessment report a summary list of the type and number of exposures, referencing Part A Question 19 and Part B Section 3 of IRAS.

> **For Radiation Assurance studies only:** CREs should also reference section F1 of the Research Exposure Form in their assessment. The HRA has already checked that the information in section F1 of the Research Exposure Form is correct and complete; therefore, it is reasonable for the CRE to accept this as an accurate summary of exposures/imaging/radiotherapy identified in the study protocol. In case of queries the CRE should contact the HRA.

3. Purpose of exposures related to study objectives; consider choice of modality

3.1 State the purpose of the exposures clearly and concisely in the context of the study e.g. CT chest-abdomen-pelvis (CAP) is performed to assess response to treatment/confirm disease progression etc, and comment on whether the exposures are of medical benefit or no medical benefit to the patient.

3.2 Comment on the appropriateness of the modality selected for the specified purpose. Where a protocol allows for different modalities to be used (e.g. CT or MRI or a combination) a comment regarding the choice of modality in relation to radiation exposure would be appropriate. However, it should also be noted that the choice of modality at a particular centre is likely to be resource dependent.

3.3 Comment on the appropriateness of the frequency of exposure(s) to ionising radiation and provide justification for this.

If the frequency cannot be justified, the lead CRE should not authorise the form in IRAS.

For studies not using Radiation Assurance: If the frequency cannot be justified the lead CRE should contact the research team.

For Radiation Assurance studies only: If the frequency cannot be justified the lead CRE should contact the HRA.

3.4 Where radiotherapy is indicated state whether this is standard of care in the cohort. If radiotherapy is the intervention under investigation state the purpose of the proposed modification of the radiotherapy from standard of care.

4. Statement/comment regarding research exposure versus standard clinical care

4.1 IRAS requires a comment regarding additional exposures versus standard care. Contextualise the exposure in terms of the study population (age, prognosis, possibility of pregnancy etc.).

4.2 It should be recognised that this may vary between centres as clinical care is rarely truly standardised.

For studies not using Radiation Assurance: The suitability of the standard of care exposures listed in Part A Question 19 of IRAS should be considered and challenged if required.

For Radiation Assurance studies only: The suitability of the standard of care exposures listed in section F1 of the research exposure form should be considered and challenged if required.

4.3 The Lead CRE should comment on the possibility of additional exposures which may be referenced in, but not required by, the protocol. Examples would include additional MUGA scans where cardiac impairment is observed during the course of the study where cardiac monitoring is by MUGA, or chest CT scans are required to check for pneumonia if participants display potential symptoms. It is not expected that these exposures are identified in Part A Question 19 of the IRAS form, in Part B Section 3 Question B of the IRAS form (all studies), or in the research exposure form (Radiation Assurance studies only) because it is not possible to identify how many exposures there might be even if any participants do have any of these exposures. Example of an appropriate statement:

Adverse events
There is potential for additional exposure as a consequence of study treatment. As a result of side effects/toxicity related to study drugs additional imaging may be required.

Such exposures are justifiable in the context of the study in this group of patients.

4.4 Where studies are open-ended in design (e.g. scanning continues until disease progression) the Lead CRE should include a comment to reflect the risks and benefits of exposures in later years of the trial. Whilst best efforts may be made by applicants, Lead MPEs and Lead CREs to identify how long participants are likely to participate in the research for, it is acknowledged that in some instances participants could survive and participate for much longer than expected.

4.5 Where any aspect of radiotherapy is the intervention under investigation comment on the differences to standard of care with particular reference to prescribed dose and fractionation, whole/partial organ irradiation, imaging type and frequency, dose delivery method.

5. Risks versus benefits; attempt to match with best fit Generic Risk Statement

5.1 Provide a statement of risks vs benefits to (a) individual participants and (b) the society in general as appropriate.

5.2 Attempt to match the study with the best fit generic statement, based on the MPE review.

> **For studies not using Radiation Assurance:** If in agreement please insert the relevant generic IRAS statement into Question D2 of Part B Section 3 in IRAS.
>
> **For Radiation Assurance studies only:** If in agreement please insert the relevant generic IRAS statement into the first box of question D2 in section F3 of the research exposure form.

5.3 For studies where radiotherapy is the intervention under investigation one of the suggested scenarios may fit the study in which case this can be used as a basis for the risk-benefit summary. If not, a bespoke summary is required. Given the complexity of studies involving radiotherapy, the addition of further detail is appropriate in either case.

5.4 Inclusion of a comment regarding variation in standard of care between centres may be appropriate to supplement the best fit generic risk statement e.g. ‘standard’ clinical care varies between individual centres - at some centres all of the exposures required by this study would be considered in line with standard clinical care and in others a proportion may be considered additional.

5.5 For studies involving healthy volunteers the Lead CRE is expected to check that the total radiation exposure is not more than 10mSv per year (based on the information in the MPE’s statement) and that participants are all over 50 years. If these are not the case, the CRE should ensure that specific justification is provided within the application by the applicant.

5.6 The Lead CRE should work with other CRE reviewers and the Lead MPE to check that the risk statement provided to participants in the Participant Information Sheet is appropriate.

For studies not using Radiation Assurance: The Lead CRE should ensure that the risk statement provided is suitable for participants with the clinical condition(s) under investigation. Where this is not the case they should request that this is amended appropriately and sent to them for review. The Lead CRE should not authorise the application form in IRAS until they are satisfied that the risk statement in the participant information sheet is suitable.

For Radiation Assurance studies only: The Lead CRE should ensure that the risk statement provided is suitable for participants with the clinical condition(s) under investigation and indicate “yes” in the appropriate check box in question D2 of section F3 of the research exposure form. Where the risk statement is not suitable for participants with the clinical condition(s) under investigation the Lead CRE should select the “no” check box and provide further comment in the second free text box in question D2. This should include confirmation of any wording to be added or removed.

6. Administrations of Radioactive Substances

6.1 Where appropriate specific clinical justification should be included in the following scenarios:

a. Where healthy volunteers aged below 50 years are to be included
b. Where healthy volunteers receive > 10mSv
c. the use of novel radiopharmaceuticals for the proposed indication

7. Summary statement

7.1 For example: “The required exposures are appropriate for the objectives/purposes identified in the study protocol. The potential benefits to the individual and/or society have been considered in relation to the risks posed by the additional radiation exposure that will or may be incurred by participating in this study. The potential benefits are felt to outweigh those risks, and the radiation exposures are justifiable in the context of the study population.”

For studies not using Radiation Assurance: The Lead CRE should provide the names, job titles, reviewing organisations and GMC or GDC registration numbers of any additional CRE reviewers in their assessment in Question D2 of Part B Section 3 of IRAS. The Lead CRE should indicate in Question D2 of Part B Section 3 in IRAS whether any of the reviewers, including themselves, are part of the research team or are named in the protocol.

For Radiation Assurance studies only: The Lead CRE should provide the names, job titles, reviewing organisations and GMC or

GDC registration numbers of any additional CRE reviewers within the first box of question D2 in section F3 of the research exposure form. The Lead CRE should indicate within the first box of question D2 in section F3 of the Research Exposure Form whether any of the reviewers, including themselves, are part of the research team or are named in the protocol.

8. Appendix 1: Guardians Group

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

CRE Guardian	Role / Job Title	Organisation
Laurence Abernethy	CRE / Consultant Paediatric Radiologist	Alder Hey Children's Hospital NHS Foundation Trust
Eleanor Lorenz	CRE / Consultant Radiologist	Sheffield Teaching Hospitals NHS Foundation Trust
Shonit Punwani	CRE / Consultant Radiologist	University College London Hospitals NHS Foundation Trust
Anju Sahdev	CRE / Director of Education and Research	Barts Health NHS Trust

9. Appendix 2: Administration of radioactive substances; guidance on situations where input can be provided by a CRE without a practitioner licence under IR(ME)R for that procedure

For some nuclear medicine procedures that are either relatively low dose or common diagnostic tests, in some scenarios it is acceptable for a CRE without a licence to adequately assess the inclusion of the administration of radioactive substances in a research study. This applies to the following four scenarios:

9.1 Isotope Glomerular Filtration Rate (GFR) measurement

Relevant indication: A more accurate measure than estimated glomerular filtration rate (eGFR) where accurate knowledge of renal function is required for patient safety.

Radiopharmaceutical: ^{51}Cr-EDTA or ^{99m}Tc-DTPA with an Effective Dose < 0.1 mSv

Isotope GFR measurements can be approved by a CRE without a licence where accurate knowledge of GFR is required.

9.2 ^{18}F-FDG-PET CT scan for whole body tumour imaging

Relevant indication: clinical staging of a cancer and then follow up of cancer on treatment.

Radiopharmaceutical: ^{18}F-FDG with an Effective Dose of 8mSv (or approximately 20mSv including the CT portion)

Studies including ^{18}F-FDG-PET CT scans can be assessed by a CRE without a licence with experience of cancer imaging for clinical trials of cancer patients including the following:

1. Scans at baseline;
2. Scans at follow up where tumours are ^{18}F-FDG positive at baseline;
3. Scans at 3-monthly or wider intervals;
4. a single early follow-up scan for clear research end-points;
5. on-going ^{18}F-FDG-PET scans after the standard 3 clinical scans (beginning, middle and end of treatment) for cases of advanced or refractory-to-treatment cancer.

9.3 ^{99m}Tc-MUGA (Multiple-gated acquisition radionuclide angiography) Scan

Relevant indication: Safety test to measure cardiac function (ejection fraction) to check for potential cardiac toxicity of standard (e.g. doxorubicin) or trial drugs. Some centres use this test in preference to echocardiography.

Radiopharmaceutical: ^{99m}Tc erythrocytes with an Effective Dose of approximately 6mSv.

Studies including MUGA scans can be assessed by a CRE without a licence if the following all apply:

1. serial cardiac function testing is required; and
2. it is standard practice for the participating site; and
3. the protocol allows echocardiogram to be used where standard management.

If the protocol insists on serial MUGA scans in centres where echocardiogram is normally used this is considered a specialist decision, and a CRE with a licence should assess the MUGA scans.

9.4 ^{99m}Tc Bone Scan (planar or SPECT)

Relevant indication: diagnosis and follow-up of bone metastases.

Radiopharmaceutical: ^{99m}Tc phosphates or phosphonates with an Effective Dose of approximately 3mSv.

Studies including ^{99m}Tc Bone Scans can be assessed by a CRE without a licence with experience of cancer imaging for:

1. clinical trials of patients with cancers for which bone scans are commonly used in standard clinical practice at staging, including, but not confined to, sarcomas, lung, breast or prostate cancer
2. scans at baseline where presence of bone metastases is relevant

3. scans at follow up at 3-monthly or wider intervals where tumours are bone-scan positive at baseline, or when new bone metastases are a significant risk e.g. prostate cancer studies.