Identified actions to be implemented as part of the project and proposed for the future

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This project has received funding from the European Commission under Service Contract N° ENER/2022/NUCL/SI2.869532.0

1. Insufficient linkage between EU pharmaceutical legislation/EMA guidance & BSSD

Suggestions for remedies in the wider context of SAMIRA

- Clarification of precedence of BSSD over pharma regulations
- Inclusion of radiopharmaceuticals in Annex VII when revised
- Revisions of guidance documents translating the BSSD's principles into practice, e.g., EMA Guideline on Radiopharmaceuticals (EMEA/CHMP/QWP/306970/2007) and Guideline on Summary of Product Characteristics (SmPC), both published in 2009. Introduce a distinct consideration of diagnostics and therapeutics as well as a differentiated discussion of posology for therapeutic radiopharmaceuticals
- Draft a clinical guideline on the development of therapeutic radiopharmaceuticals in oncology with consideration for diagnostics and therapeutics and a differentiated discussion of posology for therapeutic radiopharmaceuticals

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1. Insufficient linkage between EU pharmaceutical legislation/EMA guidance & BSSD

Suggestions for remedies in the wider context of SAMIRA

- Establish a permanent expert working group on radiopharmaceuticals, consisting of experts in medical physics, radiopharmacy, radiochemistry and clinical nuclear medicine
- Revision of CTIS to include structured radiation safety and dosimetry information for therapeutic radiopharmaceuticals
- Establish a multi-level forum concerning interaction between regulators working in the fields of pharmaceutical supervision and radiation protection both at EU and national levels

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1. Insufficient linkage between EU pharmaceutical legislation/EMA guidance & BSSD

Potential strengths, weaknesses, opportunities and threats

1. **Strengths:** A statement in the proposed new pharma directive that the BSSD's requirements should prevail in case of contradictions should provide clarity. Including radio-pharmaceuticals in the list of products that should be regulated (in article 28, annex II of the current proposal by the commission for a new directive) will allow addressing radiopharmaceutical specificities. Revised versions of the EMA Guideline on Radiopharmaceuticals and Guideline on SmPC as well as a new clinical guideline for the development of therapeutic radiopharmaceuticals that include dedicated instructions for the posology of therapeutic radiopharmaceuticals will provide the basis for a suitable description of posologies that fulfil the requirements stipulated by the BSSD
2. **Weaknesses:** The current Directive 2001/83/EC clearly mentions BSSD requirements in both a recital and in an article of the text; still the BSSD requirements are not fully recognised. The outcome of the suggested remedies may be limited

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1. Insufficient harmonisation between EU pharmaceutical legislation/EMA guidance & BSSD

Potential strengths, weaknesses, opportunities and threats

3. **Opportunities:** Inclusion of radiopharmaceuticals in annex VII according to article 28 of the EC's proposal could trigger adapted radiopharmaceutical rules in other fields (good manufacturing practice requirements, clinical trials, marketing authorisation procedures, requirements for qualified persons, ...)

4. **Threats:** The reform of the EU pharmaceutical legislation may not consider the BSSD or specifics of therapeutic radiopharmaceuticals

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1. Insufficient harmonisation between EU pharmaceutical legislation/EMA guidance & BSSD

Synthesis

The lack of intersection between pharmaceutical legislation/EMA guidance documents and Euratom BSSD requirements has clearly been identified to be a considerable challenge especially with the advances in development of new therapeutic radiopharmaceuticals. The proposal for revision of Directive 2001/83 contains an important step towards recognising the concept of justification and optimisation also in the context of marketing authorisation of radiopharmaceuticals used for therapy. This, however, must be expressed unambiguously in the legal text, complemented by additions in annexes, guidance documents and CTIS and guided by professionals in the field of therapeutic radiopharmaceuticals

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2. Interpretation and implementation of the BSSD in the context of therapeutic nuclear medicine

Suggestions for remedies during SIMPLERAD

- Guidelines or guidance documents to help users understand the possibilities of treatment adaptation based on regulatory requirements, definitions of individual planning, appropriate verification, etc.

  "Implementing Dosimetry in Clinical Practice"

  "Guidance Document on Treatment Planning and Verification for Selected Radiopharmaceuticals"

  "EANM Guidance Document: Dosimetry for First-in-Human Studies and Early Phase Clinical Trials"

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2. Interpretation and implementation of the BSSD in the context of therapeutic nuclear medicine

Suggestions for remedies during SIMPLERAD

- Modification of posologies

  Raise awareness of the possibility within the EU to administer different activities, based on dosimetry, rather than that given in the registered posology and on the requirements for doing so

  Remind competent authorities regarding the BSSD requirement to document the irradiation delivered (treatment verification) even for fixed activities, particularly in the perspective of repeated/multiple cycle treatments

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2. Interpretation and implementation of the BSSD in the context of therapeutic nuclear medicine

Suggestions for remedies in the wider context of SAMIRA

- Establish centres of excellence to mitigate the lack of knowledge and training and shortage of well-trained staff
- Establish accreditation programmes to ensure traceability of clinical dosimetry throughout Europe
- Create a regulatory network to foster interactions between radiation-protection and medicines agencies

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2. Interpretation and implementation of the BSSD in the context of therapeutic nuclear medicine

Potential strengths, weaknesses, opportunities and threats

1. Strengths

The strengths of the proposed actions for this item are that they are widely accepted and that they contain explicit proposals on how to overcome the current barriers for implementing the BSSD in the member states

2. Weaknesses

The weakness of the proposed actions is that no explicit proposals can be made on how to overcome the inequalities between the member states, as this is beyond the scope of this tender

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2. Interpretation and implementation of the BSSD in the context of therapeutic nuclear medicine

Potential strengths, weaknesses, opportunities and threats

3. Opportunities

The proposed remedies, when taken up by the different stakeholders involved, will further enhance and improve the use of radiopharmaceutical therapies throughout Europe for the benefit of the patients

A coordinated joint action for networking and improving communication, such as the grant CR-g-23-44-03 within the framework of the SAMIRA initiative, may be of great value and should be considered with high priority

4. Threats

A major threat to implementing the suggested remedies is the lack of linkage between the different authorities on a European level as well as on the national level within the member states

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2. Interpretation and implementation of the BSSD in the context of therapeutic nuclear medicine

Synthesis

This item and the corresponding annexes contain explicit proposals on the interpretation and implementation of the BSSD in the context of therapeutic nuclear medicine

It is strongly recommended that an integral effort is undertaken by the different directorate generals involved to implement these remedies on the national and European level

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3. Lack of resources for dosimetry

Suggestions for remedies during SIMPLERAD

- Update the joint EANM/EFOMP core curriculum for education and training of medical physicists in nuclear medicine

Suggestions for remedies in the wider context of SAMIRA

- Develop training in nuclear medicine therapy for all professionals involved in the field, e.g., physicians, physicists, radiopharmacists, technologists, nurses, etc.
- Introduce reimbursement for dosimetry procedures on national level
- Decrease the workload associated with clinical dosimetry by introducing quality assurance and standardisation
- Adapt procedures to less well-resourced centres

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3. Lack of resources for dosimetry

Potential strengths, weaknesses, opportunities and threats

1. **Strengths:** The lack of resources is widely acknowledged as a limiting factor for clinical dosimetry dissemination
2. **Weaknesses:** The solutions may be difficult to implement in countries with fewer resources, where the need is most pronounced. A progressive roadmap may have to be defined
3. **Opportunities:** Identifying molecular radiotherapy as a radiotherapeutic procedure paves the way for the full integration of dosimetry - and its reimbursement - as an integral part of the nuclear medicine therapy
4. **Threats:** The shortage of medical resources in the EU is not specific to molecular radiotherapy; therefore molecular radiotherapy may not be considered as a priority

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3. Lack of resources for dosimetry

Synthesis

The implementation of the individual planning mandate stated in article 56.1 of the BSSD is hampered by a lack of resources, both in terms of educated staff and funding/reimbursement

We recommend coordinated actions to increase the availability of sufficient educated staff as well as funding

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4. Differences regarding status of MPEs between member states

Suggestions for remedies

- Survey to map the roles and responsibilities for MPEs and medical physicists working with molecular radiotherapy
- A guidance document should be prepared on roles and responsibilities for MPEs and medical physicists working with molecular radiotherapy
- Staffing requirements for centres performing molecular radiotherapy should be defined and enforced
- Training of MPEs should be harmonised across Europe

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4. Differences regarding status of MPEs between member states

Potential strengths, weaknesses, opportunities and threats

1. **Strengths:** Performing a survey to map roles and responsibilities will allow identifying variations in practices across centres and countries. Aligning recommendations with the EFOMP policy statement 16 will enhance the guidance document relevance
2. **Weaknesses:** Variations in responsibilities may be tied to available resources, making it challenging to standardise roles without addressing resource disparities by enforcing staffing requirements
3. **Opportunities:** The proposed initiatives will enhance the quality and safety of molecular radiotherapy services and contribute to improve patient care and treatment outcome
4. **Threats:** Resistance from centres or countries to standardise roles, responsibilities, and staffing levels may impede the effectiveness of proposed initiatives

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4. Differences regarding status of MPEs between member states

Synthesis

There are different responsibilities for medical physicists and MPEs across Europe, as well as large variations in resources. First, the responsibilities should be harmonised by mapping the current situation followed by a guidance document with recommendations. Staffing levels should be defined and enforced

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5. Heterogeneity of dose constraints & patient release criteria between member states

Suggestions for remedies in the wider scope of SAMIRA

- Provide guidance on which individual (and in which situation) can be considered as a comforter/carer or as a member of the public, and which information and guidance relating to the benefits and risks should be provided
- Create an explanatory document summarising the concept of dose constraints in the BSSD framework, and more generally explaining concepts laid out in ICRP publications and BSSD
- Conduct risk assessment studies using state-of-the-art methods to characterise the (potential) exposure of an individual from a nuclear medicine patient

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5. Heterogeneity of dose constraints & patient release criteria between member states

Suggestions for remedies in the wider scope of SAMIRA

- Set up grant programmes for the generation of high-level dosimetry data for the optimisation of protection of the public
- Consider removal of generic patient instructions concerning radiation protection advice provided by radiopharmaceutical companies in the SmPC when such instruction is not based on robust data. Adapt to specific regulatory instruction of member states

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5. Heterogeneity of dose constraints & patient release criteria between member states

Potential strengths, weaknesses, opportunities and threats

1. **Strengths:** The proposed multi-level strategy to approach the lack of harmonisation of release criteria will enable to clarify the impact of different decision levels on the final outcome
2. **Weaknesses:** The significant variations across centres and member states indicate that harmonisation may be difficult, as different countries might set up the legal framework differently and prerequisites may vary
3. **Opportunities:** EU grant programmes present an opportunity to gather comprehensive dosimetric data, facilitating the establishment of harmonised patient release criteria. The proposal for European guidance documents offers the potential to create unified standards across member states
4. **Threats:** The reliability and quality of data generated through grant programmes may vary, impacting the effectiveness of harmonisation efforts. Developing European guidance that is universally accepted across member states is challenging

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5. Heterogeneity of dose constraints & patient release criteria between member states

Synthesis

The process of setting release criteria and patient instructions is influenced by different criteria and decision levels which include the use of the concept of comforter and carers, the use of appropriate dose constraints for optimisation, and the methodologies used in risk assessment studies

Harmonisation of patient release criteria and instructions cannot be accomplished if there is a lack of harmonisation of those specific criteria and decision levels

Future EU programmes that support the generation of scientific data can contribute to the harmonisation of risk assessment studies whereas the elaboration of European guidance documents on the medical exposure comforters/carers in nuclear medicine and the correct use of dose constraints should be considered

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6. Heterogeneity of management of radioactive waste across member states

Suggestions for remedies in the wider scope of SAMIRA

- Set up a specific EU survey on the specific criteria and methodologies used by competent authorities to set specific effluent release conditions
- Based on the results of the WP2 survey: New evaluation of the conditions on the discharge of radioactive effluent and application of exemption and clearance according to the requirements of the BSSD
- Establish a working party representing different competent authorities that could formulate a specific guidance document on effluent release and waste management related to the use of medical radionuclides

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6. Heterogeneity of management of radioactive waste across member states

Potential strengths, weaknesses, opportunities and threats

1. **Strengths:** Existing international guidance can be utilised as a foundation for harmonisation efforts, minimising the need for creating entirely new frameworks. Use this principle as a common ground for harmonisation, ensuring a focus on patient safety and environmental impact. The survey can provide insights into the specific criteria and methodologies used by competent authorities, enabling informed decision making
2. **Weaknesses:** The complexity of factors influencing effluent discharge limits, such as regional sewerage system development and wastewater treatment, may complicate harmonisation efforts. Lack of transparency on the methodologies used by authorities across member states for effluent release conditions poses a challenge

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6. Heterogeneity of management of radioactive waste across member states

Potential strengths, weaknesses, opportunities and threats

3. **Opportunities:** The acknowledgment that radioactive effluent discharge is a cross-sectoral challenge opens avenues for collaboration not only in therapeutic nuclear medicine but also in research laboratories and the nuclear industry. The proposal for a working party to elaborate a specific guidance document on effluent release and waste management provides an opportunity for standardisation

4. **Threats:** Competent authorities may resist changes to existing effluent discharge conditions, particularly if adjustments impact established practices. Engage stakeholders early in the process, demonstrating the benefits of harmonisation for patient care, environmental protection, and regulatory efficiency. Develop strategies to address financial and infrastructure challenges, potentially through phased implementation

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6. Heterogeneity of management of radioactive waste across member states

Synthesis

Further focused analysis and surveys of the conditions concerning effluent release and waste management across the EU and different sectors should be undertaken. A working party to generate harmonised guidance for medical radionuclides should be formed

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7. Differing guidance from professional societies for clinical practice

Suggestions for remedies during SIMPLERAD

- Draft guidance on what pertains to individual dose planning to reinforce the precedence of BSSD in establishing treatment regimen
- Contact relevant professional clinical societies with the accompanying guidance document, requesting that societies adapt guidelines to conform to the BSSD

Suggestions for remedies in the wider context of SAMIRA

- Set up grant programmes for the generation of high-level clinical evidence on the benefit of individual planning of various forms of radionuclide therapy using dosimetric methods
- Stimulate interdisciplinary, dedicated meetings aimed at achieving interdisciplinary consensus among experts on issues pertaining to individual planning of radionuclide therapy

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7. Differing guidance from professional societies for clinical practice

Potential strengths, weaknesses, opportunities and threats

1. **Strengths:** The current proposal will endeavour to entice clinicians and non-clinicians to look beyond traditionally established disciplinary boundaries
2. **Weaknesses:** The success of the measures proposed here relies upon cooperation of professional societies and individual professionals as well as their willingness to be open for interdisciplinary evidence gathering
3. **Opportunities:** The identification of the necessary measures for this item present an opportunity to reserve financial resources in upcoming budgets for subsidy programmes
4. **Threats:** Lack of funding for various stimulating measures presents the largest threat to the success of the measures proposed in this section

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7. Differing guidance from professional societies for clinical practice

Synthesis

Different professional societies come to different, even contradictory, guidance for the same disease/therapeutic modality on issues pertaining to the interaction between the pharmaceutical directive and BSSD as well as on interpretation of the BSSD in the clinical context. To mitigate this, we propose a number of potential remedies:

- Publication of the results of the evidence gathering process of WP1 and WP2 of the SIMPLERAD project in the form of, e.g., public reports, publications in scientific journals and presentations
- Contact by regulatory agencies with professional societies, reminding such societies of the legal precedence of the BSSD and asking such societies to ensure any guidance is compliant in this respect
- Generation of high-quality evidence on the need and benefit as well as optimal method of individual planning of various forms of radionuclide therapy using dosimetric methods
- Facilitation of interdisciplinary consensus discussion

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8. Differing regulatory procedures between member states for drug development & clinical trials

Suggestions for remedies in the wider context of SAMIRA

- Modification of CTIS to allow structured data entry on radiation-safety-related aspects for radiopharmaceuticals
- Integration of radiation associated features of radiopharmaceuticals as investigational medicinal product into the data package required for submission in CTIS
- Further evidence collection through databases, investigator-initiated studies/trials, dosimetry networks, individual dosimetry data to be included in marketing authorization dossiers, health economic studies

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8. Differing regulatory procedures between member states for drug development & clinical trials

Potential strengths, weaknesses, opportunities and threats

1. Strengths

Any modification of CTIS to allow data entry on radiation-safety related aspects will bring both pillars of relevant legislation closer together. Same applies for an obligation to incorporate radiation-safety related issues when applying for a clinical trial authorisation

2. Weaknesses

Within the scope of SIMPLERAD we will not be able to implement the proposed remedies

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8. Differing regulatory procedures between member states for drug development & clinical trials

Potential strengths, weaknesses, opportunities and threats

3. Opportunities

Regulators who are competent for the enforcement of pharmaceutical legislation only will likely pay more attention to radiation-safety-related issues when it comes to decision making on clinical trials or marketing authorisation applications. This could lead to a better alignment of pharmaceutical and radiation-protection legislation in the future. Furthermore, it will enhance cooperation with regulators enforcing radiation-protection legislation

Supporting multi-centre and especially multinational clinical trials could lead to a closer cooperation between scientists and subsequently to “better” medicines for patients in the EU

Health economics studies will almost certainly enhance the benefit–cost ratio for medicinal products and thus improve health care for EU citizens

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8. Differing regulatory procedures between member states for drug development & clinical trials

Potential strengths, weaknesses, opportunities and threats

4. Threats

Any establishment of additional databases could possibly lead to a higher level of bureaucracy

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8. Differing regulatory procedures between member states for drug development & clinical trials

Synthesis

There is a clear need to harmonise the application process for clinical trials with radiopharmaceuticals regarding the radiation safety related parts such as dosimetry and dose finding. Since there is a high heterogeneity across European member states and a risk of decrease of representation of Europe in global drug development and clinical trials with radiopharmaceuticals, specific measures should be taken

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9. Lack of specialist knowledge regarding EU pharmaceutical and medicine as well as BSSD-related regulations

Suggestions for remedies in the wider context of SAMIRA

Knowledge gaps between pharmaceutical and radiation protection legislation should be bridged by:

- Further specialist training
- More harmonised legislation or specific guidance addressed to both radiation safety and pharmaceutical authorities, ideally drafted and released by both Euratom and EMA
- Close cooperation between all stakeholders

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9. Lack of specialist knowledge regarding EU pharmaceutical and medicine as well as BSSD-related regulations

Potential strengths, weaknesses, opportunities and threats

1. **Strengths:** Established connections between national radiation protection authorities through HERCA
2. **Weaknesses:** National regulators are at different levels of knowledge in pharmaceutical and radiation protection legislation. Even if pharmaceutical and radiation protection authorities in a specific country collaborate, there can be conflicts in the interpretation of both sets of legislation as well as a lack of coordination between the different authorities
3. **Opportunities:** Specialist training in both sets of relevant legislation and improved cooperation between all stakeholders will bridge the knowledge gaps between pharmaceutical and radiation protection legislations
4. **Threats:** Linkage between the stakeholders may not be developed further

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9. Lack of specialist knowledge regarding EU pharmaceutical and medicine as well as BSSD-related regulations

Synthesis

There is a need for more extensive specialist knowledge concerning nuclear medicine within various stakeholders regarding the EU pharmaceutical directive as well as BSSD-related regulations. This will require further specialist training, more harmonised legislation/guidance and close cooperation between stakeholders

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10. Differences between opinion of professionals concerning dosimetry and the necessity stipulated in national legislation and guidance

Suggestions for remedies during the SIMPLERAD project

- Guidelines or guidance documents on applying dosimetry for radionuclide therapy
- Publication of results of SIMPLERAD WPs 1 and 2

Suggestions for remedies in the wider context of SAMIRA

- Translation of available European guidance to national level
- Collaboration between competent authorities and national societies
- Expert consultation for revision of new regulatory guidance documents

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10. Differences between opinion of professionals concerning dosimetry and the necessity stipulated in national legislation and guidance

Potential strengths, weaknesses, opportunities and threats

1. Strengths

Many of the proposed solutions also serve to solve other items defined in the SIMPLERAD project. Involvement of experts at time of establishment of guidance documents will prevent delays and difference in opinion at time of implementation. The proposed solutions build on existing guidance documents

2. Weaknesses

Coordination of the proposed solutions is not defined. Definition of 'expert' is not given and might be sensitive to interpretation

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10. Differences between opinion of professionals concerning dosimetry and the necessity stipulated in national legislation and guidance

Potential strengths, weaknesses, opportunities and threats

3. Opportunities

Improved collaboration between international societies such as EANM and EFOMP will have a positive effect on national society collaboration as well

4. Threats

Implementation on a local level while maintaining international alignment may prove challenging due to a lack of cooperation

Consultation for revision of new regulatory guidance documents

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10. Differences between opinion of professionals concerning dosimetry and the necessity stipulated in national legislation and guidance

Synthesis

Guidance and legislation on the implementation of dosimetry currently differ from expert opinion for certain therapies, which also varies between European countries. To solve this, alignment between competent authorities, national societies and experts is crucial

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“Implementing Dosimetry in Clinical Practice”

Major content

Heterogeneous recommendations on dosimetry (e.g., different levels of complexity) in:

- ICRU Report 96
- EFOMP policy statement 19
- EANM position paper on Article 56 of the Council Directive 2013/59/Euratom for nuclear medicine therapy

Discussion of:

- How to reconcile these documents with each other and with respect to BSSD

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"Guidance Document on Treatment Planning and Verification for Selected Radiopharmaceuticals"

Major content

- Resource requirements for dosimetry
- Examples on how to perform dosimetry for treatment planning or treatment verification for five of the most important use cases, based on the suggestions of the EANM enabling guide
  - $[^{131}\text{I}]\text{NaI}$
  - ^{131}I–mIBG
  - ^{177}Lu–DOTATATE
  - ^{177}Lu–PSMA
  - ^{90}Y radioembolisation

European Journal of Nuclear Medicine and Molecular Imaging (2023) 50:1861–1868
https://doi.org/10.1007/s00259-023-06226-z

GUIDELINES

EANM enabling guide: how to improve the accessibility of clinical dosimetry

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Example treatment planning using (^{131}I)NaI

Clinical indication	Benign thyroid disease without cardiovascular risk factors
Level of dosimetry	Prescription to absorbed dose
Approach A	**Approach B**
Methodological description	
Thyroid pertechnetate uptake study Target volume determined by ultrasound Tracer administration of 10 MBq of ^{131}I Thyroid uptake scintigraphy at 4 hours p.i. Thyroid uptake scintigraphy at 24 hours p.i. Thyroid uptake scintigraphy at 72 hours p.i. Thyroid uptake scintigraphy at 144 hours p.i. Absorbed dose calculation Therapeutic administration of ^{131}I	Target volume determined from pertechnetate uptake study Tracer administration of 2 MBq of ^{131}I Thyroid uptake probe measurement at 5–8 days P.I. Absorbed dose calculation Therapeutic administration of ^{131}I
Advantages	
Ultrasound scan gives accurate mass estimate Calculation of patient-specific half-life reduces uncertainty (<10%) in absorbed dose calculation. Multi-time point uptake allows uncertainty in absorbed dose to be determined. Gamma camera quantification is more accurate	If pertechnetate scan is standard of care, use for mass estimate negates the need for additional ultrasound scan. Single time point method reduces number of hospital visits Use of thyroid uptake probe does not require use of other NM resources
Disadvantages	
Additional ultrasound scan needed Extra hospital visits and measurements needed. High activity required for gamma camera measurements Gamma camera time may be limited	Large margin of error using scintigraphy for thyroid mass estimate Errors exceeding a factor of two are possible in individual patients if the uptake is measured after 1 day. The potential for error is slightly lower for uptake assessments after 2 days Gamma probe is not standard equipment in every centre

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Example treatment verification using (^{131}I)NaI

Clinical indication	Benign thyroid disease without cardiovascular risk factors
Approach A	**Approach B**
Methodological description	
Target volume determined by ultrasound Thyroid uptake scintigraphy at 4 hours p.i. Thyroid uptake scintigraphy at 24 hours p.i. Thyroid uptake scintigraphy at 72 hours p.i. Thyroid uptake scintigraphy at 144 hours p.i. Absorbed dose calculation	Target volume determined from pertechnetate uptake study Thyroid uptake probe measurement at 5–8 days P.I. Absorbed dose calculation
Advantages	
Ultrasound scan gives accurate mass estimate Calculation of patent specific half-life reduces uncertainty (<10%) in absorbed dose calculation. Multi-time point uptake allows uncertainty in absorbed dose to be determined. Gamma camera quantification is more accurate	If pertechnetate scan is standard of care, use for mass estimate negates the need for additional ultrasound scan. Single time point method reduces number of hospital visits Use of thyroid uptake probe does not require use of other NM resources
Disadvantages	
Additional ultrasound scan needed Extra hospital visits and measurements needed. High activity for gamma camera measurements could cause dead-time losses of counts Gamma camera time may be limited	Large margin of error using scintigraphy for thyroid mass estimate Errors exceeding a factor of two are possible in individual patients if the uptake is measured after 1 day. The potential for error is slightly lower for uptake assessments after 2 days Gamma probes are not standard equipment in every centre. High activity for probe measurements could cause dead-time losses of counts

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Example treatment plans using ^{177}Lu-DOTATATE and -PSMA

Clinical indication	Expression of sstr2, or metastatic or inoperable neuroendocrine tumours with poor kidney function [21] Patients with PSMA-positive mCRPC (For more details see Kratochwil et al [22])
Level of dosimetry	Prescribe to an absorbed dose constraint with post-treatment absorbed dose verification
Approach A	**Approach B**
Methodological description	
7400 MBq ^{177}Lu administered for cycle 1. SPECT–CT imaging of kidneys and lesions at 24 hours p.i. SPECT–CT imaging of kidneys and lesions at 96 hours p.i. SPECT–CT imaging of kidneys and lesions at 168 hours p.i. Organ/lesion delineation on CT Absorbed dose calculation for kidneys and lesions Provided AD_{kidney} for the 4 cycles (PRRT) or 6 cycles (PSMA-RLT) will be less than 23 Gy then administer next cycle and repeat	7400 MBq ^{177}Lu administered for cycle 1 SPECT–CT imaging of kidneys at 96 hours and use a population elimination constant for kidneys Kidneys delineation on SPECT or CT Absorbed Dose Rate calculation of kidneys Extrapolation to the absorbed dose using a population-based effective half-life Ensure AD_{kidney} x4 (PRRT) or AD_{kidney} x6 (PSMA-RLT) <23 Gy Administer next cycles with SPECT–CT imaging of kidneys at 96 hours p.i.
Advantages	
Highly accurate absorbed dose calculation using multiple SPECT–CT Multi-time point scans allow uncertainty in absorbed dose to be expressed. Risk of toxicity is decreased Probability for response is indicated by lesion absorbed doses Prediction of absorbed dose is verified at all cycles	Fairly accurate absorbed dose rate calculation Risk of toxicity is reduced ensuring kidney absorbed doses are below a toxicity threshold for most patients Low scanning burden for patient and department
Disadvantages	
SPECT–CT is time consuming and gamma camera time may be limited Protocol may require up to 18 low-dose CTs Depending on the duration of the hospitalisation, several additional hospital visits may be required for the additional scans. Treatment administration is not optimised, just kept below the 23 Gy absorbed dose constraint for the kidneys	One time point approach is less accurate Lesion absorbed doses are generally not calculated so efficacy is uncertain Biokinetics of kidney unknown. Patients with renal impairment may not follow the assumed population biokinetics Treatment administration not optimised, just kept below the 23 Gy absorbed dose constraint for the kidneys

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Example treatment plans using ^{131}I mIBG

Clinical indication	Patients with metastatic neuroblastoma with a poor response to Induction Chemotherapy
	Prescription to whole body absorbed dose with post-treatment absorbed dose verification
Approach A	**Approach B**
Methodological description	
444 MBq/kg ^{131}I administered for cycle 1. WB counting using ceiling mounted detector 4 times per day until patient activity <300 MBq SPECT–CT imaging of lesions at 24 hours p.i. SPECT–CT imaging of lesions at 72 hours p.i. SPECT–CT imaging of lesions at 120 hours p.i. Lesions delineation on CT Absorbed dose calculation of whole body and lesions Administer 2nd cycle to deliver AD_{WB} = 4 Gy and repeat dosimetry. For cycle 2: Either repeated SPECT–CT imaging or WB counting performed once per day using dose rate monitor until patient activity <300 MBq	444 MBq/kg ^{131}I administered for cycle 1. WB counting performed once per day using dose rate monitor until patient activity <300 MBq Qualitative image at 72 hours to verify treatment delivery. Absorbed dose calculation to whole body Administer 2nd cycle to deliver AD_{WB} = 4 Gy For cycle 2: WB counting performed once per day using dose rate monitor until patient activity <300 MBq
Advantages	
WB measurement system can be used by all staff groups and patient's parents, Highly accurate absorbed dose calculation using multiple SPECT–CT All scans & measurements occur whilst patient is in hospital Multi-time points allow uncertainty in absorbed dose to be expressed. Treatment efficacy is verified by determining lesion absorbed doses.	Dose rate meter readily available in NM department. All measurements occur whilst patient is in hospital Multi-time points allow uncertainty in absorbed dose to be expressed. Qualitative images can be used to ensure distribution of uptake is as expected
Disadvantages	
WB measurement system is bespoke and requires installation. SPECT–CT is time consuming and gamma camera may be time limited Potential radiation exposure to scanning staff Protocol demands up to 6 low-dose CT exposures	Dose rate measurements are less frequent Potential radiation exposure to personnel taking dose rate measurements Lesion absorbed doses are not calculated so efficacy is not verified

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Example treatment plans using ^{99m}Tc-MAA

Clinical indication	Patients with unresectable hepatic carcinoma or liver metastases.
Level of dosimetry	Prescribe to absorbed dose with post-treatment absorbed dose verification
Approach A	**Approach B**
Methodological description	
Diagnostic administration ^{99m}Tc-MAA. SPECT–CT imaging of the abdomen (liver and gastro-intestinal tract) within 1h p.i. Planar or SPECT–CT imaging for lung shunt assessment, within 1h p.i. Liver tumour and non-tumour delineation on CT, lungs on CT or planar emission imaging Voxel dosimetry (Mean absorbed dose and DVH) for tumour and non-tumour hepatic volumes and lungs (if lung shunt >0) Administer activity based on voxel dosimetry considering DVH information and mean dose threshold for efficacy (tumour) and safety (non-tumour liver) Post-treatment dosimetry based on ^{90}Y PET–CT within a few hours post-administration	Diagnostic administration ^{99m}Tc-MAA SPECT–CT imaging of the abdomen (liver and gastro-intestinal tract) within 1h p.i. Planar or SPECT–CT imaging for lung shunt assessment, within 1h p.i. Liver tumour and non-tumour delineation on CT, lungs on CT or planar emission imaging Mean absorbed dose calculations for tumour and non-tumour hepatic volumes and lungs (if lung shunt >0) Administer activity based on partition model considering mean dose threshold for efficacy (tumour) and safety (non-tumour liver) Post-treatment dosimetry based on bremsstrahlung SPECT–CT or ^{90}Y PET–CT within a few hours post-administration
Advantages	
Improved treatment personalisation and expected efficacy taking into account the spatial (intra- and inter-lesion) heterogeneity of absorbed dose distribution Risk of toxicity is limited Post-therapy dosimetry verification allows for better tailoring future therapy sessions and optimal patient management Post-therapy dosimetry provides valuable information for absorbed dose-effects studies	Reasonably accurate predictive dosimetry (mean doses in the tumour and non-tumour compartments) based on the partition model dosimetry Lower scanning burden for patient and department Risk of toxicity is limited No need for a specific dosimetry software, an electronic spreadsheet can suffice Post-therapy dosimetry verification allows for better tailoring future therapy sessions and optimal patient management
Disadvantages	
Typically requires specific software implementing 3D voxel dosimetry Not demonstrated clinical superiority of voxel dosimetry over partition model dosimetry Extra time and resources required for post-SIRT ^{90}Y dosimetry verification	Assumption of close agreement between the predicted and the actual therapeutic absorbed dose distribution. Not always true [36, 37] Neglect possible absorbed dose heterogeneity in targeted lesion and non-tumour parenchyma Extra time and resources required for post-SIRT Dosimetry verification Insufficient quantitative accuracy of the bremsstrahlung SPECT–CT imaging

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This project has received funding from the European Commission under Service Contract N° ENER/2022/NUCL/SI2.869532.0

“EANM Dosimetry Committee Guidance Document: Dosimetry for First-in-Human Studies and Early Phase Clinical Trials”

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Status

Approved by the EANM board and submitted to the EJNMMI for publication

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This project has received funding from the European Commission under Service Contract N° ENER/2022/NUCL/SI2.869532.0

“EANM Dosimetry Committee Guidance Document: Dosimetry for First-in-Human Studies and Early Phase Clinical Trials”

Major content

This document provides guidance relevant to dosimetry for first-in human and early phase clinical trials of such novel agents. The guideline includes a short introduction to different emitters and carrier molecules, followed by recommendations on the methods for activity measurement, pharmacokinetic analyses, as well as absorbed dose calculations and uncertainty analyses. The optimal use of preclinical information and studies involving diagnostic analogues is discussed. Good practice reporting is emphasised, and relevant dosimetry parameters and method descriptions to be included are listed

Three examples of first-in-human dosimetry studies, both for diagnostic tracers and radionuclide therapies, are given:

- [^{177}Lu]Lu-lilotomab satetraxetan for non-Hodgkin’s lymphoma (NHL)
- ^{223}Ra-dichloride
- ^{68}Ga-NODAGA-RGDy

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Recommendations to Advance Coherent Implementation of European Legal Requirements

Discussion
20 minutes

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Coffee break!

10:50–11:20

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