SAMIRA Study on the Implementation of the Euratom and EU Legal Bases with Respect to the Therapeutic Uses of Radiopharmaceuticals

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List of Abbreviations

ALARA	As low as reasonably achievable
BSSD	Basic Safety Standards Directive, Council Directive 2013/59/Euratom
CHMP	EMA Committee for Human Medicinal Products
CT	Computed tomography
CTIS	Clinical Trials Information System
CTR	EU Clinical Trials Regulation, Regulation (EU) No. 536/2014
EANM	European Association of Nuclear Medicine
EC	European Commission
EFOMP	European Federation of Organisations for Medical Physics
EIBIR	European Institute for Biomedical Imaging Research
EMA	European Medicines Agency
EU	European Union
EU-REST	European Union Radiation, Education, Staffing and Training study
FDA	US Food and Drug Administration
FTE	Full-time equivalent
IAEA	International Atomic Energy Agency
ICRP	International Commission on Radiological Protection
ICRU	International Commission on Radiation Units and Measurements
IFU	Instructions for use
MPE	Medical physics expert
PET	Positron emission tomography
SAMIRA	Strategic Agenda for Medical Ionising Research Applications
SGQS	SAMIRA Steering Group on Quality and Safety
SIRT	Selective internal radiation therapy
SMART	Specific, measurable, achievable, reasonable, time-bound
SmPC	Summary of product characteristics
SNMMI	Society of Nuclear Medicine and Molecular Imaging
SPECT	Single photon emission computed tomography
WP MED	Article 31 Working Party on Medical Exposures

Glossary

Activity

The number of radioactive transformations per second of an amount of a radionuclide in a particular energy state at a given time. It is the quotient of dN by dt, where dN is the expectation value of the number of nuclear transitions from that energy state in the time interval dt: A=dN/dt. The unit of activity is the becquerel (Bq)

Absorbed dose

The energy absorbed per unit mass (D = dε/dm), where dε is the mean energy imparted by ionising radiation to the matter in a volume element, dm is the mass of the matter in this volume element. The unit for absorbed dose is the gray (Gy) where one gray is equal to one joule per kilogram: 1 Gy = 1 J/kg

Dosimetry

The process of relating the administered amount of radioactivity to the absorbed (radiation) dose in tumors, and normal organs/tissues

Molecular radiotherapy

Therapies with radiopharmaceuticals, often used as a synonym for radiopharmaceutical therapy

Non-target volume

Region of tissue irradiated outside of the target volume, for which the absorbed dose is calculated. For this region, the aim is to minimise the absorbed dose

Posology

The treatment dosage of a (radio-)pharmaceutical

Radiopharmaceutical therapy

Defined by the International Commission on Radiation Units and Measurements as therapy that uses pharmaceuticals containing radioactive atoms that emit ionising radiation. Often used synonymously with molecular radiotherapy

Target volume

Region of tissue to treat, for which the absorbed dose is calculated. For this region, the aim is to maximise the absorbed dose

Treatment planning

The decision-making process that assesses a patient's suitability for treatment, defines the optimal administered activity, and establishes a dosing schedule tailored to the individual. Simultaneously, it identifies the absorbed doses likely to be received by both target and non-target tissues. This process occurs both prior to administering the radiopharmaceutical and continuously throughout the treatment course, particularly if multiple administration cycles are planned

Treatment verification

The process of checking and recording that the administration has occurred according to the plan within some pre-defined tolerances. This process must take place even if treatment planning does not vary beyond the posology specified by the summary of product characteristics

Volume of interest

Region drawn defining the image coordinates over which counts, or other quantity represented by image values, are integrated over time

Abstract

[en] The 24-month SIMPLERAD project aimed to improve the understanding of the links and interdependencies between the European pharmaceutical legislations and Euratom radiation protection requirements and highlight potential barriers to coherent implementation of radiopharmaceutical therapies in clinical practice. It proposes practical guidance and recommendations to advance a coherent implementation of these requirements and inter-linkage with respect to the therapeutic use of radiopharmaceuticals. The study further explores quality and radiation safety issues related to the current use and introduction of novel therapeutic radiopharmaceuticals into clinical practice, the role of medical physics experts, requirements for dosimetry, release of patients from hospital, and management of radioactive waste.

To achieve the specific objectives, the project included the following elements.

- Analysis of the interrelations between European Union (EU) pharmaceutical legislation and Council Directive 2013/59/Euratom's requirements for therapeutic nuclear medicine
- A survey on the implementation of the relevant European legal requirements with respect to therapeutic nuclear medicine
- Recommended actions to advance the coherent implementation of the European legal requirements with respect to therapeutic nuclear medicine
- Project workshop

[fr] Le projet SIMPLERAD, d'une durée de 24 mois, avait pour objectif d'améliorer la compréhension des liens et des interdépendances entre les législations pharmaceutiques européennes et les exigences de radioprotection d'Euratom. Il visait également à identifier les obstacles potentiels à une mise en œuvre cohérente de la radiothérapie interne vectorisée en pratique clinique. Le projet a formulé des conseils pratiques et des recommandations pour favoriser une implémentation cohérente des exigences et interconnexions qui concernent l'utilisation thérapeutique des radiopharmaceutiques. L'étude aborde également les enjeux de qualité et de radioprotection associés à l'utilisation actuelle et à l'introduction de nouveaux radiopharmaceutiques thérapeutiques dans la pratique clinique. Elle traite du rôle des experts en physique médicale, des exigences en matière de dosimétrie, de la sortie des patients de l'hôpital et de la gestion des déchets radioactifs.

Pour atteindre ces objectifs, le projet a considéré les éléments suivants :

- Analyse des interactions entre la législation pharmaceutique de l'Union européenne et les exigences de la directive 2013/59/Euratom en matière de médecine nucléaire thérapeutique ;
- Enquête sur la mise en œuvre des dispositions légales européennes relatives à la médecine nucléaire thérapeutique ;
- Recommandations pour promouvoir une application cohérente de ces exigences ;
- Organisation d'un atelier de rendu des conclusions du projet.

Executive Summary

[en] While the use of radiopharmaceuticals is paving the way towards a new paradigm especially in cancer care and towards personalised medicine for many diseases and medical conditions, challenges to ensure and maintain high standards for the quality and safety of nuclear medicine treatments are increasing. Some of these challenges relate to the complex regulatory framework regulating the preparation and use of radiopharmaceuticals in general and therapeutic radiopharmaceuticals specifically.

Nuclear medicine is a multidisciplinary specialty that involves the administration of radioactive substances in order to diagnose and treat disease in patients of every age group. Each year more than 10 million patients in Europe benefit from nuclear medicine studies relating to cancer, cardiovascular, neurovascular and endocrine diseases. Currently over 100 different nuclear medicine procedures are approved worldwide by regulators.

Therapeutic as well as diagnostic nuclear medicine applications have demonstrated an excellent clinical safety profile. Given their chemical, physical and clinical particularities, however, radiopharmaceuticals are a very special class of drugs that require specific considerations. As such, their preparation, handling and use are regulated in two separate legal frameworks. Specifically, medicinal authorisation and supervision are laid out in the EU's pharmaceutical legislation, while radiation safety is regulated under Euratom radiation protection legislation. Additional complexity is added by the fact that nuclear medicine is a highly innovative and rapidly developing field of medicine.

Objectives of the SIMPLERAD Project

SIMPLERAD is an acronym: SAMIRA Study on the Implementation of the Euratom and the EU Legal Bases with Respect to the Therapeutic Uses of Radiopharmaceuticals.

SIMPLERAD aimed to improve the understanding of the links and interdependencies between the European pharmaceutical legislation and Euratom radiation protection requirements and to highlight potential barriers to implementation. The intention of the project was to propose practical guidance and recommendations to advance a coherent implementation of these requirements with respect to the therapeutic use of radiopharmaceuticals. The intention of the study was also to explore quality and radiation safety issues related to the current use and introduction of novel therapeutic radiopharmaceuticals into clinical practice, including implementation of dosimetry, the role of medical physics experts (MPEs), release of patients from hospitals, and management of radioactive waste.

Overview of the SIMPLERAD Work Programme and Structure

This study was carried out by a consortium consisting of the European Institute for Biomedical Imaging Research (EIBIR) as project leader, European Association of Nuclear Medicine (EANM) and European Federation of Organisations for Medical Physics (EFOMP), grouping a multi-disciplinary team of professionals from the following areas of expertise: nuclear medicine (diagnosis and treatment), medical physics, radiopharmacy, regulatory expertise in pharmaceuticals and medical radiation protection, waste management, patient release, project management, and coordination. An Advisory Board, consisting of representatives nominated by relevant stakeholders such as major EU and international bodies as well as European professional societies, radiation protection platforms, competent authorities, medical product regulators, industry associations and patient organisations supported the project consortium. In addition, the project activities and results were presented to the SAMIRA Steering Group on Quality and Safety of medical applications (SGQS)[1] and the Working Party on Medical Exposures (WP MED)

[1] https://energy.ec.europa.eu/topics/nuclear-energy/radiological-and-nuclear-technology-health/samira-action-plan_en

of the Group of Experts established under Article 31 of the Euratom Treaty,[2] as well as other relevant groups and initiatives in agreement with the European Commission (EC).

The results of the literature review accompanied by an in-depth study of the current situation in seven European countries including expert interviews and a pan- European survey with more than 200 participants were used as input. An analysis of the current practices in therapeutic nuclear medicine revealed ten issues to be addressed within the project. For each of these issues, a SWOT analysis was performed. Furthermore, guidance was developed on treatment planning and verification for selected radiopharmaceuticals and for dosimetry for first-in-human studies and early phase clinical trials. The results of this analysis were presented to the Advisory Board in November 2023

A SIMPLERAD workshop held in December 2023 in Brussels focused on the key findings, conclusions and recommendations of the project, which were discussed intensively with the participants. The workshop was accompanied by an online wider stakeholder consultation. The stakeholders included were, but not limited to, the following.

- European and national authorities responsible for authorisation of radiopharmaceuticals
- Competent authorities for radiation protection
- Researchers in the area of radiopharmaceuticals
- The nuclear medicine and medical physics communities
- Patient organizations
- The radiopharmaceutical industry targeted via Nuclear Medicine Europe (NMEU)
- Relevant clinical communities

Workshop-related information was announced to relevant stakeholders through the project website at the time of the workshop. The survey was sent out to the wider stakeholder community and was open for responses until the end of December 2023.

The workshop proceedings, containing background, the target groups, session summaries and conclusions from the discussions, is available in PDF format on the project website.

Key Findings, Conclusions and Recommendations from the SIMPLERAD Project

The literature survey and in-depth analysis of the situation in seven European countries provided evidence of a missing intersection between EMA guidance documents and requirements of Council Directive 2013/59/Euratom, referred to in this report as the Basic Safety Standards Directive (BSSD) [1], for radiopharmaceutical therapies, particularly concerning the implementation of article 56 of the BSSD.

The main results of the survey identified a lack of alignment between pharmaceutical legislation and the BSSD's requirements regarding radiopharmaceuticals, leading to interpretation issues and varied legislative processes across Europe. This disparity may affect the development of and patient access to innovative radiotherapeutic compounds. Increased resources, closer collaborative working between all stakeholders and Member States, and further specialist training were identified as potential actions to advance the coherent implementation of these European legal requirements. Further regulatory guidance produced in collaboration was also identified as a means to address the observed issues and maintain high standards for quality and safety of nuclear medicine treatments without stifling development.

Based on these results, the SIMPLERAD consortium identified ten items and recommended actions to advance the coherent implementation of the European legal requirements with respect to therapeutic nuclear medicine. These actions include regulatory measures and suggestions for improvement to material and staff resources and implementation of the BSSD. Efforts to further

[2] https://energy.ec.europa.eu/topics/nuclear-energy/radiation-protection/scientific-seminars-and-publications/group-experts_en

demonstrate the added value of patient-specific optimisation of treatments are recommended. Furthermore, suggestions are made for a diverse palette of measures to improve understanding of current regulations, including a proposal for explanatory documents pertaining to the implementation of article 56.1 of the BSSD in the context of radiopharmaceutical therapy and the interconnection of the BSSD with existing and planned pharmaceutical and Medical Devices Regulation (EU 2017/745; [2]).

These items are presented below. Items 1, 2, 3, 8 and 10, denoted in **bold** below, were defined according to the stakeholder feedback in December 2023 as having the highest importance. It should be further noted that for securing a follow-up to the SIMPLERAD recommendations, major investments are needed.

1. ***Disconnection between Marketing Authorisation of Radiopharmaceuticals and the BSSD***

   The disconnect between pharmaceutical legislation, EMA guidance documents and Euratom BSSD requirements with respect to the development, authorisation and use of new therapeutic radiopharmaceuticals has clearly been identified as a considerable challenge. The legislative proposal [3] for repealing Directive 2001/83, referred to as the EU Pharma Directive [4], might contain an important step towards recognising the concept of justification and optimisation also in the context of marketing authorisation of radiopharmaceuticals used for therapy. A statement in the legislative proposal for the revision of the EU Pharma Directive that the BSSD's requirements should prevail in case of contradictions might give clarity on this point. However, this is not included in the list of proposed amendments as of September 2024. An inclusion of radiopharmaceuticals in the list of products that should be regulated by an adapted regulatory framework in article 28, annex VII, of the current proposal by the commission for a new directive, will give the needed flexibility to address the specificities of radiopharmaceuticals. Annex VII, however, is also not in the list of proposed amendments as of September 2024.

   The concept of justification and optimisation should be complemented by guidance documents published by the EMA and an update of the Clinical Trials Information System (CTIS). Achieving this will require the involvement of the responsible EC services, EMA and professionals in the field of therapeutic radiopharmaceuticals such as nuclear medicine clinicians and medical physicists.

2. ***Differences in Interpreting and Implementing the BSSD in the Context of Therapeutic Nuclear Medicine***

   The BSSD specifically includes nuclear medicine for therapeutic purposes among radiotherapeutic procedures.

   This report and reference [5] contain explicit proposals for and guidance on the interpretation and implementation of the BSSD in the context of therapeutic nuclear medicine, with specific suggestions on how individual treatment planning and appropriate verification of delivery can be implemented.

   A continuing effort by the European nuclear medicine and medical physics communities, responsible EC services and EMA is recommended to promote the guidance document on the European level. In particular, the EMA should ensure that the defined posologies do not prevent individualised treatment planning and optimisation.

3. ***Lack of Resources for Dosimetry***

   The implementation of the individual planning and verification 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.

   For this purpose, an update of the EANM/EFOMP MPE curriculum [6] is presently undertaken. Furthermore, we recommend coordinated actions by the EC and national authorities to increase the availability of sufficient educated staff as well as funding.

4. *Differences Regarding Status of MPEs (e.g., Training, Requirements, Level of Experience, Responsibilities) between Member States*
   Differing responsibilities as well as large variations in resources, e.g., training, requirements, level of experience and responsibilities, exist for medical physicists and MPEs across Europe.

   First, responsibilities should be harmonised by mapping the current situation, e.g., by a EU-sponsored tender, accompanied by a guidance document with recommendations.

   Second, the staffing levels defined in the publication Radiation Protection No. 174, European Guidelines on Medical Physics Expert [7], should be adopted by the Member States with the support of the EC and national authorities, also taking into account the forthcoming guidelines and recommendations of the EU Radiation, Education, Staffing & Training (EU-REST) study [8]. Furthermore, national authorities should ensure free circulation of MPEs within the EU.

5. *Heterogeneity of Dose Constraints and Patient-Release Criteria between Member States*
   The setting of release criteria and patient instructions is influenced by different criteria and decision levels in different countries, which include the use of the concept of comforter and carers, appropriate dose constraints for optimisation, and methodologies in risk-assessment studies.

   Future EU programmes that support the generation of scientific data can contribute to the harmonisation of risk-assessment studies. The elaboration of European guidance documents on the medical exposure of comforters and carers in nuclear medicine and correct use of dose constraints should be considered by the EC in close collaboration with HERCA.

6. *Heterogeneity of Management of Radioactive Waste across Member States*
   Conditions concerning management of radioactive waste are well-established in most countries across Europe. However, the specific conditions and practical application of such vary widely across Member States and centres.

   Future EU programmes that support focused analyses and surveys of the conditions concerning effluent release and waste management across the EU and different sectors should be undertaken and will contribute to the harmonisation of risk-assessment studies in close collaboration with HERCA.

7. *Differing Guidance from Professional Societies for Clinical Practice*
   Different professional societies come to different, even contradictory, guidance for the same disease/therapeutic modality on issues pertaining to the interaction between the EU Pharma Directive and BSSD as well as the interpretation of the BSSD in the clinical context.

   To overcome this, dialogue between national competent authorities and professional societies should be initiated to ensure that society guidance complies with the BSSD.

8. ***Differing Regulatory Procedures between Member States for Drug Development and Clinical Trials***
   Differing regulatory processes between Member States for application procedures of clinical trials concerning dosimetry aspects of radiopharmaceuticals and varying competences on the assessment of radiation- and dosimetry-related aspects of clinical trial applications were observed among Member States.

   A clear need to harmonise the application process for clinical trials with radiopharmaceuticals by the EMA is apparent in relation to radiation safety, notably dosimetry and absorbed dose finding.

9. *Insufficient Specialist Knowledge Concerning Nuclear Medicine within Competent Authorities Regarding EU Pharmaceutical and Medicine as Well as BSSD-Related Regulations*
   The SIMPLERAD consortium observed heterogeneity across Member States concerning many aspects of both sets of relevant legislation, e.g., pharmaceutical legislation and radiation

protection legislation. A lack of coordination between different competent authorities was observed along with different levels of knowledge in one or even both sets of legislation.

Therefore, more extensive specialist knowledge is needed concerning nuclear medicine for the respective competent authorities regarding the EU Pharma Directive as well as BSSD-related regulations. This will require further specialist training, more harmonised guidance and close cooperation between national competent authorities responsible for transposing and implementing the respective EU directives.

Certainly, a coordinated joint action for networking and improving communication, such as the proposed call for EU funding CR-g-23-44-03 within the framework of the SAMIRA initiative, would be of great value and should be considered with high priority.

10. ***Differences among Opinions of Professionals Concerning Dosimetry and the Necessity Stipulated in National Legislation and Guidance***
Both the EU pharmaceutical legislation and BSSD contain provisions concerning dosimetry, treatment planning, optimisation and verification in different therapies involving radiopharmaceuticals. Furthermore, the process of transposition of EU/Euratom legislation into national legislation allows a degree of variation in the respective national provisions. Consequently, regulatory guidance provided by national authorities differs between radiopharmaceutical therapies. For some therapies, positions of professionals on the role of dosimetry also differ.

Some guidance to overcome this can be found in this report (See also [5]). To reconcile these differing positions, competent authorities and national societies such as EANM and EFOMP should collaborate to implement similar guidance at the national level. This guidance should provide best practice examples and acceptable deviation whilst still complying with EU law.

Needed Mid- and Long-Term Investments

As stressed in the previous section, there is a need for significant investment in therapeutic nuclear medicine, in particular with respect to the items in **bold** in Table 1 below. Furthermore, the SIMPLERAD consortium suggests the following more general measures, encapsulating the items mentioned above and partly going beyond them.

- Create and support specialised treatment and training centres, i.e., networks of excellence, with advanced knowledge on quantitative imaging and dosimetry
- Promote and support accreditation programs for therapeutic nuclear medicine and dosimetry
- Collate dosimetric and response data from centres across Europe to develop and generate large-scale database studies
- Initiate studies on the impact of individual treatment planning of radiopharmaceutical therapy on patient outcomes

The creation of infrastructures and the development of networks of excellence and research projects should be supported by the EC research programme in the health area, in close collaboration between the EC services dealing with the EU pharmaceutical and radiation protection policies.

Most of the measures proposed here are well within the scope of existing funding instruments and regulatory frameworks. We, the SIMPLERAD consortium, therefore strongly believe that the measures will contribute to the implementation of truly personalised radiopharmaceutical therapies in compliance with all relevant regulatory frameworks.

Table 1. Measures with the highest priority to be taken in the wider SAMIRA framework

Type of Remedy	Proposed Remedy	Responsible Party	Corresponding Section
Data collection	**Establishment of national and European databases among multiple centres to collect data on clinical factors associated with molecular radiotherapy for approved radiopharmaceuticals, including dosimetry and patient outcome**	**European professional societies supported by EC or national funding**	**3.5.8**
Data collection	**Support of investigator-initiated multi-centre and multinational clinical trials on therapeutic radiopharmaceuticals to develop optimised treatments**	**Clinical researchers or networks of excellence supported by EC or national funding**	**3.5.8**
Harmonisation and training	Establishment of dosimetry expert networks to disseminate know-how for clinical trials with therapeutic radiopharmaceuticals	EANM, EFOMP	3.5.9
Data collection	Mandatory presentation of results and evidence on individual-patient dosimetry within the marketing authorisation application dossier	EMA	3.5.1, 3.5.8
Legislation and regulation	Inclusion of radiopharmaceuticals in annex VII of the EC's proposal for a revision of directive on Union code relating to medicinal products for human use (2023/0132)	Responsible EC services	3.5.1
Legislation and regulation	**Revise the EU CTIS so that structured radiation safety and dosimetry information must be provided for therapeutic radiopharmaceuticals**	**EMA**	**3.5.1**
Reimbursement	**Ensure that clinical dosimetry is explicitly integrated as part of the molecular-radiotherapy clinical process and therefore in the reimbursement scheme at the national level**	**National competent authorities**	**3.5.3**
Harmonisation and training	Increase relevant specialist knowledge within national competent authorities through further specialist training, regulatory cooperation and harmonised legislation	National competent authorities	3.5.9

Synthèse

[fr] Alors que l'utilisation de produits radiopharmaceutiques ouvre la voie à un nouveau paradigme, notamment dans le traitement du cancer, vers une médecine personnalisée pour de nombreuses maladies, les défis pour assurer et maintenir des normes élevées de qualité et de sécurité des traitements de médecine nucléaire augmentent. Certains de ces défis sont liés au cadre réglementaire complexe régissant la préparation et l'utilisation des produits radiopharmaceutiques en général et des produits radiopharmaceutiques thérapeutiques en particulier.

La médecine nucléaire est une spécialité multidisciplinaire qui implique l'administration de substances radioactives afin de diagnostiquer et de traiter des maladies chez des patients de tous âges. Chaque année, plus de 10 millions de patients en Europe bénéficient d'examens de médecine nucléaire portant sur le cancer, les maladies cardiovasculaires, neurovasculaires et endocriniennes. Actuellement, plus de 100 procédures de médecine nucléaire différentes sont approuvées dans le monde entier par les autorités règlementaires.

Les applications thérapeutiques et diagnostiques de médecine nucléaire ont démontré un excellent profil de sécurité clinique. Cependant, compte tenu de leurs particularités chimiques, physiques et cliniques, les produits radiopharmaceutiques constituent une classe de médicaments très particulière qui nécessite des considérations spécifiques. En tant que tels, leur préparation, leur manipulation et leur utilisation sont réglementées dans deux cadres juridiques distincts. Plus précisément, l'autorisation et la surveillance des médicaments sont régies par la législation pharmaceutique de l'Union européenne, tandis que la radioprotection est réglementée par la législation Euratom sur la radioprotection. La médecine nucléaire est un domaine de la médecine très innovant et en plein essor, ce qui complique encore les choses.

Objectifs du projet SIMPLERAD

SIMPLERAD est l'acronyme de SAMIRA Study on the Implementation of the Euratom and the EU Legal Bases with Respect to the Therapeutic Uses of Radiopharmaceuticals.

SIMPLERAD visait à améliorer la compréhension des liens et des interdépendances entre la législation pharmaceutique européenne et les exigences de radioprotection d'Euratom et à mettre en évidence les obstacles potentiels à leur mise en œuvre. L'intention du projet était de proposer des orientations pratiques et des recommandations pour faire progresser une mise en œuvre cohérente de ces exigences en ce qui concerne l'utilisation thérapeutique des radiopharmaceutiques. L'objectif de l'étude était également d'explorer les questions de qualité et de radioprotection liées à l'utilisation actuelle et à l'introduction de nouveaux radiopharmaceutiques thérapeutiques dans la pratique clinique, y compris la mise en œuvre de la dosimétrie, le rôle des experts en physique médicale, la sortie des patients des hôpitaux et la gestion des déchets radioactifs.

Aperçu du programme de travail et de la structure de SIMPLERAD

Cette étude a été réalisée par un consortium composé de l'Institut européen de recherche en imagerie biomédicale (EIBIR) en tant que chef de projet, de l'Association européenne de médecine nucléaire (EANM) et de la Fédération européenne des organisations de physique médicale (EFOMP), regroupant une équipe multidisciplinaire de professionnels issus des domaines d'expertise suivants : médecine nucléaire (diagnostic et traitement), physique médicale, radiopharmacie, expertise réglementaire en matière de produits pharmaceutiques et de radioprotection médicale, gestion des déchets, libération des patients, gestion de projet et coordination. Un comité consultatif, composé de représentants désignés par les parties prenantes concernées telles que les principaux organismes européens et internationaux ainsi que les sociétés professionnelles européennes, les plateformes de radioprotection, les autorités compétentes, les régulateurs de produits médicaux, les associations industrielles et les organisations de patients, a soutenu le consortium du projet. En outre, les activités et les

résultats du projet ont été présentés au SAMIRA Comité de supervision sur la qualité et la sécurité des applications médicales (SGQS) et au Groupe de travail sur les expositions médicales (WP MED) du groupe d'experts établi en vertu de l'article 31 du traité Euratom, ainsi qu'à d'autres groupes et initiatives concernés en accord avec la Commission européenne.

Les résultats de l'analyse documentaire, accompagnés d'une étude approfondie de la situation actuelle dans sept pays européens, comprenant des entretiens avec des experts et une enquête paneuropéenne auprès de plus de 200 participants, ont été utilisés comme données d'entrée. Dans cette section, une analyse des pratiques actuelles en médecine nucléaire thérapeutique a révélé dix problèmes à traiter dans le cadre du projet. Pour chacun de ces problèmes, une analyse SWOT a été incluse. En outre, des orientations ont été élaborées sur la planification et la vérification du traitement pour certains produits radiopharmaceutiques et pour la dosimétrie pour les premières études sur l'homme et les essais cliniques de phase précoce. Les résultats de cette analyse ont été présentés au conseil consultatif en novembre 2023.

Un atelier de rendu du projet organisé en décembre 2023 à Bruxelles s'est concentré sur les principales constatations, conclusions et recommandations du projet. L'atelier a été accompagné d'une consultation en ligne plus large des parties prenantes. Les parties prenantes incluses étaient, sans s'y limiter, les suivantes.

- Autorités européennes et nationales responsables de l'autorisation des produits radiopharmaceutiques
- Autorités compétentes en matière de radioprotection
- Chercheurs dans le domaine des produits radiopharmaceutiques
- Communautés de médecine nucléaire et de physique médicale
- Organisations de patients
- L'industrie radiopharmaceutique ciblée via Nuclear Medicine Europe
- Communautés cliniques concernées

Les informations relatives à l'atelier ont été annoncées aux parties prenantes concernées via le site Web du projet au moment de l'atelier. L'enquête a été envoyée à l'ensemble de la communauté des parties prenantes et était ouverte aux réponses jusqu'à fin décembre 2023.

Le compte rendu de l'atelier, contenant le contexte, les groupes cibles, les résumés des sessions et les conclusions des discussions, est disponible au format PDF sur le site Web du projet.

Principales conclusions et recommandations du projet SIMPLERAD

L'étude de la littérature et l'analyse approfondie de la situation dans sept pays européens ont mis en évidence l'absence d'intersection entre les documents d'orientation de l'EMA et la Directive 2013/59/Euratom du Conseil [1], les exigences relatives aux thérapies radiopharmaceutiques, notamment en ce qui concerne la mise en œuvre de l'article 56 de la Directive 2013/59/Euratom.

Les principaux résultats de l'enquête ont identifié un manque d'alignement entre la législation pharmaceutique et les exigences de la Directive 2013/59/Euratom concernant les produits radiopharmaceutiques, ce qui a conduit à des problèmes d'interprétation et à des processus législatifs variés à travers l'Europe. Cette disparité peut affecter le développement et l'accès des patients à des composés radiothérapeutiques innovants. Des ressources accrues, une collaboration plus étroite entre toutes les parties prenantes et les États membres et une formation spécialisée plus poussée ont été identifiées comme des actions potentielles pour faire progresser la mise en œuvre cohérente des exigences juridiques européennes. Des guides d'interprétation réglementaire produits en collaboration ont également été identifiées comme un moyen de résoudre les problèmes observés et de maintenir des normes élevées de qualité et de sécurité des traitements de médecine nucléaire sans entraver le développement.

Sur la base de ces résultats, le consortium SIMPLERAD a identifié dix points et recommandé des actions pour faire progresser la mise en œuvre cohérente des exigences juridiques européennes en matière de médecine nucléaire thérapeutique. Ces actions comprennent des mesures réglementaires et des suggestions d'amélioration des ressources matérielles et humaines et de la mise en œuvre de la Directive 2013/59/Euratom. Des efforts visant à démontrer davantage la valeur ajoutée de l'optimisation des traitements spécifiques au patient sont également recommandés. En outre, des suggestions sont faites pour une palette diversifiée de mesures visant à améliorer la compréhension de la réglementation actuelle, notamment une proposition de documents explicatifs relatifs à la mise en œuvre de l'article 56.1 de la Directive 2013/59/Euratom dans le contexte de la thérapie radiopharmaceutique et l'interconnexion de la Directive 2013/59/Euratom avec les législations, existante et prévue sur les produits pharmaceutiques et le Règlement (Union européenne) 2017/745 relatif aux dispositifs médicaux.

Ces éléments sont présentés ci-dessous. Les éléments 1, 2, 3, 8 et 10, indiqués en **gras** ci-dessous, ont été définis en fonction des commentaires des parties prenantes en décembre 2023 comme ayant la plus haute importance. Il convient de noter en outre que pour assurer un suivi des recommandations du projet, des investissements majeurs sont nécessaires.

1. **Déconnexion entre l'autorisation de mise sur le marché des produits radiopharmaceutiques et la Directive 2013/59/Euratom**
   La déconnexion entre la législation pharmaceutique, les documents d'orientation de l'EMA et les exigences de la Directive 2013/59/Euratom en ce qui concerne le développement, l'autorisation et l'utilisation de nouveaux produits radiopharmaceutiques thérapeutiques a clairement été identifiée comme un défi considérable. La proposition législative [2] visant à abroger la directive 2001/83, appelée dans le présent rapport la directive pharmaceutique de l'Union européenne [3], pourrait constituer une étape importante vers la reconnaissance du concept de justification et d'optimisation également dans le contexte de l'autorisation de mise sur le marché des produits radiopharmaceutiques utilisés à des fins thérapeutiques. Une déclaration dans la proposition législative de révision de la directive pharmaceutique de l'UE selon laquelle les exigences de la Directive 2013/59/Euratom devraient prévaloir en cas de contradiction pourrait clarifier ce point. Toutefois, cette disposition ne figure pas dans la liste des modifications proposées en septembre 2024. L'inclusion des produits radiopharmaceutiques dans la liste des produits qui devraient être réglementés par un cadre adapté à l'article 28, annexe VII, de la proposition actuelle de la Commission européenne pour une nouvelle directive, donnera la flexibilité nécessaire pour tenir compte des spécificités des produits radiopharmaceutiques. L'annexe VII ne figure toutefois pas non plus dans la liste des modifications proposées en septembre 2024.

   Le concept de justification et d'optimisation devrait être complété par des documents d'orientation publiés par l'EMA et une mise à jour du Système d'information sur les essais cliniques. Pour y parvenir, il faudra l'implication des services responsables de la Commission européenne, de l'EMA et des professionnels du domaine des produits radiopharmaceutiques thérapeutiques tels que les cliniciens en médecine nucléaire et les physiciens médicaux.

2. **Différences dans l'interprétation et la mise en œuvre de la Directive 2013/59/Euratom dans le contexte de la médecine nucléaire thérapeutique**
   La Directive 2013/59/Euratom inclut spécifiquement la médecine nucléaire à des fins thérapeutiques parmi les procédures radiothérapeutiques.

   Ce rapport et la référence [5] contiennent des propositions explicites et des conseils sur l'interprétation et la mise en œuvre de la Directive 2013/59/Euratom dans le contexte de la médecine nucléaire thérapeutique, avec des suggestions spécifiques sur la manière dont la planification individuelle du traitement et la vérification appropriée de l'administration peuvent être mises en œuvre.

   Un effort continu de la part des communautés européennes de médecine nucléaire et de physique médicale, des services responsables de la Commission européenne et de l'EMA est

recommandé pour promouvoir le document d'orientation au niveau européen. En particulier, l'EMA devrait s'assurer que les posologies définies n'empêchent pas la planification et l'optimisation individualisées du traitement.

3. Manque de ressources pour la dosimétrie

La mise en œuvre du mandat de planification et de vérification individuelle énoncé à l'article 56.1 de la Directive 2013/59/Euratom est entravée par un manque de ressources, tant en termes de personnel qualifié que de financement/remboursement.

À cette fin, une mise à jour du programme conjoint EANM/EFOMP [5] de formation des experts en physique médicale est actuellement en cours. En outre, nous recommandons des actions coordonnées par la Commission européenne et les autorités nationales pour accroître la disponibilité d'un personnel qualifié suffisant ainsi que le financement.

4. *Différences concernant le statut des physiciens médicaux (par exemple, formation, exigences, niveau d'expérience, responsabilités) entre les États membres*

Des niveaux de responsabilités différentes ainsi que de grandes variations dans les ressources, par exemple, la formation, les exigences, le niveau d'expérience et les responsabilités, existent pour les physiciens médicaux à travers l'Europe.

Tout d'abord, les responsabilités devraient être harmonisées en cartographiant la situation actuelle, par exemple, par un appel d'offres parrainé par l'Union européenne, accompagné d'un document d'orientation contenant des recommandations.

Deuxièmement, les niveaux de dotation définis dans la publication Radiation Protection No. 174 [7] devraient être adopitése par les États members avec le soutien de la Commission européenne et des autorités nationales, en tenant également compte des prochaines lignes directrices et recommandations du projet EU-REST [8]. En outre, les autorités nationales devraient assurer la libre circulation des physiciens médicaux au sein de l'Union européenne.

5. *Hétérogénéité des contraintes de dose et des critères de libération des patients entre les États membres*

La définition des critères de libération et des instructions aux patients est influencée par différents critères et niveaux de décision dans les différents pays, qui incluent l'utilisation du concept de d'accompagnant et de soignants, des contraintes de dose appropriées pour l'optimisation et des méthodologies dans les études d'évaluation des risques.

De futurs programmes de l'Union européenne soutenant la production de données scientifiques peuvent contribuer à l'harmonisation des études d'évaluation des risques. L'élaboration de documents d'orientation européens sur l'exposition médicale des accompagnants et soignants en médecine nucléaire et l'utilisation correcte des contraintes de dose devraient être envisagées par la Commission européenne en étroite collaboration avec HERCA.

6. *Hétérogénéité de la gestion des déchets radioactifs dans les États membres*

Les conditions de gestion des déchets radioactifs sont bien établies dans la plupart des pays européens. Toutefois, les conditions spécifiques et l'application pratique de ces conditions varient considérablement selon les États membres et les centres.

De futurs programmes de l'Union européenne qui soutiennent des analyses et des enquêtes ciblées sur les conditions de rejet d'effluents et de gestion des déchets dans l'Union européenne et dans différents secteurs devraient être entrepris et contribueront à l'harmonisation des études d'évaluation des risques en étroite collaboration avec HERCA.

7. *Orientations divergentes des sociétés professionnelles pour la pratique clinique*

Différentes sociétés professionnelles parviennent à des orientations différentes, voire contradictoires, pour la même maladie/modalité thérapeutique sur des questions relatives à l'interaction entre la directive pharmaceutique de l'Union européenne et la Directive

2013/59/Euratom ainsi qu'à l'interprétation de la Directive 2013/59/Euratom dans le contexte clinique.

Pour surmonter ce problème, un dialogue entre les autorités nationales compétentes et les sociétés professionnelles devrait être initié pour garantir que les orientations des sociétés soient conformes à la Directive 2013/59/Euratom.

8. **Procédures réglementaires différentes entre les États membres pour le développement de médicaments et les essais cliniques**
   Des processus réglementaires différents entre les États membres pour les procédures de demande d'essais cliniques concernant les aspects dosimétriques des produits radiopharmaceutiques et des compétences variables en matière d'évaluation des aspects liés aux rayonnements et à la dosimétrie des demandes d'essais cliniques ont été observés parmi les États membres.

   Un besoin évident d'harmonisation du processus de demande d'essais cliniques impliquant des produits radiopharmaceutiques par l'EMA est évident pour ce qui concerne la radioprotection, notamment la dosimétrie et les résultats dosimétriques.

9. *Connaissances spécialisées insuffisantes concernant la médecine nucléaire au sein des autorités compétentes concernant les réglementations pharmaceutiques et médicales de l'Union européenne ainsi que celles relatives à la Directive 2013/59/Euratom*
   Le consortium SIMPLERAD a observé une hétérogénéité entre les États membres concernant de nombreux aspects des deux ensembles de législations pertinentes, la législation pharmaceutique et la législation sur la radioprotection. Un manque de coordination entre les différentes autorités compétentes a été observé ainsi que des niveaux de connaissances différents dans l'un ou même les deux ensembles de législations.

   Par conséquent, des connaissances spécialisées plus étendues sont nécessaires en matière de médecine nucléaire pour les autorités compétentes respectives concernant la directive pharmaceutique de l'Union européenne ainsi que les réglementations relatives à la Directive 2013/59/Euratom. Cela nécessitera une formation spécialisée supplémentaire, des orientations plus harmonisées et une coopération étroite entre les autorités nationales compétentes responsables de la transposition et de la mise en œuvre des directives européennes respectives.

   Il est certain qu'une action commune coordonnée pour la mise en réseau et l'amélioration de la communication, telle que l'appel à financement européen proposé CR-g-23-44-03 dans le cadre de l'initiative SAMIRA, serait d'une grande valeur et devrait être considérée comme une priorité élevée.

10. **Différences entre les opinions des professionnels concernant la dosimétrie et la nécessité stipulée dans la législation et les orientations nationales**
    La législation pharmaceutique de l'Union européenne et la Directive 2013/59/Euratom contiennent toutes deux des dispositions concernant la dosimétrie, la planification, l'optimisation et la vérification du traitement dans différentes thérapies impliquant des produits radiopharmaceutiques. En outre, le processus de transposition de la législation de l'Union européenne/Euratom dans la législation nationale permet un certain degré de variation dans les dispositions nationales respectives. Par conséquent, les orientations réglementaires fournies par les autorités nationales diffèrent selon les thérapies radiopharmaceutiques. Pour certaines thérapies, les positions des professionnels sur le rôle de la dosimétrie diffèrent également.

    Des orientations pour surmonter ce problème peuvent être trouvées dans ce rapport (voir aussi la référence [5]). Pour concilier ces positions divergentes, les autorités compétentes et les sociétés nationales partenaires de l'EANM et l'EFOMP devraient collaborer pour mettre en œuvre des orientations similaires au niveau national. Ces orientations devraient fournir des

exemples de bonnes pratiques, et les écarts acceptables tout en respectant la législation de l'UE.

Investissements nécessaires à moyen et long terme

Comme souligné dans la section précédente, il est nécessaire d'investir de manière significative dans la médecine nucléaire thérapeutique, en particulier pour ce qui concerne les éléments en **gras** du tableau 1 ci-dessous. En outre, le consortium SIMPLERAD suggère les mesures plus générales suivantes, qui englobent les points mentionnés ci-dessus et vont en partie au-delà.

- Créer et soutenir des centres de traitement et de formation spécialisés, c'est-à-dire des réseaux d'excellence, dotés de connaissances avancées en imagerie quantitative et en dosimétrie.
- Promouvoir et soutenir les programmes d'accréditation pour la médecine nucléaire thérapeutique et la dosimétrie.
- Collecter les données dosimétriques et de réponse des centres de toute l'Europe pour développer et générer des bases de données à grande échelle.
- Lancer des études sur l'impact de la planification individuelle du traitement de la thérapie radiopharmaceutique sur le devenir des patients.

La création d'infrastructures et le développement de réseaux d'excellence et de projets de recherche devraient être soutenus par le programme de recherche de la Commission européenne dans le domaine de la santé, en étroite collaboration entre les services de la Commission européenne chargés des politiques pharmaceutiques et de radioprotection de l'Union européenne.

La création d'infrastructures et le développement de réseaux d'excellence et de projets de recherche devraient être soutenus par le programme de recherche de la Commission européenne dans le domaine de la santé, en étroite collaboration avec les services de la Commission européenne chargés des politiques pharmaceutiques et de radioprotection de l'Union européenne. La plupart des mesures proposées ici s'inscrivent dans le cadre des instruments de financement et des cadres réglementaires existants. Nous, le consortium SIMPLERAD, sommes donc convaincus que ces mesures contribueront à la mise en œuvre de thérapies radiopharmaceutiques véritablement personnalisées, dans le respect de tous les cadres réglementaires pertinents.

Tableau 1. Mesures prioritaires à prendre dans le cadre plus large de SAMIRA

Type de Recours	Recours Proposé	Partie Responsable	Section Correspondante
Collecte de données	**Mise en place de bases de données nationales et européennes entre plusieurs centres pour collecter des données sur les facteurs cliniques associés à la radiothérapie moléculaire pour les produits radiopharmaceutiques approuvés, y compris la dosimétrie et les résultats pour les patients**	**Sociétés professionnelles européennes soutenues par des financements de la Commission européenne ou nationaux**	**3.5.8**
Collecte de données	**Soutien aux essais cliniques multicentriques et multinationaux initiés par les chercheurs sur les produits radiopharmaceutiques thérapeutiques pour développer des traitements optimisés**	**Chercheurs cliniques ou réseaux d'excellence soutenus par des financement de la Commission européenne ou nationaux**	**3.5.8**
Harmonisation et formation	Mise en place de réseaux d'experts en dosimétrie pour diffuser le savoir-faire en matière d'essais cliniques avec des produits radiopharmaceutiques thérapeutiques	EANM, EFOMP	3.5.9
Collecte de données	Présentation obligatoire des résultats de dosimétrie individuelle du patient dans le dossier de demande d'autorisation de mise sur le marché	EMA	3.5.1, 3.5.8
Législation et réglementation	Inclusion des produits radiopharmaceutiques dans l'annexe VII de la proposition de révision de la directive relative au code de l'Union européenne relatif aux médicaments à usage humain (2023/0132)	Services Commission européenne responsables	3.5.1

Législation et réglementation	**Réviser le Système d'information sur les essais cliniques de l'Union européenne afin que des informations structurées sur la radioprotection et la dosimétrie soient fournies pour les produits radiopharmaceutiques thérapeutiques**	**EMA**	**3.5.1**
Remboursement	**Veiller à ce que la dosimétrie clinique soit explicitement intégrée dans le processus clinique de radiothérapie moléculaire, et donc dans le système de remboursement au niveau national**	**Autorités nationales compétentes**	**3.5.3**
Harmonisation et formation	Renforcer les connaissances spécialisées pertinentes auprès des autorités nationales compétentes grâce à une formation spécialisée plus poussée, à la coopération réglementaire et à une législation harmonisée	Autorités nationales compétentes	3.5.9

1. Analysis of the Interrelations between EU Pharmaceutical Legislation and Council Directive 2013/59/Euratom

1.1 Introduction

The SIMPLERAD consortium investigated the links and interdependencies between the European pharmaceutical legislations and Euratom radiation protection requirements, in view of highlighting potential barriers to the implementation of individual treatment planning and verification as mandated by the BSSD. In addition, a comparative analysis between the situation in EU Member States and the UK and US was conducted.

1.2 Methodology

The methodology consisted of a literature analysis, in-depth study in selected Member States on therapeutic radiopharmaceuticals and medical devices, and respective analyses of summaries of product characteristics (SmPCs) and instructions for use (IFU).

Derived from the EANM position paper on article 56 of the BSSD for therapeutic nuclear medicine [9], the most relevant radiopharmaceuticals and medical devices for selective internal radiotherapy (SIRT) were identified. An extensive literature analysis was performed, covering regulatory documents, position papers, guidance documents, international body recommendations and scientific literature as well as SmPCs and IFU for medicinal products and medical devices.

The literature provided by an in-depth review consisted of 129 references, which were grouped into the following seven categories.

1. Regulatory documents
2. Posologies
3. Medical devices
4. Position papers
5. Guidelines
6. International body global recommendations
7. Scientific references

The methodology was completed by an in-depth study of the regulatory framework in seven selected European countries, representing a range of population but also various degrees of deployment of therapeutic nuclear medicine: Finland, France, Germany, Italy, Poland, Spain and Sweden. For these countries information was gathered from competent authorities, when possible, or selected experts such as clinicians, MPEs and radiopharmacists well aware of regulatory procedures. Care was taken to keep the information as factual as possible, and national regulations were collected and explicitly referenced. For this, a list of five questions was circulated to the seven countries in order to ease the analysis of the responses.

- What are the legal bodies in charge of the marketing authorisation of a therapeutic radiopharmaceutical in your country?
- Are there institutions in charge of providing specific expertise in radiation safety and related fields to the regulatory authorities?
- What are the interactions, if any, between the institutions in charge of giving the marketing authorisation (pharmaceutical) and those in charge of the implementation of the BSSD (radiation safety and optimisation)?
- How is the BSSD, and specifically article 56 on optimisation, implemented in your country?
- What is the situation in your country for the three following specific products: [^{131}I]NaI, [^{177}Lu]Lu-DOTATATE and ^{90}Y-labelled microspheres?

These questions aimed at identifying at the national level the consequences of the different regulations at the European level governing radiopharmaceutical marketing authorisation and

the optimisation of radiation protection of the affected patients. The aim was also to try to determine if the national bodies are aware of any regulatory inconsistencies and if mitigating measures were or are being implemented to reconcile the two types of regulations.

1.3 Pharmaceutical Regulation and Guidance Documents

The EC has produced directives applicable to radiopharmaceuticals as part of medicinal products, e.g., the Pharma Directive [4].

Beyond this directive, Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency [10] presents EC procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishes the EMA, also mandatory for radiopharmaceuticals.

The Committee for Human Medicinal Products (CHMP) of the EMA has issued guidelines, e.g., [11], that do not have legal status as directives or regulations. However, EMA guidelines make explicit reference to directives issued by the EC, e.g., "*Applications for marketing authorisation in respect of radiopharmaceuticals should be accompanied, as in the case of all medicinal products, by the particulars and documents referred to in Directive 2001/83/EC, as amended*."

A very important step regarding pharmaceuticals is the ongoing revision [3] of the Pharma Directive and Regulation (EC) No 726/2004. The Pharma Directive currently makes general reference to radiation protection legislation, but a more explicit reference to therapeutic radiopharmaceuticals and treatment planning was added to the recitals of the current proposal for revision. On the other hand, references to the BSSD are proposed to be removed. Therefore, it is, at the time of publication of this report, unclear if the final text will include improvements or amendments with respect to therapeutic radiopharmaceuticals.

1.4 Radiation Protection (BSSD) Regulation

In article 56 (Optimisation), the BSSD states that "For all medical exposure of patients for radiotherapeutic purposes, exposures of target volumes shall be individually planned, and their delivery appropriately verified taking into account that doses to non-target volumes and tissues shall be as low as reasonably achievable and consistent with the intended radiotherapeutic purpose of the exposure." Furthermore, in article 4 (Definitions), the Directive states that 'radiotherapeutic' pertains to radiotherapy, including nuclear medicine for therapeutic purposes.

1.5 Medicinal Products and Medical Devices Regulation

Medical devices by definition are not pharmaceuticals. Requirements regarding the information supplied with the device are laid down in annex 1, chapter 3 of the Medical Devices Regulation [2].

1.6 Analysis

The basic principles of the pharmaceutical legislation for the EU are laid down in [4] as amended, especially by [12].

The primary text of the consolidated version of the EU Pharma Directive [4] consists of more than 130 articles plus three annexes. Annex I describes the contents and format that have to be followed for the establishment of the marketing authorisation dossier, whereas annex II and annex III are of formal content only, i.e., list of repealed directives and correlation table respectively, and therefore are of no relevance to this analysis. Recital (18) of the Directive states that any rules regarding radiopharmaceuticals must take into account the provisions of the BSSD [1]. This is further elaborated in article 4(1) of the directive stating that "*Nothing in this Directive shall in any way derogate from the Community rules for the radiation protection of persons undergoing medical examination or treatment*."

The posology of all (radio)pharmaceuticals that have obtained or apply for marketing authorisation in the EU is described in the SmPC, which must follow a predefined structure. The legal basis for this is article 11 of the Pharma Directive. This structure is further elaborated by A Guideline on Summary of Product Characteristics – SmPC [13], issued by the EC in September 2009 and which is part of the EudraLex framework.'

A scheme of all contents that must be included in the SmPC is given on slide 6 of the EMA presentation "Summary of product characteristics (SmPC)." Note that within the EMA's structure subpoint 4.2 is dedicated to the recommended posology.

For some classes of pharmaceuticals, dedicated guidelines on the content of the SmPCs have been issued by the EMA CHMP. In fact, a guideline on the SmPC and the package leaflet does exist as well for radiopharmaceuticals [14]. While the general structure given in Figure 1 is maintained, additional information that is specific to radiopharmaceuticals is requested by this guideline, i.e., the need for reconstitution before administration in case of kit-based radiopharmaceuticals, details on internal absorbed doses that are to be expected from the use of the radiopharmaceutical, use of SI values for radioactivity, etc. However, this guideline does not consider therapeutic radiopharmaceuticals separately in detail, as it does not distinguish between radiopharmaceuticals for diagnostic purposes and those for therapeutic applications. Paragraph 4.2, Posology and Method of Administration, currently requires a defined activity range to be described that as a rule of thumb should be based on a 70 kg patient, which is appropriate for diagnostic radiopharmaceuticals but is a clear contradiction to the BSSD requirements for therapeutic radiopharmaceuticals.

Because medical devices are not pharmaceuticals, no SmPC exists or must be created. This role is instead taken by the IFU.

For some radiopharmaceuticals that are well established and marketed by several marketing authorisation holders, the CHMP has established dedicated guidelines on the contents of SmPCs for those specific products. This is the case for sodium iodide (^{131}I) for therapeutic use [15].

1.7 Regulatory Situation in the Selected EU Countries

With regard to the country-specific study, it was found that although the BSSD has been 'faithfully' transposed into national law in all countries, the fixed activity posology approved by the EMA in the corresponding SmPCs is usually followed. In about half of the selected countries, the community is aware of the existence of a contradiction between the BSSD requirements and EMA posologies and is seeking guidance on how to implement dosimetry in therapeutic nuclear medicine. Examples of good practice have been identified for Na^{131}I and SIRT-related posologies, whereas posologies for ^{177}Lu-labelled compounds are approved for use with fixed activity (and therefore do not comply with BSSD requirements). However, all SmPCs for therapeutic radiopharmaceuticals contain a reference to the 'as low as reasonably achievable' (ALARA) principle and indicate the need for a positive risk/benefit assessment of the treatment.

Another major obstacle to the implementation of Article 56 of the BSSD is the lack of awareness among competent authorities of the requirements of the BSSD and the optimisation principle. In addition, there is confusion among stakeholders whether pharmaceutical or radiation protection legislation should take precedence. A lack of European guidance on how to implement the BSSD in therapeutic nuclear medicine was also identified. Although the BSSD is considered a *lex specialis* and the current EU Pharma Directive clearly states that the BSSD must be taken into account or even take precedence (recital (18) and article 4), the current practice is different.

1.8 Comparison of the Regulatory Framework between EU, UK and USA

The main findings of a comparative analysis of the legal bases for the use of radiopharmaceuticals for therapeutic purposes in the European Member States, the UK and US are as follows.

- The main legal framework for pharmaceuticals in the EU is defined by the Pharma Directive. The relation to the BSSD is provided both in a recital (recital 18) and in the legal text, i.e., an article (article 4), giving priority to the BSSD in case of conflicts.
- In the UK radiation protection aspects in the context of medical treatments are regulated in the Ionizing Radiation (Medical Exposure) Regulation, which transcribes the BSSD requirements into national law and has not been altered since the UK left the EU. In principle the framework is very similar to that of the EU. Therefore, the same basic principle of optimisation applies, but individual patient dosimetry is not routinely applied.
- In the US, two agencies provide regulatory functions, the Food and Drug Administration (FDA), which is responsible for granting marketing authorisations, and the Nuclear Regulatory Commission. In contrast to the situation in Europe, FDA regulations take precedence over those of the Nuclear Regulatory Commission. Prescribed posologies for recently approved therapeutic radiopharmaceuticals are similar to those approved in the EU, i.e., fixed activities for ^{177}Lu-labelled products such as Lutathera® and Pluvicto®, or dosage based on dosimetric calculations, either mandatory or recommended, for SIRT products. Concerning article. 56 of the BSSD, there is no correspondence in the legislative framework of the US. However, in contrast to the EU, guidelines for the industry have been issued for the development phase of therapeutic radiopharmaceuticals [16] and monitoring potential late radiation effects of therapeutic radiopharmaceuticals [17].

1.9 Specific Situation of Clinical Research and Radiopharmaceutical Development

Clinical research and radiopharmaceutical development for human use are currently governed by the need to fulfil the requirements of the pharmaceutical rules and regulations of the EU, as set out in the Pharma Directive in the amended version, Directive 2003/63/EC [12]. Furthermore, the guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products, EMEA/CHMP/SWP/28367/07 Rev. 1 2017 [18], needs to be taken into account. The requirements on preclinical studies for pharmaceuticals to progress to clinical studies are described in [19], although this document is still in a draft version. For the specific situation of anti-cancer drugs, the document [20] applies. Further analysis with respect to the relevance of these documents to radiopharmaceuticals is provided below.

As radiopharmaceuticals represent a form of administration of ionising radiation for medical purposes, the BSSD also applies. Indeed, in EC guidance on the Clinical Trials Regulation (CTR) n° 536/2014 [21] in the section Questions & Answers, the answer to question 7.53 clearly states that "*The risks of both ineffective treatment due to insufficient absorbed dose to the target lesions and risks of severe/irreversible long-term toxicity due to excessive absorbed dose to risk organs, need to be monitored and mitigated during the trial to optimise the benefits and risks for the individual trial participant*." Later in the paragraph, it is mentioned that "*In addition to the benefit/risk section, sponsors should describe dosimetric procedures in the protocol, as well as target absorbed doses (in Gy) to tumour lesions*."

Although [12] does designate radiopharmaceuticals as a "*particular medicinal product*," this document does not distinguish between diagnostic and therapeutic radiopharmaceuticals. No specific guidance is given with regard to posologies (administered activity) or dosimetry (absorbed dose to the target tissue). Rather, for lack of such specific details the general principles of dose-finding and posology must be assumed to apply, although these, i.e., substance mass expressed in units of mass, bear no direct relationship to the diagnostic or therapeutic effect. [19] does not contain any language addressing the issues of dosing in radiation-related units rather than mass.

As for the required preclinical studies, [20] does not cover radiopharmaceuticals. On the other hand, reference [19] specifically deals with radiopharmaceuticals; however, only the required preclinical testing of their non-radioactive elements in terms of substance-related safety is covered. The document does call for biodistribution studies including dosimetry but does not

provide any details on how these should be conducted. Furthermore, radiation-related toxicity is not explicitly covered by this document.

Radiation safety aspects of clinical research and radiopharmaceutical development are governed by the provision of the BSSD, more specifically chapter VII, articles 55–64. Although general terms are set out in this document, the specific methodology required, especially with regard to the methods, levels and extent of individual dosimetry in the pre- and post-treatment phase as well as development are open to interpretation. Furthermore, the BSSD relies on transposition in national law rather than on setting a specific and uniform regulations, resulting in a varied landscape of national rules within the EU when it comes to first-in-human use and clinical trials.

Concerning biomedical research, the BSSD in its article 56.3, states that:

> Member States shall ensure that for each medical or biomedical research project involving medical exposure:
> - The individuals concerned participate voluntarily;
> - These individuals are informed about the risks of exposure;
> - A dose constraint is established for individuals for whom no direct medical benefit is expected from exposure;
> - In the case of patients who voluntarily accept to undergo an experimental medical practice and who are expected to receive a diagnostic or therapeutic benefit from this practice, the dose levels concerned shall be considered on an individual basis by the practitioner and/or referrer prior to the exposure taking place.

To address these BSSD requirements, applicants to pharmaceutical studies implying the use of ionising radiation, including for imaging, are required to describe all procedures with ionising radiation that are part of the studies and the associated irradiation delivered per study so that a dose constraint can be established.

Since January 2022, all pharmaceutical studies must be handled centrally in the CTIS. The CTIS serves to centrally store information related to clinical trial applications in the EU and provide a platform for exchange of documentation and decision making [22]. Its intention is to support the flow of information between clinical trial sponsors, EU Member States, European Economic Area countries and the EC. As mentioned above, DG SANTE published an updated version of their Q&A on the EU CTR that includes a paragraph, 7.53, on how sponsors are expected to justify radiation exposure in clinical trials, with specific recommendations on therapeutic radiopharmaceuticals [21].

1.10 Conclusion

Although safety and efficiency of treatment for the patient are the ultimate aims of both the pharma legislation and BSSD, the implementation of the optimisation principle for therapeutic nuclear medicine as set in the BSSD must be improved. The SIMPLERAD comparative analysis of applicable rules and regulations uncovered a significant lack of practical guidance and recommendations to advance coherent implementation of the respective BSSD requirements. Moreover, the existing EU guidance on data acquisition and processing and the related application procedures for the preclinical phase of clinical trials and marketing authorisation does not adequately address the specificities and the needs of radiopharmaceutical development. Further recommendations to address the issues identified by the SIMPLERAD analysis of applicable legislation, regulations and guidance, as well as other issues identified under the project, are provided in section 4 of this report.

2. Survey and Analysis of the Implementation of Relevant European Legal Requirements for Therapeutic Nuclear Medicine

2.1 Introduction and Methodology

The aim of the survey conducted by the SIMPLERAD consortium was to provide insight into the practical implementation of key requirements outlined in European pharmaceutical legislation and the BSSD regarding therapeutic nuclear medicine. This encompassed aspects such as individual patient dose planning, dosimetry, involvement of MPEs, patient release protocols, and the management of radioactive effluents and waste. The primary objective was to identify existing gaps in compliance with these requirements and pinpoint the main barriers faced by European stakeholders in the development and utilisation of therapeutic radiopharmaceuticals.

The survey was comprehensive in its coverage, spanning the EU Member States, Norway and Switzerland, and targeted competent authorities, relevant professional stakeholders and treating centres within these regions. The methodology employed two tailored questionnaires and expert interviews.

The first questionnaire focused on identifying pertinent government and health authorities responsible for radiation protection regulation and pharmaceutical practices. Additionally, it aimed to collect national documentation relevant to the project. This approach, coupled with the consortium's established contacts, ensured successful outreach and elicited valid responses from the target countries.

Expert interviews were conducted with individuals possessing qualifications and regulatory knowledge specific to therapeutic nuclear medicine. These experts were selected from various fields including national competent authorities, industry representatives, MPEs, nuclear medicine physicians and radiopharmacy experts. Companies involved in the therapeutic radiopharmaceutical industry were chosen based on market volume and developmental pipeline depth.

The substantive questionnaire targeted stakeholders across different tiers of interest, including competent authorities for radiation protection and authorisation of radiopharmaceuticals, professional societies, and clinical staff with direct experience in navigating legislative constraints. A comparative analysis of regulatory knowledge and questionnaire responses from these groups was used to formulate strategies for advancing the coherent implementation of European requirements. The questionnaire incorporated case studies to explore the application of legal frameworks in different scenarios. These case studies included both well-established therapies such as ^{131}I for benign thyroid disease treatment and emerging therapies like ^{177}Lu-DOTATATE and ^{177}Lu-PSMA. Additionally, the study considered the alpha-emitter ^{223}Ra dichloride as part of its scope.

2.2 Results

The pre-survey collected 61 responses, encompassing all EU Member States except Bulgaria and Cyprus, whose contacts did not initially respond. Additionally, responses were received from six non-EU Member States, including Norway, Switzerland, the UK, Bosnia and Herzegovina, North Macedonia, and Serbia. Over 150 pertinent organisations were identified, averaging five per country, with some countries such as Austria, Germany and Italy indicating regional governance of regulations, resulting in a higher number of competent authorities. Of the 176 contact details established, 35% pertained to regulatory authorities for radiation protection, 34% to medicine and pharmaceutical authorities, and 31% to training and assessment of medical physicists. Expert interviews, comprising 22 face-to-face and 3 written communications, ensured diversity in nationality, geographical location and area of expertise, providing an unbiased and representative perspective.

The main survey received 279 responses over a 3-month period, resulting in 193 valid responses after collation and filtering. Responses were primarily from treating centres (62%), followed by national competent authorities (18%) and national societies (16%), with 4% from other organisations, including national training and assessment bodies and industry. Responses were received from 40 countries, including all 27 EU Member States as well as non-EU states such as Monaco, Norway, Turkey, Serbia, Switzerland, the UK and Ukraine. Non-European countries included Canada, India, Israel, Japan and Oman.

2.3 Findings

The survey results confirmed the disconnect between pharmaceutical legislation and Euratom BSSD requirements regarding radiopharmaceuticals and revealed further interpretation issues and varied legislative processes across Europe. The respondents identified this disparity as a barrier to the development of, and patient access to, innovative radiotherapeutic compounds. Closer collaboration and interdisciplinary expertise across regulatory frameworks, along with specialised regulator knowledge of therapeutic nuclear medicine, were identified as potential solutions.

Confusion existed among survey respondents regarding the optimisation requirement stipulated in the BSSD and adherence to posology outlined in the SmPC, exacerbated by heterogeneity across Europe. Opinions varied also among regulatory experts, with differences primarily stemming from interpretation issues and heterogeneity rather than direct conflicts between regulations. Some experts highlighted conflicts between the requirement for optimisation in the BSSD and approved posologies, leading to perceived risks in treating off-label. Suggestions for flexibility in posologies, including options for both fixed activity administration and individually optimised activity using dosimetry, were proposed. However, industry experts emphasised the need for regulatory guidance in this regard. Concerns were raised about outdated frameworks in current radiation safety and pharmaceutical legislation, with varying levels of knowledge among national competent authorities posing challenges for new developments in therapeutic nuclear medicine.

Regulatory guidance on conducting dosimetry studies and the necessity for dosimetry data from clinical trials were highlighted. Regulatory guidance on conducting dosimetry studies and the necessity for dosimetry data from clinical trials were highlighted.

Opinions on the precision level and associated methodology to comply with the BSSD were divided, with a recognised desire for dosimetry-guided optimisation and verification in most therapies. However, this practice is not widespread due to insufficient detail in legislation or national guidance. Dosimetry was more prevalent for established therapies like ^{131}I for benign thyroid disorders but varied widely across Member States. A lack of resources, including reimbursement, expertise and adequately trained staff in nuclear medicine centres, was identified as a primary barrier to dosimetry implementation and therapy development. Participants sought further recommendations on planning and verification requirements.

Insufficient medical physics support and disparities in the number of MPEs per centre were noted, influenced by centre size, national competencies and variation in MPE definition and responsibility.

Heterogeneity in implementing dose constraints and patient-release criteria was evident, with a clear desire for unified dose constraints at either the national or European level. Interpretation of comforter and carer varied, and national advice on patient release was generally lacking. Guidance provided to patients upon release varied in detail and duration. While radioactive waste and effluent management conditions were well-established across Europe, criteria for aqueous waste release varied.

The most significant barrier highlighted by experts regarding the development and delivery of radiotherapeutic products was the sustainability and management of the radionuclide supply chain. Issues such as maintenance of ageing nuclear reactors and transportation hurdles were

identified as sources of interruptions in the supply chain. Additionally, challenges in reimbursement support and commercialisation of new radionuclide therapies were noted, with licensing processes in individual EU countries contributing to delays. Regulatory constraints and differing interpretations across Europe, compared to the more streamlined process in the US, were cited in the expert interviews as barriers. The implementation of good clinical practice was highlighted as inconsistent across EU states, raising concerns about the harmonisation of clinical trial approvals under the new CTR. Regulatory framework issues, including heterogeneity and the need for harmonisation, were reiterated during expert interviews, emphasising the importance of specialist expertise in bridging the gap between pharmaceutical and radiation competent authorities.

Perception challenges surrounding therapeutic nuclear medicine, both public awareness and among professionals, were identified as significant hurdles. Resources, reimbursement, dosimetry, treatment personalisation and training were also cited as challenges to the full exploitation of the potential of therapeutic nuclear medicine.

3. Recommendations and Proposed Measures

3.1 General Methodology

As the primary output of the SIMPLERAD project, the guidance and further remedies proposed by the consortium are based on the following input during the period of study.

1. A review and analysis of the interrelations between the European pharmaceutical legislation relevant to radiopharmaceuticals, the dosimetry and optimisation requirements established under the BSSD, as presented in section 1 of this document.
2. Expert interviews and a survey on the implementation of the relevant European legal requirements with respect to therapeutic nuclear medicine, as summarised in section 2.
3. The following additional components completed the methodology to derive the most important issues.

    - Based on the literature survey as well as the identification of recent scientific developments and international recommendations, the preliminary list of issues to be addressed and actions identified in the tender application were updated.
    - A combined list of itemised results was distributed among the consortium members, Advisory Board and interviewed experts. All were asked to rank the itemised list in accordance with their assessment of priority, considering the priorities and actions as described in section 3.5.1 of the SAMIRA action plan [23]. The summed score for each item served to determine a definitive prioritisation of items. The ten highest-ranked identified issues were considered for the formulation of guidelines.
    - For the selected items, the consortium discussed and subsequently drafted a first proposal of actions and remedies, taking into account suggestions acquired in the expert interviews. The proposal was developed in accordance with the specific, measurable, achievable, reasonable, time-bound (SMART) methodology. This involved the drafting of professional and regulatory guidance. Furthermore, suggestions for support actions under the relevant EU support programmes for measures in the areas of training, research, improvement of infrastructure and access to material, and human resources as well as proposals for amending or supplementing the existing legislative basis were developed as deemed necessary.
    - Stakeholder consultation: The Advisory Board consisted of representatives of various stakeholder groups (See annex 4). Through this group as well as further additional stakeholders identified in the main survey, the suggested measures and remedies were circulated for 14 days for comment by their respective organisations, allowing the board members to receive feedback from their respective interest groups. Furthermore, various stakeholders were invited to the stakeholder workshop in December 2023, during which additional comments and feedback were received. The EC as well as SGQS and WP MED were involved in the selection of additional stakeholders.
    - Taking the comments of the stakeholders into account, the members of the consortium drafted an updated proposal in order to ensure compatibility of the proposed measures and remedies, especially those outlined in section 4, with the SAMIRA action plan. The proposals thus defined were linked to specific actors, preferably stakeholders involved in the project either directly or through involvement and representation in the Advisory Board, and included concrete practical guidance on selected issues. Furthermore, proposals for addressing those items exceeding available resources in the framework of the current project and those not receiving sufficient priority for further work in the current project were formulated.

- The consortium coordinated the writing of a draft consensus guidance document based on these recommendations. This included practical professional and regulatory guidance on selected items and a list of additional proposed actions outside the scope of this tender.
- Upon receipt of final feedback from the workshop, the consortium produced a definitive report on the guidelines and recommendations, as described below.

3.2 Analysis of Current Practices in Therapeutic Nuclear Medicine

Feedback from the Advisory Board, workshop participants and stakeholders in addition to a number of consortium-led initiatives, including a literature survey, analysis of the current practices in seven countries, survey and expert interviews, led the consortium to arrive at the following conclusions.

- The lack of interdependence between EMA guidance documents and Euratom BSSD requirements on the specific subject of radioactive compounds for use in therapeutic nuclear medicine generates:
  - Confusion between the requirement for optimisation as stipulated in the BSSD and the need to follow the posology presented in the marketing authorisation;
  - Lack of consideration in EMA guidance regarding marketing authorisations for items pertaining specifically to safety of radionuclides; and
  - Lack of guidance from European bodies for implementing the BSSD, pertaining to the specificities of therapeutic nuclear medicine beyond those encountered in external-beam radiation therapy.
- The BSSD specifically includes therapeutic nuclear medicine among radiotherapeutic procedures, yet, even though the terms planification and verification are very well adopted in external-beam radiotherapy, clarification is needed regarding:
  - The level of precision and associated methodology to comply with the individual planification of target volume exposures as required ("*shall*") by the BSSD; and
  - The definition of an appropriate delivery verification, whether qualitative or quantitative (dosimetry-based) assessment.
- The implementation of therapeutic nuclear medicine in clinics suffers from:
  - Divergent interpretation within the EU regarding the definition of standardised therapeutic procedures and their relation to dosimetry; and
  - Lack of clarity or absence of the level of optimisation required to comply with European directives on, e.g., patient selection, imaging and dosimetry.
- Differing European guidance is provided by scientific organisations concerning treatment regimen
- Concerning biomedical research, since January 2022 all clinical trials with radiopharmaceuticals must be handled centrally in the CTIS. In this system, pertinent information regarding radiation protection in biomedical research is not specifically being taken into account at the EU level. Recently, DG SANTE published an updated version of their Q&A on the EU CTR, Regulation (EU) No. 536/2014, that includes a question and answer on how sponsors are expected to justify radiation exposure in clinical trials, with specific recommendations on therapeutic radiopharmaceuticals [21].

  Furthermore, since time to complete reviews of applications on a national level within CTIS is very short and no additional documentation can be requested from applicants, it is very hard, if not impossible, to estimate risk–benefit with regard to radiation protection.

Furthermore, the survey and interview analysis identified the following issues (See also section 2 and annex 1).

- A lack of commonality between pharmaceutical legislation and Euratom BSSD requirements concerning radiopharmaceuticals. Heterogeneity was identified as leading to problems in understanding and interpretation among the stakeholders and different legislative processes across Europe.
- Confusion concerning the requirement for optimisation as stipulated in the BSSD and the need to follow the posology presented in the marketing authorisation.
- Insufficient resources in terms of reimbursement; know-how; and sufficiently trained technical, medical, radiopharmacy and physics staff in nuclear medicine centres were identified as the predominant barriers stifling dosimetry and development of therapy.
- Heterogeneity in the implementation of dose constraints and patient-release criteria was evident across Member States.
- Interpretation of definition and translation of comforter and carer appeared to vary across Europe.
- Conditions for management of radioactive waste and effluent were well established across Europe, although aqueous waste release criteria varied.
- Medical physics support was considered insufficient in most countries and also raised as a barrier to implementing dosimetry.

3.3 Prioritisation of Issues to Be Addressed

Based on the literature survey, further analysis of literature and legislation, expert interviews, and the results of the survey of the field, a preliminary list of issues to be addressed was compiled. The overlap between issues identified in the tender document and these results was discussed. Based on this list, an iterative discussion on the content of each of the 18 items was held. During these discussions, it was found that several items were part of a single, overarching main issue. In the process of iterative internal discussion within the consortium as well as with the representatives of the EC it was decided to merge such items in single issues. Upon completion of this process, a list of ten issues remained, thus obviating the need for further ranking and selection. See section 3.5 for a listing and discussion of the issues.

3.4 Stakeholder Feedback

The feedback of the Advisory Board was collected in October and November 2023 and discussed among the consortium, leading to a wider stakeholder consultation in collaboration with the EC in November and December. This consultation centred on distributing the draft proposal of the project summary, which was updated based on initial Advisory Board and EC feedback, to the workshop registrants, SAMIRA SGQS members, HERCA members, Advisory Board members and EMA. A link to a survey form on the platform Jotform was provided for submission of feedback. The form began with a request to rank the priority of the ten identified issues for implementation using a drag-and-drop format, followed by a field for suggestions on how to address the top priority. The ten issues were listed with descriptions and supplemented with fields to submit the greatest challenge for implementing the consortium's proposed remedies and additional means of remedy. Workshop participants were reminded after the event, such that the submission form was closed on 1 January 2024, to gather as much feedback as possible in a timely manner. Discussions during the two sessions on the guidelines and recommendations during the workshop were also recorded for additional input.

From the wider stakeholder consultation, a total of 34 responses, representing 16 of the project's target countries and each target group, were received. These comments were considered and applied where relevant to the text to yield a final version.

3.5 Proposed Actions and Remedies

The consensus guidelines and actions or remedies for implementation are presented below. Activities to be carried out within SIMPLERAD and those to be tackled within the wider SAMIRA framework are differentiated.

3.5.1 Disconnection between marketing authorisation of radiopharmaceuticals and the BSSD

Description of the issue

Disconnection between marketing authorisation of radiopharmaceuticals and the Euratom BSSD requirements on the specific subject of radioactive compounds for use in therapeutic nuclear medicine creates the following issues.

- Confusion between the requirement for optimisation as stipulated in the BSSD and the need to follow the posology presented in the marketing authorisation.
- Lack of consideration in pharmaceutical legislation/EMA guidance regarding marketing authorisations for items pertaining specifically to safety of radionuclides.
- Lack of European guidance for implementing the BSSD, pertaining to the specificities of therapeutic nuclear medicine beyond those encountered in radiation therapy.

Furthermore, the mandatory EU CTIS does not take into account pertinent information regarding radiation protection in biomedical research in contravention of the BSSD.

Brief summary of relevant evidence

Since radiopharmaceuticals are both medicinal products as well as products associated with effects of ionising radiation, the current legislation on radiopharmaceuticals in general is based on two different directives: one covering the pharmaceutical aspects [4] and the other dealing with associated (for diagnostics and therapeutics) or intended (for therapeutics) effects of radiation, the BSSD [1].

The EU Pharma Directive was established in 2001 and is in force in its latest consolidated version dating from 1 January 2022. When the directive was issued, the large majority of radiopharmaceuticals that were clinically applied were diagnostic compounds, especially ^{99m}Tc-labelled products that were to be compounded in-house from radionuclide generators and cold kits. The clinical application of therapeutic radiopharmaceuticals at that time was limited to mainly a few compounds like ^{131}I-labelled mIBG, [^{131}I]NaI and others. Although the application of therapeutic radiopharmaceuticals since then has been considerably extended and a variety of new agents have been introduced into clinical practice, the later amendments of the directive did not consider these developments and advances in, among others, radiopharmacy. The directive remained unchanged regarding radiopharmaceuticals and in principle still reflects the situation existing more than 20 years ago.

The current version of the BSSD was introduced in 2013 and, among other applications of radiation, covers the use of radioactive substances for therapeutic purposes. It especially requires individual treatment planning and verification for therapeutic applications of radiation, including therapeutic nuclear medicine in article 56: Optimisation.

The two directives come from two distinct legal personalities of the former European Community as defined by the Treaty of Lisbon, the EU and Euratom. The fact that radiopharmaceuticals according to the currently applicable framework are regulated by two different major pillars of the European Community that otherwise rarely share any responsibilities could potentially explain the perceived disconnection between the BSSD and Pharma Directive.

The specific requirements of the BSSD regarding optimisation of treatment by ionising radiation are reflected in the current EU Pharma Directive in one of the recitals (18), first clause:

> Any rules governing radiopharmaceuticals must take into account the provisions of Council Directive 84/466/Euratom[3] of 3 September 1984 laying down basic measures for the radiation protection of persons undergoing medical examination or treatment.

And in article 4, number 1:

> Nothing in this Directive shall in any way derogate from the Community rules for the radiation protection of persons undergoing medical examination or treatment, or from the Community rules laying down the basic safety standards for the health protection of the general public and workers against the dangers of ionising radiation.

Since therapeutic applications of radiopharmaceuticals are only covered in recital (18) in an indirect way, and otherwise throughout the remainder of the directive therapeutic radiopharmaceuticals are not distinguished from diagnostic applications[4], the possibilities for reinforcement of the BSSD requirements seem limited. In real life, competent authorities enforcing pharmaceutical legislation may not pay close attention to the second pillar of relevant legislation. This poses the risk of patients being treated in a non-optimal way with regard to the specific characteristics of this type of medicines.

The EU pharma legislation is currently under revision, and a legislative proposal for a directive repealing the Pharma Directive was published in April 2023 by the EC. This proposal, not yet ratified at the time of finalising this report, now explicitly mentions the need for treatment optimisation as requested by article 56 of the BSSD in its recital (19):

> This Directive should be without prejudice to the provisions of Council Directive 2013/59/Euratom, including with respect to justification and optimisation of protection of patients and other individuals subject to medical exposure to ionising radiation. In the case of radiopharmaceuticals used for therapy, marketing authorisations, posology and administration rules have to notably respect that Directive's requirements that exposures of target volumes are to be individually planned, and their delivery appropriately verified taking into account that doses to non-target volumes and tissues are to be as low as reasonably achievable and consistent with the intended therapeutic purpose of the exposure.

When compared to the current Pharma Directive, the new legislative proposal makes a more explicit reference to the requirements imposed on therapeutic radiopharmaceuticals by the BSSD in the recitals. However, the impact of this improvement may be limited given the fact that the recitals are only indicating the rationale of the legal text that follows. A statement like article 4, number 1, in the Pharma Directive is missing in the proposed legislative proposal.

Although at the current moment the content of the final recital is uncertain, the new EU Pharma Directive might be even less explicit with regard to BSSD demands.

Therefore, the following items need to be assured.

[3] 84/466/Euratom has been repealed by 97/43/Euratom, which has been repealed by the BSSD; thus the Pharma Directive in its current version refers to the BSSD.

[4] Radiopharmaceuticals are mentioned in Directive 2001/83 in a few other places, e.g., annex I, part III recognises specific information that must be provided additionally in the marketing authorisation dossier; annex I, article 11, Nr. 11 expresses the need for data on internal dosimetry in the SmPC. However, these parts of the directive are related to diagnostic radiopharmaceuticals. This becomes evident from the context. As stated before, therapeutic radiopharmaceuticals are not explicitly considered in the directive.

Suggested remedial actions

To be addressed in the wider context of SAMIRA

- In order to resolve any misunderstanding, it should be clarified that in case of conflicts between the BSSD and the revised EU Pharma Directive regarding the optimisation of medical treatment by means of therapeutic radiopharmaceuticals, the BSSD shall prevail.

- The current proposal for the revised EU Pharma Directive foresees the possibility to create an adapted regulatory framework for specific products listed in annex VII of the EC's draft. The adapted regulatory framework mentioned in article 28 of the EC's proposal for a revision of directive on Union code relating to medicinal products for human use (2023/0132), for products whose categorisation poses regulatory and scientific challenges, could be a promising tool to accommodate the specifics of radiopharmaceuticals. Considering the high innovation pace, especially with theranostics developments, radiopharmaceuticals would benefit from specific regulatory requirements. Therefore, the consortium recommends the inclusion of radiopharmaceuticals in annex VII, when revised, along with other medicinal products such as the currently listed phage-containing medicinal products.

- Guidance documents, such as the EMA Guideline on Radiopharmaceuticals, EMEA/CHMP/QWP/306970/2007 and Guideline on Summary of Product Characteristics (SmPC), both published in 2009, do not cover the principles of the BSSD. Ideally, such documents should introduce a distinct consideration of diagnostics and therapeutics as well as a differentiated discussion of posology for therapeutic radiopharmaceuticals. A concept paper on the evaluation of therapeutic radiopharmaceuticals in oncology is in the draft process organised by the EMA. The EMA Guideline on Radiopharmaceuticals is also currently under revision, and a concept paper on the intended content has been published by the Quality Working Party of EMA [24]. As stated in the current concept paper, the EMA does not intend to include any guidance on dosimetric data or justification of the posology for therapeutic radiopharmaceuticals. The concept paper announces merely an explanation of required radioanalytical procedures for therapeutic radionuclides and clarifications regarding the accuracy of the radiopharmaceutical dose for injection. Dose in this context is the amount of radioactivity of the radiopharmaceutical that will be administered, not the absorbed dose delivered by the radiation to target and non-target tissue. The EMA should be encouraged to include the required guidance on therapeutic radiopharmaceuticals in the revised guideline.

- A clinical guideline on the development of therapeutic radiopharmaceuticals in oncology should be drafted. This has been considered by the EMA Oncology Working Party and is mentioned in the problem statement of a recent publication by the EMA's Committee for Medicinal Products for Human Use [25]. A distinct consideration of diagnostics and therapeutics as well as a differentiated discussion of posology for therapeutic radiopharmaceuticals should be introduced.

- A permanent expert working group on radiopharmaceuticals, consisting of experts in medical physics, radiopharmacy, radiochemistry and clinical nuclear medicine should be formed to advise on new regulations as they pertain to radiopharmaceuticals.

- The EU CTIS should be revised so that structured radiation safety and dosimetry information must be provided for therapeutic radiopharmaceuticals.

- A multi-level forum concerning radiopharmaceuticals should be established for interaction between regulators working in the fields of pharmaceutical supervision and radiation protection both at EU and national levels.

Discussion of potential strengths, weaknesses, opportunities and threats of the proposed remedy with regard to the resolution of the issue

Strengths

A statement in the legislative proposal for the revised EU Pharma Directive that the BSSD's requirements should prevail in case of contradictions will give clarity on that point. However, this is not included in the list of proposed amendments as of September 2024 [3]. An inclusion of radiopharmaceuticals in the list of products that should be regulated by an adapted regulatory framework in article 28, annex VII, of the current proposal by the commission for a new directive, will give the needed flexibility to address the specificities of radiopharmaceuticals. Annex VII, however, is also not in the list of proposed amendments. 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.

Weaknesses

The current Pharma Directive does have a clear statement on the BSSD's requirements in both a recital and in article 4, number 1 of the legal text. Nevertheless, BSSD requirements are not fully recognised in all aspects, as this study has demonstrated. The outcome of this suggested remedy might be limited.

Opportunities

Inclusion of radiopharmaceuticals in annex VII according to article 28 of the EC's proposal could open the possibility of adapted rules for radiopharmaceuticals in several other fields such as good manufacturing practice requirements, clinical trials, marketing authorisation procedures and requirements for qualified persons.

Threats

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

Synthesis

In summary, 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 the Pharma Directive might contain 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.

3.5.2 Differences in interpreting and implementing the BSSD in the context of therapeutic nuclear medicine

Description of the issue

The BSSD specifically includes therapeutic nuclear medicine among radiotherapeutic procedures. Although the terms planning and verification are very well adopted in external-beam radiotherapy, the precise translation of these terms is not well defined regarding radiopharmaceutical therapy. Currently, multiple strategies are thought to be able to satisfy these requirements as shown from the survey carried out within this project. Still, a lack of clarity exists regarding the level of optimisation required to comply with European directives on, e.g., patient selection, imaging and dosimetry.

Brief summary of relevant evidence

The main findings concerning the interpretation and implementation of the BSSD in the context of therapeutic nuclear medicine were identified in the comparative analysis of Member State legal frameworks.

- Lack of European guidance for implementing the BSSD, pertaining to the specificities of therapeutic nuclear medicine beyond those encountered in radiation therapy
- A need for clarification concerning the level of precision and associated methodology to comply with the mandate that 'exposures individually planned' and 'delivery appropriately verified' of target volume exposures as required ("*shall*") by the BSSD
- Lack of clarity or absence of the level of optimisation required to comply with European directives on, e.g., patient selection, imaging and dosimetry

These issues were further confirmed by survey data. Even if these issues were to be clarified at the European level, legal implementation occurs at the national level and will have to be addressed by each Member State.

During the survey participants were asked how they interpret the phrases 'exposures individually planned' and 'delivery appropriately verified.' The highest-rated response from participants in all stakeholder groups was that 'exposures individually planned' called for the planning of an administered activity based on an individual absorbed dose assessment. A significant number of respondents also gave more than one answer to this question, indicating the phrases also meant ensuring patient treatment suitability, based on imaging and other clinical factors. A similar but somewhat broader trend was observed concerning treatment verification. A significant proportion of respondents from all stakeholder groups agreed the BSSD statement concerning verification meant an individual dosimetry assessment. However, ensuring the prescribed activity had been administered and quantitative imaging were scored highly amongst respondents. Thus, the survey showed that the field of nuclear medicine is largely in agreement that 'exposure individually planned' entails at least some form of dosimetry, and 'delivery appropriately verified' should include scanning post therapy in such a fashion that a dose assessment is possible.

Concerning the requirements for the use of dosimetry as required by the BSSD, substantial differences are evident for different treatments. The therapy where dosimetry was identified as being most readily recommended within national legislation or guidance and common practice in Member States was for ^{131}I treatment planning for benign thyroid disorders. For ^{177}Lu treatments the majority of responses pointed to national recommendations that did not include dosimetry with administrations based rather on a fixed activity prescription and ensuring the patient is suitable for treatment using diagnostic imaging. Current practice seems to reflect these recommendations, although, as identified in the survey, there was a strong desire across the community to implement dosimetry-based treatment planning.

Therefore, it is likely because of national regulations, based on EMA guidance that recommends fixed activity, that planning and verification of exposure are not done. Furthermore, the SmPCs for newer products such as Lutathera or Pluvicto in section 4.2 of their product characteristics recommends a fixed activity of 7400 MBq, likely leading physicians to follow this explicit advice and not additionally apply the provision in the special warnings section 4.4, which states that:

> For each patient, the radiation exposure must be justifiable by the likely benefit. The activity administered should in every case be as low as reasonably achievable to obtain the required therapeutic effect.

How and to what extent other factors contribute to the lack of individualisation of activity is not immediately clear from the evidence gathered.

For ^{223}Ra therapies the distribution of practice reflected national recommendations, with the majority of respondents indicating therapy was planned with an adjustment of activity based on

body weight or body surface area. When asked what they believed should be performed, responses were more heterogeneous, likely due to the lack of guidance and perceived difficulty in dosimetric planning for alpha therapy.

Discussion of potential remedies

- Guidelines or guidance documents
    - Treatment planning and verification

A summary of different recommendations by the International Commission on Radiation Units and Measurements (ICRU), EANM and EFOMP; their differences; and potential remedies are presented in annex 2.

Treatment planning in the context of radiopharmaceutical therapy with the aim to determine the individual level of activity to be administered to a patient can be defined in different ways, depending on the clinical protocol and the radiopharmaceutical used. It may also evolve as more clinical or scientific evidence becomes available.

- Administration of a tracer activity of the same radiopharmaceutical, considerably lower than the activity intended for treatment and subsequent determination of the biokinetics via either imaging or tissue sampling. Current examples are ^{131}I for the treatment of benign thyroid diseases or blood-based dosimetry for thyroid cancer treatment (See annex 3).

- In cases when tracer activities cannot be administered and when several treatment cycles are foreseen, dosimetry after each cycle should be used to determine the activity needed for future administrations. Examples for this approach could be applied to Lutathera or Pluvicto (See annex 3).

- In cases when imaging or patient material sampling, e.g., blood, cannot be carried out because of technical difficulties, administration of fixed activities based on the respective posology may be considered. A current example is the administration of Xofigo®. In those situations, documentation of irradiation delivered should nonetheless be reported, even if only cohort based.

Details on how to perform treatment planning or post-administration absorbed dose verification for selected use cases reflecting the present state of the art are presented in annex 3. Since clinical dosimetry is a rapidly evolving field, the examples presented in annex 3 should be taken with care, as recommendations may be amended to account for methodological and technical advances in quantitative imaging and absorbed dose determination.

The aim of the treatment should also be defined, as it could be either maximisation of the tumour absorbed dose (efficacy) or sparing of normal organs and tissues (safety) or both.

Treatment planning should be made possible by tested and reliable CE-labelled treatment planning software solutions. Specific quality assurance programmes should be developed, considering the whole clinical dosimetry workflow.

With respect to research, opportunities should be created for funding projects investigating dosimetry, toxicity limits to normal organs and radiobiology of therapeutic radiopharmaceuticals.

If available, absorbed dose calculations should be performed by tested and reliable treatment planning software solutions that are in compliance with the Medical Devices Regulation. Examples of how to test dosimetry software for radiopharmaceutical therapies are given in [26, 27].

For some radionuclides, however, imaging is, at present challenging due to technical difficulties. Typical examples are the radionuclides ^{90}Y or ^{223}Ra. Treatment verification is also difficult in patients presenting with a diffuse spread of the disease.

Therefore, verification should be adapted to the clinical situation and local possibilities, while putting the emphasis on traceability and reproducibility of the practice to allow for future improvement and repeated treatments.

- Early phase clinical trials

The new EANM guidance document [5] provides recommendations from the EANM Dosimetry Committee on dosimetry for first-in-human studies and early phase clinical trials.

- Modification of posologies

Posologies issued by the EMA for therapy radiopharmaceuticals should be open towards individualising treatment based on dosimetry. For example, section 4.4 of recent posologies for Pluvicto:

> For each patient, the radiation exposure must be justifiable by the likely benefit. The activity administered should in every case be as low as reasonably achievable to obtain the required therapeutic effect.

allows for deviations from the fixed activity regimes. However, details are not sufficiently specific to provide the user with adequate information on an appropriate methodology for choosing or determining the absorbed doses.

For products that are already on the market, dosimetry-driven optimisation should always be explicitly mentioned as a possibility in the package insert and therefore would not require a clinical trial or ethical committee approval before being implemented. Ideally the posology should contain instructions or a protocol on how to perform dosimetry for that specific indication. Pharmaceutical legislation or the EMA should encourage marketing authorisation applicants to submit this information. See also section 3.5.1 and annexes 2 and 3.

- Establishment of centres of excellence

Establish centres of excellence within an EU network of expertise for personalised radionuclide therapy with advanced knowledge on quantitative imaging and dosimetry as a focal point. This network should be defined based on the available human and methodological resources, type and number of treatments delivered, existence of a specific training scheme for all professional involved in the practice, and possibility to store and retrieve dosimetry data in time in a way that allows reprocessing if needed, i.e., all relevant data should be stored.

This will mitigate the current lack of knowledge and training and shortage of well-trained staff (See section 3.5.3).

- Establishment of accreditation programmes

Quantitative imaging, either with positron emission tomography–computed tomography (PET–CT) or the combination of single photon emission computed tomography with a computed tomography (SPECT–CT) scan, should be accompanied by respective accreditation programmes by, e.g., scientific organisations or radiation protection authorities such as that provided by EANM Research Limited for PET scanners [28] to foster standardisation and comparability of results. Such equipment should be made available at nominal costs in all Member States of the EU. The establishment of such a programme should ensure traceability and comparability of measurements throughout Europe, greatly simplifying European clinical studies with radiopharmaceuticals including dosimetry.

Equivalent programmes should be developed to benchmark clinical dosimetry from activity calibration to absorbed dose calculation, i.e., the whole clinical dosimetry workflow. This requires developing quality assurance programmes that cover all aspects of clinical dosimetry.

This activity should also comprise further efforts for defining a specific DICOM standard adapted to therapeutic nuclear medicine dosimetry.

- Creation of a regulatory network

Foster the creation of a regulatory network with representatives from radiation protection authorities, medicines agencies and scientific societies (EANM, EFOMP). The regulatory network would work together to clarify the regulatory landscape surrounding this field, thereby enabling international, multicentre clinical research, translational innovation, workforce training and patient access. It could also contribute to the development of a regulatory framework for marketing approvals of new therapeutic radiopharmaceuticals that takes into account both legislative areas.

Discussion of potential strengths, weaknesses, opportunities and threats of the proposed remedy with regard to the resolution of the issue

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.

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.

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 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.

Threats

A major threat to implementing the suggested remedies is the lack of linkage between the different authorities on the European level as well as on the national level of the Member States.

Concluding summary with final recommendations for remedy

This section, annexes 2 and 3, and reference [5] contain seven 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 stakeholders involved to ensure implementation of these remedies by the appropriate actors on the national and European levels. See also the tables in section 4.

3.5.3 Lack of resources for dosimetry

Description of the issue

A lack of resources in terms of finance; know-how; sufficiently trained technical, medical and physics staff; capacity of imaging equipment either because of competition for time slots with diagnostic imaging or a lack of equipment in some countries or centres; and access to CE-marked dosimetry software in nuclear medicine centres stifles BSSD implementation.

Brief summary of relevant evidence

In the project survey, the lack of reimbursement for dosimetry was highlighted as the main barrier for implementing dosimetry. This included both dosimetry for treatment planning and verification.

The current situation is that even though guidelines on clinical dosimetry exist, there are no associated clinical operating procedures, and the degree of refinement locally achievable and clinical dosimetry vary from one centre to the next due to locally available resources and history.

Identification of potential remedies

During the SIMPLERAD project

- The joint EANM/EFOMP core curriculum for education and training of medical physicists in nuclear medicine [6] was published in 2013. It is currently being updated, and the new core curriculum should be available in the next few months. It will include a specific section on nuclear medicine dosimetry in diagnostics and therapy for patients, the public and staff.

To be addressed in the wider context of SAMIRA

- Training and dosimetry

The syllabus for postgraduate specialisation in nuclear medicine is ageing. A call [29] to redesign the training of, broadly speaking, theranostic specialists was published in 2019, but to our knowledge, no specific work has been undertaken, neither in the US nor EU.

Training in therapeutic nuclear medicine should be developed for all professionals involved in the field. Curricula should be further developed and consider the highly multidisciplinary nature of the field, i.e., not only clinical education for physicians but also teaching clinical aspects for physicists or radiopharmacists, technologists, nurses, etc.

As a mitigation method to overcome the short-term lack of dosimetry expertise, specialised treatment centres that have the capability to provide training, both theoretical and practical, should be identified and created, ideally at a national level to allow the training of professionals in their native language. European networks for therapeutic nuclear medicine must be supported and expanded to share experience, expertise and resources. A hub–spoke model could be adopted for sharing resources: hub centres to support spokes. Ideally the creation of centres of excellence should be based on an accreditation scheme, considering also but not only clinical dosimetry. Centres of excellence should not only be able to perform a whole range of clinical dosimetry procedures but also deliver training in the field to all professionals.

Several levels of practice of dosimetry should be defined to allow optimised use of available resources.

The first degree would consist in ensuring that a centre is able to calibrate instruments, perform acquisitions and export to an expert centre. The second degree would involve being able to perform full dosimetry studies, including studies with data transferred from remote centres, while the third degree would entail ensuring the training of professionals in the different fields that compose therapeutic nuclear medicine.

- Reimbursement

Clinical dosimetry should be explicitly integrated as part of the molecular-radiotherapy clinical process and therefore integrated in the reimbursement scheme at the national level. Imaging and patient dosimetry must be reimbursed as is the case for external-beam radiotherapy, and some countries have enacted such broader policies for therapeutic nuclear medicine.

For example, in Norway, reimbursements for additional scanning sessions or other measurements such as whole-body measurement blood sampling for outpatient procedures used for dosimetry have recently been implemented.[5] While the current reimbursement scheme only considers measurements, work on reimbursement codes including the dosimetry calculations is in progress. Reimbursement associated with clinical dosimetry was also recently introduced in Italy by its government for outpatient procedures, considering SPECT and PET for treatment planning and dosimetry studies performed on treatment planning systems [30].

- Decreasing the workload associated with clinical dosimetry and standardisation

Concerning potential approaches to reduce the burden of dosimetry, the EANM has produced an Enabling Guide [31], which proposed that the degree of methodological refinement could be tailored to the need of a given clinical procedure and resources of a department. Recent attempts have also been reported in the literature to further reduce the number of timepoints used in pharmacokinetics assessment. However, as the required accuracy of dosimetric indices have yet to be defined, the clinical benefit of these procedures is difficult to assess. Work is therefore required to implement quality assurance programmes in nuclear medicine on the basis of what is current practice in external beam radiotherapy. This will lead to the provision of dosimetric indices associated with uncertainties. As it is widely acknowledged that the degree of refinement needed for a clinical dosimetry may vary according to the clinical situation (pathology, stage), radiopharmaceutical (isotope and vector), and clinical aim (safety or optimisation dosimetry), it can be foreseen that a clinical dosimetry procedure may be elaborated according to the acceptable uncertainty budget, defined prior to and conditioning the procedure.

Scientific and medical societies should generate guidance documents on how to further enable dosimetry, focusing on the needs of less well-resourced centres, expanding on the recent EANM document, and indicating acceptable methods currently available to reduce resource burden. Further research funding should be made available to implement and disseminate uncertainty assessments in every clinical dosimetry procedure, defining the level of uncertainty acceptable for each clinical procedure for a given clinical aim.

Discussion of potential strengths, weaknesses, opportunities and threats of the proposed remedy with regard to the resolution of the issue

Strengths

The main strength is that the lack of resources, although variable from one country or even one hospital to the next, is widely acknowledged and considered as a limiting factor for the implementation of clinical dosimetry, amongst other nuclear medicine practices.

Weaknesses

The main weakness is that the technical–methodological environment is sometimes so poor that even identifying the resources needed to implement clinical dosimetry can prove difficult. In countries where professionals are almost exclusively trained in external-beam radiotherapy, characterising the need for clinical dosimetry professionals in therapeutic nuclear medicine can be difficult to assess.

Opportunities

Recognising therapeutic nuclear medicine as a radiotherapeutic procedure paves the way for the full integration of dosimetry as an integral part of the clinical procedure and its reimbursement. Another major opportunity is that the current drought in medical physics resources has triggered the development of mitigating approaches aimed at reducing the workload required to perform clinical dosimetry. In this context, the development of centres of excellence capable of

[5] Code tsy0sn in the online tool: https://finnkode.ehelse.no/#icd10/0/0/0/-1

centralising clinical dosimetry and training professionals, not only MPEs, represents an opportunity to structure and strengthen the field.

Threats

The shortage of medical resources in the face of an ageing population in the EU is not specific to molecular radiotherapy. Implementing the need to determine irradiation, planned or delivered, in molecular radiotherapy may prove very difficult until a minimum staffing level in the field of nuclear medicine is defined and set by national competent authorities.

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.

3.5.4 Differences regarding status of MPEs (e.g., training, requirements, level of experience, responsibilities) between Member States

Description

There are differences regarding status of MPEs, e.g., training and level of experience, requirements and responsibilities, between Member States. The responsibilities for medical physicists or MPEs within molecular radiotherapy are currently not standardised across Europe and vary considerably from centre to centre. The staffing levels needed are also inadequately defined. A recent EFOMP survey reported differences in training across Europe [32].

Brief summary of relevant evidence

The requirement for MPEs is clearly stated in the BSSD article 58: "*In medical radiological practices, a medical physics expert is appropriately involved, the level of involvement being commensurate with the radiological risk posed by the practice*." EFOMP Policy Statement 16 [33] provided recommendations on what this involvement should imply. In 2014, the EC published the document Radiation Protection No. 174 [7]. This document provides detailed guidance on the education, training and staffing levels of MPEs, further elaborating on the requirements set forth in the BSSD. One of the key aspects is its emphasis on the education and qualification framework for MPEs, which should be at European Qualifications Framework level 8. Other recommendations for staffing level have previously been published in an International Atomic Energy Agency (IAEA) requirements document [34].

The EFOMP publishes competence-based core curricula to support the standardisation of education and training of MPEs across Europe. These curricula, based on the Radiation Protection Series publication, will be revised given recent technological and health practice developments to outline the essential knowledge, skills and competencies required for MPEs working in various specialties in imaging and therapy. EFOMP together with its national member organisations and European societies such as ESTRO, EANM and ESR aim to develop a single combined curriculum for all MPE specialties.

An EANM survey on time estimates and personnel responsible for main tasks in molecular radiotherapy dosimetry [35] indicated some variation in time estimates, reflecting the different experience and methods used at different centres. Medical physicists were found to be responsible for most tasks in dosimetry, in agreement with the BSSD article 83 requirements to ensure that "*The medical physics expert takes responsibility for dosimetry*." The survey identified a wide range of MPEs between centres and a lack of sufficient MPE support for molecular radiotherapy in the majority of centres. Variations in responsibilities were also indicated, as in these extracts from the survey.

- There was a substantial range of MPEs (from 0.07–9 FTE) observed, with a median value of 1.5 FTE. There was no minimum threshold identified under which molecular radiotherapy was not implemented.
- The majority (55%) responded that MPE support for molecular radiotherapy was certainly not sufficient.
- The survey did not seek to ascertain the variation in roles of the MPE across the EU, although internal dialogue and expert interviews indicated that this may vary widely from centre to centre, ranging from hands-on patient treatment to more administrative work.
- The majority of responders felt the role of the MPE was reasonably well defined, although 80% indicated there was still room for further improvement.

An EFOMP survey concerning education, training and registration of MPEs across Europe found large variations in the required training between countries [32]. Variations in individual subject areas such as nuclear medicine were not assessed directly, but the overall variation indicates that the training and level of experience also in molecular radiotherapy-related tasks may vary greatly.

- Of the 25 EU states (of 27 total) that participated in the EFOMP survey, 19 had national registration schemes for MPEs, and three were considering implementing one.
- Only in 50% of the centres was a distinction between a medical physicist and a more senior experienced MPE observed.
- Variation in the specialisation was also evident, with some MPE qualifications being granted after completion of a Master or Bachelor of Science courses covering all fields of medical physics and some with up to 6.5 years post-graduate and clinical training in a specialist subject area such as nuclear medicine.
- Only 80% of the national training schemes were government approved and only 22% by the EFOMP.

The joint EANM/EFOMP core curriculum for education and training of medical physicists in nuclear medicine was published in 2013 [6], detailing the knowledge, skills and competence needed for different activities, including internal radionuclide dosimetry. It is currently being updated. The EFOMP published recommendations on staffing levels for MPEs in its policy statement 7.1 [36], which considered the requirements of the BSSD, Radiation Protection Series No. 174 as well as the relevant publications of the IAEA. In particular, the impact on the workforce of aspects such as the increasing workload in advanced molecular radiotherapy has been made by the IAEA and in the UK [34, 37].

Identification of potential remedies, strengths and weaknesses

During the SIMPLERAD project

- The training of MPEs should be aligned with the joint EANM/EFOMP core curriculum. As demonstrated by the EFOMP survey, large variations exist in the training of MPEs, and as a first step these overarching differences should be tackled by the professional societies. Harmonisation would improve the overall quality of the profession and facilitate mobility, also for MPEs working in molecular radiotherapy. The updated joint EANM/EFOMP core curriculum for education and training of medical physicists in nuclear medicine will also facilitate harmonisation.

Discussion of potential strengths, weaknesses, opportunities and threats of the proposed remedy with regard to the resolution of the issue

Strengths

Conducting a survey to map roles and responsibilities will provide a systematic approach to identify variations in practices across centres and countries and gain valuable insights into the factors influencing these variations, including resource availability and training levels.

The proposal to create a guidance document on roles and responsibilities demonstrates a proactive approach to standardising practices. Aligning recommendations with the EFOMP policy statement and considering survey results will enhance the document's relevance and practicality.

Establishing and enforcing staffing requirements for molecular radiotherapy centres ensures a baseline level of expertise and resources. Minimum requirements for medical physicists and MPEs contribute to the overall quality and safety of molecular radiotherapy services. This will address existing variations and promote a standardised level of expertise. Harmonisation not only improves the quality of the profession but also facilitates professional mobility, supporting collaboration and knowledge exchange.

Weaknesses

Variations in responsibilities may be closely tied to available resources, making it challenging to standardise roles without addressing resource disparities. Enforcing staffing requirements may face challenges in implementation, especially if there is resistance from centres or countries. Differing national practices may pose a challenge in harmonising MPE training across Europe.

Opportunities

The survey presents an opportunity to gain a deeper understanding of the factors influencing roles and responsibilities in molecular radiotherapy and inform the development of the guidance document and initiatives, ensuring they are grounded in real-world practices.

Harmonising MPE training fosters professional mobility and collaboration, allowing practitioners to work seamlessly across European countries. Shared training standards promote knowledge exchange and the adoption of best practices from different regions.

The proposed initiatives have the potential to enhance the overall quality and safety of molecular radiotherapy services. Standardised roles, responsibilities, and staffing levels contribute to improved patient care and treatment outcomes.

Threats

Resistance from centres or countries to standardise roles, responsibilities, and staffing levels may impede the effectiveness of proposed initiatives. Implementing a comprehensive survey may face logistical challenges, including data collection and diversity across centres and countries. Balancing the need for standardisation with the diversity of centres and national practices requires careful consideration.

Synthesis

In summary, different levels of implementation are in place across Europe as well as large variations in resources.

Staffing levels should be updated by the professional societies to take into account advanced molecular radiotherapy and should be implemented by national authorities, taking into account the forthcoming guidelines and recommendations of the EU-REST study [8]. Furthermore, national authorities should ensure free circulation of MPEs within the EU by implementing mutual recognition of MPE training qualifications.

3.5.5 Heterogeneity of dose constraints and patient-release criteria between Member States

Description of the issue

There is a lack of harmonisation regarding patient-release criteria and patient instructions among EU Member States. As part of this problem there is also a lack of guidance for the establishment of dose constraints.

Brief summary of relevant evidence

The survey demonstrated variation across centres and Member States on the criteria used to hold and release patients from hospital. In some cases, specific guidance was issued by the competent authority or professional society. However, this was generally lacking for the newer lutetium therapies. Instructions provided to patients on release were similarly varied both in advice and detail.

As part of the lack of harmonisation of release criteria and instructions the survey of the SIMPLERAD project noted that responsibility for establishing dose constraints varied across Member States and were either established by the competent authority, professional bodies or societies or the treating centre. When asked to provide further information regarding these constraints many respondents were unable to provide a numerical effective dose constraint. In some instances, respondents provided a dose limit, a dose rate, patient-release criteria, reference to national regulations or indicated that it was the decision of the practitioner. In only eight countries could a public dose constraint be ascertained with typical values reported of 0.1, 0.25 and 0.3 mSv per procedure. Similar values were reported in a recent survey undertaken by HERCA [38].

Identification of potential remedies

To be addressed in the wider scope of SAMIRA

- Importance of recognising different decision levels

Final release criteria and instructions are set to optimise radiation exposure of any other person likely to be exposed as a result of a therapeutic nuclear medicine. The process of setting release criteria and patient instructions is, however, influenced by different criteria and decision levels.

Table 2: Different decision levels that influence the setting of patient-release criteria and instructions

		Individual of a Critical Group		
Level 1	Decision on type of exposure	Comforter or carer (medical exposure)		Member of the public (public exposure)
Level 2	Decision on level of dose constraint	Dose constraint (medical exposure)		Dose constraint (medical exposure)
Level 3	Risk assessment method	Exposure scenario		Patient source characterisation
	Final result	Patient release criteria	Patient instructions	

The first level is the type of exposure that should be considered for an individual that might be exposed by a nuclear medicine patient. If the individual acts as comforter or carer this exposure should be considered as a medical exposure. Comforters and carers are defined as individuals knowingly and willingly incurring an exposure to ionising radiation by helping, other than as part of their occupation, in the support and comfort of individuals undergoing or having undergone medical exposure. For a patient receiving a therapeutic administration of a radionuclide a carer

and comforter may be a friend, spouse or other family member supporting the patient whilst there is still a likelihood of exposure. The absence of specific dose constraints for this type of exposure in many countries according to the survey shows that there is a need of guidance that will help in the decision of which individual and in which situation can be considered as a comforter or carer or as a member of the public and which adequate information and guidance relating to the benefits and risks they should be provided.

The second level that influences specific release criteria and instructions is the setting of the dose constraints both for medical exposure of comforters and carers and for the public. The BSSD requires that, where appropriate, Member States shall establish dose constraints for the purpose of prospective optimisation of protection for planned exposures. Dose constraints represent a level of individual dose which should not, in normal circumstances, be exceeded. They are used in the planning process and the chosen value will depend on the circumstances of the exposure under consideration. They are not a limit and do not represent a demarcation between safe and dangerous levels of radiation exposure but are used, prospectively, as a tool for optimisation. For planned exposures that have an associated dose limit, dose constraints should be lower than the pertinent dose limit. The International Commission on Radiological Protection (ICRP) recommends that dose constraints should be set per episode for comforters/cares and per period (year) for the general public [39]. Despite this, the survey shows a variety of the use of specific values, periods and episodes such as a single procedure or a treatment cycle and indicates the need for an explanatory document summarising the concept of dose constraints in this framework.

Another level that has an impact is the risk-assessment method that is used to characterise the (potential) exposure of an individual from a nuclear medicine patient. It was already recognised in IAEA Safety Report Series No. 63 [40] that different applied methods in risk-assessment studies can lead to a variation of patient-release criteria and instructions. An important component of this risk-assessment method is the characterisation of the patient as a radioactive source for external exposure as well as contamination risk. Several studies already reported measured and calculated data on the potential exposure after ^{131}I therapy and often used different assumptions and models to estimate the retained activity which led to different source characteristics. With the increasing number of newer therapies and the better knowledge of patient biokinetics, researchers should be encouraged to conduct risk-assessment studies using state-of-the-art methods.

It is clear that harmonisation of patient-release criteria and instructions cannot be accomplished if there is a lack of harmonisation at one of the levels that influence the outcome.

- Generation of data

Establishing EU programmes for the generation of high-level dosimetric data for the optimisation of protection of the public, carers and comforters, and household members affected by radionuclide therapy should be considered to complement ongoing efforts by, e.g., the European Radiation Dosimetry Group and SINFONIA project. Examples are the following.

- An EU database of findings of measured doses to family members and comforters and carers of patients including sufficient demographic and therapy data to generalise typical exposures from therapies.
- A publicly available EU database for recording dose rate and excretion factors, including biokinetic data from patients receiving unsealed radionuclides for therapy.
- An EU programme to develop modern and appropriate models of contact pattern patients and household members.

- Guidance documents

European guidance documents to help in the decision of which individuals and in which situations can or should be considered as a comforter or carer or as a member of the public should be provided with adequate information and guidance relating to the benefits and risks. These documents ideally should be supported by similar codes of practice nationally approved by competent authorities, who could consider jointly developing them for establishment across EU regions or different Member States.

- Regulatory frameworks

Consideration should be given to the removal of generic patient instructions concerning radiation protection advice provided by radiopharmaceutical companies in SmPCs where this instruction is not founded on robust data or matches the specific regulatory instruction of a Member State.

- Demystifying dose constraints

An explanatory document summarising the concepts laid out in the ICRP publication and BSSD should be published. The document should focus on healthcare establishments performing therapeutic administrations of radionuclides and those wishing to start a service. The document should provide both the principles and good-practice examples.

An EANM/EFOMP guidance document or approved code of practice based on the SIMPLERAD survey results could explain the differentiation between limits and constraints and propose constraints for the public and comforters and carers for nuclear medicine therapies. This should involve national competent authorities and HERCA.

Discussion of potential strengths, weaknesses, opportunities and threats of the proposed remedy with regard to the resolution of the issue

Strengths

The proposed multi-level strategy to approach the lack of harmonisation of release criteria will enable clarifying the impact of different decision levels on the final outcome.

Weaknesses

The significant variations across centres and Member States on the criteria used to hold and release patients from hospital indicates that future harmonisation might result in a significant relaxing or strengthening of existing release criteria in some countries, as different countries might set up the legal framework differently and the several prerequisites may vary in each country.

Opportunities

EU grant programmes present an opportunity to gather comprehensive dosimetric data, facilitating the establishment of harmonised patient-release criteria. Such programmes would also support local or national clinical audits pursuant to article 58(e) of Council Directive 2013/59/Euratom and further described in Commission Recommendation (EU) 2024/1112 [41] and by the QuADRANT project, a European study on clinical audit of medical radiological procedures that concluded in 2022 [42]. The proposal for European guidance documents offers the potential to create unified standards across Member States. Collaboration with competent authorities and professional bodies will help to ensure widespread adoption and implementation of harmonised guidance. Explanatory documentation can demystify concepts, providing clarity on the differentiation between limits and constraints.

Threats

The reliability and quality of data generated through grant programmes may vary, impacting the effectiveness of harmonisation efforts. Challenges in developing European guidance that is

universally accepted across Member States. Fostering collaboration with competent authorities, professional societies, and Member States throughout the development process will help to address potentially diverse perspectives.

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 of comforters and carers in nuclear medicine and the correct use of dose constraints should be considered.

3.5.6 Heterogeneity of management of radioactive waste across Member States

Description of the issue

Conditions concerning management of radioactive waste are well-established in most countries across Europe. However, the specific conditions and practical application of such varies widely across Member States and centres. A consequence of these conditions is a potential hampering or limitation of patient access to treatments. The radiological assessment used to establish these conditions is also unclear.

Brief summary of relevant evidence

It was apparent from the survey that management of radioactive waste varies widely across Europe. Different systems are in place at hospitals for reducing the environmental and radiological impact of effluent discharge of therapeutic radionuclides. These include, reducing the annual or monthly aqueous radionuclide waste output from the hospital (effectively limiting the number of patients that are treated), decay storing aqueous waste prior to discharge to limit the concentration of activity at the time of release, or filtering the waste of radionuclide contaminants prior to discharge from the hospital.

The latter two solutions have financial impact and often require significant infrastructure development prior to commencing a therapeutic service. In addition, the solutions rely on the patient excretion being managed within the hospital, often necessitating the treatment to be undertaken in an inpatient setting. As such, sites where these systems were in place were generally found to keep patients in hospital longer than those that just limited the total activity administered per month or year. Radioactive waste and aqueous waste conditions therefore have an impact on patient discharge criteria which further exacerbated the financial impact.

Identification of potential remedies

To be addressed in the wider context of SAMIRA

In IAEA Technical Document 1638 [43] and General Safety Guide GSG-9 [44], the IAEA published a comprehensive overview of the different factors leading to the setting of authorised effluent discharge limits.

Current guidance documents emphasise that regulation of discharges to the environment should be based on the principle of dose optimisation of a representative member of the public and that a relevant dose constraint related to the discharge activity should be specified.

The value of a relevant dose constraint in this context might differ as multiple facilities or activities in an area where more than one source is present could contribute to the exposure of a representative person. Even setting similar dose constraints for similar installations can result in different authorised discharge limits because dose assessment studies can be influenced by

factors such as the regional extent of development of the sewerage system including the type and number of wastewater treatment plants.

Although guidance on granting an authorisation for effluent release of nuclear medicine patients is available, there is a lack of transparency on the different factors and methodologies that are used by authorities across Member States.

This accounts also for the application of the concepts of exemption and clearance in the framework of solid waste arising from the use of medical radionuclides. The EC already evaluated in 2003 the application of the concepts of exemption and clearance across Member States and concluded that there is a need to encourage harmonisation.

Due to the wide scope of topics covered by the survey it was not possible to gather more detailed information concerning these methodologies used for specific treatments or radionuclides by competent authorities. Gathering of further information on the specific criteria and methodologies used by competent authorities to set specific effluent release conditions could be established through an EU survey focused on this topic. Based on the results of this survey, the feasibility of the harmonisation of the specific conditions on the discharge of radioactive effluent and application of exemption and clearance according to the requirements of the BSSD could be studied.

Additionally, a working party representing different competent authorities could elaborate a specific guidance document on effluent release and waste management related to the use of medical radionuclides. This document should also focus on the practical management of emerging medical radionuclides such as alpha emitters and potential long-lived contaminants of new upcoming therapeutic radiopharmaceuticals, e.g., ^{177m}Lu. A review of current and emerging technology to reduce the radiological impact of medical radionuclides should also be included.

Discussion of potential strengths, weaknesses, opportunities and threats of the proposed remedy with regard to the resolution of the issue

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.

Weaknesses

The complexity of factors influencing effluent discharge limits, such as regional sewerage system development and wastewater treatment, will complicate harmonisation efforts. Lack of transparency on the methodologies used by authorities across Member States for effluent release conditions poses a challenge.

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. Ensure the guidance document considers emerging technologies, including those related to new therapeutic radiopharmaceuticals, enhancing its relevance and applicability.

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.

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.

3.5.7 Differing guidance from professional societies for clinical practice

Description of the issue

In clinical practice, treatment of patients is based on an individual assessment of a specific patient's case. However, for most diseases, the majority of patient cases show sufficient similarities that it is possible to establish a best practice applying to such patients based on evidence generated in rigorous scientific study. This best practice is often summarised in the form of guideline documents, which are written by representative societies of various medical and related professionals from different disciplines. As treatment increasingly involves multidisciplinary care, it is not uncommon that multiple professional societies each formulate an own guideline for a particular disease or treatment modality. In an ideal world, these guidelines would nonetheless contain congruent, if not identical guidance. Unfortunately, in the case of radionuclide therapy, it has been noted that different professional societies come to different, even contradictory guidance for the same disease or therapeutic modality.

Brief summary of relevant evidence

In the project's initial analysis, an overview of three products selected for focused examination was given. For newer forms of therapy, such as [^{177}Lu]Lu-DOTATATE or ^{90}Y-labelled SIRT products, thus far only guidelines from nuclear medicine societies were found. However, notably, for radioiodine therapy, which is the oldest currently administered form of radionuclide therapy, strong discrepancies were encountered between guidance from professional societies from different disciplines.

In brief, the EANM procedure guidelines provided by Stokkel et al. [45] provide guidance that a personalised approach based on dosimetry may be suitable for at least a selected subgroup of patients. Absorbed doses are also recommended for different pathologies: 100–150 Gy for multinodular goitre, 300–400 Gy for autonomous nodules and 150 Gy for restoring euthyroidism in Graves' disease. Conversely the view within the guideline from the European Thyroid Association for the management of Graves' hyperthyroidism [46] is that that whilst the ALARA policy is an important principle within radiation treatment, it has remained an elusive goal when balancing rapid relief of hyperthyroidism and postponing hypothyroidism. It is therefore observed that many have given up absorbed doses calculation and offer fixed activities based on clinical parameters, such as thyroid size.

Clinical guidance from the EANM for treatment of differentiated thyroid cancer similarly contains information concerning potential application of pre-therapeutic dosimetry concepts including remnant, lesion, and bone-marrow dosimetry [47]. Suggested absorbed doses are reported with a brief procedural instruction further described in standard operational procedures for pre-therapeutic dosimetry [48]. The European Thyroid Association statement for the indications of post-surgical radioactive iodine therapy in differentiated thyroid cancer [49] does not mention dosimetrically prescriptions and rather concentrates on an activity lead prescription based on the risk classification of patients.

The existence of such discrepancies or even contradictions between professional guidelines from different professional clinical societies, which are based on the same body of evidence in literature, suggests that the available evidence is weak and ambiguous at best, leaving room or even a need for professional opinion to fill in where higher-level or better-quality evidence is not available.

Identification of potential remedies

During the SIMPLERAD project

Beyond the project workshop organised in December 2023, the publication of the results of the evidence-gathering process of the SIMPLERAD project should be made available to the community, under as many formats as possible: public reports, publications in scientific journals and presentations.

Two issues described in this section also pertain to other issues identified and are dealt with more extensively in section 3.5.2. Professional societies should be alerted to this. Both issues are summarised below.

- Need to reinforce the precedence of BSSD in establishing treatment regimen

Article 56 of the BSSD clearly stipulates that individual dose planning and post-therapy verification of administration are mandatory. However, as discussed in section 3.5.2, additional guidance on what pertains to individual dose planning may be needed. For further details on this matter, we refer to the text of section 3.5.2.

- Contact by competent authorities with professional societies

It should be considered by national competent authorities to contact relevant professional clinical societies, with the accompanying guidance document as drafted in section 3.5.2 and annex 2 and 3 to draw attention to this issue, requesting that societies adapt guidelines to conform to BSSD as *lex specialis*.

To be addressed in the wider context of SAMIRA

- Generation of evidence

It should be considered to set up, e.g., within the Horizon Europe framework, a grant programme for the generation of high-level clinical evidence on the benefit of individual planning of various forms of radionuclide therapy using dosimetric methods. Furthermore, such a program should also involve generation of evidence pertaining to optimisation of dosimetric methods as well as minimisation of patient burden of dosimetric procedures.

For example, EFOMP Policy Statement 19 [50] makes a number of recommendations intended to assist in resolving such issues.

Statement number 1: European molecular radiotherapy networks must be supported and expanded to share experience, expertise and resources.

Statement number 2: National and European databases are required to collect data on clinical factors, dosimetry and patient outcomes from multiple centres.

Statement number 3: Codes of practice for the validation and harmonisation of dosimetry results and patient outcomes for different treatments should continue to be developed and put into practice.

Statement number 6: Research should be supported through national and European programmes to investigate treatment planning strategies for individual therapeutic procedures.

Statement number 11: Investigator-initiated multi-centre and multi-national clinical trials should be promoted to develop optimised treatments.

Statement number 13: For industry- and investigator-initiated clinical trials, individual-patient dosimetry must be incorporated to enable risk-versus-benefit analyses within drug development. Results and evidence must be presented at the time of submission for drug marketing authorisation.

- Facilitation of interdisciplinary consensus discussion

There is a need to stimulate interdisciplinary, dedicated meetings aimed at achieving interdisciplinary consensus among experts from various disciplines involved in the field on issues pertaining to individual planning of radionuclide therapy. The building of interdisciplinary consensus could be supported by the relevant EU programmes in the health area

Discussion of potential strengths, weaknesses, opportunities and threats of the proposed remedy with regard to the resolution of the issue

Strengths

The current proposal will endeavour to entice clinicians and non-clinicians to look beyond traditionally established disciplinary boundaries.

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.

Opportunities

The identification of the necessary measures in this section presents an opportunity to reserve financial resources in upcoming budgets for subsidy programmes. The proposed programmes would also support local or national clinical audits pursuant to article 58(e) of the BSSD and further described in Commission Recommendation (EU) 2024/1112 [41].

Threats

Lack of funding for various stimulating measures presents the largest threat to the success of the measures proposed in this section.

Synthesis

Different professional societies come to different, even contradictory, guidance for the same disease/therapeutic modality on issues pertaining to the interaction between the EU Pharma 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 the SIMPLERAD project in the form of, e.g., public reports, publications in scientific journals and presentations
- Contact by competent authorities 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

3.5.8 Differing regulatory procedures among Member States for drug development and clinical trials

Description of the issue

- Missing feature in CTIS for structured handling of dosimetry-related information on radiopharmaceuticals
- Differing regulatory processes between Member States for application procedures of clinical trials concerning dosimetry aspects of radiopharmaceuticals

- Varying and often unclear competences on the assessment of radiation- and dosimetry-related aspects of clinical trial applications among Member States

Brief summary of relevant literature

Since radiopharmaceuticals are both pharmaceuticals as well as products associated with effects of ionising radiation, the current set of legislation that radiopharmaceuticals have adhere to is based on two different sets of regulations: one covering the pharmaceutical aspects, the Pharma Directive and CTR, and the other dealing with associated (for diagnostics) or intended (for therapeutics) effects of radiation, the BSSD.

Before the CTR came into effect in 2022 and the transition period for the application of clinical trials under the old clinical trial directive ended in January 2023, there was considerable heterogeneity among the different Member States regarding the approval procedures for clinical trials.

This has been harmonised by the CTR and the introduction of the CTIS with a central submission portal.

However, within the CTIS itself the entry of radiation associated data, such as dosimetry, is not foreseen, although a function to upload separate files pertaining to radiation-associated data, such as dosimetry, is requested during the formal validation of the submission. There appears to be no prescribed format for this datasheet. It is unclear how this datasheet is assessed, by whom and what consequences are drawn from the information given within the file. Since these data are mandatory for a comprehensive evaluation of a clinical trial with therapeutic radiopharmaceuticals as investigational medicinal products that fall under the scope of the CTR, an additional evaluation procedure outside CTIS is often required. This additional procedure is not regulated by the CTR and, in absence of any harmonised procedure within the EU on this topic, falls back into the responsibility of the national competent authorities. This leads again to heterogeneous procedures among the individual Member States, counteracting the original intention of the CTR to harmonise clinical trial applications throughout the EU.

In some Member States, radiation protection/safety aspects are linked to the authorities handling pharmaceutical aspects. In others, the pharmaceutical and radiation protection aspects are processed by completely independent entities. As a consequence, both timeframes and processing times and the process structure, i.e., sequential vs. parallel processing, are not harmonised. This can lead to significant differences in the time needed from submission of application documents to receipt of the final decision up to several months.

Before the CTR and CTIS came into force, the processes for Germany and the Netherlands as examples differed considerably: In Germany the present application process for a clinical trial was consecutive. For a clinical trial with radiopharmaceuticals the competent authority, the Federal Institute for Drugs and Medical Devices, would process the application data except for radiation-associated aspects (dosimetry) that were to be addressed by a different authority, the Federal Office for Radiation Protection. In contrast, in the neighbouring country, the Netherlands, the CTR did not change this practice, and all aspects concerning assessment of radiation protection and pharmaceutical safety were in the responsibilities of the medical ethical committees themselves.

Since the mandatory application of CTIS fell into the progression period of the SIMPLERAD project, limited real-life experience with the application process and potentially associated problems thereof is available at the time of publication.

Identification of potential remedies

To be addressed in the wider context of SAMIRA

This issue does not allow for solutions or remedies within the scope of the SIMPLERAD project, but the consortium suggests the following remedial actions to overcome these problems.

- Integration of radiation-associated features of radiopharmaceuticals as investigational medicinal products into the data package required for submission in CTIS.
- Further evidence collection through the following:
    - Establishment of national and European databases among multiple centres to collect data on clinical factors associated with molecular radiotherapy, including dosimetry and patient outcome.
    - Initialisation and support of investigator-initiated multi-centre and multi-national clinical trials on therapeutic radiopharmaceuticals to develop optimised treatments.
    - Establishment of dosimetry expert networks to disseminate know-how for clinical trials with therapeutic radiopharmaceuticals. As an example, image processing and dosimetry may be performed at remote sites with data collected according to specified protocols.
    - Mandatory presentation of results and evidence on individual-patient dosimetry within the marketing authorisation application dossier.

Discussion of potential strengths, weaknesses, opportunities and threats of the proposed remedy with regard to the resolution of the issue

Strengths

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

Weaknesses

Within the scope of SIMPLERAD we were unable to implement the proposed remedies.

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 healthcare for EU citizens.

Threats

Any establishment of additional databases could possibly require a higher level of administrative effort.

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 EU Member States and a risk of decrease of representation of Europe in global drug development and clinical trials with radiopharmaceuticals, efforts should be made at both national and EU level to overcome national differences and ensure harmony between the applicable EU rules and regulations (Pharma Directive and BSSD).

3.5.9 Insufficient specialist knowledge concerning nuclear medicine within various stakeholders regarding EU pharmaceutical and medicine as well as BSSD-related regulations

Description of the issue

Expert interviews and the main survey carried out by the SIMPLERAD consortium identified some problems regarding the route to market as well as the administration of therapeutic radiopharmaceuticals.

- Issues concerning regulatory frameworks were generally a dominant theme.
- Heterogeneity was observed across Member States concerning many aspects of both sets of relevant legislation for pharmaceuticals and radiation protection.
- Even if a number of regulators indicated that pharmaceutical and radiation protection authorities in their country work closely together, some conflicts concerning the interpretation of both sets of applicable law as well as a lack of coordination between the different competent authorities were identified.
- It was noted that national regulators are at different levels of knowledge in one or even both sets of legislation.

Problems identified could not only lead to differences during the registration processes but also to important consequences regarding patient access to novel therapeutic radiopharmaceuticals across the 27 Member States of the EU.

This section in particular deals with a lack of sufficient knowledge regarding radiation protection legislation amongst pharmaceutical-legislation experts and vice versa. From the authors' own experience, such lack of knowledge, potentially leading to stifling development and delayed patient access to innovative radiotherapeutics, is widespread.

It also affects, e.g., the acceptance of patient-individual dosimetry. For most therapies there is a desire for such dosimetry-guided optimisation. However, because of the problem identified such optimisation probably is not common practice in some EU Member States. The survey was only able to determine a plausible dose constraint in a few countries.

Brief summary of relevant literature

As the present issue is a matter identified through the SIMPLERAD survey and is a subjective impression of the participants rather than an objective matter, there is no relevant literature to discuss.

Identification of potential remedies

To be addressed in the wider context of SAMIRA

Obviously, there is a clear need for specialist expertise in both sets of relevant legislation. Knowledge gaps between pharmaceutical and radiation protection legislation should be bridged by the following.

- Further specialist training
- Close cooperation between all stakeholders
- More harmonised legislation or specific guidance addressed to both radiation safety and pharmaceutical authorities, ideally drafted and released by the relevant EU bodies and services. A first step could be drafting a guideline on the clinical development of therapeutic radiopharmaceuticals in oncology, which has been considered by the EMA Oncology Working Party

Discussion of potential strengths, weaknesses, opportunities and threats of the proposed remedy with regard to the resolution of the issue

Strengths

Established connections between national radiation protection authorities through HERCA.

Weaknesses

National regulators are at different levels of knowledge in one or even both sets of 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.

Opportunities

Specialist training in both sets of relevant legislation bridges the knowledge gaps between pharmaceutical and radiation protection legislation. Improved cooperation between all stakeholders. International databases would further support local or national clinical audits pursuant to article 58(e) of the BSSD and further described in Commission Recommendation (EU) 2024/1112 [41], the infrastructure of which was raised as a potential barrier to implementation in in the final report of the QuADRANT project [42].

Threats

Linkage between the stakeholders is not developed further.

Synthesis

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

3.5.10 Differences among opinions of professionals concerning dosimetry and the necessity stipulated in national legislation and guidance

Description of the issue

Provided regulatory guidance differs between therapies, countries and at least for some therapies, guidance might differ from professional opinion. This item aims to describe these discrepancies and provide guidance and solutions.

If there is a discrepancy between provided guidance, requirements and the ideal situation according to professional opinion, it is important that users understand the possibilities on treatment adaptation based on legislation while taking into account expert opinion.

Brief summary of relevant literature

To summarise the SIMPLERAD project's preliminary research, information on four different therapies was specifically collected.

- A: [^{131}I]NaI for benign thyroid disorders
- B: [^{177}Lu]Lu-DOTATATE for neuroendocrine tumours
- C: [^{177}Lu]Lu-PSMA for metastatic prostate cancer
- D: [^{223}Ra]$RaCl_2$ for bone palliation of metastatic prostate cancer

Respondents were asked what guidance on dosimetry existed for these therapies, what was current practice, and also what they thought would be ideally performed.

For treatment A, guidance, current practice and ideal situation according to professional opinion were almost aligned, with exception of the individual dose assessment, for which even more respondents think it should ideally be required.

For treatments B and C, while guidance and practice were aligned quite well, there was a strong discrepancy with the ideal situation according to professional opinion, with 50% of the responders indicating they felt 'planning administered activity based on an individual absorbed dose assessment' should be required, while only 10% of the responders indicated this was provided as guidance or was current practice.

Results for treatment D were markedly different from the other three therapies studied. The distribution of practice reflected national recommendations, with the majority of respondents indicating therapy was planned with an adjustment of activity based on body weight or body surface area. When asked what they believed should be performed, responses were more heterogeneous, likely due to the lack of guidance and perceived difficulty in dosimetric planning for the alpha therapy.

Identification of potential remedies

During the SIMPLERAD project

- Guidelines or guidance documents on applying dosimetry for radionuclide therapy

Create an explanatory document to help users understand the possibilities of treatment adaptation based on legislative restrictions, e.g., *lex specialis*, how much freedom exists on the EU level to administer more or less than the registered posology, specifically also referring to text in the SmPC section 4.4, which states that:

> For each patient, the radiation exposure must be justifiable by the likely benefit. The activity administered should in every case be as low as reasonably achievable to obtain the required therapeutic effect.

The document should further stipulate specifically that this paragraph allows for deviation from the fixed-activity recommendation stated in section 4.2 of the SmPC and the requirements for this, e.g., involvement by a medical physicist. A summary of different recommendations is presented in annex 1, and details for selected use cases reflecting the present state of the art are presented in annex 2. See also section 3.5.2.

- Publication of results of the SIMPLERAD evidence-gathering process

Results from the literature review, legal analysis, survey and expert interviews provide insight into existing discrepancies and their possible consequences and can therefore serve as input for definition of solutions.

To be addressed in the wider context of SAMIRA

- Translation of available European guidance to national level

Such a document might require amendment for national situations if not elevated to EU generalised law status. There is a need for translation to national documents. If European legislation is different from national legislation, it needs to be clarified how to deal with this. EANM and EFOMP could also consider a joint guideline document to align these issues.

- Collaboration between competent authorities and national societies

National competent authorities and societies should work together to implement guidance that already exists on the European level, e.g., guidance documents or position statements. Competent authorities should provide guidance and statements on how they expect centres to comply with law, and what argumentation is acceptable in case of deviation.

- Expert consultation for revision of new regulatory guidance documents

Expert consultations are crucial to ensure minimising discrepancies in regulatory documents and professional opinion of competent experts in the field, both at European and national level. This is also crucial when revising documents, since expert opinion might evolve based on experience following current legislation. Possible revision of regulatory guidance could also be initiated as a result of establishing that there is a discrepancy between regulatory guidance and expert opinion.

Discussion of potential strengths, weaknesses, opportunities and threats of the proposed remedy with regard to the resolution of the issue

Strengths

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.

Weaknesses

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

Opportunities

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

Threats

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

Synthesis

In summary, 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.

3.6 Discussion

The present project presents a number of identified pressing issues pertaining to radiation protection, pharmaceutical legislation and the use of dosimetry in clinical practice of molecular radiotherapy and suggests potential remedies for the same. These issues stem from a variety of sources, spanning from ambiguity in the interpretation of legislative provisions, such as article 56.1 of the BSSD, to lack of resources and human factors such as communication.

Communication is also of the utmost essence when it comes to the lack of clarity surrounding the interpretation of the BSSD. It was evident from the survey and interviews conducted in the field that while the general spirit of article 56.1 was understood to pertain to the need for a form of individualisation, there was nonetheless widespread confusion on a national level what exactly pertains to individual planning.

The present project has endeavoured to clearly define this in terms that are easy to understand and provide clear guidance on how it could be applied in clinical practice. We suggest that the EC adopts this document and communicates it through all appropriate channels to the professional societies for further distribution to professionals in the field and through HERCA to the respective national authorities. Only with such clear communication and endorsement will the need for true individual therapy planning not only be a matter of good clinical practice for treating patients, but also as a matter of legal obligation to become sufficiently clear to be respected.

In the present project, a number of other factors hampering the uptake of the individual planning mandate in article 56.1 of the BSSD became evident, mostly pertaining to resources needed for the execution of this mandate. A disparity between Member States was observed in terms of the availability of staff, of equipment and of adequate funding, e.g., in the form of reimbursement within the healthcare system, and of the need to perform individual planning for molecular radiotherapy. A disparity was observed in the required and available number of MPEs supporting nuclear medicine alongside a variation across Member States in the roles MPEs play regarding patient treatment.

Certainly, as a function of the requirements of the BSSD there seems to be a role for the EU to take a variety of measures, as explained and recommended in more detail in this chapter. These measures provide a common framework for Member States to ensure more homogeneity, and in most cases an increase with regard to resources available for respecting article 56.1 of the BSSD. These measures can be of a stimulatory nature, such as providing funding for training programmes or additional resources to set up the required conditions for individual planning of molecular radiotherapy, especially to those Member States lacking sufficient funds to provide them.

Currently, as illustrated for example in section 3.5.8, the transposition of European directives into national law allows for a considerable degree of variation in the execution of such regulations in practice, which in turn has limiting consequences in terms of exchange of knowledge and skills, free movement of skilled workers between Member States, and equality of access to radiopharmaceutical therapy for patients between Member States. Currently, national law consists of a patchwork of variations of the BSSD and other EU directives. We therefore recommend that the EC support measures streamlining communication between the EU and local regulators, e.g., in the framework of the SAMIRA action plan. A good example of this can be a Joint Action subsidy for competent authorities aimed at better cooperation and communication, such as the grant CR-g-23-44-03: Direct grants to Member States' authorities to support implementation of the strategic agenda for medical ionising radiation applications (SAMIRA) — Preparatory activities for a future joint action on quality and safety of medical applications of ionising radiation under the SAMIRA initiative. Furthermore, it would be advantageous for the EC to establish a cross-policy working group with the scope to address regulatory variation and current lack of harmonisation on the assessment of radiation exposure. Establishing such a group could contribute to standardising the implementation of the BSSD.

3.6.1 Limitations

The current project provides a complete inventory and several proposals for remedies of issues related to the interrelations between the EU Pharma Directive and associated guidance documents and the BSSD as well as issues hampering implementing the requirements of the BSSD in practice. However, the project has certain limitations which to some extent may restrict the applicability and generalisability of the recommendations.

Although we endeavoured within the project consortium to interview a representative cross section of experts from a variety of Member States, not all Member States were represented equally in the expert pool. Furthermore, not all relevant national legislation information of the various Member States was available in languages that at least one member of our consortium could understand. It is conceivable that some issues of a more detailed nature may not have been observed as a result. However, considering the considerable number of different Member States represented within the expert group interviewed as well as the cross-sectional nature of the online survey of the field, it is unlikely that issues of a more structural nature have been overlooked. Thus, as the recommendations of the present project are largely aimed at resolving more structural issues, which mostly transcend national borders, it is unlikely that our suggestions for remedies and solutions will not be applicable in the EU Member States.

3.6.2 Feedback: stakeholders and workshop

SIMPLERAD was conceived to identify issues and limitations on radiation protection and radiopharmaceuticals in the context of radioligand therapy. During the written stakeholder consultation and the SIMPLERAD workshop in Brussels on 11–12 December 2024, the proposals presented in this report received extensive feedback.

In result, there was a general agreement, albeit with minor variations between the various stakeholder groups concerning their precise ranking (See also sections 3.4 and 3.5) on the five most important issues dealt with in this report, as follows.

- Disconnection between marketing authorisation of radiopharmaceuticals and the BSSD (Item 1)
- Differences in interpreting and implementing the BSSD in the context of therapeutic nuclear medicine (Item 2)
- Lack of resources for dosimetry (Item 3)
- Differing regulatory procedures among Member States for drug development and clinical trials (Item 8)
- Differences among opinions of professionals concerning dosimetry and the necessity stipulated in national legislation and guidance (Item 10)

On the content of individual issues, the commentary and opinions differed widely, especially where the implementation of individual dosimetry was concerned. Whereas the commentaries of national competent authorities appear largely to be in agreement with both the necessity for dosimetry and proposed remedies and strategies, representatives from industry as well as some from the field of clinical nuclear medicine warn against making dosimetry mandatory for clinical practice or clinical studies. Instead, some opinions were in favour of fixed-activity posology, citing a lack of evidence and high burden for patients and healthcare systems alike. Certainly, the opinions in the field are divided, and an issue frequently mentioned by stakeholders from all groups is the insufficient evidence that individual dosimetry in clinical research and daily practice provides a benefit to patients over fixed-activity posology. Sufficient evidence would show that dosimetry is not merely a tool to fulfil a regulatory purpose but rather a means to provide optimal care for patients. The commentaries differed in the causes and solutions to this issue: A lack of resources, lack of real enforcement of the requirement to implement clinical dosimetry, and limited availability of high-quality evidence as well as a reluctance from pharmaceutical companies to acquire it were mentioned. It was pointed out by stakeholders from all points of view that the availability of such evidence will greatly contribute to the acceptance of a mandate for a form of individual treatment optimisation.

The various comments in the stakeholder feedback do, however, largely focus on the identified base problems rather than on the solutions posed in this project. Within the work on the SIMPLERAD project we have endeavoured to represent a nuanced range of views. Representing the broad range of comments and opinions in the field, as also identified in the evidence-gathering process. We have specifically endeavoured to ensure that this report does not suggest making the use of either individual dosimetry or fixed-activity posology mandatory. Rather we make suggestions on what is necessary and useful to make individual treatment planning of therapeutic nuclear medicine more accessible and generate more evidence on the benefits of individual treatment planning.

In fact, also reflecting the stakeholder comments from all sides that more evidence is necessary, the present report makes important suggestions on what could and should be done to support the collection of high-quality evidence on performing individual treatment planning of radiopharmaceutical therapy to potentially benefit patients, which are more extensively detailed in sections 3.5.3 and 3.5.7.

- Promote specialised treatment and training centres
- Facilitate research by collating dosimetric and response data acquired from centres across Europe in routine clinical care, preferably in a large unified database
- Initiate studies on the impact of individual treatment planning of radiopharmaceutical therapy on relevant patient outcomes.

Certainly, an important issue which can be derived from the various commentaries is that stakeholder acceptance of mandatory dosimetry is not guaranteed in the development of novel radionuclide therapeutics by industry and even less for clinical routine. It is cited in some stakeholder and workshop comments that a mandate for individual dosimetry may lead to limitation of patient access to radionuclide therapy in Europe and that the complexity of dosimetry may deter industry from further considering the EU for development and marketing of such therapies. Another stakeholder opinion is that not realising the mandatory nature of dosimetric optimisation is hindering the acquisition of high-level evidence of the superiority of patient-specific optimisation versus fixed activity administration. From such comments, it appears evident that for any measure, guidance or regulation to succeed, prior stakeholder engagement and consultation is key to eventual success, while clearly presenting the interests of each contributing party to promote transparency in the debate.

In our opinion, this project and its stakeholder involvement have contributed to improving engagement on the issues dealt with in this project. The differences of opinion mentioned in the previous paragraphs as well as in more detail in section 3.4 considerably predated the present SIMPLERAD project and are well known in the field. In fact, these very differences of opinion between various stakeholders in the field motivated the inception of the SIMPLERAD project as part of the wider SAMIRA framework.

Over the course of the present project, the consortium has seen some positive developments with initial steps towards improving communication between various professional groups and stakeholders in the field. This in turn has fostered better understanding of the respective views and concerns on issues pertaining to the BSSD in relation to radionuclide therapy between regulators and other stakeholders. Furthermore, the discussions during the workshop as well as during the stakeholder consultation provided a clear platform for expressing differing views and concerns, thus also increasing stakeholder involvement in the issues. Next to the identification of issues and corresponding remedies, but harder to quantify and measure, this increase in communication and involvement can also be considered a success achieved through the initiation of the SIMPLERAD project.

3.6.3 Outlook

The present project was undertaken to improve the understanding of the links and interdependencies between the European pharmaceutical legislations and Euratom radiation protection requirements and highlight potential barriers to implementation of radiopharmaceutical therapies in clinical practice. The proposed practical guidance and recommendations to advance a coherent implementation of these requirements and inter-linkage with respect to the therapeutic use of radiopharmaceuticals as written in the present document can contribute significantly to the true implementation of individualised molecular radiotherapy in full compliance with the spirit of the BSSD as well as the Pharma Directive and Medical Devices Regulation.

It is imperative that further coordinated action is taken to implement the recommendations in this project. In any implementation, both EU and national competent regulatory authorities will likely be heavily involved. Certainly, 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 here and should be considered with high priority.

Also, although not all remedies may be as easy to realise, most of the measures proposed here are well within the framework of existing subsidy instruments and regulatory frameworks. It is

therefore our distinct conviction as the SIMPLERAD consortium that the measures proposed here shall contribute to implementation of truly individually planned molecular radiotherapy in compliance with all relevant regulatory frameworks.

3.6.4 Conclusion

In the present document, the SIMPLERAD project team has recommended actions to advance the coherent implementation of the European legal requirements with respect to therapeutic nuclear medicine. These actions include regulatory measures and suggestions for improvement to material and staff resources and implementation of the BSSD in addition to stimulation of further efforts to demonstrate the added value of patient-specific optimisation of treatments. Furthermore, suggestions are made for a diverse palette of measures to improve understanding of current regulations, including a proposal for explanatory documents pertaining to the interpretation of article 56.1 of the BSSD in the context of radiopharmaceutical therapy and the interconnection of the BSSD with existing and planned pharma and medical device directives.

4. Summary of Recommended Actions Following the End of the Project

4.1 Highest-Priority Recommendations

Table 3: Measures with the highest priority to be taken in the wider SAMIRA framework

Type of Remedy	Proposed Remedy	Responsible Party	Corresponding Section
Data collection	**Collect evidence through establishment of national and European databases among multiple centres to collect data on clinical factors for approved radiopharmaceuticals associated with molecular radiotherapy, including dosimetry and patient outcome**	**European professional societies supported by EC or national funding**	**3.5.8**
	Collect evidence through initialisation and support of investigator-initiated multi-centre and multinational clinical trials on therapeutic radiopharmaceuticals to develop optimised treatments	**Clinical researchers or networks of excellence supported by EC or national funding**	**3.5.8**
	Collect evidence through establishment of dosimetry expert networks to disseminate know-how for clinical trials with therapeutic radiopharmaceuticals. As an example, image processing and dosimetry may be performed at remote sites with data collected according to specified protocols	EANM, EFOMP	3.5.8
	Collect evidence through mandatory presentation of results and evidence on individual-patient dosimetry within the marketing authorisation application dossier	EMA	3.5.1, 3.5.8
Harmonisation and training	Increase relevant specialist knowledge with national competent authorities through further specialist training, cooperation between stakeholders and harmonised legislation	National competent authorities	3.5.9
Legislation and regulation	Include radiopharmaceuticals in annex VII of the EC's proposal for a revision of directive on Union code relating to medicinal products for human use (2023/0132)	Responsible EC services	3.5.1
	Revise the EU CTIS so that structured radiation safety and dosimetry information must be provided for therapeutic radiopharmaceuticals	**EMA**	**3.5.1**

Reimbursement	**Ensure that clinical dosimetry is explicitly integrated as part of the molecular-radiotherapy clinical process, and therefore integrated in the reimbursement scheme at the national level**	**National authorities**	**3.5.3**

4.2 Needed Mid- and Long-Term Investments

There is a need for significant investment in therapeutic nuclear medicine, in particular with respect to the items shown in bold in table 3. Furthermore, the SIMPLERAD consortium suggests the following more general measures, encapsulating the items mentioned above and partly going beyond them.

- Create and support specialised treatment and training centres, i.e., networks of excellence, with advanced knowledge on quantitative imaging and dosimetry.
- Promote and support accreditation programs for therapeutic nuclear medicine and dosimetry.
- Collate dosimetric and response data from centres across Europe to develop and generate large-scale database studies.
- Initiate studies on the impact of individual treatment planning of radiopharmaceutical therapy on patient outcomes.

The creation of infrastructures and the development of networks of excellence and research projects should be supported by the EC research programme in the health area, in close collaboration between the EC services dealing with the EU pharmaceutical and radiation protection policies.

Most of the measures proposed here are well within the scope of existing funding instruments and regulatory frameworks. We, the SIMPLERAD consortium, therefore strongly believe that the measures will contribute to the implementation of truly personalised radiopharmaceutical therapies in compliance with all relevant regulatory frameworks.

4.3 Additional Recommendations

Table 4: Additional recommendations of the SIMPLERAD project

Type of Remedy	Proposed Remedy	Responsible Party	Corresponding Section
Addressed through SIMPLERAD Project Deliverables and Associated Actions			
Dissemination	Dissemination of the results of the evidence-gathering process of SIMPLERAD through, e.g., public reports, publications in scientific journals, presentations • Presentations in the EU policy symposia during the EANM Congress 2024 and 2025 • Presentations at smaller workshops • Promotion through the EFOMP Special Interest Group for Radionuclide Internal Dosimetry • EFOMP webinars • Presentation during the EFOMP European Congress of Medical Physics 2026 • Publication of survey results in peer-reviewed journals	SIMPLERAD consortium, EANM, EFOMP	3.5.1–3.5.10
Guidance documents	Create an explanatory document for publication by the EC to help users understand the possibilities of treatment adaptation based on regulatory requirements, definitions of individual planning, appropriate verification, etc. This should be done on a radiopharmaceutical base, as clinical endpoint, and therefore methodology, may differ depending on the radiopharmaceutical	SIMPLERAD consortium	3.5.2, 3.5.10
	Remind competent authorities of the BSSD requirement to document the irradiation delivered (treatment verification) even for fixed activity administrations, particularly in the perspective of repeated/multiple cycle treatments	Responsible EC services	3.5.2
	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	Responsible EC services, EMA	3.5.2
	Revise the joint EANM/EFOMP core curriculum for education and training of medical physicists in nuclear medicine	EANM, EFOMP	3.5.3

Guidance documents	Publish the results of the evidence-gathering process of SIMPLERAD through, e.g., public reports, publications in scientific journals, presentations	SIMPLERAD consortium	3.5.10
	Contact relevant professional clinical societies with the accompanying guidance document as drafted in section 3.5.2 to draw attention to this issue, requesting that societies adapt guidelines to conform to BSSD as *lex specialis*	National competent authorities	3.5.7
To Be Addressed in the SAMIRA Framework			
Data collection	Gather further information on the specific criteria and methodologies used by competent authorities to set specific effluent release conditions through a specific EU survey focused on this topic. Based on the results of this survey evaluate the conditions on the discharge of radioactive effluent and the application of exemption and clearance according to the requirements of the BSSD	HERCA	3.5.6
	Develop EU grant programmes to generate more data on protection of the public from radionuclide therapy	Responsible EC services, national competent authorities	3.5.5
Guidance documents	Propose a clinical guideline on the development of therapeutic radiopharmaceuticals in oncology	EMA	3.5.1, 3.5.2
	Establish European guidance documents supported by similar national approved codes of practice by competent authorities based on such data	Responsible EC services, national competent authorities	3.5.6
	Produce an explanatory document ondose constraints for carers and comforters summarising the concepts laid out in the ICRP publication and BSSD with both principles and good-practice examples	Responsible EC services, HERCA	3.5.5
	Generate a guidance document or approved code of practice based on the SIMPLERAD survey results explaining the differentiation between limits and constraints with proposing constraints for the public and comforters and carers for nuclear medicine therapies	National competent authorities, EANM, EFOMP, HERCA	3.5.5
	Produce a specific guidance document on effluent release and waste management related to the use of medical radionuclides	Responsible EC services, national competent authorities	3.5.6
	Translate available European guidance to the national level	National competent authorities	3.5.10

Harmonisation	Form a permanent expert working group on radiopharmaceuticals consisting of experts in medical physics, radiopharmacy, radiochemistry and clinical nuclear medicine to advise on new regulations as they pertain to radiopharmaceuticals	EMA	3.5.1
	Establish a multi-level forum concerning radiopharmaceuticals to promote interactions between regulators working in the fields of pharmaceutical supervision and radiation protection both at the EU and national levels	Responsible EC services, EMA and national competent authorities	3.5.1, 3.5.8
	Establish centres of excellence to mitigate the lack of knowledge and training and shortage of well-trained staff and provide generation and dissemination of reference practice in the field	National competent authorities, EANM, EFOMP	3.5.2, 3.5.3
	Establish accreditation programmes to ensure traceability of clinical dosimetry throughout Europe	Responsible EC services, professional societies	3.5.2, 3.5.3
	Create a regulatory network to foster interaction between radiation-protection and medicines agencies	Responsible EC services, national competent authorities	3.5.2
	Decrease the workload associated with clinical dosimetry by introducing quality assurance and standardisation and produce guidance documents for less well-resourced centres	National competent authorities, professional societies	3.5.4
	Harmonise patient-release criteria and instructions at the decision levels of members of the public, dose constraints and exposure scenarios	HERCA, national competent authorities	3.5.5
	Stimulate interdisciplinary, dedicated meetings aimed at achieving interdisciplinary consensus among experts from various disciplines involved in the field on issues pertaining to individual planning of radionuclide therapy through direct action or grants	EANM, EFOMP, responsible EC services	3.5.7
	Promote collaboration between competent authorities and national societies	National competent authorities	3.5.10
	Consult experts during revision of the new regulatory guidance documents	Responsible EC services, national competent authorities	3.5.10

Legislation and regulation	Clarify the precedence of the BSSD over provisions of revised pharma regulations	Responsible EC services, national competent authorities	3.5.1
	Revise relevant EMA guidance documents to introduce a distinct consideration of diagnostics and therapeutics as well as a differentiated discussion of posology and the required guidance for therapeutic radiopharmaceuticals	EMA	3.5.1
	Consider removal of generic patient instructions concerning radiation protection advice provided by radiopharmaceutical companies in the SmPC where this instruction is not founded on robust data or matches the specific regulatory instruction of a Member State	EMA, national competent authorities	3.5.1, 3.5.5
	Integrate radiation-associated features of radiopharmaceuticals as investigational medicinal product into the data package required for submission in the CTIS	EMA	3.5.1
Training	Align the training of MPEs with the joint EANM/EFOMP core curriculum	National competent authorities	3.5.3
	Develop training in therapeutic nuclear medicine for all professionals involved in the field, with curricula that consider the highly multidisciplinary nature of the field and identification of specialised treatment centres of excellence that have the capability to dispense training, both theoretical and practical, at a national level to allow the training of professionals in their native language.	EANM, EFOMP, other professional societies	3.5.4

5. Conclusions

The main aim of SIMPLERAD was to improve the understanding of the links and interdependencies between the European pharmaceutical legislations and Euratom radiation protection requirements and highlight potential barriers to implementation of radiopharmaceutical therapies in clinical practice. The practical guidance and recommendations to advance a coherent implementation of these requirements and inter-linkage with respect to the therapeutic use of radiopharmaceuticals proposed in the present document can contribute significantly to the implementation of individualised radiopharmaceutical therapy in full compliance with the BSSD as well as the Pharma Directive and Medical Devices Regulation. Further actions include regulatory measures at the European and national levels and suggestions for improvement to material and staff resources and implementation of the BSSD in addition to stimulation of efforts to demonstrate the added value of patient-specific optimisation of treatments. Importantly, suggestions are made for a diverse palette of measures to improve understanding of current regulations, including a proposal for explanatory documents pertaining to the interpretation of article 56.1 of the BSSD in the context of radiopharmaceutical therapy and the interconnection of the BSSD with existing and planned pharma and medical device legislation.

In the future, further coordinated action is imperative to implement the recommendations developed in this project. In any implementation, both the EU and national competent authorities must be heavily involved. The consortium makes suggestions on what is necessary and useful to make individual treatment planning and verification of radiopharmaceutical therapy, as mandated by the BSSD, more accessible. Additional suggestions are intended to support the collection of high-quality evidence on performing individual treatment planning of radiopharmaceutical therapy to potentially benefit patients.

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Annex I: Summary of the Results of the SIMPLERAD Survey

I.1 Survey Overview

The aim of the survey is to provide insight on the practical implementation of the main requirements of the European pharmaceutical legislation and the BSSD concerning therapeutic nuclear medicine. This includes the relevant provisions for individual patient dose planning and dosimetry, involvement of MPEs, release of patients, and management of radioactive effluents and waste. The survey aimed to identify the existing gaps in implementing the above requirements, as well as the main barriers encountered by European stakeholders in the development and use of therapeutic radiopharmaceuticals.

I.2 Main Survey

The specific requirements of the BSSD and pharmaceutical legislation considered in the substantive survey included the following.

- Practical aspects regarding the preparation, use and distribution of therapeutic radiopharmaceuticals
- Requirements needed to achieve marketing authorisation
- Authorisation and conditions for use that may or may not restrict potential personalisation in clinics
- Relevant provisions for individual patient dose planning and dosimetry
- Relevant provisions for dosimetry verification
- Provisions for radiopharmaceutical preparation, distribution and dispensing
- Provision, training and involvement of MPEs
- Selected dose constraints for comforters, carers, volunteers and the public
- Criteria used for the release of patients from hospitals
- Implemented strategies for radioactive waste management

The survey included case studies to investigate the differing applications of the legal frameworks. These included a well-established therapy, ^{131}I for the treatment of benign thyroid disease, and less well-established therapies such as ^{177}Lu-DOTATATE and ^{177}Lu-PSMA. The alpha-emitter ^{223}Ra dichloride was also considered as a part of the study. These therapies were included for their differing posology, stages of marketing authorisation, and levels of patient and public risk regarding radiation protection. A variation regarding the implementation of the legal frameworks was therefore expected for these products.

I.3 Survey Results

I.3.1 Regulatory interpretation

Participants were asked how well they felt the main requirement of the EU pharmaceutical and medicine legislation concerning radiopharmaceuticals had been implemented in their country. Although most responders claim to be familiar with the legislation and think that it is well implemented, it is remarkable that some responses received from participants from the same country were somewhat heterogeneous. To some degree this may be attributed to a partly ambiguous question or different interpretations. However, even for clear questions some degree of heterogeneity was observed. An example of this was a question asking if there are any national pharmaceutical regulations specifically for therapeutic radiopharmaceuticals. Overall only 15% of respondents indicated that there were specific regulations, 63% that there wasn't and 22% of respondents did not know. Whereas in ten countries all respondents stated that there is no specific legislation for therapeutic radiopharmaceuticals, in several countries there was a very heterogeneous response. For example, in Germany, Switzerland and to some extent Belgium, a relatively even split was observed between yes and no responses, indicating that the relevant legislation is either potentially too complicated or insufficiently clear that knowledge of it is

lacking, or that this may differ between regions. A summary of responses from each country are summarised in Figure I.1.

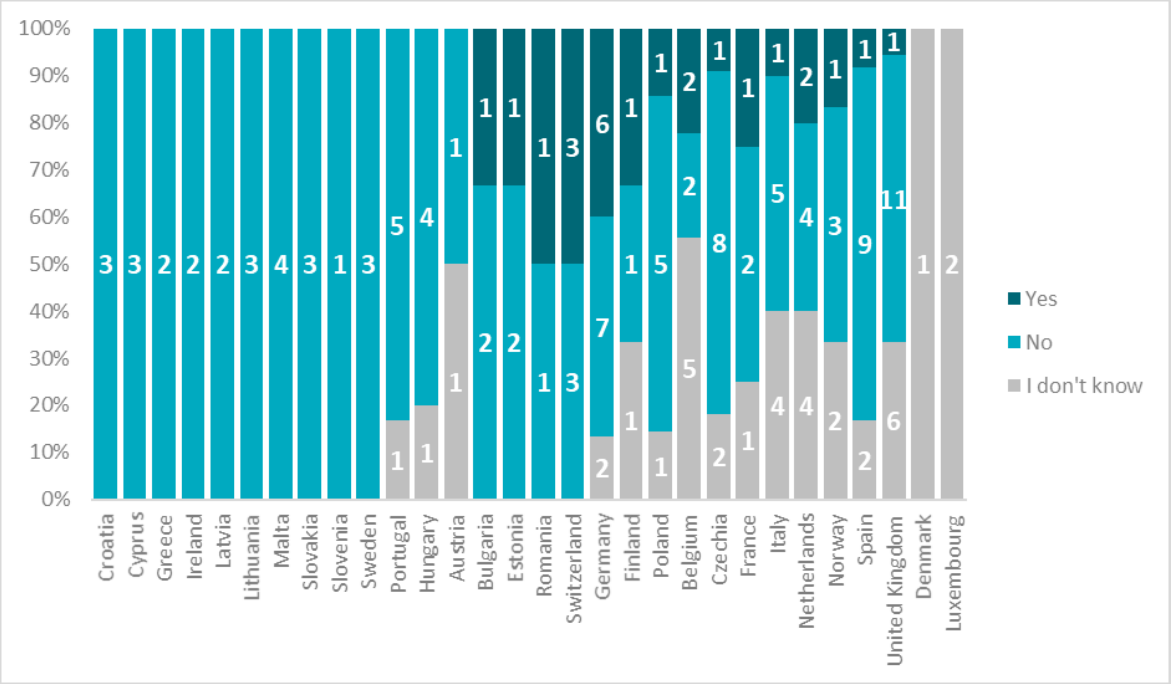


Figure I.1: Responses by survey participants when asked if there were any national pharmaceutical regulations specifically for therapeutic radiopharmaceuticals

This point is further corroborated in the responses received to the follow-up question to those that indicated specific legislation was in place. When asked to provide additional details a couple of responders quoted differences associated with radiation safety regulations. This indicated they did not fully understand the scope of the question. Other examples were very specific concerning differences between diagnostic and therapeutic radiopharmaceuticals. These included different investigational medicinal products and good manufacturing practice requirements, more stringent limits on the accuracy of activity measurements, different licensing requirements and exclusion of in-house production or distribution of radiotherapeutics. Given the responses from the survey, it can be deduced that there are likely no set of pharmaceutical regulations specific to therapeutic radiopharmaceuticals in any EU country. However, some countries have specific pharmaceutical regulations or exemptions for diagnostic radiopharmaceuticals. Examples include Germany, with a specific exemption from marketing authorisation for facilities who prepare a 'low number' of diagnostic radiopharmaceuticals [I.1], and Italy, having certain exemptions from marketing authorisation and manufacturing authorisation for 'experimental radiopharmaceuticals' if they are used in public healthcare establishments on a non-profit basis. This exemption has recently been applied to diagnostic radiopharmaceuticals exclusively.

During the expert interviews it was highlighted by some experts that the lack of specific instruction tailored specifically for radiopharmaceuticals, specifically therapeutics, in national medicine regulations hampers implementation. A regulator from the Swedish Medical Products Agency noted that there is an understandable lack of competence and know-how about radiopharmaceuticals within the national competent authorities for radiotherapeutic applications. Although clinical trials with external-beam radiotherapy have been conducted for decades, these have never been a subject of assessment by the Medical Products Agency since they did not involve systemic drugs.

Another notable result from the survey was the fact that there are some clear and relevant differences between the 27 Member States of the EU concerning preparation, administration and distribution of therapeutic radiopharmaceuticals without a marketing authorisation. Results from the survey indicated it was permissible to prepare and administer therapeutic

radiopharmaceuticals without a marketing authorisation in countries such as Austria, Belgium, Germany and the Netherlands, whilst in other Member States such as Hungary, Poland, and Spain it was not. However, even in this question different responses were received by stakeholders within the same country. Czechia is a typical example, with five respondents indicating it was allowed and four indicating it was not (See Figure I.2).

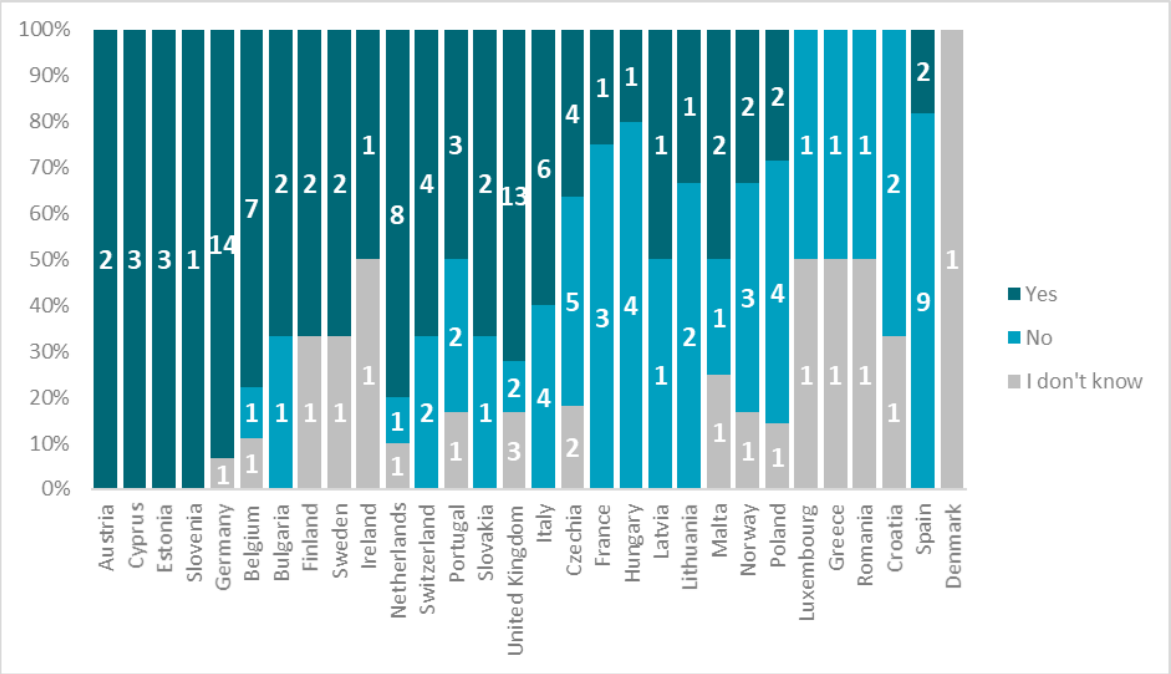


Figure I.2: Responses by survey participants when asked if it is permissible to prepare and administer therapeutic radiopharmaceuticals without marketing authorisation in their country

Contradictory answers were not just received by treating centres, but similar differences were also received by regulators and national societies regarding this point. Figure 10 filters responses received by regulators and professional societies and as can be seen, responses from the same country are still varied, indicating a potential lack of collaborative working between these stakeholders concerning this topic article 3 of Directive 2001/83/EC provides details when pharmaceuticals without marketing authorisation may be prepared and used within a hospital setting. This includes any medicinal product prepared in a pharmacy in accordance with a medical prescription for an individual patient.

In addition Member States may, according to article 5 (1) of Directive 2001/83, exclude medicinal products from the provisions of the Directive, provided they are supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorised healthcare professional and for use by an individual patient under his direct personal responsibility. Consequently, these specialties are medicines that are prescribed on a named-patient basis by a healthcare professional, i.e., the responsible nuclear medicine physician.

Implementation of this directive and the actual situation in each Member State cannot easily be determined without further in-depth review of all national legislation. With such a review, a lack of evidence may not fully guarantee the true position within a Member State. Examining survey responses restricted to those from national regulators indicates one or more aspects of this regulation are applied and in common practice in some Member States. Competent authorities from Belgium, Czechia, Estonia, Germany, Latvia, Lithuania, Slovakia, Slovenia and Sweden responded positively to being able to manufacture and use pharmaceuticals without marketing authorisation. Croatia, Hungary, Luxembourg, Norway and Poland responded in the negative. Lack of responses or knowledge from the competent authority, restricts identification of the situation in other Member States.

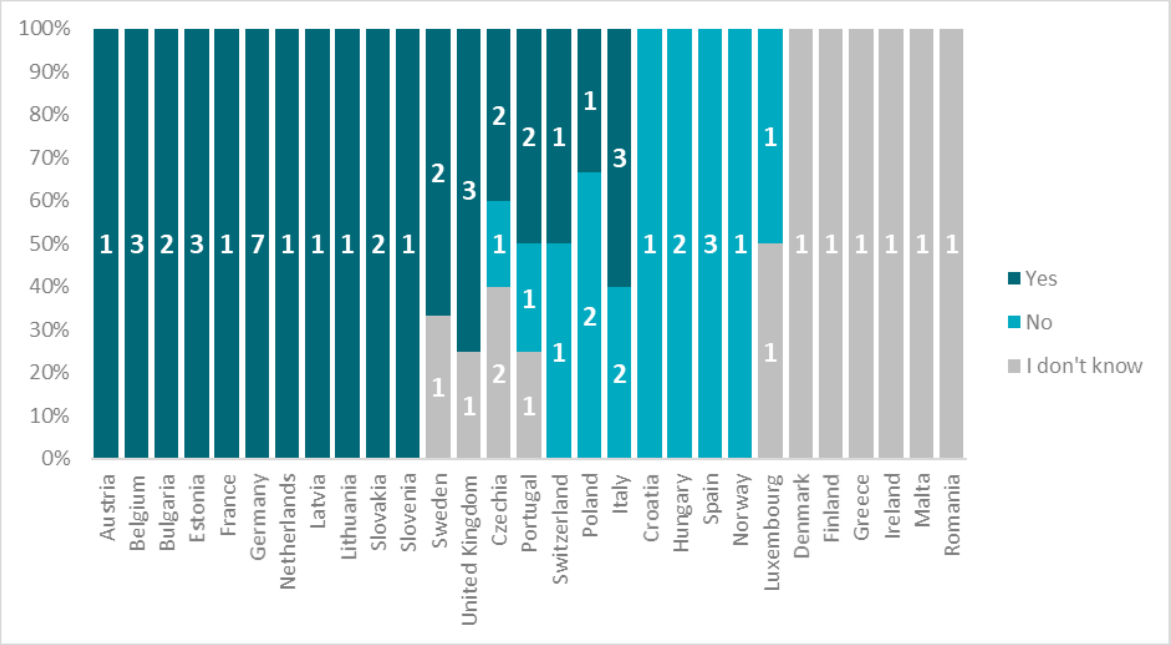


Figure I.3: Responses by national regulators and professional societies when asked if it is permissible to prepare and administer therapeutic radiopharmaceuticals without marketing authorisation in their country

Further evidence of confusion over this topic is demonstrated in the 2015 and 2016 Judgements of the Court of Justice of the EU concerning Article (2)1 of directive 2001/83/EC and the interpretation of how industrial manufacturing or industrial processes should be defined as well as the exact requirements to fulfil the exemption related to the magistral formula in Article 3(1). Concerns are therefore raised that such confusion surrounding this topic could lead to some relevant differences regarding access to innovative medicinal products and patient-centred care within the EU. This is further exacerbated in that even in Member States where it was indicated to be allowed to prepare and administer therapeutic radiopharmaceuticals without a marketing authorisation there is concern that patients do not have access to innovative radiopharmaceuticals. Participants from, e.g., Portugal stated that while basic conditions for preparing and administering are given there are neither healthcare establishments, radiopharmacies and/or any other non-commercial units preparing ^{177}Lu-PSMA for clinical use in-house nor any manufacturers preparing and distributing ^{177}Lu-PSMA for clinical use. In several countries, e.g., Austria, Belgium and Germany, in-house production is the predominant source. Note at the time of the survey ^{177}Lu-PSMA, or Pluvicto, had not received marketing authorisation in the EU. There is insufficient evidence from the survey to indicate why the difference exists across Member States. However, factors such as lack of competence or desire for clinical development and economic and societal factors cannot be eliminated.

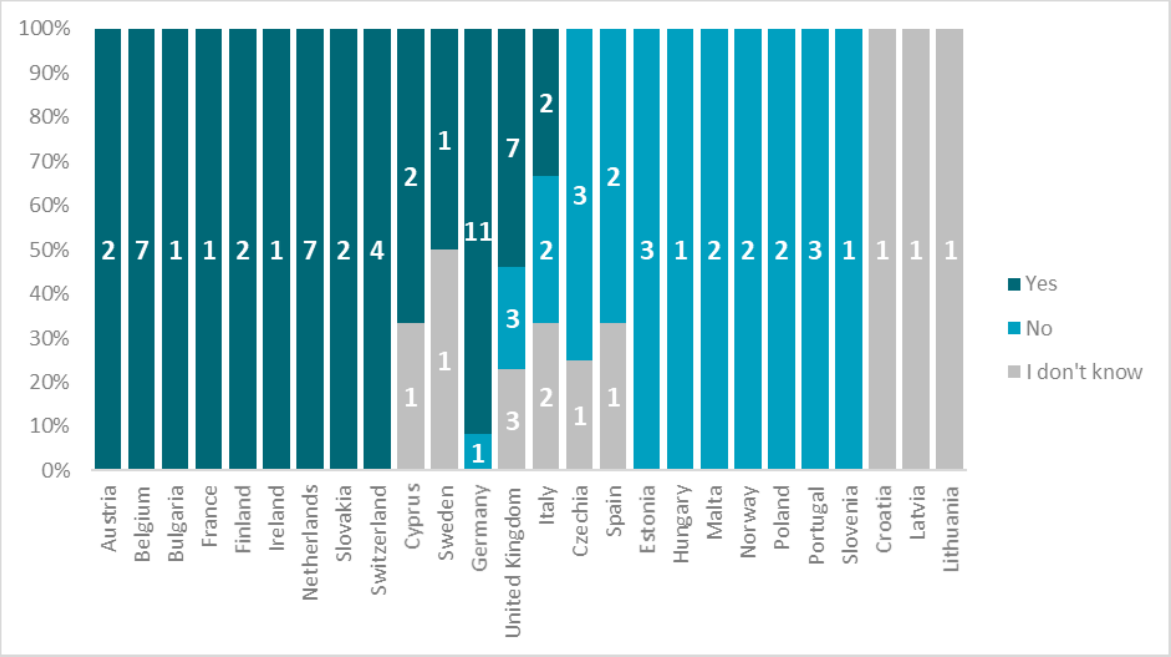


Figure I.4: Responses by survey participants when asked if there are any non-commercial units preparing ^{177}Lu-PSMA for clinical use in house

The topic of posology and instructions provided in packet insert was raised during the expert interviews which identified a clear trend in favour of treatment flexibility. Many interviewees stressed that such flexibility should be based on solid individual dosimetry, and several remarks indicated that this should be performed (only) with the necessary experience and personnel resources, particularly MPE involvement. Examining the different expert backgrounds, flexibility was overwhelmingly favoured by the MPE and physician groups. Radiopharmacy experts and regulators agree with flexibility but point out the need to base this on solid scientific data. Radiation safety regulators indicated a clear favour for flexibility, with pharmaceutical regulators showing more reluctance. Most concerns were raised by experts from industry pointing out that more regulatory guidance is first needed. Two interviewees indicated that the summary of product characteristics for metaiodobenzylguanidine already allows two approaches for posology, fixed and flexible, which could be considered as a model for other radiotherapeutic agents.

From the interviews it also became apparent that there were differing opinions on the legal obligations to follow the posology provided for marketing authorisation. One expert indicated that in their country the prescribing medic had complete flexibility in the activity prescribed, whilst another indicated a legal requirement to strictly follow the posology as given in the summary of product characteristics.

This was further demonstrated during the substantive survey which showed differences of opinion whether administration of authorised therapeutic radionuclides outside of the posology indicated on the package insert was allowed. While this seems to be possible in countries such as Germany, Netherlands, Spain and some outside of the EU, for example the UK, a substantial number of participants from other countries, particularly in Eastern Europe, answered rather in the negative. For some countries different responses were received. A good example of this is Italy, with 4 out of 9 of respondents indicating it was not allowed and 5 out of 9 that it was. This indicated either regional differences in a country or a general lack of clarity over exactly what is or is not allowed.

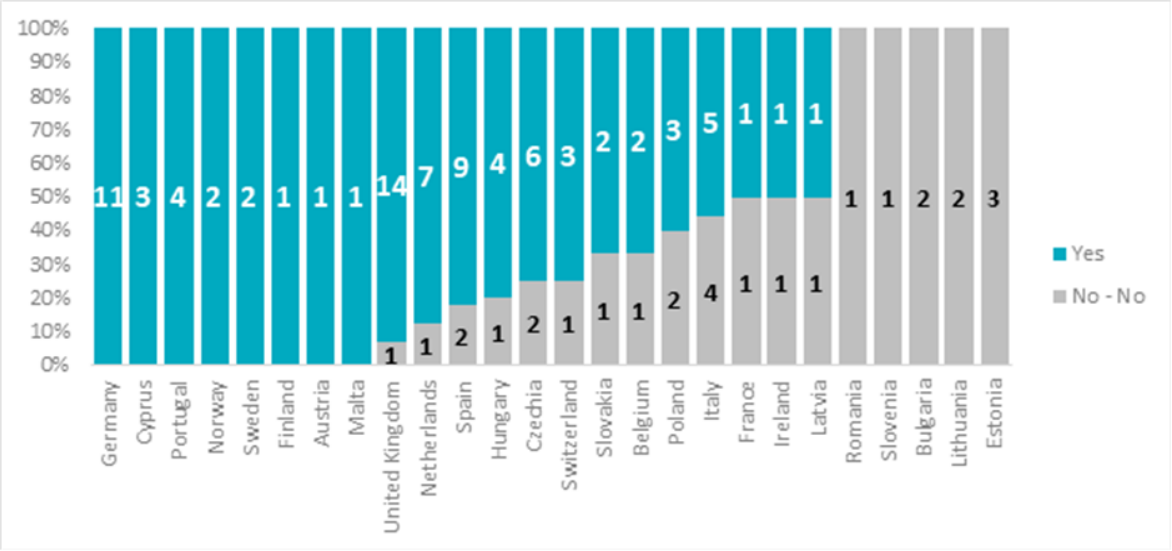


Figure I.5: Responses by survey participants when asked whether in their country administration of authorised therapeutic radionuclides outside of the posology indicated on the package insert is allowed

Taking responses from the competent authorities as a true reflection of what is the actual situation in that Member State, flexibility beyond the posology of the package insert is deemed allowable in Czechia, Germany, Hungry, Ireland, Latvia, Norway, Slovakia, Spain, Sweden and the UK. Belgium, Estonia and Slovenia responded negatively. Conflicting answers were received between the radiation protection and medicine regulators in Italy and Poland.

I.3.2 Requirements for compliance

Notwithstanding that there seems to be differences in access to innovative radiopharmaceuticals, the survey demonstrated that in nearly all Member States standards for compliance, i.e., good manufacturing practices, are in place and should be followed when preparing therapeutic radiopharmaceuticals. Moreover, healthcare establishments, radiopharmacies and any other units where preparation of therapeutic radiopharmaceuticals is carried out and where therapeutic radiopharmaceuticals are administered are subject to supervision by a competent authority all over the EU. In the vast majority of countries responses to the survey indicated supervision is carried out by both radiation safety and pharmaceutical authorities.

Concern was raised by a couple of the experts during the interviews that some aspects of the legislation were hampering development. These concerns were raised for both the radiation and medicines regulators, with one expert expressing frustration in the delays caused to initiate a service due to the regulatory necessities required to undertake therapy procedures. Another expressed frustration that they were hampered in the range of novel therapies that could be delivered due to the need for in-house good manufacturing practice compliance.

Further questions in the survey trying to delve further into the regulatory compliance for non-commercial production and use of therapeutic radiopharmaceutical on a first sight gave a more homogeneous picture. The majority of responses indicated that the use of ^{177}Lu-PSMA outside clinical trials is possible (67 yes, 14 no), based on approval of a competent authority (76 yes, 10 no). The question whether a therapeutic radiopharmaceutical can be prepared locally outside marketing authorisation even when a marketing authorisation in another country exists, was agreed by most responders (72 yes, 45 no) whereas a majority denied the question if preparations can be made using non-authorised starting materials (79 no, 28 yes). In particular the last answers were somehow contradictory, also no clear trend when looking at the answers from the different involved professionals could be extracted from these data. Overall, this outcome underlines the difference in understanding and interpretation of existing legislation, when it comes to the legal requirements for preparation of therapeutic radiopharmaceuticals.

I.3.3 Discussion summary

Overall, considering all responses in relation to pharmaceutical regulations a fairly heterogeneous overview across the EU was observed as also highlighted during the expert interviews. Some aspects seem to be clearly regulated and mutually understood. Responders indicated a good oversight from regulatory bodies for therapeutic radiopharmaceuticals and the establishment of good practices for their preparation. Conversely other answers indicated a much more heterogeneous picture. This, in particular, was becoming evident by national differences in the responses, indicating more of a difference in national interpretation and implementation of pharmaceutical regulations, especially with respect to the preparation and use of therapeutic radiopharmaceuticals without marketing authorisation, such variation could contribute to a heterogeneous practice of supply to patients. Conversely, some responses were heterogeneous without any clear national trend, e.g., on the question on posology requirements or specific legislation on therapeutic radiopharmaceuticals, indicating different views and different levels of understanding of the regulations and guidance available in Member States. The overall complexity of the regulatory framework for medicines in general with its regulations both on EU and national levels certainly is felt in the field of therapeutic radiopharmaceuticals, adding to uncertainties and variable opinions of stakeholders and different practices in the clinical application of therapeutic radiopharmaceuticals.

I.4 BSSD Legislation

Fifty questions within the survey were dedicated to the BSSD, specifically those concerning treatment optimisation and verification, dose constraints, management of radioactive waste and provision of the MPE.

I.4.1 Treatment optimisation and verification

Questions surrounding treatment optimisation and verification were concerned with the interpretation and requirements surrounding paragraph 1 of article 56 of the BSSD, namely:

> For all medical exposure of patients for radiotherapeutic purposes, exposures of target volumes shall be individually planned and their delivery appropriately verified taking into account that doses to non-target volumes and tissues shall be as low as reasonably achievable and consistent with the intended radiotherapeutic purpose of the exposure.

Paragraph 81 of Article 4 of the BSSD also specifies this, relating to nuclear medicine: "*'Radiotherapeutic' means pertaining to radiotherapy, including nuclear medicine for therapeutic purposes*."

Aspects of this article were considered into two parts, the requirement that "*Target volumes shall be individually planned*" and secondly that "*Their delivery is appropriately verified*."

Transposition and interpretation of national regulations

Participants were initially asked how well they felt the aspects of this statement were transposed into national legislation. The majority of respondents were content in how it had been transposed nationally. Six respondents, representing regulators and national societies in Bulgaria, Estonia, Italy, Spain, Sweden and Switzerland indicated such a statement was not present in their national legislation. In contradiction, translation of the respective legislation gathered during the pre-survey indicated that in some cases similar statements were present. For example in the Swiss Ordonnance sur la Radioprotection 814.501, Section 3 Optimization in Medicine, Art. 32 Optimization of Medical Exposures states:

> During all therapeutic exposures, he (the Doctor) must establish an individualised dosimetric plan. The doses applied to the organs at risk must be kept as low as possible, taking into account, however, the intended radiotherapeutic aim.

It is likely that in some cases when answering this question, some aspects of the national regulations were not considered applicable to radiotherapeutic administration of unsealed sources.

Regulatory interpretation

For the majority of cases such responses were a minority and when asked what was meant by "*exposures…individually planned*" and "*Their delivery is appropriately verified*," the highest rated response from all stakeholder groups was that it called for the planning of an administered activity based on an individual absorbed dose assessment (See Figure I.6). A significant proportion of responses were also received for other categories, with many respondants giving more than one answer indicating the statement also included, ensuring suitability of treatment based on imaging and other clinical factors.

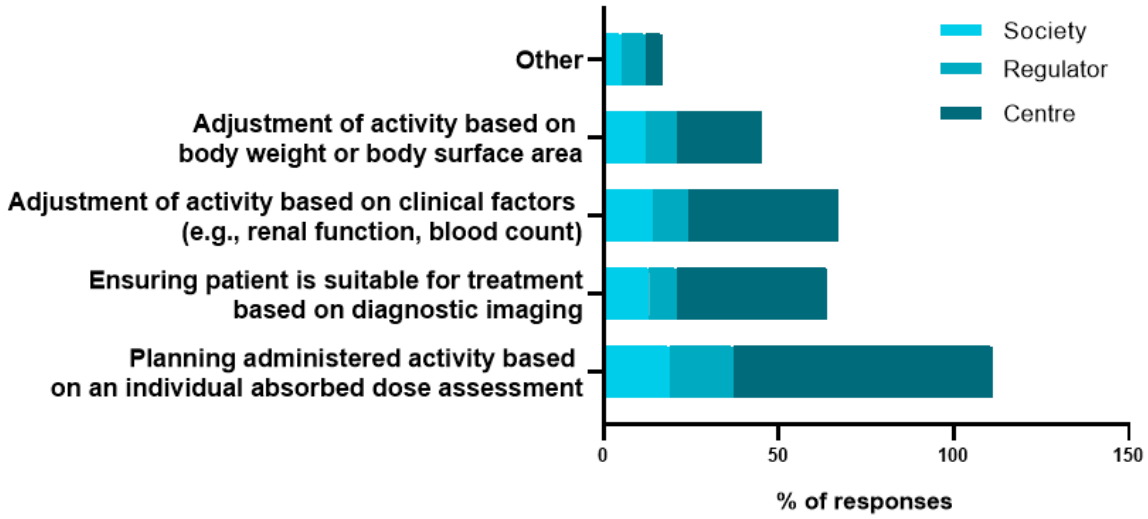


Figure I.6: Responses by survey participants when asked what they felt was meant by "exposures of target volumes shall be individually planned"

A similar but somewhat broader trend was observed concerning treatment verification. A significant proportion of respondents from all stakeholder groups agreed the BSSD statement concerning verification meant an individual dosimetry assessment. However, ensuring the prescribed activity had been administered and quantitative imaging were scored equally as high.

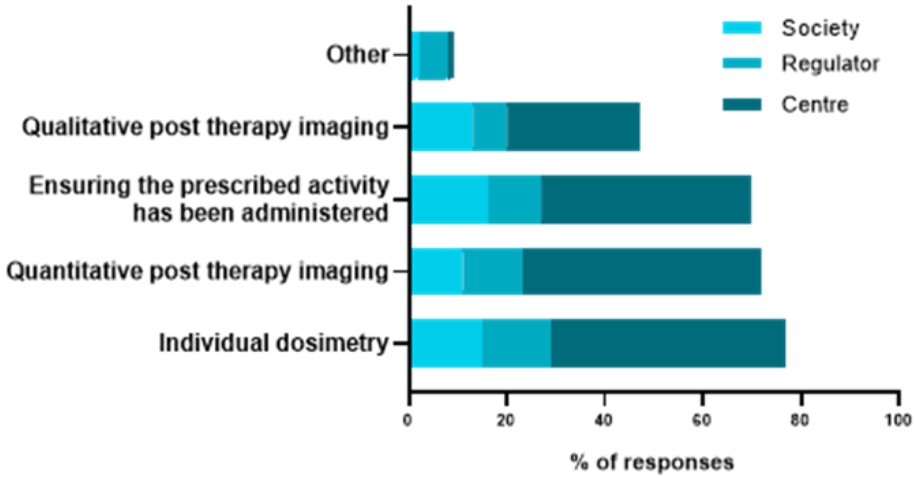


Figure I.7: Responses by survey participants when asked what they felt was meant by "delivery is appropriately verified"

For the specific treatment case studies outlined in section I.2, questions sought to further identify in situations where national recommendations did exist, what those were, what was commonly being practised and what the respondent ideally thought should be required. These questions

were asked for both the planning and verification aspects of the therapies. The therapy where dosimetry was identified as being most readily recommended and carried out was ^{131}I for benign thyroid disorders as summarised below. Respondents were given a choice of options labelled A–F in the figure and summarised below. It is clear that the current practice reflects the recommended practice except for the individual dose assessment, for which even more respondents think it should ideally be required.

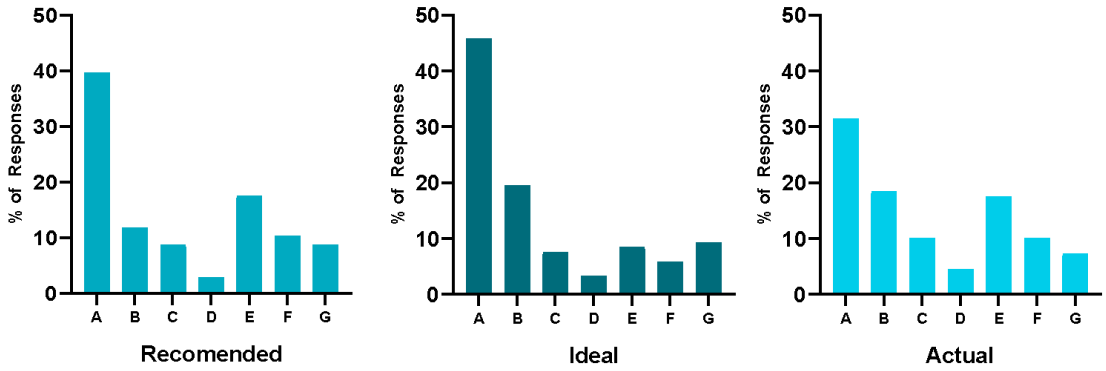


Figure I.8: Responses by survey participants when asked for cases where guidance did exist, what does guidance recommend (left), what do you think should be done (middle) and what do you do (right) for treatment planning of [^{131}I]NaI for benign thyroid disorders

A = Planning administered activity based on an individual absorbed dose assessment
B = Ensuring patient is suitable for treatment based on diagnostic imaging
C = Adjustment of activity based on clinical factors (e.g., renal function, blood count)
D = Adjustment of activity based on body weight or body surface area
E = Fixed activity based on posology
F = Other (please specify)
G = I don't know

Conversely for ^{177}Lu treatments the majority of responses from individual countries pointed to recommendations that did not include dosimetry, with administrations based rather on a fixed activity prescription whilst ensuring the patient is suitable for treatment using diagnostic imaging (See Figure I.9). Current practice seems to reflect these recommendations although there was a strong desire across the community to utilise dosimetric treatment planning.

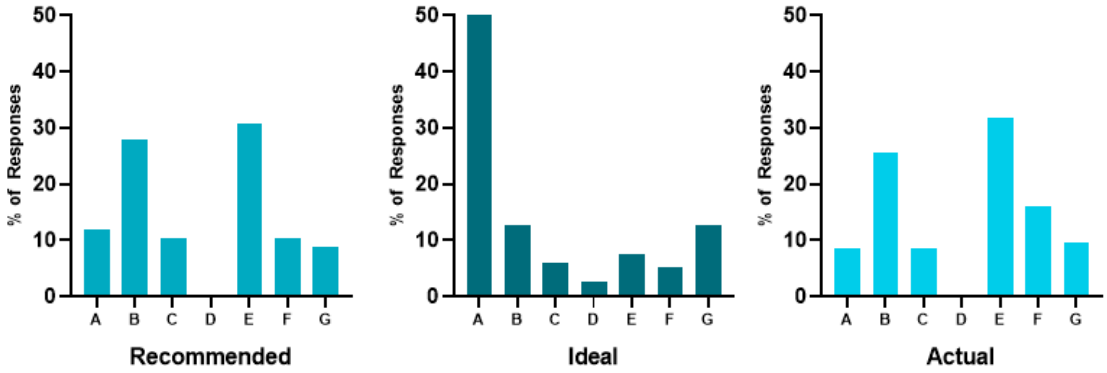


Figure I.9: Responses by survey participants when asked for cases where guidance did exist, what does guidance recommend (left), what do you think should be done (middle) and what is your current practice (right) for treatment planning of ^{177}Lu-DOTATATE for neuroendocrine tumours

A = Planning administered activity based on an individual absorbed dose assessment
B = Ensuring patient is suitable for treatment based on diagnostic imaging
C = Adjustment of activity based on clinical factors (e.g., renal function, blood count)
D = Adjustment of activity based on body weight or body surface area
E = Fixed activity based on posology
F = Other (please specify)

G = I don't know

When asked the same questions for ^{177}Lu-PSMA there was no difference observed to that obtained for ^{177}Lu-DOTATATE, indicating the fact that one product had received marking authorisation at the time of the survey did not affect national practise. Results for [^{223}Ra]$RaCl_2$ for bone palliation of metastatic prostate cancer were markedly different from the other three therapies studied. The distribution of practice reflected national recommendations, with the majority of respondents indicating therapy was planned with an adjustment of activity based on body weight or body surface area. When asked what they believed should be performed, responses were more heterogeneous, likely due to the lack of guidance and perceived difficulty in dosimetric planning for alpha therapy.

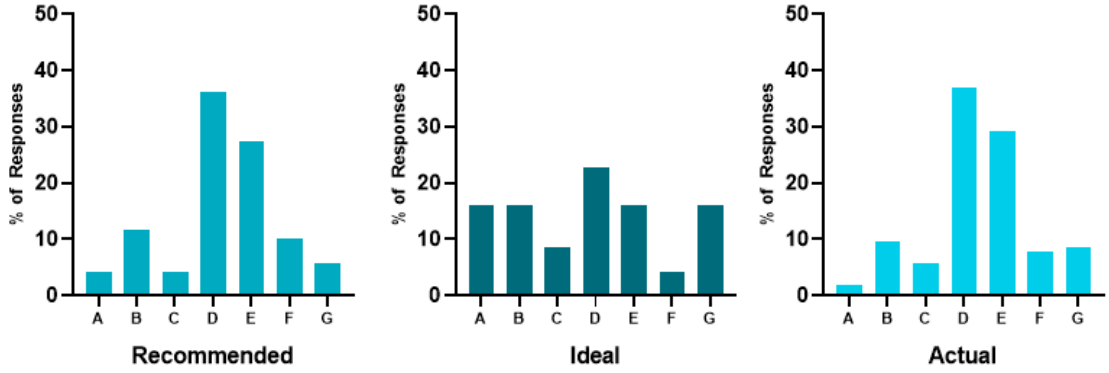


Figure I.10: Responses by survey participants when asked for cases where guidance did exist, what does guidance recommend (left), what do you think should be done (middle) and what is your current practice (right) for treatment planning of [^{223}Ra]$RaCl_2$ for bone palliation of metastatic prostate cancer

A = Planning administered activity based on an individual absorbed dose assessment
B = Ensuring patient is suitable for treatment based on diagnostic imaging
C = Adjustment of activity based on clinical factors (e.g., renal function, blood count)
D = Adjustment of activity based on body weight or body surface area
E = Fixed activity based on posology
F = Other (please specify)
G = I don't know

Barriers

Results from the survey indicated an evident desire to implement dosimetry planning and verification, although this was rarely carried out or stipulated within any national recommendations. Respondents were then asked to score what they felt was hampering the implementation. A number of potential factors detailed below were suggested in the survey question and participants asked to score from 0–5, with 5 being the most influential. The average scores for each choice, with error bars representing the standard deviation, are shown in Figure I.11 for treatment planning and 25 for treatment verification. Responses were fairly consistent between the different stakeholder groups with funding and resourcing scoring the highest of the options presented. The lack of legislative requirement, scientific evidence and patient burden were among the lowest scored factors. Treating centres indicated the possible clinical risk of treating outside the standard posology as a factor of limited importance, indicating they would feel comfortable to do so from a clinical risk perspective.

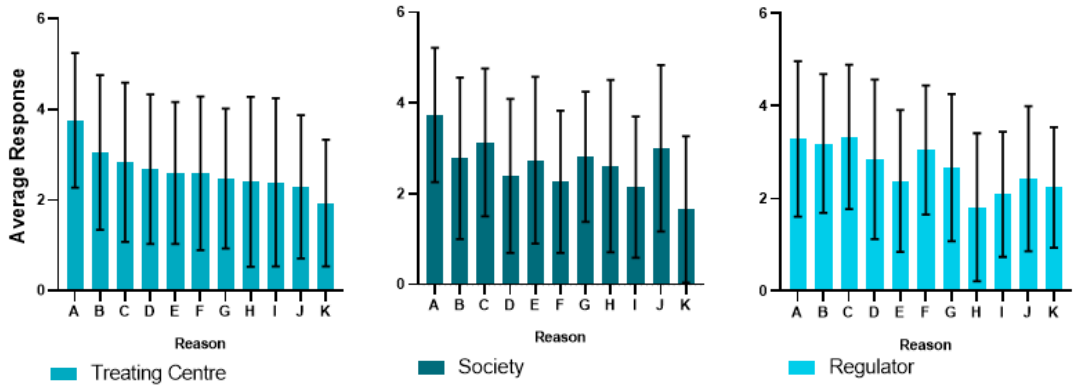


Figure I.11: Responses by survey participants when asked how strongly the specific factors limit the implementation of individual treatment planning. Score 0 (not at all) to 5 (extremely strongly)

A = Shortage of funding/reimbursement
B = Shortage of medical physicists working in nuclear medicine
C = Limited access to dedicated software
D = Lack of knowledge and know-how in performing individual treatment planning
E = Requirement to follow the posology
F = Limited access to scanners or other equipment needed
G = Shortage of other staff
H = No legislative requirement
I = Unnecessary burden to the patient
J = No scientific evidence for added value of dose planning
K = There is a clinical risk in prescribing outside the standard posology

The 2016 EANM Internal Dosimetry Task Force Survey [I.1] also touched briefly on barriers for therapy planning. Here lack of information on the tolerance levels of normal organs was raised as an obstacle for clinical implementation, others argued that prospective, randomised trials for examining the clinical value of dosimetry are needed before implementation. Others pointed at needs for resources and equipment, methodological guidance, and standardisation of dosimetry methods.

During the expert interviews the majority of interviewees agreed that the key resource required for treatment was the availability of sufficient staff to perform the therapy, dosimetry and patient care during hospitalisation. Staffing levels were felt to be below what is currently required, which would only worsen as future demand increases. Besides general availability of staff, a major point of attention raised in the interviews was the training and education of these staff groups. Other hospital resources that were indicated for attention were the availability of equipment such as SPECT–CT and PET–CT systems and appropriate in-patient facilities and waste management protocols.

For most interviewees working in treating centres the general feedback was that dosimetry can support treatment optimisation in therapeutic nuclear medicine and is essential for personalised medicine. However, it was also discussed that there is a need for better understanding of therapy mechanisms and dose-effect relations and therefore dosimetry should play a stronger role in clinical trials and should be further developed and implemented. Most regulators supported the concept of dosimetry for treatment optimization but also stressed that there is a need for better understanding of corresponding dose-effect relations. Industry feedback was more dispersed, with some interviewees stressing that they are in favour of dosimetry and think it is essential for treatment optimization, while others feel dosimetry is overrated and it should be better understood before it can prove its added value in therapeutic nuclear medicine. A pertinent point also raised during the interviews was that the role of dosimetry in therapeutic nuclear medicine should depend on the risk/cost/benefit for the patient and might be different for various therapies.

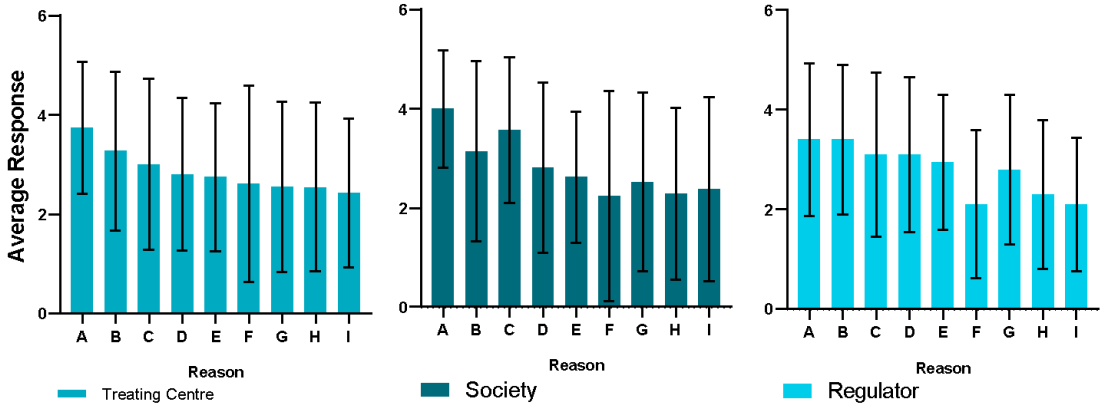


Figure I.12: Responses by survey participants when asked how strongly the specific factors limit the implementation of individual treatment verification. Score 0 (not at all) to 5 (extremely strongly)

A = Shortage of funding/reimbursement
B = Shortage of medical physicists working in nuclear medicine
C = Limited access to dedicated software
D = Limited access to scanner or other equipment needed
E = Shortage of other staff
F = No legislative requirement
G = Lack of knowledge and know-how
H = No evidence of clinical benefit of treatment verification
I = Unnecessary burden for the patient

I.4.2 Dose constraints

Dose constraints pertinent to radionuclide therapy are raised in article 6 and 56 of the BSSD. Specifically:

Article 6 1. Member States shall ensure that, where appropriate, dose constraints are established for the purpose of prospective optimisation of protection

(b) for public exposure, the dose constraint shall be set for the individual dose that members of the public receive from the planned operation of a specified radiation source. The competent authority shall ensure that the constraints are consistent with the dose limit for the sum of doses to the same individual from all authorised practices.

2. Dose constraints shall be established in terms of individual effective or equivalent doses over a defined appropriate time period.

Article 56 3. Member States shall ensure that for each medical or biomedical research project involving medical exposure:

(c) a dose constraint is established for individuals for whom no direct medical benefit is expected from exposure;

5. Member States shall ensure that: (a) dose constraints are established for the exposure of carers and comforters, where appropriate

Respondents were asked about their familiarity with this requirement, for which 75% of respondents indicated that they are either reasonably or completely familiar with the terminology of dose constraints for the public and for comforters and carers.The survey sought to identify where national dose constraints were established, and in 70% of cases respondents indicated they were established for both the public and comforters and carers (See Figure I.13).

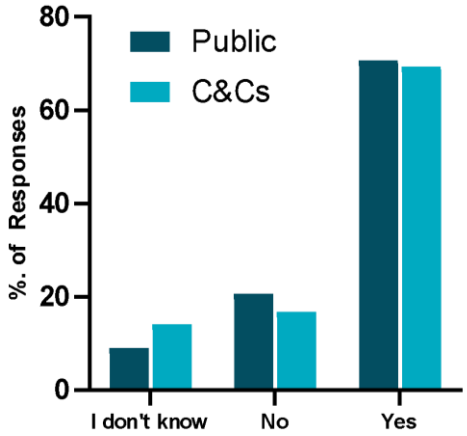


Figure I.13: Responses by survey participants when asked if there were dose constraints for members of the public and comforters and carers established in their country

However, when asked to provide further information regarding these constraints the responses received were considerably more heterogeneous. A numerical effective dose value was not always provided by respondents. The diversity of types of answer can be grouped into the following categories.

- Numerical effective dose value of the dose constraint
- Numerical effective dose value of the public dose limit
- Decision of practitioner
- Release criterion or dose rate
- Reference to national regulations

The answers indicate that perhaps a lower number of respondents are truly versed with the concept and implementation of a dose constraint. This was particularly apparent in the case of the dose constraint of the public, for which 20% of the respondents tended to confuse the concept with a specific release criterion.

More respondents were able to provide dose constraints for comforters and carers compared to that for public exposure. In five countries consistent, age-related, effective dose constraints were provided. Consistent, non-age specific values were reported in a further six countries. In some cases respondents provided dose constraints for household members and persons under the age of 18. This raised questions concerning the definition of comforter and carer and translation and implementation differences across the EU. Data from the survey indicated that in some countries the term 'carer and comforter' is well defined, as individuals knowingly and willingly incurring an exposure to ionising radiation by helping in the support and comfort of individuals undergoing or having undergone a medical exposure, such as a therapeutic nuclear medicine. In some countries it appears this is also taken to include any household member of the individual being treated, which could well include children. The consequence of this is people in some countries may receive doses above what would ordinarily be the dose limit in another Member State. Examples of the use of dose constraints in some European countries can be found in the table below.

Evidence supports the need for further clarification and harmonisation concerning dose constraints and the definition of carer and comforters. When asked if participants felt it was appropriate to establish unified dose constraints the majority of respondents agreed it was with an even split between those feeling it should be provided at the national level to those thinking it should be provided at the European level.

Table I.1: Examples of the use of dose constraints in some European countries

Country	General Public	Comforters/Carers
Germany	No specific constraint	No specific constraint
Norway [I.3]	0.25 mSv per treatment cycle	Children <18 y: 1 mSv per treatment cycle Adults >18 y and <60 y: 3 mSv per treatment cycle Adults >60 y: 15 mSv per treatment cycle
Spain [I.4]	0.3 mSv/y	Pregnant women: 1 mSv/y Children <2 y: 1 mSv/y Children between 3 and 10 y: 1 mSv per treatment cycle Children >10 y and adults: 3 mSv per treatment cycle Adults >60 y: 15 mSv per treatment cycle
UK [I.5]	0.3 mSv per procedure	5 mSv per procedure
Italy (Lombardy)	0.3 mSv per treatment cycle	<60y: 3 mSv per treatment cycle >60y: 15 mSv per treatment cycle
Belgium [I.6]	No specific constraint	No specific constraints
Netherlands	1 mSv/y [I.7]	Children <10 y: 1 mSv per treatment cycle Children >10 y and adults: 3 mSv per treatment cycle Adults >60 y: 15 mSv per treatment cycle [I.8]
Sweden	0.1 mSv per treatment cycle	Children <18 y: 1 mSv per treatment cycle Adults >18 y and <70 y: 3 mSv per treatment cycle Adults >70 y: 15 mSv per treatment cycle

I.4.3 Patient release and instructions

Strongly related to the topic of dose constraints is the need for adequate release criteria of patients from hospital and the provision of instructions to the patients to ensure exposure to other people conforms with the ALARA principle.

> Article 56(6): Member States shall ensure that in the case of a patient undergoing treatment or diagnosis with radionuclides, the practitioner or the undertaking, as specified by Member States, provides the patient or their representative with information on the risks of ionising radiation and appropriate instructions with a view to restricting doses to persons in contact with the patient as far as reasonably achievable. For therapeutic procedures these shall be written instructions. These instructions shall be handed out before leaving the hospital or clinic or a similar institution.

These instructions and the criteria for release should ideally be based upon the dose constraints within which the department is working. Survey results showed that at least for some treatments guidance on either instructions or release criteria is provided by regulatory bodies or national professional societies (See Figure I.14). It can be seen that responses from the same country were sometimes conflicting, which could indicate a lack of communication or awareness concerning specific guidelines.

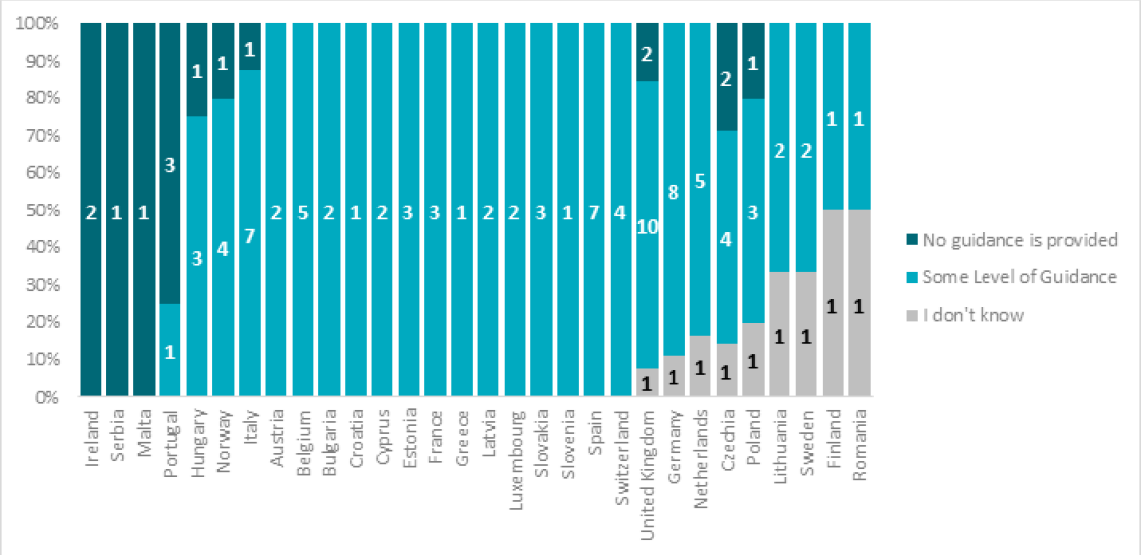
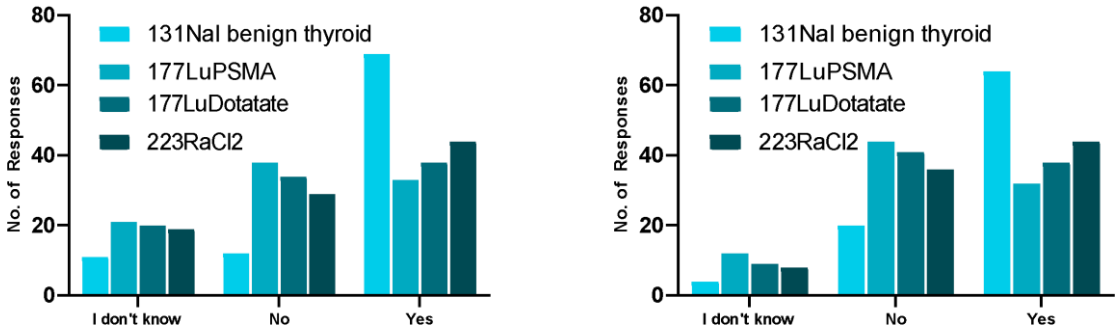


Figure I.14: Responses by survey participants when asked how much guidance is provided in their country by regulatory bodies or national professional societies concerning the information and instructions given to patients after treatment with radionuclides

When asked to comment on the level of guidance provided for specific treatments, it was evident that more is available for the established therapy using ^{131}I for benign thyroid disorders and less guidance available for the newer therapies such as for ^{177}Lu therapies.



Instructions Criteria for release

Figure I.15: Responses from participants when asked if guidance was provided concerning instructions provided to patients and criteria for release from hospital

Current practice

After the main survey was conducted, willing centres were recontacted and asked to provide further details concerning the information they provide to patients and the release criteria they use. Data from 11 centres in nine countries were analysed, each of which performed at least one of the individual treatments of interest. Most centres provided patient instructions tailored for the different treatments, and a few also personalised instructions for the individual patients depending on the treatment biodistribution. For release criteria, one centre mentioned that they have a general dose rate limit of 30 uSv/h at 1 m distance for patient release. Most centres reported specific criteria for different treatments. However, a more general threshold may be underlying these criteria which varied according to time post administration, activity retention, percentage excreted or external dose rate. Examples of release criteria in some European countries can be found in the following table.

Table I.2: Examples of release criteria in some European countries

Country	Benign ^{131}I Therapy 500 Mbq	^{177}Lu-DOTATATE	^{177}Lu-PSMA	^{223}Ra
Germany [I.9]	48 h and (<3.5 µSv/h @ 2 m or A <250 MBq)	48h	48h	None
Norway	<20 µSv/h @1 m	None	None	None
Spain	A<800 MBq	<20 µSv/h @ 1 m	<20 µSv/h @ 1 m	None
UK	None	24 h	<25 uSv/h @ 1 m	None
Italy (Lombardy)	<30 µSv/h @1 m	<30 µSv/h @1 m	<30 µSv/h @ 1 m	None
Belgium	<20 µSv/h @1 m [I.10]	24 h and <20 µSv/h @1 m [1.11]	24 h and <20 µSv/h @1 m	None
Netherlands [I.12]	<20 µSv/h @1 m	<20 µSv/h @1 m	6 h	None

Release criteria and instructions [^{131}I]NaI

Out-patient basis was the most common, but a dose rate limit, e.g., 25 µSv/h @1 m, or an allowed amount of activity left in the patient, e.g., 200 or 400 MBq, were also used by some centres. This may in practice be the same, if centres without a limit have experienced never to exceed such a dose rate threshold.

Patient instructions typically indicated to avoid close contact with others for prolonged periods after administration. However, the level of detail, e.g., distance, duration and differentiation according to the amount of activity given, varied between centres. A few centres provide personalised instructions, depending on the individual biodistribution for the patients. Also, the strictness varied. For example, some stated that the patient couldn't stay in the same room with children or pregnant women for 1–2 weeks, and others only that they should not sleep in the same bed for the first week. Also, only some instructions recommended to avoid sharing cutlery and toothbrushes due to excretion through saliva.

Release criteria and instructions ^{177}Lu-DOTATATE

Release criteria varied between centres, and was either based on a dose rate limit, such as 20 µSv/h or 25µSv/h @1 m, or isolation for a defined period of time. The isolation time varied between centres from anything from 6 to up to 48 hours after administration. Some centres also indicated treatment delivered on an out-patient basis. Instructions provided to patients were typically to avoid close contact with others for prolonged periods after administration. Most but not all centres had recommendations concerning personal hygiene due to urine excretion. The instructions regarding distance and duration of contact varied significantly between centres. However, this could also be related to differences in release criteria. As for [^{131}I]NaI, a few centres provide personalised instructions, depending on the individual biodistribution, and this could result in a range of recommendations; e.g. sleeping in the same bed as a partner to be avoided for 2–3 weeks or allowable after returning home.

Release criteria and instructions ^{177}Lu-PSMA

Release criteria varied between centres, and was based on a dose rate limit, such as 20 µSv/h @1 m, or isolation for a defined period of time, e.g., 24 hours after administration. The instructions provided resembled the instructions for ^{177}Lu-DOTATATE, and were typically to avoid prolonged contact with others, as well as recommendations on personal hygiene.

Release criteria and instructions [^{223}Ra]$RaCL_2$

All responding centres performed this treatment on an out-patient basis. Instructions were typically based on the package insert and regarded handling bodily fluids with care, such as to wash clothes, bed linen and towels stained with urine, blood or faeces separately or to sit on the toilet and flush twice. However, many of the recommendations that were reproduced in the instructions varied between centres. One centre indicated they did not provide any instructions for this therapy.

1.4.4 Waste and effluent

Article 29(4) of the BSSD states that:

> Where applicable, national legislation or a licence shall include conditions on the discharge of radioactive effluent, in accordance with the requirements laid down in Chapter VIII for the authorisation of the release of radioactive effluent into the environment.

A vast majority (>90%) of the respondents indicate that there are at least for some treatments conditions or guidelines provided by regulatory bodies concerning the clearance and storage of solid waste and the effluent release from patients. This means that specific conditions are well-established in most countries, as was also demonstrated in a recent survey of HERCA [I.13].

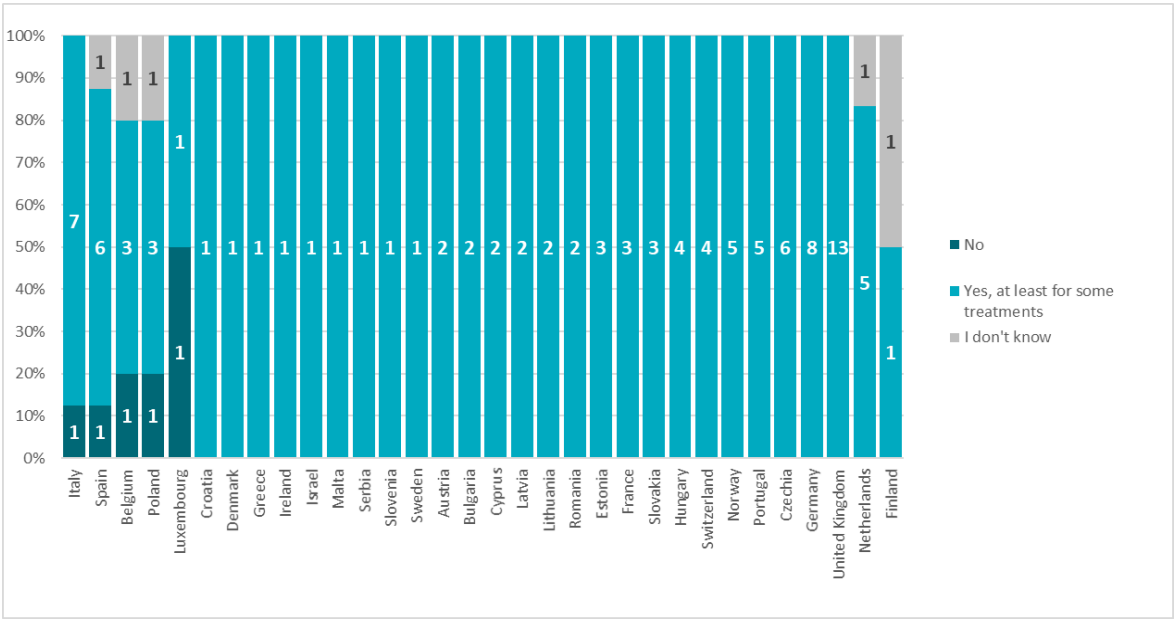


Figure I.16: Presence of specific conditions/guidelines provided for the clearance and storage of solid waste

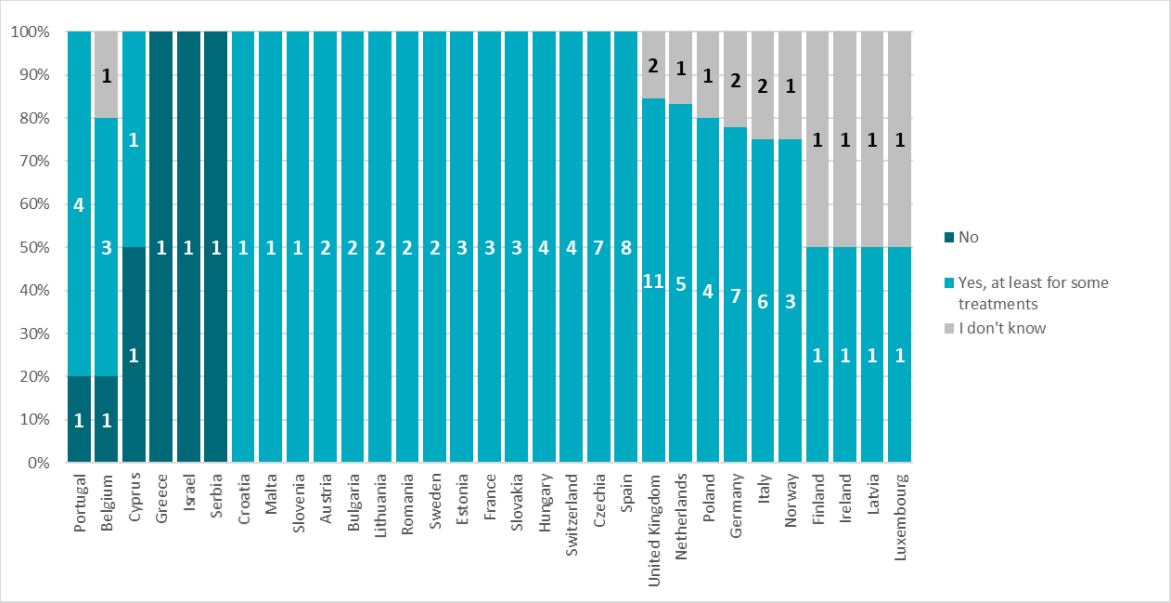


Figure I.17: Presence of specific conditions/guidelines provided for the release of effluent from patients

Due to the wide scope of topics the survey had to cover, it was not possible to gather more detailed information concerning the conditions for specific treatments or radionuclides across Member States within the substantive survey. For this reason, specific centres were contacted to provide further information on the conditions put on them for effluent and waste management.

Despite the low number of centres for which data were gathered, it was apparent that management of such waste varied widely across Europe. Different systems are in use at hospitals for reducing the environmental and radiological impact of effluent discharge of therapeutic radionuclides. These include reducing the annual or monthly aqueous radionuclide waste output from the hospital (effectively limiting the number of patients that are treated), storing aqueous waste prior to discharge to limit the concentration of activity at the time of release, or filtering the waste of radionuclide contaminants prior to discharge from the hospital. The latter two solutions have financial impact and often require significant infrastructure development prior to commencing a therapeutic service. In addition the solutions rely on the patient excretion being managed within the hospital, often necessitating the treatment to be undertaken in an inpatient setting. As such, sites where these systems were in place were generally found to keep patients in hospital longer than those that just limited the total activity administered per month or year.

Table I.3: Example data of aqueous waste discharge criteria in some European countries

Country	^{131}I	^{177}Lu	^{223}Ra
Germany	5 Bq/L leaving hospital sewage	100 Bq/L when entering the public sewage system	
Norway (centre A)	350 GBq/year	3000 GBq/year	0.1 GBq/year
Norway (centre B)	5 GBq/year	500 GBq/year	0.15 GBq/year
Spain	decay store for a few months		
UK (centre A)	900 GBq/year	1800 GBq/year	1.4 GB/year
UK (centre B)	900 GBq/year	480 GBq/year	1.2 GBq/year
Italy	The condition for effluent is "no radiological relevance," which means that no population member should absorb more than 10 uSv per year		
Belgium	45 Bq/L leaving hospital sewage	1.9 kBq/L leaving hospital sewage	1.1 Bq/L leaving hospital sewage

I.4.5 Medical physics

Shortage of medical physicists working in nuclear medicine was highlighted within the survey as a significant barrier to implementation of dosimetry. Article 58 of the BSSD concerning procedures requires that: "*In standardised therapeutic nuclear medicine practices, a medical physics expert shall be involved*."

The survey therefore set out to create an overview of the level of MPE support in centres and the levels of expertise across Europe.

A survey concerning education, training and registration of MPEs across Europe [I.14] was recently conducted by the EFOMP. Notably, among the published results, of the 25 EU states that participated in this survey, 19 had national registration schemes for MPEs and 3 were considering implementing one. Results from our survey reflected this result and well as indicating that schemes are now in place since that initial survey. Results also demonstrated that different European countries follow different paths to educate and train MPEs further reiterated in the WP data. Of interest was the distinction between that of a medical physicist and a more senior experienced MPE. Results from the WP survey showed that only in 50% of the centres was such a distinction observed.

Variation in the specialism was also evident, with some MPE qualifications being granted after completion of a Master or Bachelor of Science courses covering all fields of medical physics and some with up to 6.5 years post graduate and clinical training in a specialist subject area such as nuclear medicine. Of concern, raised also by the EFOMP survey, was that only 80% of the national training schemes were government approved and only 22% by EFOMP.

When asked how well participants felt the role of the MPE was defined concerning therapeutic nuclear medicine, the majority of participants and stakeholders felt it was reasonably well defined, although 80% indicating there was still room for further improvement. The survey did not seek to ascertain the variation in roles of the MPE across the EU, although internal dialogue and expert interviews indicate that this may vary widely from centre to centre. In some instances the MPEs take a more active role in the treatment administration and patient care, and in others are more separate from the day-to-day running of a therapy service. The EANM Internal Dosimetry Task Force survey of 2017 [I.2] indicated that MPEs were routinely involved at 75 and 90% of centres treating with ^{177}Lu-DOTATATE and ^{177}Lu-PSMA respectively decreasing to less than 50% when treating with ^{131}I for the treatment of benign thyroid disease and ^{223}Ra dichloride for bone metastasis. This difference in involvement will somewhat reflect the level of radiological risk posed by the practice as stipulated in the BSSD.

This difference in practice may explain the variation in MPE resources observed per centre across the survey. Although the number of physicists per centre was seen to vary with centre size, this did not fully explain the substantial range from 0.07–9 full-time equivalent (FTE). The medical physicists was also the most under represented staff group per centre that participated in the survey, with a median value of 1.5 FTE physicists per centre, compared to 2, 3 and 4 for radiopharmacy, nuclear medicine physician and technologist respectively.

When respondents were asked whether they felt MPE support for therapeutic nuclear medicine was sufficient, the majority (55%) responded that this was certainly not the case. This observation is in line with that received concerning treatment planning and verification, where insufficient support by MPE was identified as one of the main barriers to implementation.

Lack of MPE provision was also identified during the expert interviews raised by regulators, nuclear medicine physicians and MPEs. One regulator specified that:

> The shortage of MPE support has been a problem for years. There are lots of centres trying to recruit, but an insufficient pool to recruit from.

Similarly a nuclear medicine physician commented that:

> At present there are insufficient resources. A dedicated medical physicist should be available in all nuclear medicine departments performing therapies the same as it is for external beam radiotherapy.

and

> In my past department we had seven beds for inpatients. We performed at least 10–12 therapies per week without a dedicated nuclear medicine MPE. A MPE was in the hospital but borrowed from radiotherapy. There should be a specific nuclear medicine MPE in each department.

I.4.6 Discussion summary

Results from the expert interviews mirror the results obtained through the substantive survey. For the end users, including nuclear medicine physicians, radiopharmacy experts and MPEs, the general feedback was that dosimetry can support treatment optimization in therapeutic nuclear medicine and is essential for personalised medicine. It is mentioned that there is a need for better understanding of therapy mechanisms and dose-effect relations, therefore dosimetry should be included more in clinical trials and should be further developed with clearer regulatory guidance. Almost all experts agreed that a key issue is the availability of sufficient staff to perform therapy, dosimetry and patient care during hospitalisation. It is thought that resources are currently below what would be needed with increasing future demand. Besides general availability training and education was also raised. Other hospital resources that require attention are the availability of equipment such as SPECT–CT and PET–CT systems, especially mentioned by industry and MPEs, availability of ward rooms and improved waste management protocols, especially if therapeutic nuclear medicine numbers will increase in the future. The main survey highlighted the variation in practice concerning waste management and increased therapy load could have a significant economical impact or stifle patient access to therapy. Participants also indicated a desire for unified dose constraints, patient release criteria and guidance concerning the radiation protection instructions provided to patients.

I.5 Route to Market

I.5.1 Barriers to implementation

By far the strongest barrier raised by experts concerning development and delivery of radiotherapeutic products was the sustainability and management of the radionuclide supply chain. Planned and unplanned maintenance of old nuclear reactors was stated to be causing breaks in the supply chain and causing grievances. Transportation was also stated to represent a major hurdle for distribution of radionuclides. Prioritisation of airline logistics was raised as a means to continue this process without interruption. With the ever-increasing costs, reimbursement support was thought to be insufficiently updated and further squeezes the manufacturer between the supplier and treatment centre.

One industry representative stated that the biggest challenge facing therapeutic nuclear medicine is related to the commercialization of the new radionuclide therapies. Difficulty in conducting the licensing processes separately in each EU country and the loss of time it creates was also raised as a barrier by industry. One industry expert expressed frustration in the regulatory constraints put upon them when trying to translate a new therapeutics compound into the clinic, taking more than 4 years to open the clinical study due to questions and slow case management from the radiation protection agency and additional conditions put upon the study within the trial inclusion criteria. Some experts made reference to differences between Europe and the US. The implementation of good clinical practice was identified as being a clearly defined process in the US, whereas across EU states inconsistency was expressed as having a major impact. The new CTR, Regulation (EU) No 536/2014, that came into force in January 2022 introduced centralised submission of clinical trial applications to the CTIS, which in January 2023 became the single entry point for submission of data and information relating to clinical trials, and thus harmonisation of the approval of clinical trials will certainly develop. However,

considering previous experiences, as outlined by some experts, this approach to harmonisation within the medicine legislation might be hampered by enforcement of national regulatory requirements based on the radiation safety regulations that were not considered in the harmonisation process.

Issues concerning regulatory frameworks were generally a dominant theme of the expert interviews, reiterating what was determined from the substantive survey concerning heterogeneity across Europe and the need for harmonisation. Heterogeneity across EU and Local authorities was thought to contribute to problems in understanding and interpretation among the users in the different countries. One industry expert felt that national agencies do not have significant specialist experience with respect to new radiopharmaceuticals. It was suggested that the EMA should play a more prominent role for that reason. Again comparison to the US was raised and the important role the FDA has taken from the Nuclear Regulatory Commission concerning radiopharmaceuticals. Such an endeavour may not be suitable in the European setting, but a clear need for specialist expertise concerning radiopharmaceuticals, particularly in the therapeutic setting is evident. If such expertise were to bridge the gap between pharmaceutical and radiation regulators, this would only be a positive.

Another important challenge raised during the interviews was the overall perception of therapeutic nuclear medicine, covering both public awareness and perception in the professional field. Interviewees felt that the full potential of therapeutic nuclear medicine was not yet exploited, and a change in perception will be needed to do so. Also, resources and reimbursement are indicated as a challenge, since all aspects of therapeutic nuclear medicine require increased resources if they are to be optimally used. Dosimetry and treatment personalization were also mentioned in this regard in addition to increased training and education of all personnel.

I.5.2 Interrelations and regulatory conflicts

Opinion regarding legislative conflict was diverse among the regulatory experts interviewed. A number of regulators indicated that the radiation protection and pharmaceutical authorities in their country work closely together to find optimal solutions. However, as previously stated frustration was generally concerning interpretation, heterogeneity and lack of coordination rather than any direct conflict between the sets of regulations. One expert felt that the conflict was not between available legislations, but rather between the requirement for optimisation in the BSSD and the posology approved in certain products during the registration processes.

When asked what they would want from an approved posology, opinion from the experts was varied although the majority were in favour of flexibility, noting that this was ultimately the decision and responsibility of the treating physician. The results of the survey indicated that it is allowed in many countries to treat outside the posology described in the package insert. There is therefore an obvious perceived risk in treating off-label, which may be hindering this practise. As an alternative, some experts suggested including both planning methods within the posology during marketing authorisation. Suggestions included an option for both a fixed activity administration and an individually optimised activity using dosimetry. The mIBG package insert was given as a good example where there are two possibilities with details of how it can be implemented. Another suggestion was that both a minimum injected activity and maximum cap be quoted. Estimation of the absorbed dose to organs at risk could, for example, be used for prescription but within the limits of the two extremes. It was further raised that evidence for such prescription methods should come from clinical trials, which was particularly stressed by pharmaceutical regulators and radiopharmacy experts. However, although there was general support by industry for generating more flexible posologies, potentially with dosimetry, it was stated that guidance concerning this should come from the regulators.

Further to this, one industry expert felt that current radiation safety and pharmaceutical legislation are based on outdated frameworks that do not recognise the specific requirements of radiopharmaceuticals. It was also noted that national regulators are at different levels of

knowledge, with each new development of therapeutic nuclear medicines involving significant effort.

I.6 Discussion

A survey of European stakeholders on the implementation of the relevant European legal requirements with respect to therapeutic nuclear medicine was undertaken. As with any survey, responses attract those with specific interest in the field, and there is risk of bias in the responses received. In this survey a diverse range of stakeholders and professionals were included to alleviate any such risk. Indeed while a heterogeneity of responses were observed, there was often no clear group of respondents with differing opinions or views over that of another. As the survey sought to identify implementation to the European legal requirements, it was necessary to provide aspects of these texts in the questionnaire. It is possible, in some instances, respondents were unfamiliar with these English translations and interpretation of the question could differ. However, given the large number of responses received the impact of such translation differences is thought to be minimal. In some instances responses from a specific country were low, and as such we have refrained from making any strong conclusions concerning individual states. The pattern and diversity across Europe is felt to be adequately represented given the number and range of responses received.

The lack of commonality between pharmaceutical legislation and Euratom BSSD requirements concerning radioactive compounds for use in therapeutic nuclear medicine was identified through the work as an area needing attention. In particular the lack of specificity concerning radioactive therapeutic compounds in the legislation at both a national and European level was identified, with heterogeneous implementation across Europe in particular impacting preparation, administration and distribution of radiopharmaceuticals without a marketing authorisation. Heterogeneity was identified to lead to problems in understanding and interpretation among the stakeholders in the different countries, with different legislative processes across Europe potentially delaying and stifling development of, and patient access to, novel radiotherapeutic compounds. Closer collaboration and cross-disciplinary expertise across the regulatory frameworks and specialist regulator knowledge concerning therapeutic nuclear medicine was identified as a potential means to tackling some of these concerns.

The work identified some confusion within the community concerning the requirement for optimisation as stipulated in the BSSD and the need to follow the posology presented in the marketing authorisation. Heterogeneity across Europe and even within some countries points to lack of clarity. Lack of specific instruction and therefore a perceived risk in treating off-label may be hindering optimisation at the clinical level. Arguments for flexibility in the posology were discussed within the expert interviews. However the need for dosimetry data from clinical trials supporting such regimens was identified as were the need for regulatory guidance in how to conduct such studies.

Opinion concerning the level of precision and associated methodology to comply with the individual planification of target volume exposures as required by the BSSD and regarding the definition of an appropriate delivery verification was divided. Many participants recognised the statement of the BSSD pointing towards dosimetry applications. However some respondents felt this should not be applied in a nuclear medicine setting. For most therapies there was a recognised desire for dosimetry-guided optimisation and verification. However, in most countries this was not sufficiently detailed in legislation or national guidance to become common practice. Dosimetry was more apparent for the well-established therapy of ^{131}I for benign thyroid disorders. However, this practice was still widely variant across Member States.

A lack of resources in terms of reimbursement, know-how and sufficiently trained technical, medical, radiopharmacy and physics staff in nuclear medicine centres was identified as the predominant barriers stifling dosimetry and development of therapy. An overwhelming agreement that further recommendations would be beneficial, concerning both the requirements for planning and verification was also shown.

Heterogeneity in the implementation of dose constraints and patient release criteria was apparent across Member States. The survey was only able to determine a plausible dose constraint in a few countries, leading to concern that constraints may not necessarily be in place or advice on their derivation is lacking. Participants indicated a clear desire to see the development of unified dose constraint either at the national or European level. Interpretation, definition and translation of 'comforter and carer' appeared to vary across Europe. This could lead to significant differences in the potential exposure to household members following a patient's treatment with radionuclides. Instructions provided to patients on release from hospital were provided by most centres although national advice was generally missing for all but the more established therapies. Advice provided to patients varied in detail and duration. This may be due to heterogeneity in the dose constraint that centres are working to, but also on the length of time patients are required to remain in hospital. The social and economical implications of the hospital stay and restrictions on contact will therefore vary depending on the practise of the treating centres.

Conditions for management of radioactive waste and effluent were well established across Europe. An in-depth analysis of the conditions and the underlying radiological assessments from which they are based was not undertaken, although may be of interest in the future. For the data that was gathered it is apparent that aqueous waste release criteria take one of two forms, either based on an activity concentration limit or a maximum discharge limit per month or year. Ramifications for these criteria are either the installation of storage tanks or a limit on the number of patients that can be treated. A consequence is that patient access to treatment may be hampered with either a need to travel to a large centre with sufficient waste facilities or potentially long waiting lists as centres are confined in the number of patients they can treat.

Medical physics support was considered insufficient in most countries and also raised as a barrier to implementing treatment planning and verification. The level of training and accreditation of MPEs across Europe appears to vary, an issue currently being tackled within EFOMP. There were observed differences in the number of MPEs per centre and this may be somewhat explained by size in addition to the different competencies and responsibilities at the national level.

I.7 Conclusions

The consortium undertook a survey on the practical implementation of the main requirements of the European pharmaceutical legislation and the BSSD concerning therapeutic nuclear medicine. The survey included targeted questionnaires and expert interviews and obtained valid responses from all EU Member States with an active practice of therapeutic nuclear medicine.

The work identified a strong thematic trend. Heterogeneity was observed across Member States concerning many aspects of both sets of regulatory legislations. Increased resourcing, closer collaborative working between all stakeholders and Member States, with further specialist training were identified as potential actions to advance the coherent implementation of these European legal requirements. Further regulatory guidance produced in collaboration, was also identified as a means to address the issues identified and maintain the high standards for quality and safety of nuclear medicine treatments without stifling development.

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Annex 2: Visions on the Implementation of Dosimetry in Clinical Practice

II.1 Introduction

Nuclear medicine and the application of radiopharmaceuticals are paving the way towards a new paradigm, especially in cancer care and personalised medicine. Challenges to ensure and maintain high standards in quality and safety of nuclear medicine treatments are increasing. Nuclear medicine is a medical specialty involving the administration of radioactive substances in order to diagnose and treat disease in patients of every age group. Each year, more than ten million patients in Europe benefit from nuclear medicine studies relating to cancer, cardiovascular, neurovascular and endocrine diseases. Currently over 100 different nuclear medicine procedures are approved worldwide by regulators.

Therapeutic as well as diagnostic nuclear medicine applications have exhibited an excellent safety profile. Nevertheless, optimising and personalising treatments is still challenging. Given their chemical, physical and clinical particularities, radiopharmaceuticals are a very special class of drug that require specific considerations. As such, their preparation, handling and use are regulated in two separate legal frameworks. Specifically, medical authorisation and supervision are laid out in EU pharmaceutical legislation [II.1, II.2], while radiation safety is regulated under Euratom radiation protection legislation.

In December 2013, the EU issued the BSSD, laying down basic safety standards for protection against the dangers arising from exposure to ionising radiation. The directive integrated several previous directives on occupational, public and medical exposures and radiation protection. The system of radiation protection is based on the principles of justification and optimisation.

The BSSD defines justification as the decisions taken with the intent to ensure that the individual or societal benefit resulting from the practice outweighs the health detriment that it may cause. Decisions introducing or altering an exposure pathway for existing and emergency exposure situations should be justified in the sense that they should do more good than harm.

The optimisation of the protection of individuals subject to medical exposures applies to the magnitude of individual doses which should be consistent with the medical purpose of the exposure. For therapeutic purposes this is further described in article 56.1 of the BSSD, which states that:

> For all medical exposure of patients for radiotherapeutic purposes, exposures of target volumes shall be individually planned and their delivery appropriately verified taking into account that doses to non-target volumes and tissues shall be as low as reasonably achievable and consistent with the intended radiotherapeutic purpose of the exposure.

In article 2 radiotherapeutic is explicitly stated as pertaining to radiotherapy, including nuclear medicine for therapeutic purposes.

Although the terms ‘planning’ and ‘verification’ are very well adopted in external beam radiotherapy, the BSSD does not further specify what is intended with the term ‘individually planned’ when related to molecular radiotherapy. While the terms ‘exposure’ and ‘doses’ clearly implies implementing dosimetry, the complete definition of how this legal requirement should be fulfilled in molecular radiotherapy is left to the interpretation of experts.

Currently, multiple strategies are thought to be able to satisfy these requirements, as demonstrated from the survey carried out in the SIMPLERAD project. A lack of clarity was thought to exist regarding the level of optimisation required to comply with the BSSD, particularly concerning methodology of aspects such as patient selection, imaging and dosimetry.

This document summarises the point of view of three representative bodies, the ICRU, EANM and EFOMP, on radiopharmaceutical dosimetry implementation.

II.2 Definition of Reporting Levels According to ICRU Report 96

According to ICRU Report 96 [II.3], three reporting levels are identified for radiopharmaceutical therapies.

Level 1 represents the "*minimum standards for prescribing and reporting*." According to the ICRU, below these standards radiopharmaceutical therapy should not be performed. Level 1 is typically implemented based on administered activity. The requirement at this level is that the prescribed administered activity should be confirmed using an activity meter that has been calibrated relative to a national metrology lab. The standard uncertainty in the administered activity must be within 10% to meet this level. However, in certain cases, i.e., certain radiopharmaceuticals and clinical scenarios, absorbed-dose calculations are required even for level 1. The mean absorbed dose to the dosimetric treatment region and region-at-risk are reported, as appropriate to the treatment intent. The time activity curve and the fitted function for determining the activity biodistribution, if applicable, are to be indicated in the patient report. When possible, the absorbed dose pertinent to the region at risk should be reported.

Level 2 recommendations apply for the prescribing and reporting state-of-the-art techniques so that the calculation of the exposure of the target volume is patient-specific and that it meets pre-specified uncertainty criteria. A complete quality assurance programme is used to ensure that the prescribed treatment is accurately delivered. This translates into collecting the data required to calculate absorbed doses to the dosimetric treatment region and the region-at-risk. Depending upon the agent, clinical circumstances, and ability to accurately collect the needed data, this level should include adjustments to the prescribed activity based on the absorbed dose to the dosimetric treatment region and the region at risk.

Level 3 recommendations are indicated for reporting research and novel developments. They are used for the development of new techniques and approaches for which reporting criteria are not yet standardised. The objective here is to develop and implement new techniques that may be implemented and refined in clinical trials to evaluate their applicability for widespread deployment as level 2 recommendations.

The approaches and methodologies mentioned should be considered the minimum required to achieve a given level. The description provided does not preclude prescribing and reporting techniques that are intermediate to the descriptions provided. At all levels, the reports generated should include all input to the calculations used in arriving at the prescribed absorbed dose or administered activity.

II.3 Definition of Levels in Compliance with the BSSD According to the EANM Position Paper on Article 56

The EANM position paper on article 56 of the BSSD for therapeutic nuclear medicine [II.4] proposes to distinguish three levels in compliance to the optimisation principle in the BSSD. These three levels are to be viewed as a staircase, where above level 1, levels 2 and 3 add refinements with the purpose to decrease the uncertainty in the absorbed dose estimates for the individual patient.

Level 1 is defined as activity-based prescription and patient-averaged dosimetry. Qualitative verification of the therapy delivery should be performed at a relevant time point in therapies for which post-therapy imaging is feasible, and the results should be recorded. Absorbed dose estimates can be made for patients involved in level 1 therapies by using patient cohort–averaged dosimetry data and the administered activity.

Level 2 is defined as activity-based prescription and patient-specific dosimetry. Level 2 compliance is reached by recording and reporting of the absorbed dose to organs at risk and optionally the absorbed dose to treatment regions (regions of disease that motivate treatment

prescription) for the individual patient. This level is advised to form the minimum requirement for non-standardised therapies. If the treatment objective is to avoid toxicity, then the absorbed dose to the organs at risk should be quantified. If the objective is tumour control but also for therapy selection, then the absorbed dose to the treatment region is of relevance. The activity prescription at level 2 is not different from that in level 1. The organs at risk and treatment regions selected for the calculations need to be those that are most likely to predict biological outcome to assess safety and efficacy of the treatment. The key distinction between level 1 and level 2 is the degree to which the absorbed dose report is patient-specific and also in the degree of its uncertainty.

Level 3 is defined as dosimetry-guided patient-specific prescription and verification. Level 3 compliance is the prescription of administered activity calculated to deliver a desired absorbed dose to a treatment region or organ at risk and is appropriate in a research setting to develop new dosimetry methodologies in order to better predict response or toxicity. For level 3 studies, it is essential that dosimetry and correlations between absorbed dose and induced effects are timely identified and published in peer-reviewed literature.

According to the EANM position paper, radiopharmaceuticals in clinical development, phase 1–2 trials, should ideally comply with absorbed-dose reporting at least at level 2. This preferably applies also to off-label use with administrations of activity that are significantly higher, 25% or more, than the recommended activity, including the total activity accumulated over all cycles and treatments.

II.4 EFOMP Policy Statement No. 19

EFOMP Policy Statement No. 19 [II.5] on dosimetry in therapeutic nuclear medicine and molecular radiotherapy summarises aspects of three European directives relating to the therapeutic use of radiopharmaceuticals and medical devices and outlines the steps needed for implementation of patient dosimetry for radioactive drugs.

EFOMP policy acknowledges the regulatory dimension of BSSD, and therefore focuses on the means, resources and processes that need to be implemented to allow implementing the BSSD in clinical routine. To support the transition from administrations of fixed activities to personalised treatments based on patient-specific dosimetry, EFOMP presents the 14 recommendations below (Table 2). Close collaborations between the medical physicist and responsible practitioner are encouraged to develop a similar pathway as is routine for external beam radiotherapy and brachytherapy.

Summary of recommendations in EFOMP Policy Statement No. 19

- European molecular radiotherapy networks must be supported and expanded to share experience, expertise and resources.
- National and European databases are required to collect data on clinical factors, dosimetry and patient outcomes from multiple centres.
- Codes of practice for the validation and harmonisation of dosimetry results and patient outcomes for different treatments should continue to be developed and put into practice.
- Imaging and patient dosimetry must be reimbursed as is the case for external beam radiotherapy.
- Staffing requirements for centres offering molecular radiotherapy must be defined in compliance with the BSS directive.
- Research should be supported through national and European programmes to investigate treatment planning strategies for individual therapeutic procedures.
- Professional organisations should continue to provide joint guidelines to perform image-based dosimetry and guidance for resource requirements, for each treatment procedure.
- Initiatives are required to promote engagement and knowledge transfer between the various disciplines, including medical physics and medical specialties, competent authorities and industry.
- MPEs in training should gain experience in the implementation of dosimetry-guided treatments. Where necessary, training may be provided at remote centres.
- Molecular radiotherapy is a highly multidisciplinary field. Programmes of education are therefore required to train all disciplines in relevant areas.
- Investigator-initiated multi-centre and multi-national clinical trials should be promoted to develop optimised treatments.
- Networks for dosimetry expertise are required to enable sharing of know-how to support clinical trials. For example, image processing and dosimetry may be performed at remote sites with data collected according to specified protocols.
- For industry- and investigator-initiated clinical trials, individual-patient dosimetry must be incorporated to enable risk-versus-benefit analyses within drug development. Results and evidence must be presented at the time of submission for drug marketing authorisation.
- Health economics studies should be incorporated into clinical trials to investigate the costs of patient imaging and dosimetry relative to that of recently introduced commercial therapeutic radiopharmaceuticals and to other forms of radiotherapy.

Policy Statement 19 was adopted by EFOMP's national member organisations in September 2023. Out of 60 EFOMP delegates, 85% participated in the ballot, and 96% endorsed the document, which was then published in the European Journal of Medical Physics.

II.5 Discussion

Differences between the ICRU levels and those proposed by the EANM position paper and EFOMP Policy Statement 19 stem from their origin from different organisations and may or may not address the BSSD explicitly. Of note, none of the three documents presented have been endorsed by competent authorities.

The ICRU is a scientific compendium of state-of-the-art dosimetric approaches but is not specifically related to the BSSD. Both EANM and EFOMP documents were explicitly written as a reaction to BSSD publication. The EANM "considered it necessary to provide guidance on how to interpret the Directive statements for nuclear medicine treatments." The EFOMP policy statement focuses on the "steps needed for implementation of patient dosimetry for radioactive drugs."

In principle, the definitions of the levels defined by the ICRU and EANM show some similarities, e.g., for level 1. Differences occur with level 2, as the ICRU requests prescribing and reporting the absorbed dose, whereas the EANM position paper requests absorbed dose verification for activity-based prescriptions and treatment planning for off-label use of a radiopharmaceutical. The levels defined by the ICRU are in close agreement with the levels it has defined for several external-beam treatments, whereas the levels proposed in the EANM position paper focus on present-day clinical practice of radiopharmaceutical therapies, which is known to vary from one country or even from one department to another. The EANM position statement does not explicitly differentiate between treatment planning and treatment verification.

Therefore, the EANM started an initiative to provide enabling guidelines on how to improve the accessibility of clinical dosimetry in daily practice, culminating in the article EANM enabling guide: how to improve the accessibility of clinical dosimetry [II.6].

The EFOMP policy statement considers that the BSSD, as any regulatory document, should lead to changes in current clinical practice. The question is therefore not to identify therapies for which dosimetry should or should not be implemented, but to acknowledge the fact that dosimetry has to be implemented and identify the means to allow its dissemination in the clinics, taking into account the variety of treatments currently available.

Both EFOMP and EANM position statements acknowledge that application of dosimetry is heterogeneous across Europe. EFOMP considered this as a starting point that helps characterise the steps toward homogeneous application of the BSSD in the EU, thereby giving all patients equivalent chances in front of molecular radiotherapy procedures.

To reconcile EFOMP Policy Statement 19 and the EANM documents with respect to the BSSD, dosimetry should be implemented in compliance with the BSSD. This statement should be sent to national competent authorities as a clear reminder that therapeutic nuclear medicine is considered a radiotherapeutic procedure.

No therapy should be administered without explicitly stating how the BSSD requirements are respected. Even though cohort-based dosimetric results may be currently the only way to document the delivered irradiation, dosimetry should always be considered and the respective results reported.

It is acknowledged that not all EU countries are equivalent in terms of resources, history and practice of clinical dosimetry in molecular radiotherapy. Therefore, guidelines and recommendations should be generated to ascertain that patients throughout the EU will eventually be given the same high level of care.

The definition of the detail of dosimetry to implement may be therapy specific and should be provided by joint documents generated by scientific and medical professional associations, which are then endorsed by national competent authorities. These documents should focus on the methodology of dosimetry to implement, emphasising the requirement for clinical dosimetry. The objectives, planning or verification, of such documents should be clearly stated, even though

it is acknowledged that the distinction may be difficult to establish in some situations, e.g., when reporting helps to plan future therapies.

This is the purpose of annex 3, which presents some guidance on treatment planning and verification for selected radiopharmaceuticals.

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Annex 3: Guidance Document on Treatment Planning and Verification for Selected Radiopharmaceuticals

III.1 Introduction

Nuclear medicine and the application of radiopharmaceuticals are paving the way towards a new paradigm especially in cancer care and personalised medicine. Challenges to ensure and maintain high standards in quality and safety of nuclear medicine treatments are increasing. Nuclear medicine is a medical specialty involving the administration of radioactive substances in order to diagnose and treat disease in patients of every age group. Each year more than 10 million patients in Europe benefit from nuclear medicine studies relating to cancer, cardiovascular, neurovascular and endocrine diseases. Currently over 100 different nuclear medicine procedures are approved worldwide by regulators.

Therapeutic as well as diagnostic nuclear medicine applications have exhibited an excellent safety profile. Nevertheless, optimising and personalising treatments is still challenging. Given their chemical and clinical particularities, radiopharmaceuticals are a very special class of drug that require specific considerations. As such, their preparation, handling and use are regulated in two separate legal frameworks. Specifically, medical authorisation and supervision are laid out in EU pharmaceutical legislation [III.1, III.2], while radiation safety is regulated under Euratom radiation protection legislation.

In December 2013, the EU issued the BSSD, laying down basic safety standards for protection against the dangers arising from exposure to ionising radiation. The directive integrated several previous directives on occupational, public and medical exposures and radiation protection. The system of radiation protection is based on the principles of justification and optimisation. The BSSD defines justification as the decisions taken with the intent to ensure that the individual or societal benefit resulting from the practice outweighs the health detriment that it may cause. Decisions introducing or altering an exposure pathway for existing and emergency exposure situations should be justified in the sense that they should do more good than harm.

The optimisation of the protection of individuals subject to medical exposures applies to the magnitude of individual doses which should be consistent with the medical purpose of the exposure. For therapeutic purposes this is further described in article 56.1, which states that:

> For all medical exposure of patients for radiotherapeutic purposes, exposures of target volumes shall be individually planned and their delivery appropriately verified taking into account that doses to non-target volumes and tissues shall be as low as reasonably achievable and consistent with the intended radiotherapeutic purpose of the exposure.

In article 2 radiotherapeutic is explicitly stated as pertaining to radiotherapy, including nuclear medicine for therapeutic purposes.

Although the terms ‘planning’ and ‘verification’ are very well adopted in external beam radiotherapy, the precise translation of these terms is not well defined regarding therapeutic nuclear medicine. Currently, multiple strategies are thought to be able to satisfy these requirements, as demonstrated from the survey conducted by the SIMPLERAD project. A lack of clarity was thought to exist regarding the level of optimisation required to comply with the directive, particularly concerning methodology of aspects such as patient selection, imaging and dosimetry.

When asked on the amount of guidance provided by competent authorities concerning implementation of this aspect of the regulations, 42% of regulators answered that no guidance was provided, and 30% said they did not know. Similarly, concerning guidance from professional societies, 26% of the national societies stated that none were provided, and 11% did not know. Responses from treating centres reflected those indicated by the other stakeholders, with 35% stating no national guidance was available. However, there were discrepancies observed across countries, with responses from some centres indicating that no guidance was provided and

others affirming guidance is provided. These results indicate that whilst some national guidance may exist, perhaps not all stakeholders are fully aware or utilise it.

When asked if further guidance should be provided, there was an overwhelming agreement that further recommendations would be beneficial concerning both the requirements for planning and verification. A slightly higher proportion of respondents felt such guidance should come from the European level.

The purpose of this document therefore is to provide guidance for selected radiopharmaceutical therapies on how dosimetry can be implemented within a treatment regimen to maintain compliance with Article 56 of the BSSD with respect to both treatment planning and treatment verification. The target groups of this document are manufacturers, pharma and radiation-protection legislators, and treatment centres.

The procedures proposed are based on the EANM Enabling Guide: How to Improve the Accessibility of Clinical Dosimetry [III.3]. According to this guide, the resource requirements for dosimetry-based treatment planning and verification can be tailored appropriately to suit the clinical indication, the intent of the dosimetry and the resources of the department.

Different levels of refinement are possible for a given therapy, depending on the accuracy requirement that must be set prior to each clinical dosimetry procedure. It must be clearly understood that simplification, when required, may affect the clinical relevance of the dosimetric indices. In that respect, planning procedures are fundamentally different from verification, but both require provision of expected uncertainties.

III.2 Treatment Planning

Treatment planning is the decision-making process that assesses a patient's suitability for treatment, defines the optimal administered activity, and establishes a dosing schedule tailored to the individual. Simultaneously, it identifies the absorbed doses likely to be received by both target and non-target tissues. This process occurs both prior to administering the radiopharmaceutical and continuously throughout the treatment course, particularly if multiple administration cycles are planned.

The initial step in determining the administered activity for most modern therapeutic radiopharmaceuticals is rooted in the posology outlined in the SmPC. This information, backed by clinical trials demonstrating a net benefit, provides a baseline for treatment. Typical absorbed doses to tissues are also provided in the SmPCs based on a subset of patients.

To further optimise therapeutic outcomes, individualised clinical factors should then be considered, including examples such as renal function, blood count and disease burden. Additionally, imaging and dosimetry techniques can further be used to tailor treatment plans to the unique characteristics of each patient.

Personalised calculations regarding the likely dosage required for both target lesions and organs at risk contribute significantly to treatment plan refinement. By integrating these factors, healthcare practitioners ensure that the treatment plan is justified and optimised, with decisions taken carefully to balance the benefits against any potential health detriments associated with the exposure.

Dosimetry using patient cohort-averaged dose data requires very little resourcing beyond collating the typical absorbed doses reported in the literature for the therapy in question. This information can be gathered when first developing the therapy protocol and is often readily available in the appropriate guidance documents. For most radiopharmaceutical therapies, a range or distribution of absorbed doses have been reported, providing valuable indication of the likeliness of potential under or over-dosing in a population.

In a theranostic setting, it is often standard practice to confirm patient eligibility with a diagnostic conjugate of the therapeutic compound. There is therefore extensive interest in using the pre-

therapy images to predict therapeutic absorbed doses. This information could be used to tailor the activity prescription to deliver an optimised therapeutic absorbed dose and is an approach shown to be highly successful in SIRT [III.4].

Such methods have particular relevance in view of possible activity escalation beyond standard administered activity indications. Alternatively, with fractionated treatments dosimetry verification after an initial cycle can be used to adjust the activity or number of subsequent cycles, which considerably reduces the pre-therapy dosimetry workload. The dosimetry method for this approach does not necessarily lead to a high burden, as standard operating procedures using whole-body, blood-based and thyroid probe measurements are available for many treatments [III.5–9].

III.3 Treatment Verification

Treatment verification is the process of checking and recording that the administration has occurred according to the plan within some pre-defined tolerances. This process must take place even if treatment planning did not vary beyond the SmPC posology.

In the first instance this would be to validate that the prescribed activity was administered without incident, and a 10% tolerance is usually defined for most therapies.

Further verification of the radiopharmaceutical distribution should then be performed at a relevant timepoint, and the results recorded. When the expected distribution is confirmed, absorbed dose estimates can be made using the population dosimetry data and measured administered activity.

A more personalised absorbed dose assessment following therapy is desirable but often associated with the necessity to acquire SPECT–CT studies at multiple timepoints spanning several days. However, significant work has been undertaken to validate practical methods to reduce the burden to the patient and department [III.10–12]. In centres facing constraints on capacity and resources, image-based dosimetry calculations could be performed at alternate cycles or just on the initial cycle. Alternatively, when post-therapy imaging is being performed for treatment verification and optimisation, it is often not a substantial effort to develop this into a quantitative image. A combination of the patient-specific quantitative measurement with population effective half-lives can, for some radiopharmaceutical therapies and organs, enable a population-based absorbed dose estimate based on a single timepoint acquisition [III.5, III.12, III.13].

When camera availability is the limiting factor, multiple time-point SPECT acquisitions can be replaced with a hybrid approach that uses a combination of SPECT–CT complemented with less time-consuming yet not fully quantitative planar or whole-body imaging [III.14, III.15]. The planar data are used for temporal sampling and do not need to be diagnostic quality, enabling further reduction in acquisition time. However, region-based determination of uptake based on 2D projections is only possible for some radiopharmaceuticals and pathologies, e.g., due to overlap of different regions of interest in anteroposterior direction. In some cases, dosimetry evaluations can also be performed without any imaging: noteworthy examples include thyroid uptake measurements or whole-body dosimetry using external radiation detectors [III.5, III.6]. These have the advantage that they do not affect camera availability.

III.4 Clinical Examples

Examples on how to perform dosimetry for treatment planning and treatment verification for five of the most important use cases are presented in the following pages, based on the suggestions of the EANM enabling guide [III.3].

For other treatments the reader is referred to ICRU publication 96, which reflects the present state-of-the-art methods for performing dosimetry of the respective treatments [III.16]. Since clinical dosimetry is a rapidly evolving field, the examples presented below should be taken with

care as recommendations may be amended to account for methodological and technical advances in quantitative imaging and absorbed dose determination.

III.5 ^{131}I Sodium Iodide

The rationale behind dosimetry prior to therapy is to determine the ^{131}I activity that is most likely to lead to therapeutic success whilst limiting the radiation exposure to the amount necessary [III.7, III.17]. A prospective randomised study on radioiodine treatment in patients with Graves' disease showed a similar outcome in patients treated with 555 MBq and patients who received a target absorbed doses of 100 Gy, but also that those patients treated with 555 MBq who received absorbed doses higher than 200 Gy had a higher success rate [III.18]. Also, a retrospective study has shown that by delivering dosimetry-driven treatments, the activity to achieve the desired response can be reduced [III.19]. However, patients with cardiovascular risk factors may benefit from a definitive treatment with a fixed higher administered activity to ensure hypothyroidism is rapidly achieved [III.20]. The prospective randomised comparison in Graves' disease (or any other benign thyroid disease) using standard activities vs. personalised activities attempting to achieve 300-400 Gy has not been performed yet, hence lacking the confirmation of superiority of one another

EANM guidelines recommend that absorbed doses of 300–400 Gy should be used to ablate autonomous nodules, and in patients with Graves' disease, 200–300 Gy [III.7, III.17], supported by a systematic review by Taprogge et al [III.21].

To deliver a prescribed absorbed dose requires a pre-therapy dosimetry study. Such a study should not be associated with excessive effort, for neither the nuclear medicine department nor the patient. EANM standard operating procedures are available to aid centres in designing and implementing such a study, with sufficient scope for the centre to adjust as appropriate to the resources available [III.5].

Table III.1 highlights two possible study methodologies using ^{131}I that could be implemented, although ^{123}I could also be used as an alternative. These methods are not an exhaustive list and aspects of each approach could equally be taken to form an alternative regimen. Table III.2 provides suggestions on how to perform treatment verification.

Table III.1: Example treatment plans 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

Table III.2: Example treatment verification approaches 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

III.6 ^{177}Lu-DOTATATE and –PSMA

The Joint IAEA, EANM, and Society of Nuclear Medicine and Molecular Imaging (SNMMI) practical guidance on peptide receptor radionuclide therapy [III.22] as well as the Joint EANM/SNMMI procedure guideline for the use of ^{177}Lu-labelled PSMA-targeted radioligand therapy [III.23] indicate that patient-specific dosimetry can provide valuable information to assess organ-specific radiation absorbed doses and to assess the risk of delayed kidney toxicity, particularly in patients with known risk factors. The EANM dosimetry recommendations for dosimetry of ^{177}Lu-labelled somatostatin-receptor- and PSMA-targeting ligands [III.15] provide comprehensive guidance and information for clinical implementation.

There are numerous methods and approaches for ^{177}Lu dosimetry, each with advantages and disadvantages. The current administration regimen considers fixed, repeated activity administrations. In that context, treatment planning is limited as activity is not varied based on efficacy (tumour irradiation). Yet, since the procedure involves repeated administrations, verification can be performed on each cycle and used as planification for subsequent cycles. Hence planning and verification are dissociated here. Dosimetry of organs at risk can be used to personalise the treatment and confine toxicity to acceptable levels. Depending on the treatment, several organs-at-risk may be considered, and clinical dosimetry approaches should be defined accordingly.

The table below provides just two example regimens that could be considered for dosimetry assessment in cases where there is particular concern of kidney toxicity. In this example, an absorbed dose limit of 23 Gy over 4 cycles for peptide receptor radionuclide therapy or 6 cycles for PSMA radioligand therapy has been suggested. However, whilst extrapolated from external beam-radiotherapy [III.24], this value is not a confirmed toxicity threshold, for molecular radiotherapy as the absorbed dose rates and micro-distribution of the radiopharmaceutical can be more heterogeneous than external beam. Lower toxicity incidents have hence been observed at significantly higher absorbed doses in some retrospective studies [III.25–27]. The dissemination of clinical dosimetry will provide molecular-radiotherapy-specific dosimetric thresholds that will account for the specific nature of irradiation delivery in molecular radiotherapy.

Table III.3: Example treatment plans using ^{177}Lu

Clinical Indication	Expression of sstr2, or metastatic or inoperable neuroendocrine tumours with poor kidney function [III.22] Patients with PSMA-positive mCRPC (For more details see Kratochwil et al [III.23])
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

III.7 ^{131}I mIBG

^{131}I mIBG is used as a radiotherapeutic metabolic agent in neuroectodermal tumours of the sympathetic nervous system with prevalent use in treating paediatric neuroblastoma. The EANM procedure guidelines for ^{131}I mIBG therapy indicate that the organ that limits the activity to be administered is predominantly the red marrow [III.28]. The EANM Dosimetry Committee series on standard operational procedures for internal dosimetry for ^{131}I mIBG treatment of neuroendocrine tumours [III.6] suggests using whole-body dosimetry as a surrogate for red marrow dosimetry. Both the EANM and ICRU strongly recommend dosimetrically optimised activity prescriptions for paediatric administrations [III.4, III.29], and some centres and clinical trials now opt to treat to a target 4 Gy whole-body absorbed dose, usually delivered over two cycles [III.30–33]. The activity administered for the first cycle is determined from patient weight and subsequent whole-body dosimetry used to determine the activity of the second infusion. The table below presents two dosimetry regimens which both set out to deliver a dosimetrically optimised therapy. As with previous examples, one of these approaches requires less resources and the pros and cons of each are briefly outlined.

Table III.4: 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

III.8 ^{90}Y radioembolisation

The selective loco-regional permanent implantation of ^{90}Y loaded microspheres is a well-established therapeutic option for the treatment of the primary hepatic carcinoma and metastasis. This technique also known as SIRT, transarterial radioembolisation or ^{90}Y hepatic radioembolisation, demonstrated the key role of dosimetry in improving patient outcome [III.4, III.34]. Based on clinical results, present international recommendations for SIRT considers both predictive and post-therapy absorbed dose assessment [III.35–37], hence in compliance with the European BSSD. The determination of the patient specific ^{90}Y therapeutic activity administration relies on predictive dosimetry calculations achieved in a treatment simulation of the therapeutic ^{90}Y activity deposition by the transarterial hepatic administration of a diagnostic activity of ^{99m}Tc macro-aggregate albumins (^{99m}Tc-MAA) imaged in SPECT–CT.

For predictive dosimetry, planar imaging is currently used for extrahepatic lung and gastro-intestinal shunt assessments, but SPECT–CT has superior spatial localisation and quantification abilities and can be used for determination of uptake in lesions and normal liver.

Qualitative post-treatment verification of the appropriate deposition of ^{90}Y-labelled microspheres is performed with bremsstrahlung planar and SPECT–CT imaging or a post-treatment absorbed dose verification in lesions, and hepatic non-tumour tissues can be obtained from quantitative ^{90}Y PET–CT (typically 15–30 minutes in single bed position centred on the liver), depending on the PET system available [III.38]. This step is essential for assessing possible post-therapy extrahepatic shunt and enable appropriate and timely medication if needed.

The assumption of permanent local deposition of the ^{90}Y-loaded microspheres reduces the need of quantitative imaging to only a single acquisition. Typically, ^{99m}Tc-MAA SPECT–CT is acquired promptly within an hour after the administration, while ^{90}Y PET–CT is acquired within a few hours post-therapeutic implantation before patient discharge from the hospital.

Table III.5: 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 [III.39, III.40] • 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

III.9 Conclusions

This document aims to serve as an initial guide for the implementation of dosimetry in therapeutic nuclear medicine. The challenges in maintaining high standards of quality and safety in nuclear medicine treatments are acknowledged with a unique regulatory framework. The importance of adhering to the principles of justification and optimisation laid out in the EU's BSSD are clear, and we aim to provide practical guidance for treatment planning and verification, urging the tailoring of resource requirements to specific clinical indications and departmental resources. Individualised approaches, integrating clinical factors, imaging and dosimetry are all required to optimise therapeutic outcomes. Clinical examples for dosimetry in key therapeutic use cases are presented, demonstrating the scope for the varied treatment planning and verification approaches available for radiopharmaceutical therapy.

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Annex 4: Composition of the Advisory Board

Table IV.1: List of organisations represented in the SIMPLERAD project's Advisory Board

Organisation Name	Area of Expertise
Administration of Radioactive Substances Advisory Committee	UK relations
European Alliance for Medical Radiation Protection Research	Radiation protection
European Association of Eurology	Urology
European Cancer Organisation	Patient representative
EMA	Medicine regulation
European Neuroendocrine Tumor Society	Endocrinology
European Radiation Dosimetry Group	Dosimetry
Europa Uomo	Patient representative
HERCA	Competent authorities/BSSD expertise
IAEA Nuclear Medicine and Diagnostic Imaging Section	International organisation
International Commission on Radiological Protection	Radiation protection
Nuclear Medicine Europe	Radiopharmaceutical industry
SGQS	Medical radiation quality and safety