



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



D4.3: Workshop Proceedings

27 February 2024

Start date of project: 1 May 2022

Duration: 24 months

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Review by the coordination team

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This project has received funding from the European Commission under Service Contract N° ENER/2022/NUCL/SI2.869532.



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List of Abbreviations

AmRadV	German Regulation on Radioactive Medicines or Medicines Treated with Ionising Radiation
BfArM	German Federal Institute for Drugs and Medical Devices
BfS	German Federal Office for Radiation Protection
BSSD	Basic Safety Standards Directive (Council Directive 2013/59/Euratom)
DG ENER	EC Directorate-General for Energy
DG SANTE	EC Directorate-General for Health and Food Safety
EANM	European Association of Nuclear Medicine
EC	European Commission
EIBIR	European Institute for Biomedical Imaging Research
EFOMP	European Federation of Organisations for Medical Physics
EMA	European Medicines Agency
ESTRO	European Society for Therapeutic Radiology and Oncology
EU	European Union
GMP	Good manufacturing practice
HERCA	Heads of the European Radiological Protection Competent Authorities
IAEA	International Atomic Energy Agency
ICRP	International Commission on Radiological Protection
IFU	Instructions for use
IR(ME)R	UK Ionising Radiation (Medical Exposure) Regulations
MPE	Medical physics expert
SAMIRA	Strategic Agenda for Medical Ionising Radiation Applications
SGQS	SAMIRA Steering Group on Quality and Safety
SIRT	Selective internal radiotherapy
SmPC	Summary of product characteristics
WHO	World Health Organisation
WP	Work package
WP MED	Article 31 Working Party on Medical Exposures



1. Introduction

The 24-month SIMPLERAD project aims 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. It will propose 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 will further address quality and safety issues related to the current use and introduction of novel therapeutic radiopharmaceuticals into clinical practice, the role of medical physics experts (MPEs), requirements for dosimetry, release of patients from hospital, and management of radioactive waste.

To achieve the specific objectives, the SIMPLERAD project includes 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

The deliverable provides detailed session summaries and conclusions from the discussions of the SIMPLERAD project workshop held in December 2023. The target groups, dissemination, organisational arrangements, online streaming platform and attendance are also described.

Workshop date: 11–12 December 2023

Workshop format: in-person meeting, 1.5 days, online participation via EIBIR Zoom webinar

Venue: BluePoint Brussels, Room Archimedes

Target countries: EU27, Norway, Switzerland

2. Background

The workshop was intended to provide an opportunity to present the consortium's achievements since beginning in May 2022, with results from work packages (WPs) 1–3 to understand and compare the legal requirements for authorisation of radiopharmaceuticals and practice of therapeutic nuclear medicine in several EU and non-member countries, analyse a survey and expert interviews to collect information on the practical implementation of the legal requirements and challenges to practitioners, and develop guidance for the coherent implementation of the legal requirements in preparation of the project's final report.

The workshop gathered the consortium's crucial stakeholders, namely, the Advisory Board, European Medicines Agency (EMA), Heads of the European Radiological Protection Competent Authorities (HERCA), Article 31 Working Party on Medical Exposures (WP MED), SAMIRA Steering Group on Quality and Safety (SGQS), and the European Commission (EC) Directorate-Generals for Energy (DG ENER) and Health and Food Safety (DG SANTE) as well as regulatory authorities and medical professional and patient advocacy groups. The Advisory Board was consulted throughout the preparation process, and they along with the survey participants, SGQS and HERCA members, and EMA were asked in October and November to give feedback on the consortium's draft guidance and recommendations so a refined version could be presented during the workshop.



Detailed briefings to moderators, rapporteurs, speakers and panellists were also distributed with a release form and PowerPoint template in November. The consortium partnered with a local hotel to provide accommodations for these groups and the other consortium partners and arranged technical details with the BluePoint staff. These steps culminated in a successful workshop meeting each of the following goals.

- Presentation of the SIMPLERAD project and its results
 - Project objectives
 - Results of the analyses of legal and regulatory frameworks (WP1)
 - Results of the survey and expert interviews (WP2)
 - Draft guidance document for coherent implementation of the European legal requirements (WP3)
- Receive feedback from stakeholders
- Receive feedback from target groups
- Reach consensus on the guidance document and further actions needed
- Prepare proceedings of the workshop, consisting of session summaries and main conclusions and recommendations

3. Dissemination

3.1 Target Groups

The groups represented at the workshop included the following.

- European and national authorities responsible for authorisation of radiopharmaceuticals were reached through personalised invitations via the database built in WP2 and the consortium's pre-existing contacts
- Competent authorities for radiation protection were invited via HERCA and the consortium's pre-existing contacts.
- Researchers in the area of radiopharmaceuticals were reached through EANM's communication channels
- The nuclear medicine community were reached via EANM's membership and established communication channels, including the national nuclear medicine societies and ESTRO
- The medical physics community working in the field were reached via EFOMP's membership and established communication channels
- Patient organisations such as Europa Uomo and that of the European Cancer Organisation were contacted through the patient representation in the Advisory Board as well as the clinical societies involved
- The radiopharmaceutical industry were invited via Nuclear Medicine Europe representation on the Advisory Board
- Relevant clinical communities such as urology, endocrinology, cardiology and thyroid research were reached through Advisory Board representation
- Members of the Advisory Board were invited via personalised emails from the EIBIR office, and the WP MED and SGQS members were contacted by the EC

3.2 Dissemination

A venue for the workshop was sought from a group of five candidates in February 2023. Prior to selecting the venue, a save-the-date message was distributed in March to the consortium and Advisory Board members with relevant information available at that time.

A simple registration form was created on Jotform in May following the 2nd progress meeting, and the draft programme was posted to the SIMPLERAD website in June. Invitations to register were then distributed via the consortium partners and HERCA to their members. Similar invitations were in July distributed to the WP2 survey participants and representatives of the target groups, while potential speakers and Advisory Board members received formal invitations with venue and reimbursement information. When registration reached the venue capacity of 110, the EC was consulted to devise a policy for onsite and online invitations. These were issued to the more than 130 registrants throughout the two months preceding the workshop. The EANM office updated the website



with the final programme in December, and the social media channels of the consortium partners were utilised to promote the workshop throughout the event.

Following conclusion of the event, PDFs of all presentations were uploaded to the project website for continued interaction with participants and interested persons who were unable to attend.

3.3 Participation

Total participation, including speakers, moderators and panellists, amounted to 118, with 85 onsite and 33 online. A table of the represented countries and number of representatives follows.

Table 1: Summary of workshop representation

Austria	5	Ireland	3
Belgium	19	Italy	2
Bulgaria	1	Latvia	2
Croatia	1	Luxembourg	5
Czechia	4	Netherlands	8
Denmark	2	Norway	3
Estonia	1	Portugal	1
Finland	4	Spain	4
France	9	Sweden	6
Germany	20	Switzerland	7
Hungary	2	Other non-EU	9

4. Workshop Programme

Monday, 11 December 2023

Session 1 Opening & Setting the Scene

Moderator: M. Lassmann

Rapporteur: EIBIR Office

13:00-13:10 Welcome by the EC and consortium (G. Simeonov, DG ENER; M. Lassmann)

13:10-13:20 Introduction to the SIMPLERAD project (B.J. Krause)

- Overview of project scope and workplan
- The underlying issues, including status of the use of therapeutic radiopharmaceuticals

13:20-13:45 Presentation of the European framework relevant to therapeutic radiopharmaceuticals

- EURATOM framework (G. Simeonov, DG ENER)
- Pharma framework
 - European pharma legislation (P. Erba, DG SANTE)
 - Clinical trials legislation (A.M. Janson Lang, Clinical Trials Coordination and Advisory Group)
 - Guidance and posology (V. Fradin-Da Ros, European Medicines Agency)

13:45-14:00 Perspectives of international organisations

- World Health Organisation (L. Gwaza)
- International Atomic Energy Agency (A. Korde)
- International Commission on Radiological Protection (A. Giussani)

**Session 2 Interrelations among Legal and Regulatory Frameworks [WP1]**

Moderator: M. Lassmann

Rapporteur: M. Patt

14:00-14:20 Results of analytical work and identified regulatory and implementation issues [WP 1] (M. Bardiès)

14:20-14:40 Presentation of the outcome of comparative analysis of the legal bases in the United States, United Kingdom and EU [WP 1] (M. Lassmann)

14:40-15:15 Legal basis in the United Kingdom (L. Fraser, UK Administration of Radioactive Substances Advisory Committee)

15:15-15:45 *Coffee break***Session 3 Survey and Expert Interviews on European Legal Requirements [WP2]**

Moderator: C. Decristoforo

Rapporteur: S. Peters

15:45-16:15 Presentation of survey methodology and results of questionnaires and expert interviews (J. Gear)

16:15-17:00 Member-state field reports and good-practice examples
Germany – A. Drzezga, German Commission on Radiological Protection
Sweden – A. Sundlöf, Swedish Medical Products Agency
Czechia – P. Solný, Czech Society of Nuclear Medicine

17:00-17:45 Discussion

17:45-18:00 Wrap-up and conclusions, Day 1 (M. Lassmann)

Tuesday, 12 December 2023

09:00-09:10 Welcome to Day 2 and introduction of programme (M. Lassmann)

Session 4 Recommendations to Advance Coherent Implementation of European Legal Requirements [WP3]

Moderator: M. Lassmann

Rapporteur: J. Gear

09:10-09:40 Identification and prioritisation of issues (F. Verburg)

09:40-10:30 Identified actions to be implemented as part of the project and proposed for the future (M. Lassmann, M. Bardiès)

10:30-10:50 Discussion

10:50-11:20 *Coffee break***Session 5 Roundtable Discussion on SIMPLERAD Guidance Document and Recommendations [WP3]**

Moderator: M. Lassmann

Rapporteur: C. Stokke

11:20-12:00 Round table panel statements
European Commission (G: Simeonov, DG ENER)
EMA (V. Fradin-Da Ros)
Nuclear medicine therapy expert (K. Herrmann)
Medical physics expert (S. Peters)
Radiopharmacy expert (M. Patt)
Patient representative (E. Briers, Europa Uomo)
Industry (L. Schätz, Novartis Pharma AG)

12:00-13:00 Open discussion on actions proposed and their implementation

13:00-14:00 *Lunch break*

**Session 6 Summary**

Rapporteur: EANM Office

14:00-15:00 Conclusions and recommendations per proposed action (M. Lassmann)

15:00-15:30 Summary and wrap-up per project task (M. Lassmann)

15:30-16:00 Next steps in the project (M. Hierath)

16:00 Closing (G. Simeonov, DG ENER; M. Lassmann)

5. Session Summaries

Day 1, December 11

5.1 Session 1: Opening & Setting the Scene

Aims of the session

Session 1 welcomed the participants onsite and online and introduced the house rules and agenda for day 1 of the workshop. The context of the use of therapeutic radiopharmaceuticals in Europe and the SAMIRA Action Plan were described before the SIMPLERAD project, the consortium members and its workplan for addressing the issues in the field were presented. Supplementing the project background, the European framework, including Euratom, pharmaceutical, clinical trial, and guidance and posology legislation, relevant to therapeutic radiopharmaceuticals was described by EC agencies and advisors. Perspectives on the challenges and project methodology were given by major international organisations to conclude the session.

Key points

- The SAMIRA Action Plan aims to ensure that the EU continues to be the global leader in supplying medical radioisotopes and developing radiological diagnostics and treatments, while applying the highest quality and safety standards.
- The SIMPLERAD project is a consortium of EIBIR, EANM and EFOMP that has undertaken a survey of the practices and legal regimes for the use of therapeutic radiopharmaceuticals and formulated guidelines and recommendations to advance the coherent implementation of the European legal requirements.
- The Basic Safety Standards Directive (BSSD), Council Directive 2013/59/Euratom, is a primary source for the requirements for radiation protection of patients, staff and the public in therapeutic nuclear medicine in Europe.
- EC agencies have procedures and guidelines for each step of the manufacture, testing and use of therapeutic radiopharmaceuticals.
- The WHO, IAEA and ICRP support the creation of norms and standards in this field in addition to their own programmes for research, quality assurance and safe use.

Summary of presentations

1. Welcome by the EC and consortium (G. Simeonov, M. Lassmann)

G. Simeonov and M. Lassmann introduce themselves and welcome the participants onsite and online. B.J. Krause, project scientific coordinator, is unable to attend in person. G. Simeonov describes the objectives of the SAMIRA Action Plan and its approach to therapeutic nuclear medicine as well as the role of the 2019 Euratom Scientific Seminar as background for the proposal leading to the SIMPLERAD project. M. Lassmann reviews the house rules, agenda for day 1 and representation of the project's target countries and types of organisations.



2. Introduction to the SIMPLERAD project (B.J. Krause)

B.J. Krause thanks the contributors to the project to this point and introduces the consortium members. The main topic of compliance with the BSSD Article 56 requirement of treatment planning and verification of absorbed dose delivered to patients is given, followed by the general and specific project objectives, the latter of which are the themes of the WPs. The role of the Advisory Board, the WPs and their leads and co-leads, and the project timeline are described. B.J. Krause wishes everyone a successful workshop and notes the timely achievements of the project in the context of the increasing use of therapeutic radiopharmaceuticals.

3. Presentation of the Euratom framework relevant to therapeutic radiopharmaceuticals (G. Simeonov)

G. Simeonov highlights some of the key BSSD requirements on therapeutic nuclear medicine, with medical exposure covered in Chapter 7. Basic safety standards against the effects of ionising radiation were introduced in the Euratom Treaty, and medical exposures have been subject to Euratom regulation since the 1990s. The latest revision of the BSSD keeps most of the legal provisions from the 1990s while introducing several changes, e.g., with respect to the responsibilities of MPEs and recording and reporting of patient doses. Therapeutic nuclear medicine has been subject to the Euratom requirements for radiotherapy since the 1990s. The recent interest in the role of patient dosimetry in treatment planning and verification stems not so much from Euratom regulatory changes but rather from the introduction of new therapeutic radiopharmaceuticals in recent years. Key legal definitions are reviewed along with the Article 56 requirements on optimisation and other articles on MPEs, procedures and operational protection of members of the public. The key regulatory phrases and definitions of relevance are reviewed.

4. Presentation of the European pharma legislation relevant to therapeutic radiopharmaceuticals (P. Erba)

P. Erba explains the EU pharmaceutical reform and its impact on radiopharmaceuticals. The reform has six objectives within the EU single market for medicines but does not address reimbursement. The regulatory frameworks of several countries are compared in terms of protection and duration for innovative pharmaceuticals, and the timeline of the proposed EU modulation is illustrated. Revising the definition of radiopharmaceutical could raise problems, given variations in national law of the EU member states. Reforms to marketing authorisation, labelling and instructions, and those particular to radiopharmaceuticals contained in annex 1 and 2 are presented.

5. Presentation of the clinical trials legislation relevant to therapeutic radiopharmaceuticals (A.M. Janson Lang)

A.M. Janson Lang introduces Regulation No. 536/2014 on clinical trials, which has applied since January 2022. The Regulation has four primary objectives to ensure patient safety and generate good data, harmonise the approval process, streamline the submission and review process, and increase transparency. Assessment is still based on a balance between risk and benefit at the national level. Benefit and risk when applied to therapeutic radiopharmaceuticals entails principles such as achieving as high a target-absorbed radiation dose as safely attainable and absorbed doses to tumour target lesions and dose limits to risk organs based on the best available evidence. Eudralex Volume 10 (See link on the [slide](#)) contains questions and answers regarding radiotherapeutics in clinical trials. The Clinical Trial Coordination and Advisory Group decided recently to establish a subgroup on radiotherapeutics to clarify and harmonise requirements on trial sponsors among the member states. The subgroup is now completing its membership, and DG SANTE will collaborate with colleagues of DG ENER on the BSSD.



6. Presentation of guidance and posology relevant to therapeutic radiopharmaceuticals (V. Fradin-Da Ros)

V. Fradin-Da Ros explains the EMA's missions, activities and organisational structure within the EU. The EMA's policy for stakeholder engagement and some principles for the use of medicines in the EU are also described. Principles from section 4.2 and 4.4, as detailed in the Guideline on Core SmPC, Labelling and Package Leaflet for Advanced Therapy Medicinal Products Containing Genetically Modified Cells (See links on the [slides](#)), are presented in addition to the list of the nine therapeutic radiopharmaceuticals centrally authorised. Examples of the summary of product characteristics (SmPC) sections 4.2 and 4.4 for the four radiopharmaceuticals recently authorised centrally, i.e., LUTATHERA®, Lumark®, Pluvicto® and Lutetium (¹⁷⁷Lu) chloride Billev, are presented. The restart of the work undertaken by the EMA and experts from the EU network on radiopharmaceuticals, their planned activities, and ambitions for 2024 are mentioned as a conclusion.

7. Perspectives of the World Health Organisation (L. Gwaza)

L. Gwaza, team lead for norms and standards for radiopharmaceuticals, cites the tremendous progress in human health since the establishment of the WHO and explains its current work to address the ongoing challenges in health and access to quality radiology and medical products. Importantly, half of cancer patients in low- and middle-income countries do not have access to radiotherapy. The differentiated approach to improve health based on a state's capacity and vulnerability is a key component of its mission. Its programmes supporting regulatory systems are described, including collaborating with the IAEA to develop public standards and quality assurance guidelines for radiopharmaceuticals.

8. Perspectives of the International Atomic Energy Agency (A. Korde)

A. Korde of the IAEA's Radiochemistry and Radiation Technology Section focuses on the Technical Cooperation projects supporting member states to produce radioisotopes, develop radiopharmaceuticals, conduct preclinical testing and translate these products to safe effective use on patients. Some historic results of Technical Cooperation projects in these areas are highlighted, in addition to the IAEA's role to develop guidelines and promote best practices through technical meetings, education and publications. The outcomes of a recent technical meeting on pharmaceutical regulations for radiopharmaceuticals are highlighted.

9. Perspectives of the International Commission on Radiological Protection (A. Giussani)

A. Giussani recommends ICRP publications of interest to the project and highlights relevant portions among the recommended actions proposed in WP3. Radiotherapy with radiopharmaceuticals was one topic of interest at the recent ICRP symposium in Japan, and a working party on new radiotherapies, including radiotherapy with alpha emitters, has been recently established.

Summary of discussion

C. Decristoforo asks if the upcoming EMA concept paper on therapeutic radiopharmaceuticals and the clinical trials initiative on therapeutic radiopharmaceuticals are the same. A.M. Janson Lang replies that the Clinical Trial Coordination and Advisory Group is composed of all member states, and the initiative addresses questions regarding the legally required approval before clinical trial are conducted, while the EMA initiative concerns guidelines on the centrally approved marketing approval of therapeutic radiopharmaceuticals in oncology.



Conclusions from the session

- The SIMPLERAD project is addressing the challenges to the safe and effective use of therapeutic radiopharmaceuticals and is on track to deliver its proposed outcomes by the end of the project.
- The European legal framework for therapeutic radiopharmaceuticals is a network of laws and guidelines developed by Euratom, EC, EMA and expert groups, each with a somewhat autonomous role but collaborating where necessary.
- The WHO, IAEA and ICRP support the project's work and administer several relevant programmes in line with its objectives, with references that may help guide the consortium's response to the selected issues.

5.2 Session 2: Interrelations among Legal and Regulatory Frameworks [WP1]

Aims of the session

The aim of this session was to summarise the methodologies and results of WP1 and its presentation to the workshop audience. SIMPLERAD WP1 itself aims to analyse links and interdependencies between the European pharmaceutical legislations and Euratom radiation protection requirements and highlight potential barriers to implementation of the BSSD. In addition, the results of a comparative analysis between the situation in the EU member states and the UK and US were to be presented, supplemented by a detailed update on the situation in the UK.

Key points

- WP1 methodology consists of a literature analysis, an in-depth study in selected member states on therapeutic radiopharmaceuticals and medical devices and the respective analysis of SmPCs and instructions for use (IFU).
- Lack of awareness and consideration of Art. 56 (BSSD) requirements among regulators and EMA guidelines, respectively, was identified as one reason for insufficient implementation in the EU.
- Legal frameworks in the EU and UK are very similar regarding regulation of medical application of ionizing radiation.
- The US regulatory framework is governed by two agencies, the FDA and Nuclear Regulatory Commission (NRC). The former is in charge of granting marketing authorisation and prescribing posologies. Compared to the EU, the relationship between the two agencies is more formalised.
- Posologies in recent marketing authorizations in EU, UK and US are primarily based on fixed activities or other generic values such as body weight and body surface area but not individually calculated dose requirements.
- Guidance for industry regarding development of therapeutic radiopharmaceuticals is available in the US but not in the EU.

Summary of presentations

1. Results of analytical work and identified regulatory and implementation issues [WP 1] (M. Bardiès)

Prof. Manuel Bardiès as leader of WP1 gave an overview on the methodologies and outcomes of the work package. Derived from the EANM position paper the most relevant (n=18) radiopharmaceuticals were identified, complemented by ¹⁷⁷Lu-labelled PSMA-ligands, which were just recently approved outside the EU, and medical devices for selective internal radiotherapy (SIRT). An extensive literature analysis was performed covering regulatory documents, position papers, guidance documents, international body recommendations, scientific literature as well as SmPCs and IFU for medicinal products



and medical devices, respectively. The methodology was completed by an in-depth study of the regulatory framework in seven selected countries, i.e., Finland, France, Germany, Italy, Poland, Spain and Sweden. Although the BSSD in all countries was “faithfully” transcribed into national law, it is usually the fixed activity posology recommended in the SmPC that is followed. However, in about half of the selected countries, the community is aware of the existence of a contradiction between BSSD requirements and EU SmPC posologies and aims at establishing guidance on how to implement dosimetry in nuclear medicine therapy. Good practice examples were identified for the posologies of Na(¹³¹I) and SIRT, while posologies for ¹⁷⁷Lu-labelled compounds that were recently authorised use fixed activity, and therefore are non-compliant with BSSD requirements. However, the SmPCs of therapeutic radiopharmaceuticals in general contain reference to the ALARA principle and do point out a need for a positive risk/benefit evaluation. The lack of awareness of regulators regarding BSSD requirements and optimisation principle was identified as a major hurdle for its implementation. Moreover, the lack of intersection between pharma and radiation protection legislation results in confusion which legislation is to be given precedence. In addition, a lack of European guidance on how to implement BSSD in nuclear medicine therapy was identified. Even though the BSSD is a *lex specialis* and the current pharma directive clearly states a need for consideration or even precedence of BSSD (Dir 2001/83/EC recital (18) and article 4), the current practice is a different one. In addition, Prof. Bardiès pointed out that though the first draft of a revision of the community code directive that was published by the EC in April contained a more explicit reference to the BSSD optimisation principle and its applicability to radiopharmaceuticals, the currently tabulated amendments that will be subject to discussion and approval by the European Parliament bear the potential to weaken the BSSD’s influence and effect on medical treatment using ionising radiation.

2. Presentation of the outcome of comparative analysis of the legal bases in the United States, United Kingdom and EU [WP 1] (M. Lassmann)

Prof. Michael Lassmann summarised the main findings of a comparative analysis that was performed regarding the legal bases of the application of radiopharmaceuticals for therapeutic purposes in the European member states, the UK and US. The main legal framework for pharmaceuticals in the EU is defined by directive 2001/83/EC. 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 (IR(ME)R), which transcribes the BSSD requirements into national law and has not been altered since the UK left the EU. Since a dedicated talk about the situation in the UK was yet to come, the situation was not further elaborated by Prof. Lassmann.

In the US, there are two agencies that govern the situation, i.e., the FDA, which is responsible for granting marketing authorisations, and NRC. In contrast to the situation in Europe, the relation between these agencies is stricter, and FDA governance is given priority over NRC regulations, e.g., NRC Reg., Part 3, 5§35.7¹. Prescribed posologies for recently approved therapeutic radiopharmaceuticals are similar to the ones approved in the EU, i.e., fixed activities for ¹⁷⁷Lu-labelled products such as Lutathera and Pluvicto or dosage based on dosimetric calculations (either mandatory or recommended) for SIRT products. In contrast to the EU, guidance documents for industry applicable to the developmental phase of therapeutic radiopharmaceuticals have been issued².

¹ “Nothing in this part relieves the licensee from complying with applicable FDA, other Federal, and State requirements governing radioactive drugs or devices.”

² Nonclinical evaluation of late radiation toxicity of therapeutic radiopharmaceuticals, 2011; Non-clinical studies and labelling recommendations for oncology therapeutic radiopharmaceuticals, 2019).



3. Update on the situation in the UK (L. Fraser, UK Administration of Radioactive Substances Advisory Committee)

Dr. Louise Fraser from the UK Health Security Agency gave an overview on the regulatory framework governing the application of ionising radiation for medical applications in the UK and Northern Ireland. In principle the framework is very similar to that of the EU since the main legal act governing the medical application of ionising radiation, the IR(ME)R, represents the UK's national transcription of the BSSD before the UK left the EU. Therefore, the same basic principle of optimisation applies but nevertheless, individual patient dosimetry is not routinely applied. In addition, Dr. Fraser elaborated in more detail on the practical implementation of IR(ME)R regarding licence application processed by an independent expert committee, the Administration of Radioactive Substances Advisory Committee, and the individual duties of the different stakeholders such as employers, referrers, practitioners and operators.

Summary of discussion

The discussion started with a question of the expected impact of the health technology assessment regulation on reimbursement policies for radiopharmaceuticals. The question was addressed by G. Simeonov in a general way, stating that DG ENER is currently discussing several issues concerning radiopharmaceutical therapies with various stakeholders of DG SANTE; however, this specific topic was not investigated by the SIMPLERAD project since it is out of scope of the project. A controversial discussion evolved on the efficiency of the implementation of BSSD requirements into recently granted marketing authorisations via the central procedure by the EC. A participant hypothesised that the actions of the directorates involved in regulating the use of therapeutic radiopharmaceuticals, DG ENER and DG SANTE, are far from harmonised and that the EMA seems to be unaware of the optimisation principle stipulated by the BSSD. It was stated that since the beginning of the SIMPLERAD project several steps towards a better implementation have already been initiated, something that might serve as justification of the project on its own. Another participant emphasises that the pharma legislation explicitly expresses awareness of BSSD requirements. Even though the applicability of the optimization principle is made clear in the BSSD, it is not adequately considered by the respective competent authorities, referring to the posologies granted for Lutathera and Pluvicto. A further reason for insufficient implementation of BSSD requirements being the lack of sufficiently trained medical physics experts was suggested by another participant.

Conclusions from the session

Although safety and efficacy of treatment for the patient is the ultimate aim of both regulatory sets, i.e., pharma legislation and BSSD, the implementation of the optimisation principle needs to be improved. In addition to establishment of practical guidance and recommendations to advance a coherent implementation of the BSSD requirements, improvement of the MPE workforce, and creation of data-processing procedures during the application phase of clinical trials, collaboration between the directorates responsible for radiation protection and pharmaceutical legislation needs to be improved.

5.3 Session 3: Survey and Expert Interviews on European Legal Requirements [WP2]

Aims of the session

To summarise the (barriers to) practical implementation of regulatory requirements for therapeutic nuclear medicine, as was found in WP2. Both expert interviews as well as a survey on a European level along different stakeholders were used. In addition, some good practice examples from member states were given.



Key points

- Results of expert interviews and the survey were presented.
- Survey showed that understanding of legislation concerning radiopharmaceuticals varies widely, resulting in differences in interpretation and implementation, mainly of the BSSD Article 56 requirement.
- Three good practice examples from Germany, Sweden and Czechia showed that also in these countries the situation regarding treatment optimisation for radionuclide therapy varies widely.

Summary of presentations

1. Survey and expert interviews on European legal requirements (J. Gear)

A presentation on the work in SIMPLERAD WP2 was given. The structure of WP2 used a pre-survey to select input for the main survey of the WP and also to select relevant contacts to send the survey to. In addition, expert interviews were held, to identify gaps and barriers in implementing requirements in the development and use of therapeutic radiopharmaceuticals. A total of 25 experts were interviewed from different backgrounds, e.g., regulators, industry, MPEs, nuclear medicine physicians and radiopharmacists. Results are elaborately discussed in deliverable 2.3.

Most important results from expert interviews:

- **Biggest challenge in nuclear medicine therapy:** Supply/distribution of radiopharmaceuticals, which is outside the scope of SIMPLERAD
- **Main barriers:** Regulations, with an aspect of regulation that causes difficulty, in addition to reimbursement
- **Greatest impact:** Lack of EU harmonisation
- **Understanding of legislation:** Either not understood, not available or ignored
- **Absorbed dose calculations:** Agreement amongst stakeholders that it can support individual optimisation
- **Posology:** Should be flexible

The main survey consisted of around 100 questions, and we received a total of 193 usable responses, representing 40 countries and 27 EU member states. Questions were asked about radiopharmaceutical legislation, posology vs. dosimetry, treatment planning and verification, dose constraints and patient release, waste, and MPE training and responsibilities.

Key findings that emerged concerning these topics were the following.

Radiopharmaceutical legislation

The study revealed a lack of specificity in both national and European legislation concerning radioactive therapeutic compounds. This ambiguity led to heterogeneous implementation practices across Europe, affecting the preparation, administration and distribution of radiopharmaceuticals. Different legislative processes were identified as potential hurdles, emphasising the need for closer collaboration and interdisciplinary expertise to address these concerns, particularly within the regulatory frameworks.

Posology vs. dosimetry

Confusion within the community was noted regarding the requirement for optimization outlined in the BSSD versus the need to adhere to posology from marketing authorizations. The lack of specific instructions raised concerns about treating off-label, hindering optimisation at the clinical level. The study identified a need for dosimetry data from clinical trials and regulatory guidance on conducting such studies.



Planning and verification

Across most therapies, there was a recognized desire for dosimetry-guided optimization and verification. However, in many countries, detailed legislative or national guidance on these practices was lacking. The predominant barrier was identified as a shortage of resources, including reimbursement, know-how, and adequately trained staff. The study recommended further clarifications on planning and verification requirements.

Dose constraints and patient release

Heterogeneity in implementing dose constraints and patient release criteria was apparent across member states. Participants expressed a desire for unified dose constraints at the national or European level. Variation in the interpretation and translation of "comforter and carer" across Europe could lead to differences in potential household exposure post-treatment. Standardized national instructions for patient release were generally missing, impacting the social and economic implications of hospital stays.

Waste management

While conditions for managing radioactive waste were in place across Europe, the underlying radiological assessments were unclear. Discrepancies in activity concentration limits or discharge limits per month or year were noted. Patient access to treatment might be hindered by the need to travel to centres with proper waste facilities or face long waiting lists.

MPEs

Insufficient medical physics support in most countries emerged as a barrier to implementing treatment planning and verification. Variations in training and accreditation of MPEs were observed across Europe, with differences in the number of MPEs per centre, potentially influenced by size and national-level competencies and responsibilities. Efforts within EFOMP and EANM are aiming to address these discrepancies.

2. Member-State field report and good-practice examples: Germany (A. Drzewga, German Commission on Radiological Protection)

The involved authorities and federal agencies, e.g., [Clinical Trials Information System](#), Federal Institute for Drugs and Medical Devices (BfArM), and [Federal Office for Radiation Protection](#) (BfS) are discussed.

Clinical application options:

For non-approved diagnostic radiopharmaceuticals there are in principle two possibilities available for the legal basis of preparation. One is based on the German Regulation on Radioactive Medicines or Medicines Treated with Ionising Radiation (AMRadV), requiring manufacturing authorisation, i.e., full industrial good manufacturing practice (GMP), and the other possibility is the manufacture of non-approved drugs under the direct responsibility of the physician for his own patient. The latter possibility is also applicable to therapeutic radiopharmaceuticals. A special situation applies in Germany for the reconstitution-like compounding of diagnostic radiopharmaceutical from licensed kits and licensed generator-eluate. While in most European countries this type of preparation is considered to be different from manufacturing, thus facilitated quality assurance standards apply, in Germany there is from a legal point of view no differentiation between a complex multi-step manufacturing procedure and a kit-based compounding.

Trial application requirements:

- **Pathophysiology trials:** Ethics approval, BfS approval, no BfArM
- **Established clinical application:** No BfS, yes BfArM
- **Companion diagnostics:** BfS notification only, BfArM only for investigational drug
- **Original drug trial:** Ethics/IRB approval, BfS approval, BfArM

Issues:

- **Involvement of multiple authorities:** Risk on difference in perspective and delay
- **GMP regulations:** Heterogeneity regionally within Germany
- **BFS/radiation protection/dosimetry requirements:** unclarity on where dosimetry is required in trials
- **Paperwork**
- **Dosimetry:** discussion going on in Germany, mainly useful in non-standardized setting and first cycle treatment, not make it too extensive.
- **Recommendations of German Committee on Radiological Protection:**
 - R1 infrastructure
 - R2 inpatient treatment
 - R3 Quality assurance
 - R4 Handling of radioactive residues

- **Suggestions from the presenter:**
 - Introduction of GMP light for radionuclides and kits combination (radiolabelling)
 - Introduction of regulated pathway for local production of therapeutic radiopharmaceuticals similar to the AMRadV
 - Combination of different bodies for clinical studies approval
 - International standardisation, not following the strictest possible interpretation
 - Limitation of dosimetry requirements to a reasonable amount

3. Member-state field report and good-practice examples: Sweden (A. Sundlöv, Swedish Medical Products Agency)

Dr. Sundlöv explains that in Sweden there is a privileged situation with a long tradition of high-quality research in radiation therapies, including radionuclide therapy and internal dosimetry. Still, the optimization principle is implemented inconsistently, and mostly within clinical trials.

In 2021, a collaboration between the Radiation Safety Authority and the Medical Products Agency was started. Discussion led to the identification of common grounds. They now have regular meetings and consultations as needed, they give lectures/presentations together and conferences and meetings, and they participate in the SAMIRA project. Main message of the presentation: talking to each other, trying to understand each other, is key across all different professionals to move forward and achieve the goal of implementation of BSSD article 56 requirements.

4. Member-state field report and good-practice examples: Czechia (P. Solny, Czech Society of Nuclear Medicine)

Mr. Solny discusses the use of therapeutic radiopharmaceuticals in Czechia since the introduction of the BSSD and its translation into the Czech legal framework. The position of most nuclear medicine physicians is that the BSSD does not reflect the clinical reality for nuclear medicine, as it is mainly formulated for external beam radiation therapy, and therefore dosimetry is very limited in implementation. However, thanks to good collaboration between regulatory bodies, scientific bodies and small-scale dosimetry projects, the added value of dosimetry is now more accepted amongst all stakeholders. The problem is reimbursement, which would enable more specialists to become involved. Furthermore larger projects to unify and optimise the treatment schedule for ¹³¹I is requested. Furthermore, the dosimetric procedures need to be practical and consistent with the general radiation protection principles. Therefore, it is important to create unified guidelines and a collaborative international effort to streamline studies, research and practices in nuclear medicine, including current treatments and all new ones.



Summary of discussion

- Paddy Gilligan (MPE, EFOMP president): Requirement of 2 MPEs per radionuclide therapy per 1 million population; for implementation and standardisation. This would mean 2000 MPEs within Europe. The total MPE numbers would need harmonisation. This should be part of an extra DG GROW directive. Also, it is important to include patients into the treatment optimisation discussion. There is a need for a patient survey on their experience with dosimetry, asking, for example, the patient burden.
- John Dickson (MPE): It is important that we try to engage professional societies, we need to talk to each other.
- Anna Sundlöv (regulator): When it comes to making things happen, the SAMIRA joint action is where we are supposed to take the action items from this SIMPLERAD project. Again, talking to each other is key.
- Ann Marie Janson Lang (Clinical Trials Facilitation and Coordination Group): Initiate communication between radionuclide-therapy dosimetry experts from DG ENER with radiation therapy experts in the network of DG SANTE. Involve all stakeholders. Recognise that all regulations are relevant and talking to each other is key.
- Jonathan Gear (MPE): An important aspect in this discussion is knowledge of regulators. There are many different organisations, but within these organisations there are few expert people in this specific field. This means a high burden on a limited number of regulators (lack of resources), so collaboration on EU level is important.
- Silvano Gnesin (MPE): Limited MPE resources is a short-term problem. Many students are interested, but we need to create the conditions for training and for them to have a position in the field after their training.
- Sergejs Akuličs (regulator): Too much dosimetry is not needed, we need clinical dosimetry to be provided and monitored for the sake of patients. We should only perform meaningful dosimetry.
- Anna Sundlöv (regulator): Indeed, we should not perform dosimetry for the sake of dosimetry, but we should put it to good use by optimising the treatment and improving patient selection.
- Marianne Patt (radiopharmacist): Why is the requirement of treatment planning and verification even in the BSSD if the dosimetry data does not support this?
- Bernhard Sattler (MPE): We should recognise the parallels to external beam radiation therapy. There is no question about whether it has to be planned or not, it is the use of therapeutic ionising radiation. We have to make it bearable for the patients, it is not a question of to do or not to do, but to make the burden as low as possible. We should take into account the life expectancy of patients into this burden.
- Filip Vanhavere (EURADOS): There is a need for more research in dosimetry. It would help to increase accuracy, help to reduce the burden to patients, etc.
- Leo Schätz (Novartis): 3 thoughts I would like to share: 1) we lump all nuclear-medicine interventions into 1 thing, should we make buckets? 2) In some buckets we will have labelled posology. 3) Capacity constraints are crucial, many countries in the EU do not have infrastructure, so dosimetry should not limit the application for all these patients. Very limited added value for individual patients, we should only apply dosimetry when we know it has a lot of effect.



- Clemens Decristoforo (radiopharmacist): Would a distinction between therapeutic and diagnostic radiopharmaceuticals be beneficial?
- Marianne Patt (radiopharmacist): Yes, that should be there. For example, in Germany we now have the possibility to use diagnostic radiopharmaceuticals under special law, while for therapeutic ones this is not allowed. There is a controversy here.
- Bernhard Sattler (MPE): Do we really need animal studies to demonstrate dosimetry? This should not be needed if a similar thing has been shown earlier. We could then use a fast track for new radiopharmaceutical development.
- Manuel Bardiès (MPE): Instead of external beam radiation therapy with photons, why not use other particles like protons? Then we would need no dosimetry since there is no knowledge on this dose. This would be ridiculous right? The same holds for dosimetry in radionuclide therapy, we cannot not do it just because we have limited knowledge on the dose and dose effects. In external beam radiation therapy we are investing a lot in research and standardisation. This is what is needed for radionuclide therapy also.
- Tommi Nojonen (MPE): Right now we have a lot of discussion about dosimetry. Harmonisation is also required for more simple instructions about release criteria, waste management, etc. This would be very helpful for countries with limited resources.
- Katarina Sjögreen Gleisner (MPE): When ionising radiation is delivered to a patient, the therapeutic absorbed dose needs to be monitored individually. The absorbed dose delivered during radionuclide therapy is largely unknown. This should be concerning to those responsible for radiation protection in Europe. How can a therapeutic exposure be justified if the absorbed dose is unknown?
- Jonathan Gear (MPE): It cannot.
- Maria Luisa Ramirez Vera, Spanish Nuclear Safety Council (regulatory body): The SIMPLERAD project should answer to some extent why we have to require dosimetry? Is it because of history since it is in the BSSD? What is the added value for the patient? If there is no impact in the treatment, or the results?

Conclusions from the session

WP2 findings showed that understanding of legislation concerning radiopharmaceuticals varies widely, resulting in differences in interpretation and implementation, mainly of the BSSD Article 56 requirement. Comments from the discussion session need to be implemented into the WP3 suggested solutions if applicable. The discussion also relates to workshop session 5, the round table discussion, as general input from workshop attendees on D3.2

**Day 2, December 12****5.4 Session 4: Recommendations to Advance Coherent Implementation of European Legal Requirements [WP3]****Aims of the session**

The aims of this session were to introduce the key issues identified by the SIMPLERAD project concerning the implementation of the European pharmaceutical legislations and Euratom radiation protection requirements with respect to the therapeutic use of radiopharmaceuticals. It was the intention that the actions proposed by the SIMPLERAD consortium, to be taken to advance the coherent implementation of European Legal requirements, are introduced to the wider stakeholder audience whilst providing the opportunity for discussion concerning the raised issues and proposed remedies.

Key points

- The results of literature and legal texts reviewed for the tender and WP1 as well as the results of the interviews and survey were analysed.
- Of the topics highlighted in WP1 and WP2, 10 unique issues were identified.
- For each issue multiple suggestions were presented
- Proposals included actions to be taken within the framework of the SIMPLERAD project and those that could only be tackled in the wider context of SAMIRA.
- SWOT analysis was presented for each proposal.
- A lively discussion followed the presentations concerning the practicality of the proposals and the wider application of dosimetry in nuclear medicine therapy.

Summary of presentations

Prof Erik Verburg, WP 3 leader, provided the opening presentation summarising all the topics and issues identified through the activities of WPs 1 and 2 and explained how within work package 3 this list was itemised and condensed into a final proposal of priorities. Prof Verburg highlighted that there was often overlap in the topics and as such many items could be combined into a single unique issue. Examples were given for the different issues alongside the pertinent evidence from the other work packages. The timeline for the work was presented explaining that the draft deliverable document providing this proposal was initially sent to the project's Advisory Board and the EC in October 2023. This consultation was said to continue throughout November and December, including input from HERCA WGMA, SGQS, EMA and the Advisory Board. Feedback from the workshop would also be integrated into the proposal before a final ready-to-publish version is accepted April 2024 within the consortium's final report to the EC.

Following this initial presentation Prof Michael Lassmann and Prof Manuel Bardiès elaborated on each of the items and presented the proposal of remedies. For each of the 10 items a number of proposed actions were discussed. These suggestions were grouped between those that could be initiated as part of the SIMPLERAD project and those that were suggested for consideration for action in the wider context of SAMIRA. The strength, weaknesses, opportunities and threats of each item were also presented.

Prof Bardiès and Prof Lassmann also presented the content of three documents that have been established over the course of the SIMPLERAD project and form some of the proposed remedies. The first of these documents, Implementing Dosimetry in Clinical Practise, aimed to reconcile the content of three other documents, ICRU report 96, EFOMP policy statement 19, and the EANM position paper on Article 56. The second document presented was a guidance document, On Treatment Planning and Verification for Selected Radiopharmaceuticals, which is largely based on the recently published EANM Enabling guide How to Improve the Accessibility of Clinical Dosimetry. These documents give examples of how dosimetry can be performed for treatment planning and verification for



five of the most important use cases. The examples presented included two cases each of which require a differing level of resources with unique advantages and disadvantages.

The third document presented concerned dosimetry in clinical trials and was also a product of the EANM. Titled EANM Dosimetry Committee Guidance Document: Dosimetry for First-in-Human Studies and Early Phase Clinical Trials, the document provides recommendations on the methods for activity measurement and pharmacokinetic analyses as well as absorbed dose calculations and uncertainty analyses, emphasising good practice reporting and listing the relevant dosimetry parameters and method descriptions.

Summary of discussion

The discussion opened with questions from the online audience. This included a question concerning how industry had been included in the discussions concerning the proposed remedies. Prof Lassmann assured that Nuclear Medicine Europe were part of the Advisory Board and have been able to provide feedback concerning all aspects of the SIMPLERAD project. It was also asked if those that have received a draft copy of the deliverable could share this with additional stakeholders in their country such as competent authorities and national societies. Georgi Simeonov confirmed that this would be possible, provided that the draft nature of the document is appropriately acknowledged and the objective of further distribution, i.e., to collect further input on the draft, is fully respected. However, Ms Monika Hierath of the SIMPLERAD consortium and EIBIR office raised concerns over the short timeline that feedback is required and therefore the deadlines would first need to be discussed. Within the room Prof Ken Hermann raised concerns that some of the proposed remedies would not be easy to implement and asked what could be employed to simplify the situation. The issue surrounding scientific evidence was also raised. Prof Bardiès noted that when we discuss dosimetry we need to establish the distinction between dosimetry as a legal necessity or because it has added clinical added value. Prof Bardiès argued that there are substantial barriers initiating the Phase 3 clinical trial and waiting for such data to be available would be futile. He stated that the BSSD recognises that these therapies are a form of radiotherapy, initiating a deterministic effect, which is why the absorbed doses being delivered should be monitored. Data from such monitoring will in the future provide the clinical added value being sought. Prof Hermann was concerned that being too prohibitive in requirements for dosimetry could be detrimental to the treatment. Prof Verburg followed up highlighting the need to assess safety as well as efficacy, particularly if a practitioner wishes to prescribe beyond the activities or cycles within the package insert. Prof Hermann agreed but emphasised it shouldn't be a requirement when treating within the posology of the SmPC. U. Holzwarth again emphasised the need to distinguish between regulatory dosimetry and research dosimetry, noting that the regulations are there to protect the patient, but this should not be done to excess. A point is raised that the treatments have been approved and have demonstrated positive benefit/risk ratio, and thus patients have a right to access these treatments. It was suggested that if there is a law that requires dosimetry, when dosimetry cannot be implemented, then a change to the law is required.

Dr Anna Sundlöv from the Swedish Medical Products Agency argued that the relationship between absorbed dose and biological effect does not need to be proven, as it is already well established in all other types of radiotherapy. The burden of additional imaging and dosimetry investigations was also compared to that required for external beam radiotherapy. Dr Chiesa pointed to the results of the DosiSphere trial and evidence of dosimetry improving treatment in a randomised control trial. In opposition to the remarks of Prof Hermann, Dr Chiesa felt the proposed actions of the SIMPLERAD project were not sufficiently strong and suggested that clearer timelines for the actions be given. In addition, he asked that the report include a statement that EMA should immediately release an amendment to allow centres the possibility of treating patients according to BSSD optimisation, not mandating dosimetry for all treatments, but opening the possibility for those that are capable. The requirement for additional resources was also raised alongside the need for carefully refined reimbursement costs. Ms. Paula Santos from the Portuguese Environment Agency later emphasised this point, noting that there could be an economical benefit to including dosimetry within the treatment regimen.



Mr Leonhard Schätz from Novartis Pharma AG noted that mandating dosimetry, or attempting to generate evidence by mandating dosimetry would not work. It was suggested that a network of centres be established and a repository for dosimetry data be created. Mr Schätz argued that to know the corrected hypothesis, data must first be generated in a standardised way that can then inform prospective trials. It was stressed that it would be better to allow the network of centres to generate the retrospective data but not mandate other centres that do not have infrastructure. Concern was raised that to do so would create more barriers for treatment access. It was felt that product posology should allow sufficient freedom to reach a broad range of patients with low barriers. Mr Schätz stated that industry cannot invest resources into dosimetry clinical trials, as currently it is unclear what such a trial would look like and how it would lead to drug approval.

Prof Bardiès agreed that as a first step establishing such a network and working towards standardisation across centres of excellence was an initial step to gathering evidence. He stressed that no one is implying that dosimetry should be mandated everywhere straight away. He stressed that what is needed at this moment is a defined political direction and a plan of how to get there. Dr Sundlov also agreed with the concept of having sites that do more and sites that do less provided in the end the direction is to ensure patients get the best optimised treatment. It was again stressed that there is no need to prove the concept of dose effect, but what is required is data to quantify the magnitude of said effect. Dr Sundlöv did not feel the requirement to reach that point is too far away as many data can be extrapolated. For example, she suggested that once the dose limit for kidney is set for Lutathera a similar dose limit may be applicable to Pluvicto.

Dr Sarah Baatout from the Belgian Nuclear Research Centre commented that she was enjoying the openness of the discussion across all the different disciplines. However, she would also like to highlight the importance of radiobiology and would like to see more recommendations concerning this in the deliverable, as it is important to training and understanding data particularly when it comes to distinguishing between responders, non-responders and observed side effects. The second point raised was linked to Belgium having EU presidency in 2024, the use and supply of radiopharmaceuticals is a key point on the agenda for Belgium, particularly concerning cost recovery of reactors as much of these costs are being covered nationally. Dr Baatout would like to see more emphasis on this and would also like to invite some of the workshop speakers to a summit being organised in May or June next year. Professor Lassmann thanked the representative and stressed that radiopharmaceutical supply is a key concern of the EC and being covered extensively in the SAMIRA action plan but was outside the specific scope of the SIMPLERAD project.

Mrs Vanessa Fradin-Da Ros, representing the EMA, reminded the audience that for drug approval, decision makers have concluded from the assessed data that the benefits outweigh the risks. Georgi Simeonov clarified that the requirement for the benefit to outweigh risk corresponds to the BSSD provisions for justification. However, the BSSD also requires optimisation, meaning an effort to maximise the benefit/risk ratio both at the level of the general treatment procedure and on an individual basis. He stressed that there is no desire to impose a new layer of regulations, and instead the aim is to find a practical way of implementing what is already in the regulations.

Conclusions from the session

The consortium should ensure practical actions to the issues identified. The centres of excellence /network and generation data should be further emphasised in the report. Consideration to timelines and a roadmap to implementation should be given in the report.



5.5 Session 5: Roundtable Discussion on SIMPLERAD Guidance Document and Recommendations [WP3]

Aims of the session

The aims of this session were to discuss the key issues identified by the SIMPLERAD project concerning the implementation of the European pharmaceutical legislations and Euratom radiation protection requirements with respect to the therapeutic use of radiopharmaceuticals. Stakeholder representatives would present initial statements, followed by an open discussion on actions proposed and their implementation, including also the wider stakeholder and target group audience.

Key points

- Round table panel statements were made by:
 - EMA (V. Fradin-Da Ros)
 - Patient representative (E. Briers, Europa Uomo)
 - Medical physics expert (S. Peters)
 - Nuclear medicine therapy expert (K. Herrmann)
 - Radiopharmacy expert (M. Patt)
 - Industry (L. Schätz, Novartis Pharma AG)
 - European Commission (G. Simeonov, DG ENER)
- A discussion followed, concerning the key issues of the project, future actions and the wider application of dosimetry in nuclear medicine therapy.

Summary of presentations

The panellists had before the workshop been asked to consider three points.

- To share the three most important topics to be discussed during the 2-day workshop on the SIMPLERAD project.
- What is the greatest challenge in your view to providing access to high-quality and safe nuclear medicine and radiopharmaceuticals in the EU?
- Which is the first priority with respect to implementation of EU legislation regarding this topic?

EMA (V. Fradin-Da Ros): V. Fradin-Da Ros gave a concise statement that the challenge encountered at the EMA level, and possibly also at a member-state level in the pharma context, is to gather appropriate expertise to discuss and handle the points discussed during the SIMPLERAD workshop.

Patient representative (E. Briers, Europa Uomo): E. Briers addressed issues from the patient's perspective. He remarked that the answer to the question: "What do patients want?" is simple: "Patients want a cure for their disease;" followed by: "And if that's not possible, they want good control with good quality of life. And they want quality at the end of life." Afterwards, he discussed the issues with availability and affordability. He exemplified the points referring to medicine shortages for treatments with lutetium for patients with prostate cancer and also reimbursement issues. He also touched upon the special considerations for radioprotection, adding to both affordability and availability questions. At the end he commented that the technical discussions regarding dosimetry are challenging to comprehend for patients, who are mainly concerned with receiving the treatment.

Medical physics expert (S. Peters): S. Peters started by arguing for the importance of looking at nuclear medicine therapy as a field of its own, instead of comparing it to diagnostic nuclear medicine, external beam radiotherapy or chemotherapy. She also commented on the multidisciplinary nature of the field, concerning many different stakeholders. She remarked that the answer to the question "Do we need to apply treatment optimisation because it is written in the BSSD, or because we think it's good for the patients?" is in the end always the latter. Peters commented on the lack of conflicting



requirements between EU pharma legislation and the treatment optimisation requirement in the BSSD, stating that the issue is more in the understanding and the interpretation of these requirements and this legislation. A need for educational programmes was stated. While the resource issue was raised, S. Peters stated that we should rather think about how we can tackle these challenges and how we can set the roadmap together to implement this. "Because I think it should never be the point that we settle for suboptimal treatment, for suboptimal patient selection, just because that is what we can do now. I think we should work towards a way where we can have optimal treatment for patients." She argued that we should not settle for one-size-fits-all treatments in radionuclide therapy because we know that is not optimal. She expressed concern that this may "kill radionuclide therapy in the end because we will have not optimal results and we will have higher healthcare costs." Her final point was that proactive governance is very important to ensure implementation, also to establish reimbursement for imaging and dosimetry.

Nuclear medicine therapy expert (K. Herrmann): K. Herrmann started by addressing the issue of how to scale up. He discussed four challenges related to this issue, the first being the workforce. The second was patient referral, exemplified by how a range of centres, not only academic centres, need to be aware that the therapy is available. The third was reimbursement and the fourth striving for improvement and optimising. "Vision has only 46% of PSA-50 response. We can get better, which means we have to optimise dosing." Coming to the topics relevant to discuss, Herrmann reiterated that scale-up is one, together with ensuring that we have fast-track mechanisms to get new treatments into humans. Finally, he stated he is "a big believer in dosimetry, but not in dosimetric overkill," meaning that it has to serve a purpose and show that it affects patient outcome.

Radiopharmacy expert (M. Patt): M. Patt stated that radiopharmacists are not really involved in the questions of the SIMPLERAD project. "We have other fields where radiation protection and pharma legislation meet and where compromises have to be made." She expressed a strong desire to see DG ENER initiate a similar project to SIMPLERAD but rather on the production of radiopharmaceuticals. This would especially concern the production of radiopharmaceuticals in healthcare establishments, universities and research institutes as well as private practices, as this is largely unharmonised throughout Europe. Her examples on how radiopharmaceuticals differ from other medicines included the production area of radiopharmaceuticals, the timelines regarding the quality tests, and legislation. M. Patt argued for a thorough discussion on pharma legislation, exemplified by the emerging use of alpha emitters in the future due to the many uncertainties regarding the radiochemical purity of alpha emitters. M. Patt's last point was to vote for a dedicated legal document for radiopharmaceuticals: "What we are doing now is we try to squeeze them always into the existing laws." She acknowledged that not every single special medicinal product can have its own directive; however, for radiopharmaceuticals she argued, advocating for its own directive, that there are many special things regarding the quality control, production, verification of treatment and optimisation of treatment.

Industry (L. Schätz, Novartis Pharma AG): L. Schätz started out by stating that radioligand therapy is at a tipping point where it can become really big: "It can become a new pillar in cancer management." He mentioned several key things he believes we need to manage, the first being in the area of regulations. He mentioned differences between Europe and other geographical areas: "It would be a great pity, especially for all the patients in Europe, that they then will not have access to this new treatment modality." He argued that we should not put the bar too high in the beginning, to allow many new centres to adopt this therapy. L. Schätz advocated for centres of excellence to drive the continued research, including questions on topics like dosimetry. He also discussed radiation safety, raising questions on in-hospital stay duration vs efficient use of resources and capacity as well as impact on individual patients. His last comment was that "we need to really make it pragmatic for clinical practice and at the same time drive the initiatives that advance the science."

European Commission (G. Simeonov, DG ENER): G. Simeonov started by applauding an achievement of this project, gathering this group of people to speak on the basis of a document. He further acknowledged the initiative to invite people with such a range of



differing opinions and the intention to find a reasonable, pragmatic way to meet the regulatory requirements in force. He argued that the law should be followed but for the benefit of the patient and the development of these treatments. He noted that he personally had been convinced in the past 10 years that there is a big future in radionuclide therapies and there is a lot of room for development. He also referred to the SAMIRA action plan, where one of the three big workstreams is on the supply of isotopes. He moved on to comment on the practical recommendations in the project, both for existing treatment (e.g., of how to apply dosimetry to a number of treatments with two options, depending on the level of resources you have and what level of dosimetry you need) and also on what to do for future studies (for developing future radionuclide therapies), and expressed a hope that the project helps to formulate these recommendations. G. Simeonov advised to extend the formal consultation period for a few weeks to allow potential extra comments on the specific recommendations in the document. He reminded that even if the commission publishes it in the Radiation Protection Series, this will not be a legal requirement but a recommendation of the direction we want to be moving. Focus would then be on the implementation that takes place nationally and locally. He commented also on specific emphasised aspects in the SIMPLERAD report, like the need for generating further evidence and resources, which are supportive of future development of radiation therapies. Actions beyond the timeframes and the resources of the project were mentioned, including the need to continue the discussion in and among all relevant groups, including the SGQS, EMA groups, DG SANTE group on CTIS, etc. He emphasised the SGQS, which links the member state radiation protection and health authorities. A point was made that the discussion is mostly not restricted to regulatory issues but concerns many organisational and resources issues, i.e., all the enablers that need to be put in place to enable these developments. He expressed that it was good to see involvement and commitment from the EFOMP and EANM and hoped that they'll work further on developing some of the issues. Furthermore, he mentioned the need for communication among the national health, medicines and radiation protection authorities and stated the commission services may be able to help using their convening power. He recognised that there is much work to be done and a need to identify the priorities and the timelines. A point, stated to maybe go beyond the current project, was the need to stay engaged and turn this into a workplan, assign tasks, assign timeframes, and see under which instruments they can be implemented. He expressed an interest to help identify some of the many relevant instruments and mentioned examples of specific calls. His final remark was to again appreciate that all these opinions and different perspectives were collected and to argue that we still have quite a bit of commonalities. A larger concern is that we want to make progress and enable these therapies. Enabling entails identifying the best way to do so for all involved parties, patients, clinicians, physicians and hospital staff.

Summary of discussion

The discussion opened with questions from the online audience. The first comment came from A. Hojny of the Luxembourg Ministry of Health, stating that we need to have a vision concerning what direction we are going as well as precise and flexible legislation.

K. Herrmann addressed the need for compromises, moving the development front gradually to allow all countries/centres to be included. E. Briers remarked that dosimetry is not done for most other medicines, and how we can do the same in a pragmatic way for radionuclides as well. S. Peters responded that radionuclide therapy is not the best compared to other systematic therapies but rather to external beam radiation therapies, and it is possible to plan doses also in order to increase efficacy. E. Briers replied that he agreed and commented that classical treatments may also be improved. G. Simeonov added that with the development of therapies, he believes needs to understand better the dose delivery and optimisation of therapies will actually increase, further adding, in reply to K. Herrmann, that the next step is implementation and the heterogeneity among member states is a barrier: "So I think in the process of creating consensus guidelines, and then trying to implement them have their own merit." S. Peters also agreed to this, referring to the EANM Enabling Guide: How to Improve the Accessibility of Clinical



Dosimetry and EFOMP Policy Statement 19: Dosimetry in Nuclear Medicine Therapy – Molecular Radiotherapy. L. Schätz advocated for a roadmap to define the work.

J. Gear raised a question on inequality: As we are treating the patients differently in different centres and different countries, how can we reduce that inequality without working to a concept of a lowest common denominator? G. Simeonov mentioned the network of radiation protection authorities in Europe, highlighting the challenge of reaching agreement between individual member states and the need to work together towards agreement or at least transparency. M. Patt raised a question on how we can change the way clinical trials are performed. K. Herrmann replied to both J. Gear and M. Patt, arguing that heterogeneity should not be in treatments that are approved. He stated we need to show evidence during trials that, e.g., dosimetry can improve the response rates or survival, which will then be approved. U. Holzwarth also commented on the importance of communication between industry, regulators and clinicians.

A.M. Janson Lang from Sweden provided a perspective from the Clinical Trials Coordination and Advisory Group. She stated that for clinical trials, we need to balance the benefits versus the risks. Further arguing “The potential is that we are not using high enough doses of radiotherapies because we are playing it safe now without dosimetry,” she stated that we may need ways to clarify already at the clinical-trial level in order to have data for central marketing authorisation applications. She stated that how to consider radiopharmaceuticals is already included in the [Questions and Answers](#) document with the clinical trials guidelines of Eudralex Volume 10 and that clarity on how to achieve this is the topic to discuss. For this she argued for communication and a need to interact to promote the necessary next steps. L. Schätz agreed on the need to evolve, as rules and regulations at some points are outdated. He further commented that from a pharmaceutical perspective the cost of performing a trial, together with the potential consequence of a failed trial, needs to be considered against the risk profile of trials. V. Fradin-Da Ros contributed reflections on the assessment structure, at a centralised or national level, with national competent authorities involved in assessments in both cases and involvement of various stakeholders, including patient organisations. S. Kaijaluoto from the Finnish Radiation and Nuclear Safety Authority and also member of the HERCA medical group commented that HERCA is in the process of creating guidance for the regulators regarding article 56.

E. Briers had a statement as a member of the Prostate Cancer Guidelines Panel of the European Association of Urology that guidelines are just guidelines and need to be adopted.

K. Herrmann commented that therapies are in competition and argued that even if the level could always be higher, the level for radionuclide therapy is already high. For example, for patient selection imaging is performed. He argued strongly that improvement should be strived for but not made mandatory and it should also be hypothesis-driven. He also raised the question on real-world practice and in-house stays versus outpatient treatment. L. Schätz speculated that we have a tendency to over-scrutinize, compromising accessibility. His opinion was that the standards are incredibly high compared with other disease areas and other treatments. He exemplified the argument with waste questions, stating that waste from chemotherapy patients are probably more toxic than excretions of lutetium patients. E. Briers briefly replied that this is precision medicine, and we should be careful when lowering the bar for selection of patients receiving precision medicine based on previous experience.

T. Nojonen from Finland made a statement that we need practical simple guidelines for implementation of dosimetry and radiation protection.

M. Koole from the EANM and University Hospitals Leuven highlighted the differences between a research centre and clinical routine, asking how we can be more compliant with the BSSD from a clinical-routine perspective. He also touched upon reimbursements and the issue of quality for more peripheral centres. K. Herrmann agreed and replied that he finds the current biggest limitation to be the workforce, saying we should focus on how to move forward. S. Peters commented that it may be difficult for small centres to really



implement dosimetry in a practical way, but we have seen much improvement in the last 20–30 years, and technological advances are helping us together with research on simplification of protocols. Regarding workforce, G. Simeonov also added that in the SAMIRA action plan, one of the work packages is on workforce, which will hopefully provide data for continued discussions. He also mentioned that “Specifically the workforce gap in nuclear medicine and nuclear medicine therapy now is quite well known,” and “I hope that there will be a more concerted effort to address that in the next years.” M. Patt raised the question of whether more advanced centres can set up trials or have registers to collect data.

R. Hesselmann, working as a regulator for the Swiss Federal Office of Public Health, made a statement composed together with a colleague from SwissMedic, arguing to keep regulation flexible.

M. Bardiès stated that we revolve around the regulatory aspect of dosimetry and the added value of dosimetry and argued that a roadmap is needed. He also made the point that excess dosimetry is not an issue at the moment because dosimetry is not done. A brief discussion followed, where K. Herrmann opposed this statement, referring to current practice for a few treatments, and M. Bardiès referred to a recent survey. M. Bardiès also commented on the role of the pharma representative with a comparison: “The car manufacturer should not be the one who set the speed limit.” M. Bardiès argued that we can do better, and to prove the added value of dosimetry, we first need resources to perform this. He further argued that we should start with demonstrating added value, and then realising the potential for simplification, referring also to the demonstrated value of dosimetry for external beam radiation treatment. K. Herrmann replied, reiterating the need for evidence and a need for investments. He also commented that medical physicists are also biased, followed by a reply from S. Peters that “trained in the field” is probably rather the term. K. Herrmann elaborated that he believes everyone is biased and transparency is the key. In the discussion S. Peters also stated that “Almost no medical physicist is claiming dosimetry is good just because it creates jobs for medical physicists. It's just because we think it's better in the interest of the patients. And that is what we think from our knowledge.”

A. Sundlöv commented that the part of the SAMIRA joint action that will concern radiopharmaceuticals can hopefully continue the work of seeing a common way forward.

C. Chiesa argued that dosimetry is not complex, exemplified by a few specific protocols. Secondly, he debated whether phase three trials are really needed for implementation of dosimetry, referring to other fields where believed best practices have been introduced instead of waiting for phase three results. M. Lassmann asked K. Herrmann if they always do imaging after each treatment cycle, referring to one of C. Chiesa's examples. K. Herrmann replied that they do ^{124}I dosimetry even though there is no prospective evidence for it but because they believe in it. However, K. Herrmann further argued that they perform imaging and dosimetry for academic interest to push the frontiers. He raised the question if this would be possible to implement across Europe.

M. Lassmann asked for the audience's views on patient hospitalisation after treatment. L. Schätz replied that the regulation should be evidence-based and patient-centric and that there is room for improvement in current practice. He further argued for outpatient clinics. K. Herrmann commented that in Germany, they have patients in-house for two nights and stated that he believes this can be reduced to one. E. Briers put forward that for individual patients, not all will prefer to return home straight after the injection. B. Godthelp, from the Dutch Authority for Nuclear Safety and Radiation Protection and also part of the HERCA workgroup on medical applications, highlighted that there are differences between radionuclides and the overall need for safe radiation protection. B. Sattler argued for a one-day hospitalisation practice, referring to an ongoing local project. He also stated that this is practical since a day 1 scan is performed.

G. Flux had a question in the chat read by M. Lassmann: “The dosimetry paragraph in the BSSD applies also to radiotherapy, for which dosimetry is far more complex and the



imposition on the patient much greater. Is this exercise being performed for radiotherapy? Also, everyone agrees that evidence is needed. If industry do not support nuclear medicine nor conduct trials, where does the panel think the evidence should come from?" K. Herrmann replied, referring to a few trials ongoing, that industry will need to defend the costs. E. Briers proposed that we should revisit registries performed by groups of excellent centres doing dosimetry properly: "Analysis could learn an awful lot about efficacy, risk, and the clinical benefit of doing dosimetry."

Conclusions from the session

The round table and discussion raised important questions from people with varying opinions but also demonstrated the joint wish to enable and promote radionuclide-based therapies to the benefit of patients. A range of points were made during the discussion that should be considered by the consortium. These include the need for a roadmap and vision; issues of health economics; networking of centres for generation of robust dosimetry data and consideration for establishing registries for dose data; if radionuclide therapy should be considered a field of its own; patient hospitalisation; the level of dosimetry required and resources to implement it; and distinctions between more advanced centres and small centres for research, education and training.

5.6 Session 6: Summary

Aims of the session

The aim of Session 6 of the SIMPLERAD workshop was to summarise the presented findings and outcomes from the SIMPLERAD workshop. Further, this session summarised the main points raised by stakeholders during the discussions, and how this feedback will be incorporated by the consortium. Finally, the next steps of the project were presented.

Key points

- Summary of WPs 1–3: Conclusions and recommendations per proposed action
- Main outcomes of the stakeholder consultation: Ranking of issues identified within WP3
- Challenges to radiopharmaceutical therapies
- Next steps in the project

Summary of presentations

While summarising the recommendations per proposed action, Michael Lassmann, summarised each work package.

- In WP1, an in-depth analysis of seven EU countries and comparison with the UK and the US clarified the legal frameworks, common practices and divergence, clearly highlighting the important missing links among guidance and legislation.
- As a follow-up, the survey on the implementation of relevant European legal requirements for therapeutic nuclear medicine collected almost 200 responses with strong representation across Europe, and interviews confirmed and elaborated on common themes. Legislative issues confirmed the work of WP1 and those in the current practice were highlighted, and differing criteria and good practices in planning/verification, dosimetry, waste and patient release were important findings submitted to WP3.
- Finally, WP3 developed and analysed 10 prioritised issues, before developing specific remedies with a SWOT analysis of each. Consultation with the Advisory Board, as well as discussion with the wider stakeholder community will help to seek consensus on the final recommendations.

Based on the stakeholder consultation which was shared with workshop participants ahead of the workshop, Michael Lassmann presented the top priorities identified, based on the findings of the SIMPLERAD project.



- **Priority 1:** Insufficient linkage between EU pharmaceutical legislation/EMA guidance and BSSD
- **Priority 2:** Interpretation and implementation of the BSSD in the context of therapeutic nuclear medicine
- **Priority 3:** Differences between opinion of professionals concerning dosimetry and the necessity stipulated in national legislation and guidance
- **Priority 4:** Differing regulatory procedures between member states for drug development & clinical trials

This was an opportunity to remind everyone about the 10 identified issues, as well as the related remedies identified by the consortium.

Additionally, main aspects raised during the discussions of the workshop sessions have been summarised for them to be implemented into the outcomes of the workshop.

- A general remark was for instance the opinion, that mentioned remedies are overly complex, and therefore not fulfilling the initial expectation to facilitate the use of therapeutic nuclear medicine. This is something that the consortium agreed to further discuss to make its final recommendations easily actionable and implementable.
- Further, following the numerous points raised with regards to dosimetry, the consortium agreed with workshop participants that a discussion on the distinction between dosimetry as a tool for generating evidence to fulfil regulatory purposes and a method benefiting patients in daily practice should take place. Similarly, the audience suggested that networking between centres should be facilitated to generate robust dosimetry data. Finally, it was suggested that a holistic approach should be taken on dosimetry, also considering health economics, and therefore the economic impact of dosimetry, but also considering the resources available in different centres (advanced centres vs smaller centres).
- Also, a better understanding and a consideration of radiobiology was strongly recommended. While the EANM is already engaged in the topic, further actions were recommended.
- As a consensus was reached on the fact that today is a tipping point for the success or failure of therapy, consortium and audience agreed that communication should be improved between all stakeholders in order to build together a roadmap and a vision for therapeutic nuclear medicine, clearly stating that it should be considered as an independent field/specialty. This group of stakeholders should, not only compass healthcare professionals, industry and regulators, but also the patients. Patients' perspective should not only be considered for regulatory issues as highlighted by the consortium, but also in daily practice (i.e., hospitalisation, level of dosimetry required). On this point, the EC reminded that the optimisation principle is about maximising the benefit/risk ratio for the patients.

Michael Lassmann concluded by outlining three global challenges which will need to be addressed in the future to allow successful implementation of SIMPLERAD's recommendations.

- Europe's market share might be falling behind due to complexities related to radiopharmaceutical therapies.
- Similarly, lack of capacity of treatment slots due to inappropriate infrastructure and workforce shortages is threatening a successful development of nuclear medicine therapy across Europe.
- Finally, as highlighted in SIMPLERAD outcomes, regulations will have a massive impact on how Europe will be attractive and viable for radiopharmaceuticals therapies, especially compared to other continents and other treatment options, even though radiopharmaceuticals therapies have clinically proven to be better for the patients.



Conclusions from the session

The EIBIR office presented the next steps for the upcoming months.

- The consortium will prepare the workshop proceedings, taking into account the feedback received.
- Slides will be published on website shortly, and the attendees will be notified.
- Feedback from the workshop participants and from the stakeholder consultation will be considered by the consortium.
- The consortium will aim at producing the final consensus guidelines by April 2024; the draft will be submitted to the EC in February, and the final report will be submitted in April 2024.
- Further, the involved professionals' societies will discuss potential publications of the outcomes of WP1 and WP2, as well as future actions to be implemented as a result of the project.

6. Workshop Conclusions

The SIMPLERAD project is an important part of the SAMIRA initiative. Two medical disciplines are represented within the SIMPLERAD project, namely nuclear medicine and medical physics. These disciplines are represented by the EANM and EFOMP.

SIMPLERAD aims to study the implementation of the Euratom and the EU legal bases with respect to the therapeutic uses of radiopharmaceuticals. The SIMPLERAD WP4 hybrid workshop, focused on the findings of the project (WP1: Interrelations among Legal and Regulatory Frameworks, WP 2: Survey and Expert Interviews on European Legal Requirements), introduced a set of 10 recommendations to advance coherent implementation of European legal requirements developed in WP3. The workshop was held in December 2023 in Brussels as part of the SIMPLERAD project.

Targeted at representatives from European and national authorities responsible for authorisation of radiopharmaceuticals, competent authorities for radiation protection, the nuclear medicine and medical physics community represented by national and professional societies, researchers, patient representatives, radiopharmaceutical industry, other relevant clinical communities, and members of the Advisory Board and the WP MED and SGQS members, the WP4 workshop attendees discussed the recommendations derived during the course of the SIMPLERAD project. The attendance over the two days of the workshop was over 100 people on both days. This may be taken as a demonstration of the importance of the subject and level of interest in it.

In session 1, the European framework relevant to therapeutic radiopharmaceuticals was addressed by representatives of DG ENER, DG SANTE, the Clinical Trials Coordination and Advisory Group, and the EMA. Speakers from the WHO, IAEA and ICRP spoke of the perspectives of international organisations. The conclusion of this session was that the European legal framework for therapeutic radiopharmaceuticals is a network of laws and guidelines developed by Euratom, EC, EMA and expert groups, each with a somewhat autonomous role but with some collaboration.

The WHO, IAEA and ICRP support the project's work and administer several relevant programmes in line with its objectives, with references that may help guide the consortium's response to the selected issues.

In session 2, the interrelations among legal and regulatory frameworks were introduced, based on a literature survey and an in-depth study of the regulatory framework in seven selected countries, Finland, France, Germany, Italy, Poland, Spain and Sweden. Furthermore, the regulatory frameworks for the EC, UK and US were compared. The main difference between the European countries and the US is that, in the US, the FDA governs the process of marketing authorisation with collaboration from the NRC.



One of the conclusions of session 2 was that, although safety and efficiency of treatment for the patient is the ultimate aim of both regulatory sets, i.e., pharma legislation and BSSD, the optimisation principle set out by the BSSD needs further development. Moreover, in addition to the establishment of practical guidance and recommendations to advance coherent implementation of the BSSD requirements and improve the MPE workforce and data-processing procedures during the application phase of clinical trials, the interrelation between the directorates responsible for radiation protection and pharmaceutical legislation needs to be improved.

In session 3, the results of expert interviews and the survey on European legal requirements were presented. The survey showed that understanding of legislation concerning radiopharmaceuticals varies widely, resulting in differences in interpretation and implementation, mainly of the BSSD Article 56 requirement. Furthermore, three good-practice examples from Germany, Sweden and Czechia presented by three speakers elicited the fact that also in these countries the situation regarding treatment optimisation for radionuclide therapy varies widely.

Overall, this session showed that understanding of legislation concerning radiopharmaceuticals varies widely, resulting in differences in interpretation and implementation, mainly of the BSSD Article 56 requirement.

In session 4, 10 recommendations to advance coherent implementation of European legal requirements including actions to be completed as part of SIMPLERAD project, which were developed based on the findings of WP1 and WP2, were introduced.

- 1.** Insufficient linkage between EU pharmaceutical legislation/EMA guidance and BSSD
- 2.** Interpretation and implementation of the BSSD in the context of therapeutic nuclear medicine
- 3.** Lack of resources for dosimetry
- 4.** Differences regarding status of MPEs between member states
- 5.** Heterogeneity of dose constraints & patient-release criteria among member states
- 6.** Heterogeneity of management of radioactive waste across member states
- 7.** Differing guidance from professional societies for clinical practice
- 8.** Differing regulatory procedures between member states for drug development & clinical trials
- 9.** Sufficient specialist knowledge concerning nuclear medicine within various stakeholders regarding EU pharmaceutical and medicine as well as BSSD-related regulations
- 10.** Differences between opinion of professionals concerning dosimetry and the necessity stipulated in national legislation and guidance

These 10 recommendations were also provided to the wider stakeholder community prior to the workshop together with an opportunity to prioritise these items and further comment on them. Furthermore, three documents on practical implementations of dosimetry in clinical routine and for clinical trials were presented.

After the presentation of these items, a lively discussion took place. This included a question concerning how industry had been included in the discussions concerning the proposed remedies, which was addressed by informing the audience that Nuclear Medicine Europe is part of the Advisory Board. Furthermore, based on the discussion, the period for providing stakeholder comments to be submitted, was prolonged until 1 January 2024.

Within the participants of the discussion, there was some disagreement whether dosimetry should be performed and at what level. The discussion centred on the fact that scientific evidence has not demonstrated conclusively a benefit to performing dosimetry, the distinction between scientific and legal requirements, the necessity to distinguish between use of radiopharmaceuticals according to the posology of the SmPC and off-label use, the lack of resources, generation of dosimetry data within clinical trials, and the establishment of centres of excellence for dosimetry. Beyond dosimetry, a proposal was made to consider



research and findings in radiobiology for radiopharmaceuticals therapies and to enhance the efforts for collaborations.

The representative of the EMA reminded the audience that drugs are approved when they show that benefits outweigh the risks. The representative of DG ENER stated that for radiation protection purposes under the BSSD optimisation should show also that the benefit/risk ratio has been maximised. Moreover, there is no desire to impose a new layer of regulations, and instead the aim is to find a practical way of implementing what is already in the regulations.

The conclusion of the discussion was that the consortium should ensure practical actions to the issues identified. The centres of excellence network and data generation should be further emphasised in the report. Consideration to timelines and a roadmap to implementation should also be given in the final report.

Session 5 started with a round table discussion by a representative of the EMA, patient representative, MPE, nuclear medicine therapy expert, radiopharmacy expert, industry, and the EC, expressing their view on the topic of SIMPLERAD and the 10 action items proposed.

The general discussion afterwards raised important questions from people with varying opinions but also demonstrated the joint wish to enable and promote therapies to the benefit of patients. A number of points were raised during the discussion that should be considered by the consortium. These include the need for a roadmap and vision; issues of health economics; networking of centres for generation of robust dosimetry data and consideration for establishing registries for dose data; if radionuclide therapy should be considered a field of its own; patient hospitalisation; the level of dosimetry required and resources to implement it; and distinctions between more advanced centres and small centres for research, education and training.

Session 6 of the SIMPLERAD workshop summarised the presented findings and outcomes from the SIMPLERAD workshop and the main points raised by stakeholders during the discussions. Based on the stakeholder consultation, which was shared with workshop participants ahead of the workshop, a preliminary list of the top priorities was identified, based on the findings of the SIMPLERAD project.

- **Priority 1:** Insufficient linkage between EU pharmaceutical legislation/EMA guidance and BSSD
- **Priority 2:** Interpretation and implementation of the BSSD in the context of therapeutic nuclear medicine
- **Priority 3:** Differences between opinion of professionals concerning dosimetry and the necessity stipulated in national legislation and guidance
- **Priority 4:** Differing regulatory procedures between member states for drug development & clinical trials

This session also served the purpose to remind the stakeholders that they could still provide feedback to the recommendations by means of the stakeholder survey.

For the final report, several aspects raised during the discussions of the workshop sessions will be discussed, and, if feasible, implemented.

- The remedies mentioned should simplify the use of therapeutic nuclear medicine. The consortium will further discuss this to make the final recommendations easily actionable and implementable.
- The consortium agreed with workshop participants that a discussion on the distinction between dosimetry as a tool for generating evidence to fulfil regulatory purposes and a method benefiting patients in daily practice should take place.
- Networking between centres should be facilitated to generate robust dosimetry data.



- A holistic approach should be taken on dosimetry, also considering health economics and therefore the economic impact of dosimetry, but also considering the resources available in different centres (advanced centres vs smaller centres).
- A better understanding and a consideration of radiobiology was strongly recommended.
- As today is a tipping point for the success or failure of radiopharmaceutical therapies, consortium and audience agreed that communication should be improved between all stakeholders in order to build together a roadmap and a vision for therapeutic nuclear medicine, clearly stating that it should be considered as an independent field/specialty. This group of stakeholders should, not only compass healthcare professionals, industry and regulators, but also the patients.
- The patients' perspective should not only be considered for regulatory issues, as highlighted by the consortium, but also in daily practice (i.e., hospitalisation, level of dosimetry required).

The SIMPLERAD project needs to consider also three global challenges.

- Europe's market share of radiopharmaceutical therapies might be falling behind due to the complexities related to radiopharmaceutical therapies.
- A lack of capacity of treatment slots due to inappropriate infrastructure and workforce shortages is threatening a successful development of nuclear medicine therapy across Europe.
- New regulations will have a massive impact on how Europe will be attractive and viable for radiopharmaceuticals therapies, especially compared to other continents and other treatment options, even though radiopharmaceuticals therapies have clinically proven to be better for the patients.

The output and conclusions from the WP4 workshop, both presentations and panel discussions, combined with the findings from the previous WPs, in particular WP3, form the basis of the final conclusions/recommendations document. As a final step of the SIMPLERAD project, the consortium will aim at producing final consensus guidelines by April 2024.