FINAL PUBLISHABLE REPORT

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1 Overview

An estimated 4.3 million new cases of cancer are being diagnosed annually and treatments based on molecular radiotherapy (MRT) are being increasingly used to treat them, creating a $7.27 billion market in radiopharmaceuticals. Ensuring patients receive the prescribed therapeutic doses whilst mapping drug delivery to tumour sites is routinely performed using Single Photon Emission Computed Tomography (SPECT) or Positron Emission Tomography (PET). For clinicians to comply with EC Directive 2013/59/EURATOM, Article 56, which requires confirmation that the administered patient dose matches the prescription, whilst delivering optimised healthcare outcomes, requires the adoption of improved practices in the commissioning, calibration and quality control of these mapping instruments. This project has provided the nuclear medicine community with calibration protocols, and commissioning and quality control guidance, for quantitative SPECT imaging and absorbed dose calculations that were developed in EMPIR JRP 15HLT06 MRTDosimetry. Supported by the European Association of Nuclear Medicine (EANM), the largest organisation facilitating nuclear medicine communication worldwide, the project's goal was to increase the adoption of best practice in clinics using MRT, fostering greater harmonisation in delivery. This work has enabled improved assessments of radiopharmaceuticals during clinical trials thus speeding the introduction of more effective cancer therapies.

2 Need

One in two people will develop cancer during their life and there were an estimated 4.3 million new cases diagnosed in 2018, which lead to 1.9 million deaths. This makes cancer the second most common cause of death in Europe. Molecular radiotherapy using radiopharmaceuticals is becoming a first line cancer treatment, and it represents a global radiopharmaceuticals market that is expected to reach $7.27 billion by 2021. However, despite growing acceptance that an accurate knowledge of the radiation absorbed dose to critical tissues would provide a more effective targeted use of MRT, most patient treatments still follow the historical practice of administering a nominal activity of the radiopharmaceutical.

Delivering optimised, patient specific therapies through the clinical application of MRT dosimetry, supported by training (objective 3) and published good practice guidelines for calibrating, commissioning and QC (quality control) of quantitative imaging (objective 1) based on the outcomes from EMPIR JRP 15HLT06 MRTDosimetry will improve healthcare delivery and reduce clinical costs.

Clinical trials play a major role in the development of standardised dosimetry (including MRT). Absorbed dose is a critical parameter in both assessing treatment effectiveness and harmful side-effects, therefore a reduction in the uncertainty of the absorbed dose calculation (currently estimated to be of the order of 8 % - 40 %) will give a corresponding greater statistical power to clinical trials. In turn, this should support the incorporation of standardised dosimetry into clinical trials and hence this will lead to the greater adoption of MRT as a routine treatment.

EC Directive 2013/59/EURATOM, Article 56 introduces requirements for individual dose planning for radiotherapy patients (including MRT) which is being introduced in legislation by EU member states. Quantitative imaging using SPECT or PET enables the precise location of administered activity in the tissue to be assessed. The EMRP JRP HLT11 MetroMRT and EMPIR JRP 15HLT06 MRTDosimetry put in place the foundations for a traceable MRT calibration infrastructure. EMPIR JRP 15HLT06 MRTDosimetry developed a traceable SPECT/CT calibration protocol and demonstrated the capability for harmonising imaging across multiple centres, systems and countries. It performed the first cross comparison "ground truth" exercise between clinical centres and the project's commercial partners using "known dose" to establish uncertainties and accuracy for a given clinical dosimetry system. This project's novel range of quasi-realistic 3D printed anthropomorphic phantoms, the dataset of SPECT/CT images and the associated Monte Carlo dosimetry calculations can provide a unique tool for the validation of the dosimetry chain.

The long-term results of EMPIR JRP 15HLT06 MRTDosimetry have been extended and promoted in this project as training materials and good practice guidance providing a significant contribution to delivering more effective, better targeted cancer treatments, improved patient outcomes, a more harmonised approach to determining the dosimetry underpinning clinical trials, and significant cost savings to national and European cancer treatment centres. This project has prepared calibration, commissioning and QC best practice guidance for quantified SPECT imaging for MRT dosimetry for use in clinical centres. It also prepared a practical protocol (objective 2) for the commissioning and validation of a clinical MRT dosimetry calculation platform (with accompanying freely available validation datasets). This will allow the nuclear medicine community to set standards for dosimetry imaging with clinical equipment that commercial companies can incorporate into these

systems. It has extended the e-learning training material produced in EMPIR JRP 15HLT06 MRTDosimetry to support the use of the project developed guidance and protocols in clinical centres delivering cancer treatments (objective 3).

Just as the success of EMPIR JRP 15HLT06 MRTDosimetry was primarily due to strong engagement with the clinical MRT community as demonstrated by the 250 attendees at project workshops; the defining impact from the project, in improving outcomes for patients, will only be delivered through clinical uptake of project outputs. The support from the EANM in promoting the outputs from this project to European MRT dosimetry clinics will provide the strongest possible pathway to deliver this impact.

3 Objectives

The overall aim of this project was to deliver practical impact from the outputs of JRP 15HLT06 MRTDosimetry by incorporating them into protocols and guidelines which were promoted and made available by the project's primary supporter, EANM to MRT dosimetry clinics. The protocols were supported by training materials and by the provision of freely available datasets and 3D printed phantoms.

The objectives of this project were:

1. To prepare good practice guidance and guidelines based on the protocols developed in EMPIR JRP 15HLT06 MRTDosimetry for the calibration, commissioning and QC of SPECT dosimetry for use in clinical centres. In addition, to enable the protocol to be used, validated 3D printed phantoms will be loaned to clinical sites that do not have the capability to make their own. The project's primary supporter, EANM, will promote and make the guidance documents available to European MRT dosimetry clinics and will also assess the suitability of the guidance documents for use in a new EARL accreditation service for SPECT/CT systems analogous to those for Fludeoxyglucose-PET/CT.
2. To publish a practical protocol for the commissioning and validation of a clinical MRT dosimetry calculation platform (with accompanying freely available validation datasets). The protocol will be based on the commissioning procedure developed in the EMPIR JRP 15HLT06 MRTDosimetry and it will incorporate input from external funded partners that are experts in MRT dosimetry calculations.
3. To further develop the elearning training material produced in EMPIR JRP 15HLT06 MRTDosimetry to support the use of the protocol. These materials will be incorporated into the ESMPE lectures that are dedicated to nuclear medicine dosimetry and into other national training schemes. The Christie leads the MRT component of the UK National Health Service Higher Specialist Training Programme (HSST) through which these training materials will be disseminated.

4 Results

4.1 Objective 1. To prepare good practice guidance and guidelines based on the protocols developed in EMPIR JRP 15HLT06 MRTDosimetry.

Good practice guide for preparing phantoms with activity traceable to national standards

When calibrating a SPECT system for quantitative imaging (the conversion of detected counts to activity) all calibration methodologies depend on the preparation of a phantom or source with known activity. As such these phantoms, when combined with an appropriate calibration protocol, provide the primary route for traceability for quantitative SPECT imaging. Within the project a good practice guide on "Preparation of Radioactive Phantoms with an Activity Traceable to National Standards" has been prepared by NPL, Christie, INSERM and UKW. This work describes the methodology to prepare liquid radioactive phantoms with a total activity or activity per unit mass traceable to national and international standards when using a radionuclide calibrator. Different methodologies are suggested to suit local facilities, allowing a range of phantoms to be prepared.

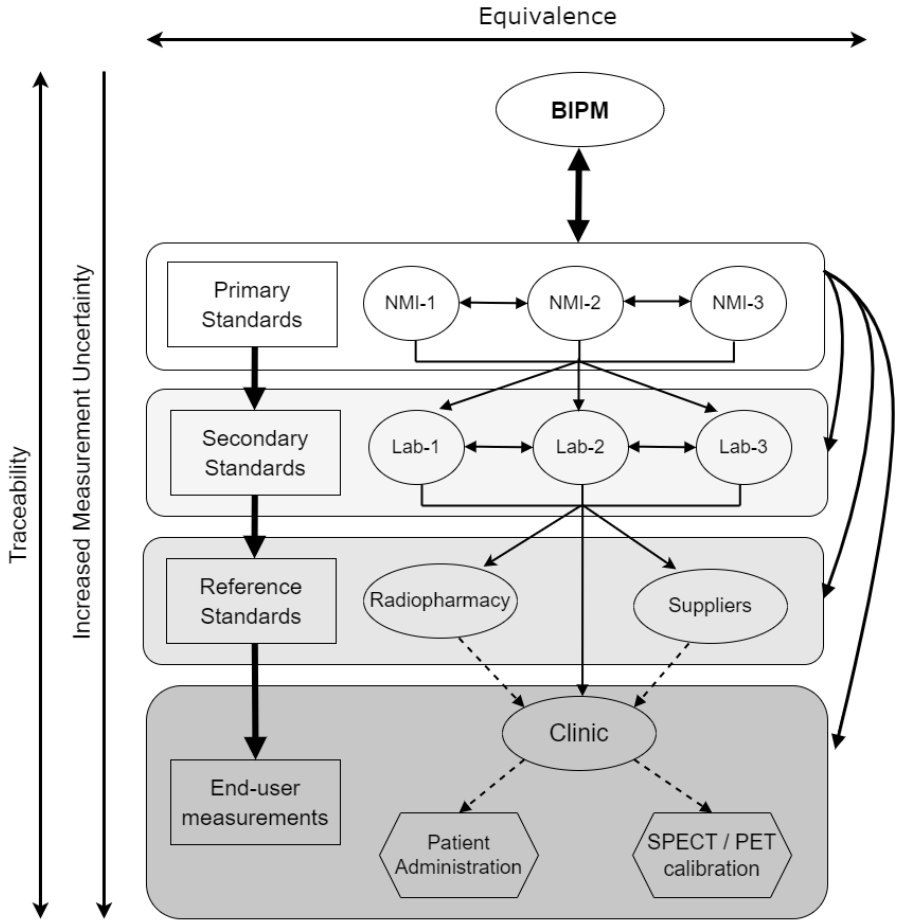

Figure 1: Traceability and equivalence in nuclear medicine. NMI-1, NMI-2 and NMI-3 correspond to different National Measurement Institutes participating in international intercomparison exercises. Lab-1, Lab-2 and Lab-3 correspond to national measurement institutes, designated institutes or other laboratories that provide secondary standards.

In this document, the equipment and methodology for the preparation of phantoms with a known-activity traceable to standards are described. The preparation of radioactive stock solutions and appropriate carrier solutions is covered. Guidance is also provided on the estimation of uncertainties, an essential step for traceability and in understanding the measurement. An example of filling a cylindrical Jaszczak phantom is provided. This good practice guide is now being prepared for publication and the current draft of the document has been made available on the project data repository [1] ahead of final publication.

A multicentre and multi-national evaluation of the accuracy of quantitative ^{177}Lu SPECT/CT imaging

The first step in dosimetry for MRT is the determination of the activity of the radiopharmaceutical taken up by an organ or tumour over time from calibrated SPECT/CT imaging. To support the uptake of guidance from the MRTDosimetry project the results of a multicentre intercomparison of the accuracy of quantitative ^{177}Lu SPECT/CT imaging have been published [2] (UKW, Christie, INSERM and NPL). In this work a common experimental protocol was used to harmonise the calibration across the participating sites. The protocol included (1) determination of an appropriate image calibration factor, (2) correction of partial volume effects (PVE) due to the finite resolution of the imaging systems, and (3) validation of quantitative imaging using a 3D printed two-organ phantom (based on kidney and spleen models from ICRP110).

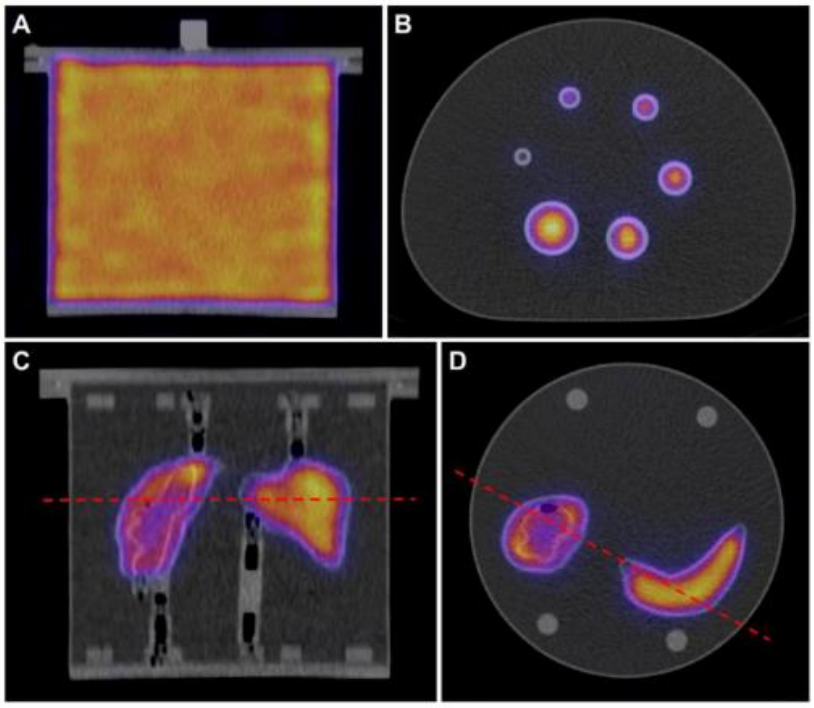

Figure 2: Example reconstructed SPECT/CT images from the intercomparison exercise (Siemens Intevo Bold system). (A) Coronal view of Jaczszak phantom. (B) Axial view of NEMA phantom used to estimate PVE.. (C) Coronal view of two-organ (kidney and spleen) phantom. (D) Axial view of Two-Organ phantom. The red lines indicate the position of the axial cut for the two-organ phantom

This work demonstrated that harmonisation of quantitative SPECT/CT imaging across multiple international sites was feasible when following a common protocol. Ensuring traceability of activity measurements to an agreed primary standard was an essential underpinning step to obtain accurate quantitative radionuclide imaging. It notable that this work brought together the expertise of clinical sites and metrology institutes to ensure traceability and assess uncertainties in the activity determination, two aspects that are rarely considered in comparison exercises in the field of nuclear medicine.

Anthropomorphic phantom designs and MRTDosimetry data repository

Two multi-organ anthropomorphic phantoms designed during the MRTDosimetry project, including the two-organ phantom used for the quantitative imaging intercomparison. The phantoms were designed to be filled with radioactive solutions, producing nuclear medicine imaging data (SPECT or PET) with a known (ground truth) activity concentration. Stereolithography (STL) files for all the MRTDosimetry project phantom designs are hosted on the project's data repository at, https://osf.io/69nge/ [1] (NPL). These files are widely compatible with slicing software for 3D printing, allowing the design to be fabricated on a range of printers.

To provide a realistic test object for validation of SPECT/CT Quantitative Imaging (QI) a two-organ phantom insert (designed for a standard cylindrical Jaszczak phantom) containing only the spleen and right kidney inserts has been designed [2]. A four-organ phantom was also designed [2]. This phantom consisted of a spleen, left and right kidneys (with two compartments as described for the "two-organ" phantom) and a liver with a 15.9 mL spherical insert (tumour). Due to the size of the organs a large bespoke elliptical phantom, with internal major and minor axes of 258 mm and 198 mm, respectively, is required to house the organ inserts. Full phantom designs, including designs for the elliptical phantom and base plates to attach the inserts to conventional phantoms can be found on the project's data repository. Further details of the phantoms have been published in [2] (NPL, Christie, INSERM and UKW).

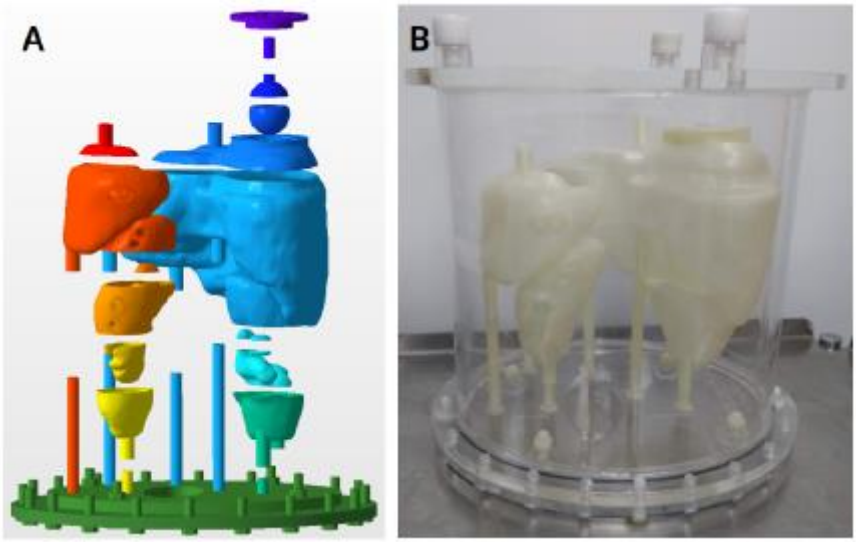

Figure 3: (A) Design of the four-organ phantom with spleen, kidneys and liver with spherical tumour. (B) Photograph showing the assembled phantom in custom Perspex© elliptical phantom.

Guidance on establishing measurement traceability for SPECT Quantitative Imaging

A guidance document to provide a practical methodology for establishing measurement traceability for SPECT Quantitative Imaging for Molecular Radiotherapy dosimetry has been prepared by NPL, Christie, INSERM and UKW. This work provides an example of the application of the methodologies presented in the quantitative imaging comparison exercise [1] and the upcoming GPG on "Preparation of radioactive phantoms with an activity traceable to national standards", to the traceable calibration of SPECT/CT for quantitative imaging with ^{177}Lu. It has been designed to complement existing and future guidance on quantitative imaging from EANM and EARL with a focus on establishing traceability.

The document covers methodologies for traceable measurements of activity in a clinical setting and for preparation of a phantom with activity traceable to a national standard. A vendor independent methodology for SPECT calibration and validation measurements is presented. A complete example of the application of these methods to the calibration of a clinical SPECT/CT system for QI of ^{177}Lu is shown, including the assessment of uncertainties. This work is currently being prepared for publication before the end of 2023. A draft version of the manuscript is available ahead of publication upon request.

SUMMARY OF OUTCOMES

A range of guidance documents based on the protocols developed in EMPIR JRP 15HLT06 MRTDosimetry have been produced. These documents, along with designs for multi-organ anthropomorphic phantoms available on the project open access repository, will assist clinical centres in establishing traceability calibration for quantitative SPECT/CT imaging. This objective was successfully achieved in this project.

4.2 Objective 2. To publish a practical protocol for the commissioning and validation of a clinical MRT dosimetry calculation platform (with accompanying freely available validation datasets).

Validation imaging dataset for Molecular Radiotherapy dosimetry

A validation imaging dataset for image based ^{177}Lu dotatate dosimetry calculations, based on the multi-organ anthropomorphic phantom designs (as described in section 4.1), was produced during EMPIR JRP 15HLT06 MRTDosimetry. The methodology for production of the dataset has been presented in [4]. The adoption of a

standard reference dataset for assessing performance and providing Quality Assurance (QA) for MRT dosimetry platforms is an important step towards harmonisation and reproducibility for clinical MRT dose calculations.

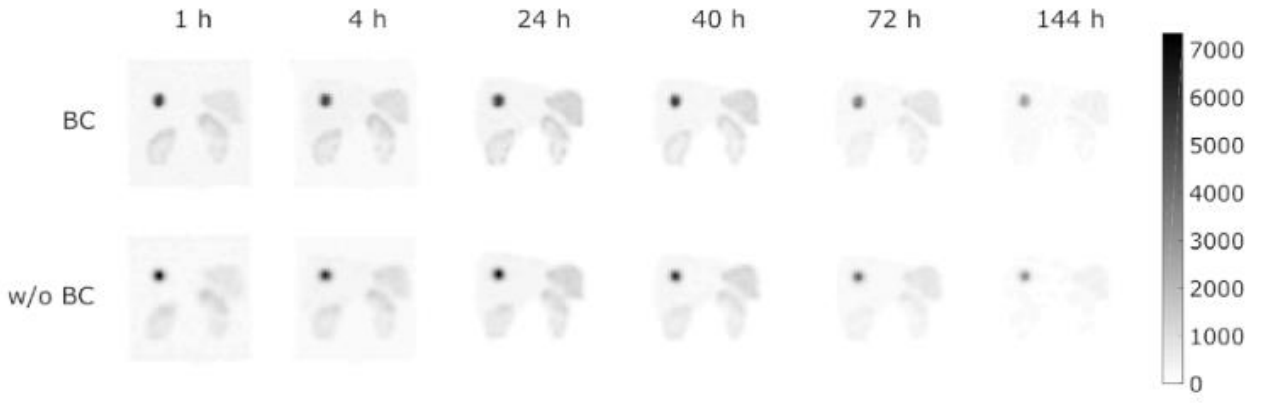

Figure 4: Two-dimensional MIPs of the reconstructed validation imaging dataset SPECT imags acquired with (top) and without (bottom) body contour enabled.

The dataset contains SPECT/CT and whole-body imaging data for the phantom filled with activity concentrations corresponding to different time points from a pharmacokinetic mode and is now available on the projects open-access data repository [2]. An accompanying SPECT/CT dataset, suitable for performing QI calibration using the methodology presented in section 4.1, was also produced. The ancillary SPECT/CT calibration data, the integrals of the time dependent activity curves generated by the pharmacokinetic model and Monte Carlo generated absorbed dose values for the phantom have also been provided, allowing for institutions to compare their calculated dosimetry values to the ground truth.

Guidance protocol for the commissioning and validation of clinical MRT dosimetry systems

A guidance protocol for the commissioning and validation of clinical MRT dosimetry calculation systems has been prepared by Christie, INSERM, NPL and UKW. This work covers the sequence of operations for clinical dosimetry workflows and defines commissioning and validation in the context of MRT absorbed dose calculations. The generation of test datasets specific to clinical dosimetry validation is considered. The check points needed for validation of a dosimetry system are discussed and results from a survey of clinical sites commissioned in this project are presented. The resources required for a successful validation are considered, including for the estimation of uncertainties. The roadmap for delivering the objective of routine and regular validation of dosimetry calculations is also discussed. This work is currently being prepared for publication before the end of 2023.

SUMMARY OF OUTCOMES

A guidance protocol for the commissioning and validation of clinical MRT dosimetry systems, based on the protocol and datasets developed in EMPIR JRP 15HLT06 MRTDosimetry, has been produced. A comprehensive validation imaging dataset for image based ^{177}Lu dotatate dosimetry calculations has been made available to support this protocol. This objective was successfully achieved in this project.

4.3 Objective 3. To further develop the e-learning training material produced in EMPIR JRP 15HLT06 MRTDosimetry to support the use of the protocol.

During the project the consortium has delivered 15 lectures as part of training courses endorsed by EFOMP, SGNM, SSRMP, BAG, DGMAP and NHS HSST, providing training to over 1500 medical physicists, physicians, technologists and researchers. These programmes included, the ESMPE European School for Medical

Physics Experts Nuclear Medicine Dosimetry, National Health Service Higher Specialist Scientist Training, the UK Internal Dosimetry Users Group IDUG dosimetry workshop and Dosimetry-Guided Treatment Planning for Radionuclide Therapy. Work from the project has also been presented at 8 international and national workshops to a combined audience of >1000 participants.

SUMMARY OF OUTCOMES

The project has successfully disseminated the finding of the in EMPIR JRP 15HLT06 MRTDosimetry project into a number of European and national training schemes for nuclear medicine dosimetry. This objective was successfully achieved in this project.

5 Impact

During the project the consortium has contributed to the development of training which has been disseminated to over 1500 participants at multiple training events courses endorsed by EFOMP, SGNM, SSRMP, BAG, DGMAP, IDUG and NHS HSST. This training has addressed a wide of career paths in medical physics including medical physicists, physicians, technologists, researchers, future consultant level healthcare scientists and Medical Physics Experts (MPE).

The project's open-access data repository, containing a range of open access data from the MRTDosimetry is available, hosted on the Open Science Framework (https://doi.org/10.17605/OSF.IO/69NGE). This repository provides a range of resources related to the calibration of quantitative SPECT imaging and commissioning of MRT dosimetry platforms. These included design for 3D printable phantoms and a validation imaging dataset with accompanying ''ground truth'' pharmacokinetic model and absorbed dose calculation [2]. Additional 3D printed designs for fillable cylindrical sources with varying diameters, suitable for measuring partial volume effects are also included. The repository also includes open access papers and good practice guidance from the consortium, released ahead of publication. This resource has seen a significant increase in unique visits throughout the project.

The consortium has presented results from the project at 8 international and national conferences during the project and provided input to 6 per-reviewed publications associated with the MRTDosimetry project. Members of the consortium have provided input and expertise to upcoming EARL accreditation for the harmonisation of 177Lu quantitative SPECT/CT to improve multi-centre research studies and clinical trials. They have also contributed to new EANM practice guidance for quantitative SPECT-CT intended to assist practitioners in improving the diagnosis and treatment of a variety of diseases using nuclear medicine imaging (https://doi.org/10.1007/s00259-022-06028-9).

The outcomes from this project are in line with EANM's mission to facilitate communication worldwide among individuals pursuing clinical and research excellence in nuclear medicine. Currently, the EANM represents more than 9,000 specialists from 41 different countries within Europe and it serves the interests of a community that goes far beyond these numbers and geographical boundaries. This project has provided the EANM and nuclear medicine standardisation bodies with easily available practical guidelines to support the robust application of MRT dosimetry in clinics. Combing the disciplines of clinical science and metrology couple traceability and a metrological treatment of the clinical measurement chain with medical expertise for the delivery of MRT across a range of European healthcare systems. This project has formed an important metrology contribution to delivering more effective, better targeted treatments, improved outcomes for the patients receiving them, and savings to the national and European health systems that are providing this care.

6 List of publications

[1] A. P. Robinson *et al.*, "MRTDosimetry data repository". *Open Science Framework*; 2021, doi: 10.17605/OSF.IO/69NG, Updated Mar 21, 2021, Accessed 21 March 2022.

[2] A. P. Robinson *et al.*, "Development of a validation imaging dataset for Molecular Radiotherapy dosimetry multicenter intercomparison exercises based on anthropomorphic phantoms," *Physica Medica*, vol. 109, p. 102583, May 2023, doi: 10.1016/j.ejmp.2023.102583.

Publications from the 19SIP01 PINICAL-MRT and 15HLT06 MRTDosimetry projects are available from the Euramet publications repository: https://www.euramet.org/repository/research-publications-repository-link/

7 Contact details

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