European Partnership on Metrology
Call 2025 – Health, Integrated European Metrology, Regulation and Research Potential

Selected Research Topic number: **SRT-h07**
Version: 1.0

Title: A metrology-driven framework for the cost-effective optimisation of personalised treatment planning for targeted alpha therapies

Abstract

The use of targeted alpha therapies continues to expand due to their efficacy in treating various cancers with minimal side effects. Despite global efforts to meet the growing demand for a reliable radionuclide supply, production capacity remains limited. Traceable personalised treatment planning and optimisation is needed to ensure safe and cost-effective clinical use of these expensive radiopharmaceuticals. However more metrology support is required such as: radioactivity standards for novel theranostics radionuclides, understanding of their biological effects, robust implementation of Artificial Intelligence (AI) methods, and incorporation of robust uncertainties and health economic metrics to guide optimisation; balancing efficacy, risks and costs.

Keywords

Nuclear medicine, radiopharmaceutical, radionuclide, theranostics, molecular radiotherapy, targeted alpha therapy, radioactivity, dosimetry, radiobiology, artificial intelligence.

Background to the Metrological Challenges

According to the World Health Organisation, the number of cancer diagnoses is projected to increase by 62 % worldwide by 2040. Europe's Beating Cancer Plan encourages the development of personalised therapies and novel treatments such as targeted alpha therapies (TAT). The use of alpha-emitting radiopharmaceuticals remains the fastest growing nuclear medicine therapy, showing remarkable efficacy in clinical trials compared with conventional treatments by taking advantage of the high energy and short range of alpha particles, which cause unrepairable DNA damage in the targeted cells as compared to conventional treatments. Despite global efforts to meet the growing demand for a reliable radionuclide supply, production capacity remains limited. Therefore, more metrology support is needed to implement traceable personalised treatment planning and optimisation which takes advantage of a theranostic approach, combining information from imaging pairs of diagnostic and therapeutic radiopharmaceuticals. This need is reinforced by the Basic Safety Standards Directive (BSSD) 2013/59/Euratom and the European Medicine Agency (EMA) requirements for medicinal products. Significant efforts have been made towards providing metrology support for the use of beta-emitting radiopharmaceuticals in previous EURAMET projects, whilst on-going Metrology Partnership project 22HLT03 AlphaMet is addressing the lack of validated radioactivity standards for the most prevalent alpha emitters, ^{225}Ac, ^{212}Pb, and ^{211}At but more work is needed.

Novel diagnostic radionuclides are now being used to enable theranostics for TAT, such as ^{132}La, ^{134}Ce, ^{203}Pb, ^{209}At, and ^{226}Ac; however, the radioactivity standards to enable traceable and accurate measurements of the activity used for pre(clinical) procedures and cross-calibration of imaging equipment are not yet available, and the uncertainties in using them to predict therapeutic efficacy remain unknown.

Biological effects are of critical importance for regulators to evaluate the potential health risks of exposure, and to set protective measures, in compliance with the BSSD. The use of relative biological effectiveness (RBE) is recommended to correct the absorbed doses delivered by the high- linear energy transfer (LET) radiation of alpha emitters, accounting for their greater radiobiological effect as compared with low-LET beta-emitting radiopharmaceuticals, X-rays or gamma-rays. However, there is a lack of universally accepted values for alpha emitters, as RBE depends on multiple factors and is further complicated by the unique complexities of alpha-

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emitting radionuclides, which decay through long decay chains emitting alpha particles, electrons, and photons with a wide range of energies. Knowledge of the radiosensitivity parameters determined from the linear quadratic model are also required to integrate radiobiological models clinically. There is a clear need to establish a method for a systematic evaluation of biological effects of alpha-emitting radiopharmaceuticals, with traceability and known uncertainties to support integration into clinical applications.

As mentioned previously, despite global investments to provide a sustainable supply of medical radionuclides to meet clinical demand, access to alpha emitters remains challenging. This reliance on expensive alpha-emitters for research, can be avoided using innovative technologies such as validated digital twins, realistic synthetic reference datasets, implementation of AI techniques, and health economic metrics to improve quantification and enable cost-effective treatment optimisation; for which metrology support is still needed. In addition, to advance personalised treatment planning for TAT, emerging AI techniques that address the current imaging limitations of alphas emitters, need to be implemented. This requires a multidisciplinary approach which faces challenges including the need for clearly defined applications, robust validation, explainability of algorithms, and standardisation of data and methods, with a focus on image processing and personalised dosimetry.

There is a recent push towards simplifying dosimetry by minimising resources, e.g. taking a single scan which ignores changes in the spatio-temporal distribution of the radiopharmaceutical. This is despite the lack of evidence on how this will affect dosimetry calculations and therefore the potential impact of establishing much needed absorbed dose-response relationships in this field; and which are also likely to lead to a lack of reproducibility of results. This can, in turn, affect clinical trial design by necessitating larger patient cohorts and resources to find statistically significant correlations with treatment response and patient outcomes. A metrology-driven framework is needed to optimise treatment protocols using decision and probabilistic modelling techniques of clinical trials guided by robust uncertainty quantification methods and embedding health economic metrics, to, for the first time, enable treatment optimisation protocols that balance accuracy, precision, efficacy, safety, and costs.

Objectives

Proposers should address the objectives stated below, which are based on the PRT submissions. Proposers may identify amendments to the objectives or choose to address a subset of them in order to maximise the overall impact, or address budgetary or scientific / technical constraints, but the reasons for this should be clearly stated in the protocol.

The proposal shall focus on the traceable measurement and characterisation of alpha-emitting nuclides for targeted alpha therapy (TAT) to support the implementation of a theranostic approach for personalising treatment planning.

The specific objectives are:

1. To develop and validate, via international comparison with recommendations for deviations below ±10%, primary and secondary radioactivity standards with minimal uncertainties and improvements to the current decay data, for novel radionuclides used for diagnostic and treatment of TAT, such as ^{132}La, ^{134}Ce, ^{203}Pb, ^{209}At, and ^{226}Ac. In addition, activity measurement capabilities will be disseminated according to the end-users needs.
2. To develop protocols and uncertainty quantification methods to investigate the relative biological effectiveness (RBE) and to quantify the impact of factors such as activity, absorbed dose, dosimetry method, biological endpoint and cell/tissue type. In addition, to generate traceable and statistically relevant data for radiosensitivity parameters describing the cellular response to high linear energy transfer (LET) radiation needed as inputs to radiobiological models for personalised therapy optimisation.
3. To establish a repository of traceable and realistic patient cohort reference synthetic datasets of relevant size using in-silico models informed by (pre)clinical data. To investigate the robustness and generalisability of implementing selected AI methods in the clinical measurement chain and to quantify output uncertainties.
4. To develop a robust methodology for personalised treatment protocol optimisation based on cost effectiveness. This will use uncertainty quantification, decision and probabilistic modelling methods, and health economic metrics and balance the need for accurate/precise dosimetry with low uncertainties.
5. To facilitate the take up of the technology and measurement infrastructure developed in the project by the measurement supply chain (calibration services), standards developing organisations, end

users (clinical stakeholders, manufacturers of medical and healthcare products), organisations developing legally and non-legally binding regulation/guidance (e.g., European Association of Nuclear Medicine (EANM), the European Federation of Organisations for Medical Physics (EFOMP) and the International Atomic Energy Agency (IAEA)) and stakeholders (European Metrology Network (EMN) for Traceability in Laboratory Medicine and European Metrology Network for Radiation Protection)

These objectives will require large-scale approaches that are beyond the capabilities of single National Metrology Institutes and Designated Institutes, and it is expected that multidisciplinary teams will be required. To enhance the impact of the research, the involvement of the appropriate user community such as medical practitioners, medical (academic) hospitals and industry is strongly recommended, both prior to and during methodology development. Where relevant, proposals are encouraged to build on, or seek collaboration with, existing projects and develop synergies with other relevant European, national or regional initiatives and funding programmes. In particular, links are encouraged with (i) the projects funded under earlier relevant topics of the Horizon Europe programme; or (ii) other relevant European Partnerships.

Proposers should establish the current state of the art and explain how their proposed project goes beyond this. In particular, proposers should outline the achievements of EMRP project HLT11 MetroMRT, EMPIR projects 15HLT06 MRTDosimetry and 19SIP01 PINICAL-MRT and Metrology Partnership project 22HLT03 AlphaMet and how their proposal will build on those.

Proposers should note that the programme funds the activity of researchers to develop the capability, not the required infrastructure and capital equipment, which must be provided from other sources.

EURAMET expects the average EU Contribution for the selected JRPs in this TP to be 2.1 M€ and has defined an upper limit of 2.6 M€ for this proposal.

EURAMET also expects the EU Contribution to the external funded beneficiaries to not exceed 35 % of the total EU Contribution across all selected projects in this TP.

Any industrial beneficiaries that will receive significant benefit from the results of the proposed project are expected to be beneficiaries without receiving funding or associated partners.

Potential Impact

Proposals must demonstrate adequate and appropriate participation/links to the ’end user’ community, describing how the project partners will engage with relevant communities during the project to facilitate knowledge transfer and accelerate the uptake of project outputs. Evidence of support from the “end user” community (e.g. letters of support) is also encouraged.

You should detail how your proposal’s results are going to:

- Address the SRT objectives and deliver solutions to the documented needs,
- Feed into the development of urgent documentary standards through appropriate standards bodies,
- Facilitate improved industrial capability, or improved quality of life for European citizens in terms of personal health, protection of the environment and the climate, or energy security,
- Transfer knowledge to the healthcare sector.

You should detail other impacts of your proposed JRP as specified in the document “Guide 4: Writing Joint Research Projects (JRPs)”

You should also detail how your approach to realising the objectives will further the aim of the Metrology Partnership to develop a coherent approach at the European level in the field of metrology and include the best available contributions from across the metrology community. Specifically, the opportunities for:

- improvement of the efficiency of use of available resources to better meet metrological needs and to assure the traceability of national standards
- the metrology capacity of EURAMET Member States whose metrology programmes are at an early stage of development to be increased
- organisations other than NMIs and DIs to be involved in the work.

Timescale

The project should be of up to 3 years duration.

Additional information

The links provided in this section are only correct at the time of publication up until the end of the Call year.

These references have been provided by EURAMET.

[1] EMN Radiation Protection Strategic Research Agenda
https://www.euramet.org/research-innovation/metrology-partnership/strategic-research-and-innovation-agendas