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Establishing traceability routes in nuclear medicine

Overview

Nuclear medicine is a versatile and widely used diagnostic and therapeutic medical technique utilising radioactivity to diagnose and treat diseases in areas such as oncology, neurology and cardiology. The measurement of radioactivity in the clinical environment prior to injection, or as part of an imaging study, relies on the use of calibrated instruments. Despite being a heavily regulated environment, calibration and traceability routes across Europe vary in both availability and design leading to a disparity in measurement capability. This project aims to establish traceability routes for nuclear medicine services and provide guidance and tools to enable its widespread adoption beyond the EU.

Need

Over 9 million patients receive injections of radiopharmaceuticals each year across Europe. The global nuclear medicine market is currently valued at around 9 billion € and is anticipated to grow to 37.6 billion € by 2032. The lack of metrology input to nuclear medicine service delivery is a common theme across Europe and partly stems from the origins of nuclear medicine as a qualitative or palliative technique. This lack of metrology has led to poor knowledge of the dose effect relationships for many treatments leading to under treatment of tumours and unsuccessful clinical trials. In nuclear medicine, the injected activity is a fundamental quantity, and at present, the accuracy in the measurement of intended activity injected to patients varies, even within the same country and can be 10 % or more from the prescribed value. This leads to variability in the diagnostic images produced (leading to an inability to compare the images) and variability in the accuracy of absorbed doses delivered to tumours. Alongside this, the lack of uncertainty assessment at the end-user level also forms a critical barrier when trying to perform traceable measurements. Whilst legislation varies between countries, there is generally a requirement for the devices used to measure activity administered to be calibrated in a manner traceable to national standards. Since not all National Metrology Institutes (NMIs) and Designated Institutes (DIs) across Europe maintain primary standards of radioactivity, direct access to calibration services is not always possible to end users despite the legal requirements and patient benefits. Improving the network of calibration services will improve measurement capability.

Objectives

The overall objective of the project is to establish traceability routes for nuclear medicine services across several European countries.

The specific objectives of the project are:

1. To establish traceability routes to provide traceable calibration services for key radionuclides with an uncertainty (at $k = 1$) of 2 % or better. The services will be developed in collaboration with the local responsible NMI/DI and partner hospitals to ensure a functional service that will operate effectively within the legislative requirements of the host country.
2. To assess and develop uncertainty evaluation methods used by calibration laboratories and clinical users to provide practical support for end-to-end uncertainty evaluation from activity determination at the calibration laboratory to quantitative imaging and dosimetry.
3. To validate effectiveness of calibration routes and to assess measurement capability by performing comparison exercises among users for key clinical radionuclides. The target is for 80 % or more of

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participants from countries with emerging metrology capabilities in this field to be able to measure activity to within 10 % of the reference value. A supplementary target is to receive uncertainty budgets from 70 % or more of participants.

4. To provide guidance documents on establishing calibration services for key radionuclides, validation of measurements and uncertainty assessment to further improve the accessibility of traceable calibration routes in Europe.
5. To facilitate the take up and long-term operation of the capabilities, technology and measurement infrastructure for nuclear medicine measurements developed in the project, by the measurement supply chain (NMIs/DIs, calibration and testing laboratories), and end users (e.g. industry, instrument manufacturers, regulators). The approach should be discussed within the consortium and with other EURAMET NMIs/DIs, e.g. via EURAMET TC-Ionising Radiation (IR) and EMN for Radiation Protection, to ensure that a coordinated and optimised approach to the development of traceability in this field is developed for Europe as a whole.

Progress beyond the state of the art and results

Establishing traceability routes to provide traceable calibration services for key radionuclides with an uncertainty (at k = 1) of 2 % or better (objective 1)

In nuclear medicine, the injected activity is a fundamental quantity. Whilst legislation varies between countries, there is generally a requirement for the devices used (typically radionuclide calibrators) to measure activity administered to be calibrated in a manner traceable to national standards. This requirement can be fulfilled in multiple ways, with the most accurate method being the use of the specific radionuclide in question in a relevant geometry. Due to operational, administrative, or financial reasons, calibration services to ensure traceability by use of the specific radionuclide are not available in every country and therefore the accuracy and traceability of these devices varies significantly across Europe. Article 56.1 of EU BSS COUNCIL DIRECTIVE 2013/59/EURATOM states that: *"For all medical exposure of patients for radiotherapeutic purposes, exposures of target volumes shall be individually planned, and their delivery appropriately verified taking into account that doses to non-target volumes and tissues shall be as low as reasonably achievable and consistent with the intended radiotherapeutic purpose of the exposure".* The same directive also states that absorbed doses should be calculated in a traceable manner. In nuclear medicine there are over 20 radionuclides used for diagnosis and therapy. Each of these requires its own primary standard and there are a variety of techniques employed to realise these standards. Furthermore, quantitative imaging is used for the classification and diagnosis of disease alongside determination of absorbed dose to target tumours and healthy organs. Without traceable calibration processes, patients may be mis-diagnosed (or wrongly classified) and calculated absorbed doses for radionuclide therapy are not traceable. The latest advancements in so-called 'theragnostics', whereby therapeutic-diagnostic radionuclide pairs are used to tailor treatment, further increase the need for traceability. By creating traceability routes the aim is to improve the accuracy of both measured activity prior to injection and the activity derived from imaging techniques.

Assessing and developing uncertainty evaluation methods used by calibration laboratories and users to provide practical support for end-to-end uncertainty evaluation (objective 2)

A common theme throughout the nuclear medicine community is the lack of consideration of uncertainties. This not only makes statistical comparisons difficult to perform, it demonstrates a gap in the traceability chain through to quantitative imaging and dosimetry which needs to be addressed to comply with legislation and improve patient outcomes. By working with clinical partners, the consortium will identify the key factors preventing routine use of uncertainties within clinical departments to enable practical guidance to be drafted. Workshops prepared in consultation with clinical partners and stakeholders will raise the profile of measurement uncertainty within the clinical environment and provide training and resources to end users.

Validating effectiveness of calibration routes and assessing measurement capability by performing comparison exercises among users for key clinical radionuclides (objective 3)

By observing the outcomes of radionuclide comparison exercises from different countries the measurement landscape can be estimated. In the UK, which has a radionuclide and geometry specific calibration service, comparison exercises over the years have indicated that for most radionuclides the majority of participants (often more than 90 %) were able to measure the activity of a reference source to within ±5 % of the true activity. In contrast, a recent study in Sweden and Norway which have no national traceability for radionuclides demonstrated that only ~23 % of participants were able to measure the activity to within 5 %. Similar trends

can be seen for comparisons performed in Belgium/Netherlands/Germany and Switzerland with participants typically doing less favourably than their UK counterparts. Validation of the measurement capability in participating countries is therefore important to determine the effectiveness of the new services, and to focus research to improve measurement capability.

Providing guidance documents on establishing calibration services for key radionuclides, validation of measurements and uncertainty assessment (objective 4)

To ensure continued performance and enable expansion of the networks, it is important to write guidance documents and produce training material that can be used beyond the end of the project. The guidance drafted as part of this project can be adopted in future projects to further improve the accessibility of traceable calibration routes in Europe. Educational resources where possible will be presented/shared at external meetings such as those organised by the International Atomic Energy Authority (IAEA), European association of Nuclear Medicine (EANM) and European Federation of Organisations for Medical Physics (EFOMP).

Outcomes and impact

Key dissemination and communication activities

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Outcomes for industrial and other user communities

This project will be the first international project which looks to improve the traceability infrastructure in nuclear medicine by creating new calibration routes and assessing measurement uncertainty throughout the whole measurement chain. This improved accessibility to traceable activity measurements is of benefit to hospitals, equipment manufacturers (radionuclide calibrators, gamma counters and imaging systems), radionuclide production sites and radiopharmaceutical companies.

Hospitals delivering nuclear medicine services will be able to administer treatments and diagnostic doses using traceable activity measurement within accuracies recommended by the IAEA. The guidance documents and workshops will enable other NMIs, DIs and commercial companies to establish traceable calibration services, leading to an increase in availability of calibration services in nuclear medicine across Europe. Ready access to calibration services across Europe will increase harmonisation of measurements and make the European theatre a more attractive prospect for multi-centre, multi-country clinical trials. Improved uncertainty assessment capability will also give increased confidence in reported results. This can speed radiopharmaceutical development by providing high-quality data with known uncertainties.

Outcomes for the metrology and scientific communities

Developing the metrological capabilities of the participating countries will increase the research power in the field of metrology for nuclear medicine. Building links with the local nuclear medicine communities will bolster knowledge transfer between clinical users and the metrology community and improve the quality and applicability of research in both areas. With an increased interest in the clinical application of nuclear medicine, particularly for novel radionuclides and the adoption of theragnostic techniques, this project will be an important stepping stone to create a larger network of metrology research in the field. By developing the measurement capability of the participating NMIs and DIs this project will lead to increased participation in future research calls, particularly in the field of health, by providing base knowledge and technical infrastructure.

Outcomes for relevant standards

The measurement traceability which will be developed in this project directly supports the EU directive 2013/59/EURATOM, 2001/83/EC (medicinal products) and 2001/20/EC (clinical trials). By providing traceable calibration routes the project will contribute to: (i) the goals of the EU Strategic Agenda for Medical Ionising Radiation Applications (SAMIRA), The EU mission on cancer and the 'Europe's Beating Cancer Plan; (ii) regulatory compliance with legally binding directives 2013/59/Euratom (article 56) for dosimetry-based nuclear medicine therapies, 2001/83/EC for medicinal products and 2001/20/EC for clinical trials (to be replaced by regulation 536/2014); as well as (iii) non-legally binding guidance from professional organisations like the European Association of Nuclear Medicine (EANM), European Federation of Organisations for Medical Physics (EFOMP), European Radiation Dosimetry Group (EURADOS) and the International Atomic Energy Agency (IAEA). The outcomes also support and reinforce the work of the ongoing IEC/ISO Joint Working Group (JWG) on Calibration and Quality Control in the Use of Radionuclide Calibrators (TC 62/SC 62C/JWG 5). The consortium will disseminate the project outcomes internationally through

interactions with the International Bureau of Weights and Measures (BIPM), the EURAMET Technical Committee for Ionising Radiation (TC-IR), and partner technical committees form other regional metrology organisations.

Longer-term economic, social and environmental impacts

Over 9 million patients receive injections of radiopharmaceuticals each year across Europe. The global nuclear medicine market is currently valued at around 9 billion € and is anticipated to grow to 37.6 billion € by 2032. Increasing access to traceable activity measurements improves the efficiency of service delivery both at a clinical level and at the point of manufacture. By improving access to traceable calibration routes the quality of healthcare will be improved and the opportunity to tailor diagnostic and therapeutic administrations more accurately can lead to improved patient outcomes. Improved accuracy in imaging studies can lead to greater confidence in diagnostic techniques and more accurate assessment of doses during therapy. Uncertainty assessment through the measurement chain will lead to greater confidence and better decision making. The accurate measurement of activity at both production and during administration will reduce the quantity of radioactive material which is currently deposited into the environment through typical waste routes.

This project will provide a framework for establishing traceability in countries which do not traditionally have standards for radioactivity, and will allow calibration laboratories in emerging metrology areas to claim traceability. The guides and workshops aim to provide a foundation for increased engagement between the user community and metrology institutions to improve measurement capability across Europe.

List of publications

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<table>
<tr><td colspan="2">Project start date and duration:</td><td>01 June 2025, 36 months</td></tr>
<tr><td colspan="3">Coordinator: Andrew Fenwick, NPL E-mail: andrew.fenwick@npl.co.uk
Project website address: tbc</td></tr>
<tr><td>Internal Beneficiaries:
1. NPL, United Kingdom
2. CMI, Czechia
3. FTMC, Lithuania
4. IST, Portugal
5. SSM, Sweden
6. STUK, Finland
7. VSL, Netherlands</td><td>External Beneficiaries:
8. HUS, Finland
9. LUND, Sweden
10. RS, Sweden
11. RSFT, United Kingdom
12. VUHSK, Lithuania</td><td>Unfunded Beneficiaries:
-</td></tr>
<tr><td colspan="3">Associated Partners:
13. CHUV, Switzerland
14. METAS, Switzerland</td></tr>
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