FINAL PUBLISHABLE REPORT

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Internal Funded Partners: 1. NPL, UK	External Funded Partners:	Unfunded Partners: 2. UTU, Finland

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1 Overview

The aim of this project was to maximise awareness and minimise the effect of the measurement uncertainties in cardiac PET (Positron Emission Tomography) perfusion imaging in the research and clinical environment.

On the research side, this has been achieved by developing software tools that quantify dynamic PET perfusion scans of a ground-truth reference object (phantom) and evaluate some of the associated measurement uncertainties building upon existing software provided by the primary supporter (https://turkupetcentre.fi/carimas/); and by designing and implementing a cardiac PET perfusion validation and calibration measurement protocol. The relevant documentation explaining the quantification and uncertainty evaluation tools as well as the measurement protocol has been provided as best practice guidance for technicians, enabling them to use protocol and practices identified by the phantom study, and also been disseminated to the wider PET perfusion community.

With respect to the impact on the clinical environment, the project has not fully addressed its objectives of developing a semi-automatic classification tool with associated clinical guidelines. Instead, the findings from the phantom imaging experiments were translated and applied to a small-scale clinical test dataset, thus providing useful and valuable conclusions regarding measurement standardisation that could be useful for clinical research in the long term.

2 Need

The quantification of perfusion in PET images is highly sensitive to acquisition parameters. However, even though this is known to be the case, the uncertainties associated with these parameters are not currently provided in software implementations of perfusion analysis. This limits the usefulness of such measures as they are not easily comparable between centres, or even between different acquisition types at a single centre. Additionally, this means that uncertainty exists in the source of variations between measurements, where it is not known whether variations in perfusion measurements come from variations within the patient or variations due to scanner parameters.

To be fully quantitative, perfusion measurements require associated uncertainty measurements, as highlighted in the EMPIR project 15HLT05 PerfusImaging. This also allows for more confident comparison of results across centres and within centres over time. Therefore, there is a need for improved access to uncertainty quantification tools; that can enable clinicians to better understand their decisions; as variations could be more accurately attributed to: either true underlying changes in patient physiology or scanning parameters.

Validated, easy to use and accessible software would provide technicians and clinicians with associated uncertainty information that would improve image acquisition, interpretation and hence, quantification. The project has addressed this need by developing a software quantification tool which includes an uncertainty package based on a Monte Carlo model as described in Supplement 1 to the Guide to the Expression of Uncertainty in Measurement (GUM); to evaluate some of the sources of uncertainty as identified in 15HLT05 PerfusImaging. The software is supplemented with an associated measurement validation and calibration protocol for dynamic PET perfusion scans of a ground-phantom. This work has enabled the end user to understand key sources of uncertainty in their measurement systems. A preliminary clinical interpretation of the uncertainty has been derived from an existing dataset of patient scans.

3 Objectives

The overall aim of the project was to create clinical and research impact from the results of the EMPIR project 15HLT05 PerfusImaging, for cardiac perfusion PET imaging. The project set out to address the following objectives:

1. To develop a Monte Carlo add-on for the Carimas software which can evaluate measurement uncertainties in a cardiac PET perfusion pipeline.
2. To establish technical validation and calibration protocol using information from a multi-centre phantom study between partners, and to produce documentation relating to the relevant acquisition protocols to extract the necessary information about the gantry used.
3. To develop a semi-automatic classification software based on the results of 15HLT05-PerfusImaging, which will consider associated uncertainties in perfusion classification.

4. To produce a recommended clinical guideline (CG) whereby the disease classification results have an associated uncertainty that will provide clinicians and researchers with more information upon which to decide treatment paths.

4 Results

A software add-on to the Carimas package and knowledge transfer to the primary supporter through the application of the software to data obtained at the Turku PET centre (Objective 1)

The work developed here addressed the need of providing associated uncertainty information to PET perfusion measurements, to improve image acquisition, interpretation and hence, complete image quantification.

Software tools that quantify dynamic PET perfusion scans of a ground-truth reference object (phantom) and evaluate some of the associated measurement uncertainties have been developed by NPL with input from UTU. In particular, and addressing Objective 1, a Monte Carlo add-on was developed by NPL which can evaluate measurement uncertainties in a cardiac PET perfusion pipeline for PET image that are analysed using the Carimas software developed by UTU and the primary supporter, the Turku PET Centre (TPC). Carimas (https://turkupetcentre.fi/carimas/) is a well-established analysis software package in the PET perfusion imaging research community. The software tools developed in this project are built upon the results of 15HLT05-PerfusImaging (in which both NPL and UTU were involved), existing Carimas software libraries (using the know-how of UTU) and include an uncertainty package based on a Monte Carlo model as described in Supplement 1 to the Guide to the Expression of Uncertainty in Measurement (GUM) (using the know-how of NPL).

The software for perfusion quantification and uncertainty evaluation has been developed by NPL and UTU in consultation with the primary supporter at TPC. It was built in a modular way, in steps that describe the whole cardiac PET analysis pipeline. The following steps were included: data acquisition and storage; pre-processing of imaging data; perfusion calculation; and data exploration; sensitivity analysis; uncertainty evaluation; and comparison to the reference flow in the phantom. Modular software, comprised of MATLAB scripts and functions, as well as an executable file that is built using Carimas libraries, was created to perform each of these steps. The software tool has been deposited on a Gitlab repository and the user guide talks through a work exampled using one of the datasets deposited on Zenodo, so that users from the PET research community can reproduce the work.

Objective 1 was successfully achieved.

Protocol from a multi-centre phantom study used to validate the software and provide research centres with enough information to carry out their own validations. (Objective 2)

The quantification of perfusion in PET images is highly sensitive to acquisition parameters, and for measurements to be comparable across centres and reproducible within centres, it is important to have standardised acquisition protocols. In this project this need has been addressed by developing a technical and calibration protocol from a multi-centre phantom study used to validate the software and provide research centres with enough information to carry out their own validations, which addresses Objective 2.

To investigate perfusion quantification accuracy, a flow phantom (DCE Dynamic Flow Phantom, Shelley Medical Imaging Technologies, Canada) was used at UTU and NPL sites on three different PET/CT systems (2 GE Discovery at UTU and 1 Mediso at NPL) using two different radiotracers (15O-H2O at UTU and 18F-FDG at NPL). The flow within the phantom was measured using a flow meter and this value was used as a reference ground-truth value to compare to the image measured flow or perfusion. The image measured flow value was estimated using the software tools developed in Objective 1.

An initial protocol defining an experimental acquisition sequence for radiowater for perfusion was prepared collaboratively by the consortium and was first tested by UTU using 15O-H2O and later adapted at NPL using 18F-FDG to investigate the feasibility of implementing multi-centre measurements using a different PET/CT system and radiotracer. Feedback from the primary supporter at TPC on the draft protocol was obtained and considered.

After this, a validation and calibration protocol for implementation of cardiac PET measurements of a test object across multiple sites and different manufacturer PET/CT systems was produced by UTU and NPL and deposited on Zenodo as a technical report. Datasets have been acquired following this protocol at two sites and on three different PET/CT systems which have also been deposited on Zenodo for the user community.

Objective 2 was successfully achieved.

A semi-automatic classifier along with associated clinical guidelines (Objectives 3 and 4)

The overall aim of this project was to maximise awareness and minimise the effect of the measurement uncertainties in cardiac PET (Positron Emission Tomography) perfusion imaging in the research and clinical environment. Objectives 1 and 2 addressed the research side and Objectives 3 and 4 were more aimed at the clinical side.

Unfortunately, the objectives of developing a semi-automatic classifier (Objective 3) with associated clinical guidelines (Objective 4) was not successfully achieved. This was due to the fact that some technical difficulties with the analysis of patient data arose mainly due to Brexit related complications. The difficulties resulted in NPL having delays accessing the volume of data (hosted at UTU) necessary to develop and validate the semi-automatic classifier, and these delays could not be resolved within the project timeframe. Thus instead, the work was carried out by NPL used an existing (smaller scale clinical fully anonymised dataset) and the lessons from the measurement of perfusion within a phantom were transferred to this clinical data. A report outlining some proposed ideas on how to bridge the gap between calibrated PET perfusion measurements in a test object and PET perfusion measurements in patients for disease classification has been delivered by NPL and reviewed by UTU, with a focus on understanding the effect of volume of interest selection within the patient images on the output measurement of perfusion. Different to what was done in in the work for Objectives 1 and 2, where phantom data was made publicly available on Zenodo, in this case no data will be made publicly available due to confidentiality reasons. For this work, the deidentified clinical data from UTU has been accessed and analysed by NPL on a Sensitive Data Desktop within Finland.

This has meant the work from these objectives has no longer been targeted at Clinicians, but instead at technicians. However, in discussion with the primary supporter at TPC it was agreed that the phantom study, combined with small scale testing on the limited available patient datasets, would be sufficient to provide useful and valuable conclusions and create best practice guidance for technicians, enabling them to use protocol and practices identified by the phantom study work to calibrate their PET scanners and imaging procedures, which in the long run will improve clinical work.

Furthermore, in relation to objectives 1, 3 and 4, an analysis of the online survey that was collaboratively created between NPL and UTU, and reviewed by TPC, and circulated to relevant stakeholders and Carimas end-users was performed, informing the community requirements for the evaluation of measurement uncertainties in the cardiac PET perfusion pipeline. In-depth stakeholder interviews were held with selected users to further refine these requirements. These, together with those assessed from the primary supporter formed the user requirements for the software and tools that were developed throughout the project.

5 Impact

Summary of dissemination activities

A joint paper has been published by the consortium in the Journal of Nuclear Cardiology. The paper is titled “Assessment of a digital and an analog PET/CT system for accurate myocardial perfusion imaging with a flow phantom” by R. Siekkinen et al. J Nucl Cardiol. 2021 May 4. doi: 10.1007/s12350-021-02631-9. https://pubmed.ncbi.nlm.nih.gov/33948894/.

A joint paper has been published by the consortium in Measurement Science and Technology. The paper is titled “Measurement uncertainty quantification for myocardial perfusion using cardiac positron emission tomography imaging” by I. Partarrieu at al. https://doi.org/10.1088/1361-6501/ac58e3.

The following joint conference presentations have been delivered by the consortium:

- Accepted abstract for oral presentation titled "Measurement uncertainty quantification for myocardial perfusion using cardiac positron emission tomography imaging" at CIM2021, September 2021, in France
- Invited oral presentation titled "Standardising Pet Cardiac Perfusion Imaging Measurements and Evaluating Their Uncertainties For More Accurate Diagnosis" at Turku PET symposium, June 2022, in Finland
- Accepted abstract for oral presentation titled "A preliminary protocol for harmonizing PET/CT systems in 15O-H2O myocardial perfusion imaging" at ECMP2022, August 2022, in Ireland
- Accepted abstract for oral presentation titled "Standardising myocardial PET perfusion imaging measurements" at IMEKO-MATHMET 2022 symposium, August 2022, in Portugal

Impact on the Primary Supporter, end-users and the wider PET community

Overall, the results reported in the project have already given the primary supporter, TPC, much insight of the various factors affecting perfusion quantification in PET. In addition, the proposed phantom protocol (Objective 2) is currently undergoing a wider evaluation at their institute, to harmonize the performance of their PET/CT systems for perfusion quantification. Once they have successfully applied the phantom protocol to harmonize all PET/CT systems, they expect that the proposed phantom protocol could be further applied in multi-center evaluation in Finland. The uncertainty quantification pipeline (Objective 1) was deemed highly beneficial as well and will undergo further evaluation with a wider patient dataset. They also expect the uncertainty quantification pipeline will be of use to multiple imaging centers performing PET perfusion studies. Finally, of most upmost importance was to establish how to bridge the gap between the perfusion measurements performed with the phantom and the patients (Objectives 3 and 4), to apply the phantom more effectively and to derive solid conclusions about the effects seen in the phantom to patient studies.

Immediate impact is expected through the distribution of the software and its user guide (Objective 1), as well as the experimental validation and calibration acquisition protocol for implementation of cardiac PET measurements (Objective 2), to all current users of Carimas as well as the Primary Supporter. This will ensure awareness of the importance of traceable and reproducible measurement, as well as measurement uncertainty quantification within a wide section of the PET perfusion community.

Moreover, beyond the usage base of Carimas users, the results could be implemented in the future as a standalone package or implemented into various imaging software packages (Objective 1). Eventually, after the initial validation with the Carimas user base, the package will be disseminated to the wider PET perfusion community. By proving a visual and quantitative estimate of the uncertainties related to a perfusion scan, the end user will be informed of the errors within modelled perfusion images. This will aid in the interpretation of how errors in the acquisition and reconstruction processes affect the calculation of perfusion values. The results of the error modelling can also be used to reduce the variability due to technical factors and thus increase the repeatability and reproducibility of the subsequent perfusion scans. In this manner, the comparability of perfusion values across different imaging systems or sites in multi-centre studies will be greatly improved (Objectives 1 and 2).

There are currently no widely available reference standards or software solutions to assess and minimise the effects of measurement uncertainties across various imaging devices or sites in myocardial PET perfusion measurements. As a result of this project, a validation and calibration acquisition protocol as well as a standard analysis software tool has been provided for harmonisation and quality control purposes which will also benefit the wider PET community (Objective 2).

Long term socio-economic impact

Longer term impact is expected to be clinical, once uncertainties become part of the diagnostic pipeline (Objectives 3 and 4). There is currently no diagnostic software which would display the quantified perfusion value with an associated uncertainty. Displaying associated uncertainties with automatic classification of suspected regions would greatly enhance the reliability of the diagnosis in cases which are borderline between healthy and ischemic states whilst also allowing clinicians to determine whether further tests are necessary to make a reliable diagnosis.

The enhanced quantification is expected to modify practice as clinicians will have more information available when deciding whether further tests are needed. This will lead to improved and cost-effective healthcare for patients thus creating social and economic impact across Europe.

6 List of publications

- "Assessment of a digital and an analog PET/CT system for accurate myocardial perfusion imaging with a flow phantom" by R. Siekkinen et al. J Nucl Cardiol. 2021 May 4. doi: 10.1007/s12350-021-02631-9. https://pubmed.ncbi.nlm.nih.gov/33948894/.
- "Measurement uncertainty quantification for myocardial perfusion using cardiac positron emission tomography imaging" by I. Partarrieu at al. https://doi.org/10.1088/1361-6501/ac58e3.

This list is also available here: https://www.euramet.org/repository/research-publications-repository-link/

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