NCRI PET Core Lab

Quality Control for PET Clinical Trials

NCRI
National Cancer
Research Institute

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Activities of the NCRI PET Core Lab 2012–2015

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Background

Having been one of three strands of work within the NCRI PET Research Network that ran from 2008–2012, the PET Core Lab was funded for a second phase of activity from August 2012 to July 2015. This funding was provided by a consortium of NCRI Partners: Cancer Research UK, the Department of Health, the Chief Scientist Office (Scotland), the National Institute of Social Care and Health Research (Wales) and the Medical Research Council.

This report summarises the activities and achievements during this phase of work, which now transitions into the Experimental Cancer Medicines Centres network in August 2015.

The functions of the NCRI PET Core Lab

Positron Emission Tomography (PET) imaging is increasingly used as an imaging modality in the UK, primarily for staging and response-assessment of cancer. As a relatively new imaging modality, a number of studies are investigating the use of PET imaging within the cancer pathway. As some diseases or treatments being investigated are rare, trials often involve multiple recruiting hospitals with different scanning centres to increase sample size. PET scanning across multiple centres has the potential to introduce variability due to the difference in PET scanner technology and protocols used across sites. Differences in scanner hardware, patient preparation and imaging/reconstruction parameters can all affect measurements of tracer uptake (Table 1), which can reduce the statistical power of the study making it harder to detect an effect.

Table 1. Summary of reported errors in PET studies. From Boellaard R. *J Nucl Med* 2009;50:11S–20S

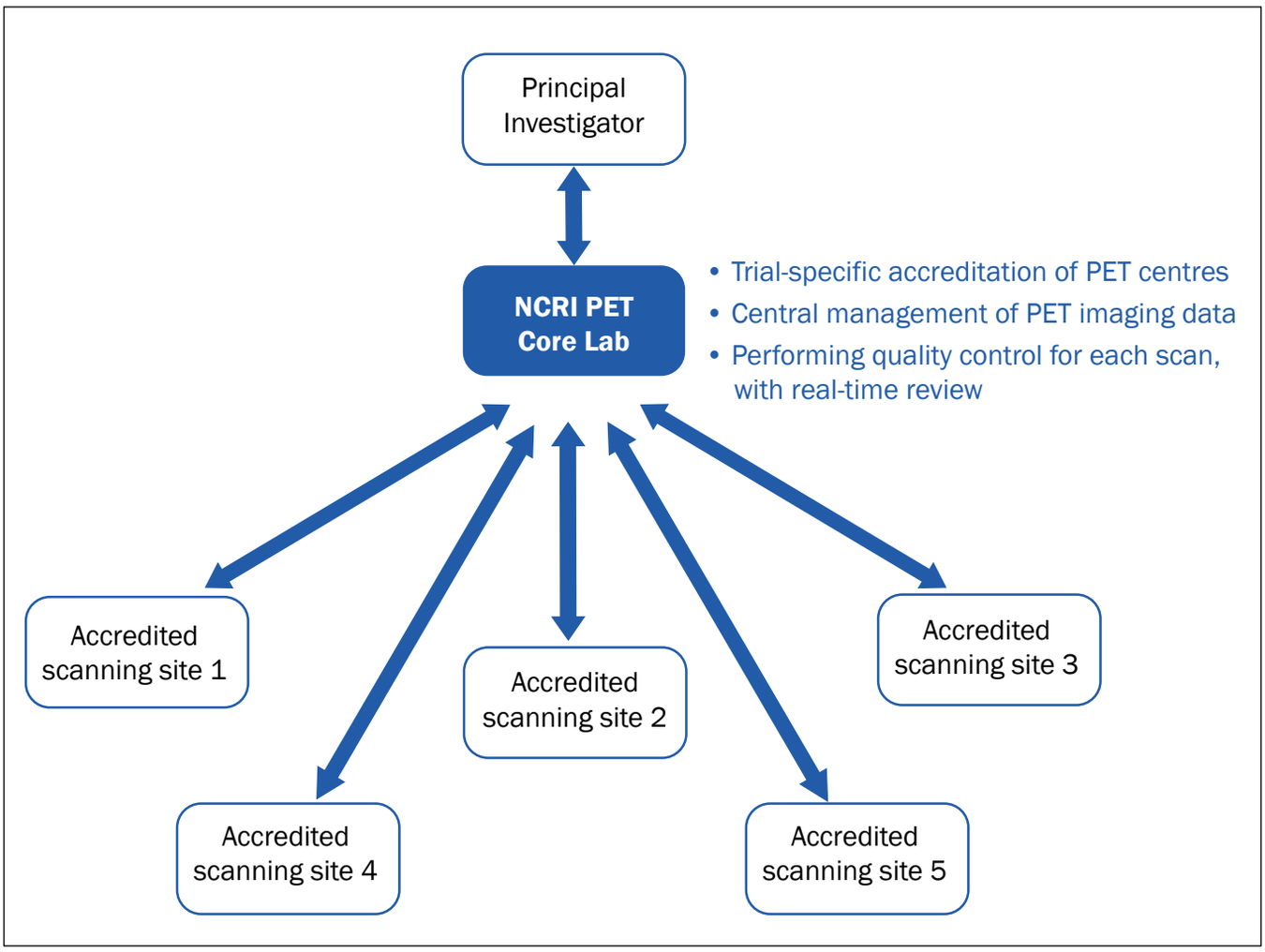
Factors contributing to variation in PET tracer uptake	Typical reported error range in tracer uptake
Error in scanner calibration used to determine uptake of radioactive tracer	–10% to +10%
Error in recorded injection and scan times used to calculate the injected activity	0% to 10%
Variation in time between tracer injection and scan start	0% to 15% at 60–90 min
Patient motion or breathing during the scan or between CT and PET scans	0% to 30%
PET scanning parameters such as scanner mode and scan duration.	0% to 15%
Image reconstruction parameters used to create the final PET images for clinical review	–30% to 0%

By standardising the various aspects of the imaging procedure, comparable and reliable data can be obtained across multiple scanning sites. This requires carefully controlled protocols, scanning sites operating to rigorous standards, and quality control (QC) of the scan data that are captured. Even greater levels of standardisation are required for studies with higher complexity, such as those involving dynamic imaging, non-FDG radiotracers or radiotherapy planning.

St Thomas' PET centre initially set up scanning standards and an accreditation process for several multicentre PET studies being co-ordinated through the department as none existed previously. These procedures were formalised with the establishment of the NCRI PET Core Lab at St Thomas' Hospital in 2009, setting the standard for sites to participate in multicentre PET trials. Since its conception the NCRI PET Core Lab has provided researchers with a single point of access to the expertise and resources required to conduct trials involving PET. The team works with PET centres across the UK, accrediting those that meet commonly agreed standards to qualify them to participate in multicentre

trials. For a given trial, the PET Core Lab then acts as a hub to perform centralised QC on every scan (Figure 1). This verifies that the scan adheres to the trial protocol and assesses image quality. The NCRI Core Lab also offers advice on the setup and running of multicentre trials to potential researchers.

Figure 1. How the PET Core Lab operates.



Implementation of electronic transfer methods by the Core Lab has allowed data turn-around times that are rapid enough to inform clinical decision-making. This real-time review also means that if PET scans do not comply with the protocol, patients can be spared future unnecessary PET scans within the trial.

Outcomes from the first study that the Core Lab implemented these standards and provided centralised PET QC for have recently been published in the New England Journal of Medicine (Radford et al 2015). The trial showed that some patients with Hodgkin's Lymphoma could be spared damaging radiotherapy and still be free from their disease three years later.

The structure of the PET Core Lab

The Core Lab is based within the KCL & Guy's and St Thomas' PET Centre providing direct access to the expertise and specialised equipment within the department. Dr Sally Barrington, Reader and Honorary Consultant in Nuclear Medicine, and Prof Paul Marsden, Professor of PET Physics, are grant holders and jointly oversee the operation and development of the Core Lab. Day-to-day management and running of the Core Lab are provided by Lucy Pike (Clinical Scientist, 0.5 FTE), supported by Donald Sinclair (Imaging Scientist, 1.0 FTE).

In addition to this, a PET scanning methodology panel was set up consisting of 15 UK and 2 international PET experts to provide input on technical and methodological issues for multicentre PET studies, helping in devising and inputting into guidelines and standards.

Advice on future direction and development of the Core Lab has also been provided by experts with extensive experience in PET imaging, oncology and clinical trials, particularly: Prof Otto Hoekstra, MD (Department of Nuclear Medicine & PET Research, VU University Medical Centre, Amsterdam), Prof Paul Kinahan (Vice Chair for Research and Professor of Radiology, UW Medical Center, University of Washington) and Prof Herbie Newell (Professor of Cancer Therapeutics, Northern Institute for Cancer Research, Newcastle).

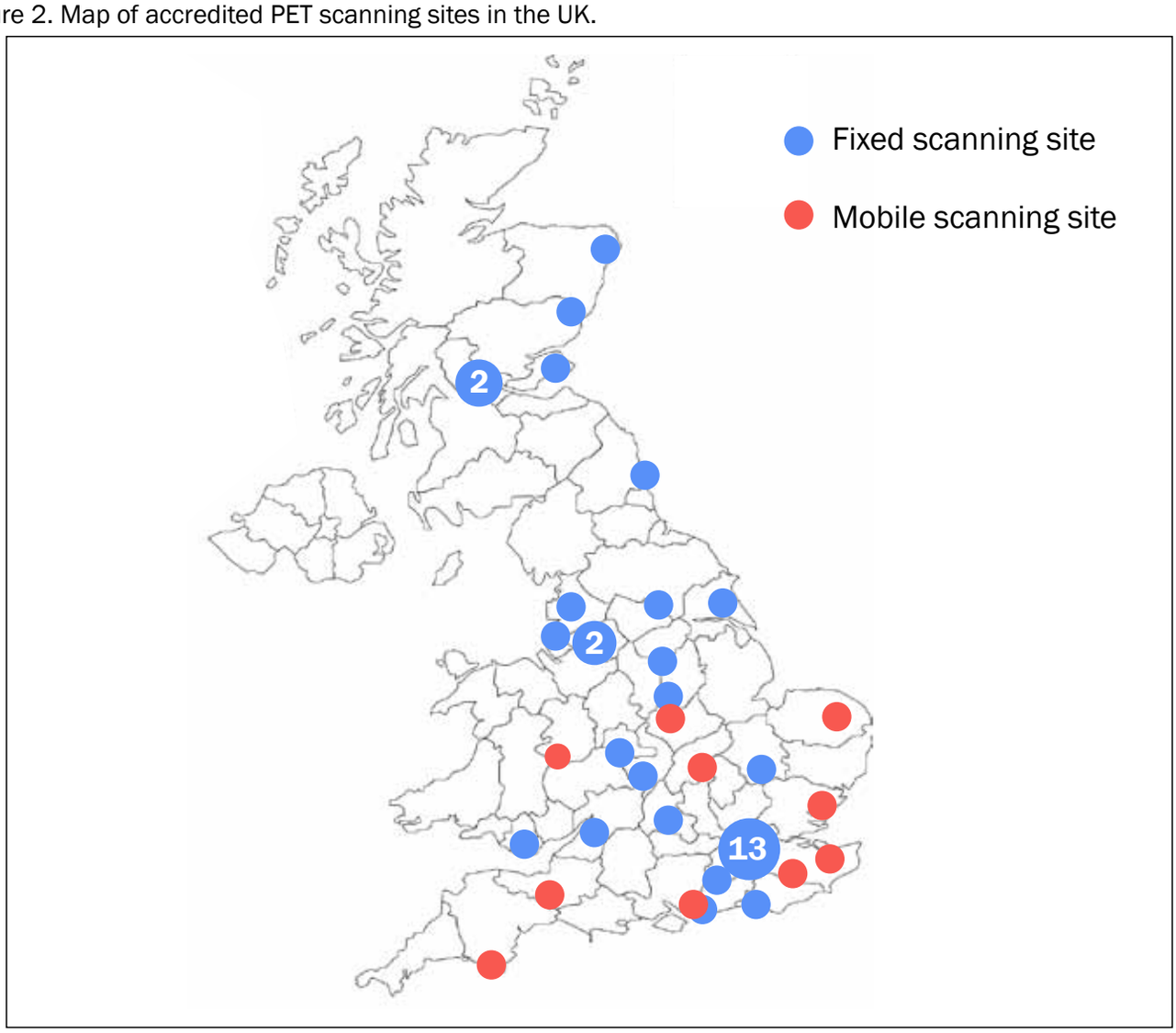
A website has been set up at **www.ncri-pet.org.uk** to provide information for researchers to access the Core Lab's expertise and seek trial technical support, and where possible the requirement for PET Quality Assurance (QA) is raised at an early stage through the NCRI Clinical Studies Group meetings.

Outputs and achievements

The NCRI PET Core Lab has two primary functions. The first is to harmonize PET scanning protocols across PET/CT scanners, to enable high quality multicentre PET trials to be conducted. An accreditation process has been established in order to institute a common standard, with 41 PET/CT scanners across the UK having submitted data to the NCRI Core Lab. By ensuring that the individual scanners in the multicentre trials acquire and reproduce images such that they conform to this standard, the reproducibility (and therefore the power) of the study is maximized.

There are currently 36 accredited static PET/CT scanners at 33 sites in the NCRI Core Lab clinical trials network. In addition, 5 mobile PET/CT scanners have been accredited for scanning at 10 sites (Figure 2). Thirty-three of these scanners have been accredited since the start of the PET Research network in 2009, and 11 since the start of the current block of funding.

Figure 2. Map of accredited PET scanning sites in the UK.



The second major function of the Core Lab is to collate and perform QC of all PET/CT data acquired as part of the multicentre trials. The Core Lab maintains close links with each of the scanning sites and once patients are recruited, the PET/CT images are sent from the scanning sites to the Core Lab for technical review. By collating the images in real-time, the Core Lab can identify technical issues with the scans promptly and raise queries directly with the site to resolve them before sending on to the central review site. Where issues cannot be resolved, the Core Lab alerts the trials management team and can provide advice on any potential consequences for the study. Table 2 provides a summary of the ongoing and completed trials for which the Core Lab has provided QA/QC.

Table 2. Ongoing and completed trials for which the Core Lab has provided QA/QC.

Trial short name	Phase	Tumour Type	Total number of scans	Duration of trial	Status
RAPID	3	Lymphoma (Hodgkin's)	602	7 years	Published
RCHOP (PET after 2 cycles in NHL)	N/A	Lymphoma (non-Hodgkin's)	464	6 years	Fully recruited and in follow-up
RATHL	3	Lymphoma (Hodgkin's)	Approx 3800	4.5 years	Fully recruited and in follow-up
PET-PANC	N/A	Pancreas	620	2 years	Fully recruited and in follow-up
PAIReD / ReACH	2	Lymphoma (Hodgkin's)	204	7 years	Fully recruited and in follow-up
POETIC: FLT-PET sub-study	N/A	Breast	170	1 year	Closed - in follow-up
TITAN	2/3	Head & Neck	150	1 year	Closed - in follow-up
BACCHUS	2	Rectum	120	1.5 years	Open
FGFR Study	2	FGFR amplified tumours (Breast, Lung, Oesophagus, Stomach)	154	2 years	Open
CHEMO-T	2	Lymphoma (non-Hodgkin's)	372	5 years	Open
SPUtNIk	N/A	Lung	750	3 years	Open
IELSG 37	3	Lymphoma (non-Hodgkin's)	400	4 years	Open
LEGEND	2	Lymphoma (non-Hodgkin's)	184	2 years	Open
ST03 PET sub-study	2/3	Stomach	520	2 years	Open
MAPPING	2	Cervix, uterus/ endometrium	300	5 years	Open
ABLE	2	Lung	138	2 years	Open
BREVITY	2	Lymphoma (Hodgkin's)	180	2 years	Open
REASURE	2	Prostate	384	2 years	Open
TORCH	2	Lymphoma (other)	144	1.5 years	In set up
SCOPE2	2	Oesophagus	584	5-6 years	In set up

In addition to these primary functions, the Core Lab has a number of additional objectives (Table 3) through which the work of the Core Lab continues to evolve and adapt as technology and guidelines change.

Table 3. List of Core Lab objectives and deliverables

Objectives	Delivery
Contribute to and implement relevant international standards as they emerge. It may be necessary to work to different standards for different types of study.	Input into imaging guidelines and standards [see reference list]: • European Association of Nuclear Medicine FDG-PET procedure guidelines [1] • Quantitative Imaging Biomarkers Alliance technical FDG-PET guidelines [2] • Institute of Physics and Engineering in Medicine PET/CT QA report [3] Input into trial QA and protocol development: • NCRI Lymphoma CSG • CTRad / RTTQA Active involvement with the following groups to inform areas of further guidance/research: • NCRI Imaging CSG • ECMC • Society of Nuclear Medicine clinical trials network. • UK PET Physics group
Implement Good Clinical Practice (GCP).	GCP guidance developed by the Core Lab specifically for PET is available via the Core Lab website **http://www.ncri-pet.org.uk/gcp.php** All sites have signed to agree that they abide by GCP guidelines as part of the PET Core Lab accreditation process
Formalise contact lists of PIs experienced in the use of PET.	List completed and updated annually, making the Core Lab able to connect chief investigators with possible collaborators during trial development. Exploring mechanisms to make this data available to researchers – possibly through ECMC network.
Develop standards that will allow multi-site mechanistic and early phase studies to be implemented at a subset of sites. Mechanistic studies are performed in order to determine, for example, the mode of action of a drug and do not fall under the clinical trials directive. Typically, mechanistic and early phase trials require more complex PET scanning protocols (e.g. including dynamic scanning protocols, blood sampling during the scan and complex data analysis).	Additional QC modules for more complex PET imaging procedures (dynamic imaging, blood sampling & radiotherapy planning) have been developed with custom designed tests. These have been incorporated into the site accreditation process to allow CIs using more complex imaging procedures to access a sub-set of scanning sites with specialist equipment and procedures. Templates have been designed by the Core Lab for incorporating these complex procedures into the trial imaging manual. As PET technology has advanced in the last 8 years, the accreditation testing procedures have been updated to reflect this to allow the widest range of systems to participate in trials with the least bias and variation between sites.

Explore ways to implement centralised data analysis.	Majority of studies now use central analysis and the Core Lab actively encourages this at the trial design stage. The Core Lab has developed a set of standard tools for testing central analysis workstations as part of the trial set up process. This ensures data from different scanner makes/models is compatible with the local software.
Set up a data archiving service on a per trial basis.	IT equipment has been upgraded and a PACS installed for image data storage. This has provided sufficient space for storage of all trial studies and QA data for the foreseeable future based on current projections and includes facility for off site backup procedures to minimize the risk of data loss. This provides a reliable central archive facility for researchers for an agreed period (usually for a fixed period beyond the end of the trial or until all data has been transferred to the central review site. Demand from researchers for longer term (beyond end of trial) data storage has been low and has such has not been pursued further.
Increase the number of industry funded PET trials handled by the Core Lab (and in the UK in general) if possible by linking with a commercial partner.	New trial in discussion with Blue Earth Diagnostics to provide Core Lab function for an industry sponsored trial.
Website maintenance and setup.	The website set up by the Core Lab has been live since May 2013; updates to information is ongoing. **http://www.ncri-pet.org.uk/** Examples of information on the website include: • Patient information video • Overview of UK cyclotron and PET scanning facilities • Site accreditation information • Data transfer instructions • Details of multicenter PET trials • Information on funding and regulations for researchers • GCP guidance On average there are 6 visits to the website per day with the PET scanning facilities being the most popular page.
Develop long term funding strategy.	Additional funding to support the core lab is received on a per trial basis, although workload is difficult to predict due to uncertainty in the number and size of trials that will receive funding. A key requirement to the ongoing success of the Core Lab is to underpin core staff salary costs.

The future of the PET Core Lab

The NCRI PET Core Lab was tasked by the NCRI Board to become self sufficient, therefore in addition to the funding received through the grant, the Core Lab has been seeking to recover costs through the individual trials for which QA is delivered.

Currently all open trials (10) and those in set up (3) have been provided with a quote to include a fee for the Core Lab work. The amount charged is modelled on:

- Fixed cost for each PET scanner to be accredited (reduced for ongoing accreditation)
- Fixed cost per scan for technical scan QC
- Number of years trial is predicted to run
- Adjusted to account for complexity of the PET components of the study (for example, a non-FDG tracer, dynamic imaging, radiotherapy etc.)

However, becoming fully self-sufficient has proven challenging. It is difficult to predict workload as this is reliant on the number of trials gaining funding and patient recruitment rate, which are highly variable. Based on current trials, the projected income would be on average £28,000 per year for the period Oct 2012-Sept 2017, assuming that all planned studies go ahead, and that the studies recruit the full number of patients in a similar timeframe to that projected. As of May 2015 85% of the projected income has been recovered.

The costs charged by the Core Lab do not cover the full cost of staffing and delivering the Core Lab activities, as this would be prohibitive to researchers using the service and to sites in becoming accredited. Furthermore, the flow of funds is not stable enough to support staff posts, as not all costs are received upfront; a setup fee is collected when the trial opens, which includes the site accreditation costs and scans are then invoiced based on work done. Staff contracts therefore require underpinning funding.

The ECMC network has agreed to provide supplemental funding to the ECMC at Kings College London for 1.5FTE of key posts until the end of the next quinquennium (31st March 2017), starting from 1 August 2015 when the NCRI funding ends. This core staffing will enable the Core Lab activities to be maintained and fulfill QC commitments to current trials. Cost recovery on a per-trial basis will continue to cover costs for non staff costs such as; technical equipment, software & network licenses, IT systems support, travel costs for accreditation & trial management meetings, training and clinical time for PET scan review as part of the accreditation process. This also provides an opportunity for the Core Lab to focus more on promoting PET within the ECMC network of centres. From the end of the quinquennium, the Core Lab aims to incorporate these posts within the ECMC future bid.

In the wider UK setting, NHS England has also provided further investment in PET scanning capability through the award of the NHS PET contract. As this is still in its infancy (contract start April 2015) the changes for patients and impact on research are yet to be seen but early indications are positive with a commitment to installing more PET-CT scanners at fixed locations across England allowing greater capacity and access for patients. The PET Core Lab team has been proactive in initiating talks with the new provider, who has shown a commitment to ensuring the quality of PET scanning is maintained for the purposes of research. The Core Lab will continue to help them to work towards accrediting all new scanning sites.

Appendix

List of guidelines the PET Core Lab has contributed to:

1. Boellaard, R., R. Delgado-Bolton, W. J. Oyen, F. Giammarile, K. Tatsch, W. Eschner, F. J. Verzijlbergen, S. F. Barrington, L. C. Pike, W. A. Weber, S. Stroobants, D. Delbeke, K. J. Donohoe, S. Holbrook, M. M. Graham, G. Testanera, O. S. Hoekstra, J. Zijlstra, E. Visser, C. J. Hoekstra, J. Pruim, A. Willemsen, B. Arends, J. Kotzerke, A. Bockisch, T. Beyer, A. Chiti and B. J. Krause (2015). "FDG PET/CT: EANM procedure guidelines for tumour imaging: version 2.0." Eur J Nucl Med Mol Imaging 42(2): 328-354.
2. Quantitative Imaging Biomarkers Alliance. FDG-PET/CT as an Imaging Biomarker Measuring Response to Cancer Therapy.
3. Pike, L. (2013). Quality Assurance of PET and PET/CT Systems. York, Institute of Physics and Engineering in Medicine. **Report 108**.

List of publications involving work by the PET Core Lab (2012-2015)

Fleming, I. N., S. J. Regel, L. C. Pike, P. K. Marsden and F. J. Gilbert (2012). "Positron emission tomography oncology research in the UK: a comparison with USA and Europe." Nuclear Medicine Communications **33**(4): 341-348.

Radford, J., T. Illidge, N. Counsell, B. Hancock, R. Pettengell, P. Johnson, J. Wimperis, D. Culligan, B. Popova, P. Smith, A. McMillan, A. Brownell, A. Kruger, A. Lister, P. Hoskin, M. O'Doherty and S. Barrington (2015). "Results of a trial of PET-directed therapy for early-stage Hodgkin's lymphoma." N Engl J Med **372**(17): 1598-1607.

Somer, E. J., L. C. Pike and P. K. Marsden (2012). "Recommendations for the use of PET and PET-CT for radiotherapy planning in research projects." British Journal of Radiology **85**(1016): e544-548.

Thomas, C. M., L. C. Pike, C. E. Hartill, S. Baker, E. Woods, D. J. Convery and A. G. Greener (2014). "Specific recommendations for accurate and direct use of PET-CT in PET guided radiotherapy for head and neck sites." Med Phys **41**(4): 041710.

Conference posters / presentations

2015, British Nuclear Medicine Society Annual Meeting:

Results of a UK survey of PET technology and imaging protocols for ^{18}FDG-PET in oncology. L.C. Pike, H.A. Williams, I.S. Armstrong and M. Burniston.

A method for the objective measurement of PET to CT alignment using the NEMA IQ phantom. D. Sinclair, L. Pike, J. O'Doherty.

2014, Society of Nuclear Medicine and Molecular Imaging Annual Meeting:

Accuracy and variability of PET activity concentration measurements for small volumes and short time frames. L. Pike, P. Schleyer, P. Marsden.

Assessment of spatial accuracy in indirect PET-CT radiotherapy planning: staging versus dedicated planning PET-CT. L. Pike, S. Barrington, T. Guerrero Urbano, A. Chalkidou, P. Marsden, E. Somer.

2013, International Conference on Malignant Lymphoma:

PET-CT for staging and Early Response- Results from the Response Adapted Therapy in Advanced Hodgkin Lymphoma (RATHL) study S. F. Barrington, M. J. O'Doherty, T. H. Roberts, A. Kirkwood, Z. N. Viney, A. Franceschetto, M. J. Fulham, M. Cucca, H. Almquist, E. Brun, K. Hjorthaug, L. C. Pike, D. A. Sinclair, P. W. Johnson.

Responses and Chemotherapy Dose Adjustment determined by PET-CT Imaging: First Results form the

International Response Adapted Therapy IN Advanced Hodgkin Lymphoma (RATHL) Study P. Johnson, M. Federico, A. Fossa, M. O'Doherty, T. Roberts, L. Stevens, P. Smith, A. Kirkwood, G. Anghel, J. Trotman, L. Berkahn, F. D'Amore, G. Enblad, S. Luminari, Z. Viney, J. Radford, S. Barrington.

Invited talks

Introduction to PET Physics and Further PET Physics Course; Assessing and Standardising Image Quality. IPEM May 2015.

National PET-CT Programme Reporters Meeting: Influence of Technical and Physical Factors on Image Quality and SUV in PET. RSM Mar 2015.

Functional Imaging in Radiotherapy: PET Fusion in Radiotherapy. British Institute of Radiology Nov 2014.

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