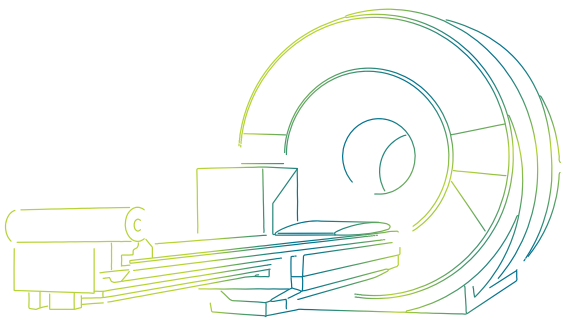
MRC Review of Positron Emission Tomography (PET) within The Medical Imaging Research Landscape

August 2017

Content

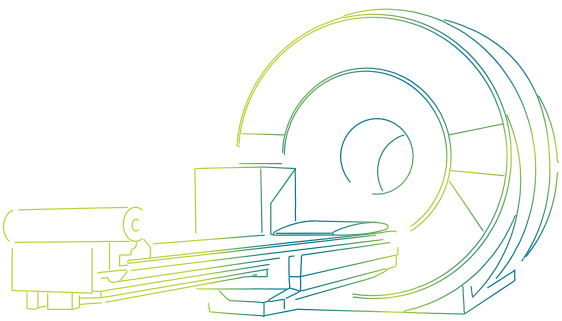


1. Introduction

This report aims to provide a review of Positron Emission Tomography (PET) within the medical imaging research landscape and a high level strategic review of the UK's capabilities and needs in this area.

The review was conducted by face-to-face and telephone interviews with 35 stakeholders from UK centres of excellence, international experts, industry and other funders (list at appendix 1). Data were also collected on facilities, resources and numbers of scans conducted across the centres of excellence using a questionnaire.

The review has focused predominantly on PET imaging, but given MRC's significant recent investment in other imaging modalities (7T Magnetic Resonance Imaging (MRI), hyperpolarised MRI) through the Clinical Research Infrastructure (CRI) Initiative, these are also considered more briefly. The review was informed by a steering panel consisting of experts in the field (Karl Herholz, University of Manchester and MRC Board member, Neurosciences and Mental Health Board (NMHB, Franklin Aigbirhio, University of Cambridge, and Phil Murphy, GSK).



2. The medical imaging research landscape in the UK

The MRC has invested heavily in imaging research over many years and a major proportion of this investment has been to address the challenges for innovation and implementation in PET research. Together with significant investments from a range of other funders (see appendix 2), the UK has strong networks across various modalities for imaging research and the number of modalities available to researchers is growing, as is the accessibility. Some of our recent investments are listed below.

2.1 Magnetic resonance imaging (MRI)

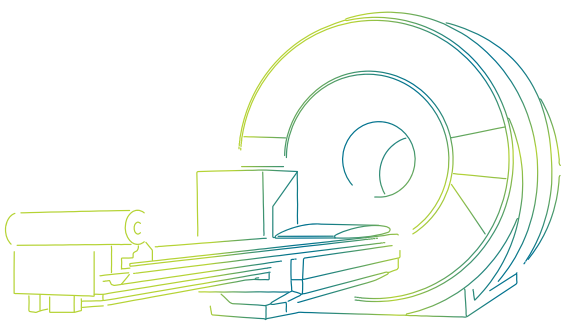
MRI has proven to be a highly versatile imaging technique that produces three dimensional detailed anatomical images without the use of radiation. It is most prominently used in diagnostic medicine and biomedical research.

7T MRI

Ultra-high field MRI is an area of intensive research and development internationally, representing the cutting edge of biomedical imaging in humans. Over the last decade, 7T MRI scanners have evolved significantly as they undergo the transition from bespoke research systems to clinical research tools within the reach of the broader imaging community. This evolution has been driven by technical developments, including advances in radiofrequency technology, imaging techniques and data analysis, along with the identification of novel contrast mechanisms. As a result, 7T MRI has greatly enhanced the range of anatomical, functional and metabolic features that can be detected *in vivo*, particularly in the brain.

The UK's contribution to this effort had been led by the Universities of Nottingham and Oxford. In 2014 MRC funded two new 7T MRI scanners at the University of Cambridge and Cardiff University, as well as a refurbishment to the existing facility at the University of Nottingham through the CRI Initiative. UK Government funding through the MRC also funded an additional 7T MRI scanner at the University of Glasgow in 2015 as part of the Glasgow & Clyde Valley City Deal. Wellcome funded a sixth scanner in King's College London.

This enhancement of national infrastructure has shifted the focus from technical development to biomedical research and requires the UK's 7T MRI sites to work together to share expertise in tackling the challenges associated with moving to clinical application. Given these challenges, in November 2015 the MRC funded the UK7T Network (PI Bowtell, University of Nottingham, £1.05m; www.uk7t.org) to share expertise, build capacity, and develop harmonised approaches to image data acquisition, sharing and analysis. The network aims to serve as a platform for future collaborative research programmes, including multi-site clinical studies across the UK's six sites.

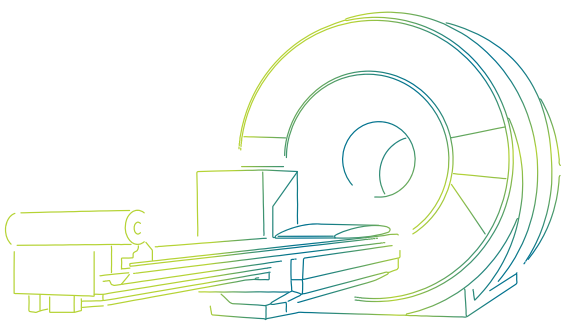


Hyperpolarisation and MRI

Hyperpolarized (HP) agents have been developed in the past 20 years for MR imaging, and they have the potential to improve MRI sensitivity for the diagnosis and management of various diseases. Most progress towards clinical translation has been made with HP gas MRI with helium (^{3}He) and xenon (^{129}Xe) isotopes. These have been successfully used for lung imaging and provide new sensitive contrast mechanisms to probe changes in pulmonary ventilation, microstructure and gas exchange. HP ^{129}Xe is also used in brain imaging and biosensors while HP ^{13}C allows imaging of tissue concentrations of simple metabolites. The CRI Initiative funded an upgrade to the HP gases and proton MRI facilities at the University of Sheffield for clinical lung imaging. The expansion also created a national hyperpolarised gas imaging facility for collaborating institutions without access to this technology.

Metabolic imaging using dynamic nuclear polarisation (DNP) with ^{13}C labelled substrates has been translated clinically in the UK within the last year. It overcomes the shortcomings of low sensitivity of MRI that has limited the potential for MR to be an effective molecular imaging technique. The methodology significantly increases the sensitivity of ^{13}C MRI to enable the study of tissue metabolic processes. Unlike PET, DNP can enable the identification of specific metabolites in tissue. However, the technique is challenged by the limited number of the substrates available for clinical use and the short measurement time possible following injection. It is likely that this technique can complement PET. Much more research is needed to optimise this methodology and explore clinical applicability. This has been largely led by Cambridge and Oxford with applications focused on oncology and cardiovascular medicine respectively.

In addition, advanced hyperpolarisation techniques are in development in the UK. The CRI Initiative also included investment in the development of a new imaging method (SABRE), that has the potential to increase the signal in a MRI image by up to 100,000 fold, at the Universities of Leeds and York. With this technique it is possible to label both drugs and substances that occur naturally in the body, making the method widely applicable. In addition, the CRI Initiative funded a second ^{13}C hyperpolariser at Cambridge and, finally, the initiative funded an upgrade to the existing 3T MRI scanner at the Dementia Research Scanner Centre, UCL.



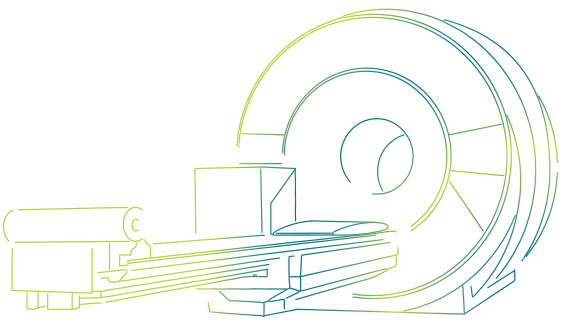
2.2 PET, including PET-MRI

The MRC has a long history of support for PET research. Initially this was through the MRC Cyclotron Unit at the Hammersmith Campus, then Imanet (an MRC-GE partnership) and, since 2011, Imanova (www.imanova.co.uk). Imanova built on an innovative alliance between MRC, Imperial College London, King's College London and University College London to act as a conduit between academia and industry and a key 'hub' for UK PET. The initial joint venture was for 5 years in the first instance; MRC's initial investment in Imanova has now ended (October 2016) and we are currently supporting PET research in Imanova on a project basis.

PET-MRI is a hybrid technology that combines the two modalities into a single machine, allowing for simultaneous MRI and PET images. This allows excellent anatomic visualisation with MRI and visualisation of functional activity via blood flow with MRI and via metabolic activity with PET. Through the CRI Initiative MRC funded five new PET-MRI scanners for the Dementia Platform UK (DPUK) imaging network at University of Cambridge, University of Edinburgh, Imperial College London (based in Imanova), University of Manchester and Newcastle University, and radiochemistry equipment at Cambridge, Cardiff, Imperial (Imanova) and Newcastle). In addition, a PET-MRI Partnership Grant (PI, Herholz, University of Manchester, £0.86m) was awarded in 2016 to establish stronger coordination between the seven UK PET-MRI centres in the field of dementia research.

MRC has also run two calls (2009 and 2012) through the Neurosciences and Mental Health Board (NMHB) to build capacity in the field of radiochemistry for PET research. The pilot scheme in 2009 aimed to allow suitably qualified post-doctoral researchers to both train in specialist PET-related disciplines and then potentially contribute towards the development of novel PET molecular imaging methodologies (for example, new molecular probes) specifically in the neurosciences. The Board committed £1.6m towards this training scheme via three awards to three universities (Cambridge, King's College London and Imperial). In 2012 the call aimed to address continuing shortfalls in specialist post-doctoral training to enable skills development for PET imaging. Two posts were awarded to King's College London and a further two to Cambridge at a cost of ~£2m to NMHB. However, following these awards the office took a view that specialist one-off training schemes had not led to a sustained change in the environment as the postdocs recruited were not retained in academia in the UK and were instead quickly recruited by either industry, or universities overseas offering permanent positions and higher salaries than those available in the UK PET centres.

The National Cancer Research Institute (NCRI) PET Clinical Trials Network and Core Lab was formed in 2008 and consists of 33 PET sites that have all been accredited and adhere to the same standards. A central 'Core Lab' based at St Thomas' provides a service that delivers independent quality control (QC) and site accreditation for PET centres participating in multicentre cancer trials, central management of image data and assessment of all acquired images to verify adherence to the trial protocol and assess image quality. The NCRI Partners (CRUK, Department of Health, MRC, Welsh and Scottish governments) last renewed the funding in 2012-2015, and they are now funded through individual research grants.

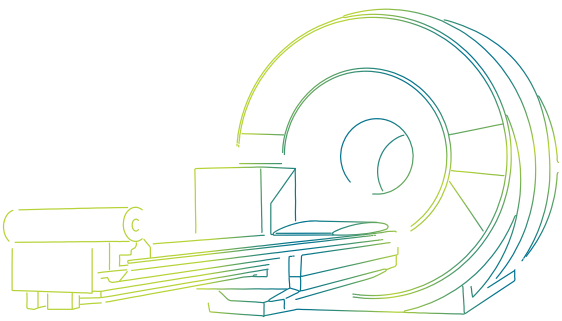


2.3 Magnetoencephalography (MEG)

MEG is a functional neuroimaging technique for mapping brain activity by recording magnetic fields produced by electrical currents in the brain, using very sensitive magnetometers. The main applications of MEG are clinical investigations and cognitive neuroscience research. In 2013 NMHB funded, jointly with EPSRC, a Partnership Grant (PI Singh, Cardiff University, £834k) to build multi-site clinical research capacity in MEG. This brings together eight UK centres in Cardiff, Oxford, UCL, Cambridge, Aston, Nottingham, York and Glasgow. The partnership funded academic networking activities, training programmes, joint studentships and the establishment of unified acquisition, analysis and data storage protocols.

Including the above initiatives, the MRC has invested approximately £167m (total value 2008-2016) in initiatives, grants and fellowships across the imaging landscape. This investment does not include our contribution to setting up and running Imanova.

The use and further development of structural and functional imaging modalities are growing across the UK. Each modality adds value scientifically rather than replicating other methods and competing for space. However, PET imaging remains the most advanced method to provide molecular level imaging although it has particular challenges associated with it which presently restricts its wider use. These include the use of radiation, complexity compared with other imaging modalities, the cost of PET scans, as well as the invasive nature of PET studies. Given MRC's significant investment in the field, the report now focuses on the scientific uses, bottlenecks for use and opportunities for PET in the future.



3. Scientific uses and demand for PET imaging

PET imaging is a unique modality for functional and quantitative molecular imaging of living tissues and organs. It relies on the emission of gamma rays from a radionuclide which is introduced into the body as part of a biological active molecule forming a tracer, e.g. a receptor ligand or a pharmaceutical agent.

3.1 Clinical practice

The adoption of PET into clinical practice is mainly limited to the use of fluorodeoxyglucose (^{18}F-FDG). In the cancer field PET imaging is well-established for diagnosis, staging, visualising the impact of treatment and monitoring metastases due to its ability to discriminate between active metabolising disease and inactive tissue. In neurology, PET imaging is effectively used to diagnose the early stages of neurological illnesses such as epilepsy, Alzheimer's disease, and other dementias. However, there has been development of more specific probes, e.g., development of a number of novel probes for misfolded protein aggregates in the brain has brought beta-amyloid imaging to the doorstep of clinical use. Cardiac PET/CT enables a high-quality examination of cardiac perfusion and/or metabolism using the radioisotope rubidium-82 (^{82}Rb) with metabolic studies of ^{18}F-FDG to evaluate glucose uptake in atherosclerotic plaques. PET has also been used to image bacterial infections clinically by using ^{18}F-FDG to identify the infection-associated inflammatory response and PET probes have been developed to image bacterial infections *in vivo.*

Limitations to the widespread clinical use of PET arise from the high costs of the required infrastructure and radiochemistry. Most clinical PET is supported by third-party suppliers of ^{18}F radiotracers that can supply many sites simultaneously – reducing costs. This limitation restricts clinical PET primarily to the use of tracers labelled with ^{18}F, or at centres using generator derived isotopes such as ^{82}Rb, zirconium-89 (^{89}Zr) and increasingly gallium-68 (^{68}Ga).These additional isotopes may overcome some of the challenges with ^{18}F distribution.

3.2 Research use of PET

PET is an enabling technology for experimental medicine and early stage clinical trials across a broad range of research areas, although its use is predominately still focused on neuroscience and oncology. In the brain, research in neurology and neuropsychiatry is increasing in areas such as schizophrenia, autism, epilepsy and neurocognitive impairment/dementia, including drug development for neurological and psychiatric indications. Oncology research addresses clinical problems in diagnosis, staging and monitoring tumour response to therapy, as well as drug development. A number of other fields could be enhanced using PET e.g. cardiology, infections, mitochondrial biology, regenerative medicine and inflammation. There is also significant opportunity within core strength areas, for example macromolecules, neurotransmission and protein mis-folding.

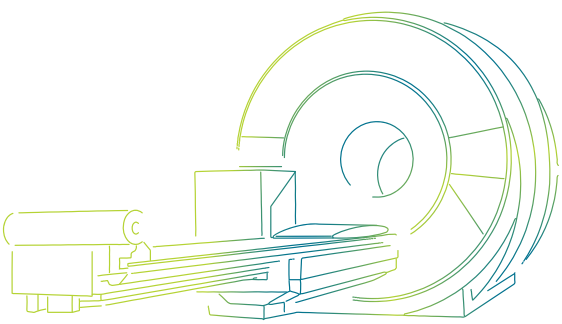
Research is also required to develop, implement and evaluate novel tracers (including new radiochemical methods), and to develop and assess new clinical PET indications and new PET technology. In data analysis, research focuses on the development and application of new tracer kinetic modelling methods and algorithms for new and existing radiopharmaceuticals, and on research in PET image reconstruction and image quantification.

PET has particular strengths when used as a research tool and outcome measure to aid drug development both in academia and industry, aiding the early selection, or elimination, of drug candidates. In pre-clinical and clinical studies, radiolabelled drugs or probe molecules can be used to interrogate whole-body biodistribution and drug-target engagement. PET has high specificity and high sensitivity and therefore meaningful results can be obtained in well-designed complex clinical studies with a few well-characterised patients. Such studies are expensive, but address important go/no go questions in drug development and can either stop or accelerate progress with a new drug and are therefore seen as highly valuable by pharma.

However, PET imaging has not yet fully achieved its potential impact in research and this is in part due to the higher cost and complexity of the technology compared with other imaging modalities, and the long timelines to develop new tracers towards clinical application. The costs of undertaking PET research include the scanning costs but also high costs for the radiosynthesis of the tracer. This requires complex radiochemistry to develop and establish a new ligand at centres, cyclotrons to generate the short-lived radioisotopes and GMP level facilities and procedures to manufacture the radioisotopes for the clinical PET scans. In addition, PET scans for research purposes can sometimes require arterial line sampling over 1-2 hours.

There is also a lack of uptake of PET imaging in research areas beyond the core areas of neuroscience and cancer and, within these, by new research teams. Novel tracers will be key in taking PET scanning into new scientific areas, such as inflammation research, but the broader research community may be unaware of this potential and of how to embark on ligand development and application.

Summaries of the facilities, research areas and numbers of research scans conducted annually across UK centres of excellence are at appendices 3 and 4.



Case study:

Dementias Platform UK (DPUK) and MRC investment in PET-MRI

DPUK is a world-leading resource for person-focused dementias research, designed to fast-track scientific understanding, treatment and the prevention of the disease. DPUK has established the world's first national research imaging network, including PET-MRI, with innovative imaging science at the core to their approach to support multicentre trials and experimental medicine for dementia. In 2014 MRC funded the purchase of five new PET-MRI scanners within the DPUK imaging network.

Fully integrated PET-MRI allows changes assessed by PET (e.g. neurotransmitter receptor occupancy, drug occupancy, innate immune activation) to be related directly to functional brain activity evaluated by MRI (e.g. resting state fMRI, arterial spin labelling perfusion). The established benefits of PET-MRI compared with PET-CT already include: reduced radiation dose (opening up the possibility of more frequent, repeat scanning); improved signal localisation for PET scanning (e.g. of sub-cortical nuclei); multimodal brain studies in short (e.g. 30 min) single scan sessions ideally suited to less cooperative subjects. Simultaneous PET-MR acquisition also promises to improve PET image reconstruction and regional quantification even with low tracer doses (e.g. with on line, MRI-constrained motion correction).

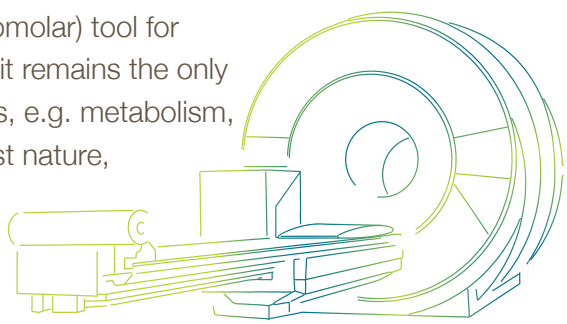
Via an MRC Partnership Grant, the five centres, together with two existing centres, have formed the DPUK PET-MRI Partnership. This aims to provide coherent and harmonised operations of the DPUK PET-MRI network. The partnership has four workstreams: communications; training; a pilot study to harmonise scanning and image reconstruction across centres and manufacturers; and governance, regulation and business development to ensure growth and long term sustainability.

Another aim of the network is to coordinate their efforts to improve access to newer radioligands for dementia research in all centres. Indeed, DPUK has leveraged an industry contribution of £1m for amyloid tracers.

3.3 Demand for PET

The demand for PET as a research tool will continue for the foreseeable future (10 years-plus), despite the bottlenecks identified below. PET remains a much more specialist and challenging modality than other types of clinical imaging and, given the use of radiation and the complexity and cost of PET scans, other alternative imaging modalities may be more straightforward.

However, PET imaging provides a highly specific and very sensitive (picomolar) tool for molecular analysis of targets and e.g. neuronal signalling pathways and it remains the only modality capable of detecting and critically quantifying certain processes, e.g. metabolism, and molecules, e.g. receptors, proteins and enzymes. Given its specialist nature, infrastructure requirements and associated costs, the broader research community may still be unaware of the potential of PET as a tool.



4. Bottlenecks

The same bottlenecks to a greater use of PET imaging in research were consistently identified across the UK centres of excellence. These focused on cost, radiochemistry requirements, the need for sufficient staff capacity and post-imaging analysis and modelling. It was widely agreed that better networking and communication across centres could address some of the issues identified.

4.1 Cost

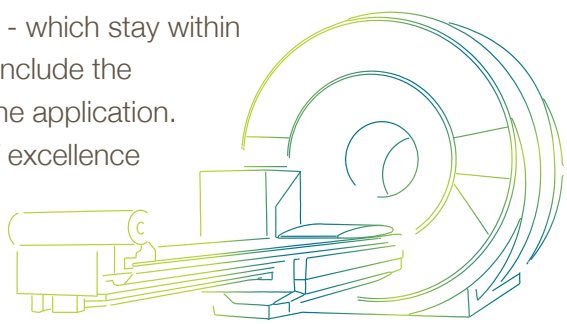
PET imaging requires a substantial capital and infrastructure investment. Therefore, facilities for research are limited to centres of excellence in specific universities, potentially a barrier to availability for the wider research community.

Funding for the investment in 2014 in five new PET-MRI machines was made available due to the one-off allocation of capital to MRC in 2014 with limited resource funding. The host universities were required to provide significant additional funding to cover, amongst other things, new staff, software and licensing, maintenance contracts and additional infrastructure works to house the scanners. For example, the University of Edinburgh received ~£5m through the CRI funding, but contributed more than £10m to install and resource the machine within the university. Maintenance contracts were considered a significant issue by all centres. At 10% of the cost of the scanners for 3 years, this is a sizable cost which will need to be resourced by the universities in future. Networking activities should mean that the universities are able to collectively negotiate better rates with manufacturers to extend the contacts.

Generally, scanners require refurbishing after approximately 5-7 years and may need replacement after ~10 years. Centres have to build depreciation costs for equipment into the on-going running costs of the machines to ensure funds are available for refurbishment or replacement. Often this is added on to commercial contracts only. Long term planning may be required by MRC, other funders and universities for reinvestment in the future when the current scanners reach the end of their lifespan concurrently.

In terms of the costs presented in grant applications, it was noted that many researchers feel unable to request the 'true' cost of imaging from funders (including MRC) due to fears about the grants being considered too expensive. Indeed, it was also noted that funders (other than MRC) have capped awards according to the available imaging budget, leaving the universities to meet the additional costs. Radiotracers are harder to cost in grants as their costs vary depending on efficiencies, such as the number of scans that can be conducted per batch, which is again dependent on patient availability. There can also be a ~10% failure rate in radiotracer manufacture which is hard to cost into grant applications, but which is a significant additional cost.

Imaging 'centres' within universities also differ in their status. Some are badged as facilities rather than academic centres and therefore don't access overheads on grants - which stay within the academic departments of the investigators. These facilities need to include the overheads in their overall costs, which increases the perceived cost of the application. A summary of the costing models and examples from the UK centres of excellence is at appendix 3.



4.2 Radiochemistry requirements

Access to radiochemistry is a key bottleneck for PET research. Seven research centres (Imanova, Cambridge, Manchester, Edinburgh, King's College London, Institute of Cancer Research and Cardiff) have access to significant GMP radiochemistry facilities and a cyclotron. Centres without a cyclotron (e.g. University College London, Oxford, Imperial College London and Newcastle) buy in radiotracers but these are limited to commercially available tracers, e.g. ^{18}F-FDG, ^{18}F-FLT, AMYViD.

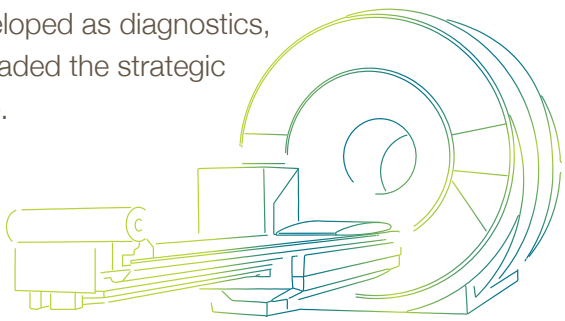
Whilst the production of ^{18}F-FDG and other ^{18}F-labelled tracers (e.g., ^{18}F-FMSIO, ^{18}F-FLT) are standard, a limited number of research centres have the capacity to manufacture a wider range of tracers, e.g. non-standard ^{18}F radiotracers, carbon-11 radiotracers and ^{15}O-water, and a yet smaller pool have the capacity for novel tracer development (e.g. Imanova, Cambridge). Facilities for novel tracer development require significant long term investment to provide equipment and the highly skilled expertise needed to staff the facility.

Given the short half-life of PET radioisotopes, geography presents an issue as the radioisotopes can't be moved significant distances. However, some radiotracers (e.g. ^{18}F labelled) can be transported approximately up to 2-3 hours travel by road (in general radiotracers are not accepted by airports) from the production centre. Hence some centres supply others e.g. Cambridge supply Oxford, Imperial and UCL. However, there is scope for better regional collaboration and coordination to maximise the efficient production and use of tracers and increase access across geographically viable regional areas. Some of these logistical challenges are specific to ^{18}F (e.g. the half-life of ^{11}C limits any distribution) and may be overcome with different chemistry. For example, ^{68}Ga can be produced locally with a generator and ^{89}Zr has a multi-day half-life that enables shipping over long distances.

There is a question about how many high level radiochemistry sites can be maintained across the UK, given the shortage in specialist staff and the difficulties in recruiting from both the UK and overseas. As mentioned earlier, investment in post-doctoral researchers in the field has not led to a sustained increase in capacity.

Stronger connectivity is needed between the clinical radiochemistry community and the breadth of chemistry expertise in the UK. There are many innovative molecular imaging tools developed in the chemistry community that fail to translate towards clinical application.

Acquiring funding for novel tracer development was also considered an issue. As stated, novel tracers will be key in taking PET scanning into new scientific areas, alongside the ability to ask novel research questions and to perform carefully designed clinical research studies using existing tracers, but securing funding for tracer development and implementation was anecdotally seen as a very challenging area. Novel tracer development requires the need to identify chemical leads, develop the radiochemistry, and carry out pre-clinical studies and subsequent clinical validation. This may, for example, cross the interests of MRC, EPSRC and BBSRC and was perceived to 'fall down the gap' between remits. It was noted that success is more likely for tracers developed as diagnostics, rather than research tool compounds. EPSRC has also recently downgraded the strategic importance of Medical Imaging through its Balancing Capability exercise.



4.3 Capacity

PET imaging research, by its nature, is multidisciplinary, requiring high level expertise in radiochemistry, physics and computational approaches, and in clinical studies using these tools for experimental medicine and drug development, and as clinical diagnostic probes.

Training, recruitment and retention of radiochemists, chemists, radiographers, academic radiologists, modellers, cyclotron engineers, physics support and people with Good Manufacturing Process (GMP)/ Quality Assurance (QA) expertise all represent a bottleneck to increased use of PET imaging for research, and indeed for clinical use. This is also the case across imaging modalities, where bottlenecks in staffing occur, particularly with new technologies. For example, in the field of 7T MRI more physicists and engineers are required who can explore the capabilities and development of the technology to stay at the cutting edge and tailor the technology for the research needs.

The complexities of the introduction of new tracers, new applications for PET imaging and the introduction of new hybrid imaging technologies represent a challenge to recruit and train individuals. For example, traditional training for technical MRI and PET staff has been organised separately with little interaction. Manufacturers of scanners often have unique technical specifications and training schedules.

In addition, more research centres may invest in PET-MRI, e.g., the University of Sheffield/Royal Hallamshire Hospital has begun procurement, which may add additional strain to the necessary recruitment across the UK. Overall, these issues pose considerable challenges in developing and maintaining a workforce with the competencies required for this novel technology and for interpretation of hybrid studies, particularly when 23% of UK radionuclide radiologists are expected to retire by 2019[1].

All centres of excellence reported issues with recruiting and retaining the necessary expertise, particularly at the more senior level, with funding that is largely project limited. Centres reported little capacity in the system to cope with sick leave, maternity leave etc. Recruitment from overseas was hard and it was anticipated that Brexit may further add to this. More often, centres train people internally rather than bring in more experienced individuals. Retention is also hard as expertise is in demand.

4.4 Analysis and modelling

Post-imaging analysis and modelling requires specific expertise, e.g. to model pharmacokinetic distribution/body compartmentalisation of PET ligands etc. Scientists are needed to integrate images who can work across modalities and tie them together. There was agreement that this is another area of expertise that is required and one where it is difficult to fill posts. There remains a national shortage of individuals with mathematical biology skills and there is consequently a need to attract mathematicians to biology.

Given the size of the files generated, infrastructure to store and share data is important. This was considered to be a significant issue for imaging studies at a centre level, and more widely, in order to provide access to others for reanalysis of data.

1. The Royal College of Radiologists. Sustainable future for diagnostic radiology: the older radiologist. London: The Royal College of Radiologists, 2015.

5. Future Opportunities

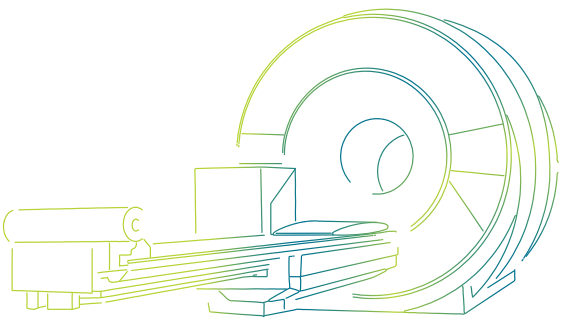
5.1 Mitigating the high costs

There are many different costing and funding models used in the PET centres across the UK with broad price differentials (see appendix 3). MRC could look at the FEC model to help with these costs. For example, funding for applications using services at Imanova are currently paid at 100% FEC under Exceptions and include VAT at 20%. This agreement was reached given that Imanova is not eligible for dual funding. To date, this arrangement does not apply to imaging conducted at other centres of excellence, but a change to make scanning costs and tracer purchase/production FEC-exempt could make these tools more attractive to a wider base of researchers and ease the cost burden on existing groups. However, new tracer development is seen as a research activity, rather than a tool, and so would still be paid at 80% like other research costs. Other examples of FEC-exempt funding on grants are items of equipment for instrument development, costs for overseas co-investigators and locally employed staff, and research costs charged by an overseas organisation.

Another option could follow MRC's current policy for mitigating the high cost of research involving non-human primates (NHP) whereby Boards currently pay 50% of the purchase costs and the remaining sum comes from a central budget. A similar approach could be considered for high-cost imaging research. It will be difficult to plan for increases in demand but costs are likely to be significantly more expensive than the funds allocated for NHP research. However, sharing the costs by offsetting them against a non-board budget may ensure that high quality applications are not seen as unaffordable.

5.2 Capacity building

The Partnership Grants awarded in the fields of PET-MRI, 7T MRI and MEG all contain components of capacity building. However, in the case of the DPUK-led award, this is necessarily focused on dementia. There is an on-going need for further investment in training across all disciplines identified, in order to increase the skills base to support medical imaging. Whilst specialised short term training schemes have not been as successful as anticipated, opportunities remain for MRC to continue to invest in this area through our own fellowship schemes and through on-going training schemes with other funders. For example, EPSRC have invested significantly in training and capacity building in the area of medical imaging. It funds two Centres for Doctoral Training (CDTs) in Medical Imaging (UCL and KCL/Imperial) and one in Biomedical Imaging (Oxford/Nottingham), along with a CDT in Optical Medical Imaging (University of Edinburgh). MRC currently co-funds the Oxford/Nottingham and Edinburgh CDTs. Together, it is hoped that these established CDTs will provide additional future capacity and capability in the identified areas of need, and will lead to future researcher leaders. The CDTs may represent an opportunity for MRC to work closer with EPSRC and to consider wider co-funding.



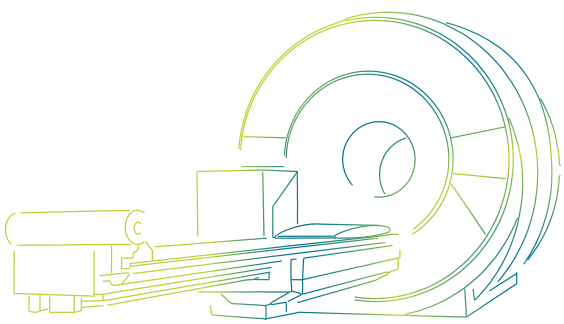
5.3 Better Networking

In 2014, MRC Strategy Board agreed a need for a hub and spoke model to enable the uptake of new radiotracers in UK centres. It was noted that better communication amongst the users about projects and tracer use would maximise the efficient use of the resources, through sharing controls and methodology and through data standardisation. It was agreed that an important role for Imanova would be the facilitation of dialogue between UK PET centres, and they were tasked by MRC to provide a hub for core communication and networking activities to complement their technological expertise and infrastructure. To date there has been slow progress on this, with limited success, due in part to focus on translation and ligand implementation at Imanova.

In the dementia field, there is reason to believe that the PET-MRI partnership will achieve the networking and some of the coordination functions that have been envisaged by MRC, at least in dementia research. However, an on-going need exists for better networking and communication more widely and provides an opportunity to address some of the issues identified in a more coordinated way rather than just on a project basis. Better coordination of tracer development, protocol sharing and tracer supply (where geographically feasible) could increase access. Different centres could specialise regionally in developing and producing particular tracers, to play to their strengths but ensure that they aren't each competing for limited research funding and trying 'to do everything'. Coordination of tracer production could also reduce costs of the radiochemistry element of PET scans. Partnership arrangements across UK centres could also be used to harness spare scanning capacity and to enable more clinical research questions to be addressed by more efficient recruitment of subjects across a network.

There was support within the community for the development of an additional partnership grant for better networking and training of radiochemists across the UK PET imaging centres. This could build on, but be wider than, the DPUK-led PET-MRI network and could build on the radiochemistry needs beyond dementia research to help improve access to tracers through better regional collaboration.

Other areas may also benefit from a similar approach, for example, the hyperpolarised MRI community.



6. Discussion and conclusions

MRC's vision for the future of PET in the UK

MRC has made a significant investment in PET imaging over several decades though previous unit funding, currently through Imanova, and more recently through the Clinical Research Infrastructure investment. There are soon to be eight UK universities (UCL, KCL, Imperial, Manchester, Edinburgh, Cambridge, Newcastle and Sheffield) with PET-MRI capabilities, aiming to make the UK leaders in the field of this relatively new technology. For the UK to fully capitalise on these investments and maintain a leading position in Europe and globally, it needs to not only lead in the innovation of technology and techniques, but also on implementation in the clinic and in clinical research. Better coordination and networking is required to maximise the use of the technology and to present the UK as 'trial ready' to industry across a number of indications, not just dementia.

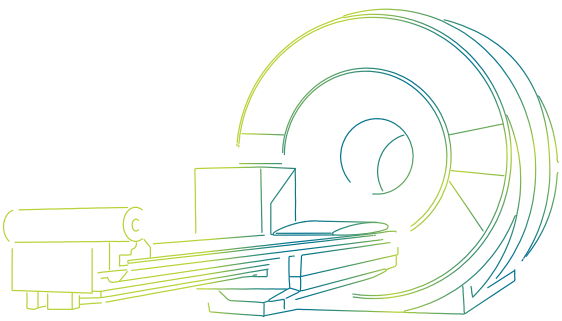
MRC alone cannot be responsible for the issues of capacity building and resourcing for PET research and NHS R&D has a key role in funding posts and creating national sustainability.

National centralisation of cutting edge imaging technology may not be the preferred way forward. The consensus within the community is that, for example, Imanova has not pulled the academic community closer together in this space, even within the three London university partners. However, greater coordination - potentially organised on a networked regional basis - could help galvanise the academic community. Centres could work together better to share tracer development, implementation and protocols, to improve training opportunities and to facilitate clinical studies both within academia and with industry. Greater facilitation and 'managing competition' between groups could ensure that centres play to their strengths but aren't each trying 'to do everything'.

Funders could also work better together to define key challenges that can best be approached using PET. This would necessitate development of new funding partnerships but also new research collaborations that would broaden opportunities and help ensure that novel research proposals aren't lost between remits. These must be strategic development areas and there should be clear leadership by experts in the field.

Providing significant capital infrastructure investment in this space has been beneficial to the UK but, longer term, the UK would benefit from a more generic approach to imaging funding where the capital funding is paired with the necessary resource funding. It should also be considered that, as the new equipment comes online, it may generate an uplift in demand for response mode funding though MRC boards and panels.

A view put forward by the community is that MRC's strategy in this area is bottom-up and reactive, and insufficiently joined up. A framework and roadmap for future investments in this area may be beneficial.



Appendix 1

Experts consulted in the review

Professor Eric Aboagye, Imperial Collage London

Professor Franklin Aigbirhio, University of Cambridge

Dr Andrew Blamire, Newcastle University

Professor David Burn, Newcastle University

Professor Richard Carson, Yale University, USA

Dr Kevin Cox, Imanova

Professor Steve Faulkner, University of Oxford

Dr Alex Gibson, GE Healthcare

Professor Fiona Gilbert, University of Cambridge

Dr Lindsey Green, Consultant

Professor Ashley Groves, University College London

Professor Karl Herholz, University of Manchester

Professor Derek Jones, Cardiff University

Professor Nick Long, Imperial College London

Professor Chris Marshall, Cardiff University

Dr Duncan Martin, University of Edinburgh

Professor Paul Matthews, Imperial College London

Professor Peter Morris, University of Nottingham

Professor Keith Muir, University of Glasgow

Dr Phil Murphy, GSK

Professor David Newby, University of Edinburgh

Dr Denise Ogden, University of Manchester

Professor Wim Oyen, Institute of Cancer Research

Professor Jeremy Pearson, British Heart Foundation

Dr Marios Politis, King's College London

Professor Geraint Rees, University College London

Professor Reza Rezavi, King's College London

Dr Marjolein Schaap, Cancer Research UK

Professor Gavin Screaton, Imperial College London

Dr Tony Soteriou, National Institute of Health Research

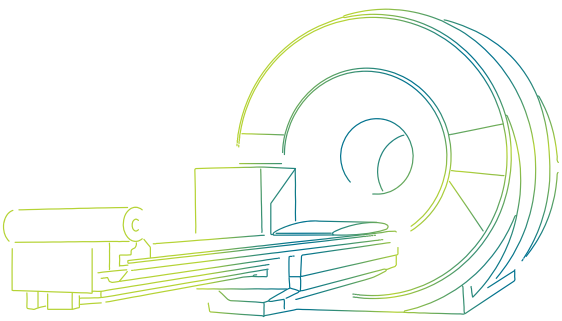
Dr Raliza Stoyanova, Wellcome

Dr Mark Tarplee, Engineering and Physical Sciences Research Council

Professor Irene Tracey, University of Oxford

Professor Edwin Van Beek, University of Edinburgh

Professor James Wild, University of Sheffield



Appendix 2
Interests of other funders

Overall, medical imaging is of strategic importance to a range of funders, to varying degrees. However, no other funder has made a specific strategic commitment to PET imaging in the same way as MRC's historical investment in this field.

Engineering and Physical Sciences Research Council (EPSRC)

EPSRC have invested significantly in training and capacity building in the area of medical imaging. It funds two Centres for Doctoral Training (CDTs) in Medical Imaging (UCL and KCL/Imperial) and one in Biomedical Imaging (Oxford/Nottingham), along with a CDT in Optical Medical Imaging at the University of Edinburgh. The CDT in Medical Imaging at KCL/Imperial funds up to 20 studentships per year and provides a comprehensive interdisciplinary PhD programme in Medical Imaging, specifically designed to meet the challenges in healthcare and medical imaging. The UCL CDT in Medical Imaging is in partnership with UCL's NIHR Biomedical Research Centres & Unit and again, trains up to 20 students a year in translational imaging research, filling a critical gap identified in academia, pharmaceutical and medical devices industries. The Oxford/Nottingham CDT in Biomedical Imaging is jointly sponsored by MRC and provides students with a broad exposure to all aspects of biomedical imaging, from cellular microscopy to clinical radiology, and from hardware development to image analysis.

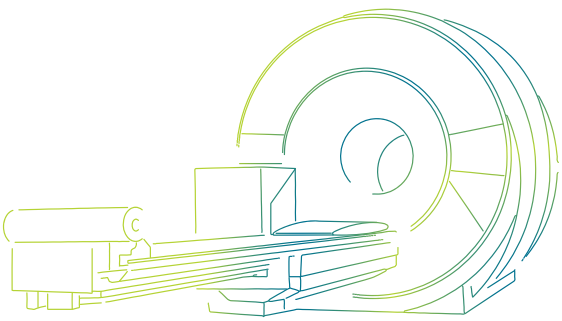
Together, it is hoped that these established CDTs will provide additional future capacity and capability in the identified areas of need, and will lead to future researcher leaders. The CDTs may represent an opportunity for MRC to work closer with EPSRC and to consider wider co-funding.

EPSRC fund response mode research in the novel chemistry and physics of imaging research. However, EPSRC's Balancing Capability strategy in 2016 has downgraded the priority of medical imaging from 'Maintain' to 'Reduce' and it is aimed to reduce funding in this area as a proportion of the EPSRC portfolio.

Cancer Research UK (CRUK)

CRUK's Cancer Imaging Initiative commenced in 2008 and has established a network of centres and research programmes to drive forward multidisciplinary cancer imaging research in the UK.

The initiative is a partnership between CRUK and EPSRC and is in its second round of funding (2013-2018). The four Cancer Imaging Centres (CICs) are involved in both pre-clinical and clinical cancer imaging, and have access to a wide range of different imaging technologies. These are based in the University of Cambridge/the University of Manchester, KCL/University of London, University of Oxford and the Institute of Cancer Research (solely funded by CRUK). The partnership also aimed to ensure the CICs work together to develop a network of excellence that will drive forward cancer imaging research in the UK.



Additionally, five Cancer Imaging Programmes were funded, each focused on one particular type of imaging technology and how it can be used in a specific area of cancer research:

- University of Birmingham Imaging Programme, investigating the use of MRI scanning for children with cancer.
- The Royal Surrey County Hospital Imaging Programme, working to improve breast cancer detection by using digital X-rays.
- Newcastle University Imaging Programme, using imaging to speed up the discovery of new cancer drugs.
- University of Sheffield, using MRI and laser imaging techniques to develop drugs that block the growth of blood vessels into tumours.
- University of St Andrews, working on optical imaging for cancer diagnosis.

However, after a recent review of the initiative, CRUK has concluded that the ring-fenced CIC funding will cease in November 2018, at the end of the current 5 year period. It was concluded that after 10 years of capacity building in this area, the centres have transformed the UK research base from almost non-existent to world-leading. Since the centres were initiated, a number of funding schemes have been introduced that can support cancer imaging (e.g. Multidisciplinary projects, Experimental medicine programmes and Centre Network Accelerator Awards). Therefore, CRUK has agreed that the centres should now be in a position to be competitive for grants through other CRUK funding routes that can support cancer imaging. CRUK will be working with the centres over the next two years to work out how best to support their work in the period when they will be transitioning to the response mode funding structure.

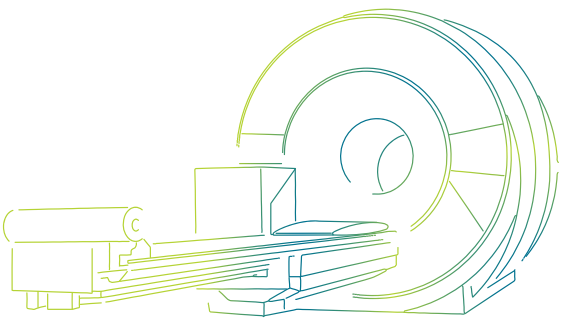
Wellcome

Wellcome's investments in imaging research focus predominantly in the MRI space and include strategic award funding for the new 7T MRI scanner at the King's College London-based London consortium. Funding for PET research represents only a small fraction of Wellcome's imaging portfolio.

In December 2016 Wellcome announced funding for 14 new research Centres over five years, including three in the field of imaging, two of which are new. The Wellcome Centre for Neuroimaging at UCL was renewed and the two new centres were the jointly funded Wellcome/EPSRC King's College Medical Engineering Centre of Research Excellence (which will include a focus on PET-MRI) and the Wellcome Centre for Integrative Neuroimaging at the University of Oxford. The Oxford centre involves the Oxford Centre for Functional MRI of the Brain (FMRIB) and the Oxford Centre for Human Brain Activity (OHBA).

National Institute of Health Research (NIHR)

NIHR has funded significant capacity in imaging modalities within the existing NIHR Biomedical Research Centres (BRCs), Biomedical Research Units and Clinical Research Facilities, and within the new round of NIHR BRCs from April 2017.

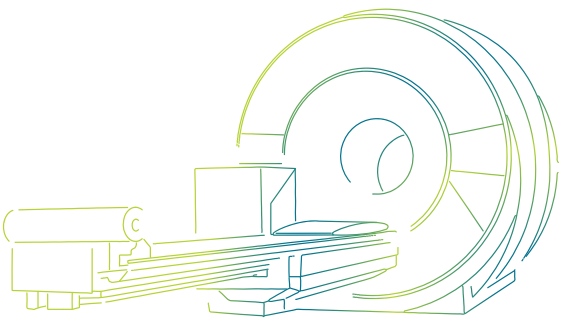


For example, the NIHR BRC at the University of Sheffield includes an Advanced Medical Imaging Theme which provides support for the new PET MRI investment made by the University (£10m). The PET-MR and associated cyclotron/dispensing laboratory will be sited at the Royal Hallamshire Hospital and used 50% for research and 50% for clinical use.

British Heart Foundation (BHF)

The BHF has made significant capital investments in MRI in the area of cardiovascular medicine. This includes £1.5m co-funding of the CRI initiative in 2014, including £1m to support the University of Leeds in the development of a new MRI method (SABRE), investment in 3T MRI at the Universities of Oxford and Glasgow, and the Centre for Translational Cardiovascular Imaging at the University of Leeds.

With regards to PET, this is funded in response mode, however BHF routinely cap imaging (PET and MRI) costs on awards due to the high cost, with the shortfall being met by the university.



Appendix 3
Usage and cost of PET in research

A questionnaire was used to collect data on facilities, resources and numbers of research scans conducted across the centres of excellence. Completed questionnaires were received from six centres and numbers of scans from a seventh.

The number of annual research PET scans varies from ~100 to ~500:

	Imaging centre						
	Cambridge	Cardiff	Edinburgh	KCL	Manchester	Newcastle	UCL
Annual no. of research scans	200 (2015/16, during refurbishment) Projected to be 400 (2017)	100 (2015/16)	300 (2015/16, scanners down for 6 months) 300 Projected to be 500 (2016/17)	192 (2015/16)	219 (2015/16)	100, due to increase with PET-MRI online	1000 clinical and research scans

Costing models and examples

Models for costing PET scans vary considerably between centres. Whilst each centre considers the full costs associated with the scans (staff salaries, maintenance contracts, capital depreciation, image analysis, estate charges, electricity, data storage, safety), different approaches are taken in costing individual studies across centres. This may be on an hourly rate, a cost per scan, a 'minimum day cost' or a bespoke cost set on a study by study basis. Costs may also be provided on a scan plus tracer basis, or as one figure. Charges also vary across most centres dependent on the funding source; several centres set academic costs at below the full economic cost, and the commercial charge at or above the full economic cost. Some centres are able to offset charges such as staff salaries by including clinical scans within their research costing model.

Costing models are more straightforward at universities that don't have their own radiochemistry facilities (e.g. Newcastle University). Scanning costs can be calculated separately and then the manufacturers cost of the radiotracer, plus any transport costs, are passed on to the researchers.

Use of in-house radiochemistry facilities and the complexity of the tracer both increase the complexity of the costing models. Again, centres vary from setting bespoke costs per tracer to applying pre-set costs for each tracer.

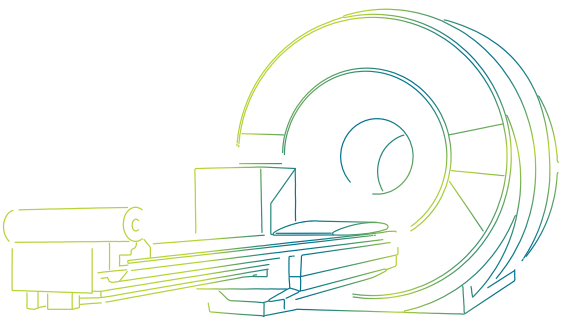
For example, at the University of Manchester, studies are costed on a study by study basis; no standard prices are set for PET scans or tracers. Costs include a study set up fee, which is also dependent on the source of funding.

King's College London use a FEC model (including depreciation) with separate agreed rates for research council, charity, EU, BRC or industry funded usage. PET-CT and PET-MRI scans are around £800 per hour with an additional £400-£1000 per dose for tracer costs.

The University of Edinburgh also modifies costs on a study basis based on the source of funding and 'scientific merit', as assessed by an internal expert review panel. Approximate scanning costs are £500-750 per hour. Tracers are manufactured internally. The batch cost of ^{18}F- FDG is £2000, which requires 8 research scans a day to charge £250 per dose. It was noted that this is achievable in a clinical department but challenging in a research facility where five research scans a day is considered efficient, representing a cost of £400 per dose. The alternative costing model is to provide a 'minimum day cost'.

For example, a cost based on 3 scans (3x£750) plus full tracer production costs (£2000) of £4250.

These compare to a total scan cost at Imanova of approximately £6500 (with ^{11}C-PE2I, ^{11}C-DASB and ^{18}F-dopa). MRC has also agreed to pay VAT at 20% on response mode funded grants though Imanova and all costs are paid at 100% FEC under exceptions, rather than at the normal 80%.



Appendix 4

Summary of facilities and capabilities across UK PET centres of excellence

	Cambridge	Cardiff	Edinburgh	Imanova	Imperial College London	Institute of Cancer Research	King's College London	Manchester	Newcastle	University College London
Location	Wolfson Brain Imaging Centre (WBIC)	Wales Research and Diagnostic PET Imaging Centre (PETIC). Cardiff University & NHS	Clinical Research Imaging Centre (CRIC), Royal Infirmary of Edinburgh campus. University-NHS partnership	Imanova Ltd	Clinical Imaging Facility (CIF)	Cancer Research UK Cancer Imaging Centre and The Royal Marsden NHS Foundation Trust.	PET Centre, St Thomas'	Wolfson Molecular Imaging Centre (WMIC) & Central Manchester University Hospitals NHS Foundation Trust (PET MR)	Centre for In Vivo Imaging (CIVI)	Institute of Nuclear Medicine, UCLH
Equipment	PET-MRI (MRC), University and NHS PET-CT	PET-CT	2 PET-CT scanners and PET-MRI (MRC)	PET-CT PET-MRI (MRC, through Imperial College)	PET-CT PET-MRI (MRC, based at Imanova)	3 PET-CT	2 PET-CTs, PET-MRI and further PET/CT under installation	2 PET-CT & PET- MRI (MRC)	PET-CT and PET-MRI (MRC)	2 PET CT and first UK PET-MRI (2012)
Cyclotron	Yes	Yes	Yes	Yes	No	Yes	Yes, and second under construction by May 2017	Yes	Preclinical only. Cyclotron planned for 2017	No
Radio chemistry facilities	Yes, Radiopharma-ceutical Unit	Standard tracer production	Yes, Radiochemistry department	Yes, world leading facilities	No	Yes	Yes, new radiochemistry laboratories	Yes	Not for tracer development	Yes, new facilities by March 2017
GMP	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Not licenced	Yes
Novel radio chemistry and ligand development	Yes. Shorter menu than Imanova, but able to develop novel tracers	No, standard tracer production only	Yes, if the demand is there	Yes, world leading capabilities	No	Yes	Yes	Yes	No, buy in tracers for clinical research	No
Science focus	Neuroimaging, dementia, mental health, traumatic brain injury, oncology, cardiovascular	Oncology, neuroimaging, dementia	Neuroimaging, dementia, inflammation, cardiovascular	Neuroimaging, dementia, inflammation, infection, cardiovascular oncology, fibrosis	Neuroimaging, oncology	Oncology, radiotherapy planning	Neuroimaging, oncology, dementia, inflammation, cardiovascular, radiotherapy planning	Dementia, neuroimaging, oncology, cardiovascular, inflammation, musculoskeletal	Neuroimaging, dementia, oncology	Oncology, cardiovascular fibrosis, inflammation, neuroimaging, dementia
Notes	Supplies Oxford, UCL and Imperial with radioligands.	Discussions with Welsh Government about new PET scanner					NCRI PET Core Lab based at St Thomas'		Plans to develop new radiochemistry facility and to purchase a cyclotron	UK's first PET-MRI facility

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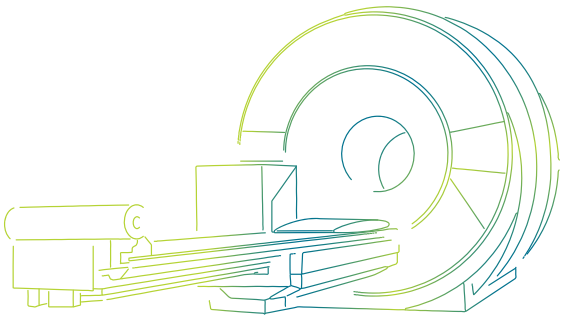

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