Imaging network MR-PET project **Start date: 1 July 2016.**			**Completion date: 30 June 2019**	
Overall work package objectives: The project is divided into 4 work packages or Task Forces: 1. Communications - Provide an effective communications framework within and beyond the network 2. Training - Organise operator training to meet the specific challenges and realise the advantages of MR-PET 3. Harmonisation study - Harmonise and optimise protocols for data acquisition, reconstruction, and analysis to maximally leverage the common investments and lower costs for all. 4. Regulatory & Governance - Address regulatory requirements for multicentre experimental medicine studies utilising novel tracers, and harmonise governance				
Deliverables	**Milestones**	**Milestone deadline**	**Work package dependencies**	**Person(s) responsible**
Objective 1:				
D1.1 Establish and maintain an SOP database	M1.1.1 Investigate similar databases and logistics of setting up such a system within the network	M1.1.1 Complete		Karl Herholz & Viki Rhodes Bradford
D1.2 Organise progress meetings on at least a monthly basis where all study sites are represented. Write and dissimilate minutes/action points to all study teams	M1.2.1 Ongoing monthly meeting	M1.2.1 Ongoing		
D1.3 Organise a yearly meeting for all members of the study partnership (each July)	M1.3.1 July 2017	M1.3.1 Complete	All Task forces to attend/present	
	M1.3.2 July 2018	M1.3.2 Complete		
	M1.3.3 July 2019	M1.3.3 Complete		
D1.4 Monthly and Bi-Annual reports for the DPUK Oversight Board	M1.4.1 Write progress reports each Month and Bi-Annually and submit to DPUK Oversight board for review	M1.4.1 Ongoing		
Objective 2:				
D2.1 Set up and recruit members	M2.1.1 Employ project coordinator	M2.1.1 Complete	None	Marius Mada (MM), John O'Brien (JO'B), John-Paul Taylor (J-PT), Adrian Carpenter (AC)
	M2.1.2 Contact PET-MR sites to identify site training representatives	M2.1.2 Complete		
	M2.2.1 Research existing resources for training	M2.2.1 Complete	None	

D2.2 Assess training needs and set up individual training schedules	M2.2.2 Design, deploy and analyse results of sites survey on training status	M2.2.2 Complete		MM, JO'B, J-PT, AC
	M2.2.3 Write and disseminate survey report	M2.2.3 Complete		
	M2.2.4 Set up training schedules for staff groups	M2.2.4 Complete		
D2.3 Coordinate shadowing visits	M2.3.1 Identify responsible persons from the sites	M2.3.1 Complete	None	MM, JO'B, J-PT, AC
	M2.3.2 Scope sites expertise for shadowing	M2.3.2 Complete		
	M2.3.3 Agree a framework for shadowing	M2.3.3 Complete		
D2.4 Coordinate local training courses	M2.4.1 Identify responsible persons from the sites	M2.4.1 Complete	None	MM, JO'B, J-PT, AC, Andrew Farrall (AF)
	M2.4.2 Scope sites expertise for local courses	M2.4.2 Complete		
	M2.4.3 Agree a framework for training courses	M2.4.3 Complete		
D2.5 Work with professional societies towards standard training curricula for MR-PET	M2.5.1 Work with professional societies towards standard training curricula for MR-PET	M2.5.1 Complete	None	MM, JO'B, J-PT, AC
D2.6 Work closely with the DPUK imaging workgroup on radiochemistry to incorporate training for distribution and use of new tracers	M2.6.1 Work closely with the DPUK imaging workgroup on radiochemistry to incorporate training for distribution and use of new tracers	M2.6.1 Jan 2020	None	MM, JO'B, J-PT, AC
D2.7 Release consolidated training curricula	M2.7.1 Release consolidated training curricula	M2.7.1 Jan 2020	None	MM, JO'B, J-PT, AC
Objective 3:				
D3.1 Phantom study	M3.1.1 Cost out and work out logistics	M3.1.1 Complete	None	Julian Matthews & Local study PIs
	M3.1.2 Run phantom scans at all sites	M3.1.2 Complete		
	M3.1.3 Collect and analyse data	M3.1.3 Complete		
D3.2 MR-PET harmonisation study, Submit & obtain local approvals (ARSAC, NHS Capability & capacity, NHS SSI approval/exemption)	M3.2.1 Prepare ethics documentation	M3.2.1 Complete		
	M3.2.2 Submit & obtain ethics approval for study	M3.2.2 Complete		
	M3.2.3 Submit & obtain local approvals (ARSAC, NHS Capability & capacity, NHS SSI approval/exemption)	M3.2.3 Complete		
	M3.2.3a Imperial /Invicro	Complete		
	M3.2.3b Manchester	Complete		
	M3.2.3c Cambridge	Complete		
	M3.2.3d Newcastle	Complete		
	M3.2.3e UCL	Complete		
	M3.2.3f KCL	Complete		
	M3.2.3g Edinburgh	Complete		
	M3.2.3h GE supply	Complete		
	M3.2.3i Subcontract between sites	M3.2.3i Complete		
	M3.2.4 Recruit participants for study (n=42)	M3.2.4 Nov 2019		
	M3.2.5 Start MR-PET scans (n=84)	M3.2.5 Feb 2019		

	M3.2.6 Analysis of collected data	M3.2.6 Jan 2020		
D4.1 Publish standardised ICF and PIS templates	M4.1.1 Investigate data sharing policies of similar networks/organisations	M4.1.1 Complete		Joanna Wardlaw & Paul Mathews (TF4 leads)
	M4.1.2 Patient/participant feedback & review	M4.1.2 Complete		
	M4.1.3 Lay-group feedback & review	M4.1.3 Complete		
	M4.1.4 Partnership feedback & review	M4.1.4 Complete		
	M4.1.5 Publish best practice documents to DPUK website	M4.1.5 Complete		
D4.2 Develop SOPs and standardised forms	M4.2.1 Collect samples from DPUK MR-PET sites	M4.2.1 Complete		
	M4.2.2 Review & collate	M4.2.2 Complete		
	M4.2.3 Partnership feedback	M4.2.3 Complete		
	M4.2.4 Publish to DPUK website	M4.2.4 Complete		
D4.3 Establish a site accreditation procedure and QC programme	M4.3.1 Using best practice protocols establish working procedures to be followed to provide QC.	M4.3.1 Complete		

Updates on delivery against milestones since last report:

- **M3.2.3 Submit & obtain local approvals (ARSAC, NHS Capability & capacity, NHS SSI approval/exemption) (Dec 18)**

All local approvals are in place

- **M3.2.3i Subcontract between sites (Dec 18)**

The radiotracer supply contract was signed by all parties.

Unfortunately, the Grove Centre, GE's production centre, closed in June 2019 and this meant that we have had to find an alternative means for supplying the southern sites, (Cambridge, Imperial/Invicro, KCL and UCL). As Manchester already produces flutemetamol in house for their local studies, we have amended our materials licence agreement with GE to permit supplying to external sites.

This contract has been fully signed.

We have also needed to amend the existing subcontract between Manchester and the other sites to reflect that the flutemetamol will be supplied from Manchester's WMIC facility rather than the Grove Centre. This amendment is currently with the Cambridge and London sites for review and signature.

- **M3.2.4 Recruit participants for study (n=42) (Nov- Jan 19)**

The study sites using Join Dementia Research for their recruitment process have all been set up in the JDR system.

We are awaiting signatures for the amendment to the radiotracer supply contract. Once we have the signature of at least one more Siemens scanner site (so KCL or UCL/H) we will open study recruitment

We anticipate the recruitment will open in November 2019.

- **M3.2.5 Start MR-PET scans (n=84) (Feb19)**

Due to the issues with the radiotracer supply, we are delayed with starting scanning. However, we anticipate that once recruitment is open, we should be able to begin scanning participants soon after.

We are co-ordinating between the sites to book in participant scans, to get all scans done as quickly as possible

Summary of plan to deliver on outstanding work (with dates)

- Obtain signatures to amendment to radiotracer supply contract with Cambridge and London sites (Nov 2019)
- Initiate study recruitment (opening study on JDR/ send out letter of approach to local cohort) Nov-Dec 2019
- Start MR-PET scans (n=84) Nov-Dec 2019)

Risks	Mitigation
1) Delays in signing amended radiotracer supply contract	1) Start the study with 4 out of 7 sites (two GE and two Siemens scanner sites minimum). PM and local teams to chase signatures with their contracts dept.

Team members funded (full or part-time) by DPUK

TF1: Karl Herholz (Manchester – PI), Viki Rhodes Bradford (Manchester, PM)

TF2: Marius Mada (Cambridge), John O'Brien (Cambridge), John-Paul Taylor (Newcastle), Adrian Carpenter (Cambridge), Andrew Farrall (Edinburgh – online MR-PET training course)

TF3: Julian Matthews (CI, Manchester), Frederik Barkhof (Cambridge), Pawel Markiewicz (UCL)

TF4: (Edinburgh): Joanna Wardlaw, Sean Denham, David Brian,
(Imperial): Paul Matthews

Team members involved with the project but not funded by DPUK

Edinburgh: Gerry Thompson, Catriona Wimberley, Laura Doull, Craig Ritchie, Gill Macnaught

Newcastle: Ross Maxwell, Alison Killen, David Brooks, Elizabeth Howell, Michael Firbank

Manchester: Jose Anton-Rodriguez, Will Lloyd, Amy Watkins, Laura Parkes

Cambridge: Tim Fryer, Martin Graves, Vicky Lupson, Franklin Aigbirhio

KCL: Alexander Hammers, Enrico da Vita, Georgios Krokos, Jane Mackewn, Paul Marsden, Andrew Reader, Sebastien Ourselin

UCL/H: John Dickson, Anna Barnes

UCL: Nick Fox, Suzie Barker, Dave Thomas, Dilek Ocal

Imperial: Paresh Malhotra, Lina Aimola

Invicro: Will Hallett, James Davies, Yvonne Lewis, Ilan Rabiner

Outcomes

- We have recently presented some of our research at the **IEEE Nuclear Science Symposium (NSS) and Medical Imaging Conference (MIC), Manchester, UK, 26th October- 2 November 2019**
- Pawel Markiewicz presented a poster on the travelling phantom study: **"Characterisation of PET/MR scanners for brain imaging in Dementias Platform UK Clinical trials" Poster M-01-340, 30th October 2019**

The purpose of this work is to characterise and compare image quality for quantitative brain PET imaging using the Dementias Platform UK (DPUK) network of seven PET/MR scanners, and which consists of three Siemens Biograph MR and four GE Signa scanners. A set of phantom scans were performed on all scanners with three main aims: (1) To provide baseline performance measurements from which future qualification standards can be set for the use of PET/MR scanners in clinical trials; (2) to provide an understanding of any differences observed with the clinical amyloid brain test-retest data, which follows this phantom study; and (3) to provide the assessment of the utility and logistics of performing phantom measurements for PET/MR. Three physical phantoms were used: (1) a long 10L uniform cylindrical phantom to assess the PET performance across the axial field of view (FOV≥25 cm), including activity outside the FOV; (2) a 5L bottle phantom to assess the PET performance with the use of head and neck coils while running simultaneously high SAR/gradient duty cycle MR sequences; (3) a 6.4L ACR-approved Jaszczak PET phantom to assess image resolution and contrast. The filling of all the phantoms and data acquisition was performed at all sites under the supervision of a single operator (PJM), to ensure scanning harmonization. The attenuation correction was performed using CT-based attenuation maps.

The preliminary results indicate good uniformity across the transaxial and axial FOV, with some mild but noticeable axial streaks, possibly due to the inaccuracies in attenuation correction for the patient bed in both scanners. The effects of intense MR sequences are detectable but within the test/retest variability of PET. The activity outside the FOV had a detectable effect on the contrast and background activity. The attenuation correction for the hardware (bed and head coils) was overall adequate for all scanners.

- Georgios Krokos will be presenting the results of our accreditation of the PET-MR scanners in the DPUK MR-PET Network: **"Qualification of the Seven Dementias Platform UK PET-MR scanners for multicentre trials" Oral session M-12-01, 1st November 2019**

Standardisation of PET scanners participating in multicentre trials is important in achieving reliable results and in maximizing the power of the study. The first multicentre clinical trial studies involving seven PET-MR scanners in the UK (four GE SIGNA and three Siemens mMR) are underway, led by Dementias Platform UK. In this study, the qualification of the seven scanners was tested using the NEMA image quality phantom. Consistent scanning methodology was followed across all sites with a 5:1 sphere-to-background contrast ratio and a CT-based μ-map used for attenuation correction. The reconstruction parameters were consistent between scanners of the same manufacturer. The SUV_{mean} and SUV_{max} for all spheres were comparable between all scanners and within EARL performance specifications. Moreover, the averaged SUV values from all scanners were similar with the averaged corresponding values from 25 PET-CT scanners across the UK currently eligible to participate in multicentre trials.
In conclusion, these preliminary results support the reliable comparison of PET performance across the PET-MR scanners.

Project narrative

In June 2019, GE Healthcare's Grove Centre closed and ceased production of our study radiotracer, flutemetamol, which meant that we have had to find an alternative means for supplying the southern sites (Cambridge, Imperial, KCL, UCLH).
Manchester had an existing material licence agreement (MLA) with GE but this only permitted the site to supply for local studies. We have therefore negotiated with GE to amend the MLA to allow Manchester to supply the other sites via their WMIC radiochemistry facility.
This amendment is now in place.
However, we additionally needed to amend the existing radiotracer supply sub-contract to reflect that flutemetamol would be supplied from WMIC and not the Grove Centre as previously stated in the contract.
An amended sub-contract was sent to the 4 southern sites for signature by their legal teams. This unfortunately is slow process but we are following up with the legal teams on a regular basis to try to keep up the impetus as we are aware of the limited amount of time we have to complete all participant scans.
At present we have 3 sites ready to begin recruitment/scanning (Edinburgh, Newcastle and Manchester). Manchester and Newcastle have GE scanners and Edinburgh has a Siemens scanner. Once we have at another Siemens scanner site with their amended supply contract signed, we will open the study.
One of the major points highlighted by this study is the precarious nature of the amyloid radiotracer supply chain in the UK. This study has been negatively impacted by industry pulling out of the UK and European market, first with the withdrawal of Lilly's florbetapir from the European market and now with the closure of GE's production centre.
If multi-centre imaging studies are to succeed in the future, there need to be a more secure radiotracer supply chain, possibly via a DPUK/academic radiochemistry network that works in conjunction with the DPUK MR-PET Imaging network.