MR-PET network Harmonisation study

Team members <u>funded</u> (full or part-time) by DPUK

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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 <u>not</u> 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, Marina Bishop

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, Gabrielle Gray

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

Location(s): Edinburgh university, Newcastle, Manchester, Cambridge, KCL, UCL, UCL Hospital, Imperial College London, Invicro

Objectives:

The project is divided into 4 work packages or Task Forces:

1. Co-ordination & 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

Dependencies to and from other work packages, networks and themes

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		KH & VRB
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		
	M1.3.1 July 2017	M1.3.1 Complete		

D1.3 Organise a yearly meeting for all members of the study partnership (each July)	M1.3.2 July 2018	M1.3.2 Complete	All Task forces to attend/present	
	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	MM, JO'B, J-PT, AC
	M2.1.2 Contact PET-MR sites to identify site training representatives	M2.1.2 Complete		
D2.2 Assess training needs and set up individual training schedules	M2.2.1 Research existing resources for training	M2.2.1 Complete	None	MM, JO'B, J-PT, AC
	M2.2.2 Design, deploy and analyse results of sites survey on training status	M2.2.2 Complete		
	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, 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	JM & 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 Jan 2020		
	M3.2.5 Start MR-PET scans (n=84)	M3.2.5 Feb 2020		
	M3.2.6 Analysis of collected data	M3.2.6 Jan 2020		
Objective 4:				
D4.1 Publish standardised ICF and PIS templates	M4.1.1 Investigate data sharing policies of similar networks/organisations	M4.1.1 Complete		JW & PM (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		

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

Complete study recruitment

Complete MR-PET scans (n=74)

Data analysis of completed scan data (10 scans completed of which 4 participants have been scanned twice)

Risks	**Mitigation**
1) Delays due to COVID-19 closures at all sites	1) Review the ongoing situation and act appropriately
2) Issues with radiotracer supply due to Wolfson Molecular Imaging Centre closing at the end of the year	2) Our Study end date is 27th September, so we intend to complete all scans by September

Lessons Learnt

For the imaging network to move forward, it needs to be self-reliant in terms of radiotracer supply. Many of the delays to the study have been a result of commercial production of amyloid imaging radiotracers such as Lily's florbetapir and GE Healthcare's flutemetamol. In addition, the University of Manchester's radiochemistry

production centre at the Wolfson Molecular Imaging Centre is due for closure at the end of 2020. This will mean that the only remaining UK site producing flutemetamol will be at the University of Edinburgh. If the imaging network is to be able to research novel radiotracers, there will need to be commitment to investment in research radiochemistry facilities.

There has been a great deal of collaboration and interaction between the 7 PET-MR research sites, which has set an excellent foundation for any multi-centre follow-on studies. From the experience that this study has brought, it would be strongly advised that any future studies attempt to streamline research contracts and have a good understanding of all research governance at all sites where possible in the set-up phase in order to cut down on delays on setting up the study. This could mean producing such as standardised collaboration agreement templates and radiotracer contracts as part of the study set-up in order to make collaborative research a little simpler.

Please tell us the most successful outcome and what it means to dementia research

The biggest achievement for the project has been in the setting up of the PET-MR imaging network, linking the 7 UK PET-MR Scanner sites. The collaboration between the research teams in setting up this pilot study and lessons learnt will be invaluable in the setting up for future multi-centre studies.

Outcomes

PUBLICATIONS

Published

- Mada M, et al. **Competencies and training of radiographers and technologists for PET/MR Imaging – a study from the UK MR-PET network,** *European Journal of Hybrid Imaging, 2020, 4:1* https://doi.org/10.1186/s41824-019-0070-6
- Gillespie, S, ***Tackling Dementia with Cutting-Edge Brain Imaging Technology*** *International Labmate* February 2020 https://www.labmate-online.com/article/microscopy-and-microtechniques/4/dementias-platform-uk/tackling-dementia-with-cutting-edge-brain-imaging-technology/2688

ENGAGEMENT ACTIVITIES

- 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.

WP 17 Project report

- Georgios Krokos presented 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.

USE OF FACILITIES & RESOURCES

- Our study has carried out 10 participant scans as of March 2020. All scans were run on DPUK MR-PET scanners.
- The scan data has been uploaded to the DPUK XNAT portal based in Swansea.

FURTHER FUNDING

- While there is currently no follow-on study planned, we secured a 6-month no-cost extension, which extends the study end date to 27th September 2020.

Project narrative

The DPUK MR-PET harmonisation project has been ground-breaking study with the aim to standardise hybrid scanning techniques between the 7 PET-MR scanner sites and to set up an imaging network to allow greater collaboration between PET-MR research teams.

It has not been without its challenges, particularly with the many issues around the supply of an amyloid radiotracer. Our initial choice of radiotracer, florbetapir was withdrawn from the UK & European market by Lily which meant we had to find a suitable alternative that could be supplied to all of the scanner sites.
Then after selecting GE Healthcare's flutemetmol, their Amersham production centre was closed in June 2019 which resulted in production for 5 out of the 7 sites being done at the University of Manchester's radiochemistry facility at the Wolfson Molecular Imaging Centre. Unfortunately, we have recently been informed that Manchester plans to close the radiochemistry labs at the end of 2020, and this will result in only one UK site, at the University of Edinburgh, being able to produce flutemetamol.
In a further setback, the COVID-19 pandemic has resulted in all research scanning activity being suspended temporarily. Due to the rapidly developing situation, we are currently uncertain when we will be able to reopen the study. Our primary concern is the safety of our study volunteers, and that of our research teams and we plan to restart recruitment and scanning activities once it is has been deemed safe for us to do so.
We have scanned a total of 6 participants, 4 of these have been scanned twice, and therefore have completed their involvement in the study. The resulting scan data for all 10 scans has been, (or is in the process of being) uploaded to the DPUK's XNAT data portal.

The next stage will be to analyse the available data, and re-opening recruitment and scanning activities.