Deep and Frequent Phenotyping
Start date: 1 October 2016 **Completion date: 30 October 2020**

Overall work package objectives:

To provide data for very deep phenotyping with established and novel biomarkers, together with very frequent phenotyping with repeated measures over a period of 12 months.

These objectives to be met through:

1) Cohort agreement – recruitment will be through pre-existing DPUK cohorts, incorporating an algorithm based on ADNI data to reduce screen failure, based on age, cognition and APOE genotype
2) Study Governance – approvals from Sponsor, Administration of Radioactive Substances Advisory Committee (ARSAC) and Health Research Authority including REC and HRA Assessment
3) Study recruitment and assessments – a 2 year study period at 7 research sites, allowing 12 months for recruitment and a further 12 for completing all participant visits
4) Participant Engagement – with Alzheimer's Society and Ethical, Legal and Social Implications work package
5) Data Dissemination – to establish a data platform and make the dataset widely available for analysis

Deliverables	Milestones	Milestone deadline	Work package dependencies	Person(s) responsible
Objective 1:				
D1.1 Recruitment process agreement from cohorts	M1.1.1 UK Biobank	M1.1.1 Complete	Dependent on UK Biobank	Simon Lovestone, Vanessa Raymont, Jennifer Lawson, Craig Ritchie, Dennis Chan, Clive Ballard
	M1.1.2 Generation Scotland	M1.1.2 Complete		
	M1.1.3 EPIC	M1.1.3 Not Completed EPIC have DECLINED		
	M1.1.4 Extend	M1.1.4 Complete		
Objective 2:				
D2.1 Sponsor Approval	M2.1.1 Protocol Finalised	M2.1.1 Complete		Simon Lovestone, Vanessa Raymont, Jennifer Lawson, Craig Ritchie, Dennis Chan
	M2.1.2 Confirmation of Sponsorship	M2.1.2 Complete		
D2.2 HRA Approval	M2.2.1 REC Approval	M2.2.1 Complete		
	M2.2.2 HRA Assessment	M2.2.2 Complete		
D2.3 ARSAC Approval	M2.3.1 Confirmation of ARSAC Licence	M2.3.1 Complete		
Objective 3:				
D3.1 Recruitment	M3.1.1 First participant recruited	M3.1.1 Complete		Simon Lovestone, Vanessa Raymont, Jennifer Lawson, Craig
	M3.1.2 Last participant recruited	M3.1.2 Feb 2021		
D3.2 Assessment Completion	M3.2.1 First participant completed study	M3.2.2 Jun 2020		
	M3.2.2 Last participant completed study	M3.2.2 Feb 2022		

				Ritchie, Dennis Chan
Objective 4:				
D4.1 Alzheimer's Society	M4.1.1 Develop short explanatory videos for CSF, MRI, PET, MEG and Cognition	M4.1.1 Complete		Simon Lovestone, Vanessa Raymont, Jennifer Lawson, Craig Ritchie, Dennis Chan
	M4.1.2 Convene Lay Members Group to review study documentation and protocol outline	M4.1.2 Complete		
D4.2 ELSI Work stream	M4.1.1 Sub study to interview DFP participants	M4.1.1 Dec 2019		
	M4.1.2 Questionnaire generated from interviews to be added to DFP study, all participants to complete at Day 300 of assessments	M4.1.2 Dec 2019		
Objective 5:				
D5.1 Data Collation	M5.1.1 Data platform established by Aridhia	M5.1.1 Complete		Simon Lovestone, Vanessa Raymont, Jennifer Lawson, Craig Ritchie, Dennis Chan
	M5.1.2 Data transfer pilot (individual modalities data)	M5.1.2 Complete		
	M5.1.3 Data transfer to platform at end of study	M5.1.3 Aug 2022		
D5.2 Data Dissemination	M5.1.1 Sage Bionetworks receive data	M5.2.1 Aug 2022		
	M5.1.2 Data made Open Access	M5.2.2 Sep 2022		

Key updates on delivery against milestones since last report

D3.1 Recruitment:

1) **UK Biobank cohort agreement/recruitment** – After some delay in UK Biobank submitting their substantial amendment, it was approved mid October 2019 and UKB is just finalising their website for recruitment. UKB recruitment should therefore start early November 2019, in Oxford and Exeter initially.

1a) **Other cohort agreements/recruitment -** Generation Scotland and EXTEND have both agreed to participate. The Edinburgh site has been unable to open as yet however, as although we finally completed the contract for the amyloid PET ligand for Edinburgh with GE healthcare at the end of May 2019, a full Caldicott Guardian review was requested by NHS Lothian R&D department, so that is currently still in process.

2) **Study Governance** – Approvals have been obtained from Sponsor and the Health Research Authority (REC and HRA assessment). All ARSAC licenses are now in place and the amendment to replace Simon Lovestone with Vanessa Raymont as CI has been approved.

3) **Study recruitment and assessments -** The first participant was recruited in October 2019 at the Oxford site via the TrialSpark website recruitment. Three more participants are now scheduled for the Oxford site. The Exeter site opened on 31 October 2019 and are ready to start recruiting in November 2019. We are currently negotiating the contractual site set up for the Imperial site, which we anticipate will open in December 2019 or early January 2020. We will then expect the Manchester, Newcastle and King's College sites to come online shortly afterwards.

Further milestones to progress in due course.

Summary of plans for the future

- Trial Spark website is open in Oxfordshire, with over 300 currently signed up. 4 people screened or scheduled for screening from this group.
- Exeter site opening from November 2019, with Imperial site to open late December 2019/early January 2020.
- UKB recruitment website scheduled to go live early November 2019.
- Initiate patient contact processes at Generation Scotland and EXTEND

Risks	**Mitigation**

1) Delay to set-up of PET Amyloid scanning 2) Further delay in recruitment via UK Biobank 3) Cost over-run. The extensive delay, the asynchronous start and the increased cost of sample curation in NIHR Bioresource vis a vis Roslin Institute costs from application and the increased cost due to salary and other inflation during the extensive delay period all contribute to a possible cost over-run.	1) LP at screening for abeta CSF analysis possible via amendment and actively chasing PET contracts. 2) Recruitment via social media platforms and from other cohorts. 3) Strict financial control with no spend from any recruitment site. Individual PI's and sites absorbing start-up costs from own resource. Use of other resource elsewhere wherever possible. However, the study was costed very tightly in the first application and the delay results in inevitable and not insubstantial cost increase.

Team members

Simon Lovestone and Vanessa Raymont; representing more than 20 Investigators. Core team includes Jen Lawson, Ivan Koychev, Clare Mackay, John Gallacher.

Outcomes

Protocol, Info sheets, website, social media adverts, amendment documents.

- Daily Express and Sunday Times articles
- Radio 4, Oxford (two news stories) and Jack FM radio reports

1. Firouzian, A., et al., *Imaging Abeta and tau in early stage Alzheimer's disease with [(18)F]AV45 and [(18)F]AV1451.* EJNMMI Res, 2018. **8**(1): p. 19.
2. Koychev, I., et al., *Abeta42/Abeta40 and Abeta42/Abeta38 Ratios Are Associated with Measures of Gait Variability and Activities of Daily Living in Mild Alzheimer's Disease: A Pilot Study.* J Alzheimer's Dis, 2018.
3. Koychev, I., et al., *PET Tau and Amyloid-beta Burden in Mild Alzheimer's Disease: Divergent Relationship with Age, Cognition, and Cerebrospinal Fluid Biomarkers.* J Alzheimer's Dis, 2017. **60**(1): p. 283-293.
4. Mc Ardle, R., et al., *Gait in Mild Alzheimer's Disease: Feasibility of Multi-Center Measurement in the Clinic and Home with Body-Worn Sensors: A Pilot Study.* J Alzheimer's Dis, 2018. **63**(1): p. 331-341.

DPUK- Outcomes from funding

References:

I. Koychev I., Lawson J., Chessell T., MacKay C., Gunn R.N., Sahakian B.J., Rowe J.B., Thomas A., Rochester L., Chan D., Tom B., Malhotra P., Ballard C., Ritchie C., Raymont V., Leroi I., Lengyel I., Murray M., Thomas D., Gallacher J., Lovestone S (2018). Deep and Frequent Phenotyping Study Protocol: An Observational Study in Preclinical Alzheimer's Disease. BMJ Open 2019;9:e024498. doi:10.1136/bmjopen-2018-024498.

i. R. Mc Ardle, R. Morris, A. Hickey, S. Del Din, I. Koychev, R. N. Gunn, J. Lawson, G. Zamboni, B. Ridha, B. J. Sahakian, J. B. Rowe, A. Thomas, H. Zetterberg, C. MacKay, S. Lovestone, L. Rochesteron, Deep, t. Frequent Phenotyping study, Gait in Mild Alzheimer's Disease: Feasibility of Multi-Center Measurement in the Clinic and Home with Body-Worn Sensors: A Pilot Study. *J Alzheimers Dis* **63**, 331-341 (2018).

ii. I. Koychev, B. Galna, H. Zetterberg, J. Lawson, G. Zamboni, B. H. Ridha, J. B. Rowe, A. Thomas, R. Howard, P. Malhotra, C. Ritchie, S. Lovestone, L. Rochester, Abeta42/Abeta40 and Abeta42/Abeta38 Ratios Are Associated with Measures of Gait Variability and Activities of Daily Living in Mild Alzheimer's Disease: A Pilot Study. *J Alzheimers Dis*, (2018).

iii. A. Firouzian, A. Whittington, G. E. Searle, I. Koychev, G. Zamboni, S. Lovestone, R. N. Gunn, Deep, t. Frequent Phenotyping study, Imaging Abeta and tau in early stage Alzheimer's disease with [(18)F]AV45 and [(18)F]AV1451. *EJNMMI research* **8**, 19 (2018).

iv. I. Koychev, R. N. Gunn, A. Firouzian, J. Lawson, G. Zamboni, B. Ridha, B. J. Sahakian, J. B. Rowe, A. Thomas, L. Rochester, D. Ffytche, R. Howard, H. Zetterberg, C. MacKay, S. Lovestone, Deep, t. Frequent Phenotyping study, PET Tau and Amyloid-beta Burden in Mild Alzheimer's Disease: Divergent Relationship with Age, Cognition, and Cerebrospinal Fluid Biomarkers. *J Alzheimers Dis* **60**, 283-293 (2017).

Additionally, to address the MRC comments above, for each publication please provide a statement which describes the significance of the publication and how it has contributed to the dementia literature, and/or broader scientific understanding. This statement can be up to 50 words per output.

i. This paper describes the protocol and processes for establishing accurate and comprehensive assessment of gait including from connected device/wearables used in DFP study. The processes were shown to be acceptable to participants and to deliver both behavioural and spatio-temporal data for use as potential biomarkers of early detection of dementia.

ii. Following from the gait protocol paper, this work shows that gait measures correlate with biochemical measures of disease processes. Specifically, CSF measures of Abeta peptide ratios correclated with step-time and step-length suggesting that early AD pathology affects the cognitive and motor control of gait.

iii. This paper describes the protocol for acquisition of concurrent PET measures of amyloid and tau. A simplified protocol with static scans showed adequate performance in comparison to dynamic scanning demonstrating a relatively low intensity protocol is acceptable and feasible in this multi-centre study.

iv. Building on the work described above, this paper compared amyloid and tau pathology markers as acquired from both CSF and PET imaging within a short window of assessment. The data suggests that even in late onset AD, those people that are relatively younger have a dementia driven more by tau than by amyloid pathology whereas those in the oldest old group have a more diverse pathological driver.

v. This paper reports on the acceptability and feasibility of a complex, high intensity, multiple modality study across multiple sites in the UK. It shows such a study is technically feasible and, using both quantitative and qualitative methods, is acceptable to participants. Learning from this experience the main DFP study protocol was developed and is reported here.

1) Details of any other significant outputs for the workpackage which you believe are worthy of mention in the progress report which will accompany the renewal proposal.

In October 2018, the DFP study and the Alan Turing Institute co-hosted a data workshop which brought together early career grade data-scientists from across the UK for three days, in order to analyse the DFP pilot data now hosted on the DPUK portal. A series of technical seminars on open data sciences and each of the modalities was held and the participants learnt how to access and analyse this complex dataset. Alongside the workshop an ATI public lecture was given by Stephen Friend, attracting over 100 paying attendees. A large amount of social media activity was associated with the event and a group of workshop attendees has been formed, which will continue to meet until the data from the main study becomes available.

Project narrative

After experiencing continued and significant delays in setting up recruitment processes through pre-existing DPUK cohorts, we have been able to recruit our first participants at the Oxford site in October and November 2019 via a web based recruitment strategy that involves engaging with the public via social media platforms. We are inviting people aged 60+ with a family history of Alzheimer's disease to take a short cognitive test on our website to assess their potential eligibility for inclusion. This has been provided by our partners TrialSpark and Cambridge Cognition and we have had over 300 people sign up as interested to date. The Exeter site opened on 31 October and will starting recruitment in November 2019.

Also, after further delays, UK Biobank have just received ethical approval of their required amendment and their dedicated website is due to go online the second week of November 2019, initially recruiting to the Oxford and Exeter sites.

The Edinburgh site has been unable to open, as although we finally completed the contract for the amyloid PET ligand for Edinburgh with GE healthcare at the end of May 2019, a full Caldicott Guardian review was requested by NHS Lothian R&D department, so that is currently still in process.

We are in the processes of agreeing the use of a Merck tau tracer, as the field has coalesced around this tracer making it most informative for clinical trials. There is an intent is that JNJ will offer additional support for this, but this is pre-contractual.