Deep and Frequent Phenotyping

Team members
Simon Lovestone and Vanessa Raymont; representing more than 20 Investigators. Core team includes Jen Lawson, Ivan Koychev, Clare Mackay, John Gallacher.
ECR: Jen Lawson
Location(s):
Oxford University
Edinburgh University

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 8 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

Dependencies to and from other work packages, networks and themes

Dependent on UK Biobank

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		SL, VR, JL, CR, DC, CB
	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	M1.1.1 UK Biobank	M1.1.1 Complete		SL, VR, JL, CR, DC, CB
	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		SL, VR, JL, CR, DC, CB
	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		
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		SL, VR, JL, CR, DC
	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		SL, VR, JL, CR, DC
	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** – UKBiobank recruitment started in February 2020, after contracts were finalised and a further review by the UKB access side committee. 1125 emails have now been sent to UKB participants and 80 have been referred to DFP as a result. Of those, 16 were potentially eligible and 14 were happy to come in from screening. We have stopped UKB emails for now, as UKB want this 'pilot' process reviewed by their access subcommittee before agreeing a continuation. We are awaiting their feedback from this in the next 1-2 months.

1a) Other cohort agreements/recruitment - We finally received Caldicott Guardian sign off for the Edinburgh site in March 2020 after submitting a good amount of modality-specific information for review and making some data adjustments at that site, so are now in the process of opening the Edinburgh site. One main additional delay has been Edinburgh contracts team reviewing the contract with GE for their amyloid PET ligand. In Oxford and Exeter (the two sites already open), 568 people have signed up on the TrialSpark website, although 234 have not completed the cognitive screening task. We are trying to optimise these numbers by contacting people individually via email to encourage their completion of the cognitive task and have worked hard to provide adequate information on the website itself. From this number, after applying the 4:1 enriching ratio, 16 of those remaining were not interested and 12 were ineligible after pre-screening. Exeter 10K cohort contracts were signed in December 2019 and they started sending out 75 invites per day in February 2020.

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.

3) **Study recruitment and assessments –** The Oxford site has now screened 5 people and enrolled 2 participants, one of whom has undergone initial amyloid PET scanning. However, all study assessments were paused in March 2020 at all sites because of the covid-19 situation. We are currently negotiating the contractual site set up for the Imperial, Manchester and Newcastle sites, and anticipate these should be ready to open soon after research can resume, pending site R&D and contract review during the shutdown. The King's College site should come online shortly afterwards.

Further milestones to progress in due course.

Summary of plans for the future

- Remaining sites to open as soon as possible once non covid-19 research restarts.
- To review UKB recruitment and continue with process once non covid-19 research restarts.
- To start Generation Scotland recruitment at Edinburgh once non covid-19 research restarts.

Risks	Mitigation
1) Further difficulties with recruitment or poor throughput from existing cohorts.	1) Recruitment via social media platforms (e.g. TrialSpark – although we are considering other options too) and from other cohorts (e.g. Join Dementia Research; JDR - this is being added in the forthcoming protocol amendment). We are also negotiating a process to actively recruit participants from the UK sites of the European Prevention of Alzheimer's Dementia (EPAD) cohort, given this is closing in June 2020 and many sites are also DFP sites.
2) Cost over-run. The extensive delay, the asynchronous start and the increased cost of sample curation in NIHR Bioresorce 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.	2) 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. We are currently exploring how existing funds can be vired to boost recruitment from specific cohorts (i.e. EPAD) in the short term.

LESSONS LEARNT

There have been a number of factors that caused the DFP study to be heavily delayed in its start. With hindsight, given the complexity of the protocol and the number of collaborators involved, this may not have been a complete surprise, but we are aware that some of these potential delays could have been managed differently in the planning stages. In particular, given the necessary recruitment and screening processes, initial planning around how to work with existing cohorts could have been discussed in greater depth prior to the protocol being finalised. In addition, unforeseen delays such as the need for Caldicott Guardian sign off for the Edinburgh site could have possibly been identified earlier, although the overarching delays may have meant such requirements could have changed over time. Further factors that could have potentially been mitigated against include several different delays in contractual agreements being reached. We are aware that other multisite studies in the UK have struggled with similar issues of late, and so wonder if a review of contractual processing across the academic and commercial sites involved would have been or still be useful.

WHAT IS THE PROJECTS MOST SUCCESSFUL OUTCOME AND WHAT DOES IT MEAN TO DEMENTIA RESEARCH?

Although the DFP study is still in its early stages, opening a study of such complexity has provided at least some evidence that such a protocol can be delivered. This reinforces that it could be feasible to expand the current protocol or develop similar approaches to help identify biomarker sets for disease tracking in early Alzheimer's disease. Given we have been able to recruit participants keen to take part also emphasizes that the public is willing to support such onerous research. When we are able to progress with the study, once the covid situation has improved, we would anticipate the most successful outcome of the study will be the recruitment of enough participants to develop a set of biomarkers that can contribute to early, disease modifying drug development

Outcomes

PUBLICATIONS

Published

- Koychev I., et al. (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.
- R. Mc Ardle, 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 Alzheimers Dis 63, 331-341 (2018).
- I. Koychev, 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 Alzheimers Dis, (2018).
- A. Firouzian, et al. **Imaging Abeta and tau in early stage Alzheimer's disease with [(18)F]AV45 and [(18)F]AV1451.** EJNMMI research 8, 19 (2018).

- I. Koychev, et al. **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).

ENGAGEMENT ACTIVITIES

- Previous Daily Express and Sunday Times articles, Radio 4, Oxford (two news stories) and Jack FM radio reports
- Oxford Medical Sciences news now advertising TrialsSpark and DFP website updated regularly.
- Talk given at Integrated Academic Training Symposium - 'Prediction and Prevention in Neurodegenerative Disease' - at Queen Mary University of London in November 2019, which highlighted DFP study.
- Talk given at Oxford Brain Day in February 2020 highlighted DFP study.
- National press coverage plan in place for first baseline visit at Oxford site, but on hold as this visit had to be postponed as a result of the covid-19 situation.

Project narrative

We have now been able to enrol initial numbers of participants and have established an efficient route for new site up, as learnt from the Oxford and Exeter sites. Unfortunately, we were at a point where the remaining sites were almost ready to be opened, when all research had to be paused because of the corona virus situation. We have now started recruitment via UKBiobank and numbers have steadily continued to slowly rise on the TrialSpark website. However, we are also aware we need to be looking at other cohorts to extend recruitment and are actively working to facilitate recruitment from the closing EPAD cohort, as well as via the JDR cohort.

We are progressing with the 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.

We anticipate a quick set up of the remaining sites once research can resume after the covid-10 situation, as most contracts are being progressed through R&D teams currently working from home.