Deep and Frequent Phenotyping – DPUK 1000

Work Package 16

Objective(s):

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

Overview Summary:

Identification of biomarkers for pre-clinical or very early disease for use in experimental medicine is the key challenge to be overcome for the successful and effective delivery of clinical trials in AD. The MRC/NIHR funded 'deep and frequent phenotyping study' is embedded in the **Dementias Platform UK** and will combine established markers, such as PET amyloid imaging and structural MRI, with novel markers, such as PET tau imaging and retinal imaging; and include potential markers which are not yet fully validated in this population, such as electrophysiology and peripheral molecular markers. These potential markers will be evaluated alone and together with conventional assessments of clinical and cognitive change, allowing the development of a multi-modal marker set for measurement of change and its prevention or modification in AD.

Executive Summary:

The Deep and Frequent Phenotyping study is a highly-focused, observational study in prodromal Alzheimer's disease. It combines both established and novel markers to establish a marker set for identification, tracking and measuring outcome in proof of concept trials and in addition, to establish a sample bank for further exploratory studies. Participants are recruited through existing parent cohorts and repeated measures of both outcome comparator modalities (cognition and pathology) and assessment modalities are performed.

Since the grant was awarded there have multiple high-profile efforts with amyloid-targeting drugs, with mixed results, such that many studies have now suggested tau may be the biological driver of the disease. Whatever the target, there is a widely shared

recognition of the need for less invasive biomarkers, for more effective markers of disease progression and for remote markers that might substitute for face-to-face assessments. DFP was conceived to provide solutions to all these challenges in the context of a repeated measures trial mimicking the size and duration of a typical proof of concept/Phase II clinical trial.

Summary of Outputs: (as per Researchfish categories)

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).
- 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).

Collaborations & Partnerships

None

Further Funding

None

Next Destinations

None

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.
- Talk given for Oxford Brookes Healthy Ageing seminar in November 2020 which highlighted DFP study.
- Oxford Mail covered first screening visit at Oxford site – plan to have press release for first baseline visit and next sites opening

Influence of policy, practice, patients & the public

None

Research Tools & Methods

None

Research Databases & Models

None
Intellectual property & licencing
None
Medical products, interventions & clinical trials
None
Artistic & creative products
None
Software & technical products
None
Spin outs
None
Awards & recognition
None
Other outputs & knowledge/future steps
None
Use of facilities & resources
None
Other:
None
Most successful outcome and what it means for future 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, even with concerns raised by COVID-19 and lockdowns. When we are able to progress further with the study, 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.
Lessons learned:
There were 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, other 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. Despite further delays as a result of the COVID-19 lockdowns in the UK, we now have our two previous sites reopened and plan to open the ICL, Manchester and Edinburgh sites in early 2021. This will be followed by the Newcastle and KCL sites. We have now also restarted recruitment via UKBiobank and numbers have continued to slowly rise again 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 are aware that the COVID situation could continue to impact recruitment and throughput for the study and so we recently obtained a no cost extension until 30 September 2022. We will review our existing recruitment plans again in mid 2021 once other sites are open, and adjust these to incorporate yet further cohorts if needed. It is too early to be firm about our plans for finishing the study, but if we are able to recruit and open sites as currently envisaged, we still hope to deliver the bulk of this study by September 2022, although further delays as a result of COVID lockdowns may force this to be reviewed again.

Date of Report:

8/03/2021