**Trials readiness**

**Start date:** 1 July 2014 **Completion date:** 30 June 2020

**Overall work package objectives:**

The dementia readiness cohort, involving the re-phenotyping (including brain imaging) of 10,000 UK Biobank participants at two years, supports the third DPUK strategic objective of re-purposing cohorts for trials readiness.

1. To establish a liaison structure with UK Biobank (UKB) to develop the readiness cohort protocol
2. The liaison group will consider all dependencies between UKB and DPUK, focusing on the imaging cohort of 100,000 and the nested readiness cohort of 10,000 participants
3. Potential dependencies with EPAD and DFP to be explored
4. To recruit 10,000 participants with two-year re-assessment for trials readiness.

**Dependencies to and from other work packages, networks and themes**

No dependencies from other WPs.
WP16 (DFP) is dependent on this WP.

| Deliverables | Milestones | Milestone deadline | Work package dependencies | Person(s) responsible |
|---|---|---|---|---|
| **Objective 1:** | | | | |
| D1.1 Regular meetings with UKB | M1.1.1 Establish a regular agenda item on DPUK at the UKB Steering Group meetings | M1.1.1 Complete | None | JG |
| | M1.1.2 Meet with UKB Steering Group annually | M1.1.2 Complete | | |
| **Objective 2:** | | | | |
| D2.1 Re-imaging protocol agreed with UKB | M2.1.1 Imaging protocol working group established | M2.1.1 Complete | None | AB |
| | M2.1.2 Re-imaging proposals submitted to UKB | M2.1.2 Complete | | |
| D2.2 A biosampling protocol agreed with UKB | M2.2.1 Biosampling working group established | M2.2.1 Complete | Samples will be assayed as a component of WP6 | SL |
| | M2.2.2 Biosample protocols agreed with UKB | M2.2.2 Complete | | |
| D2.3 Cognitive assessment and questionnaire protocol | M2.3.1 CA working group established | M2.3.1 Complete | Dependent on WP10 | JG |
| | M2.3.2 CA protocols submitted to UKB | M2.3.2 Complete | | |
| D2.4 Brain banking protocol | M2.4.1 BB protocols | M2.4.1 Complete | Dependent on WP13<br>Dependent on UKB cohort-partner policy<br>As for M2.4.2<br>As for M2.4.2 | PF |
| | M2.4.2 BB protocols submitted to UKB | M2.4.2 Nov 2020 (was Mar 2019) | | CS |
| | M2.4.3 BB pilot study | M2.4.3 Nov 2020 (was Mar 2019) | | JG |
| | M2.4.4 BB implemented in UKB | M2.4.4 Dec 2020 (was Jun 2019) | | JG |
| D2.5 Re-contact protocol | M2.5.1 Initiate discussions with UKB | M2.5.1 Complete | None | JG |
| | M2.5.2 Re-contact protocol agreed with UKB | M2.5.2 Complete | | |

| | | | | |
|---|---|---|---|---|
| | | | Dependent on UKB recontact policy | |
| D2.6 Participant selection algorithm | M2.6.1 Meet analysts to explore and test algorithms | M2.6.1 Complete | None | JG |
| | M2.6.2 Algorithm agreed with UKB | M2.6.2 Complete | | |
| D2.7 Finalise readiness cohort protocol | M2.7.1 Identify optimum repeat assessment period | M2.7.1 Complete | | JG |
| | M2.7.2 Agree intercalation of programme between baseline and repeat imaging | M2.7.2 Complete | | |
| **Objective 3:** | | | | |
| D3.1 Establish recruitment pathway for EPAD / DFP | M3.1.1 Submit EPAD and DFP data access requests to UKB | M3.1.1 Complete | None | JG |
| | M3.1.2 Acquire UKB data instance on portal | M3.1.2 Complete | Dependent on UKB data access agreement | |
| | M3.1.3 Install 'Prepad' on data portal | M3.1.3 Complete | None | ST, JS (DFP), DG (EPAD) |
| | M3.1.4 Begin EPAD / DFP recruitment | M3.1.4 Complete | Dependent on UKB recontact policy | |
| **Objective 4:** | | | | |
| D4.1 Finalise readiness cohort protocol | M4.1.1 Integrate the various components for the protocol from Objective 2 and agree with UKB a final protocol | M4.1.1 Complete | None | JG, AB |
| D4.2 Conduct pilot study | M4.2.1 Begin re-assessment of 500 participants | M4.2.1 Complete | | JG |
| | M4.2.2 Review data and adjust protocol | M4.2.2 Complete | | |
| D4.3 Conduct re-assessment on all participants | M4.3.1 Begin re-assessments | M4.3.1 Complete | | JG |
| | M4.3.2 Complete re-assessments | M4.3.2 Feb 2023 | | JG |

**Team members <u>funded</u> (full or part-time) by DPUK**
John Gallacher
**Team members involved with the project but <u>not</u> funded by DPUK**
Andrew Blamire, Cathie Sudlow, Delia Gheorghe, Simon Lovestone, Paul Francis

**Locations:**
Oxford University, Edinburgh University, Kings College London, Swansea University, Newcastle University

**Summary of plan to deliver on outstanding work (with dates)**
M2.4.2 BB protocols submitted to UKB November 2020
The International expert panel convened to sign off a proposal for submission to UKB Enhancements committee.
M2.4.3 BB pilot study

WP 3 Project report

Contingent on support from UKB Enhancements Committee
M2.4.4 BB implemented in UKB
Contingent on support from UKB Enhancements Committee
**Will you complete all your Milestones by June 2020?** *No*
*Work will continue into DPUK 2*

| **Risks** | **Mitigation** |
|---|---|
| 1) UKB will decline to conduct a brain donation pilot study | 1) We are building our request around strong arguments for the growing value of brain donation. The team developing the proposal includes John Gallacher (DPUK), Colin Smith (Edinburgh: UK Brain Banking Network), John Hardy (UCL), Jonathan Mill (Exeter University), David Bennett (Chicago) |
| 2) The no-cost extension for brain donation into DPUK2 will not be granted by MRC | 2) There is no advantage to the project in not granting the no-cost extension. The extension does not involve any financial cost and will build on what has already been achieved. |

**Lessons Learnt**

- Aligning major projects is challenging due to resourcing, planning and changing scientific priorities. Addressing these requires persistence and flexibility.
- The repeat imaging (D2.1) has proved a major success story in that the initial DPUK investment of £2.5m has realised a further £8m and is likely to release a further £20m for UKB repeat imaging. These investments will add considerably to the wider scientific value of UKB as well as to dementia research. UKB will likely be the global standard for population structural body and brain imaging for all common chronic disease. Our gratitide goes to Andrew Blamire (Newcastle) for his constructive chairing the DPUK/UKB imaging meetings that delivered D2.1.
- The biosample assays (D2.2) were not possible in UKB due to the strategic decision by UKB to reserve all samples for entire cohort analyses. Whilst this is a reasonable strategy, in that it builds on the unique strengths of UKB, it was not anticipated at the beginning of DPUK. In response, for WP 6, comparable samples were obtained from Generation Scotland and are currently being assayed. Simon Lovestone deserve much credit for his persistence in delivering D2.2.
- An enhanced cognitive assessment protocol (D2.3) was delivered (WP 9) and is being implemented at repeat imaging. This contiunues to be an impoirtant area for UKB and further discussions are underway to create opportunuties for additional, more detailed, cognitive assessent. Credit should go to Ian Deary and Chloe Fawn-Ritchie (Edinburgh) for their high quality work in delivering D2.3.
- Developing a suitable protocol (D2.4) was achieved with the valuable assistance of Paul Francis (KCL). However, the wider issue of how this might be implelented is more challenging for a number of reasons. The most important of which is lack of clarirty as to whom, and how, the invitation might be delivered. This is an important point as UKB has rapidly moved-on from repeat brain imaging of 10,000 participants to whole body imaging of 60,000 participants, and online repeat cognitive testing of 150,000 participants. A second reason is that introducing a brain donation programme is not immediately time critical; allowing time to developing a robust and low-risk protocol will be beneficial.
- Trials readiness (D2.5-D2.7) has also proven difficult. Immediately prior to implementing a pilot study to test re-contact, UKB was used as a sampling frame for a blood pressure reduction trial. This experience raised concerns for UKB, who implemented closer scrutiny of our (DPUK) proposals resulting in delays. Our response has been to continue to work with UKB, and recruitment to the Deep and Frequent Phenotyping study has been agreed, although delayed due to COVID. However, the realisation of a large trials-ready cohort recruited from UKB seems remote. In reponse we have worked with other cohorts (Airwave, Health-Wise Wales) and have recruited >50,000 to our Clinical Studies Register and >3,000 to the Great Minds register. Whilst these cohorts do not have the depth of genotyping and phenotyping available to UKB, they do provide an immediate source for re-contact that will enable precision recrutment to experimental medicine.

- The EPAD study (D2.8) has not been renewed and recrutment to EPAD has been closed. However, we have offered our research register infrastructure as a means of maintaining the English EPAD centres recruitment. This offer has been provisionally accepted and we are working through the details as part of the Trials Delivery Framework of DPUK2.

**Outcomes**

**PROTOCOLS**

- International expert panel UKB Protocol

**OTHER**

- Report

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

Repeat imaging: The added numbers, modalities, and variable duration of repeat imaging, realised by the further investments will add fundamentally to our understanding of pre-clinical disease, early detection, and disease progression.

**Project narrative**

By intention, DPUK is an investment in the long-term future of dementia research, and effort is focussed on delivering strategic initiatives. This is particularly relevant to WP3 where major scientific discoveries are not expected in the near term. Nevertheless, since the last OB, added investment in repeat imaging, assay of cohort samples, and the population of our research registers represent major progress.

We continue to pursue brain donation in UKB and would like this to extend in to DPUK2. It is our view that the value of brain donation will only increase and that in discussion with UKB we are highly likely to establish a protocol that will satisfy the needs and interest of a wide range of stakeholders.