Callum Smith: Final Report to the Neurosciences Foundation (NSF).

1. The work was largely completed as specified in the application, but some modifications were made to the methodology. Some of the clinical assessments and questionnaires specified in the application were replaced by others before recruitment started – this was generally done because further reading of the literature indicated that more psychometrically robust instruments were available. Some additions to the assessment battery were also made to increase its diagnostic utility; for example, the Cambridge Behavioural Inventory was added to explore the extent to which patients met diagnostic criteria for frontotemporal dementia.

Additionally, the final sample size was 45, which was lower than what was specified in the application. Efforts were made to maximise the sample size (e.g. participants were reimbursed for travel, home visits were offered). However, the acceptance rate still ended up below 50%, rather than the 70% that we had estimated previously. Moreover, the population were more cognitively healthy than our initial estimates, which were based on figures from earlier epidemiological studies. While the sample size was not as high as anticipated, it was still sufficient to answer the research questions. It also meant that less money was spent on consumables; this then allowed me to attend an extremely useful neuroanatomy course in London, and to disseminate my results as the Alzheimer's and Parkinson's Diseases Congress in Lisbon.

2. The study extends autopsy findings by showing that comorbid diseases, particularly Alzheimer's disease, are common in people with Parkinson's disease and cognitive decline, and that they affect the clinical presentation. This has implications for treatment, as patients with and without comorbid Alzheimer's disease may respond to different therapeutic strategies. This is especially true for the next generation of medications for neurodegenerative diseases, which are targeted against specific biological disease mechanisms (e.g. anti-amyloid drugs for Alzheimer's disease). Trials of these disease-modifying therapies in Parkinson's disease should take our findings into account, such as by stratifying participants into those with high versus low Alzheimer's pathology.

The study also showed that coexistent Alzheimer's disease can be identified relatively easily in people with Parkinson's disease using clinical strategies (which are easier and cheaper to

perform than biomarker tests). There was a distinction between patients with a Parkinsonian profile, characterised by executive dysfunction and neuropsychiatric symptoms, and those with a more Alzheimer's profile, characterised by episodic memory impairment, often with additional language dysfunction and sometimes dyspraxia. Using these findings, we made recommendations for a neuropsychological test battery for use in Parkinson's disease (such batteries are currently in development), which would have high sensitivity and specificity for detecting coexistent Alzheimer's disease. Thus, our results should also improve diagnostic strategies in Parkinson's disease, again improving treatment outcomes.

3. Results of the study were published here:

> Smith, C. R., Cullen, B., Sheridan, M. P., Cavanagh, J., Grosset, K. A., & Grosset, D. G. (2020). Cognitive impairment in Parkinson's disease is multifactorial: A neuropsychological study. *Acta Neurological Scandinavica*, *141*(6). DOI: 10.1111/ane.13226.

Other papers published during my PhD were:

> Smith, C. R., Malek N., Grosset K. A., Cullen B., Gentleman S. M., & Grosset, D. G. (2019). Neuropathology of dementia in patients with Parkinson's disease: A systematic review of autopsy studies. *Journal of Neurology, Neurosurgery, and Psychiatry*. DOI: 10.1136/jnnp-2019-321111.

> Smith, C. R., Cavanagh, J., Sheridan, M., Grosset, K. A., Cullen, B., & Grosset, D. G. (2019). Factor structure of the Montreal Cognitive Assessment in Parkinson's disease. *International Journal of Geriatric Psychiatry*. DOI: 10.1002/gps.5234.

4. Following the end of my PhD, I secured a position at the University of Glasgow as a project coordinator, supporting mental health research primarily led by clinical psychologists and psychiatrists. I was unsuccessful in my first application for the competitive clinical psychology doctorate (which I submitted shortly before my viva), but I intend to apply to the

next intake. As I have now passed my PhD and gained further relevant work experience, I hope to have more success this time.

My long-term research interests are in clinical neuropsychology, and the NSF-funded project introduced me to many aspects of this area, such as the diagnosis and measurement of psychological function. I intend to continue to focus on neurodegenerative diseases later in my career, with a particular emphasis on dementia.

5. Personally, the most important lesson learned during the project was how to interact with patients in a clinical context. Previously, I had had limited exposure to people with neurodegenerative diseases, and I initially found it difficult to manage the appointments, particularly with patients who were more prone to stress, apathetic, or otherwise uncooperative. I learned how to build rapport, respond sensitively to fatigue or stress, and ensure that the tests were applied accurately and consistently. All of these skills will be essential in my future career.

I consider the second most important learning outcome to be the interdisciplinary nature of the work. I reviewed the scientific literature on diverse topics, including genetics, pathology, and pharmacology, as well as neuropsychology. While these new areas of research were initially challenging, I found that I was relatively quick to familiarise myself with the major themes, and produce my own research in that field. This was rewarding and, again, a quality that I will try to develop in future.