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| **Rates, Risks and Routes to**  **Reduce Vascular Dementia**  **(R4VaD)**  EM8 |
| **Objective(s)**: |
| The **Rates, Risks and Routes to Reduce Vascular Dementia (R4VaD)** study focuses on risk factors for post stroke cognitive impairment (PSCI). Through assessment of cognition, functional outcome and neuropsychiatric symptoms for at least two years after a stroke, it will determine the rates of PSCI, study its progression, gain mechanistic understanding and develop better risk prediction models by studying pre-morbid and pre-stroke cognition, lifestyle, socioeconomic factors and medical history. This comprehensive study will collect blood samples to provide information on genetic and inflammatory markers and will also employ routine and advanced neuroimaging.  DPUK provided pilot funding for the initial stages of the project to 30 June 2020, allowing procedures and approvals to be put in place. A further significant investment of £1,179,476 was made by the Stroke Association, British Heart Foundation and Alzheimer’s Society with the study due to complete no earlier than the end of 2022.  The COVID-19 pandemic has caused some delay in patient recruitment but has also offered a unique opportunity to the study team. R4VaD will be one of, if not the only, national prospective study able to provide objective data on COVID-19 and stroke, in addition to its original objectives. |
| **Overview Summary:** |
| Stroke is a major risk factor for dementia and declining cognition is a major risk factor for stroke. However, the links between vascular health and brain health remain poorly understood. The “Rates, Risks and Routes to Reduce Vascular Dementia study” (R4VaD) aims to recruit 2,000 stroke survivors to shed light on vascular and brain health.  This on-going study focuses on recruiting a wide range of stroke patients presenting in UK hospitals. **Data are collected at multiple time points to** determine rates of, and risk factors for, cognitive and related impairments after a stroke. It aims to understand mechanisms and improve prediction models to reverse the current situation whereby there are currently no effective preventions or therapies.  Whilst the COVID-19 pandemic has caused some delay to patient recruitment in 2020, the study team has also taken the opportunity to plan experimentation that will provide highly informative data on COVID-19 and stroke. People with stroke may be at higher risk of COVID-19 or may experience more severe symptoms. They may also be affected by reduced access to usual stroke treatment and prevention, or have reduced social support in the community. Therefore, this study also aims to determine the rates of COVID-19 in patients with stroke and to examine the impact of the pandemic on these patients. |
| **Executive Summary:** |
| Stroke is known to affect cognition but risk factors for post stroke cognitive impairment (PSCI) are not well defined and mechanisms are not well understood. Currently there are no effective preventions or therapies.    R4VaD is a large, UK-wide, inclusive, observational study in which cognition, functional outcome and neuropsychiatric symptoms for at least two years after stroke are assessed. It aims to determine the rates of PSCI, study its progression, gain better mechanistic understanding and develop better risk prediction models by looking at pre-morbid and pre-stroke cognition, lifestyle and socioeconomic factors, along with medical history. It is a comprehensive study employing blood sampling to provide information on genetic and inflammatory markers along with routine and advanced neuroimaging.  Regulatory approvals for the study were obtained in Spring 2018 in all four UK nations. Staff were appointed, and patient recruitment started in September 2018, expanding to a total of 53 stroke centres in all four nations with 1271 patients enrolled by 23/3/20 when recruitment was interrupted due to COVID-19. Annual follow-ups started in Autumn 2019 and the advanced neuroimaging sub-study started in February 2020. During the COVID-19 pandemic, firstly all follow-ups continued using remote means, which since the follow-ups already had post/phone versions, had minimal impact on data quality or completeness during the COVID-19 lockdown. In order to continue the study recruitment and collect information on the impact of COVID-19 on patients with stroke, the team obtained ethics and R&D approvals to continue recruiting during the COVID-19 pandemic and collect data on COVID-19 exposure and infection on stroke including outcomes. The study reopened recruitment in this ‘COVID-19 substudy’ on 17/4/20 and has recruited 180 patients since then in the 13 centres that were able to continue during lockdown. As of late June 2020, other sites have started reopening to full recruitment such that 23 sites are now open with the remainder in preparation and the current total recruitment on 6/8/20 stands at 1459. Thus, R4VaD will be one of, if not the only, national prospective study able to provide objective data on COVID-19 and stroke, in addition to its original objectives.  The Study Steering Committee has met six-monthly since Spring 2018. The Protocol paper is in press and the statistical analysis plan has been prepared.  The DPUK-funded component of R4VaD ended on 30/6/20 and was key to supporting the study while it obtained approvals and put procedures in place. The success of this funding is visible in the large number of centres that have been set up (53), involving all parts of the UK to obtain a representative sample, and recruiting to target reaching 1500 of the 2000 target sample so far. The COVID-19 interruption will delay the end date of the work and discussions continue with The Stroke Association and co-funders to manage the budgetary position of the project. |
| **Summary of Outputs**: (as per Researchfish categories) |
| **Publications:** |
| The study is early stage with an anticipated end date of end 2022.  The following are in press or in preparation:   1. [Wardlaw JM, et al. (2020). **R4VaD protocol paper.** In press- European Stroke Journal,](https://app.researchfish.com/portfolio/0/publications/5db2f931a30203.28701761/view?name=5db2f931a30203.28701761&delegator=39791&filter=MRC--MR/L023784/2)   <https://journals.sagepub.com/doi/10.1177/2396987320953312>   1. [Woodhouse L, et al. (2019). **R4VaD statistical analysis plan.** In preparation for IJS,](https://app.researchfish.com/portfolio/0/publications/5db2faafea2199.08934981/view?name=5db2faafea2199.08934981&delegator=39791&filter=MRC--MR/L023784/2) |
| **Collaborations & Partnerships** |
| This study has been conducted with funding from DPUK, The Stroke Association, British Heart Foundation and Alzheimer’s Society.  It has involved Centres in the 4 nations of the UK which each have different regulatory regulations, particularly approaches to consent, including informants and for patients with incapacity. |
| **Further Funding** |
| As noted above, DPUK provided pilot funding for the initial stages of the project and further significant funding has been obtained from the Stroke Association, British Heart Foundation and Alzheimer’s Society.  Modest additional funding was obtained recently to undertake a data linkage in 2021 to ascertain COVID-19 status and other outcomes on all patients recruited before, during or after the pandemic. |
| **Next Destinations** |
| Not applicable- study in early stages |
| **Engagement Activities** |
| * R4VaD was presented as an ongoing study at the European Stroke Organisation Conference (ESOC), Milan, May 2019. * R4VaD was presented at UKSF 2018 and 2019, both at an investigator meeting and as a poster in the ongoing studies category. * Prof. Thompson Robinson gave a talk on ‘Rates, Risks and Routes to Reduce Vascular Dementia’ at the South West Peninsula and West England LCRN Meeting on 5th November 2019. * Prof. Thompson Robinson gave an update on ‘Rates, Risks and Routes to Reduce Vascular Dementia' at the West Midlands LCRN Meeting on 27th Sept 2019. * Prof. Thompson Robinson, London and KSS LCRN network meeting, 5th May 2019. Title ‘Rates, Risks and Routes to Reduce Vascular Dementia update’ * Prof. Thompson Robinson gave an update on ‘Rates, Risks and Routes to Reduce Vascular Dementia' at the West Midlands LCRN Meeting on 27th Sept 2019. * Talk by Dr Rosalind Brown ‘Rates, Risks and Routes to Reduce Vascular Dementia’ CRN Eastern Stroke network meeting, 11th November 2019. * Talk by Carol Williams ‘Rates, Risks and Routes to Reduce Vascular Dementia update’. Wessex regional stroke meeting, Basingstoke 6th March 2019. * ‘Rates, Risks and Routes to Reduce Vascular Dementia’ TSA/BHF/Alz Soc ACTVaD study meeting. Talk by Prof Joanna Wardlaw, Dr Fergus Doubal, Dr Ellen Backhouse and Dr Rosalind Brown. December 5th 2018, UK Stroke Forum, Telford 2018 * Poster by Dr Ellen Backhouse on behalf of the R4VaD study team. ‘Rates, Risks and Routes to Reduce Vascular Dementia (R4VaD)’. Organisation for Psychological Research into Stroke (OPSYRIS) meeting, Glasgow, 5th October 2018 * Poster by Dr Ellen Backhouse on behalf of the R4VaD study team. ‘Rates, Risks and Routes to Reduce Vascular Dementia (R4VaD)’. European Stroke Organisation Conference 23rd May 2019, Milan * Talk by Dr Una Clancy ‘Rates, Risks and Routes to Reduce Vascular Dementia (R4VaD)’, UK joining forces west stroke conference, Exeter, 28th June 2018 * Prof Joanna Wardlaw talk "Where next for stroke research?" at the 6th Edinburgh Stroke Winter School, 19th February 2019, Edinburgh, UK. * Prof Joanna Wardlaw talk "Cerebral small vessel disease is a relapsing and remitting neurodegenerative disorder" on the 4th Oct 2019, MRC UK Dementia Research Institute Annual Scientific Meeting (Connectome), in Birmingham, UK * Prof Joanna Wardlaw talk 'Why is one small blood vessel such a giant problem for mankind?' at the 2nd Lenstra Lecture 2019, Philanthropic Endowed Lecture, Swiss Italian Centre for Neuroscience, in Lugano, Switzerland, 1 October 2019 * Prof Joanna Wardlaw talk "Brain Health: a small matter of the blood vessels" at the Edinburgh Neuroscience Public Christmas Lecture 2018, 13th December 2018, Edinburgh, UK. * Prof Joanna Wardlaw gave a talk on "Cerebral vascular dysfunctions detected in human small vessel disease and implications for preclinical studies", at the University of Vermont, 22nd October 2018, Burlington, Vermont, USA. * Prof Joanna Wardlaw gave a talk on "Cerebral small vessel disease: novel targets for prevention" at the Dementia Prevention by Stroke Prevention' World Health Summit Satellite Symposium, 13th October 2018, Berlin, Germany * Prof Joanna Wardlaw gave a talk on "Vascular features on MRI in dementia - clinical implications and interpretation" at the 3rd UK Dementia MRI conference, 6 July 2018, Cambridge, UK. |
| **Influence of policy, practice, patients & the public** |
| This study is likely to provide significant information linking vascular and brain health, particularly linking stroke and dementia and declining cognition. The results may offer provide insight into possible preventions or therapies which could influence policy and practice.  A sub-study focusing on SARS-CoV-2 (COVID-19) pandemic, to be continued to the end of the work, is uniquely poised to deliver significant information on COVID-19 and stroke. |
| **Research Tools & Methods** |
| Cognition, mood and functioning are assessed in person or by post or phone using standardised self-report questionnaires. Blood samples are taken at baseline and/or 6 week follow up to examine genetic and inflammatory markers of stroke. Routinely conducted MRI or CT scans are collected at baseline. Those who are participating in the MRI diffusion tensor imaging (DTI) neuroimaging substudy undergo DTI MRI at 6 weeks. Baseline and 6 week follow up assessments are conducted by all participating sites whilst annual follow ups are centralised. |
| **Research Databases & Models** |
| Data are collected on electronic case record forms and stored in a secure central database held by the University of Nottingham. All brain imaging is sent to the University of Edinburgh for evaluation using online blinded evaluation methods. |
| **Intellectual property & licencing** |
| None to date |
| **Medical products, interventions & clinical trials** |
| None to date |
| **Artistic & creative products** |
| None to date |
| **Software & technical products** |
| None to date |
| **Spin outs** |
| None to date |
| **Awards & recognition** |
| None to date |
| **Other outputs & knowledge/future steps** |
| None to date |
| **Use of facilities & resources** |
| The study has support from the NIHR Clinical Research Network |
| **Most successful outcome and what it means for future dementia research**: |
| The R4VaD Study shows it is possible to recruit a large sample of patients at high risk of vascular dementia in a short time using the Clinical Research Network. Using streamlined assessment tools, cognitive domains, neuropsychiatric and related symptoms can be assessed alongside stroke outcomes in busy stroke services. Much of this has been achieved by remote procedures using adapted versions of the assessments. |
| **Lessons learned**: |
| Stroke is a major risk factor for dementia and declining cognition is a major risk factor for stroke.  Dementia research, as conducted by traditional approaches in memory clinics, is far removed in practice from the constraints under which stroke research operates, highlighting changes that are needed to better integrate vascular research in patients at risk of dementia. Dementia research and clinical practice should increase its awareness of the importance of vascular disease in routine assessments and address vascular risk factor management as routine strategies for dementia prevention. Conversely, stroke research and clinical practice should increase its awareness of the importance of assessing cognition and neuropsychiatric symptoms routinely in patients who present with stroke symptoms. By both sides taking a more integrated approach, research into causes and potential interventions to prevent and treat dementia is likely to advance more rapidly.  The team attempted to set the study up at dementia research network sites but these are often at different locations to stroke sites and operate in such a different way that this aim proved to be impossible. |
| **Other:** |
| The detailed project report can be obtained by contacting DPUK staff. |
| **Date of report**: Updated 15 October 2020 |