

## WP 25: Vascular Health

**Lead:** Atticus Hainsworth (St George's University London, SGUL)

**Aim:** To exploit the Data Portal to evaluate cerebrovascular risk from genes and modifiable multi-comorbidities, and quantify their impact via MRI, to optimise interventional trials design.

**Start Date:** Jan 21

**End Date:** Dec 25

**Team:** SM Allan (Manchester), P Bath (Nottingham), T Blackburn (TP Ventures Ltd), Z Cader (Oxford), R Carare (Southampton), K Horsburgh (Edinburgh), RN Kalaria (Newcastle), S Love (Bristol), CE MacKay (Oxford), HS Markus (Cambridge), JT O'Brien (Cambridge), J Pickett (UK Alzheimer's Society), TJ Quinn (Glasgow), RM Touyz (Glasgow), JM Wardlaw (Edinburgh), D Werring (London), S Williams (London).

**Overall objectives:** To exploit the Data Portal to evaluate cerebrovascular risk from genes and modifiable multi-comorbidities, and quantify their impact via MRI, to optimise interventional trials design. Work Package 25a will quantify brain vascular lesion progression via DPUK2's Data Portal and test the relationships of vascular and dementia risk factors with change in SVD related lesions, (WMH, lacunes, microbleeds PVS), DTI parameters and composite metrics (brain age, brain health index). Work Package 25b will perform sub-analyses of candidate genes. Work Package 25c will perform sub-analyses of mechanistic pathways.

**Background:** Work Package 25 uses the Data Portal (Work Package 21) to generate mechanistic hypotheses from big-data to optimise the design of interventional studies. Results will be used to develop proposals for an interventional experimental programme. Vascular disease increases steeply with age and combines with neurodegenerative pathologies (notably, AD) to accelerate cognitive decline<sup>27-29</sup>. Recent trials (SPRINT, INFINITY, FINGER, Ontario Health Registry, and ADNI) suggest that addressing cardiovascular risk slows cognitive decline. The most prevalent vascular cause of cognitive impairment is cerebral small vessel disease (SVD)<sup>30</sup> seen as white matter hyperintensities (WMH), lacunes, microbleeds and enlarged perivascular spaces<sup>28,31</sup>. The potential for reducing vascular cognitive impairment is rapidly emerging<sup>33</sup>. We will conduct a multi-cohort, multi-modal analysis to identify tractable targets for risk stratified groups. Using UK Biobank (UKB) as a core data set, we will link with other DPUK cohorts and search other databases, e.g. JPND Harness and MetaCohorts, for relevant data. We will use the Data Portal as a transparent repository for data access at a consortium level. UKB is ideal for this work, combining imaging with diverse and detailed antecedent data<sup>32</sup>. UKB is funded to include n=100k brain and cardiac MRI scans (n=35k to date) and n=10k repeat scans (1,000 scans to date).

This programme will deliver evidence for stratifying vascular risk and identify pharmacologically tractable vascular targets related to dementia. We will share novel imaging measures, via the Data Portal; working alongside Work Package 22 to prepare pipelines. This exemplar positions DPUK to increase industry interest in vascular treatments for dementia with a view to optimise future research partnerships.

**Objective 1:** Perform analysis of PVS and vascular lesion burden using UK Biobank and other data sources (work package 25a)

Deliverable 1: Recruit Postdoctoral Research Assistant

Deliverable 2: Obtain data from UK Biobank

Deliverable 3: Identify and obtain appropriate additional data sources

Deliverable 4: Complete analysis of vascular lesion burden

Deliverable 5: Image analysis of data sample for peri-vascular spaces

Deliverable 6: Statistical analysis of data

Deliverable 7: Share resultant dataset using the DPUK data portal

Deliverable 8: Findings from the analyses shared with the Vascular EM team

**Objective 2:** Define drug targets using Mendelian Randomisation (work package 25b)

Deliverable 9: Recruit Postdoctoral Research Assistant

Deliverable 10: Obtain data from UK Biobank

Deliverable 11: Identify and obtain appropriate additional data sources

Deliverable 12: Incorporate data from work package 5a

Deliverable 13: Complete initial Mendelian Randomisation studies looking at conventional risk factors and risk of MRI-defined small vessel disease

Deliverable 14: Complete initial Mendelian Randomisation studies looking at novel risk factors and risk of MRI-defined small vessel disease

Deliverable 15: Statistical analysis of data

Deliverable 16: Share resultant dataset using the DPUK data portal

Deliverable 17: Findings from the analyses shared with the Vascular EM team

**Objective 3:** Define drug targets using analysis of cardiovascular disease and drug history (work package 25c)

Deliverable 18: Recruit Clinical Research fellow

Deliverable 19: Obtain and analyse data from UK Biobank

Deliverable 20: Identify and obtain appropriate additional data sources

Deliverable 21: Incorporate data from work packages 5a and 5b

Deliverable 22: Complete initial scoping analyses

Deliverable 23: Choose drug targets using Delphi consensus

Deliverable 24: Complete analysis on data portal

Deliverable 25: Publish a publication on analyses conducted

Deliverable 26: Expert Consensus Panel formed

Deliverable 27: Share resultant dataset using the DPUK data portal

Deliverable 28: Consensus meeting held including input from industry partners and Clinical Trials work package

Deliverable 29: Findings from the analyses shared with the Vascular EM team

**Objective 4:** Collation of research across Vascular Health work packages

Deliverable 30: Vascular EM team to assess progress and focus subsequent directions

Deliverable 31: Vascular EM team to discuss progress with industry partners and other DPUK themes

Deliverable 32: Annual review of milestones by Work Package leads

Deliverable 33: Future studies developed and refined

Deliverable 34: DRI-DPUK Vascular theme interface maintained

**Objective 5:** DPUK/MRC project reporting

Deliverable 35: Quarterly reporting

Deliverable 36: Annual reporting

Deliverable 37: End report

Deliverable 38: Financial reporting

<b>Objective 1: Perform analysis of PVS and vascular lesion burden using UK Biobank and other data sources (work package 25a)</b>				
<b>Milestone</b>	<b>Description</b>	<b>How and who</b>	<b>Outcomes</b>	<b>Dates</b>
<b>Deliverable 1: Recruit Postdoctoral Research Assistant</b>				
M1.1.1	Recruit a Postdoctoral Research Assistant	Advertise and appoint to post (JW)	Research Assistant employed	Jul-21
<b>Deliverable 2: Obtain data from UK Biobank</b>				
M1.2.1	Submit request and receive data from UK Biobank	Apply, and receive data (JW, RA)	UK Biobank data downloaded	Nov-21
<b>Deliverable 3: Identify and obtain appropriate additional data sources</b>				
M1.3.1	Identify appropriate additional data sources	Review datasets available	Additional datasets identified	Sep-21
M1.3.2	Submit request and receive data from additional data sources	Apply, and receive data (JW, RA)	Additional datasets downloaded	Oct-21
<b>Deliverable 4: Complete analysis of vascular lesion burden</b>				
M1.4.1	Clean the downloaded datasets	Clean data (RA)	Data cleaned	Dec-21
M1.4.2	Collate the cleaned datasets	Collate data (RA)	Data collated	May-22

M1.4.3	Analysis of vascular lesion burden of data sample	Run analysis (RA)	Analysis completed	Jul-22
<b>Deliverable 5: Image analysis of data sample for peri-vascular spaces</b>				
M1.5.1	Complete image analysis of data sample for peri-vascular spaces to provide inputs into work package 25b	Run analysis (RA)	Image analysis complete	May-22
<b>Deliverable 6: Statistical analysis of peri-vascular spaces and vascular lesion burden data</b>				
M1.6.1	Complete the statistical analysis of data to provide inputs into work package 25c.	Analysis performed on DPUK data portal (RA)	Statistical analysis completed	May-23
<b>Deliverable 7: Share resultant dataset using the DPUK Data Portal</b>				
M1.7.1	Share resultant dataset using the DPUK Data Portal	Create and share Data set with DPUK Data Portal (JW, RA)	Resultant dataset available on DPUK Data Portal	May-23
<b>Deliverable 8: Findings from the analyses shared with the Vascular EM team</b>				
M1.8.1	Findings from the analyses shared with the Vascular EM team	Collate results and develop paper and presentation	Presentation of analysis findings to Vascular EM team	May-23

<b>Objective 2: Define drug targets using Mendelian Randomisation (work package 25b)</b>				
<b>Milestone</b>	<b>Description</b>	<b>How and who</b>	<b>Outcomes</b>	<b>Dates</b>
<b>Deliverable 9: Recruit Postdoctoral Research Assistant</b>				
M2.9.1	Recruit a Postdoctoral Research Assistant	Advertise and appoint to post (HM)	Research Assistant employed	Aug-21
<b>Deliverable 10: Obtain data from UK Biobank</b>				
M2.10.1	Submit request and receive data from UK Biobank	Apply and receive data (HM, RA)	UK Biobank data downloaded	Nov-21
<b>Deliverable 11: Identify and obtain appropriate additional data sources</b>				
M2.11.1	Identify appropriate additional data sources	Review datasets available (HM, RA)	Additional datasets identified	Oct-21
M2.11.2	Submit request and receive data from additional data sources	Apply and receive data (HM, RA)	Additional datasets downloaded	Nov-21
<b>Deliverable 12: Incorporate data from work package 25a</b>				
M2.12.1	Incorporate data from work package 25a	Work package 25a shares data	Data incorporated into study	May-22

<b>Deliverable 13: Complete initial Mendelian Randomisation studies looking into conventional risk factors and risk of MRI-defined small vessel disease</b>				
M2.13.1	Clean the downloaded data	Clean data (RA)	Data cleaned	Dec-21
M2.13.2	Collate the cleaned datasets	Collate data (RA)	Data collated	Jun-22
M2.13.3	Complete analysis of conventional risk factors	Run analysis (RA)	Analysis completed	Sep-22
<b>Deliverable 14: Complete initial Mendelian Randomisation studies looking at novel risk factors and risk of MRI-defined small vessel disease</b>				
M2.14.1	Complete analysis of novel risk factors	Run analysis (RA)	Analysis completed	May-23
<b>Deliverable 15: Statistical analysis of data from Mendelian Randomisation studies</b>				
M2.15.1	Complete the statistical analysis of data to provide inputs into work package 25c	Analysis performed on DPUK data portal (RA)	Statistical analysis completed	May-23
<b>Deliverable 16: Share resulting dataset using the DPUK Data Portal</b>				
M2.16.1	Share resultant dataset using the DPUK Data Portal	Create and share the dataset with DPUK Data Portal (JW, RA)	Resultant dataset available on DPUK Data Portal	May-23
<b>Deliverable 17: Findings from the analyses shared with the Vascular EM team</b>				
M2.17.1	Present findings to the Vascular EM team	Prepare findings and present to Vascular EM team (HM)	Presentation of analysis and results to Vascular EM team	Jun-23

<b>Objective 3: Define drug targets using analysis of cardiovascular disease and drug history (work package 5c)</b>				
<b>Milestone</b>	<b>Description</b>	<b>How and who</b>	<b>Outcome</b>	<b>Dates</b>
<b>Deliverable 18: Recruit a Clinical Research Fellow</b>				
M3.18.1	Recruit an Clinical Research Fellow	Advertise and appoint to post (TQ)	Research fellow employed	Apr-23
<b>Deliverable 19: Obtain data from UK Biobank</b>				
M3.19.1	Submit request and receive data from UK Biobank	Apply and receive data (TQ, RF)	UK Biobank data downloaded	Jul-23
<b>Deliverable 20: Identify and obtain appropriate additional data sources</b>				
M3.20.1	Identify appropriate additional data sources	Review datasets available (TQ, RF)	Additional datasets identified	Jun-23
M3.20.2	Submit request and receive data from additional data sources	Apply and receive data (TQ, RF)	Additional datasets received	Jul-23
<b>Deliverable 21: Incorporate data from work packages 25a and 25b</b>				

M3.21.1	Incorporate data from work package 25a	Work package 25a shares data	Data incorporated into study	May-23
M3.21.2	Incorporate data from work package 25b	Work package 25b shares data	Data incorporated into study	May-23
<b>Deliverable 22: Complete initial scoping analyses</b>				
M3.22.1	Clean the downloaded data	Clean data (RA)	Data cleaned	Nov-23
M3.22.2	Collate the cleaned datasets	Collate data (RA)	Data collated	Dec-23
M3.22.3	Complete analysis of conventional risk factors	Run analysis (RA)	Analysis completed	Jan-24
<b>Deliverable 23: Choose drug targets using Delphi consensus</b>				
M3.23.1	Initial Delphi consensus questionnaire distributed	Construct and distribute questionnaire	Questionnaire responses received	Jan-24
M3.23.2	Subsequent Delphi consensus questionnaires distributed	Review initial questionnaire responses, construct and distribute subsequent questionnaires	Questionnaire responses received	Jan-24
M3.23.3	Results from Delphi consensus determined	Review all responses and determine consensus	Consensus determined and communicated	Jan-24
<b>Deliverable 24: Complete analysis on DPUK Data Portal</b>				
M3.24.1	Complete analysis on DPUK Data Portal	Run analysis (RF)	Analysis completed	Jan-24
<b>Deliverable 25: Publish a publication on the analyses conducted</b>				
M3.25.1	Write a paper for publication on the analyses conducted	Discuss and produce a publication on the scope of the work package and the results achieved, such as protocol document or a white paper (TQ, RF)	Paper written and submitted	Jan-24
M3.25.2	Paper published	Modifications as required (TQ, RF)	Paper published	Jan-25
<b>Deliverable 26: Expert Consensus Panel formed</b>				
M3.26.1	Identify and invite members of the Expert Consensus Panel	Set up ECP (RF)	Panel meeting organised	Aug-23
M3.26.2	Feedback obtained from Expert Consensus Panel	Meet with ECP (RF)	Ideas and feedback from panel incorporated into project	Sep-23
<b>Deliverable 27: Share resultant dataset using the DPUK Data Portal</b>				
M3.27.1	Share resultant dataset using the DPUK Data Portal	Create and share Data set with DPUK Data Portal (TQ, RF)	Resultant dataset available on DPUK Data Portal	Jan-25
<b>Deliverable 28: Consensus meeting held including input from Industry partners and Clinical Trials work package</b>				

M3.28.1	Consensus meeting held including input from Industry partners and the Clinical Trials work package	Organise and host meeting	Meeting attended by Industry partners and Trial Delivery Framework leads	Oct-24
<b>Deliverable 29: Findings from the analyses shared with the Vascular EM team</b>				
M3.29.1	Findings from the analyses shared with the Vascular EM team	Prepare and present findings to Vascular EM team (TQ)	Presentation of analyses and results to Vascular EM team	Jan-25

<b>Objective 4: Collation of research across Vascular Health work packages</b>				
<b>Milestone</b>	<b>Description</b>	<b>How and who</b>	<b>Outcomes</b>	<b>Dates</b>
<b>Deliverable 30: Vascular EM team to assess progress and focus subsequent directions</b>				
M4.30.1	Vascular EM team meet at least three times per year	Organise three per year (AH)	Meeting held in 2021 Q1	Mar-21
M4.30.2			Meeting held in 2021 Q2	Jun-21
M4.30.3			Meeting held in 2021 Q3	Sep-21
M4.30.4			Meeting held in 2022 Q1	Mar-22
M4.30.5			Meeting held in 2022 Q2	Jun-22
M4.30.6			Meeting held in 2022 Q3	Sep-22
M4.30.7			Meeting held in 2023 Q1	Mar-23
M4.30.8			Meeting held in 2023 Q2	Jun-23
M4.30.9			Meeting held in 2023 Q3	Sep-23
M4.30.10			Meeting held in 2024 Q1	Mar-24
M4.30.11			Meeting held in 2024 Q2	Jun-24
M4.30.12			Meeting held in 2024 Q3	Sep-24
<b>Deliverable 31: Vascular EM team to discuss progress with Industry partners and other DPUK themes</b>				
M4.31.1	Vascular EM team to meet annually with industry partners and other DPUK themes	Organise 1 per year (AH)	Meeting held in 2021 Q4	Dec-21
M4.31.2			Meeting held in 2022 Q4	Dec-22
M4.31.3			Meeting held in 2023 Q4	Dec-23
M4.31.4			Meeting held in 2024 Q4	Dec-24
<b>Deliverable 32: Annual review of milestones by Work Package leads</b>				
M4.32.1	Annual review of milestones by Work Package leads	Review with WP leads in years 2, 3 & 4 (AH)	Meeting held in 2022 Q4	Dec-22
M4.32.2			Meeting held in 2023 Q4	Dec-23
M4.32.3			Meeting held in 2024 Q4	Dec-24
<b>Deliverable 33: Future studies developed and refined</b>				

M4.33.1	Planning for further Vascular EM studies	Look at funding and plans for the future	Planning performed	Dec-23
M4.33.2	Further refinement of planned Vascular EM studies	Review funding and refine plans	Further refinement performed	Dec-24
M4.33.3	Apply for funding for further Vascular EM studies	Specify studies and make funding applications	Funding applications submitted	Dec-24
<b>Deliverable 34: DRI-DPUK Vascular theme interface maintained</b>				
M4.34.1	Vascular EM theme meet with DRI every 6 months	Organise 2 per year (AH)	Meeting held in 2021H1	Jun-21
M4.34.2			Meeting held in 2021H2	Dec-21
M4.34.3			Meeting held in 2022H1	Jun-22
M4.34.4			Meeting held in 2022H2	Dec-22
M4.34.5			Meeting held in 2023H1	Jun-23
M4.34.6			Meeting held in 2023H2	Dec-23
M4.34.7			Meeting held in 2024H1	Jun-24
M4.34.8			Meeting held in 2024H2	Dec-24
M4.34.9			Meeting held in 2025H1	Jun-25
M4.34.10			Meeting held in 2025H2	Dec-25

<b>Objective 5: DPUK/MRC project reporting</b>				
<b>Milestone</b>	<b>Description</b>	<b>How and who</b>	<b>Outcome</b>	<b>Dates</b>
<b>Deliverable 35: Produce quarterly reports by the required dates</b>				
M5.35.1	Provide Quarterly reports detailing project deliverables and outcomes.	Online quarterly form to be completed for DPUK for MRC meetings	Quarterly report submitted	Mar-21
M5.35.2			Quarterly report submitted	Jun-21
M5.35.3			Quarterly report submitted	Sep-21
M5.35.4			Quarterly report submitted	Mar-22
M5.35.5			Quarterly report submitted	Jun-22
M5.35.6			Quarterly report submitted	Sep-22
M5.35.7			Quarterly report submitted	Mar-23



M5.35.8			Quarterly report submitted	Jun-23
M5.35.9			Quarterly report submitted	Sep-23
M5.35.10			Quarterly report submitted	Mar-24
M5.35.11			Quarterly report submitted	Jun-24
M5.35.12			Quarterly report submitted	Sep-24
M5.35.13			Quarterly report submitted	Mar-25
M5.35.14			Quarterly report submitted	Jun-25
M5.35.15			Quarterly report submitted	Sep-25
<b>Deliverable 36: Produce an annual report by the required dates</b>				
M5.36.1	Annual reports to oversee project status and updates of deliverables and outputs. Information to assess completion criteria as part of payment schedule.	Annual form to be completed for DPUK for MRC meetings. Annual reports submitted to confirm milestone completion for next payment scheduled	Annual report submitted	Dec-21
M5.36.2			Annual report submitted	Dec-22
M5.36.3			Annual report submitted	Dec-23
M5.36.4			Annual report submitted	Dec-24
<b>Deliverable 37: Provide annual financial reporting against the specified budget by the required dates</b>				
M5.37.1	Financial reports submitted at the end of each year. Information to assess completion criteria as part of payment schedule.	Yearly financial statement on spending	Financial report submitted	Dec-21
M5.37.2			Financial report submitted	Dec-22
M5.37.3			Financial report submitted	Dec-23
M5.37.4			Financial report submitted	Dec-24
M5.37.5			Financial report submitted	Dec-25
<b>Deliverable 38: Produce a final work package report by the required date to summarise the work completed and the benefits achieved</b>				
M5.38.1	Final report submitted at end of project.	Lead to complete final report and send to DPUK /MRC for final payment to be made.	Final report submitted	Dec-25

