Centre: Aberdeen IRAS Project ID: 314094

Cognitive Impairment after COVID-19 - Inflammatory and Neural Correlates: A pilot study

The ACDC study:

Assessing **C**ognitive **D**eterioration in **C**OVID-19

Sponsor	NHS Grampian
Funder	NHS Grampian Endowments
Chief Investigator	Dr Jonathan McLaughlin
Sponsor number	1-050-22
Version Number and Date	Version 1 18/8/2022

List of Abbreviations

AMARES	Advanced Method for Accurate, Robust and Efficient Spectral fitting of MRS data with use of prior knowledge
CI	Chief Investigator
CNORIS	Clinical Negligence and Other Risks Scheme
COVID-19	Coronavirus Disease 2019
CRF	Case Report Form
DMC	Data Monitoring Committee
DTI	Diffusion Tensor Imaging
DWI	Diffusion Weighted Imaging
FDG-PET	Fluoro-Deoxy-Glucose Positron Emission Tomography
FLAIR	Fluid Attenuated Inversion Recovery
GCP	Good Clinical Practice
GDPR	General Data Protection Regulations
GP	General Practitioner
HRA	Health Research Authority
ISF	Investigator Site File
MACH	Mental Health After COVID-19 Hospitalisation
MRI	Magnetic Resonance Imaging
MRS	Magnetic Resonance Spectroscopy
mTBI	Mild Traumatic Brain Injury
NHS	National Health Service
PCR	Polymerase Chain Reaction
PI	Principal Investigator
PMG	Project Management Group
PRESS	Point RESolved Spectroscopy
QSM	Quantitative Susceptibility Mapping
R&D	Research and Development
REC	Research Ethics Committee
SARS-CoV2	Severe Acute Respiratory Syndrome Coronavirus 2
SOP	Standard Operating Procedure
SWI	Susceptibility Weighted Imaging
TBSS	Tract Based Spatial Statistics
TMF/SMF	Trial/Study Master File
TSC	Trial/Study Steering Committee

PROTOCOL SUMMARY

CONSIDERED FOR ENTRY	Patients Hospitalised for COVID-19 (with a positive PCR for COVID-19) in NHS Grampian who subjectively report, and are found to have evidence of, cognitive impairment on Neuropsychological assessment.	
TRIAL ENTRY	Patients will be screened for eligibility. Written consent will be sought prior to the study.	
OUTCOME ASSESSMENT	MR imaging and spectroscopy to outline possible inflammation and neural correlates of cognitive impairment post COVID-19 hospitalisation.	
CO-ORDINATION	**Day to Day:** by the Research Nurse **Overall:** Chief Investigator	
FUNDER	NHS Grampian Endowment Fund; Florence Cumming Bequest	
TIME TABLE	Start date: Planned finish date: Planned start of recruitment: Planned end of recruitment:	September 2022 September 2024 September 2022 September2024

BACKGROUND OF PROPOSED INVESTIGATION

Overview

A heterogenous cohort of patients, who have been variably denoted as suffering from "Long COVID" or the Post COVID-19 Syndrome, will have persistent cognitive and affective symptoms. A recent large systematic review found that fatigue and objective cognitive impairment were common and persistent after COVID-19 disease with a prevalence of 24.4% and 20.2% respectively (Badenoch et al., 2022). The severity of physical illness associated with SARS-CoV2 infection does not correlate with the likelihood of these symptoms developing or persisting, raising the questions as to the nature of the processes driving post COVID-19 cognitive symptoms.

The effects of COVID-19 disease on the brain and the link to cognitive impairment has been emphasised as an area of priority research (Samkaria and Mandal, 2021). There have been proposed mechanistic explanations from case studies (Yesilkaya et al., 2021) as well as more general commentaries on the neuroimmune correlates of COVID-19 disease, (Yesilkaya and Balcioglu, 2020) but as yet no high-quality evidence exists.

It is suggested that COVID-19 disease may lead to pathologically identifiable brain changes. A large study evaluating structural brain imaging of patients before and after SARS-CoV2 infection using United Kingdom (UK) Biobank data found evidence of grey matter volume reduction compared with controls (Douaud et al., 2022). This mainly involved olfactory areas but wider limbic involvement was discussed in the context of memory impairment and reported cognitive change. A much smaller study (Hosp et al., 2021) correlated functional imaging changes, Fluoro-Deoxy-Glucose Positron Emission Tomography (FDG-PET), with cognitive impairment in patients hospitalised with COVID-19 disease.

Magnetic Resonance Spectroscopy (MRS) is an imaging technology that represents a non-invasive diagnostic tool for evaluating white matter injury in the brain and can provide valuable information regarding underlying pathogenesis. Most importantly, MRS can identify neurochemical abnormalities even in the absence of corresponding findings on structural MR brain imaging. This is important, in that many patients with persistent cognitive symptoms have normal conventional imaging (Hellgren et al., 2021).

MRS has been used in a small preliminary study to outline brain inflammation and damage linked to COVID-19 disease (Rapalino et al., 2021). This work pointed to characteristic white matter inflammatory MRS findings in patients with severe and acute COVID-19 disease. White matter changes have also been described using conventional MR imaging in patients presenting with cognitive impairment in association with COVID-19 disease (Hellgren et al., 2021) but such results were not replicated in patients describing "brain fog" symptoms after hospitalisation for COVID-19 disease (Sklinda et al., 2021).

Reviewing the nascent investigation already undertaken, there is a possibility that inflammation and other neural correlates play a role in persistent cognitive symptoms in those who have been infected with SARS-CoV2. This pilot study aims to investigate these links as a necessary and urgent first step in trying to understand how and why a significant number of patients are affected in this way.

Local relevance

NHS Grampian, along with the other health boards in Scotland, has received funding from the Scottish Government to identify and provide intervention for the mental health needs of patients hospitalised with COVID-19 disease. This follows on from *Coronavirus (Covid-19): Mental health needs of hospitalised patients - report* (https://www.gov.scot/publications/mental-health-needs-patients-hospitalised-due-covid-19/).

This has been identified as an unmet need and a clinical priority. The response has seen the creation of the Mental Health After Covid-19 Hospitalisation Team (MACH). NHS Grampian is amongst a small leading group of other boards in rolling out this service and we are currently contacting eligible patients to offer screening appointments as well as developing mental health interventions.

NHS Grampian is also moving forward with resources to help staff affected by COVID-19 disease. NHS Grampian's *We Care* programme is expanding to address the identified needs of staff affected by the pandemic, which will include the better identification, understanding and management of 'Long COVID'. There is therefore a significant overlap in the NHS Grampian corporate response for staff and the wider clinical strategy. This underlines the importance and centrality of addressing the longer-term effects of COVID-19 disease for both staff and patients alike.

Embedding research within the scope of the work of the MACH team is very important. There is a lot that remains unknown about the COVID-19 disease and meaningful inquiry about associated long term effects is an important and pressing issue.

Patients suffering with the long-term sequelae of COVID-19 disease will have a range of needs. In particular, a pressing concern for them is cognitive change. Within NHS Grampian we have heard this reported anecdotally by significant numbers of patients who have been seen in the MACH clinics so far. The prevalence of cognitive change, specifically impaired recall, has been estimated at 25% of patients from 12 to 18 months after SARS-CoV2 infection (Becker et al., 2021). In a recent large meta-analysis it was found that 32% of patients reported fatigue and 22% had evidence of cognitive impairment 12 weeks or more after SARS-CoV2 infection (Ceban et al., 2022).

We plan to offer neuropsychometric testing to all patients who report persistent cognitive symptoms in order to better understand the particular pattern, or phenotype, encountered by patients. It will be important to consider why it is that some patients report prolonged symptoms in general and prolonged cognitive symptoms specifically. Neuroimaging, and spectroscopy specifically, could start to provide answers to these questions.

The proposed project will enable research into a common adverse outcome of COVID-19 disease, which has both national recognition and significant morbidity (Ceban et al., 2022).

STUDY AIMS AND OBJECTIVES

AIMS

- To document brain structure and metabolism via spectroscopy in patients who have been hospitalised with COVID-19 disease and who subjectively and objectively evidence cognitive impairment
- To assess cognitive performance in patients reporting cognitive deterioration following hospitalisation for COVID-19 disease
- To outline associations between MR Imaging and spectroscopy data and cognitive test performance

Primary Objective
To report the association (present or not) between MR imaging and spectroscopy measures and cognitive performance following hospitalisation for COVID-19 disease.

Secondary Objectives
To report the level of cognitive performance as measured by formal neuropsychometric assessment.

ENDPOINTS

Primary Endpoint

The primary endpoint is MR imaging and spectroscopy associations with measured cognitive performance.

Secondary Endpoint

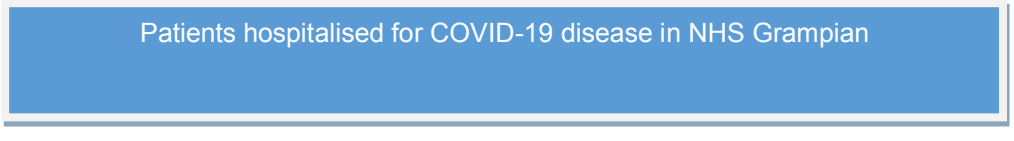
- Metabolic profile of selected brain regions via MRS
- White matter assessment via Tract Based Spatial Statistics (TBSS)
- Brain iron levels (proxy for inflammation) in regions reported to be related to memory performance

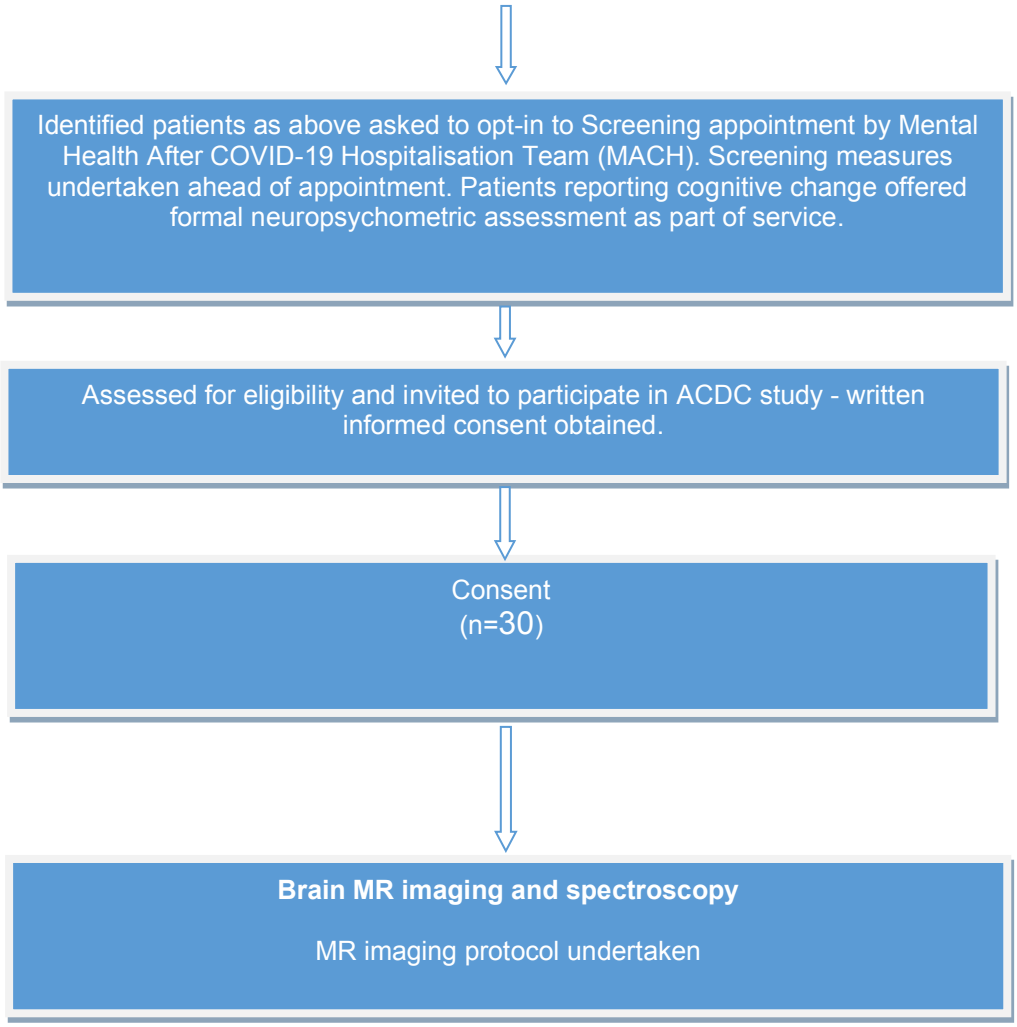
STUDY DESIGN

The project will be a pilot study. The study is cross-sectional in design.

The study design and outcomes measures are illustrated in ***Figure 1.***

Figure 1





IDENTIFYING PARTICIPANTS

Potential participants will be identified by the Mental Health After COVID-19 Hospitalisation Team (MACH) who will discuss the research with the patient. This will be done at an in-person or remote mental health screening appointment for patients who have opted in and have returned mental health and cognitive change screening measures. This represents standard care and is not study specific screening. Similarly, all patients who report cognitive change are being offered neuropsychometric testing as part of standard care. The screening measures used are as follows:

EQ-5D-5L Health Questionnaire
FACIT Fatigue Scale (version 4)
Psychological and Cognitive Changes since having COVID-19
Cognitive Change Index (CCI-20-S)
GAD-7 Anxiety
PHQ-9 Depression
Core-10 questionnaire
Trauma screening questionnaire (TSQ)

On attending their standard of care screening appointment any patient who meets the eligibility criteria for the study will be provided with a Participant Information Leaflet outlining the purpose of the research along with an Invitation Letter and several ways of contacting the research team: a pre-paid reply envelope, an email address (gram.mach@nhs.scot) and the telephone number of the MACH team (01224 551998). All patients who report cognitive change will be offered neuropsychometric testing as part of standard care. This will be organised after the initial screening appointment for eligible patients. This neuropsychometric testing will be undertaken at a further standard of care appointment and it will be face to face. The following neuropsychological tests are to be undertaken:

- Wechsler Test of Adult Reading (WTAR)
- California Verbal Learning Test, Third Edition. (CVLT-3)
- The Logical Memory subtest of the Wechsler Memory Scale, 4th Edition (WMS-I)
- Rey-Osterrieth Complex Figure Test (ROCFT)
- Digits Backwards & Forwards Span from the Wechsler Memory Scale, 4th Edition (WMS-IV)
- Elevator Counting & Elevator Counting with Distraction subtests of the Test of Everyday Attention (TEA)
- Verbal Fluency Subtest of the Delis-Kaplan Executive Functioning System (D-KEFS)
- Hayling & Brixton Tests
- Zoo Map Subtest of the Behavioural Assessment of Dysexecutive Syndrome (BADS
- Colour Trails Test

Premorbid Functioning
Wechsler Test of Adult Reading (WTAR)
This is a measure of pre-morbid functioning as vocabulary strongly correlates with overall ability level and is relatively unaffected by most non-aphasic brain disorders. 50 irregular words are presented and individuals' ability to correctly pronounce them suggests prior knowledge of them. The WTAR was co-normed among a US and UK sample for ages 16-89 years.

Memory
California Verbal Learning Test, Third Edition. (CVLT-3)
This measures both immediate and delayed memory abilities. The examiner reads List A words 5 times, followed by an interference List B. Participants engage in 'free'

and ‘cued’ recall of List A items. Thereafter, there is a 20 minute ‘long delay’ which measures recall of List A under the same two conditions of ‘free’ and ‘cued’. The measure was created to assess the use of semantic associations when learning words and as a screen for memory impairments. The 3rd edition was standardised on a large sample of adults (ages 16-90) based on the 2015 US Census data.

The Logical Memory subtest of the Wechsler Memory Scale, 4th Edition (WMS-I).
This test measures verbal memory and learning. Individuals are told a story and they are required to recall as much as possible immediately and after a 20–30-minute delay. The test is sensitive to detect subtle memory changes among individuals with mild cognitive impairment.

Rey-Osterrieth Complex Figure Test (ROCFT)
This primarily measures visual memory and visual-spatial constructional ability. Participants are shown a complex figure and asked to copy it, then the original image is removed. Participants complete an immediate recall followed by a delayed recall of 20-30 minutes. Internal reliability coefficients [Cronbach alpha (α)] for copy condition is greater than α =0.60, and greater than α =0.80 for both immediate and delayed recall conditions.

Digits Backwards & Forwards Span from the Wechsler Memory Scale, 4th Edition (WMS-IV)
This will measure working memory.

Attention
Elevator Counting & Elevator Counting with Distraction subtests of the Test of Everyday Attention (TEA)
These two subtests are widely used clinically and are ecologically valid measures of sustained and selective attention. During elevator counting, individuals establish which imagined floor they are on by counting a series of seven strings of tones. Elevator with distraction requires individuals to count the same pitched tones from the previous test while ignoring higher pitched distractor tones. This replicates the auditory distractions individuals hear in daily life.

Executive Function
Verbal Fluency Subtest of the Delis-Kaplan Executive Functioning System (D-KEFS)
Verbal fluency measures an individual’s ability to produce fluent speech as well as ‘executive’ aspects of verbal behaviour including cognitive flexibility. Assessment of this includes letter, category fluency with switching. Fluency tests have demonstrated sensitivity to acute deficits following mild-traumatic brain injury (mTBI).

Hayling & Brixton Tests
These tests include the Hayling Sentence Completion Test and the Brixton Spatial Anticipation Test as measures of inhibition and rule-attainment involving set shifting, respectively. These tests are quicker to administer and less taxing than other measures of executive functioning such as the Wisconsin Card Sorting Task or the Tower of London. The measures are normed for ages 18-80, used in a variety of populations both clinically and in research and demonstrate reliability and psychometric validity.

Zoo Map Subtest of the Behavioural Assessment of Dysexecutive Syndrome (BADS)

The Zoo Map subtest will measure planning abilities. Participants have two attempts to plan a route through a zoo while adhering to sets of rules and varying amount of instructions. Penalties are imposed for rule breaks and lack of speed. The test demonstrates adequate discriminant and ecological validity.

Processing Speed

Colour Trails Test

This test will assess processing speed as well as non-verbal aspect of sustained and divided attention. Participants are asked to connect digits within circles in ascending numerical order, beginning with 1 to 25. In Part 2, participants connect digits within circles with alternate colour and completion times are recorded for each trial. Adult version is for ages 18-89. Normative data is based on a sample of 1528 healthy volunteers across various ethnicities.

CONSENT and ENROLLMENT

Once a patient has indicated that they are interested in participating in MR imaging and analysis the research nurse or team member will contact the patient. The research team member will provide them with a written and verbal explanation of the study aims and detail on the exact nature of the study, the implications and constraints of the protocol and any risks involved in taking part. It will be clearly stated that the individual is free to withdraw from the study at any time for any reason, without prejudice to future care, and with no obligation to give the reason for withdrawal. Written informed consent will be taken by a member of the research team trained in research consent procedures. This will be done face to face on the day of the study visit. Subsequent to this the research team member will get in contact to arrange the study visit.

PARTICIPANTS:

Inclusion Criteria

- A patient who has been hospitalised with COVID-19 disease (with a positive Polymerase Chain Reaction (PCR) result for SARS-CoV2 infection) within NHS Grampian hospitals with subsequent subjective reporting and objective evidence of cognitive change.
- Patients aged over 18.
- Patient has completed neuropsychometric testing protocol as described above.
- Participant who is willing and able to give informed consent for participation in the study.

Exclusion Criteria

- Any patient whose physical condition will preclude them from lying still for the duration of the brain scan.
- Contraindication to magnetic resonance scanning such as an implantable cardiac device.
- Patients who required intensive care treatment for SARS-CoV2 infection.

- Patients with a pre-existing diagnosis of a Neurodegenerative disease (eg. Dementia), Intellectual Disability, previous moderate/severe brain injury or previous brain injury with noted cognitive change.
- Patients with a pre-existing neuro-inflammatory disorder (eg. Multiple Sclerosis).
- Patients under investigation for, or with a history of, cognitive change prior to hospitalisation with COVID-19 disease.
- Patients with a dependency on alcohol or recreational drugs.

PROCEDURE:
Participants who have expressed their interest to take part will be contacted by a member of the research team to discuss the date of their study visit, which will take place at the University of Aberdeen research MRI facility, Aberdeen Royal Infirmary Foresterhill. The potential participant will be asked about possible COVID-19 symptoms prior to proceeding with the study visit so as to ensure robust infection control measures.

Study visit:

The patient will be asked to sign an informed consent form to enter the study. This will be taken on the day of the scan.

Participants will be asked to complete an MRI safety questionnaire prior to the scanning visit and this will be checked again on the day of their study visit. They will be met by a researcher at the MRI facility and will be consented prior to scanning. The scan may involve the participant changing into some loose-fitting clothing, usually a set of scrubs. These will be provided for the participant on the day if needed.

During the study visit the following will take place:

Brain magnetic resonance imaging and spectroscopy
Brain MRIs will be performed using a Philips Ingenia dStream 3T scanner. The protocol will include high resolution structural images (3D T1-weighted, T2-weighted, susceptibility weighted imaging (QSM), fluid attenuated inversion recovery (FLAIR) and diffusion weighted imaging (DWI/DTI)) and a resting state functional sequence. These sequences allow us to detect clinically significant features such as lacunes, extended perivascular spaces, cortical and subcortical infarct, white matter hyperintensities and microbleeds. The 3D T1-weighted images will allow volumetric analysis while FLAIR images will allow quantification of white matter hyperintensity lesion load and DTI will enable computation of white matter structural integrity. Quantitative susceptibility mapping (QSM), sensitive to iron deposition, will be acquired with a multi-echo gradient-echo pulse sequence. Metabolic profile will be quantified from spectrum acquired using single voxel Point RESolved Spectroscopy (PRESS) sequence from 3 targeted regions previously reported to be involved in cognitive decline after COVID-19.

WITHDRAWAL PROCEDURES

Participants are free to withdraw at any time during the study without having to give a reason. Should this occur, additional participants will be recruited to fill in the gaps, but this is not expected to be a significant number. Some participants may consent to participate but may not wish to have a particular test done. These patients will be excluded from the study.

DATA COLLECTION

Clinical data will be entered onto a CRF and then stored electronically on University of Aberdeen managed computer systems by the research team.

Results from the analysis of scans/cognitive tests will be stored electronically on University of Aberdeen and NHS Grampian managed computer systems by the research team. Anonymised data will be transferred between servers, where necessary, using the ZendTo software facility.

Data collected from participants will be stored in an anonymised fashion with the use of unique participant identification numbers. Relevant data will be exported into a csv file and analysed using R software. Consent forms pertaining to the study will be kept in a locked filing cabinet in the Aberdeen Biomedical Imaging Centre. Data generated in the study will be kept for a minimum of 6 years and Dr Jonathan McLaughlin will act as custodian for the data.

The CI and study staff involved in this project will comply with the requirements of the General Data Protection Regulations (GDPR) and the Data Protection Act 2018. The Health Research Authority (HRA) recommended working to fulfil transparency requirements under the GDPR for health and care research has been included in the PIS.

The sponsor is responsible for ensuring that trial data is archived appropriately. Essential data shall be retained for a period of at least 6 years following close of study.

SAMPLE SIZE CALCULATION

The study, envisaged as a pilot will compare n=30 patients. We will recruit from the Mental Health After COVID-19 Hospitalisation Team (MACH). We will work to achieve full data for 30 patients and the retention rate is envisaged to be high given the single study visit. Retention should be further bolstered in that only patients who have already completed neuropsychometric testing will progress forward to have the MR imaging.

Power calculations: Sample size and power calculations are not possible at the pilot stage however our sample size of 30 will ensure a spread of measurements to allow us to estimate effects sizes and aid planning for future studies.

COMPLIANCE AND LOSS TO FOLLOW-UP

In the STRADL study (Habota et al. 2019), where 1188 participants were tested, compliance was 90% for brain imaging, 97% for laboratory samples and 99% for cognitive tests. We expect similar compliance in the current study.

POTENTIAL RISKS AND HAZARDS

Magnetic resonance imaging is very safe and there are no known side effects. The scan is noisy and we provide headphones to protect the participants' ears. The study participant will be able to speak to the radiographer during the scan..

For female participants of child bearing age where there is a possibility of pregnancy there will be a requirement for a negative pregnancy test prior to undertaking the scan. If this is not possible the scanning will not go ahead.

It is possible that an unexpected health problem could be found on the tests. However, if this is the case, the participant will be notified and the results will be passed on to the participant's General Practitioner (GP) and/or other relevant health professional, along with any recommendations for treatment that may be necessary.

PROPOSED ANALYSES

Data will be analysed using R as follows. Using the multi-echo gradient echo phase and magnitude data we will determine a marker of in-vivo brain iron concentration by Quantitative Susceptibility Mapping (QSM) (Betts et al., 2016). Cortical sub-structures where associations have previously been found between cognitive performance and iron deposition (Spence et al., 2020) will be extracted from high resolution T1-weighted MR scans by the FreeSurfer image analysis suite. The mean iron induced susceptibility (a marker of iron concentration and therefore brain inflammation) in each cortical sub-structure will be determined. Morphological brain measures such as cortical and sub-cortical volumes will also be extracted. A composite score will be determined from the cognitive tests by principal component analysis. The spectrum will be processed in jMRUI software for phase correction, apodisation, with spectral peak amplitude of brain metabolites subsequently quantified using the Advanced Method for Accurate, Robust and Efficient Spectral fitting of MRS data with use of prior knowledge (AMARES) algorithm. Associations between cognitive performance, regional iron deposition, volume, markers of small vessel disease and brain metabolism will be determined using a general linear approach while correcting for confounding variables such as age and BMI.

STUDY MANAGEMENT AND OVERSIGHT ARRANGEMENTS

The principal applicant and the co-applicants will supervise the MACH team members and Research Nurse and monitor study progress. The Research Nurse will

be responsible for the study log, storing/filing regulatory documents and patient documents as per GCP guidelines.

The Research Nurse will be responsible for checking the CRFs for completeness, plausibility, and consistency. However, this remains the overall responsibility of the CI. Any queries will be resolved by the CI or delegated member of the study team.

A study-specific Delegation Log will be prepared detailing the responsibilities of each member of staff working on the study.

The study management group will consist of Study Group detailed at the start of this document. This group will oversee the conduct and coordination of the study.

INSPECTION OF RECORDS

The CI, PIs and all institutions involved in the study shall permit study related monitoring, audits, and REC review. The CI agrees to allow the Sponsor, or representatives of the Sponsor, direct access to all study records and source documentation.

GOOD CLINICAL PRACTICE

Ethical Conduct of the Study

The study will be conducted in accordance with the principles of Good Clinical Practice (GCP). All staff must hold evidence of appropriate GCP training or undergo GCP training and this will be updated as needed throughout the study.

In addition to Sponsorship approval, a favorable ethical opinion will be obtained from the appropriate REC and appropriate NHS R&D approval(s) will be obtained prior to commencement of the study.

Confidentiality

All results, questionnaires, reports, and other records will be identified in a manner designed to maintain participant confidentiality. All records will be kept in a secure storage area with limited access to study staff only. Clinical information will not be released without the written permission of the participant, except as necessary for monitoring and auditing by the Sponsor or its designee. The CI and study staff involved with this study will not disclose or use for any purpose (other than performance of the study) any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the Sponsor or its designee will be obtained for the disclosure of any said confidential information to other parties.

The CI and study staff involved with this study will comply with the requirements of the UK Data Protection Laws with regard to the collection, storage, processing and disclosure of personal information and will uphold the Data Protection Act's core principles. The CI and study staff will also adhere, if appropriate, to the current version of the NHS Scotland Code of Practice on Protecting Patient Confidentiality. Access to collated participant data will be restricted to the CI and appropriate study staff.

Computers used to collate the data will have limited access measures via usernames and passwords.

Published results will not contain any personal data that could allow identification of individual participants.

Adverse Events

An adverse event (AE) is any untoward medical event affecting a study participant. Each AE will be considered for severity, causality or expectedness and may be reclassified as a serious event or reaction based on prevailing circumstances.

A serious adverse event (SAE) is any AE which;

- Results in death
- Is life threatening (i.e. the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect

All AEs and SAEs will be recorded from the time a participant consents to join the study until the day of completion of their scan.

The Investigators will interrogate notes and other available clinical documentation, and sometimes question participants directly, to discern details of the occurrence of AEs/SAEs. If there is any doubt as to whether a clinical observation is an AE, the event should be recorded.

This is a low-risk study and involves no interventional procedures. Only AEs and SAEs directly linked to the undertaking of the MR imaging protocol will be recorded. All safety procedures and checks around MR imaging will be implemented and adhered to. Dr Gordon Waiter serves as MR safety expert for NHS Grampian.

In the event of an AE or SAE this will be recorded initially and then reported to the sponsor as per SOP UoA-NHSG-SOP-014. Follow up information will also be reported to the sponsor in line with the aforementioned SOP.

INSURANCE AND INDEMNITY

NHS Grampian is sponsoring the study.

Insurance:

- Grampian Health Board will maintain its membership of the Clinical Negligence and Other Risks Insurance Scheme ("CNORIS") which covers the legal liability of Grampian in relation to the study.

- Where the study involves University of Aberdeen staff undertaking clinical research on NHS patients, such staff will hold honorary contracts with NHS Grampian Health Board which means they will have cover under NHS Grampian's membership of the CNORIS scheme.

Indemnity:
The Sponsor does not provide study participants with indemnity in relation to participation in the Study but has insurance for legal liability as described above.

STUDY CONDUCT RESPONSIBILITIES

Protocol Amendments, Deviations and Breaches

The CI will seek approval for any amendments to the Protocol or other study documents from the Sponsor, REC and NHS R&D Office(s). Amendments to the protocol or other study docs will not be implemented without these approvals.

In the event that a CI needs to deviate from the protocol, the nature of and reasons for the deviation will be recorded in the CRF, documented and submitted to the Sponsor. If this necessitates a subsequent protocol amendment, this will be submitted to the Sponsor for approval and then to the appropriate REC and lead NHS R&D Office for review and approval.

In the event that a serious breach of GCP is suspected, this will be reported to the Sponsor immediately using the form "Breach Report Form".

STUDY RECORD RETENTION

Archiving of study documents will be on NHS Grampian premises in line with the Sponsor's Standard Operating Procedure (SOP). At the end of the study the NHS Grampian archivist will be contacted to arrange appropriate archiving.

END OF STUDY

The end of study is defined as that point at which the final participant has undergone the scanning protocol. . The Sponsor and the CI have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the Sponsor and REC within 90 days, or 15 days if the study is terminated prematurely. The CI will ensure that any appropriate follow up is arranged for all participants.

A summary report of the study will be provided to the Sponsor and REC within 1 year of the end of the study.

REPORTING, PUBLICATION AND NOTIFICATION OF RESULTS

Authorship Policy

Ownership of the data arising from this study resides with the study team and their respective employers. On completion of the study, the study data will be analysed and tabulated, and a clinical study report will be prepared.

Publication

The clinical study report will be used for publication and presentation at scientific meetings. Investigators have the right to publish orally or in writing the results of the study.

Summaries of the results will also be made available to Investigators for dissemination within their clinical areas and clinics (where appropriate and according to their discretion). Results would also be presented at the national level to the Mental Health after COVID-19 Hospitalisation (MACH) national steering committee. Other forums for dissemination would also be envisaged including potentially to 'Long COVID' patient bodies via local and national platforms.

Peer review

Peer review of this protocol, and the antecedent funding application, has been sought from University of Aberdeen academic staff as well as NHS Grampian clinical staff.

APPENDIX 1: References

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