Statin TReatment for COVID-19 to Optimise NeuroloGical recovERy

An international, investigator initiated and conducted, pragmatic clinical trial to determine whether 40mg atorvastatin daily can improve neurocognitive function in adults with long COVID neurological symptoms

STUDY PROTOCOL

Version 12 May 2021

CONTACT DETAILS
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Investigator Agreement

I have read the following protocol:

Protocol Title: Statin TReatment for COVID-19 to Optimise NeuroloGical recovERy (STRONGER)

Version and Date: Version 2.0, 12 May 2021

I have read this protocol and associated procedure manuals and agree that it contains all the necessary details for carrying out the study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of the study. I will discuss this material with them to ensure that they are fully informed regarding the study intervention and the conduct of the study.

Name of Investigator (Printed)

Investigator's Signature | Date (Day / Month / Year)

Name of Institution (Printed)

Prof Craig Anderson **Chief Investigator**	12 May 2021	Signature
Prof Mark Woodward **Principal Trial Statistician**	12 May 2021	Signature

Contents

Glossary of Abbreviations & Terms

Abbreviation	Definition
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BP	Blood Pressure
CCC	Central Coordinating Centre
cGMP	Current Good Manufacturing Practices
COVID-19	Coronavirus Disease 2019
CRP	C Reactive Protein
D-KEF-CWIT	Delis-Kaplan Executive Functioning System "Stroop" Colour-Word Interference Test
dMRI	Diffusion-Weighted Magnetic Resonance Imaging
DSMB	Data & Safety Monitoring Board
EC	Ethics Committee
eCRF/CRF	Electronic Case Report Form – also referred to as IBM Clinical Development or database
eGFR	Estimated Glomerular Filtration Rate
EQ-5D-5L	EuroQoL 5-Dimensional 5-Level Questionnaire
FDA	Food & Drug Administration
FOD	Fibre Orientation Distribution
GAD-7	General Anxiety Disorder 7 Questionnaire
GP	General Practitioner
HDL	High-Density Lipoprotein
HR	Heart Rate
HRQoL	Health-Related Quality of Life
ICH-GCP	International Conference on Harmonisation guidelines for Good Clinical Practice
ICMJE	International Committee of Medical Journal Editors
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ITT	Intention to Treat
LDL	Low-Density Lipoprotein
Long COVID	Signs/symptoms ≥12 weeks after infection with COVID-19, not otherwise explained
MoCA	Montreal Cognitive Assessment
MRI	Magnetic Resonance Imaging
NHMRC	National Health & Medical Research Council
NPS	National Prescribing Service
OTMT-A & B	Oral Trail Making Test A & B
PCR	Polymerase-Chain-Reaction
PHQ-9	Patient Health Questionnaire-9
PISCF	Participant Information Sheet & Consent Form
PROBE	Prospective, Randomised, Open-Label, Blinded Endpoint
PSQI	Pittsburgh Sleep Quality Index
RAVLT-D	Rey Auditory Verbal Learning Test – Delayed Recall
SAE	Serious Adverse Event
SAMS	Statin-Associated Muscle Symptoms
SARS	Severe Acute Respiratory Syndrome
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SC	Steering Committee
SD	Standard Deviation
SDMT	Symbol Digit Modalities Test
SF	Semantic Fluency
SPHERE	Somatic & Psychological Health Report
STAREE	Statins in Reducing Events in the Elderly
STRONGER	Statin TReatment for COVID-19 to Optimise NeuroloGical recovERy
SUSAR	Suspected Unexpected Severe Adverse Reaction
TGA	Therapeutic Goods Administration

Abbreviation	Definition
TGI	The George Institute for Global Health
ULN	Upper Limit of Normal

1 Version History

Version Number	Version Date	Summary of Revisions
1	20 April 2021	Original
2	12 May 2021	Section 2.3.2 – Update pharmacy for study drug Section 3 – Further details added to inclusion and exclusion criteria Section 6.4 – Further details added to Inclusion criteria Section 6.6. – Further details added to Schedule of Evaluations Section 6.7.2 – Clarification and update of procedures at Visit 1 – Screening, Baseline and Randomisation Section 6.7.4 - Further details added to Visit 3 - 6 months Section 6.7.6 - Further details added to Visit 5 – End of Study 18 months Section 6.8.1 - Further details added to the SPHERE questionnaire Section 6.8.2 - New assessment details added on the Blind MoCA Section 6.8.4 – Further details and clarifications added to Other Health Assessments Section 6.9.2 – Further details added to MRI scanning Section 6.10 – Clarifications and further details added to Communications with Health Care Providers Section 7.2 – Further details added on Blinding Section 7.4 – Further details added on NPS process Section 7.5 – Further details and clarifications added on Permanent Discontinuation of Study Treatment Section 8 – Further details and clarifications added to Concomitant Medications Section 10 – Further details and clarifications added to Co-enrolment of Participants in Other Studies Section 11.2 – New section added on Assignment of Intervention Section 13.1 – Further details and clarifications made to DSMB Section 14.1 – Updates added to 14.1 Manufacturer and Packaging Section 14.3 – Updates added to Distribution and Resupply Appendices – Updates added to Appendix 2- SDMT, Appendix 7 -SF, Appendix 12 – Blind MoCA, Appendix 13 – Sleep Diary, and Appendix 14 – NPS SAMS

2 Administrative Information

2.1 Registration

Statin TReatment for COVID-19 to Optimise NeuroloGical recovERy (STRONGER) will be registered on Clinicaltrials.gov prior to enrolment of any participants.

2.2 Funding

This study is funded by National Health & Medical Research Council (NHMRC) / Rare Cancers Rare Diseases and Unmet Need – Coronavirus Disease 2019 (COVID-19) (Medical Research Futures Fund RG203341).

2.3 Study Management & Oversight

STRONGER is an investigator initiated and conducted study managed by a Central Coordinating Centre (CCC) based at The George Institute for Global Health (TGI) in Sydney, Australia. The study will be overseen by a Steering Committee (SC) comprised of international experts in the fields of neurology, infectious diseases, endocrinology, cardiovascular disease, public health, statistics, epidemiology and clinical trials.

2.3.1 Central Coordinating Centre

The Central Coordinating Centre (CCC) is based at TGI and is comprised of a team of project staff who are responsible for the day-to-day management of the study, including but not limited to: data and project management, committee coordination, assistance with ethics committee and regulatory applications, preparation of protocol and procedures for training, monitoring of data quality and safety, adherence and compliance to protocol, applicable guidelines and regulations, preparation of study data for analysis and publication.

2.3.2 Drug Distribution Centre

Study drug will be appropriately labelled, packaged and couriered to Australian trial participants by Syntro Health, Melbourne, Australia. In Chile, comparable study medication obtained locally will be distributed to participants the pharmacy of the Clínica Alemana de Santiago and Facultad de Medicina Clínica Alemana, Universidad del Desarrollo, Santiago, Chile.

2.3.3 Steering Committee

The Steering Committee (SC) is responsible for the execution of the study design, protocol, data collection and analysis plan, as well as publications. The SC has the right to appoint new members and co-opt others to add to the integrity of the conduct of the study and analyses. The SC will also include the primary grant holders and other experts. The members are: Prof Craig Anderson, Prof Sophia Zoungas, Prof Sharon Naismith, Prof Meng Law, Prof Karin Leder, Dr Ian Harding, A/Prof Ruth Peters, Prof Mark Woodward, and A/Prof Julian Elliott in Australia; and Dr Paula Muñoz Venturelli and Dr Ximena Stecher in Chile. The SC will be chaired by Prof Craig Anderson.

2.3.4 Data & Safety Monitoring Board

An independent Data & Safety Monitoring Board (DSMB) will be constituted. This committee will receive data and will have the power to recommend to the SC potential modifications to study conduct including early discontinuation of the study based on a risk/benefit assessment of the study data. The DSMB will also monitor the occurrence of serious adverse events (SAEs), adverse events (AEs) and adverse events of special interest (AESIs) throughout the study in order to monitor participant safety.

3 Protocol Synopsis

Main Sponsor: The George Institute for Global Health (TGI)	**Trial Registration Number(s):** STRONGER will be registered on Clinicaltrials.gov and ANZCTR
Title of Study: Statin TReatment for COVID-19 to Optimise NeuroloGical recovERy (STRONGER)	
Study Duration: 3 years	**Clinical Phase:** III
Objectives: To determine effectiveness of treatment with 40mg atorvastatin over 18 months on attenuating cognitive decline and neuroinflammatory biomarkers in adults with long COVID neurological symptoms.	
Number of planned participants: 410	
Study Design: Prospective, randomised, open-label, blinded endpoint (PROBE) study of atorvastatin 40mg on top of standard care, in patients with long COVID neurological symptoms.	
Study Treatment: 40mg atorvastatin + standard care or standard care alone	
Inclusion Criteria: 1. Age ≥18 years 2. History of COVID-19 that is confirmed by a positive polymerase-chain-reaction (PCR) test 3. Any ongoing neurological symptoms as a result of COVID-19 (e.g. problems with memory, concentration, sleep disturbance and fatigue) that are identified through administration of the checklist of symptoms on the Somatic and Psychological Health Report (SPHERE) questionnaire, or reported loss of smell (anosmia);[29] 4. Able to fully participate in all procedures, including cognitive assessments 5. Able and willing to provide written informed consent **Exclusion Criteria:** 1. Evidence of dementia and/or significant cognitive impairment on screening (i.e. Blind Montreal Cognitive Assessment [MoCA] score <19/22) 2. Severe co-morbid medical or psychiatric condition that prevents participation 3. History of traumatic brain injury with loss of consciousness (>30 mins) within the last 2 years 4. Ongoing long-term use for a clear indication (e.g. secondary cardiovascular prevention in high-risk individuals) or any contraindication (e.g. previous adverse reaction) of statin use 5. Evidence of severe or significant liver disease, defined as any of the following: acute viral hepatitis; chronic active hepatitis; chronic active hepatitis; cirrhosis; or elevated biochemical function markers i.e. ALT or AST >3x the ULN or eGFR <30mL/min/1.73m^2 6. Creatine kinase (CK) levels > 2x upper limit of normal (ULN) 7. Female of child-bearing potential that is unable or unwilling to use reliable method of contraception, breastfeeding, or planning a pregnancy 8. *For a sub-group of participants undergoing MRI* – any contraindication to MRI due to metallic body parts or claustrophobia 9. Medical history of a disorder that might, in the opinion of the attending clinician, put the participant at significant risk if they were to participate in the trial	
Outcome Measures: ***Primary*** – processing speed, assessed on the oral Symbol Digit Modalities Test (SDMT) ***Key Secondary*** – white matter free water measured on diffusion MRI brain imaging ***Other*** – other components of cognitive function; other health assessments; other MRI markers of cerebral white matter integrity, iron load, cerebral perfusion, and glutathione for oxidative stress; cost-effectiveness compared to standard care ***Safety*** – any SAEs, AEs or AESI including diabetes mellitus, myalgia, myositis, and biochemical abnormalities	

4 Introduction

COVID-19 Pandemic

By early 2021, the COVID-19 pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), had affected approximately 100 million people and caused over 1.8 million deaths, since it emerged in Wuhan, China in late 2019. The epidemiological pattern and clinical spectrum, pathogenesis, and complications in those infected with SARS-CoV-2 and diagnosed with COVID-19 in the acute phase have now been relatively well-described,[1, 2] but there is uncertainty over its long-term health consequences. However, there is increasing recognition that many patients have persistent symptoms, in particular ongoing impairment of cardiorespiratory, mobility, cognitive and psychological function.[3] Although post-acute syndrome is well-recognised in patients recovering from serious illness, particularly those requiring hospitalisation and admission to intensive care units, post-acute COVID-19 syndrome is not just observed in those who have had severe illness and were hospitalised. Studies have shown that up to three-quarters of patients report at least one symptom several months after onset of the infection. The most common symptoms of 'long COVID' are fatigue, muscle weakness, disturbed sleep, and anxiety/depression. Approximately 5-10% of people report neurological symptoms, such as 'brain fog', headaches, poor concentration, and dizziness.[4-8]

COVID-19 & The Brain

Evidence suggests that the brain is often involved in COVID-19,[8-13] as seen in other serious respiratory infections, such as influenza A, Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome. Many SARS patients had altered concentration, memory, and mood, which often persisted long after their physical recovery. COVID-19 patients appear to suffer a similar range of symptoms, subtle cognitive deficits,[10] and abnormalities on brain imaging.[11] This is likely to be due to a complex interplay of mechanisms related to systemic inflammation (i.e. vasculitis and hypercoagulable states), immune processes, and direct viral invasion into the brain (Fig 1). While the subset of patients with severe disease, those who require intensive care and mechanical ventilation, are at greatest risk of acute stroke and neurological complications, many with mild or absent respiratory symptoms complain of non-specific neurological symptoms, anxiety/depression, insomnia and fatigue, which persist beyond the acute infection.

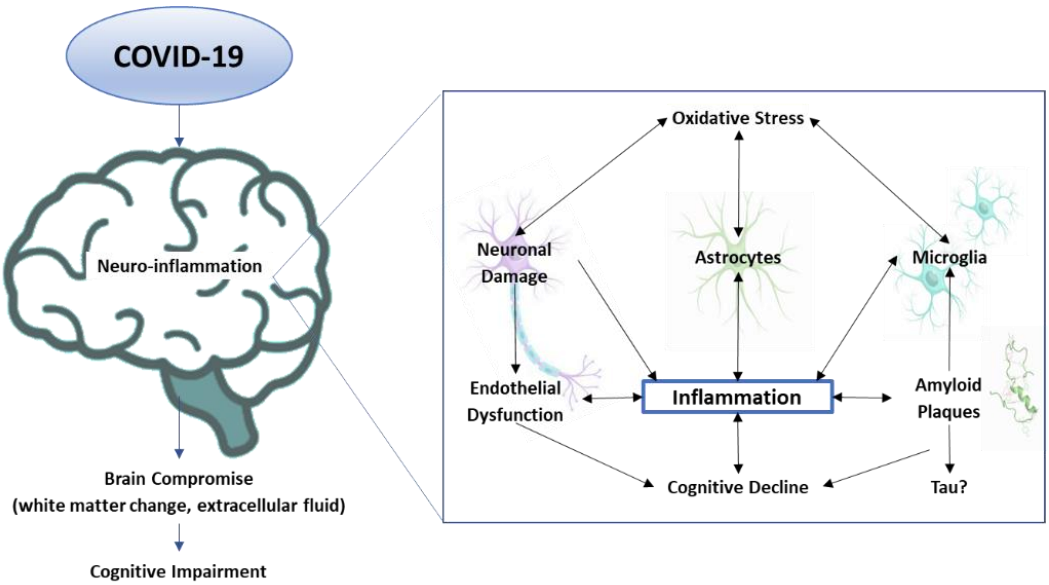


Figure 1: Neuro-Inflammation & COVID-19

COVID-19 Inflammation

Inflammatory cytokines and C-reactive protein (CRP) were important markers of ongoing inflammation in SARS, even after viral clearance. SARS-CoV-2 particles follow a similar pattern of spread via respiratory mucosa and other infected cells, to elicit a cascade of immune responses, sometimes with a detrimental cytokine storm. Direct infection of the brain is not required for neurological sequelae: systemic inflammation and cytokine elevation have been shown to be linked to subsequent hippocampal atrophy and cognitive impairment in sepsis survivors.[14] Late neurocognitive issues are likely after COVID-19 from: (i) direct non-resolving low-grade inflammation or immune reactions in the brain (Fig. 1); and (ii) indirect cerebral injury from hypotension, hypoxia, and metabolic dysfunction from effects on the heart, lungs and other organs. As in other injuries to the brain, full neurocognitive recovery may take several months or years after the initial COVID-19 diagnosis. More concerning is the potential for long-term consequences to brain health, in keeping with contemporary theories of accumulating exposures over the life-course for developing Alzheimer's disease and other neurodegenerative conditions.[15]

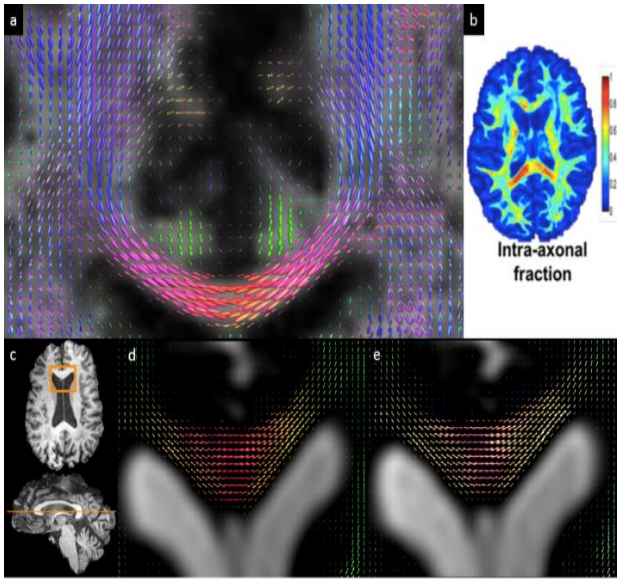


Figure 2: a) Fibre orientation distribution (FOD) estimated on multi-shell diffusion-weighted imaging (dMRI); b) FOD and compartment models allow decomposition of intra-axonal diffusion, extra-axonal diffusion and trapped water to resolve complex crossing fibre maps; c) axial and sagittal MRI showing an area of the corpus callosal genu in a subject who received the neurosteroid allopregnanolone (allo) showing d) baseline FOD and e) post-allo FOD increased intra-axonal fibre density consistent with reduced brain oedema and inflammation, and white matter regeneration. These measures are similarly relevant to the mechanisms of action of atorvastatin.

Brain Free Water & Cognition

Local extracellular fluid changes in the brain, from microglial activation and cerebral small vessel disease, can be readily quantified using non-invasive multi-shell diffusion-weighted magnetic resonance imaging (dMRI) (Fig. 2) in standard clinical settings. So-called 'free water imaging', is a sensitive marker of small vessel disease,[16] cognitive impairment (especially decision-making performance and working memory)[17] and dementia;[18] tracks cognitive function over time;[19] precedes overt white matter hyperintensities; and is a marker of vasogenic oedema, neuroinflammatory gliosis, and/or loss of neuropil or myelin.[20]

Statins & Inflammation

Statins are medications commonly prescribed for the prevention of cardiovascular disease. They inhibit 3-hydroxy-3-methylglutaryl coenzyme A reductase, which controls the rate limiting step in cholesterol biosynthesis conversion to mevalonate. However, statins also have non-lipid lowering effects that are attributed to mevalonate inhibition, which modify the activation of intracellular proteins[21] and have an essential role for intracellular inflammatory signalling and pro-inflammatory cytokine responses (Fig. 3). Human cell culture experiments and animal models have shown that statins reduce the activation of these signalling proteins, which in turn reduces the expression of cytokines, chemokines, acute phase proteins, enzymes, and adhesion molecules. Statins also affect leukocyte-endothelium interactions, modify T-lymphocyte activity, activate natural killer cells, enhance phagocytosis, and inhibit neutrophil oxidative burst and superoxide production, as well as coagulation and thrombosis.

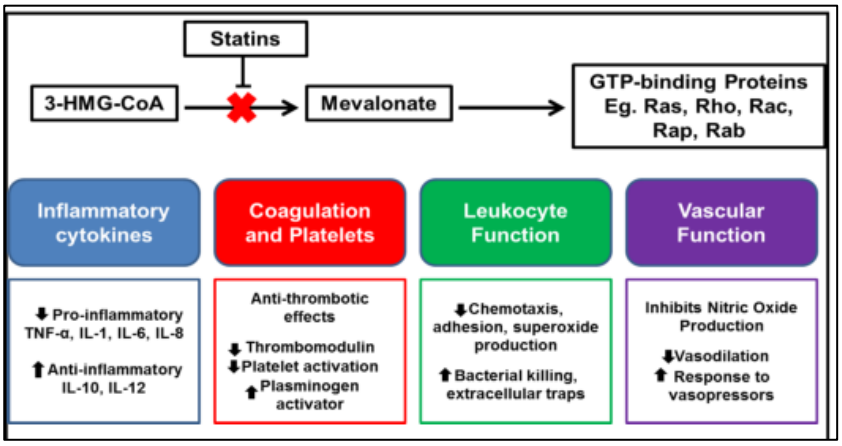


Figure 3: Pleiotropic effects of statins in the context of infection.

Statins & Cognition

Epidemiologic associations of statins and risk of dementia have been reviewed in recent publications, including an update of trials in the Cochrane library,[15, 22-24] which show a lower risk of all-cause dementia and Alzheimer's disease with statin use. However, variability across epidemiological studies and clinical trials appears related to the timing and exposure characteristics for statin therapy modulating the risks of cognitive decline and dementia.[25] There is also evidence of heterogeneity in the effects across different statins, which is missed in clustering of epidemiologic association studies.[26] Atorvastatin is highly lipophilic, which enables it to cross cell membranes including the blood brain barrier.[27] Moreover, it has the greatest effect among the statins in reducing β-amyloid deposition in rodent models of Alzheimer's disease.[28] Several important factors are, therefore, likely to influence the effects of statins in preventing cognitive decline and dementia: type, dose, length of exposure, and time of initiation within the life-course. These data are persuasive enough to justify clinical trials of statin therapy to reduce the risk and/or delay the progression of cognitive decline and degenerative dementia in at-risk individuals. Thus, given the critical role of the neurovascular unit in modifying the brain's susceptibility to injury – regulation of cerebral blood flow, blood brain barrier permeability, trophic support and repair potential – the benefits of statins are more likely to be realised if commenced soon after any acute inflammatory insult.

Summary

Pleiotropic (i.e. lipid-independent) statin effects on suppressing proinflammatory microglia activity and β-amyloid deposition, and promotion of endothelial function, are predicted to attenuate the medium and long-term consequences of COVID-19 on brain health. *Thus, STRONGER aims to determine the clinical benefit of atorvastatin to attenuate cognitive decline and reduce (or stabilise) features of neuroinflammation as evidenced by cerebral white matter free water and other cerebral changes*.

5 Research Question/Aims

Question: Does treatment with 40mg atorvastatin over 18 months attenuate cognitive decline and neuroinflammatory biomarkers in adults with long COVID neurological symptoms?

Aims: In 410 adults who report ongoing alteration of their memory, thinking, concentration or mood after COVID-19 diagnosis, this pragmatic clinical trial aims to determine the effects of standard-dose atorvastatin on improving neurological outcomes with sensitive measures of cognitive function and brain MRI.

6 Methods

6.1 Study Design

STRONGER is an international, investigator-initiated and conducted, multi-centre, prospective, randomised, open-blinded end-point (PROBE) study, with fixed time point for outcome assessments. Participants randomised to the intervention group will receive 40mg atorvastatin for up to 18 months.

6.2 Study Setting

The study sites will be established at centralised research clinics located at: The Brain and Mind Centre of the University of Sydney; Alfred Medical Centre linked to Monash University, and a research clinic associated with Clínica Alemana Universidad del Desarrollo, Santiago, Chile. Additional sites may be set up as required.

6.3 Recruitment

Participants will be recruited from the community in states of Victoria and New South Wales in Australia, and in the city of Santiago, Chile. Other states in Australia may participate if remote assessment is possible, and possibly other countries according to funding and regulatory requirements. Recruitment strategies will include screening of various COVID-19 registries and advertising campaigns via social media, community, pharmacy and community practice sites. Sources of existing registries/databases include:

- St Vincent's Hospital, New South Wales – the ADAPT study, total cohort of 167 patients to date.[6]
- Royal Prince Alfred Hospital, New South Wales – Virtual (hospital-at-home), total cohort of ~1000 patients to date.
- Royal Melbourne Hospital & West Metro, Victoria – COVID-19 Care Pathway, total cohort of ~600 patients across a catchment area covering ~25% of the Melbourne population
- Monash University – NeuroCOVID database, ~20 participants to date
- Monash Health, Melbourne – Hotel quarantine health monitoring program
- TGI/UNSW 'Join Us' – an Australia-wide electronic research registry to recruit adults with chronic disease, including those with COVID-19, to participate in research and involves extensive media outreach.

Participants who meet the eligibility criteria will progress through a 2-stage screening process involving:

a. a telephone call or online preliminary screening, and;
b. an in-person (or remote on-line) more detailed clinical assessment to assess eligibility.

If an individual is eligible, and after having provided informed consent, they will undergo a series of baseline clinical, blood and neuroimaging (a sub-group) assessments in a clinic (or remotely), before being randomised into the study. Reasonable attempts will be made to include a study population with diverse characteristics to enhance the broader generalisation of the results.

6.4 Eligibility Criteria

6.4.1 Inclusion Criteria

1. Age ≥18 years
2. History of COVID-19 that is confirmed by a positive polymerase-chain-reaction (PCR) test
3. Any ongoing neurological symptoms as a result of COVID-19 (e.g. problems with memory, concentration, sleep disturbance and fatigue) that is identified through administration of the checklist of symptoms on the Somatic and Psychological Health Report (SPHERE) questionnaire, or reported current loss of smell (anosmia) as a result of COVID-19;[29]
4. Able to fully participate in all procedures, including cognitive assessments
5. Able and willing to provide written informed consent

6.4.2 Exclusion Criteria

1. Evidence of dementia and/or significant cognitive impairment on screening (i.e. Blind Montreal Cognitive Assessment [MoCA] score <19/22)
2. Severe co-morbid medical or psychiatric condition that prevents participation
3. History of traumatic brain injury with loss of consciousness (>30 mins) within the last 2 years
4. Ongoing long-term use, or clear indication (e.g. secondary cardiovascular prevention in high-risk individuals) or contraindication (e.g. previous adverse reaction) for statin use
5. Evidence of severe or significant liver disease, defined as any of the following: acute viral hepatitis; chronic active hepatitis; cirrhosis; or elevated biochemical function markers, i.e. alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3x the upper limit of normal (ULN) or estimated glomerular filtration rate (eGFR) <30mL/min/1.73m^2
6. Creatine kinase (CK) levels > 2x upper limit of normal (ULN)
7. Female of child-bearing potential that is, unable or unwilling to use reliable method of contraception, breastfeeding, or planning a pregnancy
8. *For a sub-group of participants undergoing MRI* – any contraindication to MRI due to metallic body parts or claustrophobia
9. Medical history that might, in the opinion of the attending clinician, put the participant at significant risk if they were to participate in the trial

6.5 Informed Consent

Potentially eligible participants will be provided with basic information about the study at initial contact and the full participant information sheet and consent form (PISCF) will be provided via email or post on request. Remote consent will be collected either via telephone or via an online portal prior to commencement of the preliminary screening process. Once preliminary screening criteria have been satisfied and the PISCF has been provided, prospective participants will be provided ample time to read and discuss with family/their doctor prior to a attending an in-person clinic visit for assessments.

Participants who have provided remote consent and have agreed to attend the clinic for Visit 1, will be asked to attend the clinic in a fasting state to enable fasting blood tests to be collected. At the clinic, they will be taken through the PISCF by research staff, any potential risks and benefits will be explained and opportunity to ask questions will be provided. A copy of the consent to participate will be given to the participant and another stored on a password-protected and secured drive at each research clinic. Written informed consent must be obtained from all participants before conducting screening assessments in accordance with the International Conference on Harmonisation guidelines for Good Clinical Practice (ICH-GCP) and New South Wales Health Teletrial Standard Operating Procedures.

The PISCF, signed by the participant and the authorised person conducting the consent process, must be the current Ethics Committee (EC)/Institutional Review Board (IRB) approved version. An electronic or printed signed copy will be provided to the participant.
In the case of a remote visit, and if a participant cannot provide an electronic signature, the participant will be asked to sign the informed consent in front of a witness and ask the witness to sign and date. The signed PISCF will be mailed to the study team by the participant via a postage-paid envelope before the videoconference assessment. The process of obtaining informed consent should be documented in the participant's study records.

6.6 Schedule of Evaluations

Table 1: Schedule of Evaluations

Visit Number		0	1	2	3	4	5
Time (Weeks [w]/Months [m])		-1m to 0	0	6w	6m	12m	18m
Window Period		-	-	±1w	±1m	±1m	±1m
Visit Type		Online + Phone	Clinic*	Phone	Clinic*	Phone	Clinic*
Remote / Electronic Informed Consent		X					
In-person Written Informed Consent			X				
SPHERE Questionnaire		X	X				
Blind MoCA		X					
Eligibility – Inclusion/Exclusion Criteria		X	X				
Medical History, Demographics & Socio-Economic Status			X				
Pregnancy Test – where required			X				
Lifestyle – Smoking, Diet, Alcohol			X		X		X
History of Health Service Use for COVID-19/Visits to Medical Professionals			X		X		X
Anthropometrics – Height & Weight			X				X
Blood Pressure, Heart Rate			X		X		X
Fasting Bloods	**Haematology/Electrolytes/Renal/Liver Function** – full blood count, Na, K, urea, nitrogen, creatinine, eGFR, ALT, AST, CK		X				X
	Glucose/Lipids/Inflammation – glucose, total cholesterol, LDL, HDL, triglycerides, CRP		X				X
	Neurodegenerative Biomarkers – 220 participants		X				X
Cognitive Assessments – SDMT, RAVLT-D, OTMT-A, OTMT-B, D-KEF-CWIT, SF			X		X		X
Health Assessments – PHQ-9, GAD-7, PSQI, EQ-5D-5L			X		X		X
Actigraphy plus Sleep Diary – 7-day Capture			X		X		X
Brain MRI – 220 participants			X				X
Dispense Study Medication – treatment arm only			X		X	X	
Study Medication Adherence & Accountability – treatment arm only				X	X	X	X
Concomitant Medications			X	X	X	X	X
SAEs/AESIs				X	X	X	X

*For participants who cannot attend the clinic, efforts will be made for visit assessments to be conducted remotely via tele-/videoconference.

ALT – Alanine Aminotransferase
AST – Aspartate Aminotransferase
CK – Creatine Kinase
CRP – C-Reactive Protein
D-KEF-CWIT – Delis-Kaplan Executive Functioning System "Stroop" Colour-Word Interference Test
GAD-7 – Generalised Anxiety Disorder-7
HDL – High-Density Lipoprotein
LDL – Low-Density Lipoprotein
MoCA – Montreal Cognitive Assessment
MRI – Magnetic Resonance Imaging
PSQI – Pittsburgh Sleep Quality Index
RAVLT-D – Rey Auditory Verbal Learning Test – Delayed Recall
SDMT – Symbol Digit Modalities Test
SF – Semantic Fluency
SPHERE – Somatic and Psychological Health Report

eGFR – estimated Glomerular Filtration Rate
EQ-5D-5L – EuroQoL 5-Dimensional 5- Level Questionnaire
OTMT – Oral Trail Making Tests A & B
PHQ-9 – Patient Health Questionnaire-9

6.7 Visit Summary

In-person visits will be supplemented with telephone interviews to check on a participant's ongoing health status, adherence to study medication, and any AESIs/SAEs, as well as to provide support and appointment reminders. If participants are unable to attend in-persons visits, Zoom based (or telephone) interviews will be undertaken to assess the various health measures, where possible.

6.7.1 Preliminary Screening

Preliminary screening will be conducted via telephone or via an online portal to assess key inclusion and exclusion criteria that can be assessed remotely.

6.7.2 Visit 1 – Screening, Baseline & Randomisation

After preliminary screening, potentially eligible participants who have provided remote consent will be invited to attend a morning appointment at a research clinic in a fasting state to complete the screening process and, if eligible, baseline assessments. (If required e.g. if results of blood tests are not available on the same day, the visit can be split across 2 days). If participants are unable to attend these clinics and are otherwise eligible and willing to participate in the study, efforts will be made to conduct all assessments remotely.

At the screening visit, the following assessments will take place:

- Informed consent
- Eligibility assessment
- Review of participant's demographics, socio-economic status and lifestyle – smoking, diet and alcohol intake
- Review of participant's medical history including health service use
- Measurement of height and weight
- BP and HR
- Blood sample – following an overnight fast
    - Haematology/electrolytes/renal/liver function – full blood count, sodium, potassium, urea, nitrogen, creatinine, eGFR, ALT, AST, CK
    - Glucose/lipids/inflammation – glucose, total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides, CRP
    - *Neurodegenerative biomarkers (sub-study group: 220 participants)*
- Cognitive Assessments
    - Symbol Digit Modalities Test (SDMT), Rey Auditory Verbal Learning Test – Delayed Recall (RAVLT-D), Oral Trail Making Test (OTMT) (A & B), Delis-Kaplan Executive Functioning System "Stroop" Colour-Word Interference Test (D-KEF-CWIT), Semantic Fluency (SF)
    - Cognitive assessments will be undertaken in a separate session within 7-10 days of the clinical assessment by research personnel with skills in cognitive measures. Personnel conducting cognitive assessments will be kept blind to the participants' treatment allocation. Treatment allocation (randomisation) will be undertaken by the research coordinator using the study database following review of the participant's routine blood tests.
- Health Assessments
    - Patient health questionnaire 9 (PHQ-9), generalised anxiety disorder 7 (GAD-7), Pittsburgh sleep quality index (PSQI), EuroQoL 5-Dimensional 5-Level Questionnaire (EQ-5D-5L)
- Provision of actigraphy watch and sleep diary

  - Actigraphy watches and a sleep diary will be mailed to all participants for recording of their physical activity and sleep over a 7-day period in the next 2 weeks, and then returned by courier to a central office for downloading of data.
- *Brain MRI (sub-study group: 220 participants)*
- Randomisation – if eligible
  - After confirmation of eligibility, participants are randomised to receive standard care or study medication (atorvastatin 40mg) according a stratification scheme that involves (see Section 11.2) country, time since the acute COVID-19 illness, age, current anosmia, and participation in the MRI/biomarker substudy ,.
  - Participants will only be informed of their treatment allocation once they have completed all baseline assessments, in order to reduce the risk of differential withdrawal between the two arms.
- Dispense study medication – treatment arm only
  - Study medication will be dispensed in person or via courier in each country; if the latter, an SMS message will be sent by the participant to the regional research office to confirm receipt of study medication. If no message is received, the office will contact the participant by telephone for confirmation.
- Record of concomitant medications

Visit 1 will take approximately 3-4 hours.

All women of child-bearing potential must have a confirmed menstrual period and a negative highly sensitive pregnancy test 7 days or fewer before starting run-in medication and must use a highly effective method of contraception throughout their participation in the study. Highly effective contraceptive methods include hormonal contraception (oral, intravaginal, transdermal, injectable, implantable) or intrauterine device. These methods are not required in the case of bilateral tubal occlusion, vasectomised partner or true sexual abstinence (i.e. within line of the person's preferred and usual lifestyle).

A subset of participants (n=220) will be invited to participate in a sub-study involving:

- the collection and storage of blood for future neurodegenerative biomarker studies, and
- Brain MRI scanning (45 mins).

These additional assessments will be undertaken either the same day or within the next 7-10 days of the baseline clinical assessment, according to booking availability. See Section 6.10 for further information.

6.7.3 Visit 2 – 6 Weeks (± 1 Week) – Telephone

The following will be assessed at the 6-week phone call:

- Review of any SAE/AESIs since last visit
- Adherence to study medication (participant-reported) – treatment arm only
- Changes to concomitant medications

6.7.4 Visit 3 – 6 Months (± 1 Month) – Clinic

The following will be assessed at the 6-month clinic visit:

- Review of any SAE/AESIs since last visit
- BP and HR
- Adherence to study medication (pill count) – treatment arm only
- Changes to concomitant medications
- Review health service use and lifestyle questions
- Cognitive Assessments
    - SDMT, RAVLT-D, OTMT-A, OTMT-B, D-KEF-CWIT, SF
    - Cognitive assessments will be undertaken in a separate session within 7-10 days of the clinical assessment by a separate blinded research person with skills in cognitive measures.
- Health Assessments
    - PHQ-9, GAD-7, PSQI, EQ-5D-5L
- Download of actigraphy watch data
- Collect sleep diary
- Fasting blood tests – routine measures of haematology, biochemistry, renal function, lipids, glucose, and inflammatory markers
- Dispense of study medication (to be sent via courier/mail) – treatment arm only

This visit will take approximately 2-3 hours.

6.7.5 Visit 4 – 12 Months (± 1 Month) – Telephone

The following will be assessed at the 12-month phone visit:

- Review of any SAE/AESIs since last visit
- Adherence to study medication (participant-reported) – treatment arm only
- Changes to concomitant medications
- Dispense of study medication (to be sent via courier/mail) – treatment arm only

6.7.6 Visit 5 – End of Study 18 Months (± 1 Month) – Clinic

The following will be assessed at the 18-month End of Study clinic visit:

- Review of any SAE/AESIs since last visit
- Measurement of height and weight
- BP and HR
- Adherence to study medication (pill count) – treatment arm only
- Changes to concomitant medications
- Review medical history and lifestyle questions
- Blood sample – following an overnight fast
    - Haematology/electrolytes/renal/liver function – full blood count, Na, K, urea, nitrogen, creatinine, eGFR, alanine aminotransferase (ALT), aspartate aminotransferase (AST), CK
    - Glucose/lipids/inflammation – glucose, total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides, CRP
    - Neurodegenerative biomarkers (220 participants)

- Cognitive Assessments
    - SDMT, RAVLT-D, TMT-A, OTMT-B, D-KEF-CWIT, SF
    - Cognitive assessments may be undertaken in a separate session within 7-10 days of the clinical assessment and/or by a separate research person with skills in cognitive measures who remains blind to the treatment allocation.
- Health Assessments
    - PHQ-9, GAD-7, PSQI, EQ-5D-5L
- Download of actigraphy watch data
- Collect sleep diary
- Brain MRI with biomarkers (subset of 220 participants)

This visit will take approximately 3-4 hours.

6.8 Assessment Details

6.8.1 Screening Questionnaire 'SPHERE'

The SPHERE questionnaire will be administered at screening to assess for long COVID symptoms. It is a 34-item self-report questionnaire that was developed to assess symptoms of mental distress and persistent fatigue, with questions selected from other common scales. Participants respond to each of the items, choosing from one of three fixed options ('sometimes/never', 'often', and 'most of the time', which are coded 0, 1, and 2, for calculating a sum score) to describe the frequency of their symptoms over the 'past few weeks'.

This study will use the original 34-item scale to identify any positive response to the three arms of SPHERE: anxiety-depression, somatic distress and persistent fatigue. There is no score threshold for inclusion.

People with anosmia will be included as this is a heterogeneous condition with uncertain relationship to olfactory neuronal circuitry and encephalitis, where neuroimaging and long-term follow-up are required.[30]

6.8.2 Blind MoCA

The Blind MoCA will be administered at screening via telephone to assess for any significant cognitive impairment. The MoCA is a brief screening test for cognitive impairments that has been validated as a remote alternative to the full MoCA that can be administered over the telephone. It is scored out of 22 with a cut-off of N <19 indicating significant cognitive impairment for which subjects will be excluded from participating in the study.

6.8.3 Cognitive Assessments

Cognitive assessments will be administered between 9:30am and 12:30pm. Completion of all assessments will take approximately 40 mins.

Name	Format	Purpose	Assessment	Scoring	Normative Data	Test-Retest Reliability
SDMT	Oral	Assesses frontal lobe executive processing.	Requires participants to match numbers to symbols according to a key, containing 9 abstract symbols each paired with a number. Participants verbalise the correct number.	The number of correct symbols within the allowed time, usually 90 seconds[28]	There are Australian normative data available for the oral SDMT.[29]	The oral SDMT demonstrates excellent test-retest reliability (an intraclass correlation coefficient of 0.89) and only has a small learning effect (Cohen's d = 0.26) within a 1-week interval.[30]
RAVLT-D	Oral No difference in videoconferencing and face-to-face RAVLT–D have been reported.[31]	Assesses memory and learning.[32]	Requires participants to learn a 15-item word list over 5 learning trials, followed by a distractor list, and short and long-delayed recall.	Max score = 15	Australian normative data is available in Carstairs, Shores and Myors (2012).[33]	Test-retest reliability of the RAVLT has been reported, with the most reliable measures being the total number of words learned over the learning trials (r = 0.77), and performance on the retention trial of the learning list following the presentation and performance of the distractor list (r = 0.70).[32]
OTMT-A & B	Oral	Provides information on visual search, scanning, speed of processing, mental flexibility, and executive functions. The OTMT is a sensitive measure of early cognitive decline in relation to vascular-related factors.[34, 35]	Part A – participant is asked to count from 1 to 25 as quickly as possible. In Part B – participant is asked to progressively alternate between counting numbers up to 13 and reciting letters of the alphabet up to L as quickly as possible.	Scores relate to time for completion. The primary performance metric is the time in seconds required to complete each of the two parts of the test.	Age-based norms (for ages 20 to 90) are available in Mrazik, Millis, and Drane (2010).[36]	The OTMT-B demonstrated moderate test–retest reliability Scores showed significant agreement (intraclass correlation = .62, p < .0001), a significant correlation (Pearson r = .62, p < .0001), and similar mean scores (M = 41.85, SD = 32.55; M = 43.40, SD = 30.18) across administrations.[37]

Name	Format	Purpose	Assessment	Scoring	Normative Data	Test-Retest Reliability
D-KEF-CWIT	Oral	A battery of neuropsychological tests designed to measure executive functions in children and adults, ages 8–89. It is based on the Boston process approach[38] which stipulates that there is a primary function that each test is designed to measure, but also that component functions contribute to performance on a particular test.[39]	Four parts: colour naming, word reading, inhibition, and inhibition/switching.[39]	Performance is measured by completion time on each of the four trials. In addition, colour naming and word reading times may be summed for a composite score representing component functions. Three contrast scores (inhibition vs. colour naming, inhibition/switching vs. combined colour naming and word reading, and inhibition/switching vs. inhibition) may be calculated to determine whether there is a disproportionate impairment in a higher-level function than the component function(s).	Australian normative data not available.	The majority of contrast measures demonstrated low reliabilities: of the 51 reliability coefficients calculated in the present study, none exceeded 0.7 and hence all failed to meet any of the criteria for acceptable reliability proposed by various experts in psychological measurement.[40]
SF	Category fluency to animals is valid and reliably assessed via videoconference compared to assessed via traditional face-to-face assessment.[41]	Assesses language processing.	Requires the generation of as many 'animal names' in 1-minute.	Counting the number of correct unique semantic category items produced.	Normative data is available in Chami et al. (2018)[42]	Category fluency to animals demonstrated intraclass correlation coefficient = 0.98.[43]

6.8.4 Other Health Assessments

PHQ-9 & GAD-7

- Brief and validated measures of the presence and severity of depression and generalised anxiety, respectively.[42]
- PHQ-9 is a brief, self-administered, screening questionnaire for depression, which scores each of the nine DSM-V major depression criteria as '0' (not at all) to '3' (nearly every day). It can be used to make a tentative diagnosis of depression in at-risk populations (e.g. those with coronary heart disease or after stroke), whereby participants who score ≥10 are likely to have clinically significant depression.
    - In this study, the PHQ-9 will be used as a continuous measure to monitor the severity of depression and response to treatment.
    - If a participant has scored >10 on Q9 of the PHQ-9, or positively responded to the final question 9 'thoughts that you would be better off dead, or of hurting yourself in some way', a member of the study team will advise them to see their GP (or alternate health care professional as applies in the local context) and a letter will be sent to the treating doctor informing them of the result.
- GAD-7 is a valid and efficient, brief tool for screening for generalised anxiety disorder and assessing its severity in clinical practice and research.[43] A score of ≥10 represents a reasonable cut point for identifying cases of generalised anxiety. Cut points of 5, 10, and 15 might be interpreted as representing mild, moderate, and severe levels of anxiety GAD-7.

PSQI

- Designed to assesses overall sleep quality in clinical populations, covering 19 self-reported items across seven sub-categories: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction;[44] with five additional questions rated by the respondent's roommate or bed partner, if available.
- Administration by self-report and it generally takes 5-10 mins to complete. Scores >5 are generally indicative of poor sleep quality. In this study, the PSQI will be analysed as a continuous measure.

EQ-5D-5L

- Measures HRQoL across five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), each rated according to five levels, as well as providing an integrated utility score for calculating an overall score against population-based preference weights.

Mobility & Sleep

- Participants will also be invited for the home application of actigraphs and a completion of a sleep diary to monitor their sleep-wake and activity patterns over 7-days in the next 2 weeks according to established protocols. These data will be analysed centrally to compute sleep efficiency, nocturnal awakenings, sleep timing, total sleep and activity time. The Sleep diary data are used to assist interpretation of actigraphy results in accordance with recommendations of the American Academy of Sleep Medicine. Actigraphy will also provide a measure of activity, as a proxy for physical activity. Both sleep and physical exercise may be important potential mediators of the primary outcome.

6.9 Sub-Study – Neurodegenerative Markers & MRI

The following assessments will occur in a subset of 220 participants. The assessments will take place at Visit 1 and Visit 5.

6.9.1 Neurodegenerative Markers

Bloods will be collected for measurement of apolipoprotein E, inflammatory and other neurodegenerative markers. The bloods will be collected after an overnight fast (>8 hours) and drawn at 08:00-11:00am according to standardised procedures. The blood will then be immediately centrifuged, and the plasma locally stored at -80°C within 2 hours of collection. The bloods will be shipped at the end of the study for subsequent storage and analysis on a SIMOA immunoanalyser at the Department of Neuroscience (Alfred Hospital Precinct), Monash University, Melbourne, Australia. Key markers of neurodegeneration to be measured include Ptau-181, neurofilament light chain (NfL) and Aβ42/40, and DNA extraction for apolipoprotein E genotype. Peripheral markers of oxidative stress and inflammatory markers relevant to neurodegeneration (IL-6, IL-1β, NAD+, TNF-α, hsCRP) will also be collected for subsequent exploratory analyses.

6.9.2 MRI Scanning

MRI scanning will be undertaken on 3-Tesla clinical scanners at the Alfred Hospital (Melbourne, Australia), Brain and Mind Centre (Sydney, Australia), and the Clínica Alemana (Santiago, Chile). Scan sessions will take approximately 45 minutes and will include acquisition of:

- whole brain 3D T1-weighted, T2-weighted, and fluid-attenuated inversion structural images;
- 2D diffusion-weighted microstructural images;
- 3D pseudo-continuous arterial spin labelling perfusion images;
- 3D susceptibility-weighted images; and
- magnetic resonance spectroscopy in the posterior cingulate.

All scans will be acquired with the participant at rest, with no requirements for contrast or other injections, breath holds or other active engagement. Participant screening and data acquisition will be performed by clinical radiographers at all sites. Following local acquisition, all scans will be securely transferred in DICOM format, and housed on the Monash University XNAT imaging informatics server, Melbourne, Australia.

According to standard procedures , where an abnormal finding is detected on the MRI scan that is deemed by the site radiologist to require clinical follow-up or monitoring (e.g. small cerebral aneurysm, plaque suspicious of multiple sclerosis, small meningioma), the participant will be notified and the report forwarded to the participant's primary care or other physician (i.e. in Australia, a general practitioner [GP]) unless a more urgent follow-up is necessary (e.g. primary or secondary tumour, cerebral aneurysm, arteriovenous malformation); in which case we arrange for a direct referral to a neurologist in addition to GP. In other countries, appropriate follow-up will be arranged in accordance with the local clinical pathways) . Asymptomatic incidental findings (e.g. small spot-like abnormalities in the cerebral white matter) that are not deemed to have clinical relevance are not reported back to participant; because there is variability in what different radiologists will include in their report and it can cause a lot of anxiety for participants without any commensurate benefit.

6.10 Communications with Health Care Providers

The study team will communicate with GPs or alternate designated health care provider (according to local context) via telephone, mail or email (if available), at least three times throughout the study.

1. Prior to participant participation. The study procedures will be briefly explained, including information about the study medication, and any concerns regarding participation will be sought.
    - If at the screening stage, a participant is ineligible for the study or a physical, mental or social health issue has been identified, the GP (or alternate health care provider) will also be advised particularly if further investigations or consultation with the participant may be required.
2. When the participant is randomised to the study.
3. At the end of the trial, regardless of whether the participants have dropped out or completed the trial, GP (or alternate health care providers) will be provided with their participants blood test results and interpreted neuropsychological test results.

7 Study Treatment & Adherence

7.1 Study Treatment

Participants who meet the eligibility criteria will be randomised to receive standard care or 6-monthly supplies of atorvastatin 40mg on top of standard care for a period of 18 months.

7.2 Blinding

Study treatment is open-label. The randomisation allocation will be blinded to researchers conducting cognitive assessments and endpoint adjudicators. All participants, physicians and other study team members will be aware of participant treatment allocation. However, participants will only be informed of their allocation after all the baseline assessments have been completed in order to reduce the risk of differential withdrawal between the two arms.

7.3 Treatment Adherence

To maximise participant adherence to study medication, the following procedures will be implemented:

- Participant education on the importance of taking study medication, including timing, storage, and what to do in the event of a missed dose;
- Returned tablets will be counted and recorded by the study team;
- Participants will be provided with contact details of the responsible researcher so that they can make contact if for any reason they are unable to continue their study medication or have missed multiple doses and are unsure whether to continue.

7.4 Management of Possible Treatment Related Side-Effects

The following strategies (Table 2) can be employed for participants with side-effects deemed due to study medication and sufficiently severe to warrant a change of treatment.

Table 2: Strategies for change in treatment due to side-effects

Clinical Scenario	Strategy
Clear contraindication to a statin	Ineligible
Mild symptoms of myalgia, nausea, dizziness	Temporarily stop study medication. If symptoms improve, restart study medication – subject to investigator's discretion. If symptoms persist, study medication can be permanently stopped.
Moderate-severe symptoms of abdominal pain or myalgia, with/without biochemical or haematological abnormalities	Temporarily stop study medication. Factors to consider include renal impairment and other medications. On improvement, consider re-challenging with study medication and review. If symptoms persist, study medication can be permanently stopped. If severe reaction, permanently cease study medication and begin appropriate alternate treatment in accordance with local guidelines.

For possible or suspected Statin-Associated Muscle Symptoms (SAMS), the National Prescribing Service (NPS) process will be followed (see Appendix 14).

7.5 Permanent Discontinuation of Study Treatment

Permanent discontinuation of study medication is not considered withdrawal from the study and participants should continue to complete all study assessments in accordance with the intention to treat (ITT) principle. Participants who have temporarily stopped study medication for any reason other than the above should be encouraged to restart study medication as soon as practically, and medically appropriate at the discretion of the investigator.

The investigator must not deviate from the protocol, except when there is a contraindication, due to the participant's condition or the participant is intolerant of the study medication, in these cases, the study medication should be temporarily stopped. Study medication should also be temporarily or permanently stopped if:

- there is an SAE, which in the opinion of the investigator, is related to the study medication; **and/or**
- the investigator assesses that it is in the participant's best interest"

8 Concomitant Medications

Investigators are directed to consult the Product Information for atorvastatin for consideration of listed contraindications, special warnings and precautions.

All concomitant medications taken by the participant at screening, baseline and during the study period will be recorded in their study files and entered in the electronic case report form (eCRF). Further instructions about capturing these data will be provided in a procedure manual.

9 Study Withdrawal

If a participant wishes to withdraw or the study team/responsible investigator decides it is in the best interest of the participant to withdraw from further participation in the study, every effort should be made for the participant to report any SAEs to the study team that occur within 4 weeks of their last dose of study medication (as applies), and to attend an end of study visit prior to withdrawal.

10 Co-Enrolment of Participants into Other Studies

Co-enrolment in another investigative drug intervention trial may be considered provided there is agreement between the steering committees of both trials that there are no contraindications or adverse impact on outcomes of either trial. Participants who are enrolled in investigational device, lifestyle trial or observational cohort study, may be included into the STRONGER study at the discretion of the investigator. Co-enrolment of participants into this study is allowed where participants are informed, and there are strategies in place to avoid undue burden on them and/or duplication of research effort through co-operation with other research (trial/s) leaders.

11 Statistical Methods

11.1 Sample Size

A sample of 410 patients will provide 90% power (α=0.05) to detect at least a 0.3 standard deviation (SD) effect size difference between groups, assuming equal group participation. These calculations assume a modest 5% non-compliance and 5% dropout over 18-months of follow-up. The SDMT age-adjusted mean score is estimated at 60 (SD = 13) at baseline (based on healthy control data).[32] The effect is based on statin dementia prevention and multiple sclerosis trials, where achieved effect sizes of 0.3-0.4 are clinically meaningful and likely to confer public health benefits.[45]

11.1.1 Sub-Study Sample Size

For the sub-study, a sample size of 220 (110 per group) is estimated (α=0.05) to provide 80% power to detect effect sizes of relative differences of 5.0-6.5 (variance between groups/variance within groups) for the imaging endpoints, assuming a 20% drop out.

11.2 Assignment of Intervention

Participants will be registered and randomised via a secure web-based database. The randomisation will be stratified by the following factors: (i) country; (ii) time (<6 vs. ≥6 months since acute COVID-19 illness), (iii) age (<60 vs. ≥60 years), (iv) Current anosmia that has occurred in relation to COVID-19, and (v) participation in the MRI/biomarker substudy.

11.3 Statistical Analysis

The study follows the ITT principle for analysis. Baseline characteristics will be summarised by treatment group. The primary endpoint of change on the SDMT score will be summarised by means (SD)/medians (interquartile range), with the treatment effect tested by a Wilcoxon test. Continuous endpoints will be summarised by means/medians. The primary analysis will be through logistic regression models adjusted for region, age and sex. A sensitivity analysis will be undertaken with adjustment for baseline imbalances and clinically meaningful confounders. Descriptive statistics will be provided for safety data, where SAEs and treatment discontinuation will be tabulated using standard terminology. Heterogeneity of treatment on the primary endpoint will be assessed in pre-defined subgroups, such as age, time since COVID-19 diagnosis, baseline CRP levels, ethnicity, and prior cardiovascular risk. Analyses will be specified a priori in a full statistical analysis plan. A modelled cost-utility analysis using trial data (HRQoL, captured by EQ-5D-5L; drug costs; and health service utilisation costs, including AEs) will be conducted comparing use of atorvastatin and

standard care. A 5-year time horizon will be undertaken, with analyses conducted in line with accepted Australian standards for use of economic evaluation in decision-making.

12 Outcomes

12.1 Primary Outcome

The primary outcome is processing speed, assessed by the oral SDMT.

12.2 Key Secondary Outcome

The key secondary outcome is total white matter free water (dMRI) undertaken using data collected in standard procedures using multi-shell diffusion spectral imaging with fibre orientation and compartment modelling. SC members from Monash University have developed a novel computational framework to accurately characterise multi-shell diffusion spectral imaging signals from high b-values whilst retaining the capability of reliably resolving crossing fibres. Three compartments are used to associate brain microstructure to the diffusion signal: an intra-axonal compartment, an extra-axonal compartment, and a third compartment representing the fraction of trapped water molecules with essentially negligible diffusion.

12.3 Other Outcomes

Various other components of cognition; other health assessments and MRI markers of white matter hyperintensity volume, enlarged peri-vascular space volume, total grey matter volume, white matter microstructure (fractional anisotropy), basal ganglia iron load and total cerebral perfusion, and spectroscopy-derived glutathione as a marker of oxidative stress; cost-effectiveness compared to standard care.

12.4 Safety Outcomes

AEs, AESIs and SAEs.

13 Safety

13.1 DSMB

The DSMB will review the safety, ethics and outcomes of the study. The DSMB is responsible for monitoring cognitive and safety outcomes for early dramatic benefits or potential harmful effects and provide reports to the SC on recommendations to continue or temporarily halt recruitment to the study. The DSMB will be governed by a charter that will outline their responsibilities, procedures and confidentiality. They will review unblinded data from the study at regular intervals during follow-up and monitor treatment adherence differences between the two groups, drop-out, and event rates. It is anticipated that the first data review will be conducted after the first 50 participants have achieved 6 months of follow-up, and 6- monthly reviews thereafter.

13.2 Definitions & Reporting

13.2.1 Adverse Events

An AE is defined as any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product at any dose and which does not necessarily have a causal relationship with this treatment. Therefore, an AE can be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational medicinal product (IMP), whether or not it is considered related to the IMP. This definition includes intercurrent illnesses or injuries, and an exacerbation of a pre-existing condition.

13.2.2 AESI

The expected adverse reactions to the study medication that will be used in this study that are of special interest are listed below. To better assess participants' tolerability to the study medications, the following AESIs and whether they are new or ongoing from baseline, will be reported in the eCRF at specified visits, regardless of severity and seriousness:

- myalgia
- nausea
- elevation in blood glucose
- elevation in creatinine kinase
- abdominal pain
- new-onset diabetes mellitus
- rhabdomyolysis

13.2.3 SAEs

An SAE is defined as any untoward medical occurrence that at any dose:

- results in death
- is life-threatening in the opinion of the attending clinician (i.e. the participant was at risk of death at the time of the event; it does not refer to an event that might hypothetically have caused death had it been more severe)
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity
- results in congenital anomaly or birth defect (Note that females in the study are required to take effective contraception)
- is an important medical event in the opinion of the attending clinician that is not immediately life-threatening and does not result in death or hospitalisation, but which may jeopardise the patient or may require intervention to prevent one of the other outcomes listed above.

AEs which do not fall into these categories are defined as non-serious.

If treatment is discontinued as a result of any AE, serious or non-serious, the site study team will document all events leading to the discontinuation of treatment.

If an SAE is unresolved at the conclusion of the study or if the participant withdraws early from the study, a clinical assessment will be made by the medical monitor as to whether continued follow-up of the SAE is warranted.

13.2.4 Suspected Unexpected Serious Adverse Reactions

An unexpected adverse reaction is an adverse reaction, the nature or severity of which is not consistent with the listed side effects in accordance with the applicable product information for atorvastatin.

A suspected unexpected serious adverse reaction (SUSAR) is any unexpected adverse reaction that at any dose meets the definition of an SAE. TGI will be responsible for reporting all SUSARs to regulatory authorities in accordance with country-specific requirements and in compliance with the *International Conference on Harmonisation's Clinical Safety Data Management: Definitions and Standards for Expedited Reporting*.

13.2.5 SAE Reporting Period

All SAEs will be collected from the time the participant is enrolled in the study until the end of the final follow-up visit. To ensure SUSAR reporting requirements are met, site investigators are required to report all SAEs in the study database within 24 hours of becoming aware of an event.

14 Study Drug Management

14.1 Manufacturer & Packaging

The study medication, atorvastatin, will be sourced from Syntro Health, Richmond, Australia, a community pharmacy that specialises in direct to patient (DTP) services and clinical trials in particular. Atorvastatin 40mg has TGA and United States Food and Drug Administration (FDA) approval for general marketing for the treatment of hypercholesterolaemia and cardiovascular prevention under a number of manufacturer names. Although no particular manufacturer will be chosen for this study, the sourced study medication will be consistent across sites where practical. The study medication selected will be the atorvastatin 40mg (Lorstat) which is scored, and allows down-titration to 20mg should a participant develop symptoms. The study medication will be packaged, labelled and dispensed directly to particpants by the Syntro Health pharmacy in Australia. A comparable atorvastatin 40mg is being sourced in Chile, and will be dispensed from the pharmacy of the Clínica Alemana de Santiago and Facultad de Medicina Clínica Alemana, Universidad del Desarrollo, Santiago, Chile.

14.2 Labelling

Country-specific labelling requirements will be followed. Labels will include: (a) name of the sponsor; (b) pharmaceutical dosage form, route of administration, quantity of dosage units (and name/identifier of the product and strength/potency); (c) the batch and/or code number to identify the contents and packaging operation; (d) the trial participant identification number, where applicable; (e) directions for use; (f) “for clinical trial use only”; (g) the name of the investigator (if not included as a code in the trial reference code); (h) a trial reference code allowing identification of the trial site and investigator; (i) the storage conditions; (j) the period of use (use-by date, expiry date or re-test date as applicable), in month/year); (k) “keep out of reach of children”.

14.3 Distribution & Resupply

Syntro Health will manage distribution and resupply of study medication via courier either direct to participant in Australia.

14.4 Storage

The study medication will be stored at ambient temperature (<25°C) and protected from excessive light exposure in a secure area with limited access before distribution to participants.

14.5 Drug Dispensing & Accountability

All study medication dispensed to and returned from participants will be recorded on a dispensing and accountability log, maintained by the STRONGER study staff. Specific details on IMP management will be included in study-specific manuals and plans.

14.6 Disposal & Destruction

All unused and/or expired study medication will be returned to the appropriate STRONGER site for destruction at a suitable facility following accountability, and confirmed and written authorisation from the study team at TGI. A copy of the final signed confirmation of destruction will be provided to TGI by the facility for filing in the Trial Master File. Destruction will be carried out in compliance with the regulatory requirements.

15 Data Management & Quality Assurance

All data entry will be completed via a secure web-based data management system called IBM Clinical Development. Data entry will be performed at the participating sites by authorised site staff who have completed training and been given appropriate role-based access to the system. Data logic and consistency checks will be programmed into the data entry forms so that data entry errors can be caught in real-time and queries auto-generated. Authorised electronic signatures will be used to lock completed data entry forms once all data queries have been resolved within the system. Data entry and all subsequent changes or deletions will be captured in an accessible audit trail. Coding of outcomes will be centrally performed either automatically via the IBM coding module or manually by the CCC. All coding will be reviewed and verified by the Medical Monitor. Reporting within the system will be used for regular data reviews and overall trial monitoring. Data will be stored and backed up on the IBM's cloud servers in the United States.

16 Monitoring & Auditing

16.1 Monitoring

Trial data will be monitored, using central risk-based monitoring principles, to detect any unusual patterns of data that would require further investigation.

During the study, representatives of the CCC will monitor site performance and quality via remote methods including via videoconference to ensure that the study is conducted in accordance with the protocol, ICH-GCP guidelines and relevant ethical and regulatory requirements. Relevant data and source documentation will be archived for a minimum of 15 years.

16.2 Auditing

The study may be audited by third parties and inspected by government regulatory authorities. Paper CRFs, source documents and other study documentation must be accessible at all study sites at the time of auditing for inspection during and after the completion of the study. If an inspection is requested by a regulatory authority, the investigator must inform TGI immediately after this request has been made.

17 Regulatory & Ethical Considerations

17.1 Regulatory & Ethical Compliance

This study protocol was designed, and shall be implemented and reported, in accordance with the ICH-GCP, NHMRC National Statement on Ethical Conduct in Human Research, and with the ethical principles laid down in the World Medical Associations Declaration of Helsinki.

The protocol and the proposed PISCF and any subsequent modifications will be reviewed and approved by an EC before any participants are enrolled. Prior to study start, investigators are required to sign a protocol signature page confirming their agreement to conduct the study in accordance with these documents and all the instructions and procedures found in this protocol and to give access to all relevant data and records to TGI monitors, auditors, EC, and regulatory authorities as required.

17.2 Protocol Amendments

A protocol amendment is a written description of change(s) to, or formal clarification of a study protocol which may impact on the conduct of the clinical study, potential benefit of the clinical study, or may affect participant safety, including changes of study objectives, study design, participant population, sample size, study procedures, or significant administrative aspects. An administrative change of a study protocol is a minor correction or clarification that has no significant impact on the way the study is to be conducted and no effect on participant safety (e.g. change of telephone number(s), logistical changes). Protocol amendments must be approved by the SC and the EC. In cases when the amendment is required in order to protect participant safety, the amendment can be implemented prior to EC approval. Notwithstanding the need for formal approval of a protocol amendment, the investigator is expected to take any immediate action required for the safety of any participant included in this study, even if this action represents a deviation from the protocol. In such cases, TGI should be notified of this action.

17.3 Informed Consent

Before the start of the study, a member of the study team will have the PISCF and any other materials that will be provided to the participants reviewed and approved by the EC. This review and approval will be documented and stored with other study documents.

Potential participants may only be included in the study after providing in-person written or online/remote verbal and written informed consent. The responsible study team member must fully inform the participant of all relevant aspects of the trial. The participant must be allowed ample time to ask details about the study, and to make a decision as to whether or not to participate. The participant must personally or electronically sign the PISCF indicating their agreement to participate in the study. An electronic copy of the signed PISCF will be provided to the participant.

17.4 Confidentiality

Every precaution will be taken to respect the privacy of participants in conduct of the study. Only de-identified data will be entered in the study database to maintain participant confidentiality. All information will be de-identified in reporting data and results to protect the confidentiality of participants.

17.5 Post-Study Care

Following completion of the study, participants will be referred back to their primary care/treating physician for ongoing management. Neuropsychological scores will be interpreted and provided to GP and participants in appropriate forms.

17.6 Reimbursement

It is anticipated that most participants will be of working age and be required to attend clinics for assessments. The baseline and end of study visits will each last 3-4 hours, which may require time away from work or daily activities. Participants will therefore be reimbursed for their time (AUD$100) at the baseline and end of study visits, and any reasonable travel expenses for these and other study visits.

18 Document Retention

The study team will retain all study records required by TGI and by the applicable regulatory bodies in a secure and safe facility for a minimum period of 15 years.

19 Publications Policy & Data Sharing

Writing Committees, with oversight by the SC, will be formed from members of the various committees, statisticians, research fellows and investigators. They will prepare all reports of the study to be published in the name of "STRONGER Investigators" with credit assigned to the collaborating investigators and other research staff. Presentations of the study findings will be made at national and international meetings concerned with the management of cognitive assessments, mild cognitive impairment and dementia.

Authors of publications must meet the following International Committee of Medical Journal Editors (ICMJE) guidelines for authorship. Authors must:

a. Make substantial contributions to the conception and design of the study, acquisition of data, or analysis of data and interpretation of results.
b. Draft the publication or, during draft review, provide contributions (data analysis, interpretation, or other important intellectual content) leading to significant revision of the manuscript with agreement by the other authors.
c. Provide approval of the final draft version of the manuscript before it is submitted to the journal for publication.

All contributors who do not meet the 3 criteria for authorship will be listed in an acknowledgments section within the publication, if allowed by the journal, per ICMJE guidelines for acknowledgement.

At the completion of the study, requests for secondary analysis will be in accordance with a defined protocol from an experienced research group with an agreed analysis plan with TGI. In addition, data will be shared with other investigators on the study, and investigators from other institutions around the world, according to a strict data sharing agreement. Data sharing will be available from 12 months after publication of the main results. The PISCF will include information as to the purpose of this activity. Investigators are to make a formal request for data sharing through the Research Office of TGI, Australia and get approval from the SC.

20 Appendices

20.1 Appendix 1 – SPHERE Questionnaire

Initials: ☐☐☐☐ (First name Surname) **Subject ID:** ☐☐☐☐☐ (Interviewer to complete)

Date of birth: ☐☐ / ☐☐ / ☐☐☐☐ (Day Month Year) **Time of day:** ☐☐ : ☐☐ (Please use 24hr time)

Today's date: ☐☐ / ☐☐ / ☐☐☐☐ (Day Month Year) **Sex:** male female (Circle one)

SPHERE Questionnaire

We would like to know about your general health. For ALL questions, please tick, cross or colour the circle that most closely matches your response. There are no right or wrong answers. Please answer ALL questions.

Over **the past few weeks** have you been troubled by:

	Never or some of the time	A good part of the time	Most of the time
1. Headaches?	○	○	○
2. Feeling irritable or cranky?	○	○	○
3. Poor memory?	○	○	○
4. Pains in your arms or legs?	○	○	○
5. Joint pain?	○	○	○
6. Waking up tired?	○	○	○
7. Rapidly changing moods?	○	○	○
8. Fainting spells?	○	○	○
9. Nausea?	○	○	○
10. Arms or legs feeling heavy?	○	○	○
11. Weak muscles?	○	○	○
12. Muscle pain after activity?	○	○	○
13. Needing to sleep longer?	○	○	○
14. Prolonged tiredness after activity?	○	○	○
15. Poor sleep?	○	○	○
16. Poor concentration?	○	○	○
17. Tired muscles after activity?	○	○	○

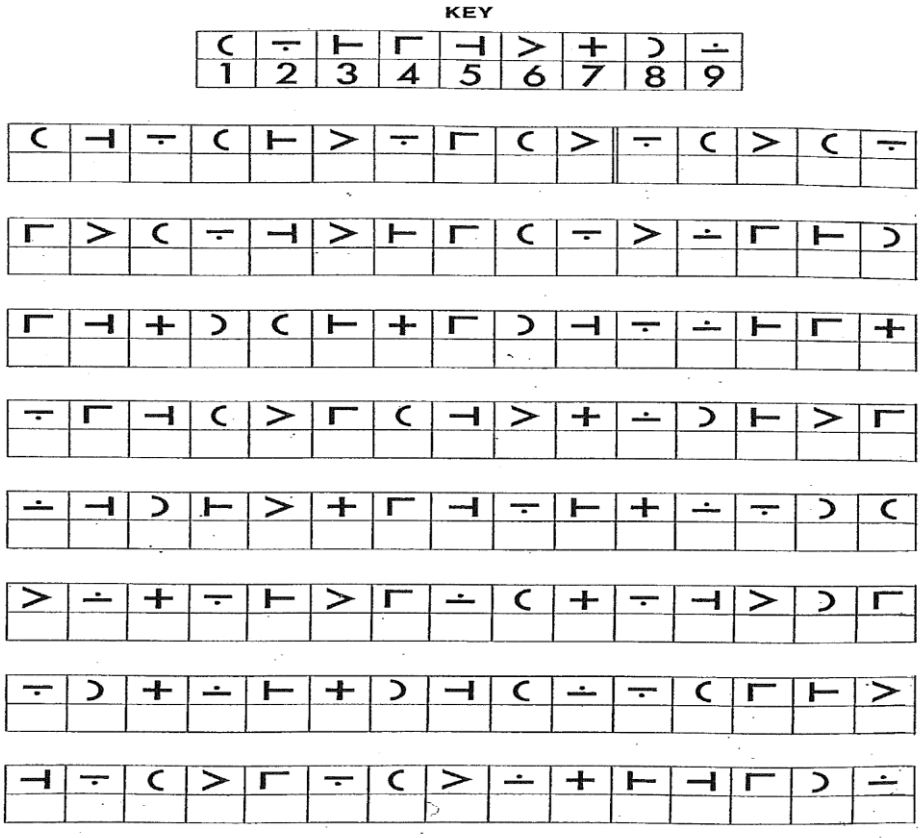
	Never or some of the time	A good part of the time	Most of the time
18. Feeling nervous or tense?	○	○	○
19. Feeling unhappy & depressed?	○	○	○
20. Feeling constantly under strain?	○	○	○
21. Everything getting on top of you?	○	○	○
22. Being unable to overcome difficulties?	○	○	○
23. Losing confidence?	○	○	○
24. Getting annoyed easily?	○	○	○
25. Dizziness?	○	○	○
26. Feeling tired after rest or relaxation?	○	○	○
27. Feeling lost for the word?	○	○	○
28. Diarrhoea or constipation?	○	○	○
29. Gas or bloating?	○	○	○
30. Fevers?	○	○	○
31. Back pain?	○	○	○
32. Sore throat?	○	○	○
33. Numb or tingling sensations?	○	○	○
34. Feeling frustrated?	○	○	○

20.2 Appendix 2 – SDMT

Please look at these boxes at the top of the page. You can see that each box in the upper row has a little mark in it. Now look at the boxes in the row just underneath the marks. Each of the boxes under the marks has a number. Each of the marks in the top row is different, and under each mark in the bottom row is a different number.

Now look at the next line of boxes (point) just under the top two rows. Notice that the boxes on top have marks, but the boxes underneath are empty. You are to fill each empty box with the number that should go there according to the way they are paired in the key at the top of the page and tell me what the number is. For example, if you look at the first mark, and then look at the key, you will see that the number 1 goes in the first box. So, you call out the number 1 for the first box. Now, what number should you put in the second box? Just call it out to me (number 5) That's right. So, you would say "5" to me. What number goes in the third box? (number 2). Two, right. That's the idea. You are to fill each of the empty boxes with the numbers that should go in them according to the key and call out the numbers to me. Now for practice, tell me the numbers and fill in the rest of the boxes until you come to the double line. When you come to the double line, stop.

No when I say "go" call out the numbers just like you have been doing until I say "STOP". I will write the numbers down for you. When you come to the end of the first line, go quickly to the next line without stopping, and so on. If you make a mistake, tell me what you think the correct answer is. Do not skip any boxes and work as quickly as you can. Ready? Go. **Allow 90secs.**



20.3 Appendix 3 – RAVLT-D

Rey Auditory Verbal Learning Test

Trial A1: "I am going to read out a list of words. Listen carefully, for when I stop, you are to repeat back as many words as you can remember. It doesn't matter in what order you repeat them. Just try to remember as many as you can."
Read list A with a 1 second interval between words. Record the exact sequence in which the words are recalled by then examinee.

Trial A2-A5: "Now, I am going to read the same words again, and once again, when I stop, I want you to tell me as many words as you can remember, including words that you said the first time. It doesn't matter in what order you say them. Just say as many words as you can remember whether or not you said them before."
Read list and record responses as with Trial A1. Instructions may be shortened for Trial A3-A5. Praise may be given as the patient recalls more words.

Trial B1: "Now I am going to read another list of words, once only. Again listen carefully, for when I stop, you are to repeat back as many words as you can remember. It doesn't matter in what order you repeat them. Just try to remember as many as you can." Read list B

Trial A6: "Now try to recall as many words from List A (the list I read to you 5 times) as possible." Do not repeat the words again.

Trial A7: "How many words can you recall from list A?"

	Recall Trials						Recall Trials		20-min delay	
LIST A	A1	A2	A3	A4	A5	LIST B	B1	A6	A7	LIST A
drum						desk				drum
curtain						ranger				curtain
bell						bird				bell
coffee						shoe				coffee
school						stove				school
parent						mountain				parent
moon						glasses				moon
garden						towel				garden
hat						cloud				hat
farmer						boat				farmer
nose						lamb				nose
turkey						gun				turkey
colour						pencil				colour
house						church				house
river						fish				river
#Correct										

Total A1 to A5=_____ Record Clock Time:_____
Trail A6-A5=_____

Recognition: "Now I am going to read out another list of words. You need to respond YES every time you recognize the word as being from list A, the list I read out to you 5 times. You can say NO if the word was not from the list."

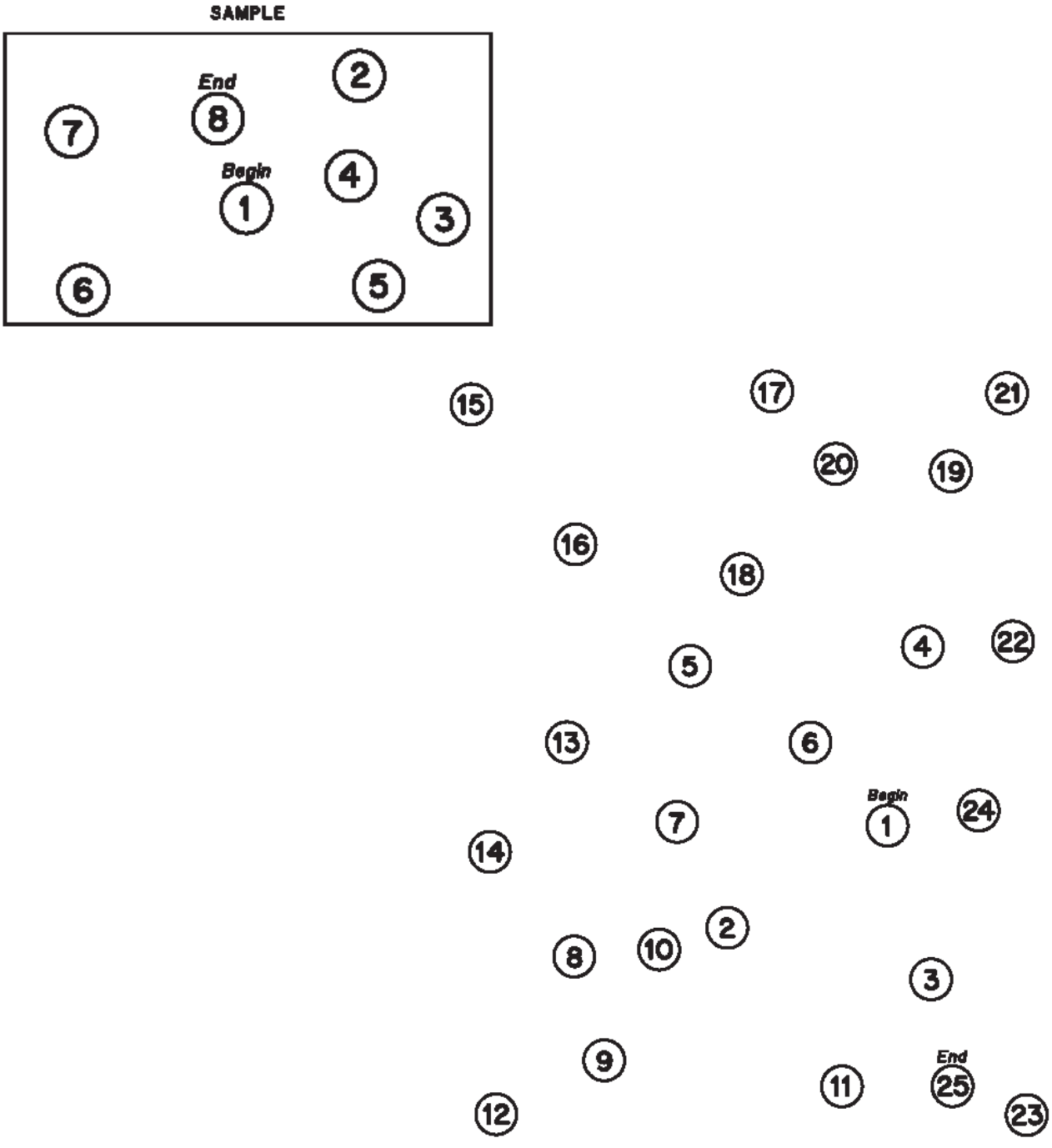
bell (A)		home (SA)		towel (B)		boat (B)		glasses (B)	
window (SA)		fish (B)		curtain (A)		hot (PA)		stocking (SB)	
hat (A)		moon (A)		flower (SA)		parent (A)		shoe (B)	
barn (SA)		tree (PA)		colour (A)		water (SA)		teacher (SA)	
ranger (B)		balloon (PA)		desk (B)		farmer (A)		stove (B)	
nose (A)		bird (B)		gun (B)		rose (SPA)		nest (SPB)	
weather (SB)		mountain (B)		crayon (SA)		cloud (B)		children (SA)	
school (A)		coffee (A)		church (B)		house (A)		drum (A)	
hand (PA)		mouse (PA)		turkey (A)		stranger (PB)		toffee (PA)	
pencil (B)		river (A)		fountain(PB)		garden (A)		lamb (B)	

#Correct:_____
False Positives:_____

20.4 Appendix 4 – OTMT A

TRAIL MAKING

Part A

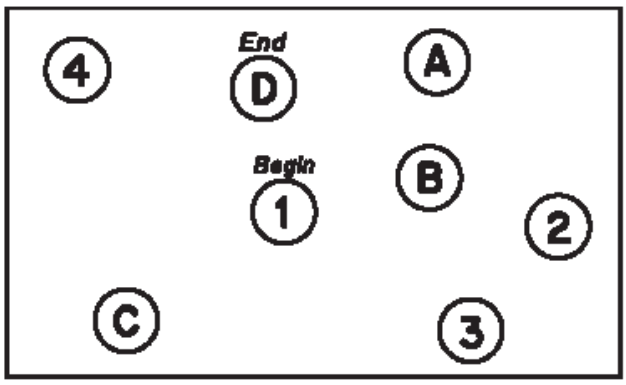


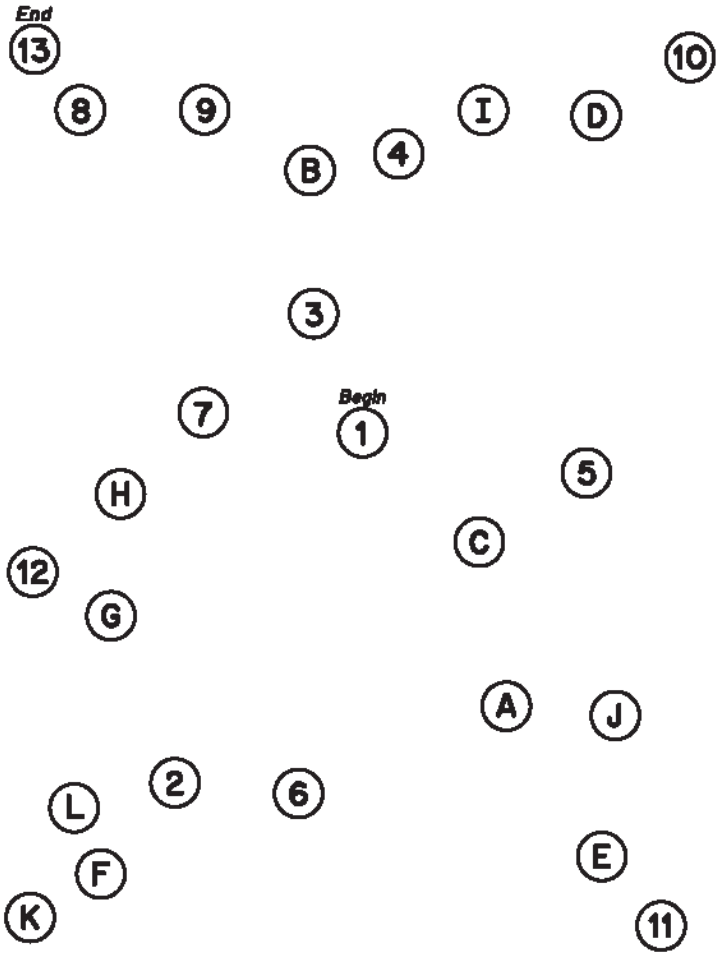
20.5 Appendix 5 – OTMT B

TRAIL MAKING

Part B

SAMPLE





20.6 Appendix 6 – D-KEF-CWIT

D-KEFS Color-Word Interference Test

Ages 8–89
Materials: Record Form, Stimulus Booklet (Flat Position), Stopwatch

Condition 1: Color Naming

Discontinue

Discontinue if the examinee has marked difficulty or makes four uncorrected errors on the practice lines. Otherwise, discontinue the scored task after 90 seconds.

Administration and Recording

Place the stimulus booklet flat on the table in a horizontal (landscape) position directly in front of the examinee so that the two practice lines of Condition 1 are positioned at the top of the page from the examinee's perspective. Say,

> **This page has patches of color on it. I'd like you to say the colors as quickly as you can without skipping any or making mistakes. When you finish this line (sweep across the first practice line of five squares with your finger), go on to this one (point to the first square of the second row). Now try these first two lines for practice.**

If the examinee is able to complete the two practice lines, say, **Good. Now, when I say begin, I want you to say the rest of the colors. Begin here (point to the first square on the first line of 10 squares below the practice lines) and say each color, one after the other, without skipping any. When you finish this line (sweep across the first row with your finger), go on to this one (point to the first square of the second row). Keep saying the colors until you reach the end of the last line (point). Say the colors as quickly as you can without making mistakes. Ready? Begin.**

Start timing. Follow the examinee's progress item by item. Record errors by writing the first letter of the incorrect color name beneath the correct response and record any nonsense words (e.g., "bleen") verbatim. Indicate self-corrections by drawing a slash mark through the letter or word. Record total completion time in seconds.

Allow the examinee to use a finger to maintain his or her place on the stimulus page. If the examinee skips a line accidentally, point out the error immediately and redirect the examinee to the correct line. Keep the stopwatch running while pointing out line-skipping errors.

If the examinee does not complete the task at the end of 90 seconds, say, **Stop.** Indicate the last item attempted and record 90 seconds as the total completion time. Items to which the examinee did not respond because the time limit was reached are not counted as errors. Turn the page in the stimulus booklet to Condition 2: Word Reading.

green red blue green blue
red blue green blue green
red blue red green red blue green blue red green
blue green red green red green blue red blue green
red green blue red green red green blue green red
blue red green blue red green blue red blue green
red blue red green blue green blue red blue green

Condition 1: Color Naming

Total Uncorrected Errors

Total Self-Corrected Errors

Total Time To Complete

8

Color

20.7 Appendix 7 – SF

COWAT

"I will say a letter of the alphabet. Then I want you to give me as many words that begin with that letter as quickly as you can. For instance, if I say B, you might give me 'BAD', 'BATTLE' or 'BED'.
I do not want you to use words which are proper names such as 'BOSTON', 'BOB' or 'BONOX'. Also, do not use the same word with a different ending, such as 'EAT' and 'EATING'. Any questions?
Begin when I say the letter. The first letter is F. Go ahead."
"Now I want you to tell me as many animal names that you can think of – Go ahead."

	F	A	S	Animals
1-15				
15-30				
30-45				
45-60				

20.8 Appendix 8 – PHQ-9

PATIENT HEALTH QUESTIONNAIRE (PHQ-9)

NAME: _____ **DATE:** _____

Over the *last 2 weeks*, how often have you been bothered by any of the following problems?
(use "✓" to indicate your answer)

	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead, or of hurting yourself in some way	0	1	2	3
add columns:		+	+	
(Healthcare professional: For interpretation of TOTAL, please refer to accompanying scoring card.)	**TOTAL:**			

10. If you checked off *any* problems, how *difficult* have these problems made it for you to do your work, take care of things at home, or get along with other people?

- **Not difficult at all** _____
- **Somewhat difficult** _____
- **Very difficult** _____
- **Extremely difficult** _____

20.9 Appendix 9 – PSQI

INSTRUCTIONS: The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. Please answer all questions.

1. During the past month, when have you usually gone to bed at night?

   USUAL BED TIME _____

2. During the past month, how long (in minutes) has it usually take you to fall asleep each night?

   NUMBER OF MINUTES _____

3. During the past month, when have you usually gotten up in the morning?

   USUAL GETTING UP TIME _____

4. During the past month, how many hours of actual sleep did you get at night? (This may be different than the number of hours you spend in bed.)

   HOURS OF SLEEP PER NIGHT _____

INSTRUCTIONS: For each of the remaining questions, check the one best response. Please answer all questions.

5. During the past month, how often have you had trouble sleeping because you...

	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
(a) ...cannot get to sleep within 30 minutes	☐	☐	☐	☐
(b) ...wake up in the middle of the night or early morning	☐	☐	☐	☐
(c) ...have to get up to use the bathroom	☐	☐	☐	☐
(d ...cannot breathe comfortably	☐	☐	☐	☐
(e) ...cough or snore loudly	☐	☐	☐	☐
(f) ...feel too cold	☐	☐	☐	☐
(g) ...feel too hot	☐	☐	☐	☐
(h) ...had bad dreams	☐	☐	☐	☐
(i) ...have pain	☐	☐	☐	☐
(j) Other reason(s), please describe				
_____				
_____				
How often during the past month have you had trouble sleeping because of this?	☐	☐	☐	☐

	Very good	Fairly good	Fairly bad	very bad
6. During the past month, how would you rate your sleep quality overall?	☐	☐	☐	☐

	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
7. During the past month, how often have you taken medicine (prescribed or "over the counter") to help you sleep?	☐	☐	☐	☐
8. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?	☐	☐	☐	☐

	No problem at all	Only a very slight problem	Somewhat of a problem	A very big problem
9. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?	☐	☐	☐	☐

	No bed partner or roommate	Partner/ roommate in other room	Partner in same room, but not same bed	Partner in same bed
10. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?	☐	☐	☐	☐

If you have a roommate or bed partner, ask him/her how often in the past month you have had...

	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
(a) ...loud snoring	☐	☐	☐	☐
(b) ...long pauses between breaths while asleep	☐	☐	☐	☐
(c) ...legs twitching or jerking while you sleep	☐	☐	☐	☐
(d) ...episodes of disorientation or confusion during sleep	☐	☐	☐	☐
(e) Other restlessness while you sleep; please describe	☐	☐	☐	☐

20.10 Appendix 10 – GAD-7

NAME DATE

1. Over the last 2 weeks, how often have you been bothered by the following problems?	Not at all sure	Several days	Over half the days	Nearly every day
• Feeling nervous, anxious, or on edge	☐ 0	☐ 1	☐ 2	☐ 3
• Not being able to stop or control worrying	☐ 0	☐ 1	☐ 2	☐ 3
• Worrying too much about different things	☐ 0	☐ 1	☐ 2	☐ 3
• Trouble relaxing	☐ 0	☐ 1	☐ 2	☐ 3
• Being so restless that it's hard to sit still	☐ 0	☐ 1	☐ 2	☐ 3
• Becoming easily annoyed or irritable	☐ 0	☐ 1	☐ 2	☐ 3
• Feeling afraid as if something awful might happen	☐ 0	☐ 1	☐ 2	☐ 3
Add the score for each column				
TOTAL SCORE *(add your column scores)*				
	Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
2. If you checked off any problem on this questionnaire so far, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?	☐ 0	☐ 1	☐ 2	☐ 3

Scoring *Add the results for question number one through seven to get a total score.*

If you score 10 or above you might want to consider one or more of the following:

1. Discuss your symptoms with your doctor,
2. Contact a local mental health care provider or
3. Contact my office for further assessment and possible treatment.

Although these questions serve as a useful guide, only an appropriate licensed health professional can make the diagnosis of Generalized Anxiety Disorder.

A score of 10 or higher means significant anxiety is present. Score over 15 are severe.

GUIDE FOR INTERPRETING GAD-7 SCORES

Scale	Severity
0-9	None to mild
10-14	Moderate
15-21	Severe

GAD-7 developed by Dr. Robert L. Spitzer, Dr. K. Kroenke, et.al.

20.11 Appendix 11 – EQ-5D-5L

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

- I have no problems in walking about ☐
- I have slight problems in walking about ☐
- I have moderate problems in walking about ☐
- I have severe problems in walking about ☐
- I am unable to walk about ☐

SELF-CARE

- I have no problems washing or dressing myself ☐
- I have slight problems washing or dressing myself ☐
- I have moderate problems washing or dressing myself ☐
- I have severe problems washing or dressing myself ☐
- I am unable to wash or dress myself ☐

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

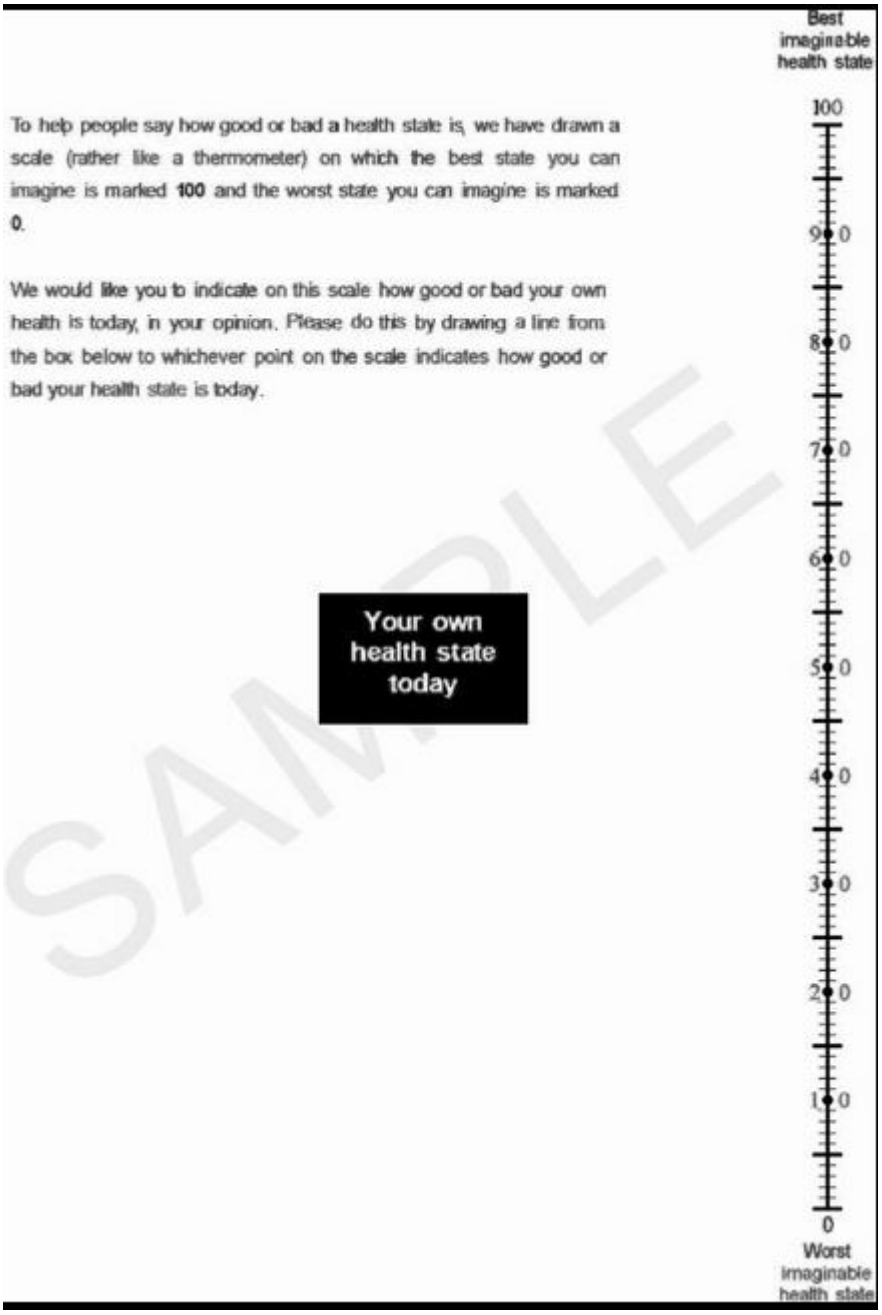
- I have no problems doing my usual activities ☐
- I have slight problems doing my usual activities ☐
- I have moderate problems doing my usual activities ☐
- I have severe problems doing my usual activities ☐
- I am unable to do my usual activities ☐

PAIN / DISCOMFORT

- I have no pain or discomfort ☐
- I have slight pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have severe pain or discomfort ☐
- I have extreme pain or discomfort ☐

ANXIETY / DEPRESSION

- I am not anxious or depressed ☐
- I am slightly anxious or depressed ☐
- I am moderately anxious or depressed ☐
- I am severely anxious or depressed ☐
- I am extremely anxious or depressed ☐


Best imaginable health state
100
90
80
70
60
50
40
30
20
10
0
Worst imaginable health state
To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.
We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.
Your own health state today
SAMPLE

20.12 Appendix 12 – Blind MoCA

MONTREAL COGNITIVE ASSESSMENT / MoCA-BLIND
Version 7.1 Original Version

Name:
Education:
Sex:
Date of birth:
Date:

MEMORY		FACE	VELVET	CHURCH	DAISY	RED	**POINTS**
Read list of words, subject must repeat them. Do 2 trials even if 1st trial is successful. Do a recall after 5 minutes.	1st trial						No points
	2nd trial						

ATTENTION

Read list of digits (1 digit/sec.) Subject has to repeat them in the forward order [ ] 2 1 8 5 4
Subject has to repeat them in the backward order [ ] 7 4 2 ___/ 2

Read list of letters. The subject must tap with his hand at each letter A. No point if ≥ 2 errors
[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B ___/ 1

Serial 7 subtraction starting at 100
[ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65
4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt** ___/ 3

LANGUAGE

Repeat: I only know that John is the one to help today. [ ]
The cat always hid under the couch when dogs were in the room. [ ] ___/ 2

Fluency / Name maximum number of words in one minute that begin with the letter F.
[ ] _____ (N ≥ 11 words) ___/ 1

ABSTRACTION

Similarity between e.g. banana - orange = fruit
[ ] train - bicycle
[ ] watch - ruler ___/ 2

DELAYED RECALL	Has to recall words **With no cue**	FACE [ ]	VELVET [ ]	CHURCH [ ]	DAISY [ ]	RED [ ]	Points for UNCUED recall only	___/ 5
Optional	Category cue							
	Multiple choice cue							

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City ___/ 6

© Z. Nasreddine MD **www.mocatest.org** Normal ≥ 18 / 22

TOTAL ___/ 22
Add 1 point if ≤ 12 yr edu

Administered by:_____

20.13 Appendix 13 – Sleep Diary

SLEEP DIARY

stronger
Statin TReatment for COVID-19 to Optimise NeuroloGical recovERy

IMPORTANT: Please complete the following sleep diary for the days that you wear an actigraphy watch.

	Day #	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Today's date:	E.g. Wed 30/06/2021							
1. What time did you get into bed last night?	10:15PM							
2. What time did you try to go to sleep?	11:30PM							
3. How long did it take you to fall asleep?	1hr. 15m.							
4. How many times did you wake up, not counting your final awakening?	3 times							
5. It total, how long did these awakenings last?	1hr 10m							
6. What was your sleep disturbed by (i.e. what caused these awakenings)?	Barking Dog							
7. What time was your final awakening?	6:30AM							
8. What time did you get out of bed for the day?	7:20AM							
9. When you woke, did you feel? - Refreshed - Tired - Other (please specify)	Refreshed ☐ Tired ☐ Other: _____	☐ ☐ _____	☐ ☐ _____	☐ ☐ _____	☐ ☐ _____	☐ ☐ _____	☐ ☐ _____	☐ ☐ _____
10. Did you nap or doze yesterday? If NO, please leave blank. If YES, please specify time of nap and total time spent napping/dozing.	Yes ☐ 11am & 3pm. 45mins	Yes ☐	Yes ☐	Yes ☐	Yes ☐	Yes ☐	Yes ☐	Yes ☐
11. What did you do before you went to sleep? (e.g. watched TV, read a book etc.)	Watched TV on the lounge							
12. In the 3-hours before bed, did you consume any alcohol or caffeine?	Alcohol ☐ Caffeine ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐
13. Did you exercise yesterday? If NO, please leave blank. YES, note duration in mins & intensity (1-10)	Yes ☐ 30 mins Level 6	Yes ☐	Yes ☐	Yes ☐	Yes ☐	Yes ☐	Yes ☐	Yes ☐
14. Comments relating to sleep quality or other important things we should consider when assessing your sleep.	I have a cold							

20.14 Appendix 14 – NPS SAMS

NPS MEDICINEWISE PROFESSIONAL

Statin-associated muscle symptoms (SAMS)

Use a systematic approach to assess suspected statin intolerance

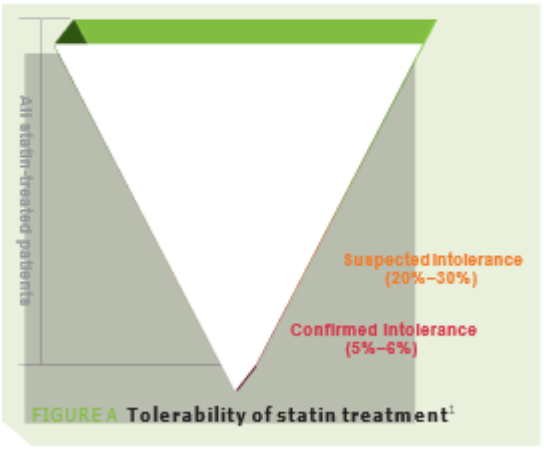


FIGURE A. **Tolerability of statin treatment**[1]

- Statin intolerance is rarely life-threatening and may have a lower incidence than is commonly reported.[2-4]
- Statins have been associated with a nocebo effect, whereby patients experience adverse effects based on the expectation of harm from a treatment.[5]
- For muscle-related adverse effects:
  - Incidence of statin-associated myalgia is lower in blinded RCTs (1% to 5%)[6] compared to observational studies (7% to 29%).[4]
  - Myopathy incidence is ≈ 1 in 10,000 per year.[4]
  - Rhabdomyolysis incidence is ≈ 1 in 100,000 per year.[4]
- Involve patients in assessing and managing adverse effects.
- Advise patients to contact you if they experience muscle symptoms, and not to stop taking their statin.[6]

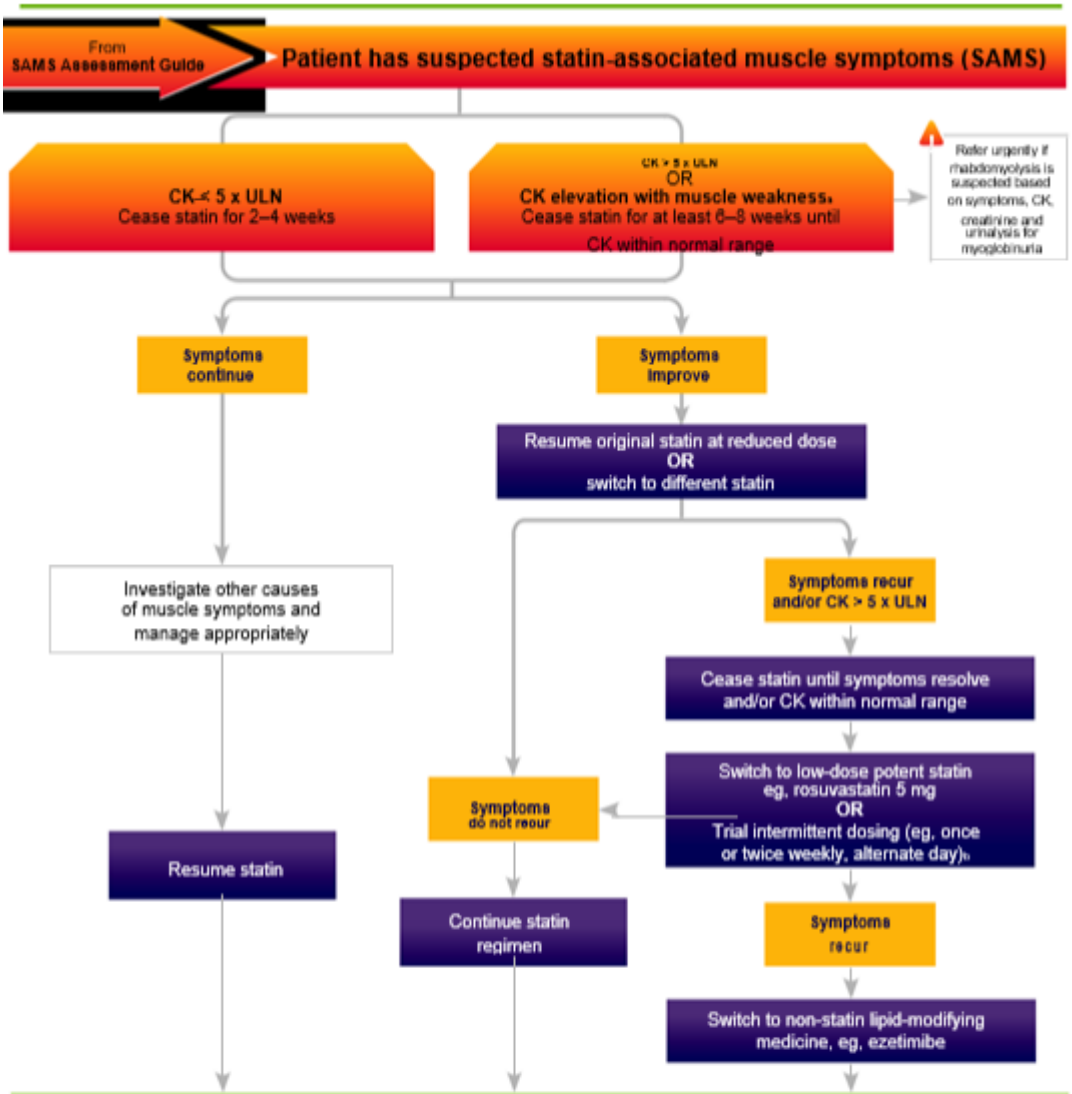
SAMS Assessment Guide

SAMS LESS LIKELY		SAMS MORE LIKELY
Unilateral Non-specific distribution Tingling, twitching, shooting pain, nocturnal cramps or joint pain	**Nature of symptoms**[4,6,7]	Bilateral Large muscle groups (eg, thighs, buttocks, calves, shoulder girdle) Muscle ache, weakness, soreness, stiffness, cramping, tenderness or general fatigue
Onset before statin initiation Onset > 12 weeks after statin initiation	**Timing of symptoms**[4]	Onset 4–6 weeks after statin initiation Onset after statin dosage increase
Non-statin causes of muscle symptoms including: • conditions eg, hypothyroidism, polymyalgia rheumatica • vitamin D deficiency • unaccustomed/heavy physical activity • medicines eg, glucocorticoids, antipsychotics, immunosuppressant or antiviral agents	**Other considerations**[4,7]	Risk factors for SAMS including: • medicine or food interactions • high-dose statin therapy • history of myopathy with other lipid-modifying medicines • regular vigorous physical activity • impaired hepatic or renal function • substance abuse (eg, alcohol, opioids, cocaine) • female • low BMI
	CK levels[4]	Elevated (> ULN; but may also be normal) Elevated CK levels decrease after statin ceased

If SAMS is likely, proceed to the **SAMS Management Algorithm (see overleaf)**

References available online at:
nps.org.au/statins-card-refs

SAMS Management Algorithm



CK = creatine kinase, LDL-C = low density lipoprotein cholesterol, ULN = upper limit of normal
[a] CK > ULN and weakness demonstrated upon physical examination. [b] Higher potency statins with a long half-life are preferred for intermittent dosing eg, rosuvastatin and atorvastatin

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