PLAGIARISM DECLARATION

1. I know that plagiarism is wrong. Plagiarism is to use another's work and to pretend that it is one's own.

2. I have used the *American Psychological Association (APA)* convention for citation and referencing. Each significant contribution to, and quotation in, this essay / report / project / from the work, or works, of other people has been attributed, and has cited and referenced.

3. This essay /report /project / is my own work.

4. I have not allowed, and will not allow, anyone to copy my work with the intention of passing if off as his or her own work.

5. I acknowledge that copying someone else's assignment or essay, or part of it, is wrong, and declare that this is my own work.

SIGNATURE Juliet Stromin, Michaela Manasse (20/12/2021)

Long-term Neuropsychological Outcomes in Severe COVID-19: A Feasibility Study

Juliet Stromin & Michaela Manasse

Supervisors: Dr Donne Minne and Prof Mark Solms

Department of Psychology

University of Cape Town

Date: 2/01/2022

Word count:

Abstract: 230

Main body: 9,994

Abstract

Since the outbreak of the coronavirus disease (COVID-19), neuropsychological sequelae have emerged, especially in patients who develop acute respiratory distress syndrome (ARDS). Studies on short-term outcomes indicate deficits in cognition and quality of life. However, few studies have investigated longer-term neuropsychological outcomes. The current pilot study investigated the feasibility of conducting a quantitative assessment of cognitive functioning in COVID-19 patients and ARDS patients one-year post hospitalisation. More specifically, this study explored the practicalities of running a large-scale investigation in Cape Town, during the current wave of infection and in anticipation of further waves. Results suggested that participant recruitment was hindered due to the vulnerability of the cohort, the uncertainties surrounding recovery and due to new legal Acts governing access to personal participant information. The duration and mental demand of the testing sessions was overwhelming for some participants, regardless of prior COVID-19 status. Findings also indicated logistical challenges related to accessing the testing venue. Despite limitations in sample size and representativeness, the findings provide a clear road map for fine-tuning the full-scale protocol. Specifically, adjusting participant eligibility criteria to broaden the age range and intensified networking within the broader medical community to foster trust and mutual benefit will be critical for meeting recruitment targets. These revisions to the protocol will aid in successfully completing a full-scale study aimed at addressing knowledge gaps regarding the effects of COVID-19 on long-term neuropsychological outcomes.

Key words: COVID-19, feasibility study, neuropsychology, ARDS, acute respiratory distress syndrome

The novel severe acute respiratory syndrome coronavirus (SARS-CoV-2), which is responsible for the coronavirus disease 2019, has taken a hold of the world, resulting in a global-wide pandemic and the death of over 1.5 million people (World Health Organization, 2021). The described hallmarks of the disease include shortness of breath, fever, and coughing; however, in severe cases it is known to cause acute respiratory distress syndrome (ARDS; Rabinovitz et al., 2020), which may present consequences to the functioning of the brain (Mikkelsen et al., 2012). In the sections that follow we highlight evidence demonstrating the neurological involvement of COVID-19. We then pose the question, what are the cognitive ramifications of COVID-19-induced ARDS, one-year post infection, before highlighting the need for a feasibility study to address the methodological complexities that this investigation would present.

Neurological and Cognitive Impacts Associated with COVID-19

Based on reports of neurological damage in cases of other coronaviruses, including severe acute respiratory syndrome (SARS) and Middle East Respiratory Syndrome (MERS), it is suspected that those infected with COVID-19 will have similar central nervous system (CNS) ailments (Rabinovitz et al., 2020). Autopsy studies have revealed that infiltration of the brain may occur following SARS infection (Beghi et al., 2020; Rabinovitz et al., 2020) and others have demonstrated signs of cerebral swelling and meningeal vasodilation (Wu et al., 2020). During the MERS-CoV outbreak, many studies showed evidence of neuro invasiveness and neurological symptoms including mental disturbances and ischemic strokes (Mikkelsen et al., 2012; Wu et al., 2020; Zangbar et al., 2021). Rogers et al. (2020) found in a 72-study meta-analysis that those with SARS and MERS presented with impaired memory and concentration, difficulty sleeping and fatigue. These findings give researchers an indication of the type of symptoms COVID-19 patients may experience.

Corresponding with findings in SARS, recent studies have detected SARS-CoV-2 in cerebrospinal fluid (CSF) (Lewis et al., 2021; Neumann et al., 2020; Nuzzo & Picone, 2020). COVID-19 is a neurotropic virus which is thought to use sensory and motor neuronal pathways to invade the central nervous system. This includes the olfactory nerve which may allow COVID-19 to reach the brain and CSF, leading to demyelination and neuroinflammation (Kumar et al., 2020). Another study suggests that the virus may also enter the CNS through the vasculature and trigeminal nerves or the lymphatic system, however, a distinct route is yet to be identified (Nuzzo & Picone, 2020). Moreover, it is thought that neurological deficits are a result of the body's immune response to COVID-19 (Chowdhury et al., 2020; Liu et al., 2021; Paces et al., 2020). The response can cause changes in cell metabolism, a drop in blood pressure and a lack of oxygen to the brain (Polito et al., 2011; Troyer et al., 2020).

The most common early neurological signs of COVID-19 appear to include hyposmia, seizures, headaches, ataxia, stroke, and a range of encephalopathies including hypoxic-ischemic and hypertensive (Anand et al., 2020; Herridge et al., 2016; Mikkelsen et al., 2012; Montalvan et al., 2020; Troyer et al., 2020; Zangbar et al., 2021). Many of these symptoms have been corroborated by other studies across the world (Helms et al., 2020; Mao et al., 2020).

Cognitive deficits including early signs of interference in executive functions, memory, and attention (Kumar et al., 2020; Rabinovitz et al., 2020; Zhou et al., 2020) have also been reported. Upon discharge, Helms et al. (2020) found that 33% of patients complained of lasting neurological symptoms and cognitive deficits such as inattention, ataxia, and disorientation. However, one study investigating cognitive dysfunction in COVID-19 survivors revealed a significant deficit in the domain of attention, while all other domains including memory and reaction speed proved insignificant (Zhou et al., 2020). It must be noted, however, that of the

studies reviewed, there are discrepancies in findings and samples consisted of those mere weeks post infection. Therefore, there is a pressing need to investigate long-term outcomes to fully understand the relationship between COVID-19 and lasting cognitive impacts.

Despite the accumulating reports, it remains unclear as to whether severe COVID-19 illness is associated with generalised brain dysfunction because of a system-wide disturbance or a unique profile of cognitive and neuropsychiatric complaints. Given the heterogeneity of symptoms in COVID-19 (Helms et al., 2020; Kumar et al., 2020; Wu et al., 2020), it is likely that cognitive disturbance will stem from multiple pathways (Bougakov et al., 2021; van Eijk et al., 2021) without a strict linear relationship to illness severity. To further complicate the issue, prior research has shown that ARDS from non-COVID-19 causes is associated with cognitive deficits at the one-year follow-up in up to 55% of patients (Carlson & Huang, 2013; Davydow et al., 2013; Mikkelsen et al., 2012; Sasannejad et al., 2019). This means that it will be difficult to get a clear sense of any specific contribution that COVID-19 may have on cognitive functioning in the most severe cases which usually involve ARDS.

ARDS and Cognitive Functioning

ARDS resulting from COVID-19-related pneumonia has been documented in 42% of patients and presents in 60-80% of those in critical condition, making the syndrome highly prevalent (Wu et al., 2020). ARDS is characterised by inflammation and inadequate oxygen supply to the arteries and bodily tissue (Rabinovitz et al., 2020). Furthermore, pulmonary vascular resistance and high pulmonary arterial pressure results in poor blood circulation which can cause a loss of oxygen to the brain (Iodice et al., 2021; Revercomb et al., 2021; Simonneau et al., 2019; Wu et al., 2020). Tissue factor, which is also released in response to endothelial cell damage, causes the clotting of blood which, furthermore, disrupts blood flow (Revercomb et al., 2021; Ryan

et al., 2014). Chen et al. (2020) reported that of 113 post-mortem COVID-19 patients, approximately 20% were found to have brain damage due to hypoxemia.

The inflammatory nature of ARDS attacks endothelial cells, which in turn releases a slew of proteins and molecules, including that of cytokines (Prince & Wort, 2017). Some theories propose that it is the immune system, particularly the release of cytokine proteins in response to the virus, that results in some of the neurological symptoms mentioned (Koralnik & Tyler, 2020; Mehta et al., 2020; Ragab et al., 2020; Troyer et al., 2020). In patients with COVID-19, there is a proliferation of cytokines due to heightened inflammation (Mehta et al., 2020) and this is especially dangerous as cytokines can infiltrate the blood brain barrier, resulting in neuroinflammation and possible brain atrophy, leading to deficits in cognition (Hopkins & Bigler, 2012; Iwashyna et al., 2012; Kempuraj et al., 2020).

Studies have conducted one-year follow ups with those who suffered from ARDS due to causes other than COVID-19 (Bein et al., 2018). One study found significant executive dysfunction and motor difficulties in their sample (Alemanno et al., 2021; Mikkelsen et al., 2012). This finding is corroborated with a study done by Carlson and Huang (2013) which reported cognitive deficits in more than half of their sample, also following one-year of initial illness. Survivors of ARDS have additionally reported lasting deficiencies in memory and concentration (Adhikari et al., 2011; Mikkelsen et al., 2012; Wilcox et al., 2013).

Regarding the current pandemic, little research has been made available that investigates the unique interaction between COVID-19-induced ARDS and its corresponding cognitive deficits and whether COVID-19 ARDS patients are at any greater risk for lasting impairment compared to patients who develop ARDS from other causes, such as trauma. A notable concern is that coronaviruses have been known to affect the respiratory tract by reaching the ACE2-enzymes in

the respiratory epithelial cells and the olfactory nerve (Kumar et al., 2020). Studies have found that the ACE2-enzymes and the neuronal pathway that runs via the olfactory nerve appear to be one of the main pathophysiological mechanisms contributing to neuropsychiatric and cognitive deficits in COVID-19 (Burks et al., 2021; Klingenstein et al., 2020; Kumar et al., 2020). This suggests that ARDS in COVID-19 likely carries risk of central nervous system damage that exceeds the risks of ARDS alone or less severe cases of COVID-19.

The methodological requirements of addressing this question in the context of the ongoing pandemic are complex and might explain why most studies on the neuropsychological outcomes in COVID-19 lack appropriate experimental control. For instance, in Italy, Alemanno et al. (2021) exclusively studied those who were in the sub-acute phase (within days of contraction) of their COVID-19 illness, dividing participants into groups based on amount of respiratory support received, and did not include a healthy control. In the United Kingdom, Hampshire et al. (2021), conducted online cognitive assessments and compared results of a healthy control with those with COVID-19 over the course of a year. The COVID-19 group was confounded by comprising participants with both confirmed and suspected COVID-19. Most importantly, neurological deficits presenting at the sub-acute phase are often transient (Desai et al., 2021), making it difficult to report on lasting cognitive changes. These results may then differ greatly from those tested months following infection. Daroische et al. (2021), in a systematic review, further noted number of participants tested, severity of COVID-19 illness, medium of testing, and assessments used as areas of great methodological variability, making it difficult to establish robust findings in COVID-19 neuropsychological research.

Factors unique to the pandemic compound the difficulty of running large-scale investigations. Hospital resources and staff have been spread thin during the COVID-19 pandemic,

affecting patient care, and determining resource allocation (Mehta et al., 2021). The pandemic has also brought about new patient profiles that hospital administration and staff are struggling to navigate and attend to (Cox, 2020). Anecdotal reports from local clinicians in Cape Town indicate that patient databases for COVID-19 patients are not readily available and that neurological symptoms have been unreliably and inconsistently documented. Moreover, in South Africa we face the unique situation that neuropsychology as a discrete discipline within the healthcare system has only recently been promulgated in law meaning that government hospitals do not have neuropsychologists on staff to routinely track and record patient cognitive outcomes. These factors suggest that full-scale investigations into long-term neuropsychological outcomes in COVID-19 patients within South Africa are needed but will pose several challenges and must be carefully considered.

Feasibility Studies

Feasibility studies, also known as pilot studies, are then crucial for determining and navigating these challenges to produce efficacious findings in these unprecedented investigations. Feasibility studies are used extensively in clinical research to assess the feasibility of large-scale studies (Arnold et al., 2009; Thabane et al., 2010). Areas of a study that are typically assessed for feasibility involve the logistics, including participant recruitment and retention rate; appropriateness of available resources, including budget allowances and time availability of a study; management requirements, including data surveying and matters relating to study personnel; and scientific matters, including sample size calculations and efficacy of trial results (Van Teijlingen & Hundley, 2002; Van Teijlingen et al., 2001). Feasibility studies are not designed to statistically test hypotheses and instead function to adequately prepare for large, full-scale studies (Drummond, 2017; Leon et al., 2011). In doing so, feasibility studies prevent wastage of

limited resources on a large scale and allow funders and researchers to assess the appropriateness of a research design (Drummond, 2017). These decisions also have bearing on proper ethical conduct when it comes to the use of participants for data that does not end up producing statistically valid findings (van Wijk & Harrison, 2013).

Challenges of Conducting COVID-19 Research

The Food and Drug Administration (FDA) of the United States has produced new standards for the publication of clinical research trials during the COVID-19 pandemic (FDA, 2021). New standards are, in part, a response to the challenges we are seeing in clinical research and therefore provide insight into these challenges. This includes the quarantining of participants or study personnel, the infection of participants or study personnel with COVID-19, testing site inaccessibility, travel restrictions and interruptions to the delivery of the intervention or treatment. Indeed, at the start of the pandemic there was an expected increase in observational studies and a decrease in experimental study designs in clinical research (Caputo et al., 2021). This is largely due to face-to-face research prohibitions and stay-at-home orders by national governments (Islam et al., 2020). As a result, we are seeing large losses to participant follow-ups and imbalances in sample representativeness because of inaccessibility to online platforms in lower to middle income countries such as South Africa (Caputo et al., 2021).

Rationale

On this basis, a feasibility study is required before implementing a full-scale study to investigate the differences between cognitive functioning between COVID-19, non-COVID-19 ARDS, and control at the one-year follow-up. Amid the ongoing COVID-19 pandemic, it is crucial that feasibility studies are conducted to improve the evidence base developing around COVID-19. As there is still much unknown about COVID-19, large-scale studies will benefit from feasibility

research that informs appropriate methodology to ensure validity and reliability. This would furthermore aid in directing resources within the health sciences that are already scarce due to the pandemic (Weiner et al., 2020).

Research Aims and Objectives

This feasibility study aimed to evaluate and comment on the process of conducting neuropsychological research in COVID-19 and ARDS cohorts. Areas of interest included research design, participant recruitment, and materials and measures. In doing so we hoped to strengthen the methodology of a future costly randomised control trial (RCT) that will improve our understanding of long-term neuropsychological outcomes in severe COVID-19.

Data from participant feedback and researcher observations during the study as well as recruitment rate and retention rate were used to evaluate the following:

1. Participation eligibility criteria.
2. Willingness of the participants in partaking in the research.
3. Feasibility of the testing location.
4. Appropriateness of the session structure in terms of time and participant coping.
5. Appropriateness of the battery of assessment tools to comprehensively measure neuropsychological functioning without overwhelming the participant.
6. Feasibility of test scoring and study outcomes in determining efficacy of tests in a future definitive RCT.

Method

Design

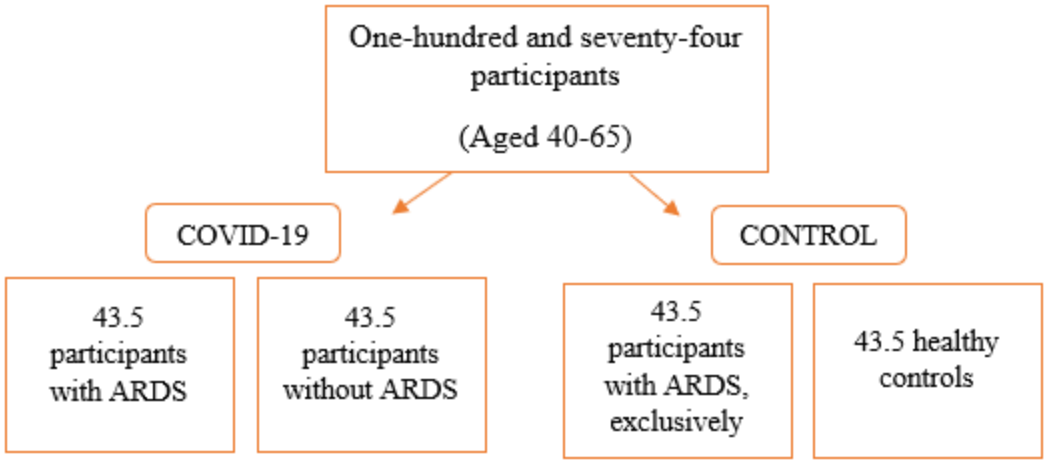
Based at Groote Schuur Hospital (GSH) in Cape Town, this feasibility study adopted a mixed-methods approach and was qualitative in nature, gathering data via observation, field notes, cognitive tests, and a semi-structured debriefing interview.

Participants

Sampling for this feasibility study was guided by the target sample for the full-scale study, which aims to include four subgroups (see Figure 1).

Figure 1

Participant Groupings for the Full-scale Study



Note. Excluding the healthy controls, all participants will have been in the ICU for their respective conditions 12-months prior to data collection and all participants will be matched according to education, sex, and age. All participants with a history of pre-morbid neurological illness or injury, stroke, major psychiatric illness, learning disability or intellectual impairment, illiteracy, or premorbid visual or auditory impairments that cannot be corrected-to-normal with glasses/hearing aids are excluded.

For the full-scale investigation, a priori power analysis was conducted for sample size estimation, using a two-tailed test to compare the difference between two independent group means. An alpha of .05 and a medium effect size (d = .55) was established, and the result indicated that a target sample of 174 with four equal sized groups of n = 43.5 would be needed to attain a power of .95 and is recommended for a larger-scaled study.

Pilot studies investigating similar research questions in COVID-19 groups reported sample sizes ranging from 24 to 54 persons (Raghavan et al., 2021; Repišti et al., 2021). However, for the purposes of this study, we were less interested in statistically testing questions relating to neuropsychological outcomes in the efforts of determining effect, and more so in assessing the feasibility of implementing a lengthy and costly research initiative. In fact, there appears to be a general misconception in the literature regarding the role of pilot studies in clinical research: Power analyses can be used to determine the number of participants necessary to produce statistically significant findings and therefore, only sufficiently powered pilot studies can assess statistically relevant outcomes (Van Teijlingen & Hundley, 2002). Pilots with smaller samples are only appropriate for evaluating feasibility.

A sample of n=12 (3 per group) was deemed reasonable to evaluate the feasibility of recruiting and testing each subgroup, however, the current study only managed to recruit 5 participants in total. Furthermore, the current pilot relaxed the age range for participant eligibility to include those between the ages of 35 and 65 years. Reasons for these adjustments will be discussed in detail in ‘Results and Discussion’. Three participants were recruited via the Long Covid clinic at GSH. One participant joined by word-of-mouth, while a fifth participant was alerted to the study via the department of student affairs at the University of Cape Town (UCT).

Materials and Measures

Overt Observations and Field Notes

Observations and field notes were taken throughout the research design that provided insight into study feasibility. Overt observations, wherein the participant was aware that they were being observed by the researcher (Smit & Onwuegbuzie, 2018), were recorded in a notebook at the time of testing. Performance on some of the cognitive tests were recorded and observed via audio and video playbacks. Field notes were recorded both on paper and electronically.

Cognitive Tests

The measures listed below were obtained from the Neuropsychology department at UCT and were translated into Afrikaans and isiXhosa copies. The tests were scored using standardised instructions, as outlined in the battery manuals. Tests that required drawings were done on paper.

Language. Boston Naming Test (Goodglass et al., 1983): Measures confrontation naming that takes into account that patients with dysnomia often have greater difficulties with the naming of low frequency objects. Line drawings of objects are presented to participants, requiring them to correctly name each target object within a 20-second interval per trial. Object naming begins with simple vocabulary and increases in difficulty to more rare words. If no response is made within the 20-second period, one phonemic and one semantic prompting cue can be given. The number of correctly produced object names, the number of cues given, and the number of responses that follow the phonemic cue and semantic cue is factored into calculating the score. The total score is the sum of correct spontaneous answers plus correct answers followed by a semantic clue. This test has been used extensively to detect language deficits and has been validated in South Africa (Mosdell et al., 2010; Thomas et al., 2019).

Boston Cookie Theft Picture Test (Goodglass & Kaplan, 1972): Requires the participant to verbally describe what is happening in a detailed picture. Permission to audio-record responses

was requested to facilitate scoring. Scoring is done by adding the total number of complete words spoken and information units. Responses are marked as correct if participants produced acceptable responses without a phonological cue being given. This test has been adapted to eliminate western cultural, language and education bias in neurocognitive screening and has been validated in South Africa (Mosdell et al., 2010).

Memory. Rey Auditory Verbal Learning Test (Rey, 1964): Participants are given a list of 15 independent words (list A) five times, each followed by attempted recall. A second 15-word list (list B) is then presented as an interference trial, before participants are asked to attempt to recall list A. Following a 20-minute interval, delayed recall and recognition of list A is also tested. The test is widely used in the assessment of memory and learning both internationally and in South Africa (Blumenau & Broom, 2011).

Rey-Osterrieth Complex Figure (Rey, 1941): Participants are first asked to replicate a complex geometric line drawing on a blank piece of paper by freehand, and then reproduce it from memory after brief distractions, and again after 20 minutes (delayed recall). Drawings are timed and scored based on accuracy and placement criteria that applies to all three drawing trials (copy trial, 3-minute immediate recall trial, and 20-minute delayed recall trial). Participants receive 2 points when the item is placed and reproduced correctly; 1 point for partially correct locations and reproductions; and 0.5 point for poor placements or reproductions. No point is given when an item is missing or unidentifiable. All points will be added to provide a total score. The test is widely used in South Africa to evaluate visuospatial constructional ability and visual memory in clinical settings and research (Blumenau & Broom, 2011; Ramlall et al., 2014).

Attention. Digit Span forwards (Wechsler, 2008): Participants are required to repeat back increasing lists of numbers in the given order. Each item consists of two trials, each scored 2, 1 or

0 points. Each correct response receives one point out of a total 14. Previous research supports the validity of this test (Clark et al., 2019) and its common usage in South Africa to assess attention deficits in patients (Blumenau & Broom, 2011; Ostrosky-Solís & Lozano, 2006; Peltzer & Phaswana-Mafuya, 2012).

Executive Functioning. Delis-Kaplan Executive Function System (D-KEFS) Trail Making Test (Delis et al., 2001) – Set shifting & psychomotor speed: Involves a series of 5 timed conditions (Visual Scanning, Number Sequencing, Letter Sequencing, Number-Letter Sequencing, Motor Speed). The Visual Scanning condition requires participants to mark all the 3s on the answer page. The Number Sequencing condition requires participants to connect numbers 1 to 16 in order, with the inclusion of distractor letters on the same page. The Letter Sequencing condition requires participants to connect letters A to P in order, with the inclusion of distractor numbers on the same page. In the Number-Letter Switching condition, participants must draw a line that connects alternating numbers and letters (i.e., 1-A-2-B, through to 16-P). The final Motor Speed condition measures basic visuomotor speed. Participants are asked to draw a line over a dotted line that connects squares on the page, as quickly as they can. Each condition includes a short practice trial and participants are asked to complete all trials as fast and precisely as they can. In all conditions except for Visual Scanning, the researcher will identify errors by drawing an "X" over incorrect connections. Participants are required to resume from their last correct connection and the timer will carry on during the connection period. This is scored by how long it takes the participant to complete the test. If the participant makes an error, there is no change in score other than that it will extend the completion time. Several South African-based studies have used the D-KEFS Trail-making Test in identifying cognitive impairments and confirmed its efficacy when applied

to a South African context and culture (Andrews et al., 2012; Chalermchai et al., 2013; Joska et al., 2011; Rosin & Levett, 1989).

D-KEFS Colour-Word Interference Test (Lippa & Davis, 2010) – Response inhibition: This includes four parts. Word task (names of colours printed in black); colour task (rows of blocks printed in coloured ink), inhibition (mismatched colour names and ink colours) and inhibition-switching task (some words have a square around them, while others do not. The words with the squares around them require the name of the word, while the words without the squares, require the name of the coloured ink). In the word task, participants are asked to identify a series of colour words printed in black ink. The colour task requires participants to identify the colour of rows of blocks (e.g., blocks in green, blue or red ink). The word-colour task includes names of colours presented in conflicting ink colours (e.g., the word "red" in blue ink) and requires participants to identify the colour of the ink instead of the word, aiming to inhibit certain responses. The word-colour inhibition task includes a mixture of naming words and naming ink colours. Four scores, as well as an interference score, are generated using the number of items completed on each page, with higher scores reflecting better performance and less interference on reading ability. The D-KEFS colour-word interference test is commonly used in South Africa and has been validated in previous research (Andrews et al., 2012; Blumenau & Broom, 2011; Joska et al., 2011; Skuy et al., 2001).

Controlled Oral Word Association Test (COWAT) (Benton et al., 1983) – Verbal fluency/mental generativity: The COWAT measures verbal creativity in phonemic fluency followed by semantic fluency. Permission to audio record the participant's responses was requested to facilitate scoring. For phonemic fluency, participants are asked to verbally generate as many words as possible that begin with a given alphabet letter (F, A & S), with 60 seconds of

responding allowed for each letter. Participants are asked not to state proper names or places and to avoid giving the same words with different endings (e.g., swim, swimmer, swimming). One point is given for each correct word and the total phonemic fluency score is calculated by adding the number of correct responses for the three pooled letters. For semantic fluency, participants are asked to verbally generate as many words as possible that correspond to a given category (animals, fruits, and colours), with 60 seconds of responding allowed for each category. One point is given for each correct word and the total semantic fluency score is calculated by adding the number of correct responses for the three pooled categories. The total fluency score is the sum of the phonemic and semantic fluency scores. Previous research conducted in South Africa has used this study to distinguish cognitively healthy individuals from those cognitively impaired (Ramlall et al., 2014).

Digit Span backwards (Wechsler, 2008) – Working memory: The participant is read increasing lists of numbers and asked to repeat back the lists in reverse order. For example, if the researcher says “12-11-10-9”, the correct response would be “9-10-11-12”; if the researcher says “5-1-4-8-6”, the correct response would be “6-8-4-1-5”. Both trials for each item are administered, even if the participant gives an incorrect response in trial 1. For each trial, 1 point is awarded for a correct response and no point is given for an incorrect or missing response. The item score is the combined score from the two trials for that item (ranging from 0 to 2). The total score is the sum of item scored out of 16. The Digit Span backwards test has been used widely in South Africa to assess executive functioning in individuals (Blumenau & Broom, 2011; Ostrosky-Solís & Lozano, 2006; Peltzer & Phaswana-Mafuya, 2012).

Weschler Adult Intelligence Scale-IV (WAIS) similarities Test (Wechsler, 2008) – Abstract verbal reasoning: Participants are asked to identify the qualitative relationship or relevant

similarities between a pair of words. For example, participants may be asked how an apple and a pear are alike. Participants get 1 point for each correct similarity. This test is commonly used in South Africa to assess logical thinking, verbal concept formation and verbal abstract reasoning (Cockcroft et al., 2015).

Psychomotor Speed. The Symbol Digit Modalities Test (SDMT) (Pyle, 1913; Whipple, 1910): Involves a simple substitution task in which the participant is given 90 seconds to match numbers with geometric figures. Both written and verbal responses are accepted. Scoring includes the number of correct substitutions made within the given 90 seconds, with a maximum attainable score of 110.

Debriefing Interviews

Debriefing in qualitative research refers to the process whereby feedback is obtained from those involved in the research process about the research design (Lavrakas, 2008). No existing debriefing assessment tool was found to be suitable for the purposes of our design. Therefore, a customised, open-ended interview schedule was administered over the telephone to participants, following the conclusion of the cognitive testing (see Table 1).

Table 1

Questions asked during Debriefing Interviews

Objectives assessed	Questions
1, 2, 3 and 4	What was your experience/ thoughts and feelings during recruitment for the study?
3	What was your experience/ thoughts and feelings locating the testing venue?
4, 5, and 6	What was your experience/ thoughts and feelings before the cognitive testing session began?

4, 5, and 6	What was your experience/ thoughts and feelings during the cognitive testing session?
4, 5, and 6	What was your experience/ thoughts and feelings after the cognitive testing session concluded?
1, 2, 3, 4, 5, and 6	What was your experience/thoughts and feelings towards the study process overall?
1, 2, 3, 4, 5, and 6	What did you enjoy the most about the study?
1, 2, 3, 4, 5, and 6	What did you enjoy the least about the study?
1, 2, 3, 4, and 5	Why might other participants not want to participate in the study?
1, 2, 3, 4, 5, and 6	Do you have any suggestions as to how we might improve this study?
1, 2, 3, 4, 5, and 6	Do you have any other comments or concluding thoughts?

Procedure

Once ethical clearance was granted by the UCT Human Research Ethics Committee (reference number HREC 482/2021) (Appendix A), the study began its participant recruitment. Participant recruitment advertisements were developed and posted at GSH and on social media platforms (Appendix B). Other local hospitals, clinic waiting rooms, and pharmacies were approached to disseminate the advertisement. Additionally, UCT's department of student affairs was utilised to reach all currently registered UCT students in the chance that they may make referrals on behalf of their family/community members. Potential participants were furthermore approached on foot in the respiratory and post-COVD clinic waiting rooms at GSH. Outsourced research assistants, proficient in isiXhosa and Afrikaans, as well as four other researchers were involved in the recruitment of participants and in data collection. Relevant stakeholders and staff

members were contacted via telephone through which they received a thorough brief of the study. An email was additionally sent to each party involved with all the necessary information regarding the study.

Interested participants next filled out a basic online eligibility questionnaire (https://docs.google.com/forms/d/e/1FAIpQLSdVjI1TCKVKrvjT1xg8m3-RWiIxTTwykLRp-fcTWRVkyEgs_w/viewform). This Google Form furthermore asked for participants' contact details as well as their next of kins'. As part of the questionnaire, participants indicated their availability for testing and accessibility of transport to the testing site. Those who qualified were notified via email. This email additionally contained information concerning their ability to consent and the role of the next-of-kin in data collection.

Next-of-kin were contacted via email or telephone and were requested to participate in the research by establishing the primary participant's ability to consent to participate and undergo cognitive testing. Next-of-kin were sent an informed consent form (Appendix C), outlining the study procedure and its aims to facilitate this decision, and were asked to sign it.

Participants were tested approximately one-year (11-18 months) following hospital discharge and each session of testing lasted between 90 and 120 minutes. Testing sessions took place throughout the week and on weekends, and remuneration for transport to the venue was provided.

Researchers met participants at admissions of the New Main Hospital at GSH and then accompanied them to the testing room. Rooms allocated for testing changed throughout data collection but were either situated in the Neurology ward (E7) or the Neuroscience Institute. Once inside the allocated room, participants were given a general overview of what the session would involve and were provided with consent forms (Appendix D). The participants were required to

carefully read and sign these before testing commenced. Participants were encouraged to ask questions at that point. Participants were also made aware, both on paper and verbally, that the outcomes of their results would not form part of their medical records and would not be disclosed to any other individual.

Shortly after, the cognitive testing began. The order of these 11 measures were administered as they are written under 'Material and Measures'. Halfway into testing, a break was issued, and snacks and beverages were made available.

Following this round of testing, participants received a telephonic debriefing in which they were informed about the background information for the current study and their contribution to furthering our understanding of COVID-19. Participants were then administered the debriefing interview.

Theoretical Framework

Criteria for interpreting data output from the current feasibility study was informed by Leon et al. (2011). Becker et al. (2019), Eldridge et al. (2016) and Thabane et al. (2010) have additionally utilised this criterion to evaluate feasibility of RCTs with pilot trial designs. Feasibility criteria includes quantitative measures of participant recruitment and retention, participant screening, randomisation, treatment adherence and fidelity as well as assessment process. For the current design, randomisation, treatment adherence and treatment fidelity were not applicable measures and were therefore discarded. See Table 2.

Table 2

Aspects of Feasibility that can be Examined with a Pilot/Feasibility Study (Leon et al., 2011)

Study component	Feasibility quantification
Screening	Number screened per month
Recruitment	Number enrolled per month

Randomization	Proportion of screen eligible who enrol
Retention	Treatment-specific retention rates
Treatment Adherence	Rates of adherence to protocol for each intervention
Treatment Fidelity	Fidelity rates per unit monitored
Assessment Process	Proportion of planned ratings that are completed; duration of assessment visit

In addition to quantitative measures of feasibility (Leon et al., 2011), Becker et al. (2019) furthermore adopted qualitative measures that assessed acceptability of trial design. Acceptability measures may include a range of standardised tests that gauge the practicality of the research process. However, acceptability measures can also be tailored to feasibility trials, and these typically include questionnaires, interviews, and surveys (Becker et al., 2019; Leon et al., 2011). For the purposes of this study, qualitative data relating to psychological factors that shed light on individual decisions surrounding participation and recruitment were also sought.

Analysis

Outcomes were reported descriptively and narratively. Descriptive statistics, including means and standard deviations were reported for socio-demographic factors and clinical history of participants while raw scores were reported for cognitive test scores. Participant recruitment rate and retention rate was used to assess objectives 1 and 2 which refer to participant eligibility criteria and participants' willingness to partake in the study. Participant recruitment rate was defined as the total number of participants recruited, divided by the number of months spent recruiting. Acceptability of cognitive testing and the study was assessed using both descriptive statistics (participant recruitment rate and retention rate) and narrative reports. Narrative reports were analysed using thematic analysis, a systematic strategy widely used in qualitative data for

identifying and assessing patterns in data (Braun & Clarke, 2006). This method assessed objectives 4, 5 and 6 which refer to feasibility of participants' willingness to undergo the cognitive testing portion of the study, acceptability of assessment tools and feasibility of test scores and study outcomes to inform a future definitive RCT. Lastly, objective 3, which refers to feasibility of testing space location, was assessed using narrative reports. Due to the nature of the design and its small sample size, inferential statistics to compare groups was not conducted.

Reflexivity

As with qualitative data, it is important that researchers evaluate their positionality, beliefs, and biases and how this impacts the integrity of the research design (Dodgson, 2019). As two young Honour's students, conducting research at this scale was a new experience and this inexperience influenced interpretation, test scoring and administration, researcher-participant communication, researcher-administrator communication, and therefore, results. The researchers' positionality as two first language English-speaking able-bodied females, one white and one coloured, additionally influenced our research design and results. Efforts were made to account for positionality by ensuring participants understood what was asked of them throughout the research design and by asking participants to clarify what was not immediately understood by researchers. Researchers were additionally aware that the cohort was potentially cognitively vulnerable and great care was taken in navigating this. Notes were taken throughout the research process to allow us to reflect on how the research design was influenced by our positionality and how the research influenced us.

Results and Discussion

The COVID-19 pandemic broke out in late 2019 and has since resulted in the emergence of long-term cognitive and neuropsychological symptoms in some severely ill patients. Studies

reporting these findings have been conducted under highly irregular and challenging circumstances brought about by the pandemic and its associated regulations, which may explain why few studies have incorporated appropriate control in their designs. Therefore, the current pilot study evaluates the feasibility of executing a study that is sufficiently powered to statistically compare long-term cognitive functioning between patients with COVID-19-induced ARDS, patients with COVID-19 but without ARDS, a subgroup with ARDS from a cause other than COVID-19 and a healthy control sample over the course of a year.

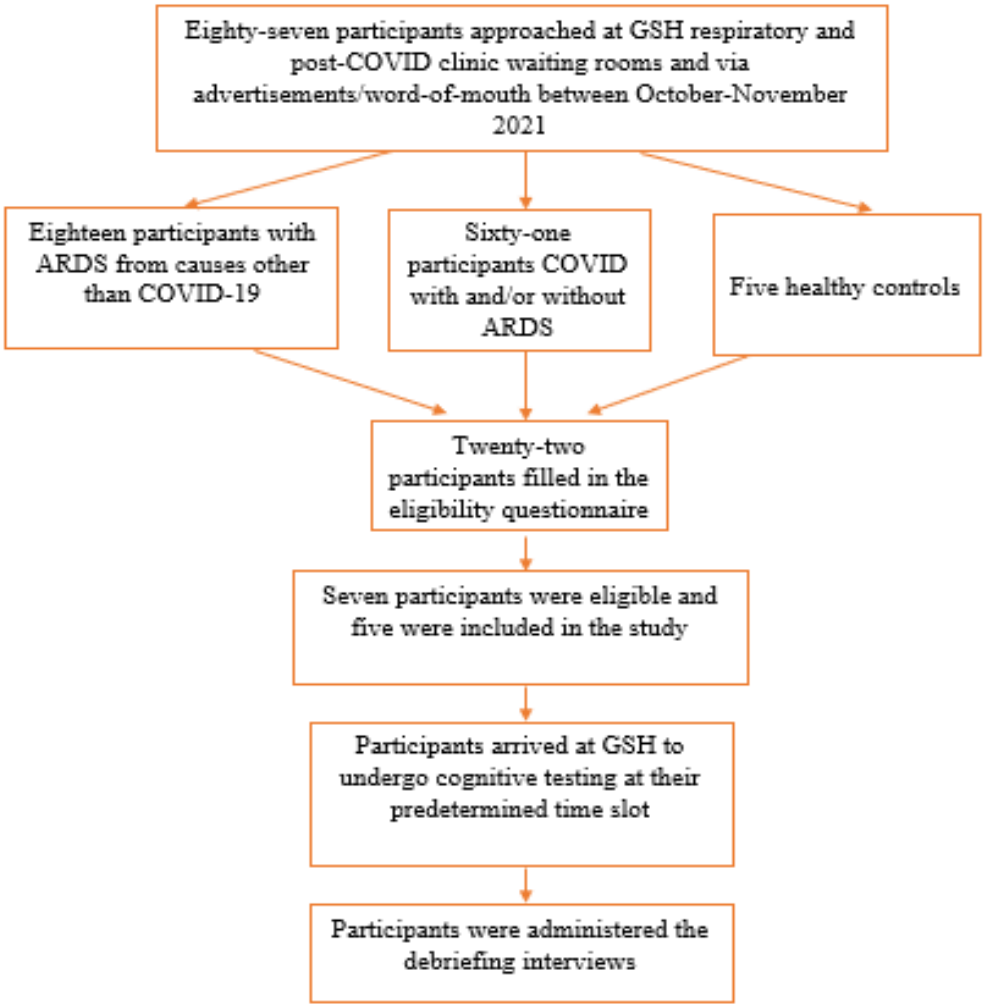
In keeping with convention in many qualitative studies, the results and discussion sections have been combined (Anderson, 2010; Sutton & Austin, 2015; Tremblay et al., 2021).

Participant Recruitment

Sixty-three patients with COVID-19 with and/or without ARDS, 18 patients with ARDS from causes unrelated to COVID-19 and six healthy controls were approached from the beginning of October to the middle of November 2021. Twenty-two participants completed an eligibility questionnaire and from those responses, seven were deemed eligible. Those who could be tested within the window for data collection were included in the final study. See Figure 2.

Figure 2

Flow Diagram of Participant Progression through the Trial



Participants who filled in the questionnaire (14.76%) and were eligible for the study were calculated at 8.05%. Participant recruitment rate was calculated at 3.33%. Retention rate of all five participants was calculated at 100%. All five participants were used to assess all 6 objectives (refer to Table 3 and 4).

Table 3

Socio-demographics and Overview of COVID-clinical History of Sample

Sample	Age	Sex	Race	Education (in years)	Treatment	Group	ICU stay (in days)
Participant 1	49	Female	Coloured	11	High flow oxygen	COVID-19 without ARDS	21
Participant 2	35	Female	White	15	High flow oxygen, CPAP, intubated	COVID-19 with ARDS	141
Participant 3	63	Female	Coloured	18	Ventilation	COVID-19 with ARDS	11
Control 1	54	Female	White	16	N/A	N/A	N/A
Control 2	39	Female	Black	25	N/A	N/A	N/A
Mean (SD)	52 (11.31)	N/A	N/A	17 (5.15)	N/A	N/A	57.67(72.34)

Table 4

Hospital Notes and Course of Illness for COVID-19 Group

Sample	Admission Date	Pre-existing Conditions	Initial Symptoms	Developments	Lasting Symptoms
Participant 1	01/21	Hypertension, asthma, and arthritis	Tight chest, high fever, low oxygen levels and diarrhoea	N/A	Joint and body pain, shortness of breath, severe hair loss, insomnia, and permanently scarred lungs
Participant 2	01/21	6-months pregnant, hyperemesis due to pregnancy.	Severe fatigue, nausea, and coughing	Induced coma, double pneumonia, collapsed lungs leading to tracheotomy, Klebsiella septicaemia, kidney failure and resuscitation four times	Hair loss, fibromyalgia in the legs and nerve damage on much of their right side, deafness in the left ear and tinnitus in the right
Participant 3	12/20	Asthma	Fatigue, cough, and fever	Pneumonia	Severe motor difficulties, hair loss, skin discolouration, 'brain fog', shortness of breath, and difficulties generating and processing language

There were several challenges that arose with regards to participant recruitment. The following points address objectives 1-6, relating to participation eligibility criteria, willingness of participants to partake in the research, feasibility of the testing location, appropriateness of the session structure in terms of time and participant coping, appropriateness of the battery of assessment tools to comprehensively measure neuropsychological functioning without overwhelming the participant, and feasibility of test scoring and study outcomes in determining efficacy of tests in a future definitive RCT: Firstly, recruiting participants from the desired clinical populations and within clinical spaces proved difficult. Based on field notes and observations, it appeared that patients were put off by the location of the testing venue within a hospital. For example, when patients were made aware that testing would take place at GSH, they physically pulled back from researchers and their attention became difficult to sustain. Other patients chose to end the conversation with the researcher immediately following this information. This observation is consistent with studies that report that nearly 50% of those with COVID-19 and ARDS reported symptoms of post-traumatic stress disorder (PTSD) at the one-month follow up (Alemanno et al., 2021). Parker et al. (2015) reported that 25% of ICU patients go on to develop PTSD-like symptoms following discharge. The likelihood of experiencing PTSD-like symptoms is thought to increase with COVID-19 ICU survivors (Murray & Ehlers, 2021). The occurrence of PTSD-like symptoms was said to be especially true for those who experienced more invasive procedures.

Based on our findings and those from the literature, the lack of willingness to participate in the study is expected to be especially pronounced in the cohort of individuals aged 40 to 65 years of age. Indeed, there is a documented decrease in interest to participate in clinical research as age increases (Forsat et al., 2020). The reasons for why this relationship exists is not entirely

clear. However, particularly in the context of the current COVID-19 cohort, it is believed that an older cohort are more likely to have experienced severe illness and therefore might find being within a clinical space triggering and/or traumatising.

Additionally, it appeared that the cohort was dissuaded from partaking due to the length of the testing session. For instance, when patients became aware that the testing session was expected to last two hours, there was visible surprise on patients' faces and their body language communicated a lack of interest. Some patients additionally turned away from researchers, indicating their wish for the conversation to end, and others verbally suggested that the testing session was too long. In fact, older patients were more likely to express these negative responses than younger ones. These reactions are suspected to be particularly true for those who experienced COVID-19 and/or ARDS: Rao et al. (2021) found that more than half of their COVID-19 sample experienced fatigue in the months following hospital discharge. Moreover, their COVID-19 sample experienced greater fatigue than their healthy counterparts. Indeed, literature surrounding 'post-covid fatigue' is fast emerging (Rao et al., 2021; Rudroff et al., 2020) and is strongly associated with changes in mental faculties (Arnold et al., 2020; Goërtz et al., 2020; Mandal et al., 2020). This lasting fatigue is particularly debilitating in those with neurological conditions (Rao et al., 2021). This finding furthermore emphasises the possibility of COVID-19-related trauma within the current cohort and this trauma could be additionally by triggered by thoughts about possible cognitive damage (Arnold et al., 2020).

Indeed, struggling to come to terms with lasting cognitive changes was identified during the debriefing interviews: "If anything, [there is] an emphasis on frustration with my personal progress and trying to gauge them [*sic*] against what I was before the coma and ICU, right after it, and now." The measuring up of oneself was echoed by another participant who additionally felt

nervous about what realisations might come from the session. They further suggested that this fear might be preventing participants from enrolling in the study: “There is a yearning to know for me, but I think fear can keep people away- what will the results be? There could be frustration and people might find it daunting. Fear of being right of [*sic*] the cognitive difficulties.”

Whilst the fear of cognitive changes was evident for some participants, there was still a great curiosity for insight into their current cognitive states:

> [I] feel that it would be nice for the patient to get some insight as to how it went. So that they get the benefit of seeing signs of improvement in their health and abilities or see where they are struggling and need to focus a little more energy going forward.

Another participant suggested that one way to improve recruitment efforts would be to emphasise what participants might gain from participating, that is, feedback about individual levels of functioning. This seems to suggest that while there is the possibility of confronting trauma for participants, this anxiety might be overridden by the desire to know more about one’s cognitive performance. This finding highlights the importance of debriefing in research for critically ill patients and for those with suspected trauma (van Wijk & Harrison, 2013).

The next few points address objectives 1 and 2: Due to the introduction of the protection of personal information act (POPIA), which commenced in early June of 2020 (South African Department of Health, 2020), the current study experienced great difficulties in accessing eligible participants via telephone or email. In previous years, healthcare staff have aided in the recruitment of potential participants by allowing research teams some degree of access to patient databases and contact details. Instead, our approach was to ask our medical collaborators to discuss the study with their patients during their consultations, but this presented challenges. Four doctors expressed

willingness to assist in the recruitment process, but when followed up with, stated that their workloads were so high that there was not enough consultation time to discuss the study.

Thus, for the most part, the current study recruited participants on foot, visiting different clinics within the hospital. Researchers were stationed in respiratory clinic waiting rooms at GSH and approached each patient individually, collecting their names and details. Although care was taken to approach people without being intrusive, researchers found that some patients did not want to engage with recruiters during their visits. Many patients appeared to be asleep whilst waiting for their appointment times and some patients declined to engage with researchers when they approached. This may have been due to a lack of established trust between recruiter and patient.

Indeed, in an investigation of clinical trial recruitment strategies, it was found that 68% of participants were recruited via established community correspondents (Peters-Lawrence et al., 2012). A lack of engagement with participants may have also been because recruitment took place during a time and within a space wherein the patient felt potentially vulnerable. For instance, one researcher approached a patient just before a scheduled operation whereby part of the patient's lungs was to be drained. The patient expressed great fear and anxiety at that moment. Moreover, by conducting our recruitment in public clinic waiting rooms, all those present were made privy to the names and contact details of patients. It then appears that eliciting the help of trusted medical personnel to act as gatekeepers could mitigate disengagement and vulnerability of patients and thereby improve recruitment (van Wijk & Harrison, 2013).

On reflection, whilst the POPIA is designed to uphold and establish ethical communication between parties, clinical studies gearing up to conduct their research just prior to the commencement of the act are having to broach other means of communication that might be

deemed unethical. It is then this ethical conundrum and the POPI Act that requires assessment within the framework of clinical research and consideration by future definitive RCTs. This is especially important as this is believed to have greatly hindered participant recruitment.

A proposed alternative to engage potential participants might be to hand out flyers, advertising the study. However, in clinical research, flyers are not found to be an effective means of recruitment (Peters-Lawrence et al., 2012). Instead, educating participants on the topic that the research team is undertaking has been found to increase recruitment rates. Given that participants were approached whilst waiting for their appointments at the various clinics, researchers were given little time to adequately educate patients on the details of the research. This further emphasises the role of medical personnel in recruiting participants by discussing the research opportunity during consultations.

Indeed, debriefing interviews made it clear that three of our participants were unaware of what our cognitive testing sessions would entail: "...I didn't know too much about what I'm [*sic*] expected to do and I wasn't aware that it's [*sic*] a brain testing thing." Both participant one and a control stated that they thought it would consist of some physical testing, with the control stating they believed it would involve a COVID-19 screening test: "...I was thinking like the testing will be cognitive including the blood and saliva testing as is for COVID-19 testing."

Importantly, the study was unable to acquire any participants with ARDS from causes other than COVID-19. Evidently, there was more engagement from those with COVID-19 related ARDS (see Figure 2). This may be because, during recruitment, researchers introduced the study as a "COVID-19 study". It is also possible that our advertisement caused confusion due to the by-line of both "COVID-19" and "ARDS" alongside each other. This is consistent with researchers' interactions with patients: Patients often asked for clarity about what the study was investigating

and what ARDS was. Therefore, there appeared to be a lot of misinformation surrounding the study for both those enrolled and potential participants. Indeed, there is a need to improve communication between researchers and participants and these findings might further suggest that the initial advertisement needs to be revised.

Thus, findings gathered regarding participant recruitment suggest that establishing a relationship with medical personnel to circumvent the legal and social barriers of participant recruitment is required for producing successful outcomes in the main study. Moreover, the main study should revise its advertising as well as relax its age range to include a younger cohort that is likely to promote recruitment, such as the current study has done.

Cognitive Performance

Digit Span Test Forwards and Backwards

All participants reported difficulty with the Digit Span backwards task. Difficulty was characterised by long pauses that were present between reading sequences and receiving answers. Participant two expressed dread when faced with both the Digit Span forwards and backwards task as they reportedly had a ‘weak’ spot in their cognition for numbers. Two participants asked for sequences to be repeated despite being informed that that would not be allowed. This might indicate the level at which participants were able to attend to information and instruction. Given prior research on how anxiety can interfere with working memory tasks (Lukasik et al., 2019; Moran, 2016), these findings indicate that great care must be taken by the researcher to introduce tasks in a non-threatening manner.

The Rey Auditory Verbal Learning Test

All participants expressed drawing a blank on the Rey Auditory Verbal Learning Task, with three out of five participants taking long to recall words and getting frustrated when they

could not. Two participants asked for the list to be repeated and when they were denied, appeared anxious.

The Rey-Osterrieth Complex Figure

Four out of the five participants expressed fatigue when asked to redraw the Rey-Osterrieth Complex Figure at the twenty-minute delay mark. However, this fatigue and exasperation was not present when asked to immediately recall the drawing. Participant three took particularly long to complete both conditions of this task.

The Symbol Digit Modalities Test

No difficulties were observed or reported during or after the completion of this test.

The D-KEFS Trail-Making test

The D-KEFS Trail-making test was met with little difficulty from the participants with only one control and one patient struggling to orient themselves about the testing paper. This elicited some moments of visible and audible frustration.

The D-KEFS Colour-Word Interference Task

Overall, the participants expressed some fatigue and exasperation towards the D-KEFS colour-word interference task. Participant two made audible groans when presented with the testing placards which might have indicated fatigue and/or frustration. One control was very quick to correct their mistakes and became increasingly annoyed with their errors. The other control found this test and its conditions to be very enjoyable as per their own report.

The Boston Cookie Theft Picture Test, Boston Naming Test, WAIS Similarities, and Controlled Oral Word Association Test (COWAT)

Participant three expressed dread when faced with the language-orientated tests as they had described identifying this area of their cognition to be particularly compromised. One of the

controls appeared anxious when they were informed that the “language portion” of the test would be commencing. Alternatively, participants one and two appeared calm and confident during these tests.

Performance on Tests Overall

While some tests were certainly met with frustration and difficulty, the debriefing interviews revealed that one participant found the testing “...not too challenging.” Overall, participants reported feeling comfortable during the cognitive session: “It was non-threatening.” Most participants reported the testing session to be a positive experience. One participant even compared the testing session to playing a children’s game and used that to evaluate their cognitive progression: “It was playful as well. It reminded me of my childhood, and I could compare my childhood with where I am now.”

Evidently, the tasks themselves did not appear to be too mentally challenging for the cohort and were sometimes even enjoyable. This finding suggests that the number of tests and tests chosen for the study are appropriate for the desired cohort. Although, because of the observed frustration and anxiety of participants, it is recommended that researchers of the main study adopt and strategize encouraging approaches that guide participants through the testing sessions and keep their morale high.

However, it must be noted that disparities existed between what researchers are observing and noting and what is reported by participants. This, again, may speak to the lack of established trust between researcher and participant and perhaps the degree to which trauma is felt and has been experienced by participants. Trust and familiarity between researchers and participants have been documented to facilitate the sharing process in clinical research (Guillemin et al., 2018; Tan, 2011).

Testing Session

Locating the Testing Space

Whilst there was ease during and after the testing session for some participants, interviews revealed that there were difficulties in locating the testing space. One participant stated: "… security tried to send me to a different building." Another participant stated: "[It was] a little frustrating with regards to actually locating the building but once there, I was met at the building entrance, and it was smooth sailing." It is then worth revising the accessibility of the testing venue by providing participants with maps and more precise directions.

Length of Testing Sessions

The following findings were observed via field notes and observation: The length of the cognitive testing sessions and the mental strain demanded by tasks appeared to be an issue for some participants but not others. Breaks were made available at the halfway point of testing for each participant, however, all but one declined. This was despite some participants expressing fatigue, inattention, and irritability during some parts of the testing session. Participant two did require pauses throughout to sip on water. Snacks and beverages were also made available to the participants. Two participants accepted water and a snack while the remaining participants declined. This might suggest that some participants do not require restoration or refuelling during the testing session itself. Subsequently, it appears that participants are initially put off by the idea of undergoing various cognitive tests for a minimum of 90 minutes in one sitting, however, when they are present for the session, fatigue and mental strain does not seem to significantly affect participants. This finding speaks to the poor participant recruitment rate but the 100% participant retention rate. Evidently, it appears beneficial to emphasise that breaks will be issued, and refreshments will be offered during participant recruitment.

Limitations

The current findings should be interpreted within the context of several limitations that make drawing conclusions on the feasibility of conducting the research design difficult. Firstly, it was believed that participant eligibility in terms of language fluency requirements was too broad for the purposes of this study: Controls recruited for the study reported to be fluent in English (and so were assessed by English speakers) but were not first language English speakers and this appeared to affect their performance on various cognitive tests, particularly those that assessed language. This was best demonstrated by the results of the Boston Cookie Theft Picture test in which the controls reported far greater utterances for time spoken than the other participants. For other language tasks, the controls performed on par and sometimes even worse than one of the participants. See Table 5. This might explain the feelings and expressions of anxiety for the controls during the tests that tapped into language functioning, which would not necessarily be a factor in the full-scale study given that first-language isiXhosa and Afrikaans researchers will conduct the sessions when required.

This same finding was reported by Kisser et al. (2012) who investigated neuropsychological performance of native English speakers versus non-native English speakers. In their sample, there were no significant differences between performance on tests of executive functioning, verbal memory, visuo-spatial tasks, and psychomotor speed, only those that were mediated by, or tapped into, language. Siedlecki et al. (2010) further reported that performance on some neuropsychological language tests were dependent on language, with English speakers outperforming Spanish speakers. However, it was hypothesised that cognitive performance was mediated by education. Moreover, Zhang et al. (2019) noted how some of the same tests used for the current study are designed by, and biased, towards a western population. Because there remains

little research on the issue of native English speakers versus non-native English speakers in South Africa and the small sample size of the current study, we were unable to make conclusions on participant eligibility and whether this might pose a problem for a large-scale future definitive RCT (objective 1). Moreover, the broad language requirements for participant eligibility further restricted our ability to appropriately assess objectives 5 and 6 which refer to acceptability of assessment tools and our ability to determine efficacious study outcomes in a future RCT.

Table 5

Cognitive Test Results of Participants

Sample	WAIS Similarities	COWAT			Digit Span Forwards	Digit Span Backwards	D-KEFS Colour-Word Interference		Complex-figure Drawing	
		Letter fluency	Categories	Category-switching			Inhibition (in seconds)	Inhibition/switching (in seconds)	Immediate recall	20-min delay
Participant 1	13	36	17	7	9	7	113	157	13	21
Participant 2	21	36	26	8	11	8	102	138	23.5	20.5
Participant 3	16	38	18	8	9	3	66	100	3.5	5.5
Control 1	18	47	23	6	9	4	55	45	27	27
Control 2	11	31	17	6	7	7	65	73	36	36

Sample	Boston Naming Task	Boston Cookie Theft Picture Task			Symbol Digit Modalities Test	D-KEFS Trial-Making Task	Ray Auditory Verbal Learning Task	
		Time spoken (sec.)	Total syllables	Utterances		Number-letter sequencing (in seconds)	Trial 5	Trial 7
Participant 1	23	32	59	3	56	93	6	11
Participant 2	30	39	104	4	56	97	15	15
Participant 3	26	129	534	15	51	160	9	10
Control 1	30	99	475	15	58	58	13	14
Control 2	25	60	71	10	53	95	11	12

Overall, the study struggled to ascertain a homogenous sample between groups. For instance, our sample was not matched for education. Although it appears that education levels and number of years of study did appear to affect performance on some of the cognitive tasks, the current investigation was not concerned with test results. It is hypothesised that even with a larger sample size, homogeneity will be difficult to ascertain due to the variation in medical history of participants (see Table 3 and 4). Great variability of clinical journeys in COVID-19 patients have been noted by (Daroische et al., 2021; Li et al., 2020). Moreover, variations in medical histories are likely to result in differing cognitive performance, as per the literature (Daroische et al., 2021). Furthermore, variations in medical history, including comorbidities, is likely to increase as a population ages (Knechel, 2013) and is therefore a caveat for the main study which consists of an older cohort. As such, variations in medical history between participants impacted our ability to assess the test scores in determining effects between groups (objective 6). One possible solution to this problem would be to increase the sample size so that analyses can be performed on subgroups within subgroups and therefore, this limitation might not exist for the greater sample size of the full-scale study.

Further areas of the feasibility design remain unclear: Although none of our participants overtly reported fatigue, because of our small sample size, we could not conclude that participants in a full-scale investigation will not feel the effects of testing fatigue as this is a well-documented phenomenon in clinical research (Adesope et al., 2017; Dunlosky et al., 2013; Greving & Richter, 2018; Karpicke, 2017; Rowland, 2014; Schwieren et al., 2017). If testing fatigue does become an issue associated with the cohort of the main study, it is recommended that tests are grouped together according to the domains of cognition that they measure and split among different testing sessions. Caputo et al. (2021) suggested that shortening testing sessions may improve participant

recruitment as there are already so many barriers that hinder clinical research participation during the COVID-19 pandemic. Cutting down the scope of the cognitive tests, however, is not recommended. This is to ensure that a wide and comprehensive range of tests are still utilised to investigate the new phenomenon of COVID-19 neuropsychological sequelae. Therefore, due to our small sample size, we were hindered in our assessment of objectives 4, 5 and 6, that is feasibility of participants' willingness to undergo several and long cognitive tests in one sitting, particularly the potentially cognitively-vulnerable sample, appropriateness of the battery of assessment tools to comprehensively measure neuropsychological functioning without overwhelming the participant and the feasibility of test scoring and study outcomes in determining efficacy of tests in a future definitive RCT. While the sample size for our study was small, we encountered, and collected data from, many people during recruitment which we believe helps validate our findings, especially with regards to objectives 1,2, and 4 (see Figure 2).

On further reflection, it is believed that the researchers' and participants' positionality resulted in some limitations: While both researchers and participants were women, which we believe controlled for a gender-based power dynamic, data may have been influenced by cultural differences between participants and researchers. Researchers were also of different ethnic and cultural backgrounds which could have led to discrepancies in data recording, such as observations and field notes, and test scoring. A participant may have been more comfortable in an environment with a researcher who was of the same ethnicity and culture and could have influenced the quantity and quality of experiences shared, particularly during the debriefing interviews. It was noted that some participants could have been uncomfortable sharing certain traumas, especially with students who could be considered exploiting vulnerable participants (i.e., using their data) for personal gain (i.e., the completion of an Honour's degree).

Lastly, because the study was unable to acquire a patient with ARDS from causes unrelated to COVID-19, the study is limited in generalising its results to those that include patients with ARDS exclusively, such as that of the main study. That being said, both ARDS from causes other than COVID-19 and COVID-19-induced ARDS have been found to have similar clinical outcomes, treatments, levels of inflammatory biomarkers, respiratory levels and gas exchange (Bain et al., 2021; Haudebourg et al., 2020; Wilson et al., 2020). These similarities suggest that COVID-19-induced ARDS and ARDS from other causes are not two distinct phenotypes (Bos et al., 2020; Ziehr et al., 2020). Subsequently, failing to include a patient with ARDS from causes other than COVID-19 is not believed to have significantly affected findings and generalisability.

Conclusion

The results from this study suggest that a large-scale future definitive RCT may be feasible following several amendments, namely concerning participant eligibility and participant recruitment. The creation of a multidisciplinary research network will be pivotal to successful recruitment in the current legal and socio-medical climate. An important avenue of inquiry for future feasibility studies will be to focus on healthcare professionals who form a vital part of the recruitment process to gain more nuanced insight into the barriers associated with actively collaborating. This study has also brought to light the potentially unforeseen challenges to clinical research that the POPIA has brought and future research in South Africa is needed to clearly map its repercussions, weighing these up against the barriers that POPIA presents to critical healthcare research. It is also worth revising the length of testing sessions to mitigate potential harm to participants.

Although this study was unable to appropriately assess all its objectives due to the small sample size, the data gathered was sufficient to appropriately guide amendments to the full-scale

protocol in question. Given the many barriers to recruitment and testing in the current clinical cohort during pandemic times, this study provides strong support for the use of feasibility studies in designing large-scale investigations of neuropsychological functioning and recovery.

References

Adesope, O. O., Trevisan, D. A., & Sundararajan, N. (2017). Rethinking the use of tests: A meta-analysis of practice testing. *Rev. Educ. Res.* 87, 659–701. https://doi.org/10.3102/0034654316689306

Adhikari, N., Tansey, C. M., McAndrews, M. P., Matté, A., Pinto, R., Cheung, A. M., Diaz-Granados, N., & Herridge, M. S. (2011). Self-reported depressive symptoms and memory complaints in survivors five years after ARDS. *Chest, 140*(6), 1484–1493. https://doi.org/10.1378/chest.11-1667

Alemanno, F., Houdayer, E., Parma, A., Spina, A., Del Forno, A., Scatolini, A., Angelone, S., Brugliera, L., Tettamanti, A., Beretta, L., & Iannaccone, S. (2021). COVID-19 cognitive deficits after respiratory assistance in the subacute phase: A COVID-rehabilitation unit experience. *PloS one, 16*(2), e0246590. https://doi.org/10.1371/journal.pone.0246590

Anand, P., Al-Faraj, A., Sader, E., Dashkoff, J., Abdennadher, M., Murugesan, R., Cervantes-Arslanian, A. M., & Daneshmand, A. (2020). Seizure as the presenting symptom of COVID-19: A retrospective case series. *Epilepsy & Behavior, 107335.* https://doi.org/10.1016/j.yebeh.2020.107335

Anderson, C. (2010). Presenting and evaluating qualitative research. *American journal of pharmaceutical education, 74*(8), 141. https://doi.org/10.5688/aj7408141

Andrews, K., Shuttleworth-Edwards, A., & Radloff, S. (2012). Normative indications for Xhosa speaking unskilled workers on the Trail Making and Stroop Tests. *Journal Of Psychology in Africa, 22*(3), 333-341. https://doi.org/10.1080/14330237.2012.10820538

Arnold, D. M., Burns, K. E., Adhikari, N. K., Kho, M. E., Meade, M. O., Cook, D. J., & McMaster Critical Care Interest Group (2009). The design and interpretation of pilot trials in clinical research in critical care. *Critical care medicine*, *37*(1 Suppl), S69–S74. https://doi.org/10.1097/CCM.0b013e3181920e33

Arnold, D. T., Hamilton, F. W., Milne, A., Morley, A. J., Viner, J., Attwood, M., Noel, A., Gunning, S., Hatrick, J., Hamilton, S., Elvers, K. T., Hyams, C., Bibby, A., Moran, E., Adamali, H. I., Dodd, J. W., Maskell, N. A., & Barratt, S. L. (2020). Patient outcomes after hospitalisation with COVID-19 and implications for follow-up: results from a prospective UK cohort. *Thorax*, *76*(4), 399–401. https://doi.org/10.1136/thoraxjnl-2020-216086

Bain, W., Yang, H., Shah, F. A., Suber, T., Drohan, C., Al-Yousif, N., DeSensi, R. S., Bensen, N., Schaefer, C., Rosborough, B. R., Somasundaram, A., Workman, C. J., Lampenfeld, C., Cillo, A. R., Cardello, C., Shan, F., Bruno, T. C., Vignali, D., Ray, P., … Kitsios, G. D. (2021). COVID-19 versus non-COVID-19 acute respiratory distress syndrome: Comparison of demographics, physiologic parameters, inflammatory biomarkers, and clinical Outcomes. *Annals of the American Thoracic Society*, *18*(7), 1202–1210. https://doi.org/10.1513/AnnalsATS.202008-1026OC

Becker, K., Park, A., Boustani, M., & Chorpita, B. (2019). A pilot study to examine the feasibility and acceptability of a coordinated intervention design to address treatment engagement challenges in school mental health services. *Journal Of School Psychology, 76,* 78-88. https://doi.org/10.1016/j.jsp.2019.07.013

Beghi, E., Feigin, V., Caso, V., Santalucia, P., & Logroscino, G. (2020). COVID-19 infection and neurological complications: Present findings and future predictions. *Neuroepidemiology, 54*, 364-369. https://doi.org/10.1159/000508991

Bein, T., Weber-Carstens, S., & Apfelbacher, C. (2018). Long-term outcome after the acute respiratory distress syndrome: Different from general critical illness? *Current opinion in critical care*, *24*(1), 35–40. https://doi.org/10.1097/MCC.0000000000000476

Benton, A. L., Hamsher, K. D., Varney, N. R., & Spreen, O. (1983). *Judgment of Line Orientation*. New York: Oxford University Press.

Blumenau, J., & Broom, Y. (2011). Performance of South African adolescents on two versions of the Rey Auditory Verbal Learning Test. *South African Journal of Psychology, 41*(2), 228–238. https://doi.org/10.1177/008124631104100211

Bos, L., Paulus, F., Vlaar, A., Beenen, L., & Schultz, M. J. (2020). Subphenotyping acute respiratory distress syndrome in patients with COVID-19: Consequences for ventilator management. *Annals of the American Thoracic Society*, *17*(9), 1161–1163. https://doi.org/10.1513/AnnalsATS.202004-376RL

Bougakov, D., Podell, K., & Goldberg, E. (2021). Multiple Neuroinvasive Pathways in COVID-19. *Molecular Neurobiology*, *58*(2), 564–575. https://doi.org/10.1007/s12035-020-02152-5.

Braun, V., & Clarke, V. (2006). Using thematic analysis in psychology. *Qualitative Research in Psychology, 3 (*2), 77-101. https://doi.org/10.1191/1478088706qp063oa

Burks, S. M., Rosas-Hernandez, H., Alejandro Ramirez-Lee, M., Cuevas, E., & Talpos, J. C. (2021). Can SARS-CoV-2 infect the central nervous system via the olfactory bulb or the

blood-brain barrier?. *Brain, behavior, and immunity*, *95*, 7–14. https://doi.org/10.1016/j.bbi.2020.12.031

Caputo, E., Feter, N., Rombaldi, A., Silva, M., & Reichert, F. (2021). What are the challenges of epidemiological research during the COVID-19 pandemic?. *Motriz: Revista De Educação Física*, *27*. https://doi.org/10.1590/s1980-657420210000200

Carlson, C., & Huang, D. (2013). The adult respiratory distress syndrome cognitive outcomes study: Long-term neuropsychological function in survivors of acute lung injury. *Critical Care*, *17*(3), 317. https://doi.org/10.1186/cc12709

Chalermchai, T., Valcour, V., Sithinamsuwan, P., Pinyakorn, S., Clifford, D., Paul, R. H., Tipsuk, S., Fletcher, J. L., Degruttola, V., Ratto-Kim, S., Hutchings, N., Shikuma, C., Ananworanich, J., & The SEARCH 007 and 011 study groups (2013). Trail Making Test A improves performance characteristics of the International HIV Dementia Scale to identify symptomatic HAND. *Journal of neurovirology*, *19*(2), 137–143. https://doi.org/10.1007/s13365-013-0151-4

Chen, T., Wu, D., Chen, H., Yan, W., Yang, D., Chen, G., Ma, K., Xu, D., Yu, H., Wang, H., Wang, T., Guo, W., Chen, J., Ding, C., Zhang, X., Huang, J., Han, M., Li, S., Luo, X., … Wang, T. (2020). Clinical characteristics of 113 deceased patients with coronavirus disease 2019: Retrospective study. *BMJ*, *368*. https://doi.org/10.1136/bmj.m1091

Chowdhury, M. A., Hossain, N., Kashem, M. A., Shahid, M. A., & Alam, A. (2020). Immune response in COVID-19: A review. *Journal of Infection and Public Health*, 13(11), 1619–1629. https://doi.org/10.1016/j.jiph.2020.07.001

Clark, H., Martin, P., & Schroeder, R. (2019). Digit Span forward as a performance validity test in dementia evaluations: Specificity in mild cognitive impairment, mild dementia, and

moderate dementia. *Archives of Clinical Neuropsychology*, *34*(6), 837. https://doi.org/10.1093/arclin/acz035.05

Cockcroft, K., Alloway, T., Copello, E., & Milligan, R. (2015). A cross-cultural comparison between South African and British students on the Wechsler Adult Intelligence Scales, Third Edition (WAIS-III). *Frontiers in Psychology. 6.* https:dx.doi.org/10.3389/fpsyg.2015.00297.

Cox, C. L. (2020). 'Healthcare Heroes': problems with media focus on heroism from healthcare workers during the COVID-19 pandemic. *Journal of Medical Ethics,* 46, 510-513. http://dx.doi.org/10.1136/medethics-2020-106398

Daroische, R., Hemminghyth, M., Eilertsen, T., Breitve, M., & Chwiszczuk, L. (2021). Cognitive impairment after COVID-19—A review on objective test data. *Frontiers in Neurology*. https:dx.doi.org/10.3389/fneur.2021.699582

Davydow, D. S., Hough, C. L., Levine, D. A., Langa, K. M., & Iwashyna, T. J. (2013). Functional disability, cognitive impairment, and depression after hospitalization for pneumonia. *The American Journal of Medicine*, *126*(7), 615-624.

Delis, D. C., Kaplan, E., & Kramer, J. H. (2001). *D-KEFS Executive Function System: Examiners Manual.* San Antonio: Psychological Corporation.

Desai, I., Manchanda, R., Kumar, N., Tiwari, A., & Kumar, M. (2021). Neurological manifestations of coronavirus disease 2019: exploring past to understand present. *Neurological sciences: Official Journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology*, *42*(3), 773–785. https://doi.org/10.1007/s10072-020-04964-8

Dodgson, J. E. (2019). Reflexivity in qualitative research. *Journal of Human Lactation, 35*(2), 220–222. https://doi.org/10.1177/0890334419830990

Drummond, A. (2017). Feasibility and pilot studies: Why are they important? *British Journal of Occupational Therapy, 80*(6), 335–336. https://doi.org/10.1177/0308022617697743

Dunlosky, J., Rawson, K. A., Marsh, E. J., Nathan, M. J., & Willingham, D. T. (2013). Improving students' learning with effective learning techniques: Promising directions from cognitive and educational Psychology. *Psychological science in the public interest: A journal of the American Psychological Society*, *14*(1), 4–58. https://doi.org/10.1177/1529100612453266

Eldridge, S. M., Lancaster, G. A., Campbell, M. J., Thabane, L., Hopewell, S., Coleman, C. L., & Bond, C. M. (2016). Defining feasibility and pilot studies in preparation for randomised controlled trials: Development of a conceptual framework. *PloS one*, *11*(3), e0150205. https://doi.org/10.1371/journal.pone.0150205

Food and Drug Administration. (2021). *Conduct of clinical trials of medical products during the COVID-19 public health emergency: Guidance for industry, investigators, and institutional review boards* [White paper]. https://www.fda.gov/media/136238/download.

Forsat, N., Palmowski, A., Palmowski, Y., Boers, M., & Buttgereit, F. (2020). Recruitment and retention of older people in clinical research: A systematic literature review. *Journal of the American Geriatrics Society*, *68*(12), 2955-2963. https://doi.org/10.1111/jgs.16875

Goërtz, Y., Van Herck, M., Delbressine, J., Vaes, A., Meys, R., Machado, F., Houben-Wilke, S., Burtin, C., Posthuma, R., Franssen, F. M. E., van Loon, N., Haijan, B., Spies, Y., Vijlbrief, H., van ‘t Hul, A. J., Janssen, D. J. A., & Spruit, M. A. (2020). Persistent

symptoms 3 months after a SARS-CoV-2 infection: the post-COVID-19 syndrome?. *ERJ Open Research*, *6*(4), 00542-2020. https://doi.org/10.1183/23120541.00542-2020

Goodglass, H., & Kaplan, E. (1972). *The assessment of aphasia and related disorders*. Lea & Febiger.

Goodglass, H., Kaplan, E., & Weintraub, S. (1983). *Boston naming test*. Philadelphia, PA: Lea & Febiger.

Greving, S., & Richter, T. (2018). Examining the testing effect in university teaching: Retrievability and question format matter. *Frontiers In Psychology*, *9*. https://doi.org/10.3389/fpsyg.2018.02412.

Guillemin, M., Barnard, E., Allen, A., Stewart, P., Walker, H., Rosenthal, D., & Gillam, L. (2018). Do research participants trust researchers or their institutions? *Journal of Empirical Research on Human Research Ethics*, *13*(3), 285-294. https://doi.org/10.177/155626418763253

Hampshire, A., Trender, W., Chamberlain, S. R., Jolly, A. E., Grant, J. E., Patrick, F., Mazibuko, N., Williams, S. C. R., Barnby, J. M., Hellyer, P., & Mehta, M. A. (2021). Cognitive deficits in people who have recovered from COVID-19. *The Lancet, 39*(101044). https://doi.org/10.1016/j.eclinm.2021.101044

Haudebourg, A. F., Perier, F., Tuffet, S., de Prost, N., Razazi, K., Mekontso Dessap, A., & Carteaux, G. (2020). Respiratory mechanics of COVID-19- versus non-COVID-19-associated acute respiratory distress syndrome. *American Journal of Respiratory and Critical Care Medicine*, *202*(2), 287–290. https://doi.org/10.1164/rccm.202004-1226LE

Helms, J., Kremer, S., Merdji, H., Clere-Jehl, R., Schenck, M., Kummerlen, C., Collange, O., Boulay, C., Fafi-Kremer, S., Ohana, M., & Anheim, M. (2020). Neurologic features in

severe SARS-CoV-2 infection. *New England Journal of Medicine, 382,* 2268-2270. https://www.nejm.org/doi/10.1056/NEJMc2008597

Herridge, M. S., Moss, M., Hough, C. L., Hopkins, R. O., Rice, T. W., Bienvenu, O. J., & Azoulay, E. (2016). Recovery and outcomes after the acute respiratory distress syndrome (ARDS) in patients and their family caregivers. *Intensive care medicine, 42*(5), 725-738.

Hopkins, R. O., & Bigler, E. D. (2012). Neuroimaging of anoxic injury: Implications for neurorehabilitation. *NeuroRehabilitation*, *31*(3), 319-329. https://doi.org/10.3233/NRE-2012-0799

Iodice, F., Cassano, V., & Rossini, P. M. (2021). Direct and indirect neurological, cognitive, and behavioral effects of COVID-19 on the healthy elderly, mild-cognitive-impairments and Alzheimer's disease populations. *Neurological Sciences*, *42*, 455-465. https://doi.org/10.1007/s10072-020-04902-8

Islam, N., Sharp, S. J., Chowell, G., Shabnam, S., Kawachi, I., Lacey, B., Massaro, J. M., D'Agostino, R. B., & White, M. (2020). Physical distancing interventions and incidence of coronavirus disease 2019: Natural experiment in 149 countries. *BMJ, 370* (m2743). https://doi.org/10.1136/bmj.m2743

Iwashyna, T. J., Cooke, C. R., Wunsch, H., & Kahn, J. M. (2012). Population burden of long-term survivorship after severe sepsis in older Americans. *Journal of the American Geriatrics Society*, *60*(6), 1070–1077. https://doi.org/10.1111/j.1532-5415.2012.03989.x

Joska, J. A., Westgarth-Taylor, J., Hoare, J., Thomas, K. G., Paul, R., Myer, L., & Stein, D. J. (2011). Validity of the international HIV dementia scale in South Africa. *AIDS patient care and STDs*, *25*(2), 95–101. https://doi.org/10.1089/apc.2010.0292

Karpicke, J. D. (2017). “Retrieval-based learning: a decade of progress,” in *Cognitive Psychology of Memory, of Learning and Memory: A Comprehensive Reference*, Vol. 2, ed. J. T. Wixted (Oxford: Academic Press), 487–514. https://doi.org/10.1016/B978-0-12-809324-5.21055-9

Kempuraj, D., Selvakumar, G. P., Ahmed, M. E., Raikwar, S. P., Thangavel, R., Khan, A., Zaheer, S. A., Iyer, S. S., Burton, C., James, D., & Zaheer, A. (2020). COVID-19, Mast cells, cytokine storm, psychological stress, and neuroinflammation. *The Neuroscientist, 26*(5-6), 402-414. https://doi.org/10.1177/1073858420941476

Kisser, J., Wendell, C., Spencer, R., & Waldstein, S. (2012). Neuropsychological performance of native versus non-native English speakers. *Archives Of Clinical Neuropsychology, 27*(7), 749-755. https://doi.org/10.1093/arclin/acs082

Klingenstein, M., Klingenstein, S., Neckel, P., Mack, A., Wagner, A. P., Kleger, A., Liebau, S., & Milazzo, A. (2020). (2020). Evidence of SARS-CoV2 entry protein ACE2 in the human nose and olfactory bulb. *Cells Tissues Organs, 209*(4-6), 155-164. https://doi.org/10.1159/000513040

Knechel, N. A. (2013). The challenges of enrolling older adults into intervention studies. *The Yale journal of biology and medicine, 86*(1), 41–47.

Koralnik, I. J., & Tyler, K. L. (2020). COVID-19: A global threat to the nervous system. *Annals of Neurology, 88*(1), 1-11. https://doi.org/10.1002/ana.25807

Kumar, M., Patel, A. K., Shah, A. V., Raval, J., Rajpara, N., Joshi, M., & Joshi, C. G. (2020). First proof of the capability of wastewater surveillance for COVID-19 in India through detection of genetic material of SARS-CoV-2. *Science of The Total Environment, 746*, 141326.

Lavrakas, P. J. (2008). *Encyclopedia of survey research methods* (Vols. 1-0). Thousand Oaks, CA: Sage Publications, Inc. doi: 10.4135/9781412963947

Leon, A., Davis, L., & Kraemer, H. (2011). The role and interpretation of pilot studies in clinical research. *Journal Of Psychiatric Research*, *45*(5), 626-629. https://doi.org/10.1016/j.jpsychires.2010.10.008

Lewis, A., Frontera, J., Placantonakis, D. G., Lighter, J., Galetta, S., Balcer, L., & Melmed, K. R. (2021). Cerebrospinal fluid in COVID-19: A systematic review of the literature. *Journal of the Neurological Sciences*, *421*, 117316. https://doi.org/10.1016/j.jns.2021.117316

Li, L. Q., Huang, T., Wang, Y. Q., Wang, Z. P., Liang, Y., Huang, T. B., Zhang, H. Y., Sun, W., & Wang, Y. (2020). COVID-19 patients' clinical characteristics, discharge rate, and fatality rate of meta-analysis. *Journal of medical virology*, *92*(6), 577–583. https://doi.org/10.1002/jmv.25757

Lippa, S., & Davis, R. (2010). Inhibition/switching is not necessarily harder than inhibition: An analysis of the D-KEFS color-word interference test. *Archives of Clinical Neuropsychology*, *25*(2), 146-152. https://doi.org/10.1093/arclin/acq001

Liu, Y., Sawalha, A. H., & Lu, Q. (2021). COVID-19 and autoimmune diseases. *Current Opinion in Rheumatology*, *33*(2), 155–162. https://doi.org/10.1097/BOR.0000000000000776

Lukasik, K. M., Waris, O., Soveri, A., Lehtonen, M., & Laine, M. (2019). The relationship of anxiety and stress with working memory performance in a large non-depressed sample. *Frontiers in psychology*, *10*, 4. https://doi.org/10.3389/fpsyg.2019.00004

Mandal, S., Barnett, J., Brill, S., Brown, J., Denneny, E., & Hare, S., Heightman, M., Hillman, T. E., Jacob, J., Jarvis, H. C., Lipman, M. C. I., Naidu, S. B., Nair, A., Porter, J. C.,

Tomlinson, G. S., & Hurst, J. R. (2020). 'Long-COVID': A cross-sectional study of persisting symptoms, biomarker and imaging abnormalities following hospitalisation for COVID-19. *Thorax, 76*(4), 396-398. https://doi.org/10.1136/thoraxjnl-2020-215818

Mao, L., Jin, H., Wang, M., Hu, Y., Chen, S., He, Q., Chang, J., Hong, C., Zhou, Y., Wang, D., Miao, X., Li, Y., & Hu, B. (2020). Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurology, 77*(6), 683–690. https://doi.org/10.1001/jamaneurol.2020.1127

Mehta, P., McAuley, D. F., Brown, M., Sanchez, E., Tattersall, R. S., & Manson, J. J. (2020). COVID-19: Consider cytokine storm syndromes and immunosuppression. The Lancet, 395(10229), 1033–1034. https://doi.org/10.1016/S0140-6736(20)30628-0

Mehta, S., Machado, F., Kwizera, A., Papazian, L., Moss, M., Azoulay, E., & Herridge, M. (2021). COVID-19: A heavy toll on health-care workers. *The Lancet, 9*(3), 226-228. https://doi.org/10.1016/S2213-2600(21)00068-0

Mikkelsen, M. E., Christie, J. D., Lanken, P. N., Biester, R. C., Thompson, B. T., Bellamy, S. L., Localio, A. R., Demissie, E., Hopkins, R. O., & Angus, D. C. (2012). The adult respiratory distress syndrome cognitive outcomes study: Long-term neuropsychological function in survivors of acute lung injury. *American Journal of Respiratory and Critical Care Medicine, 185*(12), 1307-1315.

Montalvan, V., Lee, J., Bueso, T., De Toledo, J., & Rivas, K. (2020). Neurological manifestations of COVID-19 and other coronavirus infections: A systematic review. *Clinical Neurology and Neurosurgery, 194*, 105921.

Moran, T. P. (2016). Anxiety and working memory capacity: A meta-analysis and narrative review. *Psychological Bulletin, 142*(8), 831–864. https://doi.org/10.1037/bul0000051

Mosdell, J., Balchin, R. M., & Ameen, O. S. (2010). Adaptation of aphasia tests for neurocognitive screening in South Africa. *South African Journal of Psychology*, http://hdl.handle.net/11427/28890

Murray, H., & Ehlers, A. (2021). Cognitive therapy for moral injury in post-traumatic stress disorder. *The Cognitive Behaviour Therapists, 14*(e8), 1-19. https://doi.org/10.3233/ADR-200194

Neumann, B., Schmidbauer, M. L., Dimitriadis, K., Otto, S., Knier, B., Niesen, W. D., Hosp, J. A., Günther, A., Lindemann, S., Nagy, G., Steinberg, T., Linker, R. A., Hemmer, B., & Bösel, J. (2020). Cerebrospinal fluid findings in COVID-19 patients with neurological symptoms. *Journal of the Neurological Sciences*, *418*, 117090. https://doi.org/10.1016/j.jns.2020.117090

Nuzzo, D., & Picone, P. (2020). Potential neurological effects of severe COVID-19 infection. *Neuroscience Research*, 158, 1-5. https://dx.doi.org/10.1016%2Fj.neures.2020.06.009

Ostrosky-Solís, F., & Lozano, A. (2006). Digit span: Effect of education and culture. *International Journal of Psychology*, *41*(5), 333-341. https://doi.org/10.1080/00207590500345724

Paces, J., Strizova, Z., Smrz, D., & Cerny, J. (2020). COVID-19 and the immune system. *Physiological Research*, *69*(3), 379–388. https://doi.org/10.33549/physiolres.934492

Parker, A., Sricharoenchai, T., Raparla, S., Schneck, K., Bienvenu, O., & Needham, D. (2015). Posttraumatic stress disorder in critical illness survivors. *Critical Care Medicine*, *43*(5), 1121-1129. https://doi.org/10.1097/ccm.0000000000000882

Peltzer, K., & Phaswana-Mafuya, N. (2012). Cognitive functioning and associated factors in older adults in South Africa. *South African Journal of Psychiatry, 18*(4), 7. https://doi.org/10.4102/sajpsychiatry.v18i4.368

Peters-Lawrence, M., Bell, M., Hsu, L., Osunkwo, I., Seaman, P., Blackwood, M., Guillaume, E., Bellevue, R., Krishnamurti, L., Smith, W., Dampier, C., & Minniti, C. (2012). Clinical trial implementation and recruitment: Lessons learned from the early closure of a randomized clinical trial. *Contemporary Clinical Trials, 33*(2), 291-297. https://doi.org/10.1016/j.cct.2011.11.018

Polito, A., Brouland, J., Porcher, R., Sonneville, R., Siami, S., Stevens, R., Guidoux, C., Maxime, V., de la Grandmaison, G., Chrétien, F., Gray, F., Annane, D., & Sharshar, T. (2011). Hyperglycaemia and apoptosis of microglial cells in human septic shock. *Critical Care*, 15(3). https://dx.doi.org/10.1186%2Fcc10244

Prince, L. C., & Wort, S. J. (2017). Pulmonary hypertension in ARDS: Inflammation matters! *Thorax, 72*(5), 396-397. http://dx.doi.org/10.1136/thoraxjnl-2015-208067

Pyle, W. H. (1913). The examination of school children: A manual of directions and norms. New York: Macmillan.

Rabinovitz, B., Jaywant, A., & Fridman, C. B. (2020). Neuropsychological functioning in severe acute respiratory disorders caused by the coronavirus: Implications for the current COVID-19 pandemic. *The Clinical Neuropsychologist.* https://doi.org/10.1080/13854046.2020.1803408

Ragab, D., Salah Eldin, H., Taeimah, M., Khattab, R., & Salem, R. (2020). The COVID-19 cytokine storm; what we know so far. *Frontiers in Immunology, 11* (1446). https://doi.org/10.3389/fimmu.2020.01446

Raghavan, K., Dedeepiya, V., Suryaprakash, V., Rao, K., Ikewaki, N., Sonoda, T., Levy, G. A., Iwasaki, M., Senthilkumar, R., Preethy, S., & Abraham, S. J. K. (2021). Beneficial effects of novel aureobasidium pullulans strains produced beta-1,3-1,6 glucans on interleukin-6 and D-dimer levels in COVID-19 patients; results of a randomized multiple-arm pilot clinical study. *Biomedicine & Pharmacotherapy*, *145*, 112243. https://doi.org/10.1016/j.biopha.2021.112243

Ramlall, S., Chipps, J., Bhigjee, A. I., & Pillay, B. J. (2014). Sensitivity and specificity of neuropsychological tests for dementia and mild cognitive impairment in a sample of residential elderly in South Africa. *South African Journal of Psychiatry*, *20*(4), 153-159. https://dx.doi.org/10.7196/sajp.558

Rao, S., Benzouak, T., Gunpat, S., Burns, R., Tahir, T., Jolles, S., & Kisely, S. (2021). Fatigue symptoms associated with COVID-19 in convalescent or recovered COVID-19 patients; A systematic review and meta-analysis. *Annals of Behavioral medicine: A publication of the Society of Behavioral Medicine,* 1-16. dx.doi.org/10.1093/abm/kaab081.

Repišti, S., Stevovic, L., & Radojičić, T. (2021). Scale of neuropsychological and psychiatric symptoms of the post-COVID-19 syndrome (SNP-PC19): *A pilot study. Savremena Psihijatrija I Medicina / Contemporary Psychiatry & Medicine*, 3(1), 46–55. https://doi.org/10.5281/zenodo.5208014

Revercomb, L., Hanmandlu, A., Wareing, N., Akkanti, B., & Karmouty-Quintana, H. (2021). Mechanisms of pulmonary hypertension in acute respiratory distress syndrome (ARDS). *Frontiers in Molecular Biosciences, 7* (624093). https://doi.org/10.3389/fmolb.2020.624093

Rey, A. (1941). Psychological examination of traumatic encephalopathy. *Archives of Psychology, 28,* 286-340.

Rey, R. A. (1964). *L'examen Clinique en Psychologique.* Presses Universitaires de France, Paris.

Rogers, J. P., Chesney, E., Oliver, D., Pollak, T. A., McGuire, P., Fusar-Poli, P., Zandi, M. S., Lewis, G., & David, A. S. (2020). Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: A systematic review and meta-analysis with comparison to the COVID-19 pandemic. *The Lancet Psychiatry., 7*(7), 611-627. https://doi.org/10.1016/S2215-0366(20)30203-0

Rosin, J., & Levett, A. (1989). The Trail Making Test: Performance in a non-clinical sample of children aged 10 to 15 years. *South African Journal of Psychology, 19*(1), 14–19. https://doi.org/10.1177/008124638901900103

Rowland, C. A. (2014). The effect of testing versus restudy on retention: a meta-analytic review of the testing effect. *Psychol. Bull.* 140, 1432–1463. https://doi.org/10.1037/a0037559

Rudroff, T., Fietsam, A. C., Deters, J. R., Bryant, A. D., & Kamholz, J. A. (2020). Post-COVID-19 Fatigue: Potential Contributing Factors. *Brain Sciences, 10*. https://doi.org/10.3390/brainsci10121012

Ryan, D., Frohlich, S., & McLoughlin, P. (2014). Pulmonary vascular dysfunction in ARDS. *Annals of Intensive Care, 4*(28). https://doi.org/10.1186/s13613-014-0028-6

Sasannejad, C., Ely, E. W., & Lahiri, S. (2019). Long-term cognitive impairment after acute respiratory distress syndrome: A review of clinical impact and pathophysiological mechanisms. Critical care, 23(1), 352. https://dx.doi.org/10.1186/s13054-019-2626-z

Schwieren, J., Barenberg, J., & Dutke, S. (2017). The testing effect in the psychology classroom: a meta-analytic perspective. *Psychol. Learn. Teach.* 16, 179–196. https://doi.org/10.1177/1475725717695149

Siedlecki, K. L., Manly, J. J., Brickman, A. M., Schupf, N., Tang, M. X., & Stern, Y. (2010). Do neuropsychological tests have the same meaning in Spanish speakers as they do in English speakers?. *Neuropsychology, 24*(3), 402–411. https://doi.org/10.1037/a0017515

Simonneau, G., Montani, D., Celermajer, D. S., Denton, C. P., Gatzoulis, M. A., Krowka, M., Williams, P. G., & Souza, R. (2019). Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Respir J, 53*(1801913), 1-13. https://doi.org/10.1183/13993003.01913-2018

Skuy, M., Schutte, E., Fridjhon, P., & O'Carroll, S. (2001). Suitability of published neuropsychological test norms for urban African secondary school students in South Africa. *Personality and Individual Differences, 30*(8), 1413–1425. https://doi.org/10.1016/S0191-8869(00)00123-9

Smit, B., & Onwuegbuzie, A. (2018). Observations in qualitative inquiry: When what you see is not what you see. *International Journal of Qualitative Methods. 17*(1). https://dx.doi.org/10.1177/1609406918816766.

South African Department of Health. (2020). *Protection of Personal Information Act (POPI Act)* [White paper]. https://popia.co.za/.

Sutton, J., & Austin, Z. (2015). Qualitative research: Data collection, analysis, and management. *The Canadian journal of hospital pharmacy*, *68*(3), 226–231. https://doi.org/10.4212/cjhp.v68i3.1456

Tan, C. N. (2011). Culture and trust in fostering knowledge-sharing. *Electronic Journal of Knowledge Management (EJKM), 9.* 328-339.

Thabane, L., Ma, J., Chu, R., Cheng, J., Ismaila, A., Rios, L., Robson, R., Thabane, M., Giangregorio, L., & Goldsmith, C. H. (2010). A tutorial on pilot studies: The what, why and how. *BMC Medical Research Methodology*, *10*(1). https://doi.org/10.1186/1471-2288-10-1

Thomas, K. G., Baerecke, L., Pan, C. Y., & Ferrett, H. L. (2019). The Boston Naming Test-South African short form, part I: Psychometric properties in a group of healthy English speaking university students. *African Journal of Psychological Assessment, 1*(a15). https://doi.org/10.4102/ajopa.v1i0.15

Tremblay, S., Castiglione, S., Audet, L., Desmarais, M., Horace, M., & Peláez, S. (2021). Conducting qualitative research to respond to COVID-19 challenges: Reflections for the present and beyond. *International Journal of Qualitative Methods*, *20*, 160940692110096. https://doi.org/10.1177/16094069211009679

Troyer, E. A., Kohn, J. N., & Hong, S. (2020). Are we facing a crashing wave of neuropsychiatric sequelae of COVID-19? Neuropsychiatric symptoms and potential immunologic mechanisms. *Brain, behavior, and immunity*, *87*. https://dx.doi.org/10.1016/j.bbi.2020.04.027

van Eijk, L. E., Binkhorst, M., Bourgonje, A. R., Offringa, A. K., Mulder, D. J., Bos, E. M., Kolundzic, N., Abdulle, A. E., van der Voort, P. H., Olde Rikkert, M. G., van der Hoeven, J. G., den Dunnen, W. F., Hillebrands, J. L., & van Goor, H. (2021). COVID-19: Immunopathology, pathophysiological mechanisms, and treatment options. *The Journal of Pathology*, *254*(4), 307–331. https://doi.org/10.1002/path.5642.

Van Teijlingen, E., & Hundley, V. (2002). The importance of pilot studies. *Nursing standard (Royal College of Nursing (Great Britain): 1987). 16*. 33-6. https://dx.doi/10.7748/ns2002.06.16.40.33.c3214.

Van Teijlingen, E., Rennie, A. M., Hundley, V., & Graham, W. (2001). The importance of conducting and reporting pilot studies: The example of the Scottish Births Survey. *Journal of Advanced Nursing, 34*, 289-295. https://doi.org/ 10.1046/j.1365-2648.2001.01757.x

van Wijk, E., & Harrison, T. (2013). Managing ethical problems in qualitative research involving vulnerable populations, using a pilot study. *International Journal of Qualitative Methods, 12*(1), 570–586. https://doi.org/10.1177/160940691301200130

Wechsler, D. (2008). *Wechsler Adult Intelligence Scale-Fourth Edition: Administration and scoring manual*., San Antonio, TXNCS Pearson.

Weiner, D. L., Balasubramaniam, V., Shah, S. I., Javier, J. R., & on behalf of the Pediatric Policy Council. (2020). COVID-19 impact on research, lessons learned from COVID-19 research, implications for pediatric research. *Pediatr Res* 88, 148–150 (2020). https://doi.org/10.1038/s41390-020-1006-3

Whipple, G. M. (1910). Manual of mental and physical tests. Baltimore, MD: Warwick & Sons.

Wilcox, M. E., Brummel, N. E., Archer, K., Ely, E. W., Jackson, J. C., & Hopkins, R. O. (2013). Cognitive dysfunction in ICU patients: Risk factors, predictors, and rehabilitation interventions. *Critical Care Medicine*, *41*(9 Suppl 1), S81–S98. https://doi.org/10.1097/CCM.0b013e3182a16946

Wilson, J. G., Simpson, L. J., Ferreira, A. M., Rustagi, A., Roque, J., Asuni, A., Ranganath, T., Grant, P. M., Subramanian, A., Rosenberg-Hasson, Y., Maecker, H. T., Holmes, S. P.,

Levitt, J. E., Blish, C. A., & Rogers, A. J. (2020). Cytokine profile in plasma of severe COVID-19 does not differ from ARDS and sepsis. *JCI Insight, 5*(17), e140289. https://doi.org/10.1172/jci.insight.140289

World Health Organization. (2021). *WHO Coronavirus (COVID-19) Dashboard.* WHO. https://covid19.who.int/

Wu, Y., Xu, X., Chen, Z., Duan, J., Hashimoto, K., Yang, L., Liu, C., & Yang, C. (2020). Nervous system involvement after infection with COVID-19 and other coronaviruses. *Brain, Behavior, and Immunity, 87,* 18-22. https://doi.org/10.1016/j.bbi.2020.03.031

Zangbar, H., Gorji, A., & Ghadiri, T. (2021). A review on the neurological manifestations of COVID-19 infection: A mechanistic view. *Molecular Neurobiology, 58,* 536-549. https://doi.org/10.1007/s12035-020-02149-0

Zhang, J., Wang, L., Deng, X., Fei, G., Jin, L., Pan, X., Cai, L., Albano, A. D., & Zhong, C. (2019). Five-minute cognitive test as a new quick screening of cognitive impairment in the elderly. *Aging and Disease, 10*(6), 1258–1269. https://doi.org/10.14336/AD.2019.0115.

Zhou, H., Lu, S., Chen, J., Wei, N., Wang, D., Lyu, H., Shi, C., & Hu, S. (2020). The landscape of cognitive function in recovered COVID-19 patients. *Journal of Psychiatric Research, 129*, 98-102. https://doi.org/10.1016/j.jpsychires.2020.06.022

Ziehr, D. R., Alladina, J., Petri, C. R., Maley, J. H., Moskowitz, A., Medoff, B. D., Hibbert, K. A., Thompson, B. T., & Hardin, C. C. (2020). Respiratory pathophysiology of mechanically ventilated patients with COVID-19: A cohort study. *American journal of respiratory and critical care medicine, 201*(12), 1560–1564. https://doi.org/10.1164/rccm.202004-1163LE

Appendices

Appendix A

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room G50- Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: hrec-enquiries@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

01 October 2021

HREC REF: 482/2021

Prof M Solms
Department of Psychology
PD Hahn Building-UCT
Email: Mark.solms@uct.ac.za
Student: Trnalt001@myuct.ac.za

Dear Prof Solms

PROJECT TITLE: A MIXED METHODS INVESTIGATION OF THE MENTAL ASPECTS OF POST-COVID/LONG COVID FATIGUE (MASTER'S DEGREE - MR ALTAY TURAN)

Thank you for your response letter, addressing the issues raised by the Faculty of Health Sciences Human Research Ethics Committee (HREC).

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

This approval is subject to strict adherence to the HREC recommendations regarding research involving human participants during COVID -19, dated 17 March 2020: 06 July 2020 & 01 July 2021.

Approval is granted for one year until the 30 October 2022.

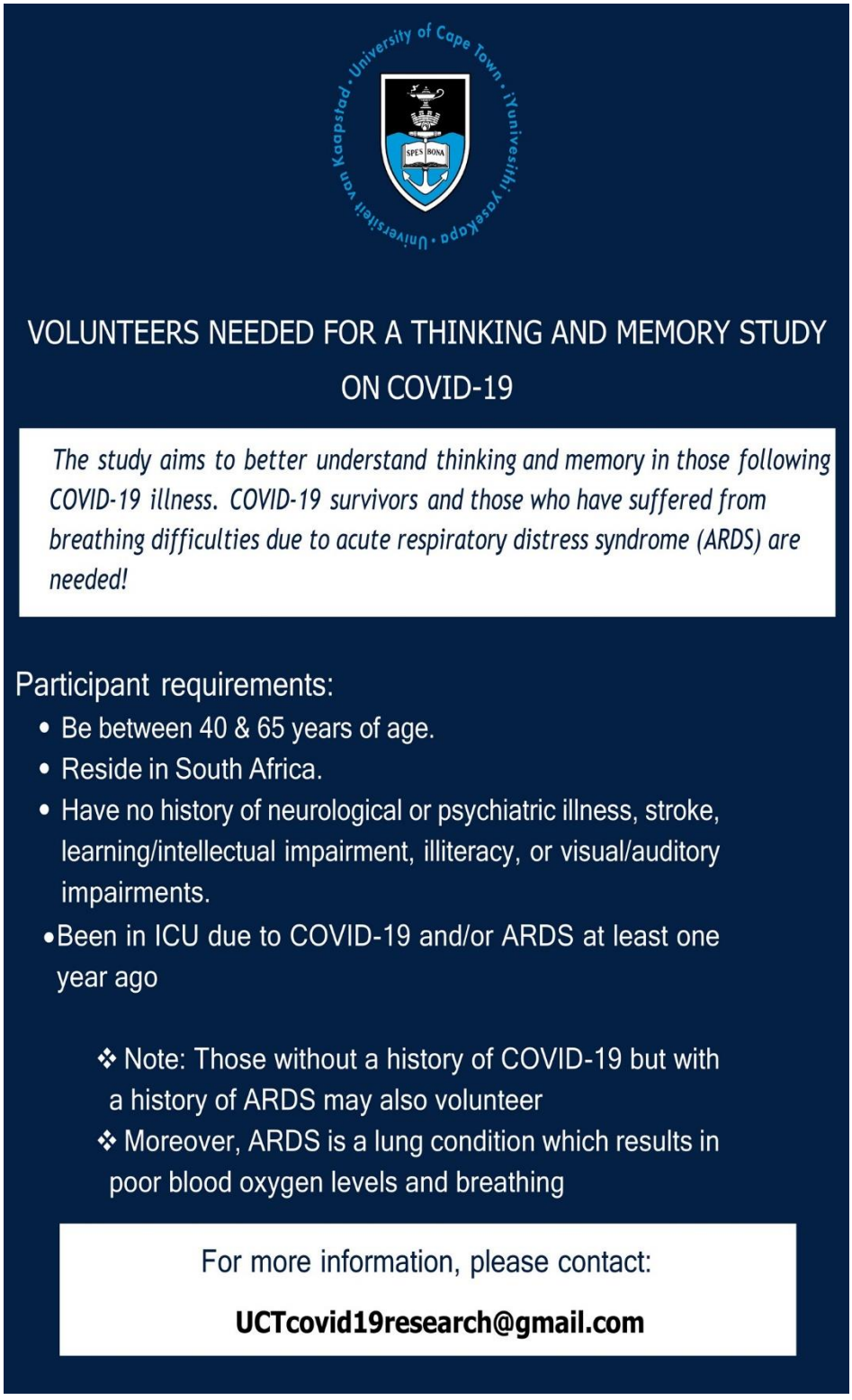
Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

The HREC acknowledge that the student: Mr Altay Turan will also be involved in this study.

Please quote the HREC REF 482/2021 in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Appendix B


University of Cape Town • iYunivesithi yaseKapa • Universiteit van Kaapstad
SPES BONA
VOLUNTEERS NEEDED FOR A THINKING AND MEMORY STUDY ON COVID-19
The study aims to better understand thinking and memory in those following COVID-19 illness. COVID-19 survivors and those who have suffered from breathing difficulties due to acute respiratory distress syndrome (ARDS) are needed!
Participant requirements:
• Be between 40 & 65 years of age.
• Reside in South Africa.
• Have no history of neurological or psychiatric illness, stroke, learning/intellectual impairment, illiteracy, or visual/auditory impairments.
• Been in ICU due to COVID-19 and/or ARDS at least one year ago
❖ Note: Those without a history of COVID-19 but with a history of ARDS may also volunteer
❖ Moreover, ARDS is a lung condition which results in poor blood oxygen levels and breathing
For more information, please contact:
UCTcovid19research@gmail.com

Appendix C

Next-of-kin Information Sheet and Consent Form

Next-of-kin Information Sheet and Informed Consent Form

This Informed Consent Form is for men and women who are invited to participate in research on the neuro-cognitive implications of severe COVID 19 illness.

Name of Organization: University of Cape Town
Names of Study leaders: Prof M Solms (University of Cape Town), Prof JL Marnewick (CPUT), Prof P Engel-Hills (CPUT), Dr D Minné (CPUT)
Name of Project proposal: Neuropsychological Sequelae in COVID-19 Survivors

This Informed Consent Form has two parts:

- **Information Sheet (to share information about the research with you)**
- **Certificate of Consent (for signatures if you agree to take part)**

You will be given a copy of the full Informed Consent Form

PART I: Information Sheet

Introduction

We are a team of researchers studying the effects of the COVID-19 virus on brain function. The aim of this research is to investigate whether or not severe COVID-19 illness causes any lasting changes to memory or the way a person thinks and processes information. This form gives you information about the study and what kinds of questions and activities you will be requested to respond to and perform. There may be some words that you do not understand. Please ask the researcher with you to stop as you go through the information and she will take time to explain it. If you have questions later, please ask any member of the study team present here today.

Purpose of the research

The purpose of this research is to describe any changes to how you think that have occurred as a result of COVID-19 illness. This information will help health practitioners and family members better support and care for individuals who were hospitalised for their COVID 19 illness.

Type of Research

This research involves the completing of a questionnaire by you, as the indicated next-of-kin of the participant.

Participant selection

To participate in this study, we are inviting next-of-kin adults to complete a questionnaire regarding the functioning of the participant. The study participant has given us permission to contact you.

Voluntary Participation
Your participation in this research study is entirely voluntary. It is your choice whether to participate or not. Even if you have agreed to take part in the study, you may still stop participating at any time you want without any consequences to you and request that your data be withdrawn.

Procedures and Protocol
If you volunteer to take part in this study, you will be asked to complete the *COVID-19 Family Questionnaire.* We can go through this questionnaire with you over the phone, or you can complete it via email.

Risks
There are no known risks to participate in this study. However, the recall of memories related to the participant's illness and other emotional experiences may cause you distress.

Benefits
There are no specific benefits for you, but your participation is likely to help us find the answer to the research question. Any participant requesting or found to be requiring appointment for further neuropsychological, psychiatric or neurological assessment will be referred onwards to the appropriate department at Groote Schuur Hospital or other community clinics.

Confidentiality
Your personal information that we collect during this research study will be kept confidential. It will be stored in a locked filing cabinet and/or a password protected computer by the team members responsible for collecting data. Any information about you will have a unique code on it instead of your name. In other words, your data will be anonymous. After all your data has been collected, only study leader, Dr Donné Minné will know what your code is in case we need to contact you.

Sharing the Results
The knowledge that we get from doing this research will be shared at public meetings such as conferences and we will also publish the results in order that other interested people may learn from our research. You should note that this is a long process and may take up to 4 years after the study has been completed. Confidential information about your identity will never be shared and it will not be possible to identify you in any reports or presentations about this research.

Right to Refuse or Withdraw
You do not have to take part in this research if you do not wish to do so. You may also stop participating in the research at any time you choose. It is your choice and all of your rights will still be respected.

Who to Contact?
If you have any questions you may ask them now or later, even after the study has started. If you wish to ask questions later, you may contact Dr Donné Minné at donneminne.za@gmail.com or on 0728005230, or Prof Mark Solms at mark.solms@uct.ac.za.

This research study has been approved by the Human Research Ethics Committee at the University of Cape Town; a committee tasked to make sure that research participants are

protected from harm. If you wish to find more about UCT'S Human Research Ethics Committee, contact hrec-enquiries@uct.ac.za

PART II: Certificate of Consent

Declaration by study participant:

I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I consent voluntarily to participate as a participant in this research. I may choose to leave this study at any time and will not be penalised or prejudiced in any way. I may be asked to leave the study before it has finished if the study doctor or study leader feels it is in my best interest or if I do not follow the study plan as agreed to. Additionally, I recognise that I may be called upon to pick up the study participant if they are deemed unable to consent to, and partake, in the study.

Print Name of Next-of-kin_____

Signature of Next-of-kin_____

Date_____

Place_____

Signature of witness_____

Declaration by investigator:

I declare that I have explained the information in this document to the study participants and encourage them to ask questions and took adequate time to answer them. I am satisfied that he/she adequately understands all aspects of the research study as discussed above. The participant has been deemed able to give consent to partake in the study by myself. I did/did not use an interpreter. (If an interpreter is used the interpreter must sign the declaration below).

Print Name of Investigator_____

Signature of Investigator _____

Date_____

Place_____

Signature of witness_____

Declaration by interpreter:

I declare that I assisted the investigator to explain the information in this document to the participant using the language medium of Afrikaans/Xhosa. We encouraged him/her to ask questions and took adequate time to answer them. I conveyed a factual correct version of what was related to me. I am satisfied that the participant fully understands the content of this information and informed consent document and has had all his/her questions satisfactorily answered.

Print Name of Interpreter_____

Signature of Interpreter _____

Date_____

Place_____

Signature of witness_____

Thumb print of participant

Appendix D

Participant Information Sheet and Consent Form

Participant Information Sheet and Informed Consent Form

This Informed Consent Form is for men and women who are invited to participate in research on the neuro-cognitive implications of severe COVID 19 illness.

Name of Organization: University of Cape Town

Names of Study leaders: Prof M Solms (University of Cape Town), Prof JL Marnewick (CPUT), Prof P Engel-Hills (CPUT), Dr D Minné (CPUT)

Name of Project proposal: Long-term neuropsychological outcomes in severe COVID-19: A pilot study

This Informed Consent Form has two parts:

- **Information Sheet (to share information about the research with you)**
- **Certificate of Consent (for signatures if you agree to take part)**

You will be given a copy of the full Informed Consent Form

PART I: Information Sheet

Introduction

We are a team of researchers studying the effects of the COVID-19 virus on brain function. The aim of this research is to investigate whether or not severe COVID-19 illness causes any lasting changes to memory or the way a person thinks and processes information. This form gives you information about the study and what kinds of questions and activities you will be requested to respond to and perform. There may be some words that you do not understand. Please ask the researcher with you to stop as you go through the information and she will take time to explain it. If you have questions later, please ask any member of the study team present here today.

Purpose of the research

The purpose of this research is to describe any changes to how you think that might occur as a result of COVID-19 illness or from non-COVID-induced ARDS. This information will help health practitioners and family members better support and care for individuals who were hospitalised for COVID-19-induced ARDS.

Type of Research Intervention

You will be requested to complete a series of thinking assessments, which will take the form of pen-and-paper tasks and mental exercises that require you to listen and respond to various questions. Additionally, you will be requested to complete some questionnaires that ask questions about your emotions and feelings.

Participant selection

To participate in this study, we are inviting adults within the age range of 40 to 65 years old who fall into any one of the following four groups:

Group 1: The inclusion criteria for participants for this group is a previous admission to an ICU ward with COVID-19 positive test result, approximately 18-month prior.

Group 2: The inclusion criteria for this group is a previous admission to an ICU ward with *non-COVID-19* related acute respiratory distress syndrome, approximately 18-month prior.

Group 3: The inclusion criteria for this group is a previous admission to an ICU ward with *COVID-19* related acute respiratory distress syndrome, approximately 18-month prior.

Group 4: The inclusion criteria for this group is adults with no existing medical history of *COVID-19* and/or acute respiratory distress syndrome.

Participants will not be able to participate if they have a history of pre-existing neurological illness or injury, cerebrovascular accident, developmental intellectual impairment, major impairing psychiatric illness, illiteracy, or visual or auditory dysfunction that cannot be corrected-to-normal with glasses/hearing aid.

Voluntary Participation

Your participation in this research study is entirely voluntary. It is your choice whether to participate or not. Even if you have agreed to take part in the study, you may still stop participating at any time you want without any consequences to you and request that your data be withdrawn.

Procedures and Protocol

If you volunteer to take part in this study, you will be asked to do the following:

.

1) Take part in round of cognitive testing during which we will assess your performance on thinking and memory tests. This research session will require your physical participation at the Neuroscience Institute at Groote School Hospital and is expected to last 90 minutes. Breaks will be issued.

2) Answer questions, and capture data, about demography, physical and mental health, medical and psychiatric history, personality and daily routines, lifestyle choices, relationships, occupation and education history. Questions concerning your medical, mental health and psychiatric history will be asked over telephone or answered via email in the days following the cognitive testing.

3) Grant us permission to use your medical records from the time of your COVID 19 hospital admission to record biomarkers related to oxygen levels, inflammation and cell health.

4) Grant us permission to audio and video record your responses for some cognitive tests test to facilitate scoring. All recordings will remain anonymous and will only be accessed by the research team. Recordings will be permanently deleted once scores are calculated.

5) Grant us permission to your indicated next-of-kin and to ask them to complete a questionnaire that concerns you and your experience of your illness and how this may have affected, or continues to affect, the people around you.

6) The questions and tests are not for diagnostic purposes and will not be included in your medical folder.

Risks

There are no known risks to participate in this study. However, the recall of memories related to your COVID 19 illness and other emotional experiences may cause you distress. Given the ongoing COVID 19 pandemic, risk of infection or re-infection remains a possibility and we will take every precautionary activity available to us to minimise this risk, including frequent hand, surface and object sanitisation, wearing of masks, ventilation and social distancing.

Benefits

There are no specific benefits for you, but your participation is likely to help us find the answer to the research question. Any participant requesting or found to be requiring appointment for further

neuropsychological, psychiatric or neurological assessment will be referred onwards to the appropriate department at Groote Schuur Hospital or other community clinics. Those that travel to the testing site at Groote Schuur Hospital by their own means will be compensated with R50. Next-of-kin that accompany primary participants will receive a coffee voucher that is redeemable at the Neuroscience Institute foyer/coffee lounge.

Confidentiality

Your personal information that we collect during this research study will be kept confidential. It will be stored in a locked filing cabinet and/or a password protected computer by the team members responsible for collecting data. Any information about you will have a unique code on it instead of your name. In other words, your data will be anonymous. After all your data has been collected, only study leader, Dr Donné Minné will know what your code is in case we need to contact you.

Sharing the Results

The knowledge that we get from doing this research will be shared with the other researchers attending to this study. However, all data that is made public, such as at conferences, will be anonymous and therefore, this data cannot be traced back to you. We will also publish the results in order that other interested people may learn from our research. You should note that this is a long process and may take up to 4 years after the study has been completed. Confidential information about your identity will never be shared. That being said, identified low cognitive or psychological functioning may result in a referral to the appropriate department at Groote Schuur Hospital for further assistance.

Right to Refuse or Withdraw

You do not have to take part in this research if you do not wish to do so. You may also stop participating in the research at any time you choose. Moreover, you may withdraw your data from the study at any time point without fear of repercussion. It is your choice and all of your rights will still be respected.

Who to Contact?

If you have any questions you may ask them now or later, even after the study has started. If you wish to ask questions later, you may contact Dr Donné Minné at donneminne.za@gmail.com or on 0728005230, or Prof Mark Solms at mark.solms@uct.ac.za.

This research study has been approved by the Faculty of Health and Wellness Research Ethics Committee (H&W REC); a committee tasked to make sure that research participants are protected from harm. If you wish to find more about the Faculty of Humanities REC, contact Ms Kerewin Parfitt, kerewinparfitt@uct.ac.za.

PART II: Certificate of Consent

Declaration by study participant:

I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I consent voluntarily to participate as a participant in this research. I may choose to leave this study at any time and will not be penalised or prejudiced in any way. I may be asked to leave the study before it has finished if the study doctor or study leader feels it is in my best interest or if I do not follow the study plan as agreed to.

Print Name of Participant_____
Signature of Participant _____
Date_____
Place_____

Signature of witness_____

Additionally, I give consent for the research team to contact my indicated next-of-kin and to ask them to complete a questionnaire that concerns me and my experience of my illness and how this may have affected, or continues to affect, the people around me.

Print Name of Investigator_____
Signature of Investigator _____
Date_____
Place_____

Signature of witness_____

Declaration by investigator:

I declare that I have explained the information in this document to the study participants and encourage them to ask questions and took adequate time to answer them. I am satisfied that he/she adequately understands all aspects of the research study as discussed above. I did/did not use an interpreter. (If an interpreter is used the interpreter must sign the declaration below).

Print Name of Investigator_____
Signature of Investigator _____
Date_____
Place_____

Signature of witness_____

The researcher has judged the participant as being able to give informed consent on the basis of his/her adequate understanding of

1) The purpose of the study, ☐
2) the potential risks involved and ☐
3) the potential benefits ☐

Print Name of Investigator_____

Signature of Investigator _____

Date_____

Place_____

Signature of witness_____

Declaration by interpreter:

I declare that I assisted the investigator to explain the information in this document to the participant using the language medium of Afrikaans/Xhosa. We encouraged him/her to ask questions and took adequate time to answer them. I conveyed a factual correct version of what was related to me. I am satisfied that the participant fully understands the content of this information and informed consent document and has had all his/her questions satisfactorily answered.

Print Name of Interpreter_____
Signature of Interpreter _____
Date_____
Place_____
Signature of witness_____

Thumb print of participant