**The long-term impacts of COVID-19 on confirmed cases in Wellington, New Zealand: An observational, cross-sectional study.**

**Internal Reference Number / Short title:** MRINZ/21/02 / Long COVID Study

**Ethics Ref: ANZCTR number:**

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# KEY STUDY CONTACTS

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# SYNOPSIS

|  |  |  |  |
| --- | --- | --- | --- |
| **Study Title** | | The long-term impacts of COVID-19 on confirmed cases in Wellington, New Zealand: An observational, cross-sectional study | |
| **Internal ref. no.** | | MRINZ/21/02 | |
| **Study Design** | | Observational, cross-sectional study | |
| **Study Participants** | | Adults with diagnosis of COVID-19 | |
| **Planned Sample Size** | | No planned sample size | |
| **Planned Study Period** | | March 2021 to November 2022 | |
|  | **Objectives** | | **Outcome and *Instrument*** | |
| **Primary** | 1. To determine the rating of overall current health in confirmed cases at 12 months post-infection | | Percentage of participants with better current overall health than before getting COVID-19  Percentage of participants with same current overall health as before getting COVID-19  Percentage of participants with worse current overall health than before getting COVID-19  *Overall Health Questionnaire*  *Compared to your overall health before getting COVID-19, how would you rate your overall health now?*   * *My overall health is much better than it was before getting COVID-19* * *My overall health is a little better than it was before getting COVID-19* * *My overall health is the same as it was before getting COVID-19* * *My overall health is a little worse than it was before getting COVID-19* * *My overall health is much worse than it was before getting COVID-19* | |
|  | 1. To determine prevalence of anaemia in confirmed cases after a minimum of 12 months post- infection | | Haemoglobin level | |
| 1. To determine prevalence of lymphopaenia in confirmed cases after a minimum of 12 months post- infection | | White Cell Count  Lymphocyte Count | |
| 1. To determine prevalence of renal impairment in confirmed cases after a minimum of 12 months post- infection | | Serum Sodium level  Serum Potassium level  Serum Creatinine level  eGFr (glomerular filtration rate)  Serum Albumin level | |
| 1. To determine prevalence of new-onset diabetes in confirmed cases after a minimum of 12 months post- infection | | Glycated haemoglobin (HbA1c) level | |
| 1. To determine prevalence of thyroid dysfunction in confirmed cases after a minimum of 12 months post- infection | | Free T3 level  Free T4 level  TSH level | |
| 1. To determine prevalence of liver dysfunction in confirmed cases after a minimum of 12 months post- infection | | AST level  ALT level  GGT level  Bilirubin level | |
| 1. To determine COVID-19 antibody status after a minimum of 12 months post- infection | | COVID-19 IgG, COVID-19 IgM, COVID-19 total antibody levels | |
| 1. To determine self-reported health state in confirmed cases after a minimum of 12 months post- infection | | Proportion of participants with issues with mobility  Proportion of participants with issues with self-care  Proportion of participants with issues with conducting usual activities  Proportion of participants with issues with pain/discomfort  Mean score on Visual Analogue Scale  *EQ-5D-5L* | |
| 1. To determine prevalence of dyspnoea in confirmed cases after a minimum of 12 months post- infection | | Proportion of participants with breathlessness above Grade 1  Proportion of participants with breathlessness at each of Grade 2-5.  *MRC Dyspnoea Scale* | |
| 1. To determine the presence and/or severity of depression in confirmed cases after a minimum of 12 months post- infection | | Proportion of participants with no signs of depression  Proportion of participants with symptoms of mild, moderate, moderately severe and severe depression  *Patient Health Questionnaire 9 (PHQ9)* | |
| 1. To determine the presence of fatigue in confirmed cases after a minimum of 12 months post- infection | | Mean total score  *Fatigue Severity Scale* | |
| 1. To determine the presence and/or severity of anxiety in confirmed cases after a minimum of 12 months post- infection | | Proportion of participants with no signs of anxiety  Proportion of participants with symptoms of mild, moderate and severe anxiety  *Generalised Anxiety Disorder-7 (GAD7)* | |
| 1. To determine the presence of sleep problems in confirmed cases after a minimum of 12 months post- infection | | Proportion of participants with poor sleep quality  *Pittsburgh Sleep Quality Index (PSQI)* | |
| 1. To determine prevalence and nature of ongoing symptoms in confirmed cases after a minimum of 12 months post- infection | | Proportion of participants with at least one ongoing symptom  Proportion of participants with two or more ongoing symptoms  Proportion of participant with each ongoing symptom  *Symptom questionnaire* | |
|  | 1. To assess feasibility of conducting a study on Long-COVID remotely | | *Participant Satisfaction Questionnaire* | |

# ABBREVIATIONS

|  |  |
| --- | --- |
| ACC | Accident Compensation Corporation |
| AE | Adverse Event |
| ALT | Alanine Aminotransferase |
| AST | Aspartate Aminotransferase |
| BNP | Brain Natriuretic peptide |
| COVID-19 | Coronavirus Disease 19 |
| CRF | Case Report Form |
| CRP | C-Reactive Protein |
| eGFR | Estimated Glomerular Filtration Rate |
| EpiSurv | New Zealand’s national notifiable disease surveillance database |
| ESR | Erythrocyte Sedimentation Rate |
| FSS | Fatigue Severity Scale |
| GAD-7 | Generalised Anxiety Disorder -7 |
| GGT | Gamma-Glutamyl Transferase |
| mMRC Dyspnoea Scale | Modified Medical Research Council Dyspnoea Scale |
| MRINZ | Medical Research Institute of New Zealand |
| NZ | New Zealand |
| PHQ-9 | Patient Health Questionnaire 9 |
| PSQI | Pittsburgh Sleep Quality Index |
| REDCap | Research Electronic Data Capture |
| RPH | Regional Public Health |
| T3 | Triiodothyronine |
| T4 | Thyroxine |
| TMG | Trial Management Group |
| TSH | Thyroid Stimulating Hormone |
| WBC | White Blood Cell |
| WHO | World Health Organisation |
| NHI | National Health Index |
| NCTS | National Contact Tracing System |
| GP | General Practitioner |

# BACKGROUND AND RATIONALE

Long-term sequelae of COVID-19 are unknown but there is increasing evidence that people who have recovered from COVID-19 report lasting effects of the infection or have had the usual symptoms for far longer than would be expected, namely ‘Long COVID’. Long-term consequences have been reported with other viral infections. It is reported that approximately 30% of people with SARS or Middle East respiratory syndrome had persisting lung abnormalities after their acute illness but it is unknown whether lessons from SARS are applicable to COVID-19. 1

Data from the UK COVID-19 Symptom Study app, which collects symptom information from nearly four million users, state their data show that one in 10 people with COVID-19 were sick for three weeks or more.2 In a US cohort, 35% of respondents with symptoms at testing reported not having returned to their usual state of health after a median of 16 days following testing.3  Short-term observational studies have shown the persistence of symptoms with 87% of patients discharged from a Rome hospital after recovering from COVID-19, still experiencing at least one symptom 60 days after onset.4 At 2-6 months from disease-onset, patients have reported breathlessness, fatigue, sleep difficulties, anxiety and depression post discharge from hospital.5,6 Similar ongoing symptoms have also been reported by patients who were diagnosed with COVID-19 but did not require hospital admission.7

Given the paucity of comprehensive data surrounding longer-term outcomes past the initial six months following infection, particularly in non-hospitalised patients, Wellington is in a unique position to undertake a follow-up of confirmed cases past 12 months post-infection. This study will be done remotely and participants will be able to get blood sampling done at the local blood collection centre. The decision to run the study remotely was taken due to the active community cases of COVID-19 in New Zealand and to mitigate the risks to the study, participants and staff given the potential unexpected changes in Alert Levels

# STUDY DESIGN

This is an observational, cross-sectional study. Cases from the first wave (01/01/20 – 16/6/20) will be followed up at least 12 months post-infection.

## Study Participants

Adults aged 18 and over with a laboratory diagnosis of COVID-19 notified to Regional Public Health in the preceding 12-18 months, with the option of extending to other Public Health Units.

## Recruitment

All COVID-19 PCR positive patients will be contacted by study staff at RPH. RPH staff will explain study details and send potential participants a Participant Information Sheet detailing no less than: why the study is being conducted, procedures to be performed by participants, total duration of the study, participant benefits of being involved; the known risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, without affecting their legal rights and with no obligation to give the reason for withdrawal. If a potential participant is willing to consider the study, verbal consent will be gained to pass on contact details to a MRINZ study investigator. Contact details will be entered onto a secure REDCap database only accessible by study investigators.

### Informed Consent

Informed consent will be obtained remotely in these cases. The person obtaining the consent must be suitably qualified and experienced, and have been authorised to do so by the Principal Investigator. This will occur via telephone, during which study documentation will be signed by the participant digitally using an electronic consent form provided via email using REDCap.8 The participant will be required to sign the Study Consent Form in order to take part in the study.

This study will also collect a blood sample to store for future unspecified research. In order to do this, a signature on a second consent form, specifically for storing blood for future research will be sought. Blood storage for future use is voluntary and participants may refuse. Refusal for blood storage will not affect a participant’s right to take part in the main study.

The consent form(s) will be delivered, reviewed, and signed whilst the investigator is on the telephone. A copy of the signed Informed Consent will be given to the participant. Informed consent will be obtained in accordance with Good Clinical Practice (GCP).

## Screening and Enrolment

Potential participants who have consented to taking part will be assessed against the eligibility criteria below. A participant is considered to be enrolled if they have provided informed consent and meet eligibility criteria.

### Inclusion Criteria

1. Aged 18 years and above
2. Laboratory PCR confirmed SARS-CoV2 infection
3. Between 12 months and 17 months since the first onset of COVID-19 symptoms

### Exclusion criteria

1. Have had symptoms of an acute infection in the past two weeks
2. Have been asked to self-isolate, quarantine or stay at home by Public Health officials
3. Have any other condition which, at the investigator’s discretion, is believed may present a safety risk or impact the feasibility of the study or the study results.

# STUDY PROCEDURES

The schedule of procedures is outlined in Appendix A.

## Consent and baseline information

**Pre-screening (RPH)**

**Contact 1:** RPH will identify COVID-19 cases from the first wave via local database and/or National Contact Tracing System. RPH study team will make contact via telephone with the potential participant to describe the study and send through the participant information sheet (PIS) for the main study as well as the optional Participant Information Sheet for the Use of Tissue for Future Unspecified Research for review. If the potential participant agrees to consider the study then consent will be taken by RPH to send their contact details to MRINZ via the secure REDCap platform.

**Screening and consent (MRINZ)**

**Contact 2:** A second follow up contact will be made by MRINZ to gauge interest will be scheduled for after a minimum 24-hour period from having sent the participant information sheet, or as much time as wished depending on participant preference. We will aim to address individual participant’s requirements for consideration time and schedule the follow up contact accordingly. The participant will be given the opportunity to discuss with their GP or other independent parties to decide whether they will participate in the study.

If the participant agrees to enrol in the study, full discussion and screening to assess eligibility will be undertaken and informed consent will be obtained.

Consent will be specifically obtained to access hospital including Regional Public Health records, National Contact Tracing records (NCTS) and Medical records (GP and hospital records) using National Health Index (NHI). This will be used to record any pre-existing medical conditions and to cross-check any relevant previous blood tests results.

Once consent has been obtained, participant specific data (see below) will be collected. Once enrolled, a letter to the participants GP will be sent, along with all available results upon completion or withdrawal.

## Participant Specific Data

The information collected will include the following:

* Name, date of birth, age, ethnicity, sex (self-report)
* NHI (EpiSurv, self-report or medical records)
* Contact details (self-report)
* Smoking history: smoking status (ex, current, never), pack years. Ex-smoker is defined as not having had tobacco containing products in the preceding 30 days. (self-report)
* Complete Medical History (self-report + medical records)
* Complete Drug History (self-report)
* Date of COVID-19 acute symptom onset (EpiSurv)
* Date of symptom resolution (EpiSurv)
* Vaccine Status (self-report + medical records)

There are three parts to the study. Part 1 and 2 can be done in any order.

## Part 1: Questionnaires

All questionnaires will be undertaken within 12-18 months from the first onset of COVID-19 symptoms. Links to questionnaires will be sent out on the day of enrolment, if investigators are reasonably able to do so, or within 48 hours.

### Overall Health Questionnaire - Appendix 2

This questionnaire compares overall health prior to getting COVID-19 with current overall health.

### Modified Medical Research Council Dyspnoea Scale (mMRC Dyspnoea Scale) - Appendix 3

The mMRC dyspnoea scale9 is a questionnaire that consists of five statements about perceived breathlessness: grade 0, “I only get breathless with strenuous exercise”; grade 1, “I get short of breath when hurrying on the level or up a slight hill”; grade 2, “I walk slower than people of the same age on the level because of breathlessness or have to stop for breath when walking at my own pace on the level”; grade 3, “I stop for breath after walking 100 yards or after a few minutes on the level”; grade 4, “ I am too breathless to leave the house or I am breathless when dressing or undressing”.

### Patient Health Questionnaire-9 (PHQ9) - Appendix 4

PHQ-910 is a rapid and effective 9 question tool for detection as well as for monitoring the severity of depression. Participants are asked how often they were bothered by 9 problems over the preceding 2 weeks and required to select one of “not at all”, “several days”, “more than half the days” and “nearly every day”

### Generalised Anxiety Disorder-7 (GAD7) - Appendix 5

The GAD-712 is a self-administered 7 item instrument that uses some of the DSM-V criteria for GAD (General Anxiety Disorder) to identify probable cases of GAD along with measuring anxiety symptom severity. Participants are asked how often they were bothered by 7 problems over the preceding 2 weeks and are required to select one of “not at all”, “several days”, “more than half the days” and “nearly every day”.

### Pittsburgh Sleep Quality Index (PSQI) - Appendix 6

The Pittsburgh Sleep Quality Index13 is a self-rated questionnaire which assesses sleep quality and disturbances over a 1-month time interval.

### EQ-5D-5L - Appendix 7

This descriptive system comprises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems and extreme problems. The patient is asked to indicate his/her health state by ticking the box next to the most appropriate statement in each of the five dimensions. This decision results in a 1-digit number that expresses the level selected for that dimension. The digits for the five dimensions can be combined into a 5-digit number that describes the patient’s health state.

### Fatigue Severity Scale (FSS) - Appendix 8

A self-report scale of nine items about fatigue, its severity and how it affects certain activities. The items are scored on a 7 point scale with 1=strongly disagree and 7=strongly agree.

### WHO Symptom Questionnaire - Appendix 9

Section 2.6 of the WHO’s Global COVID-19 Clinical Platform Case Report Form for Post COVID condition (Post COVID-19 CRF)14.

## Part 2: Laboratory Tests

All blood tests will be undertaken within 12-18 months from the first onset of COVID-19 symptoms. Blood tests will be ordered on the day of enrolment if investigators are reasonably able to do so.

### Specified tests

The following laboratory tests will be analysed:

* Haematology: Haemoglobin, WBC count, Lymphocyte count
* Chemistry Panel: Serum Sodium, Serum Potassium, Serum Creatinine, eGFR, Serum Albumin, Glycated haemoglobin (HbA1c), AST, ALT, GGT, Bilirubin, Free T3, Free T4, TSH
* COVID-19 Serology: COVID-19 total antibody, COVID-19 IgG, COVID-19 IgM

Participants will be requested to attend their local blood collection centre for venepuncture. Blood sampling, processing and destruction will be according to the laboratory’s local protocol. If a participant withdraws from the study, samples obtained for specified tests up to the point of withdrawal will be analysed.

### Storage for unspecified tests

An additional blood sample will be taken at the collection centre and sent to MRINZ for storage. Additional consent will be obtained at the time of obtaining initial informed consent for sampling and storing a blood sample for 24 months from end of study for unspecified future use, related to COVID-19 only. No genomic analysis will be undertaken. This will be voluntary and refusal of consent for blood storage will not impact a participant’s ability to take part in the study. Participants may choose to withdraw consent for blood storage at any point.

Unused blood samples will be available for collection at MRINZ by the participant either at the end of the 24 month period or upon withdrawal. If a sample is not collected within a month of notifying the participant, it will be destroyed as per MRINZ protocol.

## Part 3: Follow Up (Study Completion Procedures)

The following will be undertaken by a study investigator within 10 working days after a participant completes or withdraws from a study. Study Completion Date is defined as the date on which the last remaining blood or questionnaire result is available.

1. A summary of results for all bloods tests and questionnaires undertaken will be sent to the GP, with any abnormal results highlighted if applicable. If the participant is not enrolled with a GP, a copy will be sent to the participant and they will be encouraged to register with a GP.
2. An investigator will make three attempts to phone the participant within 10 working days following completion of study. During the phone call, the investigator will explain the results of the study procedures. If any results are abnormal, this will be explained to the participant and they will be encouraged to go see their GP if applicable. The participant will also be made aware that a copy of their results have been sent to the GP.
3. A REDCAP survey link to the Participant Satisfaction Survey (Appendix 10) will be sent via email, to be filled out by the participant. The link will be valid for 4 weeks after which it will no longer be accessible.

## Discontinuation/Withdrawal of Participants from Study

Each participant has the right to withdraw from the study at any time. In addition, the Investigator may withdraw a participant from the study at any time if the Investigator considers it necessary for any reason including:

* Any medical condition that the Investigator determines may affect the participant’s safety if they continue in the study
* Investigator determines it is in the best interest of the participant
* Sponsor determines it is in the best interest of the participant
* Withdrawal of Consent

The reason for withdrawal will be recorded. The data of all participants will be included in the data analysis. For participants that withdraw consent, their data will be included up until the point of withdrawal, where applicable.

# Definition of End of Study

The end of study is the date is four weeks after the enrolment of the last participant.

# SAFETY REPORTING

## Adverse Events

Adverse events will not be collected given the observational nature of this study and no use of any investigational products or devices. Abnormal study results will be managed as per section 6.5.

# STATISTICS

## Description of Statistical Methods

Data description principles are that categorical data will be described by counts and proportions; survival data will be described by Kaplan-Meier survival curves and estimates of 25th, median, and 75th percentiles of survival; count data will be described by rates and total counts in relation to observation time; ordinal data will be described by cross-tabulation and summaries as described for continuous data; and continuous data by mean and standard deviation (SD), median and 25th and 75th percentiles as the inter-quartile range (IQR), and minimum (min) to maximum (max) as the range.

The following baseline characteristics will be presented:

* Age
* Sex
* Ethnicity
* Smokers (current/past)
* Time from symptom onset to resolution
* Vaccine Status

## Sample Size

There is no planned sample size. We aim to recruit all consenting adults diagnosed with COVID-19 in the Greater Wellington Region during the first wave.

## Criteria for the Termination of the Study

Early termination may occur at the discretion of the Investigators for any reason that is believed may present a safety risk.

* **Investigator**: If the investigator terminates or suspends a study without prior agreement of the Sponsor, the investigator should inform the institution where required, by the applicable regulatory requirements and the investigator/institution should promptly inform the sponsor and the HDEC, and should provide the sponsor and the HDEC a detailed written explanation for the termination or suspension.
* **Sponsor**: If the Sponsor terminates or suspends a study, the Sponsor should promptly inform the investigator. The investigator should then promptly inform HDEC and provide the HDEC a detailed written explanation for the termination or suspension.
* **HDEC**: If the responsible Health and Disability Ethics Committee terminates or suspends its approval/favourable opinion of a study, the investigator should inform the Institution where required, by the applicable regulatory requirements, and the investigator/institution should promptly notify the sponsor and provide the sponsor with a detailed written explanation for the termination or suspension.

## Inclusion in Analysis

All enrolled participants will be included in the analysis. There will also be a secondary analysis performed for all laboratory test outcomes using a data set that does not include patients who had PDVs.

# DATA MANAGEMENT

## Source Data

Source data refers to where data are first recorded, and from which participants’ study data are obtained. Source documents include, but are not limited to, hospital and GP records (from which medical history and previous and concurrent medication may be summarised), NCTS records, laboratory records and results and online questionnaires. Study data are collected into a Clinical Data Management Application (CDMA) in which entries will be considered source data if the CDMA is the site of the original recording (e.g. there is no other written or electronic record of data).

## Access to Data

Direct access to source and study data will be granted to authorised representatives from the Sponsor, and the regulatory/ ethics authorities to permit trial-related monitoring, audits and inspections.

## Data Recording and Record Keeping

Data will be entered into the REDCap electronic data capture tool hosted and supported by the MRINZ. REDCap is a secure, HIPAA (United States Health Insurance Portability and Accountability Act 1996) compliant web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages, including de-identified data sets; and 4) procedures for importing data from external sources.

Participants will be identified by a unique study ID in any data export from the eCRF database. The name and any other identifying detail will not be included within the eCRF.

Source and Essential documents will be stored at Site for a minimum of 10 years after the completion of the trial, in accordance with GCP. Study Data held within the eCRF and Essential Documents held in the Trial Master File (TMF) will be stored by the Sponsor for a minimum of 10 years after the completion of the trial, in accordance GCP.

# QUALITY ASSURANCE PROCEDURES

The study will be conducted in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures.

Regular monitoring will be performed according to GCP, as defined within the study Monitoring Plan developed by the Sponsor. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. Following written standard operating procedures/ the Monitoring Plan, the Monitors will verify that the clinical study is conducted, and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

The Study Management Group (TMG) will meet regularly to discuss the progress of the study and for the purpose of assuring quality, in their role of executing the function of Sponsor. The Study Management Group will be formed of MRINZ staff with relevant expertise in conducting study.

The appropriate manuals and guidelines will be issued investigators in order that they are able to perform the study as per protocol. Any additional training for study procedures will be performed as necessary.

# SERIOUS BREACHES

A serious breach is defined as “A breach of GCP or the study protocol which is likely to affect to a significant degree:

* + Participant rights
  + Participant safety or well-being
  + Integrity of research data
  + The conduct or management of the study
  + Participant's willingness to continue study Participation

In the event that a serious breach is suspected the Sponsor must be informed within 1 working day. In collaboration with the PI, the serious breach will be reviewed by the Sponsor, if appropriate, the Sponsor will report it to the HDEC committee, and appropriate regulatory authority within seven calendar days.

# ETHICAL AND REGULATORY CONSIDERATIONS

## Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

## Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

## Approvals

Ethics submission will be made to one of the Health and Disability Ethics Committees of New Zealand. The opinion of the Ethics Committee will be given in writing. Locality approval must be granted at each site before any participants are recruited, as per Ethics Committee guidelines. The Ethics Committee should approve all participant facing material for the study.

Māori consultation will also be performed prior to any locality being activated in accordance with HRC and HDEC guidelines.

The Sponsor will approve all modifications to the Protocol and/or Participant Information Sheet and Consent Form/s that are needed.

The PI or delegate will submit all substantial amendments to the original approved documents to the HDEC.

## Reporting

The PI shall submit once a year throughout the clinical study, or on request, an Annual Progress Report to the HDEC. It is expected that only the final report will be submitted due to the fast completion of the study.

An End of Study notification and final report will be submitted to the HDEC and Sponsor as required.

## Protocol amendments

Any changes to this protocol will be circulated to the relevant parties and to the HDEC for review if mandated. Protocol version changes and reasons will be listed as an Appendix of this document, ‘Amendment History’.

## Participant Confidentiality

The study staff will ensure that the participants’ confidentiality is maintained. The sensitivity of COVID-19 infection status and risk for anti-social consequences and discrimination is recognised and all appropriate steps will be taken to maintain confidentiality. The REDCap system used to capture source and study data is an encrypted secure system that is protected by unique username and password requirements for log-in, which are only provided to trained study staff. Data is kept in server farms located offshore in Sydney, Australia within the Amazon Web Services (AWS) network, amongst the more secure digital environment globally.

Any paper CRF (if used) will only have participant study ID numbers associated with it. The list of participant identifiable data and the allocated participant study ID number will be kept within the REDCap CDMA to allow investigators to identify participants in the event there are findings from laboratory analysis that require further assessment. Study documents (apart from letters to the participant’s GP) sent out from the study site will only bear the participant study ID number and will not have any participant identifiable data on them.

All source documents/ CDMA, CRF, and REDCap eCRF will be stored securely and only accessible by study staff and authorised personnel. The Sponsor (via the Study Monitor) will have access to all identifiable source data at site, for on-site monitoring purposes, to ensure the study is being run in compliance with GCP and the protocol.

## Expenses and Benefits

Participants will be eligible for a reimbursement of $100. This is to account for any study related costs such as parking. In the event that the costs of taking part in the study are particularly prohibitive (e.g. a long distance to travel), then special payments reflective of costs incurred may be made. Such events will be reviewed by the TMG in a case-by-case basis.

## Other Ethical Considerations

The study protocol will be submitted to the first available Health and Disability Ethics Committee and conducted in accordance with the National Ethics Advisory Committee Standards, Health Information Privacy Code and Health and Disability Code of Rights. The study context creates challenges for a paper based, in person, informed consent process. Electronic (or remote) consent is acceptable in New Zealand, provided it contains the same elements of an in person, paper based, consent process.15 One limitation is the requirement for access to a computer device with an internet connection.

# FINANCE AND INSURANCE

## Funding

The MRINZ will fully fund the study. The study sponsor is the MRINZ.

## Insurance

The study is not being performed principally for the benefit of a medicinal product manufacturer or commercial Sponsor and therefore on the basis of applicable ethics approval participants will be eligible to apply for compensation from ACC, for any study related injury.

The MRINZ will maintain relevant insurance for the duration of the study in accordance with its obligations as study Sponsor.

# PUBLICATION POLICY

The study site(s), represented by the principal investigator (PI), will take responsibility to report the results in a scientific peer reviewed journal, according to the International Committee of Medical Journal Editors recommendations. The Investigators listed on page one will be listed as authors, in recognition of their contribution to the design, implementation and oversight of the study.

Publication of the study outcomes will comprise publication of the study as a whole and is encouraged by the Sponsor regardless of outcome. The Sponsor retains editorial rights to protect the Sponsor’s proprietary information and intellectual property.

Results of the study will be sent to participants on request (once available) and will be made available on a publicly available study registry website, recognised by the World Health Organisation International Clinical Study’s Registry Platform (WHO ICTRP) as a Primary Registry.

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# Appendices

Appendix 1: Schedule of Procedures

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Contact Session** | **1**  **Pre-consent**  **(RPH)** | **2**  **Consent & Enrolment**  **(MRINZ)** | **3** | **4**  **Follow-up** |
| **Week** | ≤1 | ≤1 | 1 | ≥1 |
| **Day** | ≤1 | ≤1 | 1 | ≥1 |
| **Window (Days)** | N/A | N/A | ±2 | ±10 |
| PIS sent | X |  |  |  |
| Verbal consent to pass contact details to MRINZ | X |  |  |  |
| Main Study Written informed consent |  | X |  |  |
| Optional Blood Storage Written informed consent |  | X |  |  |
| Inclusion/Exclusion criteria check |  | X |  |  |
| Demographics |  | X |  |  |
| Medical history and concomitant medication |  | X |  |  |
| Smoking history |  | X |  |  |
| Vaccination status |  | X |  |  |
| E-mail link to questionnaires sent |  |  | X\* |  |
| Blood sampling requests sent via email and/or post |  |  | X\* |  |
| Telephone call to participant to explain study results |  |  |  | X |
| Results sent to GP |  |  |  | X |
| Participant Satisfaction Survey |  |  |  | X+ |
| \*Participants are required to complete questionnaires and blood sampling within 12-18 months from the first onset of COVID-19 symptoms.  +Link to survey will be valid for 4 weeks | | | | |

Appendix 2: Overall Health Questionnaire

Compared to your overall health before getting COVID-19, how would you rate your overall health now?

* My overall health is much better than it was before getting COVID-19
* My overall health is a little better than it was before getting COVID-19
* My overall health is the same as it was before getting COVID-19
* My overall health is a little worse than it was before getting COVID-19
* My overall health is much worse than it was before getting COVID-19

Appendix 3: mMRC Dyspnoea Scale

|  |  |
| --- | --- |
| **Grade** | **Description of Breathlessness** |
| Grade 0 | I only get breathless with strenuous exercise |
| Grade 1 | I get short of breath when hurrying on the level or up a slight hill |
| Grade 2 | I walk slower than people of the same age on the level because of breathlessness or have to stop for breath when walking at my own pace on the level |
| Grade 3 | I stop for breath after walking 100 yards or after a few minutes on the level |
| Grade 4 | I am too breathless to leave the house or I am breathless when dressing or undressing |

Appendix 4: PHQ-9

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **PATIENT HEALTH QUESTIONNAIRE-9**  **(PHQ-9)** | | | | |
| **Over the last 2 weeks, how often have you been bothered by any of the following problems?** *(Use “*✔*” to indicate your answer)* | **Not at all** | **Several days** | **More than half the days** | **Nearly every day** |
| **1.** Little interest or pleasure in doing things | 0 | 1 | 2 | 3 |
| **2.** Feeling down, depressed, or hopeless | 0 | 1 | 2 | 3 |
| **3.** Trouble falling or staying asleep, or sleeping too much | 0 | 1 | 2 | 3 |
| **4.** Feeling tired or having little energy | 0 | 1 | 2 | 3 |
| **5.** Poor appetite or overeating | 0 | 1 | 2 | 3 |
| **6.** Feeling bad about yourself — or that you are a failure or have let yourself or your family down | 0 | 1 | 2 | 3 |
| **7.** Trouble concentrating on things, such as reading the newspaper or watching television | 0 | 1 | 2 | 3 |
| **8.** Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual | 0 | 1 | 2 | 3 |
| **9.** Thoughts that you would be better off dead or of hurting yourself in some way | 0 | 1 | 2 | 3 |

PHQ-9 Additional Question: Apart from getting COVID-19, has anything significant happened in your life that could affect the above responses?

-Yes

-No

Appendix 5: GAD-7

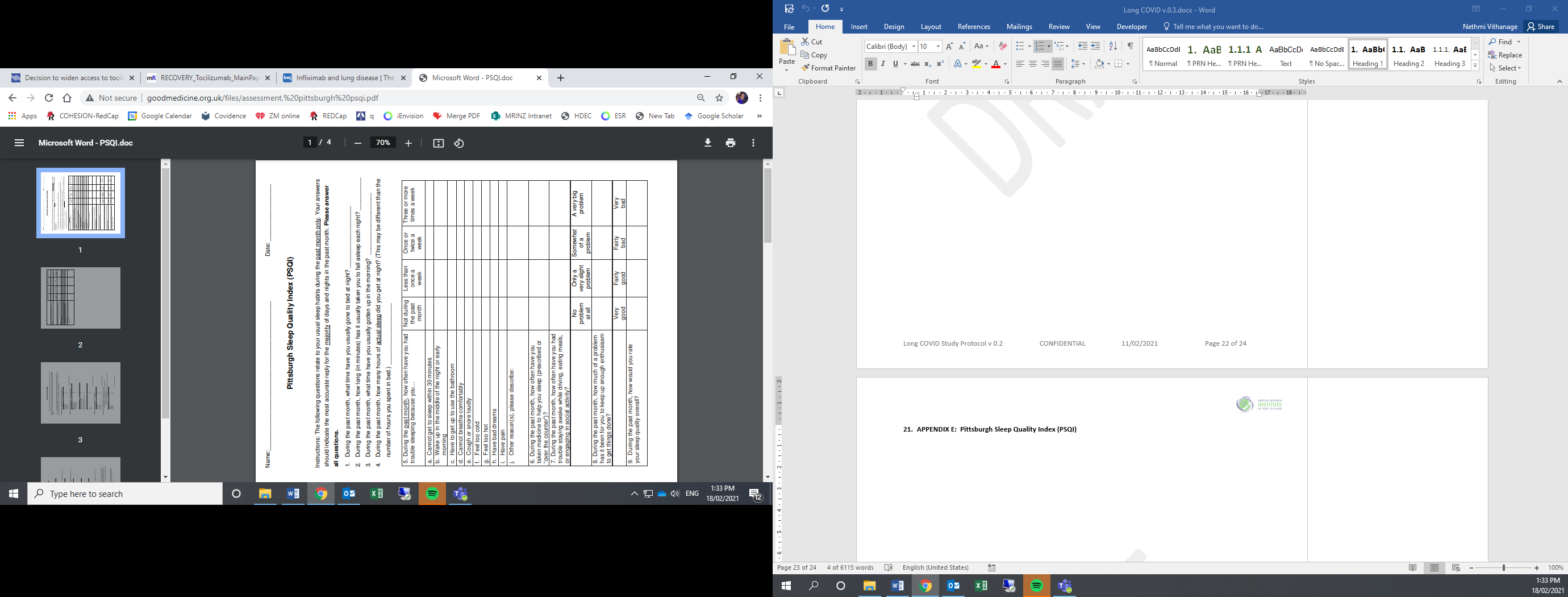
|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Over the last 2 weeks, how often have you been bothered by the following problems? | Not at all sure | Several days | Over half the days | Nearly every day |
| 1. Feeling nervous, anxious, or on edge | 0 | 1 | 2 | 3 |
| 2. Not being able to stop or control worrying | 0 | 1 | 2 | 3 |
| 3. Worrying too much about different things | 0 | 1 | 2 | 3 |
| 4. Trouble relaxing | 0 | 1 | 2 | 3 |
| 5. Being so restless that it's hard to sit still | 0 | 1 | 2 | 3 |
| 6. Becoming easily annoyed or irritable | 0 | 1 | 2 | 3 |
| 7. Feeling afraid as if something awful might happen  *Add the score for each column*  Total Score *(add your column scores)* = | 0 | 1 | 2 | 3 |
| + | + | + |  |
|  |  |  |  |

GAD-7 Additional Question: Apart from getting COVID-19, has anything significant happened in your life that could affect the above responses?

-Yes

-No

Appendix 6: Pittsburgh Sleep Quality Index (PSQI)



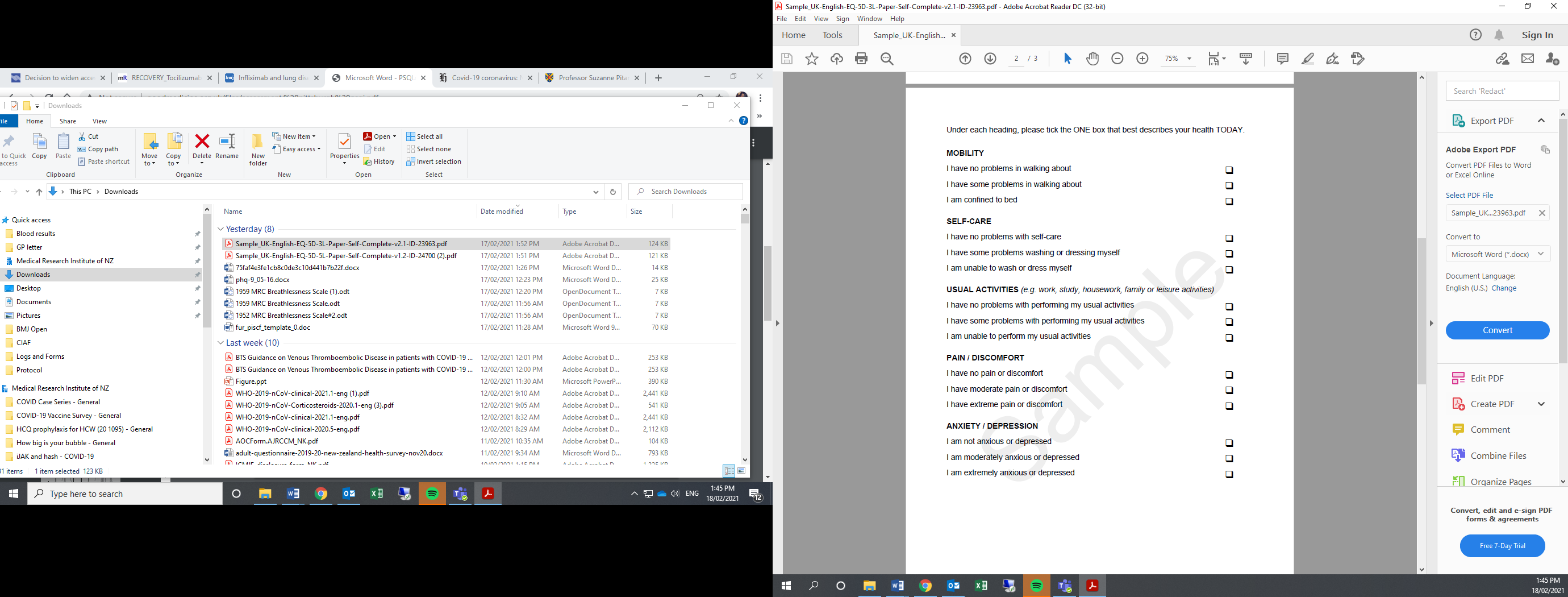
# 

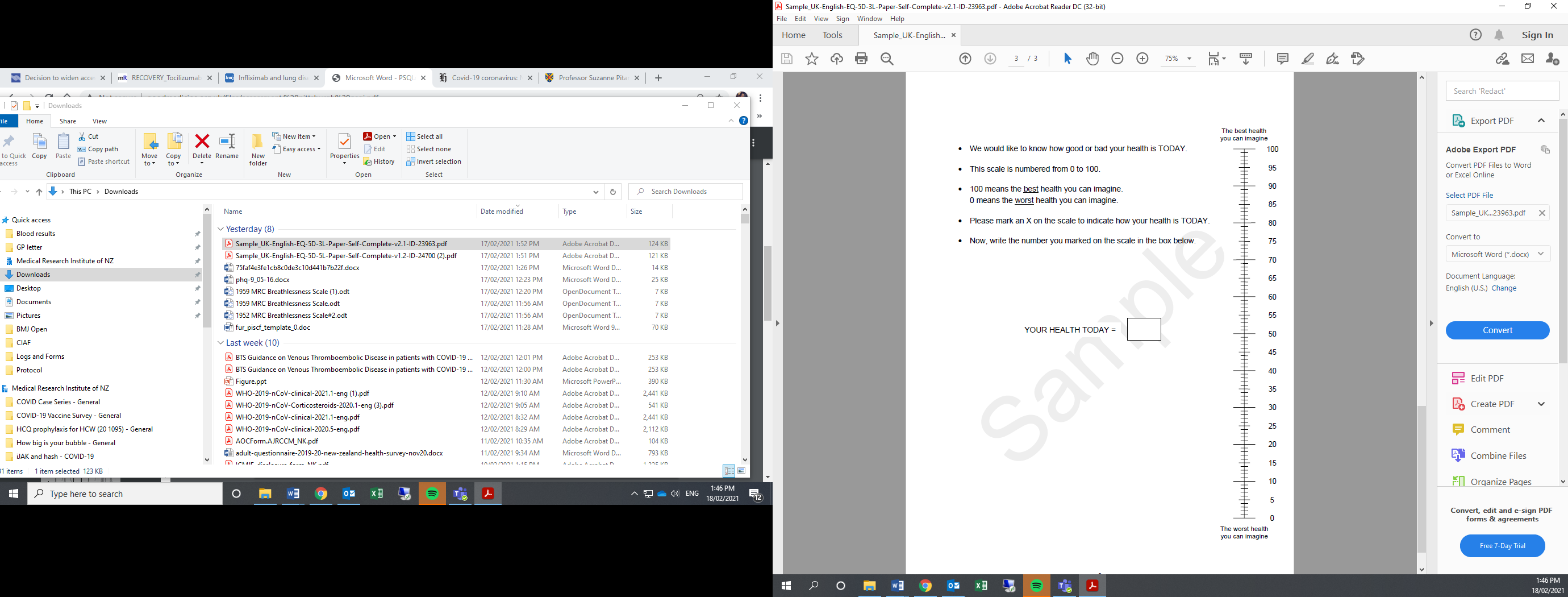
PSQI Additional Question: Apart from getting COVID-19, has anything significant happened in your life that could affect the above responses?

-Yes

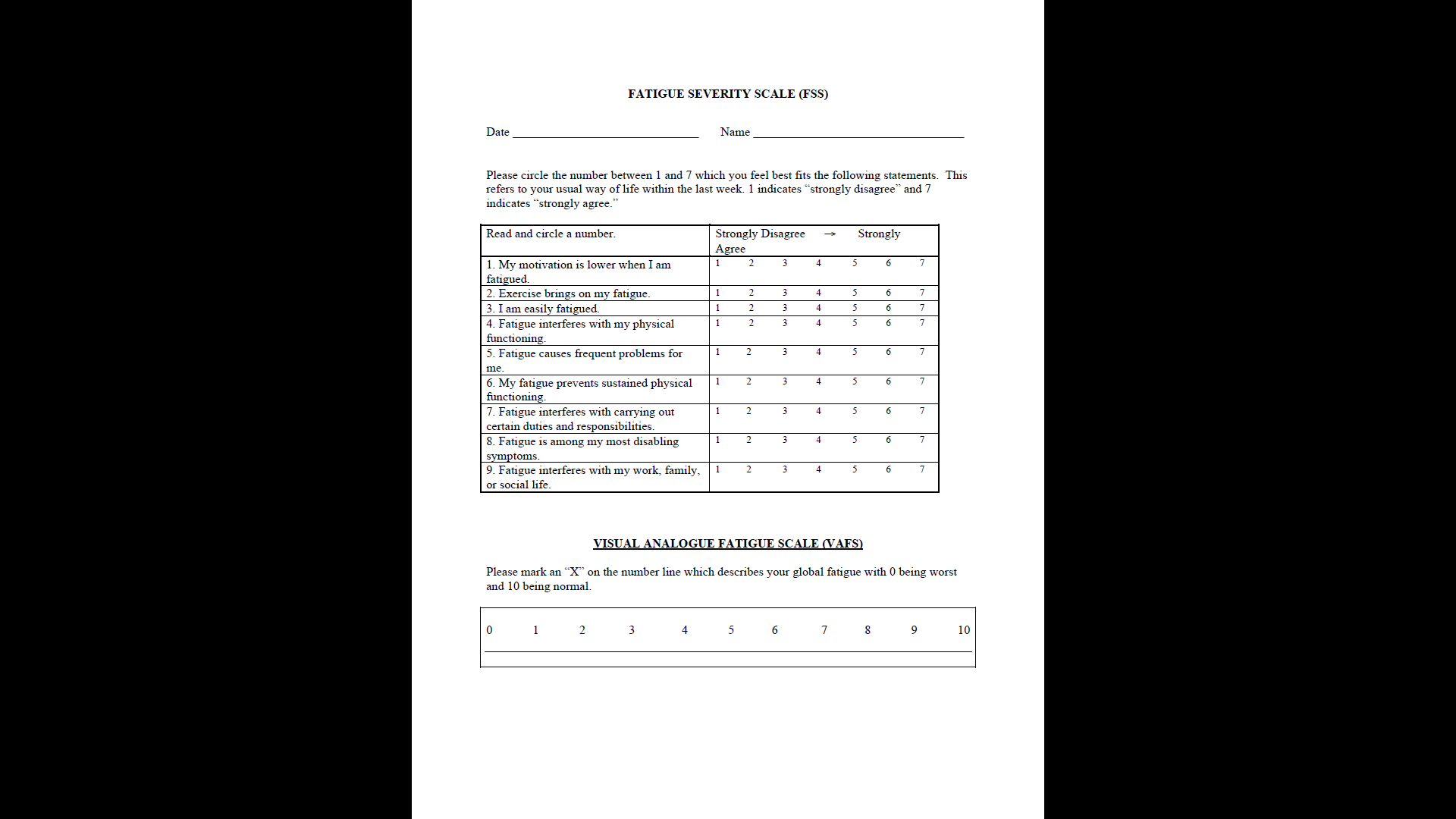
-No

Appendix 7: EQ-5D-5L





Appendix 8: Fatigue Severity Scale

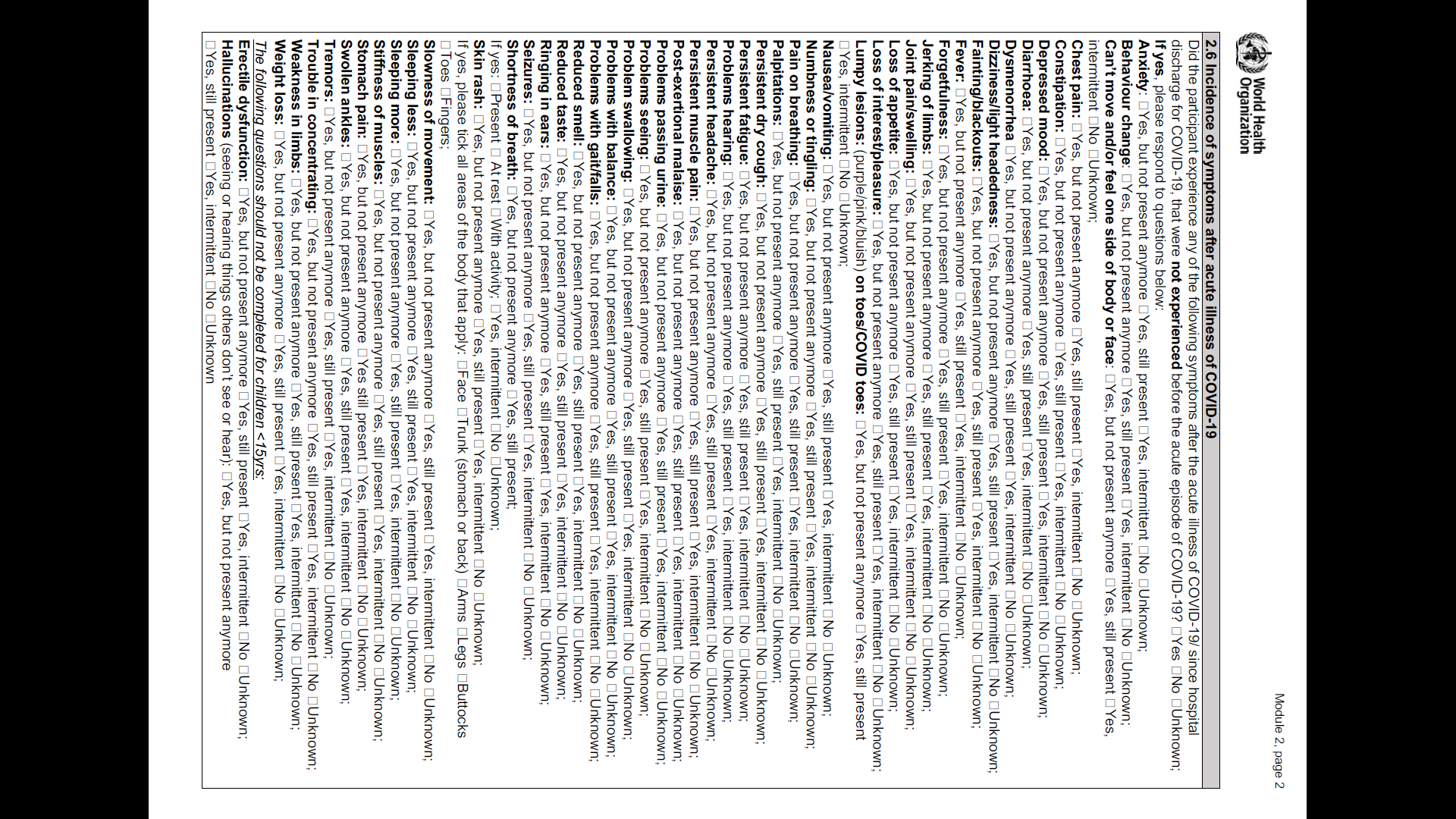


FSS Additional Question: Apart from getting COVID-19, has anything significant happened in your life that could affect the above responses?

-Yes

-No

Appendix 9: Symptom Questionnaire



Appendix 10: Participant Satisfaction Survey

We are looking to see how participants found being enrolled in a study that was done remotely. We value your feedback as it will help us with future studies. Thank you for your answers and for taking part in this study.

|  |  |
| --- | --- |
| **The following two statements are about how you felt giving consent to take part over the phone.** | |
| I was able to get all the information I needed about the study over the phone | Strongly Agree| Agree | Neutral | Disagree | Strongly Disagree |
| I would have preferred to have the study explained to me in person | Strongly Agree| Agree | Neutral | Disagree | Strongly Disagree |
| **The following two statements are about how you felt giving blood at your local blood collection centre** | |
| I was able to easily get my blood sample taken at my local collection centre | Strongly Agree| Agree | Neutral | Disagree | Strongly Disagree |
| I would have preferred to come to the Medical Research Institute of New Zealand at Wellington Hospital to get my blood sample taken | Strongly Agree| Agree | Neutral | Disagree | Strongly Disagree |
| **The following three statements are about how you felt doing the questionnaires online** | |
| I was able to easily access the internet to do the questionnaires | Strongly Agree| Agree | Neutral | Disagree | Strongly Disagree |
| I would have preferred to do the questionnaires on paper | Strongly Agree| Agree | Neutral | Disagree | Strongly Disagree |
| I would have preferred to do the questionnaires face-to-face with a study investigator | Strongly Agree| Agree | Neutral | Disagree | Strongly Disagree |
| **The last two statements are about how you feel taking part in future studies** | |
| We are planning a follow-up study in one year’s time that may include more detailed tests to investigate specific symptoms/problems. | |
| Would you consider taking part if you were experiencing long COVID symptoms in one year’s time? | Yes| No |Not sure |
| Would you consider taking part if you were NOT experiencing long COVID symptoms in one year’s time? | Yes| No |Not sure |