**RESEARCH PROTOCOL: 88587**

***Update****: This protocol updates Version 1.9 which received ethics approval on 8 September 2022 and related to a survey 3 months after a PCR test for COVID-19 or influenza. This survey was undertaken in September 2022. This updated protocol Version 2.5 reflects the ongoing nature of this research via a survey at 12 months after a PCR test for COVID-19 or influenza.*

**Project Title**

Post-Viral Recovery: COVID-19 and Flu

**Project Team (alphabetical order)**

Professor Ross Andrews (Consultant Epidemiologist; Co-Investigator)

Mr Matthew Brown (Director; Principal Investigator)

Dr John Gerrard (Chief Health Officer; Co-Investigator)

Ms Teneika Sparrow (Senior Project Officer; Co-Investigator)

**Background**

This research aims to determine rates of “long COVID” compared with influenza and a PCR-negative cohort. It is an observational cohort study that will survey people 12 weeks and 12 months after a PCR test for COVID-19 or influenza. The Office of the Chief Health Officer seeks to to understand any differences between recovery rates 12 weeks and 12 months after infection by COVID-19 or influenza. It will be managed within this unit’s core business and does not require external resourcing.

There are two target cohorts in this ongoing research:

1. those participants who, in the first survey 12 weeks after the PCR test for COVID-19 or influenza, selected the option whereby they consented to being followed up by Queensland Health on this subject.
2. those who had a PCR test for COVID-19 and/or influenza in the fortnight from Sunday 29 May to Saturday 11 June 2022 OR from Sunday 26 June to Saturday 9 July 2022 (this group was not part of the initial survey).

Post-viral syndromes – referring to a range of lingering symptoms after a viral infection – have been widely reported in the literature following viral outbreaks, epidemics and pandemics1.

The current SARS-CoV-2 (COVID-19) pandemic has seen numerous reports across the world of long-term impacts arising from this virus. These lingering impacts have been described as post-COVID-19 condition and post-acute sequelae of COVID-19, with the term “Long COVID” now in general usage across the media and literature.

Much has been written about Long COVID, but it remains little understood. Importantly, it is not clear if there are substantial differences between the rates and impacts of prolonged recoveries from COVID-19 and influenza. An opportunity exists to examine and compare post-viral recovery at two intervals: 12 weeks and 12 months after the 2022 COVID-19 and influenza outbreaks in Queensland, together with a control group.

There is considerable interest in Queensland’s response to Long COVID. However, studies on this condition, and the relevance of these to Queensland, are hampered because there is a lack of quality evidence and comparisons with other significant viruses. The differential course and fluctuating nature of the symptoms has further complicated the understanding of Long COVID. The symptomatology of Long Covid is difficult to define, and recent studies claim over 200 potential symptoms5.

The WHO’s case definition for Long COVID4 is as follows: “Post COVID-19 condition occurs in individuals with a history of probable or confirmed SARS CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms and that last for at least 2 months and cannot be explained by an alternative diagnosis. Common symptoms include fatigue, shortness of breath, cognitive dysfunction but also others and generally have an impact on everyday functioning”.

Overseas reports about Long COVID show a significant proportion of people experience ongoing symptoms 12 weeks after their infection, with some symptoms persisting for 12 months or more.

The Office of the Chief Health Officer has the opportunity to follow up with people 12 weeks after they had PCR test for COVID-19 or influenza (which was completed in 2022), and again 12 months after their test.

This creates significant challenges in understanding prevalence of Long COVID in specific contexts, and therefore in supporting health systems to respond to the issue6. It is further exacerbated by the paucity of control groups in these studies7, few comparisons with other post-viral syndromes, and a lack of understanding of functional impact. It is therefore exceedingly difficult to understand Long COVID, including if or how Queensland Health may need to plan for the management of this condition.

**Aims**

1. To estimate and compare the frequency of persistent symptoms at 12 weeks and 12 months after infection with COVID-19 or influenza.
2. To estimate and compare the severity of functional impact at 12 weeks and 12 months after infection with COVID-19 or influenza.
3. To inform Queensland Health about the potential scale of post-viral impacts arising from COVID-19 or influenza, and any system-wide response that may be required.

**Methods**

A short survey questionnaire will be sent via text message to people who:

* Tested positive to COVID-19 with this recorded in the Notifiable Conditions System.
* Tested positive to Influenza with this recorded in the Notifiable Conditions System.
* Received a negative PCR result for COVID-19, influenza and any other respiratory virus (where tested and data is available) with this recorded in the Notifiable Conditions System.

Prior to commencing the survey, recipients will review essential “participant information” (see separate attachment) that provides context and background to the project.

This protocol reflects ongoing research to build on the completed survey conducted 3 months after the relevant PCR tests. It seeks information from two cohorts:

1. People who participated in the survey conducted 12 weeks after a PCR test were asked if they consented to Queensland Health contacting them again to understand more about their recovery. Cohort 1 for the 12 month survey would be those who consented to this follow up.
2. Cohort 2 would be people had a PCR test for COVID-19 and/or influenza in the fortnight from Sunday 29 May to Saturday 11 June 2022 OR from Sunday 26 June to Saturday 9 July 2022 – with a record of this test in the Notifiable Conditions System.

*Exclusions*

The following people will not receive the survey:

* Those who did not consent to be followed up following Queensland Health’s survey of the initial project cohort at 12 weeks after infection;
* Among the additional cohort, the same exclusions will apply as per the survey at 3 months:
	+ Those under 18yo at the time of the survey;
	+ Those who are recorded in the Notifiable Conditions System to have deceased. The research team will ensure there is current data linkage between NoCS and the Registry of Births, Deaths and Marriages;
	+ Those who do not have a mobile phone number recorded in Notifiable Conditions System.

*Date of test, and date of survey*

The previous survey was sent to people with the requisite PCR tests undertaken over the below period:

* Sunday 12 June to Saturday 18 June 2022;
* Sunday 19 June to Saturday 25 June 2022.

For the cohort from this previous survey who consented to follow-up, the survey will be sent between 19 June 2023 and 2 July 2023 to ensure 12 months has elapsed since the PCR test.

For the cohort who had a PCR test for COVID-19 or influenza in the fortnight from Sunday 29 May to Saturday 11 June 2022 OR from Sunday 26 June to Saturday 9 July 2022, they will be sent a survey between 4 and 17 June 2023 (former) OR between 2 to 16 July 2023 (latter).

One initial text message and one reminder text message will be sent to each eligible participant. The survey will close 48hrs after the initial text message. See further information below.

*Potential sample size*

The potential volume of recipients is approximately 20,000.

*Use of the Post COVID Functional Status tool*

The survey will be based on the validated “Post COVID Functional Status” 8 (PCFS) screening tool, which is a very brief self-assessment survey. Please see the separately attached “Participant Survey” for the survey questions.

There are some minor-but-essential modifications to the PCFS to suit this project’s context. The PCFS includes only one reference to COVID-19 and that is in its framing of the tool. In this project, the introductory framing of the survey does not refer specifically to COVID-19 because of the inclusion of influenza and PCR-negative cases. As a result, the survey refers to participants’ “recovery after your PCR test” for either COVID or for influenza. It is noteworthy that the validated PCFS does not refer specifically to COVID-19 beyond its introduction, including when asking respondents about any symptoms or impacts.

If participants declare they have ongoing symptoms, they will be asked to select from a list of 7 symptom domains to enhance Queensland Health’s understanding of potential differences or similarities between viral illnesses.

Participants will be asked a maximum of seven survey questions, including the last question which asks if Queensland Health can contact the respondent again to understand more about their recovery. The number of questions aligns to the degree of self-reported impact: participants who declare they are free of symptoms or impacts answer only two survey questions, whereas those with ongoing symptoms or impacts answer three four questions.

*Participants and Data*

Participants (except the above exclusions) are identified because they either:

* participated in the previous survey at 12 weeks after their PCR test, and consented to further follow up by selecting this option as that survey’s final question; or
* had a PCR test for COVID-19 and/or influenza in the fortnight from Sunday 29 May to Saturday 11 June 2022 OR from Sunday 26 June to Saturday 9 July 2022, with a record in the Notifiable Conditions System (ie same methodology as original 3 month survey).

Note that all project team members are part of Queensland Health’s Office of the Chief Health Officer, where it is core business to use Notifiable Conditions System. The data custodian has provided endorsement to utilise this system for this purpose, with this attached to the ethics application.

Where available, the following personal data would be exported to a secure excel spreadsheet from the Notifiable Conditions System: first name, last name, date of birth, gender, mobile phone number, date of test, test result, hospitalisation status, vaccination status, comorbidities. Each person would then be assigned a unique identifier to allow data matching with responses.

From this, the participant’s first name, mobile phone number and unique identifier are loaded into the WHISPIR system (see next section), together with the survey questions and associated participant information (see separate attachments).

*Survey and WHISPIR System*

The survey will be managed through the WHISPIR system, for which Queensland Health has a licence and which has been used previously by Queensland Health to support its previous Long COVID survey.

Participants who are identified via the above will be sent a text message with a short statement about the purpose of the project. They will be informed that it is a short, voluntary survey, and invited to participate by clicking a link. If they click the link to participate, they then can review information on the survey (purpose, background, privacy, risks, ethics, data security, contact details for assistance). Upon acknowledgement/acceptance of this information they commence the survey. They can exit the survey at any time.

Alternatively, people are able to avoid participating by ignoring the texts.

*Analysis*

When respondents answer each question, their response is allocated a code to enable subsequent aggregation of responses. This is shown in the separately attached “Participant Survey” but will not be displayed to the participant.

During data cleansing, the unique identifier will be used to match responses from the WHISPIR Report to the details exported from NoCS and the First Name, Last Name and date of birth will be removed.

Subsequent data analysis will enable comparisons between ongoing symptoms and functional impact arising from COVID-19 and influenza, with PCR negative respondents as a control group. Further analysis will include non-identifiable demographic and clinical information (eg vaccination status, hospitalisation) to support Queensland Health’s understanding of post-viral recovery, and whether there is any difference between COVID-19 and influenza recovery.

Subject to sample size and maintenance of non-identifiability, the responses will be disaggregated according to:

1. Gender [Male, Female, Other]
2. Age [in brackets 18-39, 40-65, >65]
3. Date of test [including registration of RAT]
4. COVID-19 Vaccination Status at time of diagnosis [0, 1, 2, 3 or more; date of most recent vaccination, if available]
5. Influenza Vaccination Status at time of diagnosis [if available]
6. If the patient been hospitalised for COVID or influenza since testing positive [Yes, No, Unknown]
7. If the patient record of co-morbidities or disability [Yes, No, Unknown]
8. Symptom domain recorded in the survey response.

The data will be analysed by the project team, including the Senior Consultant Epidemiologist within the unit. This will be presented as descriptive epidemiology in the form of aggregated numbers and proportions.

**Findings and Reporting**

It is the intention of the project team to present and publish (aggregated) findings from this research. Likewise, there may be findings that may prompt further research questions for the project team (or others).

In addition, the findings may be used by Queensland Health to improve health advice to clinicians and the general public, to update health policies, and to change practice.

If there is anything significant in the findings that warrants further communication with the participants, then Queensland Health will be able to do so. The findings may assist Queensland Health to understand if or how it needs to resource any additional post-viral recovery support services. The individual deidentified data will not be shared.

**Risks**

As described above, this survey uses the validated Post-COVID Functional Status (PCFS) screening tool. It is worth noting that the validation of the PCFS was reviewed by the medical ethics committee of Maastricht University, which stated that “*the Medical Research Involving Human Subjects Act does not apply for this study and that an official approval of this study by the committee was not required (METC2020-1978)*”9.

Notwithstanding this, the project team acknowledges that risks still exist as part of the survey. It has considered the risk that respondents may experience distress arising from the questions. However, this is unlikely.

Prior to issuing the survey, the research team will ensure there is current data linkage between NoCS and the Registry of Births, Deaths and Marriages. Deceased individuals will be removed.

The validation of the PCFS9 did not report distress as a risk or outcome in the tool’s use, nor has it ever been reported in its subsequent world-wide use. Furthermore, the PCFS is freely available to the public to review and utilise8,10,11,12, and it is extremely benign when considered against the likelihood of people finding worst-case Long COVID or influenza scenarios from reputable media publications and websites that appear authoritative.

Nevertheless, to manage this risk, participants are advised to contact 13HEALTH or their doctor if they have questions or concerns. Those who report ongoing impacts are also advised to contact 13HEALTH or their doctor if they are concerned about their recovery. Potential participants can review information on the survey prior to commencing, and this includes data usage, confidentiality, and privacy. Contact details for the ethics body and the Project Manager are also provided (see separate attachment for “Participant Information”).

The distribution of the text message assumes the mobile numbers are correct for the person with a record in NOCS. As shown in the survey, the text message will include reference to the recipient's first name and the date of their test for COVID-19 or flu. It does not describe the result. There is a risk the mobile number is wrong and the text is received by an unintended person. However, the information provided in the text is not identifiable.

It also assumes the recipient possesses a “smart phone” with internet capability. If the recipient does not possess this capability, they will be unable to participate. The project team has collaborated with 13HEALTH to ensure its call centre operators are aware of this risk and will be able to advise callers of this limitation. Likewise, the project team has collaborated with 13HEALTH to prepare for calls from people who may otherwise be able to participate. The call centre operators will have access to the participant information and survey templates to appropriately advise callers. The Principal Investigator will also be available to 13HEALTH staff for additional advice once the survey is live.

There is also a risk a family member may have put their number down for another person, and they will receive the survey. Note the exclusions will mean this is unlikely to happen where the person tested was under 18yo. If the person tested was an adult, it is possible the other family member may elect to complete the survey on this person's behalf. Likewise, they may receive this on someone else's behalf and elect not to undertake the survey. The PCFS tool has been used previously in similar surveys where the above risks also existed. However, when used previously these issues were not considered to have posed significant risk.

For those who respond while the survey is open, they will be unable to edit their responses after submission. It is not administratively feasible to enable individuals to edit responses after submission owing the limitations of the software, the volume of potential participants, and the assignment of a unique identifying number. This is explained in the participant information sheet.

All project data will be kept within the secure Queensland Health system and server, and further protected by WHISPIR's two-factor authorisation. The excel sheet will sit within the data analyst / epidemiologist's individual account which is protected by a unique username and password known only to these individuals. At the conclusion of the project, the data is securely archived on Qld Health's servers.

Participants are informed of the protection of their information via the participant information sheet. If people have questions or concerns, they are able to call 13HEALTH, the MSHHS ethics team, or the Project Manager. In addition, participants can elect to not participate in the survey if they so choose. The self-reported nature of respondents' health and functional impact will be securely housed in the WHISPIR system, and only aggregated data will be released.

This short survey is aligned with Queensland Health's policy on Research Management, ensuring the safe and ethical conduct in research activities. All members of the research team have experience in research.

**Data Management**

At the end of the survey, Queensland Health will analyse the information to understand more about the population’s recovery from illness. All personal or identifying elements are removed. The information from this survey will be stored on a secure, password-protected Queensland Health server for 5 years. It may report and publish these findings at a “population level”. Participants will not be able to be identified.

**Public Health Importance:**

This project is being conducted as part of standard Public Health COVID-19 response activities. It is aimed at increasing understanding of the prevalence of post-viral syndromes associated with COVID-19 (Long COVID) and influenza in Queensland’s context. It will assist Queensland Health is designing an appropriate and proportionate response to these health issues.

As noted earlier, the lack of control groups in Long COVID research is important. This survey is significant in that it will enable comparisons between COVID-19, influenza and a control group of PCR-negative respondents.

**Plain Language Description**

While there is a lot of current discussion about “Long COVID” it remains poorly understood, especially when comparing it to the prolonged recovery from other significant viruses like influenza and when thinking about its impact upon the Queensland population.

This study aims to find out more about the Queenslanders’ recovery from COVID-19 and influenza, and the burden of ongoing symptoms and impacts from these illnesses. It will help Queensland Health understand its options to respond to post-viral impacts of COVID-19 and influenza.

**References**

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