OpenPROMPT – Long COVID and quality of life protocol

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Aim and Objectives

Evaluate the health and economic impact of long COVID on people's Health Related Quality of Life (HRQoL) among patients across demographic groups.

1. Use the UK value set for EQ-5D-5L scores to obtain HRQoL values for five dimensions of participants' mobility, self-care, usual activities, pain/discomfort and anxiety/depression
2. Compare longitudinal EQ-5D data in respondents from: (1) participants never reporting being infected with COVID-19 and never reporting long COVID; (2) participants with a previous history of COVID-19, but never reporting developed into long COVID; and (3) people who reported developing long COVID
3. Convert these results into quality-adjusted life-years (QALYs) lost due to long COVID
4. Estimate the impact of long COVID on HRQoL in patients from different sociodemographic categories
5. Assess the impact of long COVID on productivity losses

Background

Following a symptomatic infection of SARS-CoV-2, a majority of patients will recover from common symptoms such as shortness of breath, fatigue, losses of smell and taste and joint and muscular pains within 4 weeks of infection. The minority of patients who do not recover, with symptoms persisting beyond 4 weeks, may face significant impacts on their health-related quality-of-life (Tabacof, et al., 2022). The National Institute for Health and Care Excellence (NICE) has developed three clinical definitions for the effects following infection of SARS-COV-2: 'acute COVID-19' for those with signs and symptoms of COVID-19 between 0 and 4 weeks, 'ongoing symptomatic COVID-19' for people with symptoms between 4 to 12 weeks, and 'post COVID-19 syndrome' with symptoms persisting for 12 weeks or longer that are not explained by an alternative diagnosis (NICE, 2022). The latter two definitions refer to long COVID. Patients with a diagnosed case of long COVID syndrome mostly test negative when conducting polymerase chain reaction (PCR) tests for SARS-CoV-2 90 days after infection, which suggests microbiological recovery, but still experience symptoms (Líška, et al., 2022). The mechanisms of long COVID are still largely unknown.

The symptoms which may occur after infection are wide-ranging and varied, with Aiyegbusi et al. (2021) finding the most common being fatigue, dyspnoea or shortness of breath, myalgia or muscle pain, joint pains, headache, persistent cough, chest pain, and altered senses of smell and taste. Long COVID symptoms have impacted patients across a range of systems, including cardiopulmonary, gastrointestinal, musculoskeletal and neuro-psychological systems. As of 2nd January 2023, Office for National Statistics (2023) figures of the prevalence of self-reported long COVID estimate that 2 million people were experiencing symptoms persisting longer than four weeks which were not explained by other diagnoses. An estimated 1.5 million people, or 77% of those with self-reported long COVID stated symptoms adversely affected their day-to-day activities, and 380,000 or 19% reporting ability to undertake day-to-day activities had been 'limited a lot'. Given that long COVID symptoms are diverse, the impact on health-related quality of life (HRQoL) can be significant, however the impact on quality-adjusted life-years (QALYs) has not yet been quantified.

Initial research during the early phase of the COVID-19 pandemic focused on the effect of acute COVID-19 on the development of subsequent sequelae, which has since developed into investigations

for demonstrating impacts on HRQoL. Results from an online global survey on individuals diagnosed with COVID-19 requesting completion of EQ-5D-3L showed 64% of the respondents experienced impacts on quality of life across all domains within the EQ-5D survey (mobility, self-care, usual activities, pain and discomfort & anxiety and depression) more than 12 weeks after the onset of COVID-19 symptoms (Shah, et al., 2021). Our analysis will expand upon these results, using the expanded EQ-5D-5L: five dimensions and five levels of severity describes 3,125 (5^5) unique health states, significantly higher than the 243 (3^5) provided within the three levels. Furthermore, the survey within Shah et al. (2021) was completed during 2020, before a greater level of understanding had developed on the problem of long COVID, and without a control group, it is unclear whether these impacts were causally attributable to COVID-19.

Risk factors for long COVID have been partially identified. There is clear evidence of association with sociodemographic characteristics including older age, female sex, and white ethnicity individuals in the UK. Meta-analysis performed by Thompson et al. (2022) showed females had a higher risk than males of both symptoms lasting 4+ weeks versus 0-4 weeks (Odds Ratio=1.49, 95% Confidence Interval:1.24-1.79) and lasting 12+ weeks versus 0-12 weeks (OR=1.6, CI:1.23-2.7). For ethnicity, non-white ethnicity was not significantly associated in either direction with having symptoms for 4+ weeks compared to white individuals (OR=0.80; CI:0.54-1.19), but was associated with less risk of symptoms persisting 12+ weeks specifically (OR=0.32; CI:0.22-0.47). Lower educated individuals who had not attained a degree were associated with lower chances of symptoms lasting 12+ weeks (OR=0.73;CI:0.57-0.94), but again not when considering symptoms lasting 4+ weeks (OR=0.95; CI:0.80-1.14). Common associations of characteristics of ethnicity and lower educational achievement with lower morbidity have not been shown to be causal, with results suggestive that cases of long COVID were more likely to be reported for white individuals and degree educated individuals.

The majority of the current COVID literature focuses on the effect of acute COVID-19 on health-related quality-of-life rather than long COVID. Sandmann et al. (2022) examine EQ-5D-5L survey results in the UK after six months for non-hospitalised PCR test positive and negative test individuals with a specimen date 26-27 November 2020. With the study performed during 2021 prior to extensive analysis of long COVID, one in six cases report ongoing symptoms after 6 months, with 10% reporting a continued loss of function compared to pre-COVID. With an estimated 22.2 million cases of COVID-19 as of May 2022, the burden of long COVID, in terms of health effects and economic costs may be wide ranging for the NHS (GOV.UK, 2023).

The extent with which studies have developed this quality of life assessment to include quality adjusted life years (QALYs) attributable to long COVID is limited compared to estimating the effect on HRQoL. Previous attempts to quantify the effect on quality-adjusted life-years from HRQoL scores were only limited to small numbers of respondents, for example in Sandmann et al. (2022) estimating losses for 548 positive cases against a control group of 651 respondents. This is where our analysis with OpenPROMPT aims to fill a gap in the research literature, beyond analysing EQ-5D figures by attempting to assign QALY values lost due to long COVID for a significant sample size. Furthermore, for patients experiencing long COVID, the impact on healthcare costs and work-related productivity and non-related activity can be significant. The presence of symptoms for 4 months and above can have considerable impacts on participant healthcare attendance as well as productivity, both in terms of more absences and impairment in work (Jacobson, et al., 2021). Attempting to quantify the cost of healthcare and of productivity losses due to long COVID can provide more understanding of the wider long-term economic impact it may have on the prospective workforce.

Methods

Data Description

Practices which use the TPP SystmOne software will be actively recruited to participate in the study. An email will be sent to GPs informing them about the study and inviting them to participate, and once practices have confirmed their participation, they will be asked to send out email and text messages to all adults in their system they have permission to contact. Included in the messages will be a link to the study website, and a guide on how patients can participate using the Airmid app. OpenPROMPT uses Airmid, a smartphone application, to ask study participants with and without long COVID to complete questionnaires on a range of themes including quality of life, productivity and common symptoms of long COVID. The four validated questionnaires participants are requested to complete are: (1) EuroQoL EQ-5D-5L for HRQoL; (2) the Work Productivity and Activity Impairment Questionnaire: Specific Health Problems 2.0 for impact on productivity; (3) MRC Dyspnoea scale measuring breathlessness; and (4) the Functional Assessment of Chronic Illness Therapy (FACIT) tool measuring fatigue. The active data collection phase occurs across 3 months, with questionnaire data completed at the point of recruitment, then at 30, 60, and 90 days, prompted by a push notification through Airmid. For incomplete results, an additional push notification will be sent to participants to invite them to complete the questionnaires, however partially complete data will be available for the analysis. The Airmid app was developed by TPP, a GP software provider, to provide a patient-facing mobile platform that allows easier access for patient needs, including GP appointments, accessing personal records, and managing their medical record (TPP, 2020). For patients not linked to a practice using TPP, and not included in the OpenSAFELY-TPP patient population, questionnaire data will be linked with age, sex and region via the NHS login. For participants in the study who are registered with a TPP SystemOne practice, one of the biggest software providers in England holding patient records for 40% of the population in England, results from the app questionnaire data will be linked with data held in OpenSAFELY, a data analytics platform created by our team on behalf of NHS England to address urgent COVID-19 research questions (https://opensafely.org).

This analysis will be performed using pseudonymised data analysis through OpenSAFELY-TPP, a secure platform for analysis of 24 million peoples electronic health records in a Trusted Research Environment, to link data on primary care, COVID-19 testing, treatment, inpatient hospitalisations and mortality data. Coded diagnoses, medications and physiological parameters are included within this pseudonymised data. No free text data are included. OpenSAFELY provides a secure software interface allowing the analysis of pseudonymized primary care patient records from England in near real-time within the electronic health record vendor's highly secure data centre, avoiding the need for large volumes of potentially disclosive pseudonymized patient data to be transferred off-site. This, in addition to other technical and organisational controls, minimises any risk of re-identification. Similarly pseudonymized datasets from other data providers are securely provided to the EHR vendor and linked to the primary care data.

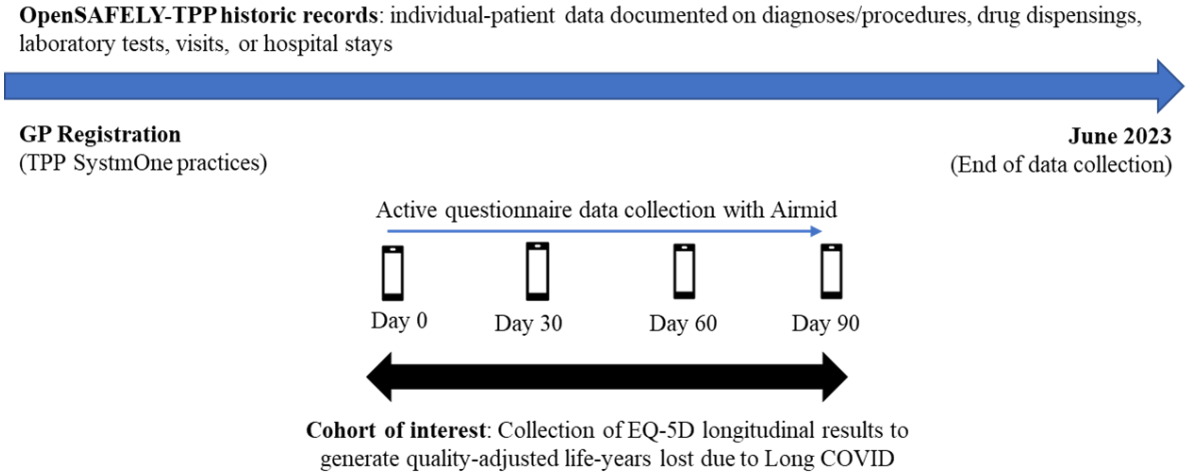
Study design

Any adult in England can participate in the study if they are able to download and use the Airmid app, and can understand English. For those with the app already downloaded, a study page will be visible where they will be able to enrol in the study. A push notification will be sent to all current users of the app advertising the study. To increase the reach of the study, advertisements across social media platforms will be shared to invite recipients to download the app and opt-in to the study. Recruitment

is monitored weekly to assess the targets for sample size and establish whether further recruitment campaigns will be required to achieve an appropriate cohort (Herrett, et al., 2023).

Day 0 is the enrollment date for each participant and where active data collection begins. Patients are required to provide a response that they have read and understood the information in the Patient Information Leaflet and consent to their information being recorded. Demographic data is collected only at the baseline recruitment, to obtain information on age, sex, relationship status, geographic region via postcode and socioeconomic status. It is also the first of the four times where information on HRQoL is collected, with EQ-5D, MRC Dyspnoea scale, FACIT fatigue, WPAI scale, and a set of closed answer questions related to long COVID. This final questionnaire set is where patients are defined as having long COVID, with a question asking "for how long have you had/did have COVID-19 symptoms overall?" The results from the symptom questionnaires aim to allow a valid comparison between those with and without long COVID. Severity of COVID-19 will also be analysed by using linkage to ongoing routinely collected data on GP records, hospitalisations, and COVID-19 tests, through TPP records. Figure 1 below shows the cohort of interest for the HRQoL assessment, collecting the EQ-5D questionnaire results four times across 90-days to generate firstly HRQoL scores, and subsequently to generate quality-adjusted life-years. Note Airmid data collection can occur anytime between the start date of OpenPROMPT recruitment and the end of data collection which is estimated for June 2023.

Figure 1: Primary Cohort



We will identify those with and without long COVID as reported in questionnaires to compare their subsequent QALY values. The UK value set for the EQ-5D-5L set will be used together with the EQ-5D-5L scores collected in the questionnaire to generate individual participant level QALYs lost due to long COVID over 3 months as the area under the curve (AUC) following the trapezium rule using the utility scores. This loss is based on disutility, which is the difference of a utility value indicating perfect health. Long COVID will be defined by patient self-reports through the closed answer question responses on how long participants experienced COVID-19 symptoms, specifically 4-12 weeks and more than 12 weeks, in line with NICE definitions. The primary cohort of interest refers to individuals who completed questionnaires across four timepoints recruited between November 2022 and May 2023. There may be non- differential loss to follow up of participants during the study as they may not complete all questionnaires every 30 days. The definition of long COVID will be assessed in the sensitivity analysis, but will be primarily based upon self-reporting and secondly in diagnosis and referral codes through TPP when performing sensitivity analysis.

Given the collection of questionnaire data occurs across 30 day timepoints, we intend to calculate the number of QALYs lost due to long COVID over time. The longitudinal EQ-5D data captures the

nesting and clustering of observations at the patient level. This will be used to compare the HRQoL across patients who may have no history of COVID-19, a previous history of being a COVID-19 case but who have not developed a case of long COVID according to the NICE definition, and finally those who developed long COVID. The expectation for the cohort completing questionnaire data is a mixture of participants who were both hospitalised and non-hospitalised with acute COVID-19.

A power calculation was performed using estimates that the EQ-5D score for participants without long COVID was 0.979 and with long COVID was 0.9360 (Ping, et al., 2020). The prevalence of long COVID in the UK is around 2.7%, but since we are recruiting through long COVID Facebook groups and other focused recruitment methods, we assumed that over-recruitment will produce 5% with long COVID. Assuming this percentage, a sample size estimate of 1172 participants is needed to achieve 80% power. This has already been reached as of 27th February 2023 and is continually increasing, as there is no additional cost to the study, and it increases the power to address research questions.

Exposure & Comparator groups

The exposure group will be participants with long COVID, identified through self-reporting in questionnaires or through a recorded diagnosis in primary care records. For patients who have 'recovered' from long COVID after a referral in historic diagnostic codes, they are part of the comparator groups, but sensitivity analysis will explore this further. This identification for long COVID will use a list of SNOMED-CT codes (Walker, et al., 2021). The comparator group will be participants without long COVID, who either have been diagnosed with acute COVID-19 which has not developed into long COVID, or who have never had a diagnosis of COVID-19. Assessment will be made in the sensitivity analysis on the impact of only limiting exposure groups to those who are either a self-reported case or who have a clinical code of long COVID in primary historic data.

Descriptive Analysis

As utilising methods of data collection such as smartphone applications can exclude some groups from participating, we will assess the overall representativeness of the surveyed population through age, gender, ethnicity, region, and the first part of participants' postcode to calculate their socioeconomic status through the index of multiple deprivation at medium super output area. Producing descriptive statistics to compare to OpenSAFELY data, irrespective of study participation, will determine whether bias may exist. This will help determine the extent of any potential biases, in terms of comparability to the general population and the observation of case-mix differences distorting the effect of the exposure group, long COVID patients, leading to confounding. Imbalances in the sample can be observed with descriptive estimates to compare with general population estimates for the prevalence of long COVID among cohorts. This will be performed at both day 0 when participants join and complete their first questionnaires, as well as at the end of the 3 months of follow-up to see whether the characteristics of patients during the active data collection process is consistent throughout.

Covariates

With risk factors for having long COVID identified within Thompson et al. (2022), we intend to analyse the impact of similar covariates on the resulting HRQoL score for long COVID patients. These demographic characteristics will be collected through questionnaires in OpenPROMPT. Categories for covariates such as age and ethnicity may be grouped together when there are low counts of participants; for example there are 19 possible categorisations for ethnicity. These will be simplified to five categories of "White, Black, South Asian, Mixed, Other." The responses to the question on the first section of postcode will be used to categorise into nine English regions: North

East, North West, Yorkshire & the Humber, East Midlands, West Midlands, East of England, London, South East and the South West. Socioeconomic status is assessed with the Index of Multiple Deprivation at lower super output area. A further covariate will be having none, one, or two or more of the comorbidities of diabetes; cancer; haematological cancer; asthma; chronic respiratory disease; chronic cardiac disease; chronic liver disease; stroke or dementia; other neurological conditions; organ transplant; dysplasia; rheumatoid arthritis; systemic lupus erythematosus or psoriasis; and other immunosuppressive conditions. These are the underlying chronic diseases used in Thompson et al. (2022). They will be identified using OpenCodelists, which is a tool created by OpenSAFELY for generating and sharing codelists. The number of COVID-19 vaccine doses received will also be included based on responses to questionnaire.

Outcomes

EuroQol EQ-5D-5L

To measure HRQoL, the participant is asked to complete the EuroQoL EQ-5D-5L. This then enables calculation of quality-adjusted life-years (QALYs) lost due to long Covid. The EQ-5D-5L questionnaire is widely used in obtaining patient-reported outcomes, asking patients to indicate whether they have no, slight, moderate, severe, and extreme problems across the five domains of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. This assigns a 1-digit number to express the level for that dimension of HRQoL, and combining these into a 5-digit health status profile describes the overall patient health state across the dimensions. Including five levels of severity allows a greater descriptive sensitivity of the more refined HRQoL data. The EuroQol Index Value set for the UK is applied using the mapping EQ-5D-5L to 3L model from Hernandez Alava et al. (2023). Using such value sets allows comparability and consistency for assessments of HRQoL across patient groups in a wide range of contexts to summarise the data from the EQ-5D-5L. To elicit preferences for the five dimensions of health-related quality-of-life, Time Trade-Off (TTO) and Discrete Choice Experiment (DCE) methods are used. For TTO, respondents were given a choice between remaining in a poor state of health for a period of time, or returning to full health but having lower life expectancy. DCE is used to assess preferences between differing health states with no time aspect to assess the weighting in terms of quality-of-life that respondents give to mobility over pain/discomfort for example. The TTO methodology elicits a value for each health state where 1 and 0 are defined as anchor points, and the DCE results generate binary data to allow the derivation of a scale of relative values. Value sets are produced where the Discrete Choice Experiment data are anchored to the QALY scale using composite Time Trade-Off data (EuroQol, n.d). This results in a single digit linear score between -0.285, with negative values indicating a state worse than death, and a maximum value of 1 indicating perfect health.

Work Productivity and Activity Impairment Questionnaire: Specific Health Problem V2.0

The Work Productivity and Activity Impairment questionnaire corresponds to four subscales of productivity: absenteeism, presenteeism, overall work impairment and activity impairment. Respondents will be asked, during the previous seven days, how many hours of work they missed attributable to their condition, missed because of other reasons, how many hours they worked, and how much they felt their condition affected productivity whilst both working, and other regular daily activities. Using the results from hours lost using WPAI and income using linked postcode, age and gender responses, the productivity loss can be estimated using the human capital approach to attempt to quantify the cost due to long COVID. The human capital approach combines the number of hours

missed from work due to the condition, in this case long COVID, and the estimated market wage, which will be collected in the demographic questionnaire. It is the predominant method for estimating economic losses due to absenteeism and presenteeism in productivity assessments (Pritchard & Sculpher, 2000).

Statistical Analysis

Individual-level analysis will be undertaken in determining the effect from key demographic variables of age, ethnicity, socioeconomic status and pre-existing health conditions on EQ-5D scores. The analysis will estimate the effect on the longitudinal EQ-5D data across the four 30-day questionnaire results for patients with long COVID, assessing the effect for living with the condition, whilst controlling for demographic indicators. EQ-5D scores will be used to calculate the QALYs lost due to long COVID, but there are alternative models to consider that describe this relationship. Given the multiple points of data collection, an option to consider is to use a generalised estimating equation with the main outcome of HRQoL score using the EQ-5D UK value set. Generalised estimating equations allow for control of repeated observations in the sample, with individuals being assessed across timepoints. This can be used to estimate QALYs lost by integrating the outcome variable of the generalised estimating equation over a given time period. We will use generalised estimating equation models with indicator terms for the time since COVID-19 episode, chronological time of questionnaire results and personal characteristics. Assessments on the number of individuals who are not linked to a TPP controlled GP will also be evidenced to show for how much of the sample's historic records of GP contacts can be utilised in estimating the effect on QALYs lost due to long COVID.

Another option that will be considered is to calculate the QALYs lost at the per-person level, and to subsequently estimate the impact of personal characteristics in a Generalised Linear Model, where QALYs are the dependent variable, with one observation per individual. The choice of model depends on the data collected, where if there is little variation in the longitudinal EQ-5D data at the participant level, then QALYs can be calculated individually. The decision to choose either the estimating equations or linear generalised model will be taken on the basis of closer analysis of the results when they become available. If participants do not complete all the questionnaires at the 30-day intervals, and there is not the possibility of interpolation between data points, then the calculation of individual QALY estimates may not be possible. This could point to the use of the estimating equations with an unbalanced panel as the basis for statistical analysis.

The exposure group will be those with long COVID, as self-reported in the questionnaires or diagnosed and recorded in OpenSAFELY. Depending on the sample collected, there may be a need to utilise a two-part model to firstly model the probability of a disutility where HRQoL score departs from 'full-health' score. An exposure variable for a long COVID diagnosis will be used as an explanatory variable across both parts of the model. The effect of key covariates including ethnicity, age, and socioeconomic status will be assessed to determine the impact on loss of HRQoL scores for participants with long COVID.

Sensitivity Analysis

Assessment will be made on the impact of only analysing the HRQoL scores for those with a historic diagnosis of long COVID compared to participants who self-reported long COVID, i.e. responded that symptoms of COVID-19 persisted either 4-12 weeks or beyond 12 weeks. Patients may find it hard to get a diagnosed case of long COVID, whilst those with a historic diagnosis may do so because of

severe and multiple symptoms that require contact with GP's to receive a referral. Patients with a historic case which has persisted over months and possibly years before participation in the study may also report differing impacts on their quality-of-life compared to patients who were diagnosed or self-reporting a case more recently before participating. Performing sensitivity analysis on HRQoL score for those with self-reported long COVID against those with a classification of long COVID can draw from information in historical records where possible for patients linked to a TPP GP. This can help to evidence whether participants experiencing long COVID for a longer period of time result in higher QALY loss, directing where interventions would provide the most benefit.

Significant impacts could emerge on the corresponding HRQoL scores from a heavily weighted sample towards those at the more severe end of the long COVID scale. Overrepresentation of patients highly affected by long COVID through recruitment in Facebook groups will be assessed in the sensitivity analysis by excluding those who were enlisted through such groups, as reported in their questionnaire response. The collection of participants beyond the targeted sample size may help balance out the cohort between the three groups of no COVID records, a case of COVID-19 which did not develop into long COVID, and the exposure group of long COVID patients.

Limitations

The use of a smartphone app inherently produces a sample which may be unrepresentative due to inequalities in access to technology, and with higher educated and higher income individuals responding to a greater degree to surveys. This inequality in access to healthcare and health professionals through technology is a consideration within the analysis (Bambra, et al., 2020). Comparison with OpenSAFELY-TPP data, irrespective of study participation, will allow us to determine the extent of selection bias, through summaries of the representativeness of population and sample age, gender, geographic region, ethnicity, socioeconomic status amongst other characteristics. Propensity score matching and weighting will be explored to achieve comparability by controlling and adjusting for observed differences leading to confounding.

There may be disparities which arise from misclassification of long COVID. Patients may have an incorrect code of long COVID in GP records. Alternatively, patients can report that symptoms have lasted beyond 12 weeks without a history of a diagnosis of long COVID in GP records. It is harder to distinguish in the experience of COVID, long COVID and vaccination questionnaire results whether the symptoms being reported were severe, including shortness of breath and fatigue, or more widely including loss of smell or taste. Less severe symptoms are non-specific and prevalent in the general population without a diagnosis of long COVID, such that there may be misclassification of long COVID. FACIT and MRC Dyspnoea questionnaire results can to some extent limit the long COVID sample, but this is not going to be possible with missing responses.

The broad recruitment strategy for participants intends to provide a sample of those with and without long COVID but specifically targeted advertisements in long COVID Facebook groups may provide an over representation of patients highly affected by the symptoms of long COVID. Patients who are highly affected in their day-to-day activities may more likely actively engage with medical research and have a higher need for medical care. Participants are asked where they heard about the study, so sensitivity analysis will be conducted to assess the impact of limiting the sample to not include those who heard through long COVID Facebook groups.

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