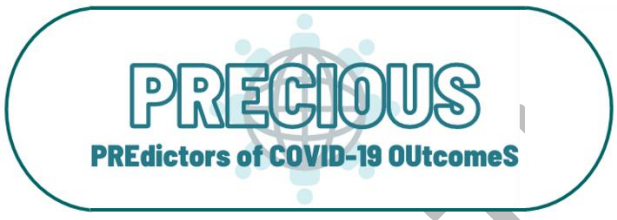
Study Title: PREdictors of COVID-19 OUtcomeS (PRECIOUS): Protocol for a systematic review-informed individual participant data meta-analysis of long-term outcomes after COVID-19

Short Title: PRECIOUS



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Chief Investigator Signature:

Confidentiality Statement:

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, HRA, host organisation, and members of the Research Ethics Committee, as appropriate, unless authorised to do so.

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Lay Summary:

BACKGROUND:

More than 767 million people worldwide have had COVID-19. More than 6.9 million people have died, and millions will need health and social service support. COVID-19 has cost more than $16 trillion USD. In the UK, more than 2 million people have Long-COVID: when symptoms last more than 3 weeks. These numbers continue to grow.

At first, researchers aimed to stop COVID-19 from spreading and to save lives. Now, we urgently need information about the long-term effects of COVID-19 to provide better care, including identifying who needs support, what kind of support and how much it costs.

AIM:

To bring together international researchers and their COVID-19 data to create a large, anonymised database with information from thousands of people that have had COVID-19 to describe long-term effects, what predicts a good (or poor) recovery and what health, and social service support people need.

DESIGN:

Searching for all existing studies that included people with COVID-19, we will organise the information relating to peoples age, health, socio-economic status, work, length of stay in hospital and long-term recovery. We will consider how independent and mobile they are, whether they have any breathing problems, tiredness or reduced quality of life.

METHODS:

We will use individual anonymised patient information instead of summaries of people's health. This is more powerful, as it allows us to look at specific patterns and plan care and support for individuals.

We will:

1. Gather information on long-term recovery from COVID-19.
2. Examine which people have good (or poor) long-term recovery from COVID-19.
3. Determine the cost of COVID-19 to the person, health services and to wider communities.

OUTPUTS:

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We will produce information on

1. long-term recovery after COVID-19
2. what predicts whether people will have long-term problems
3. the individual, healthcare and community costs of COVID-19

IMPLICATIONS:

Better understanding of long-term COVID-19 recovery and the people that experience poor recovery will help people with COVID-19 and healthcare staff understand and identify problems earlier, organise suitable support, advice and treatment for those who need it most.

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Synopsis

Study Title	PREdictors of COVID-19 OUtcomeS (PRECIOUS): Protocol for a systematic review-informed individual participant data meta-analysis of long-term outcomes after COVID-19
Internal ref. no. / short title	PRECIOUS
Study registration	PROSPERO Registration Number: CRD42020224323 IRAS Project ID: 293578 Glasgow Caledonian University (GCU) Ethics Ref: HLS/NCH/20/04
Sponsor	Glasgow Caledonian University, Cowcaddens Rd, Glasgow G4 0BA UK
Funder	National Institute of Health Research
Study Design	Individual Participant Data Meta-Analysis
Study Participants	People with COVID-19 in existing primary research datasets, where an outcome assessment exists ≥28 days of symptom onset
Sample Size	n/a
Planned Study Period	5th July 2021- 31st October 2023
Planned Recruitment period	n/a
Objectives	To describe: 1. long-term COVID-19 outcomes across ICF domains and time 2. the predictors of long-term outcomes, across outcome domains and time 3. the financial costs of COVID-19.

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Abbreviations

CI	Chief Investigator
Co-I	Co-Investigator
GCU	Glasgow Caledonian University
ICF	International Classification of Functioning, Disability and Health
ICU	Intensive care unit
IPD	Individual participant data
IRAS	Integrated Research Application System (IRAS)
NIHR	National Institute of Health Research
PI	Principal Investigator
PROSPERO	International Prospective Register of Systematic Reviews

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Glossary

The following definitions will be used throughout PRECIOUS:

Long-COVID	Describes signs and symptoms extending beyond the acute phase of infection[1] that are not explained by an alternative diagnosis[2].
COVID-19 Outcome	Describes an impact of COVID-19. In PRECIOUS, this will be operationalised for example using clinical scales in current use (e.g. the Barthel Index, capturing activities of daily living (ADLs) and can include (but is not limited to) endpoints such as death, hospital discharge, discharge location, return to work and quality of life.
Long-Term	defined as a timepoint ≥ 28 days of initial symptom onset[3] for the purposes of our analyses. Assessment ≥ 28 days will be used as it aligns with symptom manifestation and an infectious period of ~2-3 weeks[4], after which, recovery is expected and presence of ongoing problems could be considered "longer-term." This will permit the examination of trajectory of recovery across available domains beyond 28 days after infection.
COVID-Positive	defined as described in each contributed dataset; common definitions will be grouped together. Definitions may include but are not limited to: • diagnosis as COVID-positive on a Polymerase Chain Reaction (PCR) test; • diagnosis with COVID-Positive with a Lateral Flow Test (LFT); • suspected COVID-positive/clinical diagnosis • Multiple methods of diagnosis

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Introduction

Background

Globally, as of the July 2023 the multi-system disease COVID-19 has affected more than 767 million people[5], with more than 6.9 million deaths, and costing the global economy more than $16trillion[6]. While early efforts were focused on reducing the spread and managing acute infections, attention is now focused on prevention, reducing the severity of symptoms, and establishing and managing the long-term effects of COVID-19.

Reports from Germany indicate that up to 36% of people with COVID-19 have persistent problems more than 2 months after onset[7], while the Office for National Statistics estimates that 1 in 5 will have persistent symptoms for 5 weeks, and 1 in 10 will have persistent symptoms for 12 weeks or longer[1]. Initial data was based on small samples and disparate data mainly from hospitalised populations in single countries[3,8,9], reflecting the most severe cases. Community-based COVID-19 populations or those with milder symptoms were typically under-represented[10], despite indications of a higher incidence of persistent symptoms in the community based COVID-19 population compared with those that were hospitalised[11]. Data are needed that extend beyond an inventory of the persistent symptoms, to describe their impact on everyday life.

Furthermore, as the pandemic has progressed, the definitions of acute and long-term COVID-19 infections have been developed, providing reference time points for development of interventions, and for defining "long-term" support needs. The National Institute for Health and Care Excellence (NICE) has described COVID-19 timeframes in terms of acute: encompassing symptoms within the first 4 weeks of infection; ongoing symptomatic signs between 4-12 week; and as post-COVID syndrome, where symptoms persist for more than 12 weeks[12]. Increasingly, COVID-19 research includes examination of Long-COVID. Redeployment of existing services and tailored management of the emerging complex, multidomain consequences of COVID-19 is required to avoid or limit significant impact for individuals and society[4,13]. This should be informed by a robust evidence base. However, significant gaps exist in the evidence underpinning long-term COVID-19 rehabilitation efforts, including the identification of those that have the greatest rehabilitation need and what those needs are. Rehabilitation responses such as specialist Long-COVID services are being developed and delivered despite these uncertainties, and in the absence of high-quality information.

Comprehensive mapping of the full range and longevity of long-term COVID-19 outcomes across the International Classification of Functioning, Disability and Health (ICF; Figure 1) is urgently needed describing impacts on activities and participation, aspects such as return to work, quality of life, overall health and emotional wellbeing, and relationships**.**

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The relevance of demographics (e.g. ethnicity, sex, age, socio-economic status and co-morbidities) and COVID-19 history (e.g. severity, hospitalisation, length of stay, intensive care unit (ICU) admission, ventilation, catheterisation, positioning) on long-term outcomes also remain unclear. It is vital to establish the predictors related to poorer long-term outcome, thereby enabling the rehabilitation response to be tailored, ensuring that services and resources address individuals with the greatest need, those who can make important gains and those experiencing the greatest impacts. Additionally, information on the long-term impact of COVID-19 is needed to inform appropriate referral of people with persistent problems.

Analysis of large samples with varied demography, geographic diversity, and using a range of clinically relevant assessments are essential to reflect the varied long-term impacts of COVID-19[14]. With existing individual studies examining different aspects of the disease, collation and synthesis of these individual datasets would develop an overall picture of long-term COVID-19 outcomes, support description of factors related to long-term outcome, recovery potentials and optimal tailoring of rehabilitation interventions across ages, sex, comorbidities, socioeconomic and ethnicity subgroups and will complement and augment existing COVID-19 research activities.

Aims

To create an international, multidisciplinary COVID-19 database, and synthesise long-term outcomes, predictors and costs.

Objectives

To describe

1. long-term COVID-19 outcomes across ICF domains and time
2. the predictors of long-term outcomes, across outcome domains and time
3. the financial costs of COVID-19

Research Questions

1. What are the long-term outcomes of people after COVID-19 in relation to the ICF and over time?
2. What are the predictors of long-term COVID-19 outcomes over time?
3. What are the financial costs associated with the long-term health outcomes of COVID-19 for individuals, health services and society?

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Methods

Registrations and Approvals

PRECIOUS systematic review is registered with PROSPERO (CRD42020224323) while the PRECIOUS database has been registered with the Integrated Research Application System (IRAS project ID 293578). Ethical approval for the PRECIOUS study has been granted by Glasgow Caledonian University's Ethics Committee (HLS/NCH/20/04). Eligibility for inclusion in the PRECIOUS database requires all that primary research datasets adhered to the national or regional ethical agreements in place at the time the data set was gathered. We will require confirmation of those approvals from the relevant primary research contributors. We anticipate that some datasets may have consent processes which include permission for sharing of anonymised datasets.

Design

A systematic review-based identification of COVID-19 datasets and meta-analysis of IPD on long-term outcomes after COVID-19, using an established methodology[15].

Patient and Public Involvement (PPI)

Aim of PPI in PRECIOUS:

To conduct research which is of direct relevance to people with COVID-19 and their carers.

Methods:

Recruitment*:* PPI partners submitted their interest to join the PRECIOUS PPI group following an advertisement on www.peopleinresearch.org/.

Eligibility: Potential PPI partners were asked to complete a consent for to join the PPI group, and return forms to the PRECIOUS group. Eligible PPI partners were those who had COVID-19, or were closely involved in the care of those with COVID-19, or experienced, or cared for someone who experienced persistent problems due to COVID-19.

Meetings: PPI meetings will take place over Zoom and are scheduled throughout the project lifespan to ensure that PPI partners are able to contribute to each stage of data gathering, analyses and interpretation. PPI partners will be sent documents for review and comment prior to each meeting and will be invited to take an active role in dissemination via social media. Partners and remunerated based on guidance agreed with the Department of Health in 2009.

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Group Composition: The PRECIOUS PPI groups includes 8 partners who met the eligibility criteria.

Tasks:

Our PPI group have reviewed proposed activities, documents, and have advised on selection and refinement of the PRECIOUS research questions. Ongoing PPI involvement will include:

- informing content, delivery and accessibility of project communication and emerging findings on the project website
- refinement of dataset selection criteria
- refinement of outcomes for assessment, drawing on their experiences with persistent COVID impacts.
- identification of the health professions, timepoints, methods and settings most relevant for effective dissemination
- informing strategy, messaging and accessibility of all outputs

Evaluation and Reflections:

PPI partners will be sent brief evaluation forms to permit evaluation of how their recommendations have been implemented throughout the project and highlight areas of improvement.

Systematic identification of datasets

Target participant population

Adults with COVID-19, as reported in each dataset and according to the COVID-Positive definitions above.

Eligibility Criteria

We will seek raw IPD from studies relating to COVID-19 according to the eligibility criteria (Table 1).

Search Strategy & Information Sources

We will conduct a systematic search using the strategy described in Appendix 1. The search strategy will be developed by an information specialist and peer reviewed. We will systematically search electronic databases from December 2019 to 15 September 2021, with no language restrictions**.** The main searches for datasets will be conducted between 15 July 2021 – 15 September 2021; updated searches of targeted databases, supplementary searches (e.g. clinical trial databases,

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funding agencies) and backward and forward citation tracking will continue until 15th November 2021 to capture any new, relevant studies.

Selection Process

Records from electronic searches will be imported into Endnote and de-deduplicated using the method recommended by Bramer (2016)[16]. Records will be imported into Covidence following de-duplication-, and two researchers (PC, SR) will independently screen record titles and abstracts of each study against the inclusion criteria (Table 1). Full text studies will be obtained for all studies that meet the inclusion criteria and are potentially relevant and these will be screened independently by 2 researchers, using a third reviewer to resolve any disagreement. Supplementary searches and additional citation tracking will be conducted by one reviewer (PC, SR), and key details of records identified as potentially relevant will be extracted into an excel file and discussed by two reviewers (from PC, SR, MA).

Data Collection Processes

IPD from primary research studies will be sought; datasets will not be included where only summary statistics are recorded. The systematic-review informed identification and recruitment of datasets will be facilitated by strategic partnerships, collaboration and links with initiatives such as the Cochrane Rehabilitation Group and the WHO Rehabilitation Programme.

PIs of identified studies will be invited to contribute anonymised datasets as per established processes[17]. Briefly, PIs will be sent an invitation email, a PRECIOUS study information sheet (see appendix 2), will be asked to confirm dataset eligibility and invited to contribute eligible datasets. They will be contacted up to a maximum of 3 times before the 15th December 2021. They will be asked to confirm interest and ethical approvals to share data, complete a Data Contribution Form, sign a Data Sharing Agreement, and contribute fully anonymised data using a secure file transfer protocol (https://transfer.gla.ac.uk/security). Communication with primary research dataset PIs at this stage will be managed using an excel database, recording contacts made, decisions on eligibility, inclusion and a file transfer checklist.

Data Items

One reviewer will extract the following data for each included study (study level summaries) and this will be checked by a second reviewer:

- Dataset Information
- Demography

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- Outcomes using formal assessment tools
- Mortality
- Time to event (e.g. death or recovery)
- Intervention descriptions
- Health Economics data
- Risk of Bias

IPD data extraction and data cleaning

IPD will be extracted from all available contributed datasets and supplemented by published and unpublished material and information relating to the research; this will be ascertained through close collaboration with the contributing PIs. Selection of data extraction items have been informed by recent consensus work to develop a post-COVID core outcome set (COS)[18]. Items selected for data extraction include demography variables, details of active interventions that were administered to treat COVID-19, resource use within hospital (including use of ventilation, length of stay, use of ICU and corresponding length of stay) and out-with hospital (e.g. use of aids, referrals, and rehospitalisations); additional impact variables such as return to work will also be extracted where these were available.

Study Design

Study design will be informed by the Cochrane Effective Practice and Organisation of Care (EPOC) group[19].

- Randomised controlled trials (RCTs)
- Cohort studies
- Longitudinal studies
- Surveys
- Other

Countries

Countries and income categories will be described according to the World Bank's list of economies (https://databank.worldbank.org/data/download/site-content/CLASS.xls).

Age

Age will be described as a continuous variable. Where an age range is given in the original dataset, we will take a mean value.

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Time

Time data will be described as a continuous variable, and where a range is given in the original dataset, a mean will be taken.

COVID-19 Positivity

COVID Positivity will be described as:

- Positive at study baseline
- Negative at baseline with unknown prior-COVID
- Negative at baseline with known prior-COVID
- Not recorded

Diagnosis Method

- Diagnosis method will be described as:
- Antibody test
- Clinical diagnosis
- Polymerase Chain Reaction (PCR) test or Serology
- PCR / antigen based method

COVID-19 Severity

COVID-19 severity will be defined according to the degree of oxygen support required by the participant. Categories included:

- Hospitalised, high flow O2
- Hospitalised, high flow O2, unknown ventilation status
- Hospitalised, low flow O2
- Hospitalised, low flow O2, unknown ventilation status
- Hospitalised, no further O2 requirement details reported
- Hospitalised, no oxygen treatment
- Hospitalised, ventilated
- Not hospitalised

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Hospitalisation data

We will extract data related to hospitalisation for initial COVID-19 infection. This will take into consideration long COVID studies where recruitment may have taken place months after COVID-19 infection. Hospitalisation for that prior infection will be coded, where this is available.

Symptom Data

Where symptom variables can be amalgamated, this will be considered. For example, certain studies assessed anosmia and ageusia separately, while others assessed these together. We will code data pragmatically according to how the majority of data have been described. Synonymous symptoms will be amalgamated, e.g. myalgia and muscle ache.

Employment data

Employment data will be standardised to:

- employed
- Unemployed due to disability/ ill health
- Retired
- Managing households
- Student
- Not reported

Comorbidities

Comorbidities will be mapped to the ICD10. Obesity data will be extracted and informed by raw BMI measurements where this is available. Where BMI is used to impute obesity, we will use the World Health Organisation definitions of BMI cut points for obesity.

Socioeconomic status (SES)

Owing to the disparate nature of SES data, aggregation may be challenging. We will describe these data narratively.

Education

Education data will be described according to the highest level of education completed.

Health Economics Data

1. Resource use data will be extracted and will include information on resources used in hospital and out of hospital, where this is available. This includes but is not limited to referrals, GP and other health care contacts, discharge medications/ supplemental oxygen and discharge destination.

2. Length of stay data: data include but are not limited to length of hospitalisation, length of ICU stay, days of oxygen or other organ support.

3. Return to Work: this includes but is not limited to original occupation, return to work status and time to return, return with modified tasks, burnout, pre-and post-COVID employment status

4. Rehospitalisation: rehospitalisation for COVID-19 versus other admissions

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Long-Term Outcome Assessments

Assessment tools will be described verbatim and then linked to the appropriate ICF domain of assessment according to https://icd.who.int/dev11/l-icf/en (Figure 1) and informed by the recent paper by Patel et al (2020)[20]. These will include **Body Functions:** mental functions, sensory functions and pain, voice and speech functions, functions of the cardiovascular, haematological, immunological and respiratory systems, functions of the digestive, metabolic and endocrine systems, genitourinary and reproductive functions, neuromusculoskeletal and movement-related functions, functions of the skin and related structures; **Activities & Participation:** learning and applying knowledge, general tasks and demands, communication, mobility, self-care, domestic life, interpersonal interactions and relationships, major life areas, community, social and civic life; **Environmental Factors:** products and technology, natural environment and human-made changes to environment, support and relationships, attitudes, services, systems and policies; **Body Structures:** structures of the nervous system, the eye, ear and related structures, structures involved in voice and speech, structures of the cardiovascular, immunological and respiratory systems, structures related to the digestive, metabolic and endocrine systems, structures related to the genitourinary and reproductive systems, structures related to movement and skin and related structures [21]. If appropriate, we map outcomes to ICF level 3 or lower.

Acknowledging that an assessment tool can sit within multiple categories of the ICF, we will develop operational definitions of broad, overarching outcome domains. This will be generated through consensus decision with the co-applicant, collaborative and PPI groups. We will additionally extract data on mortality, time to death, and time to recovery, where these are available.

All extracted data will be reviewed by the original PIs and amended as needed. Data from open access datasets for whom a PI is not represented, will be reviewed by an investigator who was not involved in the data extraction.

Study Risk of Bias Assessment

Over 500 tools for appraising methodological quality have been identified[22]. We anticipate that the PRECIOUS study will identify a variety of different study designs and in order to meaningful appraise and synthesise the potential risk of bias across all of the included studies, we have selected the Mixed-Methods Appraisal Tool (MMAT 2018)[23]. The MMAT allows the appraisal of five study categories including RCTs, non-randomised studies, quantitative descriptive studies, qualitative research and mixed methods studies will be initially assessed using two screening questions to ensure that the MMAT is a suitable appraisal tool for that study. The algorithm in Hong (2018) guidance notes will be used to guide the appropriate category of questions.

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Three possible judgements (based on five key criteria relevant to study design category) are possible and will be recorded as either: Yes, No, Can't tell. Judgements on the MMAT criteria will be conducted independently by two reviewers, and consensus meetings will be held to discuss any discrepancies. Because of the dynamic nature of COVID-19 research and the likelihood of multiple publications linked to individual studies, we have also planned to send the appraisal decisions (plus comments supporting each judgement) to study authors to ensure that all relevant publications linked to their unique study have been captured and assessed.

Effect Measures

Effect measures will be presented as mean differences, hazard ratios and odds ratios, where appropriate.

Synthesis Methods

We plan analyses of pooled, international, anonymised COVID-19 datasets including cohort, case control, RCT, observational studies and registry datasets. Analyses will take the form of meta-analyses of subsets of the pooled available IPD specific to the research question (see Appendix 3; Logic Models). The proposed analyses will be quantitative in nature, employing generalised linear regression models (of the form appropriate to the outcome) and summary statistics of complete raw datasets as described in more detail below. Analysis datasets for each research question will be compiled based on the availability of key, pre-specified variables of interest.

Data transformation

With the rapid and parallel implementation of several initiatives to collect data on the COVID-19 population, there is a risk of uncoordinated data collection, lack of overlap in common data elements[26] and use of diverse definitions of COVID-19 positive participants. We will mitigate this by using a data transformation algorithm (developed in the RELEASE study [HS&DR–14/04/22][17]). This involves grouping outcome measurement instruments that measure the same outcome (e.g. independence, ADL, cognition, psychological outcomes, quality of life and cardiorespiratory outcomes). Consideration will be given to the contents of each of the assessment tools, purpose and direction of scoring. The most commonly used outcome measurement instrument across datasets within each outcome (e.g. Barthel Index for ADL) will serve as an "anchor measure" to which all other measures within the same category (e.g. Nottingham Extended ADL [NEADL] Score) will be transformed (matching value ranges for the BI, but preserving the original NEADL distribution)[17].

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Therefore, we will maximise the usable data that is pooled within common outcomes and presented on a clinically relevant assessment scale.

Analyses will consider data collection setting (hospital, community, other); definition of COVID-19 population (confirmed positive, negative with prior-COVID, negative with unknown prior-COVID); study design (RCT, cohort, case-control, survey); time post-symptom onset; follow up time as a continuous variable, or stratified by time points as appropriate; healthcare system (e.g. developed and developing countries) and level of evidence. Published RCT data in confirmed COVID-19 cases will represent the highest level of evidence.

For all outcome domains, descriptive statistics will be tabulated showing proportions for binary and categorical data (e.g. proportions for each level of care) and means and standard deviations, or medians and IQRs for continuous data as appropriate. Data within each domain with be transformed to the appropriate anchor measure[17].

The primary IPD meta-analyses will adopt a one-stage method rather than a two-step[27], as this is more appropriate when it is possible that some of the datasets will be small (<30 participants) or the outcome is binary or time-to-event[28]. The one-stage method involves data from all included and relevant datasets being combined in a single analysis. Individual dataset and/or country will be assessed as random effects. Appropriate generalised linear models will be used (e.g. analysis of covariance where outcome measures are continuous, binary logistic regression for dichotomous outcomes, Cox Proportional Hazards for time to event outcomes). Effect sizes (e.g. mean differences, odds ratios, hazard ratios) will be estimated and reported with corresponding 95% confidence intervals. Models will be adjusted for baseline values, where possible.

Variables of interest

RQ 1& 2: Participant profile items include individual characteristics (age, sex, ethnicity); comorbidities (e.g. diabetes mellitus, cardiac, liver or kidney disease, malignant neoplasm, obesity, chronic pulmonary disease, immunosuppressive medications or illnesses), setting (hospital, community) and health equity factors; COVID-19 severity; time since onset, type of intervention (e.g. dexamethasone, remdesivir, tocilizumab, sarilumab, other trial medication, if appropriate), presence of ongoing symptoms and long-term outcomes according to each available overarching outcome domain.

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RQ3: Cost descriptions include but are not limited to length of inpatient stay, outpatient visits, GP appointments, nurse/ GP appointments, physiotherapy, speech and language therapy, occupational therapy appointments, change in employment and rehospitalisation, where possible.

Analyses

RQ 1: What are the long-term outcomes of people after COVID-19 in relation to the ICF and over time?

Outcome categories will be described according to the ICF using linking rules[29,30] in the first instance using an Eppi map. These will be described in terms of time scales (time since symptom onset, time in hospital/ICU etc), demographic, socio-economic and clinical variables, if appropriate. Outcome data will then be described according to the overarching outcome domain generated through consensus decisions with the co-applicant, wider collaborative and PPI groups. These will be summarised as appropriate to the data type (tabulation and percentages for categorical data, mean and SD or median and IQR for continuous data). Symptom prevalence data will be described as % present over time.

RQ 2: What are the predictors of long-term outcome across ICF domains and over time?

We will explore the effect of baseline variables (e.g. age, sex, ethnicity, deprivation, comorbidities, and type of healthcare system, where available) on the health state at ≥28 days after COVID-19 onset. A one-stage meta-analysis approach will combine all available IPD within each outcome category, preserving participant clustering within each dataset. Meta-analysis with fixed demographic and recovery effects will include dataset and/or country as a random effect; variance will be evaluated for dataset heterogeneity. Continuous outcome scores (transformed to anchor measures), time to recovery and mortality will be regressed onto baseline demographic, socioeconomic and clinical variables. Significant variables at univariable level ($p<0.1$) will be included in multivariable analysis, to limit the number of predictors to a manageable level. The presentation of results will be clustered into groups of related overarching outcome domains:

- Overall Health, Wellbeing & Life, Sleep
- Cognition & Thinking, Anxiety & Depression, Stress
- Energy & Fatigue, Strength, Pain and Frailty
- Coping with Daily Life, Physical Activity & Performance
- Breathing & smell

Results will be presented as mean and 95% confidence limits on the transformed scales at each relevant timepoint. Where possible, trajectory of outcomes will be described over time. Data

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permitting, we will develop and validate a prediction algorithm that can provide prognostic information on outcome trajectory.

RQ 3: What are the financial costs associated with the long-term health outcomes of COVID-19 for individuals, health services and society?

IPD on resource use including length of hospital stay, use of primary and secondary health care, social care services, return to work and informal care will be extracted and summarised where available. We will estimate the impact of predictors identified in RQ2 on healthcare resource utilisation, return to work and rehospitalisation. Data permitting, we will explore utility loss related to poor outcomes using quality of life data. Resource use will be presented in natural units to account for differing healthcare systems. Costs will also be attached to resource use using UK sources[31], allowing each category to be compared in a common currency. It is noted that this will not be the 'cost' to the NHS or any health care system of COVID-19 but is included to provide information on what are the drivers of resource use which may inform future investment decisions for long-term rehabilitation.

The economic analysis will include resource use data for all related healthcare costs and also non-health related costs with a societal viewpoint. The costs that are deemed relevant for this study will be assessed from a societal perspective and an individual perspective when data exists for out-of-pocket payments. In that way, there will be potential to cover a wide range of costs to be used in future studies.

All findings will be reported according to existing reporting guidelines for systematic reviews (e.g. the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [PRISMA]) IPD meta-analysis[32] and Guidance for Reporting Involvement of Patients and the Public (GRIPP-2)[33] will be used to support high quality reporting of our methodologies and findings.

Heterogeneity

Given the diversity in the proposed data, we anticipate issues relating to heterogeneity, particularly in relation to methodology. Consequently, we might expect to observe some statistical heterogeneity (τ^2) in our proposed analyses when treatment effects are more different from each other than might be expected to occur through chance alone. Where statistical heterogeneity is identified we will consider the magnitude of the inconsistencies observed, as significance will depend on the number of available studies, and where appropriate adopt the following strategies:

- identify the source of heterogeneity and exclude studies that cause significant heterogeneity in a sensitivity analysis

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- consider the clinical importance of identified heterogeneity and whether it is important to the outcome
- consider sensitivity analysis and explore the impact of a fixed effects model.

Sample size

Sample size calculations are primarily used in primary research studies and are of lower importance in meta-analysis where there is less ability to control the number of patients being examined. However, sample size considerations for a meta-analysis are very similar to that of a primary-effects analysis and depend on the size of the effect to be detected, the precision of this effect size, the power and the significance level. The effect size to be detected, the power and significance level are under the control of the researcher. The latter two are often 80% or 90% and 5% or 1%, respectively. The unknown aspect is the level of precision and is a function not only of the number of participants in the individual studies, but also the number of studies, and whether we have adopted a fixed or random effect for the meta-analysis. With a random effects model, the estimate of precision (variance) is inflated by the between-studies variance, and thus greater than in a fixed effects model. Since our proposed datasets will have multiple outcomes, and multiple levels within multiple predictors (e.g. a primary predictor with 4 levels), we will set a conservative significance level of 1% and a power of 90%. Thus, for each outcome, we will require 121 participants per level to explore a difference of 0.5SD, where the SD is the square root of the joint variance within and between studies and the correlation between variables. Thus ideally, we would need 500 IPD per outcome, with approximately equal proportions of IPD per group. Domains with fewer IPD than this will be estimated but treated with caution, or excluded, as appropriate.

Missing Data

The main analyses will be complete case analyses.

Study Quality Assessment

Quality of the study and risk of bias will be assessed (e.g. inspection of funnel plots to examine publication bias). We will initially code studies according to publication status (pre-print / unpublished / peer-reviewed) as well as using Sackett's Level of Evidence[34]. We will also conduct risk of bias using relevant quality assessment tools e.g. the Joanna Briggs Institute critical appraisal checklist. Final decisions about methodological assessment may involve the PPI group, but we anticipate that we will assess studies for publication bias, reporting bias and detection and performance bias.

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Data Management

All identified IPD datasets will be collated into a single database. Variables will be cleaned and decisions recorded to ensure consistency across datasets and researchers (e.g. age in years, length of hospitalisation in days); any missing data will be investigated in collaboration with the original PIs. A master database will be compiled from all contributed data using SAS; common and overlapping variables will be standardised and the rationale for combination/standardisation will be fully explained. Data samples for each research question will be generated based on the availability of pre-specified variables. An analysis dataset will be made for each research question; each dataset will include all eligible patients' data for whom data are available for each of the essential variables.

Full details of the data management process are described in the PRECIOUS Data Management Plan. Briefly, data management will be undertaken by PC (Research Fellow) and SR (Research Assistant) who will ensure that data management systems are in place from the start of the study, and are reviewed and revised as appropriate. SR will lead data collation, storage, backup, data extraction, data archiving and data sharing. PC, SR and MA will liaise with the statisticians who will oversee the planned analyses to ensure that data are available in an appropriate format for analysis. Existing infrastructure at GCU will readily accommodate the proposed data management systems. The Data Management Plan provides a comprehensive description of the following the two-phase data processing system:

- Phase 1 covers the systematic search, screening and recruitment of eligible datasets; the inclusion and exclusion criteria; data management and administration processes covering anonymisation, data encryption and storage, security and access control, data retention and disposal and adherence to data sharing standards.
- Phase 2 utilizing the data extraction table which collates all sources of study information (published and unpublished) within the numeric IPD data will facilitated feasibility checking of planned analyses. All relevant documents are used in tandem with published reports and datasets to ensure quality assurance and to inform conversion of IPD from their existing format to the standardized format in preparation for statistical analyses.

We will ensure that all datasets provided for the PRECIOUS database are tracked and saved on the GCU server. A working copy of each dataset will be created and saved using a unique ID along with supporting documents in a unique ID folder accessible on to the Project Management Team. In accordance with GCU practice, all files will be backed up daily.

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Recruitment management

We will maintain an excel record of communication with primary researchers and research teams including the number of invitations sent and responses (agreement to contribute, declined, data no longer available, no response). We will document all invitations to participate and subsequent expressions of interest in contributing data. Each study will be tracked using the author name and study DOI reference.

Anonymisation

We will request the contribution of fully anonymised patient data only. A database-wide unique identifier will be allocated for each participant, comprising a unique study number and the study name. This will ensure that the inclusion of specific participants in subsequent analysis datasets can be traced back to the original trial source for quality assurance and data verification.

Data Documentation

Each dataset that is contributed electronically will be accompanied by an annotated Data Collection Form which will detail each of the variables collected, the time points for collection and the codes used for each of these variables. A full publication will be requested along with the dataset, where available. These documents will be used to clean the data and apply standard data labels to the master dataset(s). These documents will also be available as data descriptors on a common drive which can be accessed by the analyst/statistician.

Data Storage

Data will be stored at the NMAHP Research Unit, GCU, UK, according to university procedures. A single, anonymised project master database will be generated from these original datasets and will be stored separately on the NMAHP Research Unit's designated portion of the university server. Adjustments to this database will not affect the original study data. Analysis datasets will be generated from the master dataset and will be stored on a common, encrypted hard drive. Based on previous experience of collating similar datasets, storage of contributed datasets will not exceed standard external hard drive capacity (1TB).

Security & Access Control

During the project, data will not be accessible to those out-with the project collaboration. Access to data in a legacy database can only take place at the end of the project and will be governed through a PRECIOUS Steering Committee comprising contributing PIs and co-applicants of the current proposal. The PRECIOUS Steering Committee will govern use of research data, participate in analyses and review

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manuscripts based on the planned analyses. These contributing PIs will thereby retain control of use of their own data and have an opportunity to contribute to the planned secondary analyses. Analysis plans will be prespecified and the contributing researchers will retain the option to join the research group and contribute to the peer-reviewed publication.

Formatting Data and Data Conversions

The Data Manager and statistician will oversee the conversion of datasets into compatible formats, liaise with contributing PIs to ensure the completeness of contributed data and to check variable ranges for accuracy. Data will likely be contributed in various formats including SAS, SPSS, Excel and Access. Before commencing secondary analyses, all data will be converted into a uniform format (e.g. SAS). This will be determined by the Data Manager, bearing in mind future use, long term storage and compatibility with other forms of data storage. All contributed datasets will be combined into a single master database, merging common variables such as patient age, sex and medical history variables. Where possible, outcomes will be merged according to the assessment tool used and documenting interventions. Some translation of variable labels may be required for international datasets. We will ensure the completeness and accuracy of data with contributors. Simultaneously, we will build a map of outcome assessments and the ICF domain to which they belong.

Quality Assurance

Quality assurance and verification of variables will be performed by cross-checking the dataset against the trial source, published papers & other outputs, any unpublished data (e.g. protocols or clinical trial registrations) checking the acceptable ranges of variables and where possible through correspondence with the contributing PIs. After checking with these sources, any entries that cannot be reconciled will be excluded from analyses.

Version Control and Backups

Version control will be used for analysis datasets which are stored on a common hard drive. Milestone datasets will be identified and updated as necessary (e.g. <Filename version 1.0date>). Analysis datasets will be stored in a separate folder from the master datasets. Master datasets will only be updated when new data are contributed. In this case, the master dataset will be renamed with a new filename, version number and date. The analyst will save their on-going work under new analysis dataset file names, rather that re-naming existing master datasets. Data stored on the common or departmental hard drives are backed up daily according to University practice.

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Data Retention and Disposal

After the requested PRECIOUS funding period, researchers who have contributed data may choose to lodge their data in a central repository hosted at GCU, UK for additional data sharing activities. In this way, data can be reused beyond the scope of the current application and will be made available to a wider research community for the purposes of novel exploratory analyses (see Security & Access Control). Anonymised data will be preserved within these databases for an initial period of at least 15 years for further re-use. These potential secondary analysis activities might include re-use in validation studies, teaching, exploratory analyses and prognostic modelling.

Adherence to Data Sharing Standards

The foundational principles for data sharing aim to "promote health and wellbeing, respect individuals, families and communities, advance research and the fair distribution of benefits and foster trust, integrity and reciprocity". Elements essential for responsible data sharing include transparency, accountability, data security and quality, privacy, data protection and confidentiality, minimising harm and maximising benefits, recognition and attribution, sustainability, accessibility and dissemination. We will ensure that our data sharing activities adhere to the Framework for Responsible Sharing of Genomic and Health-Related Data (2014)[35].

The International Committee of Medical Journal Editors' (ICMJE) has also proposed requirements for ethical clinical trial data sharing[36]. It proposes that researchers conducting clinical trials must be required to include a data sharing plan as part of their registration. In order to meet the needs of authors requesting data and to protect the rights of researchers and trial sponsors, the ICMJE proposes that certain safeguards should be adhered to. The first of these is that deposition of data in a registry does not constitute prior publication. Secondly, researchers using secondary analyses must stipulate, at the time of receipt, that the use of the data will be in accordance with the stated aims of their project. Thirdly, that due credit is given to the providers of the clinical trial data by using a unique identifier which will also enable studies it has supported to be located. Fourth, that researchers conducting secondary analyses provide full details of how their own analyses differs from previous analyses. The ICMJE also states that the efforts of the researchers who create and share clinical trial data should be credited and additionally, as data sharing is a shared responsibility, collaboration between these researchers and those using the collected data should be sought.

Intellectual Property

Our proposed research builds upon previously conducted research where the study results and data gathered in relation to those primary research studies (Background IP) belongs to each individual

study sponsor and investigators. All co-applicants and collaborating partners contributing data to the PRECIOUS database are aware of the plans to re-use this historical data for the purposes of the investigations described in this protocol. Our proposed research study will, through the pre-specified secondary analysis of the PRECIOUS database, develop and build upon substantial background IP from each of the contributing studies. All PRECIOUS study database, analysis datasets and results will be newly generated (Foreground IP), this will be led by GCU. While we do not anticipate any new statistical data analysis techniques or data management procedures it is possible that new methodologies may arise from the PRECIOUS study. Any such new developments will be led by GCU and disseminated in the public domain and shared with other researchers for wider research and public health benefit.

Authorship

Each dataset contributor to this proposed project has been contacted prior to the submission of this proposal to ascertain whether they have any intellectual property issues. These details are requested in full within our on-line contribution form. Output will be presented "on behalf of the PRECIOUS Collaborators." Each researcher, funder or research group will also be named as a co-author or acknowledged in subsequent publications from PRECIOUS as appropriate (Appendix 4: Publication Policy).

Dissemination

Outputs

We will describe the long-term impacts of COVID-19 across available ICF domains, the trajectory of long-term COVID-19 outcomes, develop a clinically applicable long-term outcome predictors algorithm and describe the cost of and resource allocation needs after COVID-19. Data will also be entered into a legacy dataset for long-term COVID-19 outcomes, housed at Glasgow Caledonian University. Permission to retain data in a legacy dataset will be sought from PIs of original research. They will join a Steering Committee and will be able to review proposed uses of their datasets by the wider scientific community, thereby retaining governance over how their data are used. All research findings will be made available in an accessible format on a project website. This will be separate from planned publications, and may include use of infographics, for example. We will disseminate all findings to health professionals through use of information sheets on long-term outcomes, in addition to our planned publications.

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Findings will direct where future research is needed to capture impacts on under-represented populations, provide information for people with COVID-19, families, GPs, clinicians, allied health professionals, nurses, researchers and policy makers on what to expect (e.g. effects on activities of daily living, participation, return to work, and quality of life), when to expect poorer outcomes and the populations affected. We will additionally inform resource allocation through our analysis of long-term outcomes and costs.

Acknowledgements

Notifying funders of planned outputs

As required by the NIHR, all publications and other outputs will be submitted to the NIHR funders at the same time as submission for publication. As requested by NIHR, when presenting ongoing PRECIOUS research activities, the terminology "emerging findings" will be used instead of "results", particularly if the work has not been peer reviewed.

Governance

Project management team

The Project Management Team comprises Myzoon Ali (MA; CI; IPD Meta-Analyses), Marian Brady (MB; Co-CI, Systematic Reviewer, IPD Meta Analyses), Pauline Campbell (PC; Research Fellow, Systematic Reviewer), Scott Rooney (SR; Research Assistant; Systematic Reviewer), Linda Williams (LW; Senior Statistician) and Helen Mason and Sarkis Manoukian (Health Economists).

Co-applicants

Co-applicants comprise experts in respiratory medicine (Andrew Smith & Manish Patel), care of the elderly (Mark Barber), infectious diseases (Claire McGoldrick), immunology (Neil Basu), research into long-term conditions (Lorna Paul) and Patient and Public Involvement representatives (Charlie Chung).

Collaborators

Following contribution of datasets, primary research PIs will join the PRECIOUS collaborative group, inform data cleaning, planned analyses, publication preparation and dissemination. Communication will take place via email and Zoom meetings to review and resolve issues related to the primary datasets contributed and the PRECIOUS dataset. They will take part in quarterly meetings with the whole research team to review progress, contribute to analyses and interpretation and will review and comment on all outputs. PIs will be able to contribute to analyses processes, and interpretation; all analyses will follow the pre-specified research objectives. An expert advisory group

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will supplement the contributing PIs and will comprise multidisciplinary experts involved in the care of people with COVID-19, where expertise are not already represented within the existing contributing PIs.

Responsibilities of co-applicants and collaborators:

The core project management team, co-applicants and collaborators will each contribute their unique expertise to project development, methods, dataset recruitment, development of the analysis plan, key decision making and dissemination throughout the project.

Publication Access

All papers will be open access. A copy of the final manuscript of any research papers supported in whole or in part by the NIHR will be deposited with UK PubMed Central upon acceptance for publication, to be made freely available as soon as possible and in any event within six months of the journal publisher's official date of final publication to meet the NIHR's open access commitment.

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Table 1: Eligibility Criteria

Eligibility criteria
Inclusion

• Cohort studies, case-control studies, surveys and RCTs with more than one time point for assessment
• Any setting
• Minimum IPD of 10 people
• Adults with COVID-19 reflecting a range of severities, symptoms and durations with outcomes assessed at ≥ 28 days post-onset
• Outcomes assessments including (but not limited to) presence of:
  o A formal tool capturing an ICF domain.
  o Reporting of presence of a post-COVID complication (e.g. fatigue) ≥ 28 days of initial symptom onset
  o Morbidity or continued hospitalisation beyond ≥28 days of initial symptom presentation
  o Residence in, or discharge to a long-term care/ rehabilitation facility ≥28 days of initial symptom presentation, or discharge to another location.

Exclusion
• Studies with no available IPD • Single case studies • Studies of COVID-19 in children • Studies focused only on the impact on caregivers • Healthcare process evaluations • Qualitative data

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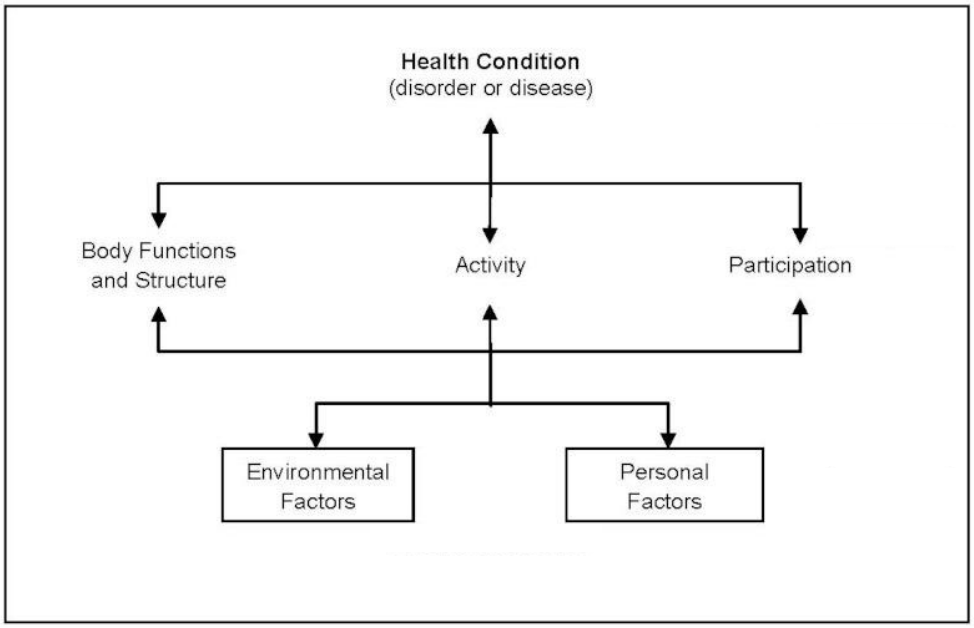
Figure 1: The International Classification of Functioning, Disability and Health (ICF)



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Appendix 1: Search Strategy

Covid-19 has resulted in an unprecedented number of publications. In order to capture the most relevant evidence in a systematic and efficient manner, we have planned to conduct our searches using a hierarchical three-stepped approach.

- Step 1: will involve the searches for all relevant systematic reviews and meta-analyses which include studies which met our eligibility criteria. We will use these high-level studies to rapidly identify any relevant study included within these publications that meet the eligibility criteria, so that invitations can be sent to potential collaborators as quickly as possible.
- Step 2: will involve systematic searching of relevant electronic databases and clinical trial databases to identify all relevant clinical trials that meet the eligibility criteria.
- Step 3: will involve a systematic supplementary search of relevant grey literature, pre-publication websites and forward and backward citation tracking.

The core search strategy will consist of coronavirus (COVID-19) terms (see lines 1-11 below) and a relevant study design filter to locate systematic reviews and meta-analyses for step 1 (see search strings) and another filter to identify randomised controlled trials for step 2 [37]. Our searches will be peer reviewed in accordance with PRESS guidelines[38].

1. coronavirus/ or betacoronavirus/ or betacoronavirus 1/ or middle east respiratory syndrome coronavirus/ or sars virus/
2. coronavirus infections/ or severe acute respiratory syndrome/
3. (coronavirus$ or corona virus$ or OC43 or NL63 or 229E or HKU1 or HCoV$ or ncov$ or covid$ or sars-cov$ or sarscov$ or Sars-coronavirus$ or Severe Acute Respiratory Syndrome Coronavirus$).mp.
4. 1 or 2 or 3
5. (20191$ or 202$).dp. or 20191117:20301231.(ep).
6. 4 and 5
7. sars-cov-2/ or covid-19/
8. (2019-ncov or ncov19 or ncov-19 or 2019-novel CoV or sars-cov2 or sars-cov-2 or sarscov2 or sarscov-2 or Sars-coronavirus2 or Sars-coronavirus-2 or SARS-like coronavirus$ or coronavirus-19 or covid19 or covid-19 or covid 2019 or ((novel or new or nouveau) adj2 (CoV or nCoV or covid or coronavirus$ or corona virus or Pandemi$2)) or ((covid or covid19 or covid-19) and (outbreak or crisis or pandemic$2)) or (coronavirus$ and pneumonia)).mp.

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9. COVID-19.rx,px,ox. or severe acute respiratory syndrome coronavirus 2.os.
10. 7 or 8 or 9
11. 6 or 10

Electronic searches

These search strategy described above will be adapted for the following major databases:

- Cochrane Central Register of Controlled Trials (CENTRAL), and the Cochrane Database of Systematic Reviews (CDSR) in the Cochrane Library (https://www.cochranelibrary.com)
- MEDLINE (Ovid)
- EMBASE (Ovid)
- Web of Science – Core Collection (Indexes= Science Citation Index Expanded (SCI-EXPANDED), Social Sciences Citation Index (SSCI), Arts & Humanities Citation Index (A&HCI), Conference Proceedings Citation Index- Science (CPCI-S), Conference Proceedings Citation Index- Social Science & Humanities (CPCI-SSH) , Book Citation Index– Science (BKCI-S), Book Citation Index– Social Sciences & Humanities (BKCI-SSH), Emerging Sources Citation Index (ESCI);
- PsycINFO (Ovid)
- CINAHL (EBSCO) (Cumulative Index to Nursing and Allied Health Literature)
- WHO Global Index Medicus databases;
- Epistemonikos (https://www.epistemonikos.org/)
- COVID19 systematic search strategies and resources including real-time dashboards of clinical trials (e.g. LitCovid)[38,39].

Additional supplementary searches

Supplementary searches will systematically identify potentially relevant studies from:

- Registers of ongoing trials (US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov) and World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch), OpenTrials, and European Medicines Agency,
- Grey literature sources (e.g. Publish or Perish software for Google Scholar searches (https://scholar.google.com/) and prepublications from MedRxiv (https://www.medrxiv.org)).

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- Searches of national and international funding agencies (e.g. NIHR, NIH Reporter, Canadian Institutes of Health Research), third sector and government websites to identify other relevant funded studies
- Forward citation tracking using Google Scholar (https://scholar.google.com/) will be completed together with searching reference lists of included studies for all included studies.
- We will also set up alerts and notifications for social media websites, electronic databases and citation alerts for included / relevant studies.

Step 1: Search strings for Systematic Reviews and Meta-analyses

Cochrane Database of Systematic Reviews Issue 7 of 12, July 2021 (last searched 15 July 2021) n=42;

#1 MeSH descriptor: [Coronavirus] this term only
#2 MeSH descriptor: [Betacoronavirus] this term only
#3 MeSH descriptor: [Betacoronavirus 1] this term only
#4 MeSH descriptor: [Middle East Respiratory Syndrome Coronavirus] this term only
#5 MeSH descriptor: [Middle East Respiratory Syndrome Coronavirus] this term only
#6 MeSH descriptor: [Coronavirus Infections] this term only
#7 MeSH descriptor: [Coronavirus Infections] this term only
#8 (coronavirus* or corona virus* or OC43 or NL63 or 229E or HKU1 or HCoV* or ncov* or covid* or sars-cov* or sarscov* or Sars-coronavirus* or Severe Acute Respiratory Syndrome Coronavirus*):ti,ab,kw (Word variations have been searched)
#9 {or #1-#8} with Cochrane Library publication date from Oct 2019 to present
#10 MeSH descriptor: [COVID-19] this term only
#11 MeSH descriptor: [SARS-CoV-2] explode all trees
#12 ("2019-ncov" or ncov19 or ncov-19 or "2019-novel CoV" or sars-cov2 or sars-cov-2 or sarscov2 or sarscov-2 or Sars-coronavirus2 or Sars-coronavirus-2 or SARS-like coronavirus* or coronavirus-19 or covid19 or covid-19 or covid 2019 or ((novel or new or nouveau) near/2 (CoV or nCoV or covid or coronavirus* or corona virus or pandemi*)) or ((covid or covid19 or covid-19) and (outbreak or crisis or pandemic*)) or (coronavirus* and pneumonia)):ti,ab,kw
#13 {or #9-#12}
#14 #9 OR #13

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions(R) 1946 to July 13, 2021 ("NOT Children" filter added; last searched 15 July 2021) n=3547.

1. coronavirus/ or betacoronavirus/ or betacoronavirus 1/ or middle east respiratory syndrome coronavirus/ or sars virus/
2. coronavirus infections/ or severe acute respiratory syndrome/
3. (coronavirus$ or corona virus$ or OC43 or NL63 or 229E or HKU1 or HCoV$ or ncov$ or covid$ or sars-cov$ or sarscov$ or Sars-coronavirus$ or Severe Acute Respiratory Syndrome Coronavirus$).mp.

4. 1 or 2 or 3
5. (20191$ or 202$).dp. or 20191117:20301231.(ep).
6. 4 and 5
7. sars-cov-2/ or covid-19/

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8. (2019-ncov or ncov19 or ncov-19 or 2019-novel CoV or sars-cov2 or sars-cov-2 or sarscov2 or sarscov-2 or Sars-coronavirus2 or Sars-coronavirus-2 or SARS-like coronavirus$ or coronavirus-19 or covid19 or covid-19 or covid 2019 or ((novel or new or nouveau) adj2 (CoV or nCoV or covid or coronavirus$ or corona virus or Pandemi$2)) or ((covid or covid19 or covid-19) and (outbreak or crisis or pandemic$2)) or (coronavirus$ and pneumonia)).mp.9. COVID-19.rx,px,ox. or severe acute respiratory syndrome coronavirus 2.os.
10. 7 or 8 or 9
11. 6 or 10
12. meta-analysis/ or "systematic review"/
13. systematic reviews as topic/
14. exp meta-analysis as topic/
15. (meta analy$ or metaanaly$ or meta synthes$).ti.
16. (systematic adj3 (review$1 or overview$1)).ti.
17. or/12-16
18. exp animals/ not humans.sh.
19. 17 and 11
20. 19 not 18
21. exp Adolescent/
22. exp Child/
23. exp Infant/
24. exp Minors/
25. exp Pediatrics/
26. exp Puberty/
27. exp Schools/
28. (baby$ or babies or infant$ or infancy or neonat$ or newborn$ or postmatur$ or prematur$ or preterm$).ti.
29. (boy$ or girl$ or teen$).ti.
30. (child$ or kid or kids or preschool$ or school age$ or schoolchild$ or toddler$).ti.
31. (elementary school$ or high school$ or highschool$ or kindergar$ or nursery school$ or primary school$ or secondary school$).ti.
32. minors$.ti.
33. (paediatric$ or peadiatric$ or pediatric$).ti.
34. (prepubescen$ or pubescen$ or pubert$).ti.
35. (youth or adolescen$).ti.
36. or/21-35
37. 20 not 36

Embase 1980 to 2021 Week 27 (last searched 15 July 2021) n=n=6812;
1. betacoronavirus/ or coronavirinae/ or betacoronavirus 1/ or middle east respiratory syndrome coronavirus/ or sars-related coronavirus/
2. coronavirus infection/ or severe acute respiratory syndrome/
3. (coronavirus$ or corona virus$ or OC43 or NL63 or 229E or HKU1 or HCoV$ or ncov$ or covid$ or sars-cov$ or sarscov$ or Sars-coronavirus$ or Severe Acute Respiratory Syndrome Coronavirus$).mp.

4. 1 or 2 or 3
5. (20191$ or 202$).dp.
6. limit 5 to dd=20200118-20200626
7. 5 or 6
8. 4 and 7
9. exp severe acute respiratory syndrome coronavirus 2/ or coronavirus disease 2019/

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10. (2019-ncov or ncov19 or ncov-19 or 2019-novel CoV or sars-cov2 or sars-cov-2 or sarscov2 or sarscov-2 or Sars-coronavirus2 or Sars-coronavirus-2 or SARS-like coronavirus$ or coronavirus-19 or covid19 or covid-19 or covid 2019 or ((novel or new or nouveau) adj2 (CoV or nCoV or covid or coronavirus$ or corona virus or Pandemi$2)) or ((covid or covid19 or covid-19) and (outbreak or crisis or pandemic$2)) or (coronavirus$ and pneumonia)).mp.
11. 9 or 10
12. 8 or 11
13. evidence based medicine/ or exp meta analysis/ or "systematic review"/
14. exp meta analysis/ or "systematic review"/
15. methodology/ or "meta analysis (topic)"/ or "systematic review (topic)"/
16. (meta analy$ or metaanaly$).ti.
17. (systematic adj3 (review$1 or overview$1)).ti.
18. or/13-17
19. (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.)
20. 18 not 19
21. 12 and 20
22. exp *adolescence/
23. exp *adolescent/
24. exp *child/
25. *high school/
26. *kindergarten/
27. *middle school/
28. exp *newborn/
29. *nursery school/
30. exp *pediatrics/
31. *primary school/
32. exp *puberty/
33. *school/
34. adoles*.ti.
35. (baby* or babies or infant* or infancy or neonat* or newborn* or postmatur* or prematur* or preterm*).ti.
36. (boy* or girl* or teen*).ti.
37. (child* or kid or kids or preschool* or school age* or schoolchild* or toddler*).ti.
38. (elementary school* or high school* or highschool* or kindergar* or nursery school* or primary school* or secondary school*).ti.
39. minors*.ti.
40. (paediatric* or peadiatric* or pediatric*).ti.
41. (prepubescen* or pubescen* or pubert*).ti.
42. or/22-41
43. 21 not 42

CINAHL EBSCO (Cumulative Index to Nursing and Allied Health Literature; 1982 to present) ("Limiters - Publication Year: 2019-2021"; last searched 15 July 2021) n=1181;

S1 (MH "Coronavirus") OR (MH "Coronavirus Infections") OR (MH "Severe Acute Respiratory Syndrome") OR (MH "SARS Virus")

S2 TI (coronavirus* or corona virus* or OC43 or NL63 or 229E or HKU1 or HCoV* or ncov* or covid* or sars-cov* or sarscov* or Sars-coronavirus* or Severe Acute Respiratory Syndrome Coronavirus*) OR AB (coronavirus* or corona virus* or OC43 or NL63 or 229E or HKU1 or HCoV* or ncov* or covid* or sars-cov* or sarscov* or Sars-coronavirus* or Severe Acute Respiratory Syndrome Coronavirus*)

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S3 S1 OR S2
S4 (MH "COVID-19") OR (MH "COVID-19 Pandemic") OR (MH "SARS-CoV-2")
S5 TI (("2019-ncov" or ncov19 or ncov-19 or "2019-novel CoV" or sars-cov2 or sars-cov-2 or sarscov2 or sarscov-2 or Sars-coronavirus2 or Sars-coronavirus-2 or SARS-like coronavirus* or coronavirus-19 or covid19 or covid-19 or covid 2019 or ((novel or new or nouveau) N2 (CoV or nCoV or covid or coronavirus* or corona virus or pandemi*)) or ((covid or covid19 or covid-19) and (outbreak or crisis or pandemic*)) or (coronavirus* and pneumonia))) OR AB (("2019-ncov" or ncov19 or ncov-19 or "2019-novel CoV" or sars-cov2 or sars-cov-2 or sarscov2 or sarscov-2 or Sars-coronavirus2 or Sars-coronavirus-2 or SARS-like coronavirus* or coronavirus-19 or covid19 or covid-19 or covid 2019 or ((novel or new or nouveau) N2 (CoV or nCoV or covid or coronavirus* or corona virus or pandemi*)) or ((covid or covid19 or covid-19) and (outbreak or crisis or pandemic*)) or (coronavirus* and pneumonia)))
S6 S4 OR S5
S7 S3 OR S6
S8 (MH "Scoping Review") OR (MH "Systematic Review")
S9 (MH "Meta Analysis") OR (MH "Meta Synthesis")
S10 TI ((systematic N3 (review* or overview*))) OR TI (meta analy* or metaanaly* or meta synthes*)
S11 S8 OR S9 OR S10
S12 S7 AND S11

APA PsycArticles Full Text (last searched 15 July 2021) n=109;
1. coronavirus/ or severe acute respiratory syndrome/
2. (coronavirus$ or corona virus$ or OC43 or NL63 or 229E or HKU1 or HCoV$ or ncov$ or covid$ or sars-cov$ or sarscov$ or Sars-coronavirus$ or Severe Acute Respiratory Syndrome Coronavirus$).mp.

3. limit 2 to yr="2019 -Current"
4. (2019-ncov or ncov19 or ncov-19 or 2019-novel CoV or sars-cov2 or sars-cov-2 or sarscov2 or sarscov-2 or Sars-coronavirus2 or Sars-coronavirus-2 or SARS-like coronavirus$ or coronavirus-19 or covid19 or covid-19 or covid 2019 or ((novel or new or nouveau) adj2 (CoV or nCoV or covid or coronavirus$ or corona virus or Pandemi$2)) or ((covid or covid19 or covid-19) and (outbreak or crisis or pandemic$2)) or (coronavirus$ and pneumonia)).mp.
5. 1 or 3 or 4
6. "systematic review"/ or "literature review"/ or meta analysis/
7. (meta analy$ or metaanaly$ or meta synthes$).ti.
8. (systematic adj3 (review$1 or overview$1)).ti.
9. 6 or 7 or 8
10. 5 and 9

Web of Science - Book Citation Index – Science (BKCI-S), Book Citation Index – Social Sciences & Humanities (BKCI-SSH), Conference Proceedings Citation Index – Science (CPCI-S), Emerging Sources Citation Index (ESCI), Science Citation Index Expanded (SCI-EXPANDED) (last searched 15 July 2021) n=2863;

#1 TS=(coronavirus* or corona virus* or OC43 or NL63 or 229E or HKU1 or HCoV* or ncov* or covid* or sars-cov* or sarscov* or Sars-coronavirus* or Severe Acute Respiratory Syndrome Coronavirus*) and 2019 or 2020 or 2021 (Publication Years)
#2 TS=("2019-ncov" or ncov19 or ncov-19 or "2019-novel CoV" or sars-cov2 or sars-cov-2 or sarscov2 or sarscov-2 or Sars-coronavirus2 or Sars-coronavirus-2 or SARS-like coronavirus* or coronavirus-19 or covid19 or covid-19 or "covid 2019" or ((novel or new or nouveau) NEAR/2 (CoV or nCoV or covid

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or coronavirus* or "corona virus" or pandemi*)) or ((covid or covid19 or "covid-19") and (outbreak or crisis or pandemic*)) or (coronavirus* and pneumonia))
#3 (#1) OR #2
#4 TI=((meta analy* or metaanaly* or meta synthes*))
#5 TI=((systematic near/3 (review* or overview*)))
#6 #4 OR #5

WHO Global Index Medicus (last searched 15 July 2021) n=119, n=400;

Updated 15 July 2021_PRECIOUS_final search Search strategy is pre-written by World Health Organisation Global Index Medicus

((("2019-2020" OR 2019 OR da:202*) ("New Coronavirus" OR "Novel Coronavirus" OR "Nuevo Coronavirus" OR "Novo Coronavirus" OR "Coronavirus disease" OR "Enfermedad por Coronavirus")) OR (2019-ncov OR covid19 OR covid-19 OR covid2019 OR covid-2019 OR "COVID 2019") OR ((srag-cov-2 OR sars2 OR sars-cov-2 OR coronavirus OR mh:betacoronavirus OR mh:"Coronavirus infections") AND (tw:2019 OR da:202*) AND NOT da:201*) OR ((srag-cov-2 OR sars2 OR sars-cov-2 OR coronavirus* OR mh:betacoronavirus OR mh:"Coronavirus infections") AND (tw:2019 OR da:202*) AND NOT da:201*) OR ("Coronavirus 2" da:202*) OR (wuhan market virus) OR (virus mercado wuhan) OR "Wuhan Coronavirus" OR "Coronavirus de Wuhan") AND NOT (ti:"Middle East respiratory syndrome" OR ti:mers-cov OR mh:"Middle East Respiratory Syndrome Coronavirus") AND (type_of_study:("systematic_reviews" OR "policy_brief" OR "overview"))

WHO COVID-19 Global literature on coronavirus disease
db:("COVIDWHO") AND type_of_study:("systematic_reviews" OR "overview")

LitCovid-19 (https://www.ncbi.nlm.nih.gov/research/coronavirus/; last searched 15 July 2021) n=4110;

LitCovid-19 (https://www.ncbi.nlm.nih.gov/research/coronavirus/)

Chen Q, Allot A, Lu Z. Keep up with the latest coronavirus research. Nature. 2020 Mar;579(7798):193. doi: 10.1038/d41586-020-00694-1. PMID: 32157233.

systematic review OR systematic overview OR meta-analysis OR meta-synthesis

Epistemonikos: Database of the best Evidence-Based Healthcare (https://www.epistemonikos.org/; last searched; 15 July 2021) n=4840;

(title:((title:((coronavirus* OR corona virus* OR HCoV* OR ncov* OR covid* OR sars-cov* OR sarscov* OR sars-coronavirus*)) OR abstract:((coronavirus* OR corona virus* OR HCoV* OR ncov* OR covid* OR sars-cov* OR sarscov* OR sars-coronavirus*)))) OR abstract:((title:((coronavirus* OR corona virus* OR HCoV* OR ncov* OR covid* OR sars-cov* OR sarscov* OR sars-coronavirus*)) OR abstract:((coronavirus* OR corona virus* OR HCoV* OR ncov* OR covid* OR sars-cov* OR sarscov* OR sars-coronavirus*)))))

Added to Database: From: 1-11-2019 to 15-7-2021 Publication Type: systematic Review

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Appendix 2: Collaborators' Information Sheet

XX Dear XX

PREdictors of COVID-19 OUtcomeS (PRECIOUS- National Institutes of Health Research Ref: 132895)

Our Project: We aim to use individual participant data (IPD) to examine the range of long-term outcomes after COVID-19. We are sourcing fully anonymised data from existing research studies. We are defining "long-term" as assessment ≥28 days of initial infection and includes outcomes across the International Classification of Functioning, Disability and Health (ICF), as well as death, complications or discharge to long-term care facilities.

Research Questions:

1. What are the long-term outcomes of people after COVID-19 in relation to each of the domains of the ICF and what is the trajectory of these outcomes over time?
2. What are the predictors of long-term COVID-19 outcomes across the ICF domains?
3. What are the financial costs associated with the long-term health outcomes of COVID-19 for individuals, health services and society?

Dataset Eligibility Criteria

Inclusion:

- Cohort studies, case-control studies, surveys with more than one time point for assessment and RCTs
- Any setting
- Minimum IPD of 10 people
- People with COVID-19 reflecting a range of severities, symptoms and durations
- Outcome assessed ≥ 28 days post-onset
- Outcomes including (but not limited to) presence of:
    - A formal tool capturing an ICF domain.
    - Reporting of presence of a post-COVID complication (e.g. fatigue) ≥28 days of initial symptom onset.
    - Morbidity or continued hospitalisation beyond 28 days of initial symptom presentation
    - Residence in, or discharge to a long-term care/ rehabilitation facility ≥28 days of initial symptom presentation, or discharge to another location.

Exclusion criteria:

- Studies with no available IPD
- Single case studies
- Studies of COVID-19 in children
- Studies focused on impact on caregivers
- Healthcare process evaluations
- Qualitative datasets

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How to participate/how to collaborate/how to get involved:

1. Please review the eligibility criteria. If your data are eligible for inclusion, please email PRECIOUS@gcu.ac.uk with your expression of interest.
2. We will then send you a Data Sharing Agreement and a link for a Data Contribution Form. Please sign the data sharing agreement and complete the contribution form and email these to precious@gcu.ac.uk.
3. **Contribute fully anonymised data** to us using secure File Transfer Protocols. Details can be found here https://transfer.gla.ac.uk/security.
4. If you are interested in collaborating, we invite expressions of interest by the 1st September 2021, as we require the contribution of physical datasets by the 15th December 2021.

What we can offer you:

1. A collaborating primary research team representative will have the opportunity to become a member of the PRECIOUS collaboration.
2. Representatives will review, comment and contribute to planned analyses.
3. Subject to meeting IJCME criteria, representatives will have the opportunity to become co-authors on outputs (for example manuscripts, reports, abstracts and posters) resulting from the analyses. The publication plan will be circulated with the Data Sharing Agreement.

Project duration: PRECIOUS commenced on the 1st July 2021. The project will end on the 30th June 2023.

After the Project ends: subject to individual dataset representatives' agreement, the pooled, fully anonymised dataset will be made available as a COVID resource to which other investigators can apply to carry out novel exploratory analyses. In this way, data will not be wasted and can continue to be used to answer questions beyond the aims of our current study. Contributing researchers will sit on a steering committee and can govern how their data are being used and contribute to future analyses.

Please email precious@gcu.ac.uk for further details.

Our Team:

Dr Myzoon Ali, Senior Research Fellow, NMAHP Research Unit, Glasgow Caledonian University, UK
Prof. Marian Brady, Professor of Rehabilitation, NMAHP Research Unit, Glasgow Caledonian University, UK
Dr Pauline Campbell, NMAHP Research Unit, Glasgow Caledonian University, UK
Dr Scott Rooney, School of Health and Life Sciences, Glasgow Caledonian University, UK
Prof. Lorna Paul, School of Health and Life Sciences, Glasgow Caledonian University, UK
Prof. Helen Mason, Professor of Health Economics, Deputy Director, Yunus Centre for Social Business and Health, Glasgow Caledonian University, UK
Dr Sarkis Manoukian, Research Fellow in Health Economics, Glasgow Caledonian University, UK
Dr Linda Williams, Senior Statistician, Usher Institute, University of Edinburgh, UK
Dr Mark Barber, Geriatrician and Stroke MCN Lead Clinician. Honorary Clinical Associate Professor, University of Glasgow.
Dr Claire McGoldrick, Consultant Physician in Infectious Diseases. Monklands District General Hospital, UK

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Dr Neil Basu, Clinical Senior Lecturer in Rheumatology/Honorary Consultant, University of Glasgow, UK
Dr Manish Patel, Consultant Physician, Respiratory Medicine, Wishaw Hospital, UK
Dr Andrew Smith, Consultant Physician in Respiratory Medicine at Wishaw Hospital, UK
PRECIOUS is led by Glasgow Caledonian University, Scotland.

Our Collaborators

For up-to-date information on our expanding collaborative group, please visit www.preciouscovidoutcomes.org.

Our Experience: Our team has extensive research and clinical experience in IPD meta-analysis. For example, we recently completed a UK-National Institutes of Health Research (NIHR) funded analysis of post-stroke impairment data based on 174 rehabilitation datasets from 28 countries which investigated recovery, predictors and therapy efficacy (see RELEASE Protocol: https://www.tandfonline.com/doi/full/10.1080/02687038.2019.1643003; IPD Meta-Analysis of Predictors: https://www.ahajournals.org/doi/10.1161/STROKEAHA.120.031162).

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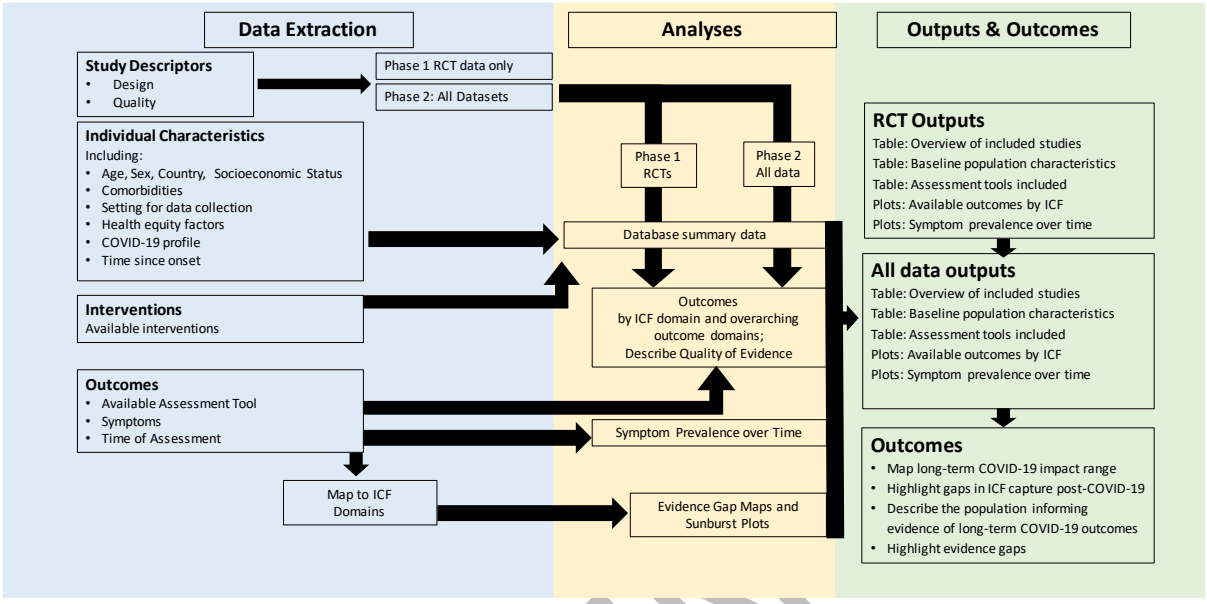
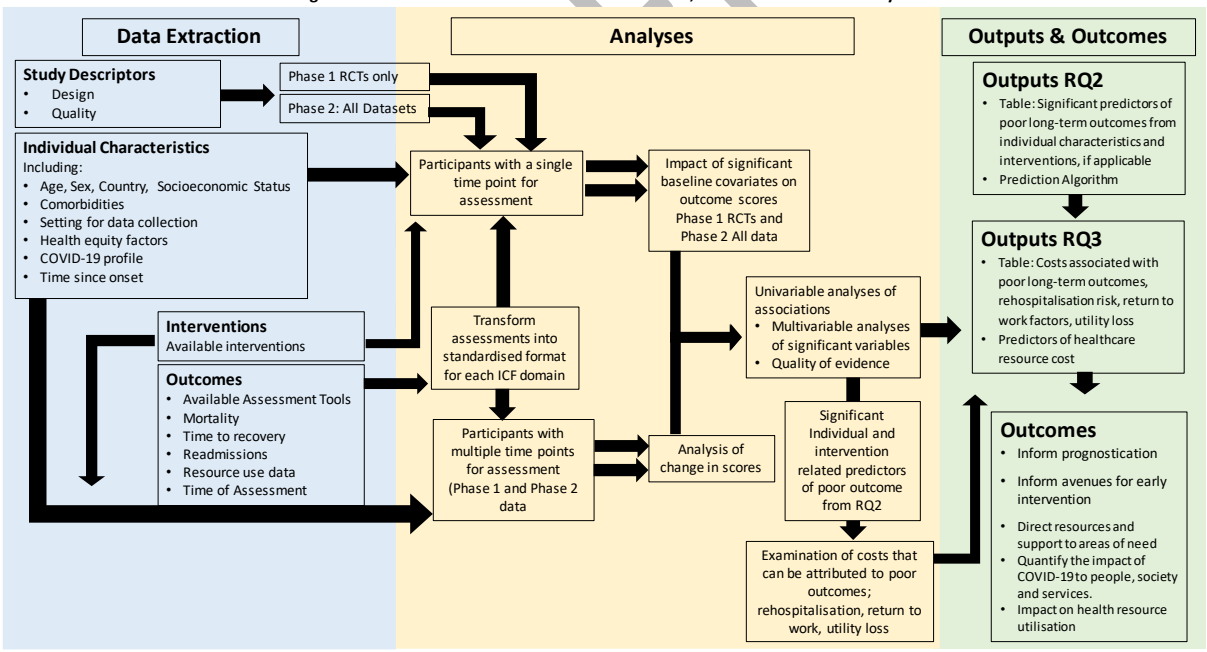
Appendix 3: Logic Models

RQ 1: Long-term outcomes of people after COVID-19 in relation to the ICF and over time



RQ 2: What are the predictors of long-term outcome across ICF domains and over time? RQ 3:What are the financial costs associated with the long-term health outcomes of COVID-19 for individuals, health services and society?



Appendix 4

Publication and Authorship Plan

Publication Plan

The following papers are planned in relation to PRECIOUS:

1. A protocol paper.
2. Description of participants, available outcomes and gaps in the capture of the International Classification of Functioning, Disability and Health (ICF) domains within the PRECIOUS dataset.
3. Predictors of long-term COVID-19 outcomes.
4. Costs of COVID-19 on individuals, health services and society.

These peer-reviewed publications have been specified in the original application to the NIHR and will be reported as a minimum. However, we anticipate that additional findings from PRECIOUS will warrant additional peer-reviewed publications. All PRECIOUS papers will adhere to the authorship plan detailed below.

Authorship plan

One person, (or where justified, a maximum of 2 named people) will represent each contributed dataset as a PRECIOUS collaborator. All PRECIOUS Collaborators will be offered co-authorship on all dissemination activities, provided that they meet the criteria outlined by the International Committee of Medical Journal Editors (ICMJE). Namely, those who:

- Substantially contribute to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
- Draft the work or revising it critically for important intellectual content; AND
- Grant final approval of the version to be published; AND
- Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

All those designated as authors should meet all four criteria for authorship, and all who meet the four criteria will be identified as authors. Those who do not meet all four criteria will be acknowledged.

Group authorship will be used (e.g. “on behalf of the PRECIOUS Collaborators”). An appendix will list the core writing group first, then each collaborating author/ data contributor alphabetically, and end with the Chief Investigator.

Collaborators/ data contributors can opt out of being listed in dissemination activities if they so choose, however the default position will be to include all collaborators/contributors in all activities. Should the collaborator wish to opt out of being included in the authorship list, they should notify precious@gcu.ac.uk at any time. They will still receive copies of all analysis drafts and dissemination materials for review and reference.

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