CVD-COVID-UK: Cardiovascular disease and COVID-19

UK-wide linked routine healthcare data to address the impact of cardiovascular diseases on COVID-19 and the impact of COVID-19 on cardiovascular diseases

Study Protocol
Version 1
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SUMMARY

The COVID-19 pandemic is a major global challenge, whose impacts on population health, healthcare services and the wider economy will be apparent for many years.

Patients with cardiovascular disease have an elevated risk of symptomatic infection and mortality. This could be due to cardiovascular conditions themselves (e.g., heart disease, stroke), their risk factors (e.g., age, raised blood pressure, obesity), medications, or combinations of these. Understanding which patients are affected and why will be a major step towards developing strategies to reduce this excess risk.

Just as important as the effects of pre-existing cardiovascular disease on COVID-19, are the impacts of COVID-19 on cardiovascular disease.

The *direct* impacts include immediate complications (e.g., acute cardiac injury, stroke) as well as the potential for increased risk of heart attack, stroke and other cardiovascular events in the longer term, through inflammation, blood clotting risk or other factors. However, the nature and extent of these direct effects is far from fully understood.

Crucially, the response by the government and health services to the COVID-19 pandemic has *indirect* impacts on the presentation, diagnosis, management and outcomes of cardiovascular diseases. There has been a dramatic decline in the numbers of people attending hospital with heart attack and stroke in recent weeks. Further, patients are more often arriving too late for beneficial acute treatments (e.g., clot busting drugs or mechanical clot removal) and after potentially preventable complications have developed. To inform government and NHS policy, we urgently need a deeper understanding of these unintended consequences, including the range of conditions affected, variation by age, sex, ethnicity, deprivation and geography, effects on different in- and out-patient services, and response to mitigating actions (e.g., regional and national government advice).

CVD-COVID-UK will address these issues through analyses of de-identified, linked, nationally collated, whole population, healthcare data across the four nations of the UK. Linked, de-identified data will be accessed and analysed by approved researchers within trusted research environments (TREs) provided by:

(1) SAIL Databank for Wales.

(2) The National Data Safe Haven in Scotland.

(3) NHS Digital for England.

(4) The Honest Broker Service in Northern Ireland.

OBJECTIVES

To interrogate nationally collated, population level, linked healthcare data across the UK population to address the following questions:

1) What are the effects of cardiovascular diseases, their risk factors and medications on susceptibility to and outcomes from COVID-19 disease?
2) What is the direct impact of SARS-CoV-2 infection on acute cardiovascular complications as well as on medium and longer term cardiovascular risk?
3) What is the indirect impact of the COVID-19 pandemic and the government and NHS response to it on the presentation, diagnosis, management and outcomes of cardiovascular diseases?

BACKGROUND

The COVID-19 pandemic is a major global challenge, whose impacts on the population's health, healthcare systems and services and the wider economy will be apparent for many years.

Patients with pre-existing cardiovascular disease have a disproportionately elevated risk of symptomatic infection and mortality. The reasons are not fully understood but could be due to cardiovascular conditions per se (angina, myocardial infarction, heart failure, stroke, peripheral arterial disease etc.); their risk factors (e.g., age, hypertension, obesity, raised cholesterol, diet and lifestyle) or medications (e.g. ACE inhibitors, angiotensin receptor blockers); or combinations of these. Understanding the drivers of this excess risk (i.e., which patients are affected and why) will be a major step towards developing strategies to reduce it.

Just as important as the effects of cardiovascular disease, and its risk factors and medications, on COVID-19 disease, are the direct and indirect impacts of COVID-19 on cardiovascular disease.

The *direct* impacts include acute cardiovascular complications of SARS-CoV-2 infection, such as acute cardiac injury, stroke and venous thrombo-embolism. In addition, the inflammatory, pro-coagulant and other effects of COVID-19 may, like influenza and other respiratory virus infections, be associated with increased risk of MI, stroke and other cardiovascular events in the short, medium and long term. However, the nature and extent of these direct effects is far from fully understood.

Crucially, there are also *indirect* impacts on the presentation, diagnosis, management and prognosis of cardiovascular diseases resulting from the response by governments and health services to the COVID-19 pandemic. For example, in the UK and elsewhere, the numbers of people attending hospital with acute myocardial infarction and stroke have declined dramatically in recent weeks, while patients who do present to hospital are frequently arriving too late to receive acute treatments proven to improve outcomes (e.g., primary angioplasty, thrombolysis or mechanical thrombectomy) or after potentially preventable complications have developed. Anecdotal reports from clinicians suggest that referrals to specialist outpatient services of patients with milder symptoms (e.g., transient ischaemic attacks, angina), who would benefit from cardiovascular preventive medication and advice, have also plummeted. A deeper understanding of the nature and extent of these unintended consequences, including the range of conditions affected, variation by patient characteristics (such as age, sex, ethnicity, and deprivation) and geography (both within and between countries), effects on different in- and out-patient services and interventions (e.g. primary angioplasty for acute myocardial infarction, thrombolysis/thrombectomy for acute ischaemic stroke), including delays in diagnosis caused by cancelled diagnostic tests, and changes over time in response to mitigating actions (e.g. regional and national government advice), is urgently needed to inform government and NHS policy.

We propose to address these questions by performing analyses of linked, nationally collated healthcare data across the four nations of the UK.

PROJECT PLAN

The project is currently set to run for three years from 1st June 2020 to 1st June 2023. There are four work packages (WPs) as outlined below:

WP 1: Coordination, Approvals and Data Access

This work package will be led by the BHF Data Science Centre. It involves:

- the identification of relevant nationally collated data across the UK.
- the coordination of applications for ethics approval.
- the coordination of applications for access to linked data within national trusted research environments.
- the coordination of rapid development of a cardiovascular TRE in partnership with NHS Digital to support the CVD COVID UK project, ensuring future proofing of this development so that it can in due course enable work beyond COVID-19 and beyond cardiovascular-related research.
- the coordination of specialist inputs from data custodians, data scientists with methodological and analytical expertise (statisticians, epidemiologists, health informaticians, bioinformaticians, computer scientists and others) and clinicians (including cardiologists, stroke physicians, vascular surgeons and others).
- administrative support for and coordination across all work packages.
- the coordination of reporting to the UK Government's Scientific Advisory Group for Emergencies (SAGE) and equivalent bodies in the devolved nations via established HDR UK processes.

Table 1 shows the relevant generic and disease-specific data being assembled for access, linkage and analysis in each of the four nations, and their priority rating with respect to the range of clinical and public health relevant research questions they can support. Regular updates (weekly to monthly, depending on what is possible for each data source) of the data will be obtained. All data will be accessed by named, approved researchers (certified to have successfully completed safe researcher training, e.g., https://saildatabank.com/application-process/following-approval/#safe-researcher-training) in the national TREs provided by:

- the SAIL Databank for Wales (population around 3 million).
- the National Data Safe Haven in Scotland (population around 5.4 million).
- NHS Digital (who are rapidly developing a TRE specifically for this project) for England (population around 56 million).
- the Honest Broker Service in Northern Ireland (population around 1.6 million).

Figure 1 shows the flows of data into the Cardiovascular TRE being developed within NHS Digital for this project. Similar data flows are in place for the TREs in the devolved nations (although Northern Ireland lags behind the other UK nations).

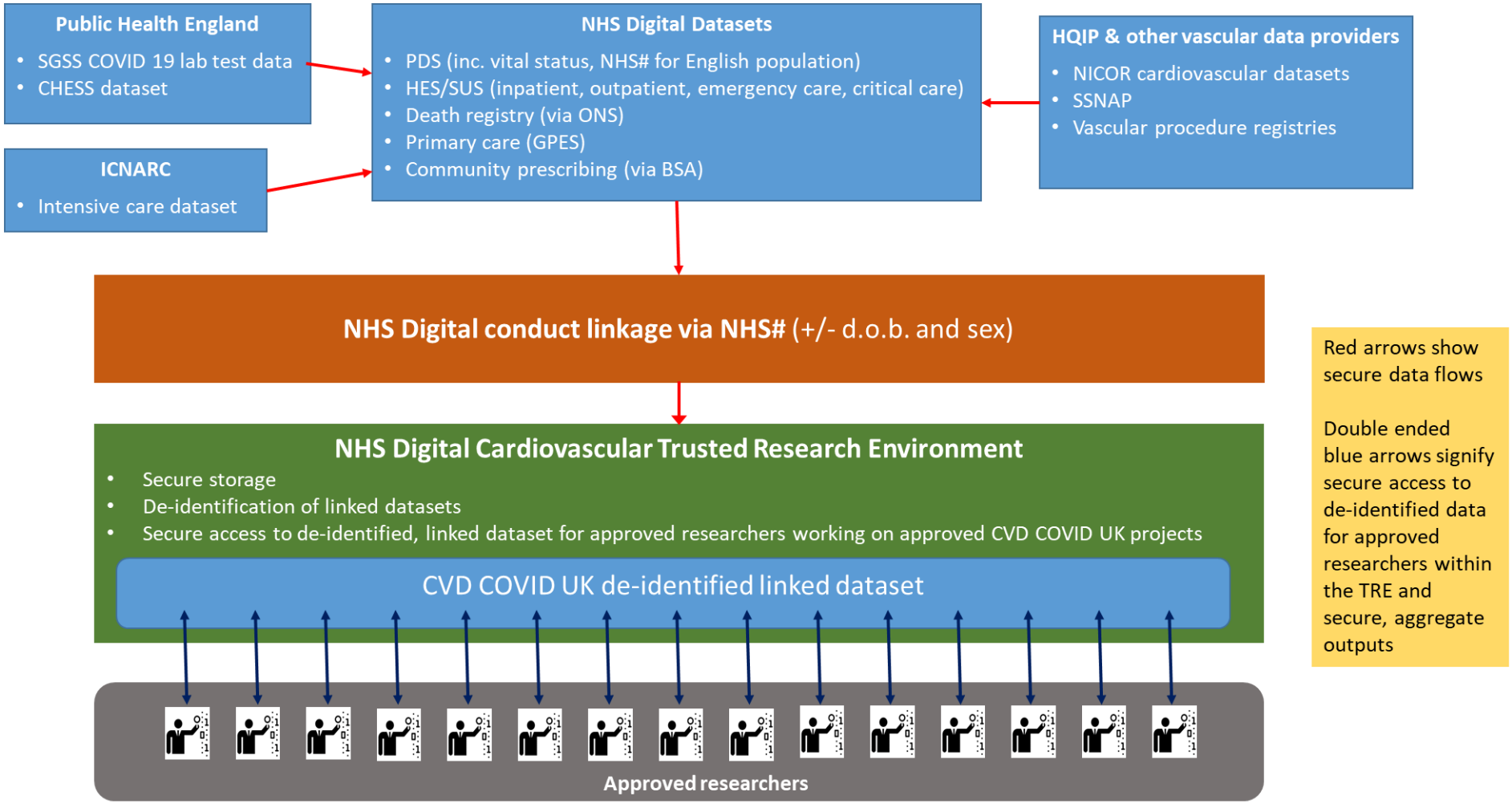
The data accessed for research analyses will be record level data but it will be de-identified and pseudonymised. The organisations providing the TREs will strip direct identifiers from each record, apply a pseudo-ID to each record and link the data. No direct identifiers will be accessed by any researcher working in the CVD-COVID-UK consortium. Following similar principles to those already used by the SAIL Databank for Wales (https://saildatabank.com/saildata/data-privacy-security/#secure-access) and the Scottish National Data Safe Haven (https://www.isdscotland.org/Products-and-Services/EDRIS/Use-of-the-National-Safe-Haven/), only summary, aggregate results data will be extracted from the TREs by approved researchers, subject to the approval of the organisations providing the TREs through respective disclosure control processes and rules. The objective of this will be to ensure that no output contains information which could be used either on its own or in conjunction with other data to breach an individual's privacy.

Table 1. Data sources for CVD COVID UK

Data type	Priority level	Country			
		England (NHS Digital cardiovascular TRE)	**Scotland (National Data Safe Haven)**	**Wales (SAIL)**	**Northern Ireland (Honest Broker Service)**
Hospital	1	Hospital episode statistics* (HES and SUS+)	Hospital data* (SMR and RAPID)	Hospital data* (PEDW, OPDW, EDDS, CCDS)	?
COVID labs	1	COVID-19 lab testing data (SGSS and data from non-NHS sources)	COVID-19 lab testing data (ECOSS and data from non-NHS sources)	COVID-19 lab testing data (including data from non-NHS sources - LIMS)	?
Primary care	1	Primary care data (GPES data for pandemic planning and research)	Primary care data (via Albasoft)	Primary care data (WLGP)	?
Death	1	Mortality/death registry data (via ONS)	Mortality / death registry data (via NRS)	Mortality / death registry data (via ONS (Office of National Statistics) - ADDE)	Mortality/death registry data (via NRIS)
ITU	2	ICNARC (ITU data)	SICSAG (ITU data)	ICNARC (ITU data)?	ICNARC (ITU data)?
ITU/HDU admissions	2	CHESS	No direct equivalent	No direct equivalent?	No direct equivalent?
Prescribing	2	Community prescribing / dispensing data (from BSA)	Community prescribing / dispensing data (PIS)	-	?
CV specialist	3	NICOR HQIP commissioned cardiovascular audit data	? some include Scotland	NICOR HQIP commissioned cardiovascular audit data?	NICOR HQIP commissioned cardiovascular audit data?
CV specialist	3	NICOR TAVI data	? covers Scotland	NICOR TAVI data?	NICOR TAVI data?
CV specialist	3	SSNAP (English and Welsh stroke audit) data	Scottish Stroke Care Audit	SSNAP (English and Welsh stroke audit) data	SSNAP (English and Welsh stroke audit) data
CV specialist	3	National Vascular Registries	National Vascular Registries?	National Vascular Registries?	National Vascular Registries?

* including, where available, inpatient, outpatient, ED/A&E and critical care data

Figure 1. Data flows for Trusted Research Environment for CVD COVID UK in England



WP2: Data analyses to address key research questions:

This work package will refine the research questions to be addressed, incorporating appropriate clinical specialist input, to draw up analysis plans for the different data sources (individually and linked), to assess data completeness and quality, conduct analyses, interpret results, report results and, where necessary, refine and extend analyses to incorporate new or updated data.

The analysis work is sub-divided into five sub-work packages, each with a separate lead from within the consortium membership:

- WP 2.1 (interim lead Prof Cathie Sudlow, BHF Data Science Centre) will assess the indirect impacts of COVID-19 on cardiovascular diseases.
- WP 2.2 (lead Assoc Prof Ami Banerjee, UCL & HDR UK London) will assess the influence/associations of cardiovascular conditions on COVID-19 outcomes.
- WP 2.3 (lead Prof Ronan Lyons, University of Swansea & HDR UK Wales/N Ireland) will assess the influence/associations of cardiovascular risk factors on COVID-19 outcomes.
- WP 2.4 (lead Prof Jonathan Sterne, University of Bristol & HDR UK South West) will assess the influence/associations of cardiovascular medications on COVID-19 outcomes.
- WP 2.5 (lead Dr Will Whiteley, University of Edinburgh & HDR UK Scotland) will assess the direct impact of COVID-19 disease on cardiovascular disease occurrence, re-occurrence and outcomes in short, medium and long term.

Given that data custodians in each of the four UK nations will bring together and make available their nationally collated data within separate TREs, and given the differences between countries in the data sources available, our general approach for each analytic work package is to develop a master protocol from which nation-specific protocols will be developed, aiming for maximum consistency but allowing for nation-specific differences in data. Where appropriate, results of nation-specific analyses will be combined in meta-analyses.

Analyses based on routinely collected, national healthcare data have the advantages of large scale and comprehensive coverage, maximising statistical power as well as inclusiveness and representativeness (e.g. across all age groups, ethnicities, geographies and socioeconomic settings).

More detailed analysis plans for each analysis sub-work package are outlined below:

- WP 2.1: An immediate priority for informing government policy across the UK is to assess the indirect impact of COVID-19 on cardiovascular diseases. This will be done via analyses of time trends in hospital activity (admissions by diagnosis, treatments, procedures) using hospital and disease audit data, registered deaths by cause and primary care activity before, during and after the COVID-19 pandemic. Analyses of trends will build on initial work commenced in partnership with NHS Digital by a small subset of consortium members, and will be made available in rapidly produced reports for government advisory groups across the UK as soon as they start to become available (aiming to commence in June) with regular updates provided as the coverage of conditions and geographies expands.

- WP 2.2: The influence/associations of pre-existing cardiovascular diseases (ischaemic heart disease, stroke etc) on COVID-19 incidence and outcomes will be studied through multivariable regression analyses of linked population wide data that contain information on previous medical history with COVID-19 test results, hospitalisation, critical care and mortality data, with adjustment for multiple confounders (including risk factors and co-morbidities).

- WP 2.3: The influence/associations of cardiovascular risk factors on COVID-19 incidence and outcomes will be studied through multivariable regression analyses of linked population wide data sources that contain information on cardiovascular risk factors such as blood pressure, body mass index and smoking status with COVID-19 tests, hospitalisation, critical care and mortality data,

with adjustment for multiple co-morbidities. Preliminary work has started in Wales and will be developed and extended across the four nations.

- WP 2.4: An immediate priority is to provide information to enable government agencies (e.g., MHRA and NICE) to give evidence-based advice to healthcare professionals and patients on drug regimens and risk of COVID. We will study the effects of ACE inhibitors, angiotensin receptor blockers and other cardiovascular medications on COVID-19 outcomes (hospitalisation, admission to ICU, mechanical ventilation and mortality) by using primary care physicians' preferred antihypertensive drug class as an instrumental variable (IV). This approach will enable us to deal with the potential for confounding by measured and unmeasured factors, including the indication for which these drugs are prescribed, health-promoting behaviours associated with receipt of one of these medications, and the effects of drugs such as statins and anticoagulants which are often used in combination. We will compare the results of IV analyses with multivariable logistic regression analyses, controlling for measured confounding variables.
- WP 2.5: Linkage of population routine data sources (demography including mortality, primary care, hospital) and audit data will enable comprehensive assessment of the impact of COVID-19 disease on cardiovascular disease occurrence, reoccurrence and outcomes in short, medium and long term. With SARS-CoV2 potentially circulating for at least several years in the population, it will be important to estimate the short-, medium- and long-term effects of infection on incidence of stroke, myocardial infarction, venous thromboembolic disease and other cardiovascular diseases. There are several potential mechanisms of increased long-term risk, including longer-term pro-coagulant and inflammatory effects as well as the recognised increased risk of many chronic health conditions among survivors of intensive care. We will estimate the risk of MI, stroke, heart failure and other cardiovascular conditions associated with COVID-19, using a self-controlled case-series design with shorter and longer periods of risk, along with other epidemiological analysis approaches.

WP3: Patient and public involvement and engagement and communications:

This work package is led by Sinduja Manohar and Fran Lord in the HDR UK public engagement and communications team. They will work with existing HDR UK and BHF public, patient and professional panels and the leads and members of each of the analysis sub-work packages to provide input into refining and prioritising the research questions in each sub-work packages, assessing the impact of the results and preparing reports for lay audiences. This work package will also coordinate communications of the consortium's activity and emerging results through websites, social media and other outlets, and will lead on interactions with the press and other media.

WP 4: Analysis methods:

This work package is led by Dr Angela Wood (University of Cambridge) and Dr Benjamin Bray (IQVIA and Kings College London). It will coordinate discussions amongst the epidemiological, statistical, informatics and computer science members of the CVD-COVID-UK consortium to address methodological challenges arising during the development and implementation of analysis plans. As part of CVD-COVID-UK's partnership with NHS Digital, members of the group will provide user input into the development of the researcher environment for the newly established cardiovascular TRE for England. They will also provide input and advice on the newly acquired NHS Digital GP Extraction Service Primary Care data for Pandemic Planning and Research, in particular as regards data quality, coverage and missingness.

RESEARCH OUTPUTS

Through addressing questions about the impacts of cardiovascular disease on COVID-19 and the impacts (both direct and indirect) of COVID-19 on cardiovascular diseases, we expect the outputs of this work to inform public health policy and clinical care, benefiting:

- patients with a history of cardiovascular disease (stroke, heart attack, peripheral arterial disease etc.) who are at increased risk of poor outcomes with COVID-19 as a result of their cardiovascular condition, cardiovascular risk factors or cardiovascular medications;
- patients now and in the future who become unwell with COVID-19 and are at risk of short, medium and long term cardiovascular complications;
- the population as a whole whose cardiovascular health services are being affected by the government and health service response to the COVID-19 epidemic.

Outputs providing these benefits are expected to start to emerge within weeks of data becoming available for analyses by the research consortium. Outputs will continue to be produced and to provide benefits as outlined throughout the three year period of the project through to June 2023. By their nature, those outputs providing information on the longer-term impacts and implications of these for clinical care and public health policy will take at least several months to start emerging.

Emerging insights will be reported to SAGE and equivalent bodies in the devolved nations as well as (especially in WP 2.4) to the National Institute of Health and Care Excellence (NICE), Medicines and Healthcare Products Regulatory Agency (MHRA) and Scottish Medicine Consortium, so helping to drive evidence-based policy decisions for health service providers and clinical professional groups. Outputs will also form the basis of manuscripts for publication in peer-reviewed scientific and medical journals, presentations at national and international scientific and medical professional conferences, and reports aimed at lay audiences, available through websites, in particular those of Health Data Research UK and the British Heart Foundation.

WIDER BENEFITS

Whilst being developed with the initial intent of supporting the CVD-COVID-UK consortium research programme, the cardiovascular TRE for England established in partnership with NHS Digital is being designed to enable its extension to support cardiovascular research more broadly beyond COVID-19 and research beyond the cardiovascular domain.

The coordination work for WP1 will provide knowledge about linked health care data and routes to their access and so will benefit other UK-wide initiatives that require linkage to routinely collected healthcare data. These include: the ISARIC-CCP (UK-wide study of the clinical characteristics of patients hospitalised with COVID-19) and its CAPACITY-COVID extension; collaborative efforts to address the determinants of COVID-19 susceptibility, severity and outcome through analyses of population-based cohorts with bio-samples linked to routinely collected healthcare data; the RECOVERY trial; and COG-UK.

In addition, the consortium is aware of initiatives in a wide range of other countries, including Italy, Sweden and Korea, that are starting to derive policy-relevant insights from analyses of routine linked data, especially on the indirect impacts of COVID-19 on cardiovascular diseases. Through the consortium's connections with international consortia and organisations, including the European Society of Cardiology, European Stroke Organisation and others, the research group will engage in the bilateral sharing of emerging results, to learn from others as well as to maximise the international reach and relevance of findings.

CONSORTIUM PRINCIPLES

CVD-COVID-UK commits to the 'Five Safes' (http://www.fivesafes.org/) and to a transparent and inclusive approach, enabling additional researchers and research groups to join the consortium as the work progresses and evolves.

All analysis plans, protocols and reports arising from this consortium's work will be made publicly available via the HDR UK website (linking to additional institutional documentation if appropriate), HDRUK github repository and open access publications.

All reports for government advisory groups and policy makers, the lay public and academic publications will be written in the name of the collaborative group (CVD-COVID-UK) with all relevant individual contributions (coordination, writing, analysis, interpretation etc.) listed.