COG-UK HOCI

COG-UK Project Hospital-Onset COVID-19 Infections Study

A phase III prospective, interventional, cohort, superiority study to evaluate the benefit of rapid COVID-19 genomic sequencing (the COVID-19 GENOMICS UK project) on infection control in preventing the spread of the virus in United Kingdom NHS hospitals.

Version	V2.0
Date	19-May-2020
Sponsor	University College London (UCL)
Comprehensive Clinical Trials Unit Trial Adoption Group #	CTU/ 2020/353
Trial registration	ISRCTN50212645
IRAS	283014
REC #	20/EE/0118

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Table of Contents

1 Administrative information 6
1.1 Sponsor 6
1.2 Structured study summary 6
1.3 Roles and responsibilities 9
1.3.1 Protocol contributors 9
1.3.2 Role of study sponsor and funders 9
1.3.3 Trial Team 9
1.3.4 Trial Management Group 9
1.3.5 Sequence Reporting Development Group 10
1.3.6 Sequence Reporting Users Implementation Group 10
1.3.7 Combined Trial Steering / Data Monitoring Committee 11
2 Study Diagram 12
3 Abbreviations 13
4 Glossary 14
5 Introduction 15
5.1 Background and Rationale 15
5.2 Objectives 16
5.3 Study Design 18
5.3.1 Study timeline 18
6 Methods 18
6.1 Site Selection 18
6.1.1 Study Setting 19
6.1.2 Site/Investigator Eligibility Criteria 19
6.2 Site approval and activation 20
6.3 Participants 20
6.3.1 Eligibility Criteria 20
6.3.2 Hospital Onset COVID-19 Infection (HOCI): Patient Diagnosis Pathway 22
6.3.3 Hospital Onset COVID-19 Infection (HOCI): Healthcare Worker Diagnosis Pathway 23
6.4 Intervention 24
6.4.1 Genomic sequencing report 24
6.4.2 Compliance and Adherence 25
6.5 Outcomes 26
6.5.1 Primary Outcomes 26

6.5.2 Secondary Outcomes 26
6.5.3 Exploratory Outcomes 26
6.5.4 Data collection flowchart 27
6.6 Study Timeline 28
6.6.1 Early Stopping of Follow-up 29
6.6.2 Loss to Follow-up 29
6.6.3 Study Closure 29
6.7 Sample Size 29
6.8 Recruitment and Retention 30
6.8.1 Recruitment 30
6.9 Assignment of Intervention 30
6.9.1 Allocation 30
6.10 Data Collection, Management and Analysis 30
6.10.1 Data Collection Methods 30
6.10.2 Data Management 31
6.10.3 Statistical Methods 32
6.10.4 Health Economics 33
6.11 Data Monitoring 33
6.11.1 Data Monitoring Committee 33
6.11.2 Interim Analyses 33
6.11.3 Data Monitoring for Harm 34
6.11.4 Quality Assurance and Control 38
7 Ethics and Dissemination 39
7.1 Ethics Committee (EC) Approval 39
7.2 Competent Authority (CA) Approvals 40
7.3 Other Approvals 40
7.4 Protocol Amendments 40
7.5 Consent or Assent 40
7.6 Confidentiality 40
7.7 Declaration of Interests 41
7.8 Indemnity 41
7.9 Finance 41
7.10 Archiving 41
7.11 Access to Data 41

7.12 Ancillary and Post-trial Care 41
7.13 Publication Policy 41
7.13.1 Study Results 41
7.13.2 Authorship 42
7.13.3 Reproducible Research 42
8 Ancillary Studies 42
8.1 Sub-study 1: Process Evaluation 42
9 Protocol Amendments 43
10 References 44
11 Appendices 45
11.1 Compliance 45
11.2 Protocol template and development 45

1 Administrative information

1.1 Sponsor

UCL is the study sponsor and has delegated responsibility for the overall management of the COG-UK HOCI study to CCTU. Queries relating to UCL sponsorship of this study should be addressed to the CCTU Director or via the Trial Team.

1.2 Structured study summary

Primary Registry and Trial Identifying Number	ClinicalTrials.gov: TBC
Date of Registration in Primary Registry	TBC
Secondary Identifying Numbers	ISRCTN: ISRCTN50212645 REC #: 20/EE/0118 UCL R & D ID # (Sponsor): 132181 CTU Trial Adoption Group #: CTU/2020/353 IRAS #: 283014
Source of Monetary or Material Support	UKRI
Sponsor	University College London with sponsor responsibilities delegated to CCTU.
Contact for Public Queries	ctu.enquiries@ucl.ac.uk
Contact for Scientific Queries	Prof Judith Breuer Division of Infection and Immunity, UCL. j.breuer@ucl.ac.uk
Public Title	COG-UK HOCI
Scientific Title	A phase III prospective, interventional, cohort, superiority study to evaluate the benefit of rapid COVID-19 genomic sequencing (the COVID-19 GENOMICS UK project) on infection control in preventing the spread of the virus in United Kingdom NHS settings.
Countries of Recruitment	United Kingdom (England and Scotland)
Health Condition(s) or Problem(s) Studied	COVID-19 viruses from infected patients and healthcare workers.

Intervention(s)	The study intervention is delivery of a COVID-19 genomic sequencing data report either: - within 48 hours from local sequencing hub to the NHS site's virology lab for dissemination to Infection Prevention and Control (IPC) teams; - or the same delivered within 5-10 days from centralised sequencing facility
Key Inclusion and Exclusion Criteria	**Inclusion criteria** - Participants must have confirmed COVID-19 infection and either: a) be a potential hospital-onset COVID-19 infection (HOCI); or b) potential workplace infection from COV-SARS-2 for site-based healthcare workers. - Participants must have provided nasal swab/pharyngeal swab / combined nasal and pharyngeal swab / nasopharyngeal aspirate or broncho alveolar lavage sample for evaluation in the COG-UK project. - Participants may be of any age to be included in study *For clarity, in the above criterion a potential HOCI is an admitted patient at site with first confirmed test for COVID-19 >48 hours after admission, where they were not suspected to have COVID-19 at time of admission.* **Exclusion Criteria** *- (There are no exclusion criteria for COG-UK HOCI)*
Study Type	COG-UK HOCI is a phase III prospective, interventional, cohort, superiority study.
Date of First Sampling	W/c 04-May-2020
Target Sample Size	2 sites initially to pilot, Maximum of 4 sites, and a total of 2,000 patients with potential hospital-onset COVID-19 infection (HOCIs)
Primary Outcome(s)	1. The contribution of viral sequencing to defining the occurrence and transmission location of HOCI 2. Does the real-time (<48 hours) availability of COVID-19 sequence data reduce the incidence rate of IPC-defined HOCIs compared with delayed (>4 days) and no sequence data.

	3. Does the real time (<48 hours) availability of COVID-19 sequence data identify previously undetected nosocomial transmission in potential HOCIs compared with delayed (>4 days) and no sequence data.
Key Secondary Outcomes	1. Does the real-time (<48 hours) availability of COVID-19 sequence data reduce the incidence rate of IPC-defined hospital outbreaks compared with delayed (>4 days) and no sequence data. 2. Does the real time (<48 hours) availability of COVID-19 sequence data identify previously undetected hospital outbreaks compared with delayed (>4 days) and no sequence data 3. Impact of the real time availability of COVID-19 sequence data on IPC actions 4. Impact of real time availability of COVID-19 sequence data on IPC workload 5. Health economic benefit of both standard and rapid sequencing reports to IPC against baseline 6. Impact of both standard and rapid sequencing reports on number of HCW days off work.
Key exploratory Outcomes	1. Rates following the intervention compared to baseline for each of the interpretative sequence categories (1-4): • 1, No evidence of COVID-19 nosocomial transmission • 2, Potential evidence of COVID-19 nosocomial transmission • 3, Sequence not informative • 4, Sequence identifies unexpected potential nosocomial transmission 2. Descriptive analysis of IPC actions before and after delivery of a sequencing report 3. Descriptive analysis of IPC workload before/after delivery of a sequencing report 4. The influence of turnaround times (TATs), if any, on exploratory outcomes 1, 2 and 3.

1.3 Roles and responsibilities

These membership lists are correct at the time of writing; please see terms of reference documentation in the TMF for current lists.

1.3.1 Protocol contributors

Name	Affiliation	Role
Prof Judith Breuer	Immunity, UCL	Chief Investigator
Dr James Price	Imperial	Expertise in Infection control and genomics
Prof Alison Holmes	Imperial	Expertise in healthcare associated infections
Mr James Blackstone	CCTU, UCL	Protocol development
Prof Nick Freemantle	CCTU, UCL	Clinical trial design and statistical analysis
Ms Gemma Jones	CCTU, UCL	Clinical trial design and operations
Dr Andrew Copas	MRC CTU, UCL	Clinical trial design and statistics
Dr Laura Shallcross	IHI, UCL	Clinical trial design, health care associated infection and electronic patient record linkage
Dr Oliver Stirrup	IGH, UCL	Statistical analysis

1.3.2 Role of study sponsor and funders

Name	Role
University College London	Sponsor
UKRI	Funder

1.3.3 Trial Team

Name	Affiliation	Role and responsibilities
Prof Judith Breuer	Immunity, UCL	Chief Investigator
Dr Andrew Copas	MRC CTU, UCL	Senior Statistician
Mr James Blackstone	CCTU, UCL	Clinical Project Manager
Dr Oliver Stirrup	IGH, UCL	Statistician
Dr Leanne Hockey	CCTU, UCL	Trial Manager
Ms Georgia Marley	CCTU, UCL	Data Manager
Mr Garrie Powers	CCTU, UCL	Programmer
Ms Monica Panca	CCTU, UCL	Health Economist
Dr Fiona Mapp	IGH, UCL	Qualitative researcher

1.3.4 Trial Management Group

Name	Affiliation	Role
Prof Judith Breuer	Immunity, UCL	Chief Investigator
Professor Nick Freemantle	CCTU, UCL	Director of CCTU
Dr Andrew Copas	MRC CTU, UCL	Senior Statistician
Ms Gemma Jones	CCTU, UCL	Head of Clinical Trial Operations
Professor Alison Holmes	Imperial College	Professor of Infectious Diseases
Prof Sharon Peacock	Public Health England	Director of COG-UK
Mr James Blackstone	CCTU, UCL	Clinical Project Manager

Dr Leanne Hockey	CCTU, UCL	Clinical Trial Manager
Dr Laura Shallcross	IHI, UCL	Consultant in Public Health Medicine
Dr James Price	Imperial College	Consultant in Infectious Disease
Dr Thushan de Silva	Univ. of Sheffield	Senior Clinical Lecturer/Consultant in Infectious Disease
Dr David Partridge	Sheffield NHS Trust	Consultant in Microbiology and Infection Control
Prof Emma Thomson	QEUH, Glasgow	Professor in Infectious Diseases
Dr Christina Price	QEUH, Glasgow	Consultant in Infection Prevention and Control
Dr Jonathan Edgeworth	Guys and St Thomas Hospital	Consultant Microbiologist
Dr Gaia Nebbia	Guys and St Thomas Hospital	Consultant in Infection prevention and control
Ms Monica Panca	CCTU, UCL	Health Economist
Dr Fiona Mapp	IGH, UCL	Qualitative Research Associate
Prof Paul Flowers	Strathclyde Univ.	Senior Qualitative Researcher

1.3.5 Sequence Reporting Development Group

Name	Affiliation	Responsibilities
Prof Judith Breuer	UCL	Development of sequencing reporting tool
Dr James Price	Imperial College	Development of sequencing reporting tool
Prof Alison Holmes	Imperial College	Development of sequencing reporting tool
Prof Emma Thomson	QEUH, Glasgow	Development of sequencing reporting tool
Prof Andrew Rambaut	Edinburgh	Development of sequencing reporting tool
Prof David Aanensen	Oxford	Development of sequencing reporting tool
Dr Pantelis Giorgiou	Imperial college	Development of sequencing reporting tool
Dr Laura Shallcross	UCL	Development of sequencing reporting tool
Dr Sunando Roy	UCL	Development of sequencing reporting tool and local implementation
Dr Josh Singer	Glasgow	Development of sequencing reporting tool and local implementation
Dr Matt Parker	Sheffield	Development of sequencing reporting tool and local implementation
Dr Ali Anwer	GSTT	Development of sequencing reporting tool and local implementation
Dr Oliver Stirrup	IGH, UCL	Probabilities expertise for sequence reporting

1.3.6 Sequence Reporting Users Implementation Group

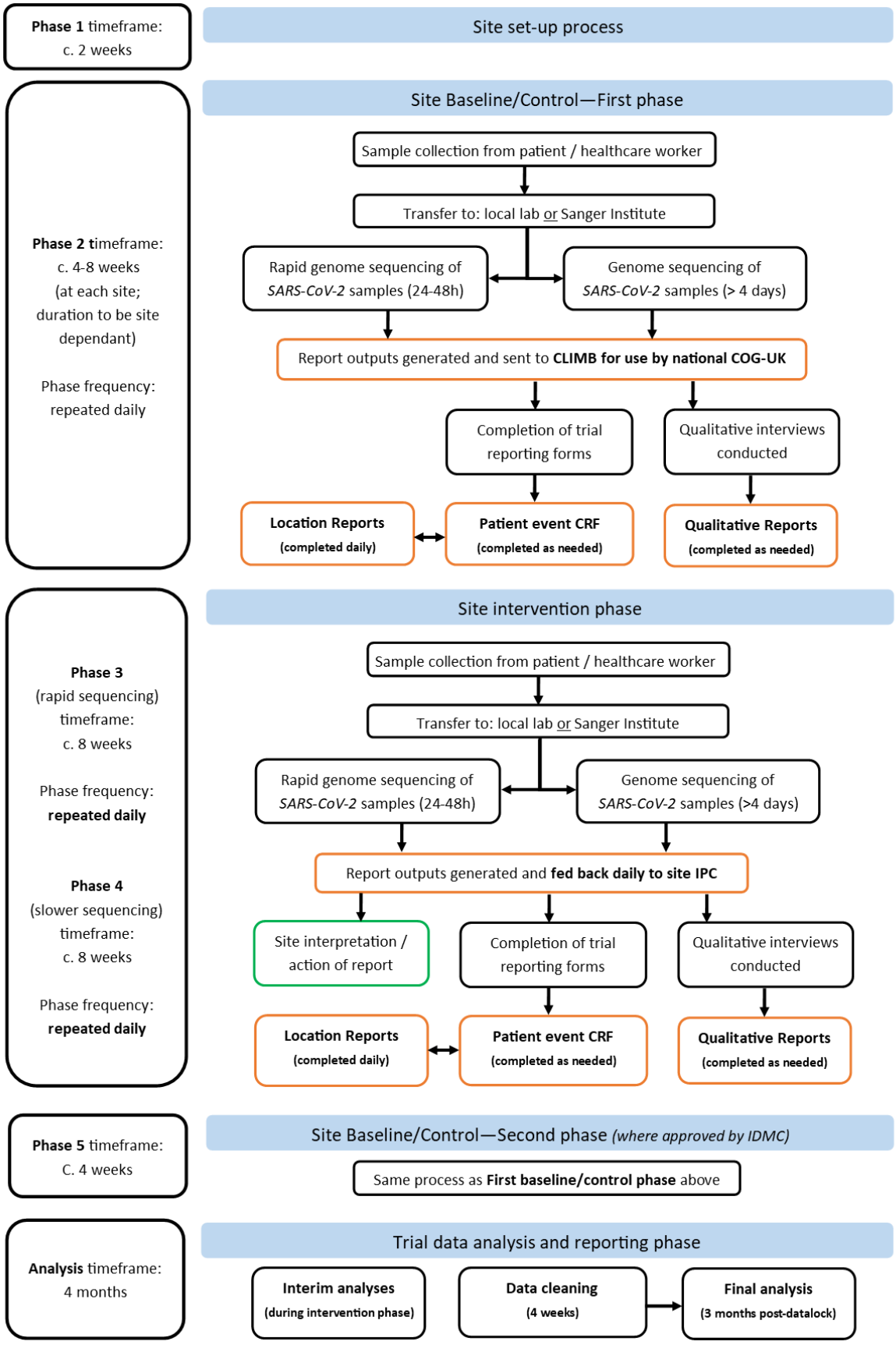
Name	Affiliation	Role
Prof Judith Breuer	UCL	Advising on application of sequencing reporting tool
Dr James Price	Imperial College	Advising on application of sequencing reporting tool
Prof Alison Holmes	Imperial College	Advising on application of sequencing reporting tool
Prof Emma Thomson	QEUH, Glasgow	Advising on application of sequencing reporting tool
Dr Alistair Leonard	QEUH, Glasgow	Advising on application of sequencing reporting tool
Dr Thushan de Silva	Sheffield	Advising on application of sequencing reporting tool
Dr Dave Partridge	Sheffield	Advising on application of sequencing reporting tool
Prof Jonathan Edgeworth	Guys and St Thomas. Trust	Advising on application of sequencing reporting tool

Dr William Newsholme	Guys and St Thomas. Trust	Advising on application of sequencing reporting tool
Dr Luke Snell	Guys and St Thomas. Trust	Advising on application of sequencing reporting tool
Mr James Blackstone	CCTU, UCL	Study reporting / data collection
Dr Leanne Hockey	CCTU, UCL	Study reporting / data collection
Dr Oliver Stirrup	IGH, UCL	Statistical aspects arising from reporting tool

1.3.7 Combined Trial Steering / Data Monitoring Committee

Name	Affiliation	Role and responsibilities
Prof Marion Koopmans	Erasmus MC	Independent Chair (Clinical)
Prof Walter Zingg	Uni. Geneva	Independent member (Clinical)
Professor Colm Bergin	TCD	Independent member (Clinical)
Prof Karla Hemming	Birmingham	Independent member (Statistician)
Prof Katherine Fielding	LSHTM	Independent member (Statistician)

2 Study Diagram



3 Abbreviations

AE	Adverse Event
ANTT	Aseptic Non Touch Technique
AR	Adverse Reaction
BMS	Biomedical scientist
CA	Competent Authority
CCTU	Comprehensive Clinical Trials Unit
CI	Chief Investigator
CLIMB	Medical Research Council CLIMB data server holds key datasets for the substantive COG-UK project
COG-UK	COVID-19 Genomics UK Consortium
CRF	Case Report Form
DHSC	UK Department of Health and Social Care
DIPC	Director of Infection Prevention and Control
EC	Ethics Committee
EHR	Electronic Health Record
EPR	Electronic Patient Record
EU	European Union
GCP	Good Clinical Practice
HAI	Hospital-acquired infection
HCAI	Health care-associated infection
HO	Hospital Outbreak
HOCI	Hospital onset COVID-19 infection
HCW	Health care worker
ICC	Infection Control Committee
ICD	Infection Control Doctor
ICN	Infection Control Nurse
ICH	International Conference on Harmonisation
ICT	Infection Control Team
IPC	Infection Prevention and Control
ISF	Investigator Site File
ITT	Intention to Treat
MHRA	Medicines and Healthcare products Regulatory Agency
PI	Principal Investigator
PIS	Participant Information Sheet
PPE	Personal Protective Equipment
PROM	Patient-reported Outcome Measure
QA	Quality Assurance
QC	Quality Control
QMG	CCTU Quality Management Group
QMMP	Quality Management and Monitoring Plan
R&D	Research and Development
RCA	Root Cause Analysis
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SSA	Site Specific Approval
SUSAR	Suspected Unexpected Serious Adverse Reaction
TAT	Turn around time
TMF	Trial Master File
TMG	Trial Management Group
TMT	Trial Management Team
ToR	Terms of Reference
TSC	Trial Steering Committee
UICP	Universal Infection Control Precautions
UCL	University College London

4 Glossary

- **Aerosol risk procedure –** any medical and patient care procedure that results in the production of airborne particles (aerosols).
- **Antimicrobial stewardship –** the optimal selection, dosage, and duration of antimicrobial treatment that results in the best clinical outcome for the treatment or prevention of infection, with minimal toxicity to the patient and minimal impact on subsequent resistance.
- **Case Report Form** a paper or electronic document designed to record all events within the study protocol required on each study subject.
- **CA-COVID-19 (community acquired COVID-19) -** patient who is positive on admission or ≤48 hours after admission
- **COVID-19 Sequence** the complete list of the nucleotides that make up the single-stranded RNA of the SARS-CoV-2 virus.
- **Doffing and donning of PPE** – the putting on and removal of personal protective equipment in line with Public Health England instructions for aerosol generating procedures.
- **Hand hygiene** – the application of good handwashing technique is applied based on trust policy for HCWs. Specifically, a hygienic handwash refers to the cleaning of hands with antimicrobial or medicated soap and water.
- **HCW (health care worker)** a clinical or non-clinical patient-facing NHS employee**.**
- **Hospital Outbreak** Linkage of two or more confirmed cases of COVID-19 within the hospital with assumed nosocomial transmission to one or more person. This may be defined by conventional IPC investigations (**IPC-defined Hospital Outbreak**), or IPC investigation following evaluation of the viral sequencing report (**IPC+sequencing-defined Hospital Outbreak**).
- **Potential HOCI** a confirmed COVID-19 infection where the onset of symptoms was determined to be within a hospital setting (i.e. standard definition of >48h post admission) or where a healthcare HCW has been diagnosed.
    - A potential HOCI may be considered to be a likely case of hospital-based transmission at evaluation by the IPC team (**IPC-defined HOCI**). The IPC team may reclassify a HOCI as a community-acquired COVID-19 patient instead (CA-COVID-19)
    - Likewise, any staff member with COVID-19 work contacts within the previous 5-14 days may be considered to be a likely case of hospital-based transmission by the IPC team (**IPC-defined HOCI**)
    - Following IPC investigation it may be that a HOCI is considered to be linked to one or more other specific COVID-19 patients (constituting an **IPC-defined Hospital Outbreak** event)
    - Following further investigation due to genomic sequence data when available, the IPC may reclassify a potential HOCI as a community-acquired COVID-19 (**CA-COVID-19**) or conclude that there was nosocomial infection (**IPC+sequencing-defined HOCI**) after re-evaluation of linkage to other cases.
- **TAT (turnaround time)** – the time taken between sampling the participant and the sequence report arriving back to the site IPC team.

5 Introduction

5.1 Background and Rationale

Hospitals are recognised to be a major risk for the spread of infections despite the availability of protective measures. Under normal circumstances, staff may acquire and transmit infections, but the health impact of nosocomial infection is greatest in vulnerable patients. For COVID-19, like SARS-CoV, MERS-CoV and Ebola virus, the risk of nosocomial spread of infection presents an additional and significant health risk to healthcare workers (HCW). During epidemics, normal infection prevention and control (IPC) practice is further complicated by the difficulties of distinguishing community- and hospital-acquired infections. This can lead to erroneous identification of nosocomial transmission, involving unnecessary IPC efforts, while true nosocomial transmissions are missed thereby putting patients and HCW at increased risk.

There is now good evidence that genome sequencing of epidemic viruses, together with standard IPC, better excludes nosocomial transmissions and, depending on the virus, better identifies routes of transmission, than IPC alone[1-3]. To date, all studies have been retrospective. However, the development of rapid nanopore sequencing methods enables identification of potentially linked or unlinked viruses within 24-48 hours: this timescale is short enough to inform clinical IPC decisions in near-real-time. Although COVID-19 has a low mutation rate estimated at around 2.5 changes per genome per month, it is generally agreed that sufficient viral diversity now exists to identify where patient and staff infections that are apparently clustered in time and space, are in fact due to different COVID-19 genotypes[4]. Such information would rapidly exclude nosocomial transmission as the cause of the cluster, reduce the need for IPC intervention and provide reassurance to healthcare workers that IPC measures including personal protective equipment (PPE), had not been breached. However, confirmation of COVID-19 transmission to patients and healthcare workers may be more difficult with a single observed mutation between two genomes feasibly representing anything between one and ten transmissions. Identical genomes will not necessarily provide evidence of a link between two cases. Nonetheless by placing genotypes detected within the framework of all the genotypes detected within the hospital setting, the surrounding community and COG-UK as a whole, it may be possible to postulate nosocomial transmission where comparatively uncommon genotypes are apparently linked or cluster in time and space.

The COG-UK initiative, which aims to sequence as many COVID-19 viruses as possible across the UK thus provides an **important and unique opportunity** to test whether viral sequence data produced in near-real-time, in addition to providing valuable information for public health planning, could also reduce uncertainties around nosocomial transmission events, better target IPC effort, improve hospital functioning and reduce the role of hospitals as a source of infection to the community.

To address this, we propose an adjunctive study, COG-UK HOCI. COG-UK HOCI will take advantage of the COG–UK design, with its mixed model of smaller sequencing hubs located close to hospitals and a large centralised hub sequencing most viruses, to identify not only whether rapid viral sequencing is useful for patient management but how time-critical this might be; turnaround times for sequence data from the central hub are likely to be longer (5-10 days) than those from local sequencing hubs (<48 hours).

COG-UK HOCI, by defining and reporting COVID-19 genotype frequencies within its participating hospitals, as compared to those in the wider community, will also have the potential to overcome some of the inherent barriers to identifying the likely sources of HOCI. The data generated will provide as accurate as possible a picture, given the constraints of viral genetic diversity, of numbers of COVID-19 infections being acquired by nosocomial transmission and where these transmissions are occurring. While COG-UK will provide data on the utility of viral genomics for national public health planning, COG-UK HOCI will quantify the utility of the same data for local management of nosocomial infection, whether observed benefits are time dependent and deliver the best estimates of how viral sequence data can be used to quantify HOCI.

The outputs from COG-UK HOCI will further inform decisions about the likely future use of viral genome sequencing for the management of epidemics and pandemics and how it might best be organised, centralised or diversified, to deliver maximal impact.

5.2 Objectives

The overarching aim of this study is to determine the utility of whole-genome sequencing to provide additional insight into hospital-onset COVID-19 infections (HOCI) which, in turn, can optimise IPC measures. In addition, the project aims to provide early data to help quantify HOCI events and where these are occurring. These will contribute to local trust level planning and to understanding of the role of HOCIs in contributing to COVID-19 outcomes and spread.

Specifically, the study will determine the role of real-time availability of COVID-19 sequence data:

- In conjunction with routine IPC data, to identify and characterise HOCI
- To identify and characterise HOCI not previously identified by routine IPC data
- To generate estimated numbers of HOCI and where these are occurring
- To identify linked HOCI and hospital outbreaks
- To identify ways to reduce the incidence of HOCI
- In optimising IPC actions, e.g. by reducing the need for extra cleaning, ward closures etc where a hospital outbreaks are excluded
- In changing workload, e.g. by reducing the need for extra cleaning, ward closures etc where a hospital outbreaks are excluded

Augmenting these approaches, we will measure whether the above are influenced by the time to sequence data result.

5.3 Study Design

COG-UK HOCI is a phase III prospective, interventional, cohort, superiority study.

Allocation to either rapid local sequencing (c.24-48h) or lack of rapid local sequencing (i.e. via Wellcome Sanger Institute at 5-10 days) will be dependent on the time of the study (see timelines).

Proposed study duration: 12 months; comprising 8 months of set-up, baseline data collection, interventional data collection) and up to 4 months of data cleaning, data analysis and reporting.

5.3.1 Study timeline

Phase 1 (2 weeks)	Site set-up and training
Phase 2 (4-8 weeks)	Baseline (control) data collection i.e. in the absence of COVID-19 sequence data availability to IPC team
Phase 3 (8 weeks)	Intervention (receipt of rapid (<48 hours) COVID-19 sequence data on hospital cases) and data collection
Phase 4 (8 weeks)	Intervention (receipt of delayed >4 days) COVID-19 sequence data on hospital cases) and data collection **INDEPENDENT DATA MONITORING COMMITTEE: Review data to see whether intervention should continue, or stop to allow data gathering within a second control period without intervention**
Phase 5 (4 weeks)	Control period data gathering i.e. in the absence of COVID-19 sequence data availability to IPC team (if approved by TSC-DMC).

It is confirmed that **Imperial College, London with Imperial College Healthcare NHS Trust** (St Mary's, Charing Cross and Hammersmith) will participate in the pilot stage, Thereafter **Sheffield** (Sheffield Teaching Hospitals NHS Foundation Trust) and **Glasgow** (Queen Elizabeth University Hospital) and **Guy's and St Thomas' NHS Trust** (St Thomas' Hospital) will participate.

6 Methods

6.1 Site Selection

The study sponsor has overall responsibility for site and investigator selection and has delegated this role to CCTU.

6.1.1 Study Setting

This study will take place in United Kingdom NHS hospital centres only.

Centres eligible to participate (see Section 6.1.2) will be those already participating in the COG-UK project.

COG-UK (the COVID-19 Genomics UK Consortium) intends to deliver a large scale and rapid SARS-CoV-2 sequencing capacity to local NHS centres and the UK government at pace. This Consortium intend to generate actionable data which when combined with epidemiological and clinical information has the potential to inform interventions and policy decisions during the UK COVID-19 epidemic. This sequencing capacity will enable real time evaluation of novel treatments and non-pharmacological interventions on SARS-CoV-2 populations and spread, and provide information on introductions versus community transmission and outbreaks. It will also evaluate signals of changing transmissibility and virulence. In the longer term, the full integration of UK population level SARS-CoV-2 genomics data, with matching NHS electronic health records, patient outcomes, human genomics and metagenomics data has the potential to generate insights into susceptibility to COVID-19 disease. Finally, the substantial new nationwide capacity in sequencing infrastructure, informatics and personnel that will be built by COG-UK will remain at the end of the COVID-19 pandemic as significant asset for the NHS, UKRI and UK Government.

6.1.2 Site/Investigator Eligibility Criteria

Once a site has been assessed as being suitable to participate in the study, the study team will provide them with a copy of this protocol.

To participate in the COG-UK HOCI study, investigators and study sites must fulfil a set of criteria that have been agreed by the COG-UK HOCI Sponsor and Trial Management Group (TMG) and that are defined below.

Site eligibility criteria:

- A named clinician is willing and appropriate to take Principal Investigator responsibility
- The Site is participating in the COG-UK project,
- The Site is able to deliver sequencing of all hospital samples with rapid sequencing turnaround (c24-48h)
- Suitably trained staff are available to collect study data (funding will be available via the study)

6.1.2.1 Principal Investigator's (PI) Qualifications and Agreements

The investigator(s) must be willing to sign an Investigator Agreement to comply with the study protocol (confirming their specific roles and responsibilities relating to the study, and that their site is willing and able to comply with the requirements of the study). This includes confirmation of appropriate qualifications, by provision of a CV, expertise in the appropriate use of any investigational datasets or reports, agreement to comply with the principles of GCP, to permit monitoring and audit as necessary at the site, and to maintain documented evidence of all staff at the site who have been delegated significant study related duties.

6.1.2.2 Resourcing at site

The investigator(s) should be able to demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period (i.e. the investigator(s) regularly treat(s) the target population).

Funding for several key site staff will be provided, though it is anticipated these roles will already exist at sites and staff be reassigned (where resource permits). Staff are anticipated to be: a research nurse, a data manager, a project manager, support from a bioinformatician and potentially additional BMS support to enable comprehensive sequencing.

Sites will be expected to complete a delegation of responsibilities log and provide staff contact details.

6.2 Site approval and activation

On receipt of the signed Clinical Trial Site Agreement or Investigator Agreement, approved delegation of responsibilities log and staff contact details, written confirmation will be sent to the site PI. The trial manager or delegate will notify the PI in writing of the plans for site activation. Study-specific activities are not be permitted to commence until a letter of activation has been issued. The Trial Manager or delegate will be responsible for issuing this after a green light to recruit process has been completed.

The site must conduct the study in compliance with the protocol as agreed by the Sponsor, and which was given favourable opinion by the Ethics Committee (EC). The PI or delegate must document and explain any deviation from the approved protocol, and communicate this to the trial team at CCTU.

A list of activated sites may be obtained from the Trial Manager.

6.3 Participants

6.3.1 Eligibility Criteria

The COG-UK HOCI study will evaluate sample data for those patients who have had a sample taken for genome sequencing analysis as part of the COG-UK project.

6.3.1.1 Participant selection

There will be **NO EXCEPTIONS** (waivers) to eligibility requirements.

The eligibility criteria for this study have been carefully considered and are the standards used to ensure that only medically appropriate participants are entered. Participants not meeting the criteria should not be entered into the study for their safety and to ensure that the study results can be appropriately used to make future treatment decisions for other people with similar diseases or conditions. It is therefore vital that exceptions are not made to these eligibility criteria.

Participants will be considered eligible for enrolment in this study if they fulfil all the inclusion criteria and none of the exclusion criteria as defined below.

6.3.1.2 Participant Inclusion Criteria

The following criteria define index patients for the purpose of data collection, reporting and statistical analysis for the COG-UK HOCI study:

- Participants must have confirmed COVID-19 infection and either:
    a) be a potential hospital-onset COVID-19 infection (HOCI); or
    b) potential workplace infection from SARS-COV-2 for site-based healthcare workers.
- Participants must have provided a nasal swab/pharyngeal swab/combined nasal and pharyngeal swab/nasopharyngeal aspirate or Broncho alveolar lavage sample for evaluation in the COG-UK project.
- Participants may be of any age to be included in the study.

For clarity, in the above criterion a potential HOCI is an admitted patient at site with first confirmed test for COVID-19 >48 hours after admission, where they were not suspected to have COVID-19 at time of admission.

The COG-UK HOCI study will also make use of the full set of available hospital- and community-obtained SARS-CoV-2 viral sequences, with associated meta-data, in generating the sequence report for the index patients in the intervention periods.

6.3.1.3 Participant Exclusion Criteria

- *(There are no exclusion criteria for COG-UK HOCI)*

6.3.1.4 Eligibility Criteria for Individuals Performing the Interventions

Guidance provided by the COG-UK Consortium covers those individuals that will perform the viral sampling and genome sequencing.

Study-specific staff at site should be adequately trained and qualified for their respective roles. Confirmation of site-held evidence of a curriculum vitae and Good Clinical Practice (GCP) training or GCP equivalent training appropriate to the staff's role to the Sponsor team will be required prior to confirmation of these staff as appropriate for addition to the local site study delegation log.

6.3.1.5 Co-enrolment Guidance

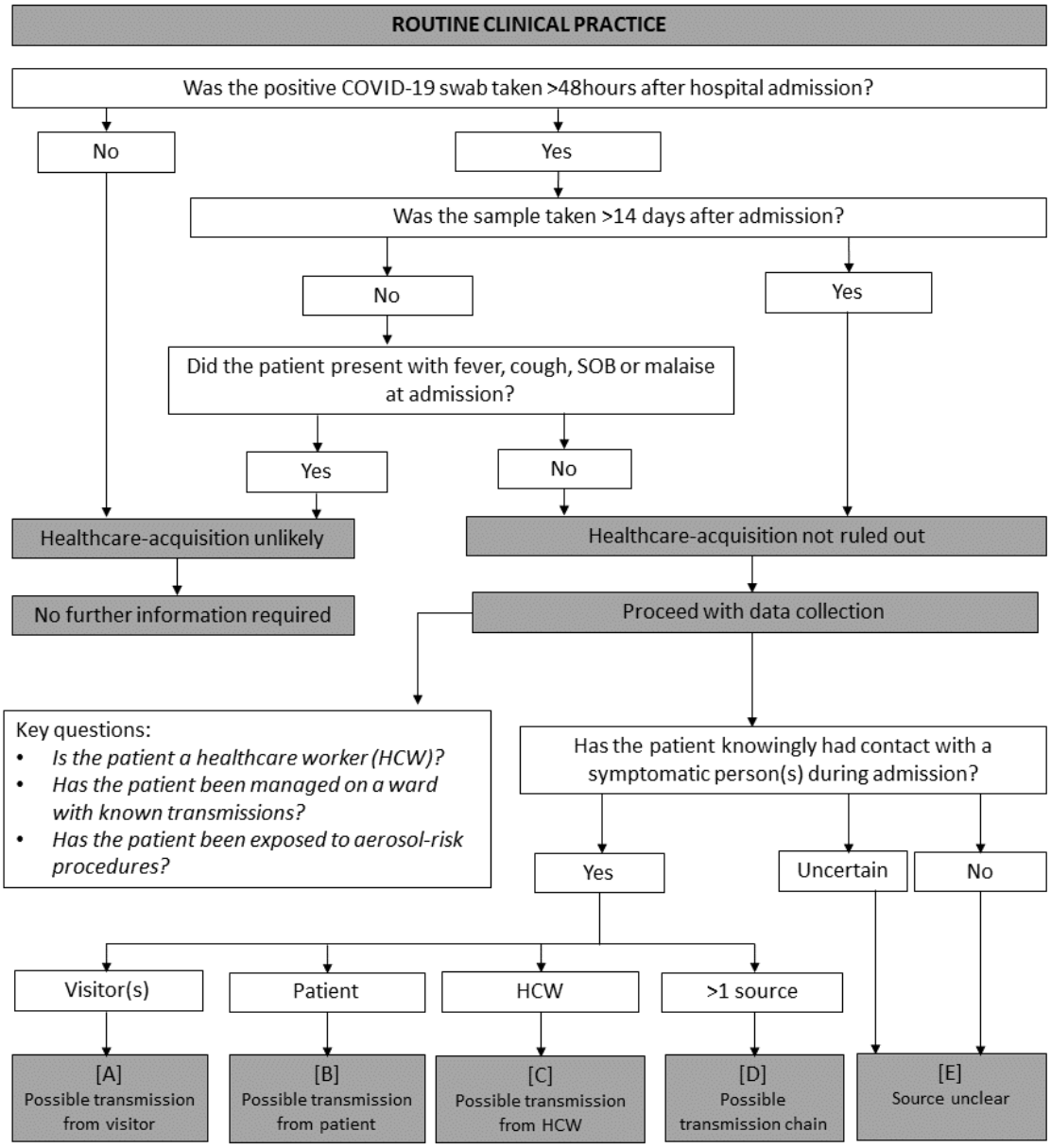
There are no restrictions on co-enrolment in other clinical trials.

6.3.1.6 Screening Procedures and Pre-randomisation Investigations

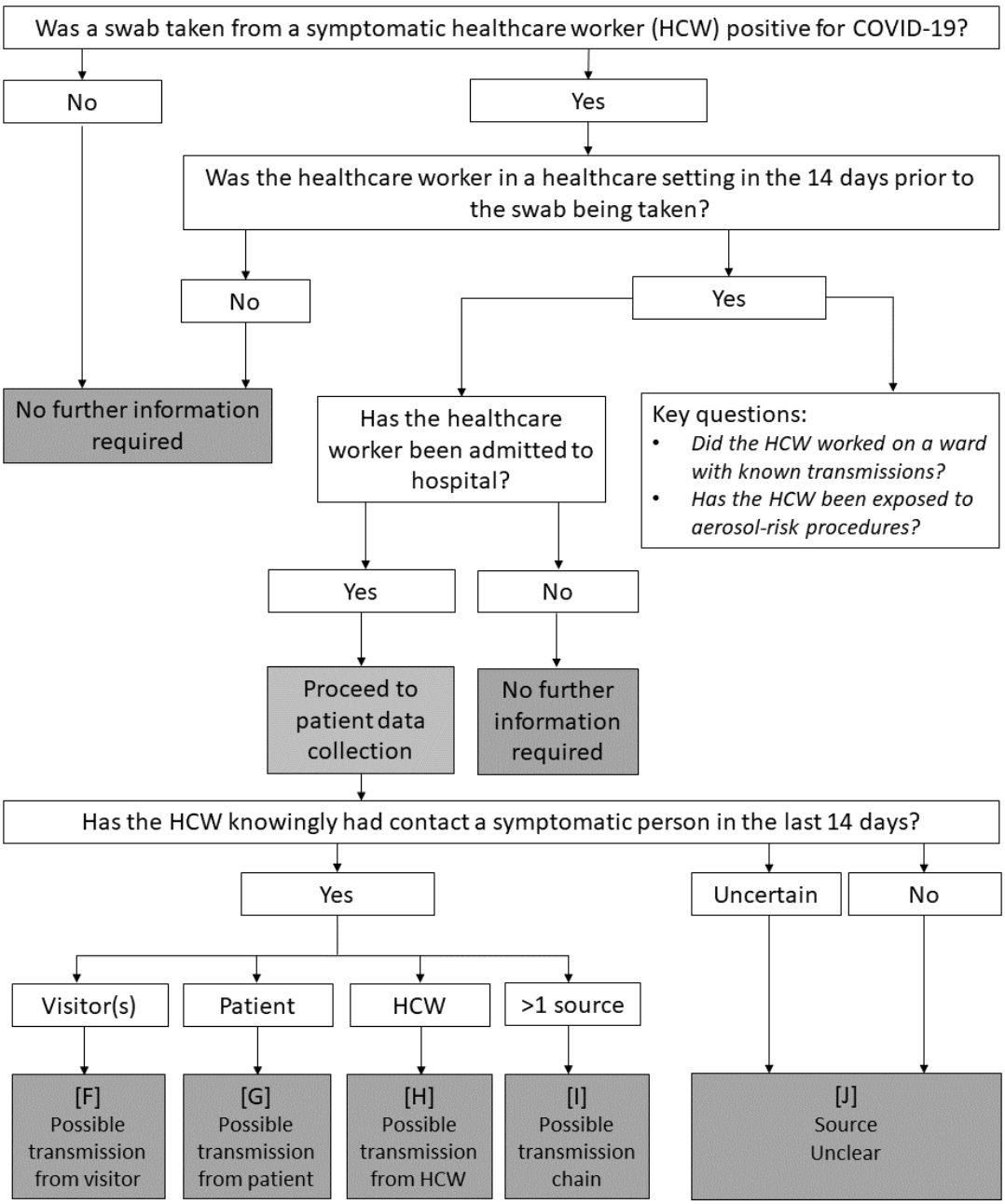
Only those patients who have received a COVID-19 positive diagnostic test will have their viral genome sequenced under the COG-UK project.

Consent will not be taken for participating in this research, except in cases where permission is requested from HCWs providing their sample outside of the Trust (e.g. at a COVID-19 community testing centre) for it to be linked back to their Trust's electronic healthcare records (see protocol Section 7.5).

6.3.2 Hospital Onset COVID-19 Infection (HOCI): Patient Diagnosis Pathway



6.3.3 Hospital Onset COVID-19 Infection (HOCI): Healthcare Worker Diagnosis Pathway



6.4 Intervention

The study intervention is a COVID-19 genomic sequencing data report delivered to the NHS site's virology lab for dissemination to Infection Prevention and Control (IPC) teams, either within 24-48 hours of sampling (rapid genomic sequencing locally) or within 5-10 days (via the Wellcome Sanger Institute).

Microbiology and IPC teams will be trained to interpret the results. An expert sequence interpretation team (a sub-set of the Trial Team) will be available 7 days a week by phone and online to discuss results where required with IPC teams, and to provide guidance on best practice.

This will be a sequential study, with each trust acting as its own control.

It is possible that some trusts will only complete the intervention aspect of the study; these data will still be valuable for the study's qualitative research into the benefit of the sequencing reports to IPC.

6.4.1 Genomic sequencing report

6.4.1.1. Report Details

The report for each sequence will comprise:

1. A frequency plot of the reported genotypes (defined a sequence sharing 1 or more mutation that are phylogenetically linked) and other genotypes sequenced from the hospital /community/country
2. A map of the hospital showing the location of other identical variants and the date on which they were sampled
3. One of the two following statements:
   - **This virus is genetically different from all other viruses sequenced from your hospital trust.** This suggests that the likelihood of this representing a short term in-hospital transmission is low**.**

   OR

   - **This virus is identical to other viruses so far sequenced from your hospital trust and occurs at a frequency *of x.* The location and time of sampling for other identical viruses is shown (hospital map and dated samples)**

     A phylogenetic tree with the strain identified related to other strains in hospital will be provided.

6.4.1.2. Report Interpretation

Interpretation

- **No evidence of nosocomial transmission** :Sequence refutes IPC HOCI or IPC-defined HO (sequences different from others defined by IPC as potentially part of a hospital outbreak)

    - Action : Stand down IPC intervention associated with this patient and associated hospital outbreak.
- **Potential evidence of hospital outbreak**: sequence potentially supports HOCI linkage to another COVID-19 patient. Identical variants are RARE in the rest of the hospital and IPC establishes individuals are NOT connected by other factors e.g. shared post code
    - Action: reinforce implementation of IPC intervention
- **Sequence not informative** (e.g. cluster of identical variants which are common in hospital/ community).
    - Action: No further use of sequence. Proceed with IPC as previously decided
- **Sequence identifies unexpected result** e.g. linked rare variants not on same ward and not connected by other factors e.g. postcode.
    - Action: Consider gathering further IPC data e.g. time spent in common areas, physician in common, staff living together, staff sharing tea room etc

6.4.2 Compliance and Adherence

The intervention reports generated will be periodically reviewed by the Sequence Reporting Users Implementation Group against the underlying data for fidelity. A selection of reports from each of the above categories will be discussed at a fortnightly Sequence Reporting Users Implementation Group meeting.

Quantitative and qualitative research will also be conducted throughout the study to evaluate the adherence of IPC teams implementation of intervention reports recommendations. This will be covered by the Processes Evaluation project (see Sub-study 1).

6.5 Outcomes

6.5.1 Primary Outcomes

1. The contribution of viral sequencing to defining the occurrence and transmission location of HOCI
2. Does the real-time (<48 hours) availability of COVID-19 sequence data reduce the incidence rate of IPC-defined HOCIs compared with delayed (>4 days) and no sequence data.
3. Does the real time (<48 hours) availability of COVID-19 sequence data identify previously undetected nosocomial transmission in potential HOCIs compared with delayed (>4 days) and no sequence data.

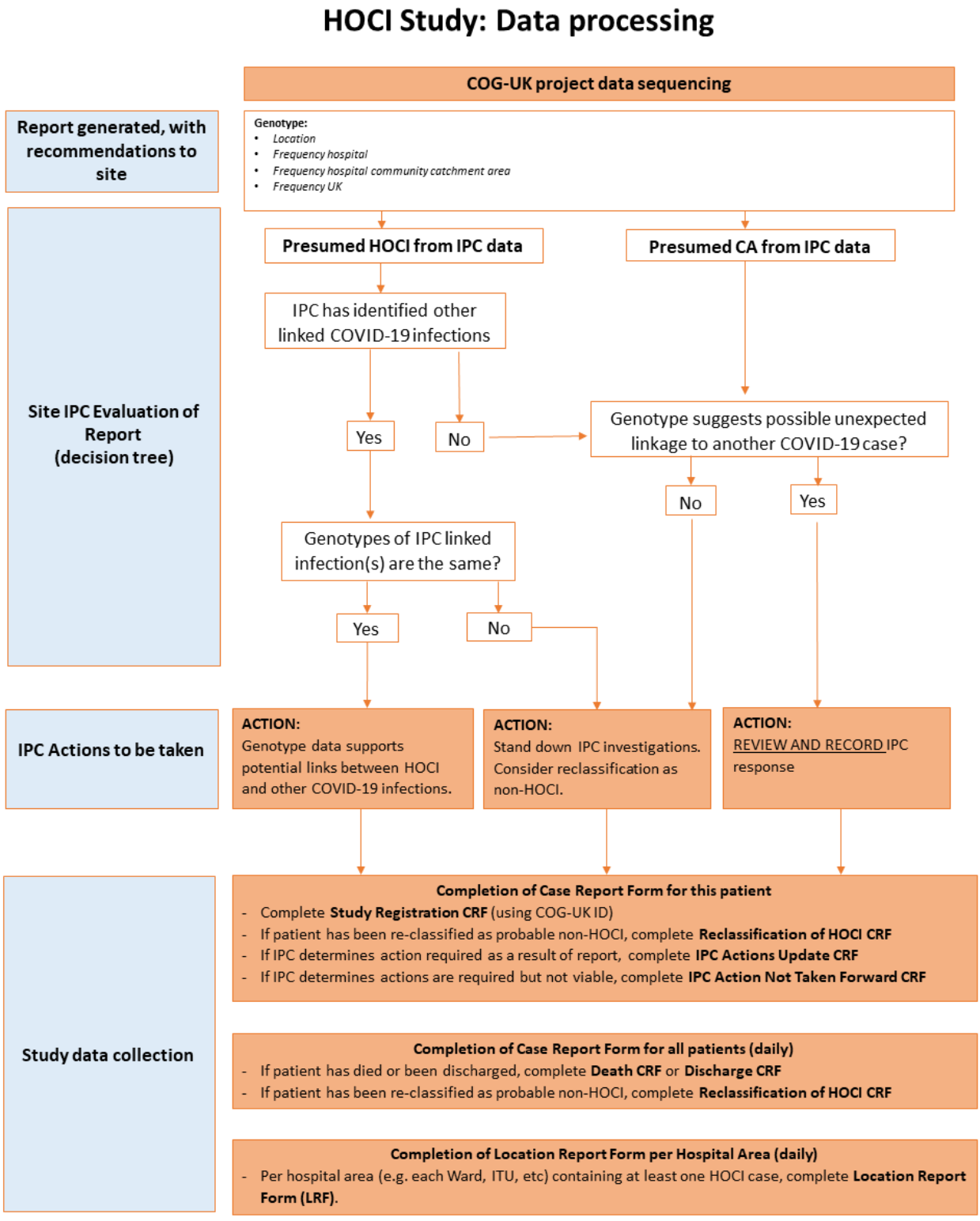
6.5.2 Secondary Outcomes

1. Does the real-time (<48 hours) availability of COVID-19 sequence data reduce the incidence rate of IPC-defined hospital outbreaks compared with delayed (>4 days) and no sequence data.
2. Does the real time (<48 hours) availability of COVID-19 sequence data identify previously undetected hospital outbreaks compared with delayed (>4 days) and no sequence data
3. Does the real time availability of COVID-19 sequence data change IPC actions as measured by the possible actions listed in the list of defined outcomes.
4. Does real time availability of COVID-19 sequence data change workload as measured by the possible actions listed in the list of defined outcomes.
5. Health economic benefit of both standard and rapid sequencing reports to IPC against baseline
6. Impact of both standard and rapid sequencing reports on number of HCW days off work.

6.5.3 Exploratory Outcomes

1. Rates following the intervention compared to baseline for each of the interpretative sequence categories (1-4):
    - 1, No evidence of COVID-19 nosocomial transmission
    - 2, Potential evidence of COVID-19 nosocomial transmission
    - 3, Sequence not informative
    - 4, Sequence identifies unexpected potential nosocomial transmission
2. Descriptive analysis of IPC actions before and after delivery of a sequencing report
3. Descriptive analysis of IPC workload before/after delivery of a sequencing report
4. The influence of turnaround times (TATs), if any, on exploratory outcomes 1, 2 and 3.

6.5.4 Data collection flowchart



6.6 Study Timeline

Timepoint (site dependent)	Week 0-2	Week 3-6	Week 7-14	Week 15-18	Week 19-22	Week 22-52
Study stage (site dependent)	**Set up**	**First Baseline / Control (daily)**	**Intervention sequencing result <48 hours (daily)**	**Intervention: sequencing result >4 days (daily)**	**Second Baseline / Control (where justified, daily)**	**Data cleaning, analysis and reporting**
Site identification	X					
Site team discussion on sampling ability, staffing availability, and logistics	X					
Initiation of contracts, R&D approvals	X					
NHS samples begin to be processed locally under COG-UK approvals (not study-related)	X					
NHS samples to be processed under COG-UK approvals, either locally or at Sanger		X	X	X	X	
Intervention reports generated		X	X	X	X	
Intervention reports returned to site ICTs (<48h)			X			
Intervention reports returned to site ICTs (>4 days)				X		
ICTs evaluate reports, seeking Expert Sequence Interpretation Team views if needed			X	X		
Aggregated locality-based data collected		X	X	X	X	
Case reports for potential HOCIs for patients		X	X	X	X	
Case reports for potential HOCIs for HCWs		X	X	X	X	
Qualitative interviews and case reports		X	X	X	X	
Interim analysis and views from TSC-DMC whether second baseline/control state acceptable					X [A]	
Data cleaning		X	X	X	X	X
Final data lock and analysis						X
Reporting/publication						X

[A] TSC-DMC review should take place to determine whether it would be considered ethical to request sites have a second period of baseline/control (where sequencing data is not provided to IPC teams). This would only be on the basis that it is unclear from the initial baseline and intervention comparison whether there is a significant benefit; in cases where it is clear there is a either benefit to the intervention or no benefit, then the second baseline would not take place.

6.6.1 Early Stopping of Follow-up

It is possible that some patient data will not be collected until the point of discharge/death or end of planned study data collection, on the basis of either reduction in available site staffing resource (e.g. due to sickness) or a decision by the site to pause sequencing.

It is not expected that follow-up of patients will be interrupted otherwise.

6.6.2 Loss to Follow-up

Not expected for this study due to the nature of the single-instance sample collection.

6.6.3 Study Closure

The end of the trial will be defined as the date of database lock. Database lock will only occur once the last participant's last CRFs have been returned, data cleaning has been completed and all data queries are closed.

The REC will be notified within 90 days of study closing. A summary report of the research will be sent to the REC within 12 months of the end of the study.

A site may be deemed 'closed' once all study-related activities at that site are reconciled and/or complete, all outstanding data queries have been resolved and a letter confirming that close down is complete has been sent to the site PI from UCL CCTU.

6.7 Sample Size

The planned sample size is 4 sites all of which will implement rapid testing, followed by slower turnaround testing, followed by a second period without sequence data.

There is uncertainty in the number of potential HOCIs that will be identified at each site during each of the intervention periods, with the rapid testing phase being roughly 8 weeks' duration. We assume there may be conservatively be an average of 40 potential HOCIs/week per site, a total of 320 per site. Within a typical site this will allow us to estimate the proportion of potential HOCIs with genotypic linkage to another case(s) not detected by IPC processes with minimum precision of +/- 5.5%. Similarly we can estimate the proportion of potential HOCIs where an action is taken that would not have occurred without sequencing within +/-5.5%. We shall also calculate a pooled estimate of key proportions across the 4 sites implementing rapid sequencing, leading to estimation within +/- 11.3% for previously undetected linked cases for potential HOCIs and actions taken that would not have occurred, assuming an intracluster correlation coefficient of 0.05.

Within the internal pilot phase for rapid testing, we shall record outcomes from around 160 potential HOCIs assuming a 4 week intervention period at the first site to initiate. This will permit us to estimate the proportion of previously undetected linked cases for potential HOCIs within +/- 7.7%.

Comparing the proportion of potential HOCIs with genotypic linkage to another case(s) not detected by IPC processes between rapid testing and delayed testing within each site, the study would have at least 80% power to detect a percentage point difference of 14% (two-sided test with alpha=0.05,

considering proportions of 57% vs 43% which would be associated with minimum power for a difference of this magnitude).

If a second control phase is conducted of 4 weeks and assuming in this phase 50 IPC-defined HOCIs per week are observed in a site then, using an approximate Normal distribution for weekly counts, there is 80% power to demonstrate a reduction due to intervention of 13 IPC-defined HOCIs per week, under 5% significance level two-tailed testing. Pooling data across 4 sites and assuming the same reduction in all, there is 80% power to demonstrate a reduction of 6 IPC-defined HOCIs per week. In practice power will however be lower in the pooled analysis due to heterogeneity between sites. The same power calculations would also apply to the incidence rates of IPC-defined hospital outbreaks, although the study will have less power to detect a difference for this outcome due to the lower number of distinct outbreak events.

6.8 Recruitment and Retention

6.8.1 Recruitment

Viral sequencing will be undertaken for every confirmed case of COVID-19 in hospital patients and staff, but it is not possible to assess clinical and infection control outcomes for every confirmed case. This study will therefore focus on the subset of patients and HCW with potential hospital-onset COVID-19, since this is where IPC is likely to have the greatest impact.

Based on initial figures discussed with key site teams (during late March 2020), and national and international evidence on likely shape of daily infections curve (and thereby hospitalisations), the team are confident that sufficient participant numbers will be available via the existing COG-project UK at the NHS sites highlighted in the protocol.

6.9 Assignment of Intervention

6.9.1 Allocation

Allocation of intervention group will be made on a site-level basis, and determined from site ability to perform rapid sequencing of COVID-19 samples.

Initially University College London will perform sequencing for Imperial College Healthcare NHS Trust as sole site to determine best practice, and subsequent sites will then be rolled out within 2-4 weeks.

It is expected that eventually there will be 4 sites but a 5th may join.

6.10 Data Collection, Management and Analysis

6.10.1 Data Collection Methods

There will be two forms of data collection mechanism for the COG-UK HOCI study. At individual participant level, Case Report Forms (CRFs) will be completed; while the collection of aggregated data

(covering data series such as ward/ITU on a given day) will be captured on locality-level reporting forms.

Each participant will use the same identifying number as is allocated to them on the COG-UK project. Data will be collected at the time-points indicated in the Study Schedule (Section 6.6).

Coded data will be collected from the study sites using paper Case Record Forms (CRFs) and Locality-level Report Forms (LRFs) and transcribed on to a CCTU database, stored on secure servers based at UCL. Training on paper CRF completion and storage for site staff listed on the delegation of responsibilities log will be provided at the site initiation meeting(s).

Data collection, data entry and queries raised by a member of the COG-UK HOCI study team will be conducted in line with the CCTU and study specific Data Management Standard Operating Procedure.

Study documentation will be kept at the study site in a locked cabinet within a secured room.

Clinical study team members will receive study protocol training. All data will be handled in accordance with the Data Protection Act 2018.

6.10.2 Data Management

Data will be entered in the approved COG-UK HOCI database by a member of the clinical study team at site and protected using established CCTU procedures.

Coded data: Participants will be allocated the same identifying number as they are given on the COG-UK project. Data will be entered under this identification number onto the central database stored on the servers based at CCTU. The database will be password protected and only accessible to members of the COG-UK HOCI study team at CCTU, and external regulators if requested. The servers are protected by firewalls and are patched and maintained according to best practice. The physical location of the servers is protected by CCTV and security door access.

The database and coding frames have been developed by members of the COG-UK HOCI Trial Management Group and the Expert Data Sequencing Group, in conjunction with CCTU. The database software provides a number of features to help maintain data quality, including: maintaining an audit trail, allowing custom validations on all data, allowing users to raise data query requests, and search facilities to identify validation failure/ missing data.

After completion of the study the database will be retained on the servers of UCL for on-going analysis of secondary outcomes.

The enrolment logs, linking participant identifiable data to the pseudoanonymised PIN, will be held locally by the study site. This will either be held in written form in a locked filing cabinet or electronically in password protected form on hospital computers. After completion of the study the enrolment logs will be stored securely by the sites for 10 years unless otherwise advised by CCTU.

6.10.3 Statistical Methods

6.10.3.1 Statistical Analysis Plan

A Statistical Analysis Plan (SAP) will be prepared for the study and each draft will be approved by an independent statistician on the TSC-DMC. The first draft will be prepared in the first month of the intervention period.

6.10.3.2 Statistical Methods – Outcomes

We shall present summary statistics for each study phase as applicable (baseline, intervention, etc.) and each site, which will be percentages for binary outcomes such as whether transmission linkage for each potential HOCI was previously undetected and counts per week for outcomes such as the total number of potential HOCIs. The numbers of potential HOCIs, IPC-defined HOCIs and IPC+sequencing defined HOCIs will also be expressed as rate per week per 100 inpatients, and as a proportion of all COVID-19 cases.

The outcomes of genotypic identification of a previously undetected linked HOCI, genotypic identification of a previously undetected hospital outbreak and whether an action occurred that would not have occurred without sequencing are only defined for the intervention periods. For such outcomes the focus of analysis is to calculate summary statistics for each site, which can be informally compared with the degree to which it is thought each site was able to fully implement the intervention. Variation over time within each site will also be explored, and the proportions will be compared between the rapid testing and delayed testing intervention periods.

For outcomes defined in both the baseline and intervention periods such as total number of IPC-defined HOCIs and the number IPC-defined hospital outbreaks this can be informally compared between the baseline, intervention and (possibly) final control periods within sites. A more formal analysis will be conducted based on Poisson regression (or negative binomial depending on model fit) to detect the change in the incidence rate of each event type between baseline, intervention and control phases within site, including site and weekly number of COVID-19 cases as a fixed effect and exposure ‘determined’ by the weekly number of inpatients. This will lead to an adjusted rate ratio for the intervention effect, presented with 95% confidence interval. Based on weekly data through the intervention period and into the second control period an estimate of the intervention effect will also be estimated using interrupted time series analysis approaches. Interpretation of these results will acknowledge the potential for the studied intervention to demonstrate effects that are delayed and /or sustained beyond intervention period, due to the nature by which IPC procedures may be adjusted over time.

All analyses will be repeated considering only potential HOCIs in HCWs and then only potential HOCIs among patients.

6.10.3.3 Analysis Population and Missing Data

In the event that some sites are unable to implement the intervention fully during the intervention period then analysis will be repeated excluding such sites to provide a ‘per protocol’ analysis.

6.10.4 Health Economics

6.10.4.1 Economic evaluations

The aim of the economic analysis will be to examine whether the rapid COVID-19 genomic sequencing might lead to measurable economic advantages. A cost-benefit analysis will be conducted looking at the incremental cost or savings for the two testing approaches in the group of sites influenced by the time to sequence data result.

The cost of generating the report (intervention) will be reviewed in conjunction with the COG-UK project team and will be evaluated.

Additional intervention cost will include Microbiology and IPC teams training, and expert sequence interpretation team who provide phone/on-line guidance.

HOCI resource use will be obtained from electronic hospital records (patients) and CRFs (HCW). Direct cost will be evaluated from the NHS setting perspective over the study period considering resources directly related to COVID-19 testing and hospital length of stay, treatment and IPC team actions (testing, disposables, cleaning), as well as indirect costs incurred by nosocomial transmission (HCW).

Economic benefit includes the attributable cost savings from averted HOCI cases, an estimate of the hospital cost savings due to excess bed days and days off work by HCW.

Deterministic sensitivity analysis will be performed to assess the impact of varying resource use and other relevant parameters to identify variables with the highest impact on costs.

6.10.4.2 Health Economic Analysis Plan

A HEAP will be prepared for the study at the same time an SAP will be produced, and each draft will be approved by the TSC-DMC team.

6.11 Data Monitoring

6.11.1 Data Monitoring Committee

Further details of the roles and responsibilities of the Independent Trial Steering and Data Monitoring Committee (TSC-DMC), including membership, relationships with other committees, decision making processes, and the timing and frequency of interim analyses (and description of stopping rules and/or guidelines where applicable) are described in detail in the COG-UK HOCI's TSC-DMC Terms of Reference (ToR).

6.11.2 Interim Analyses

At the end of the intervention period a data monitoring committee will consider whether the study should either (i) continue data collection with sites in the intervention condition, (ii) continue data collection but in control period without the intervention i.e. stop the return of sequencing data to sites, or (iii) stop data collection.

The decision will be partly informed by the quantitative interim analysis of the study outcomes, but also informed by process evaluation and other information concerning the experience of sites in implementing the intervention. In the event that information is strongly positive concerning the

intervention then the TSC-DMC is expected to recommend option (i). In the event that the information is more mixed then the TSC-DMC may recommend option (ii) so that higher quality estimation of the intervention effect can be derived from a within-site analysis. In the event that the intervention is seen to have little effect, for example because the sequencing results are rarely informative or because sites are unable to implement suitable actions based on sequencing, then the TSC-DMC is expected to recommend that the study stops (option iii).

6.11.3 Data Monitoring for Harm

6.11.3.1 Safety reporting

For the purposes of the HOCI study the only adverse events that need to be reported are ones considered a) to meet the 'seriousness' threshold, and b) to be related to the intervention.

Low grade adverse events that do not meet the seriousness criteria do no need to be reported.

Defining adverse events that: **- meet the 'seriousness' threshold,** **- are considered related to the intervention**	An adverse event is any untoward medical or psychological occurrence in a participant which does not necessarily have a causal relationship with this intervention. An adverse event can therefore be any unfavourable and unintended sign, symptom, or disease in any participant (including those in the control group), whether or not considered related to the intervention. Adverse events may include non-medical events such as self-harm. An adverse event meeting the 'seriousness' threshold (i.e. SAE) is one that: • results in death • is life threatening* • requires hospitalisation or prolongs existing hospitalisation** • results in persistent or significant disability or incapacity • is a congenital anomaly or birth defect • or is another important medical condition*** An SAE may be considered as 'being related' based upon the Causality scale as defined in section 6.11.3.
* the term life threatening here refers to an event in which the patient is at risk of death at the time of the event; it does not refer to an event that might hypothetically cause death if it was more severe (eg a silent myocardial infarction)	

** Hospitalisation is defined as an in-patient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisation for pre-existing conditions (including elective procedures that have not worsened) do not constitute an SAE

*** Medical judgement should be exercised in deciding whether an AE or AR is serious in other situations. Important AEs or ARs that may not be immediately life threatening or result in death or hospitalisation, but may seriously jeopardise the participant by requiring intervention to prevent one of the other outcomes listed in the table (eg a secondary malignancy, an allergic bronchospasm requiring intensive emergency treatment, seizures or blood dyscrasias that do not require hospitalisation, or development of drug dependency).

Adverse events include:

- an exacerbation of a pre-existing illness
- an increase in the frequency or intensity of a pre-existing episodic event or condition
- a condition (regardless of whether PRESENT prior to the start of the study) that is DETECTED after participant's sampling.
- continuous persistent disease or a symptom present at baseline that worsens following administration of the study treatment

Adverse events do NOT include:

- Medical or surgical procedures: the condition that leads to the procedure is the adverse event
- Pre-existing disease or a condition present before treatment that does not worsen
- Hospitalisation where no untoward or unintended response has occurred eg elective cosmetic surgery
- Overdose of medication without signs or symptoms

6.11.3.2 Investigator responsibilities relating to safety reporting

AEs that are considered to meet the 'seriousness' threshold and are also considered related to the study intervention should be notified to CCTU immediately the investigator becomes aware of the event (in no circumstance should this notification take longer than 24 hours).

6.11.3.2.1 Seriousness assessment

When an AE occurs, the investigator responsible for the care of the participant must first assess whether or not the event is serious using the definition given in the table in Section 6.11.3.1.

6.11.3.2.2 Causality

The investigator must assess the causality of all serious events in relation to the study intervention using the definitions below:

Table 2: Causality definitions

Relationship	**Description**
Unrelated	There is no evidence of any causal relationship

Unlikely to be related	There is little evidence to suggest that there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the study intervention). There is another reasonable explanation for the event (e.g. the participant's clinical condition or other concomitant treatment)
Possibly related	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the study intervention). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition or other concomitant treatment)
Probably related	There is evidence to suggest a causal relationship and the influence of other factors is unlikely
Definitely related	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

6.11.3.2.3 Expectedness

If there is at least a possible involvement of the trial intervention, the sponsor must assess the expectedness of the event. An unexpected related adverse event is one that is not reported in in this section of the protocol as expected to occur.

Expected serious adverse events are:

- The identification of a 'super-spreader' through the genomic sequencing process. That is an individual who is found to have a significantly higher rate of disease transmission to others than is typical for COVID-19.

Where serious adverse events are considered related to the intervention and unexpected (i.e. not listed above), they will be emailed to the Research Ethics Committee (REC) within 15 of the Chief Investigator (or CCTU staff) become aware of the event.

6.11.3.3 Notifications

6.11.3.3.1 Notifications by the Investigator to CCTU

CCTU must be notified of all **SAEs related to the study intervention** within 1 working day of the investigator becoming aware of the event.

Investigators should notify CCTU of any related SAEs occurring from the time of sampling until the point of discharge or death.

The SAE form must be completed by the investigator (the consultant named on the delegation of responsibilities list who is responsible for the participant's care) with attention paid to the grading, and causality of the event. In the absence of the responsible investigator, the SAE form should be completed and signed by a member of the site study team and emailed as appropriate within the

timeline. The responsible investigator should check the SAE form at the earliest opportunity, make any changes necessary, sign and then email to CCTU. Detailed written reports should be completed as appropriate. Systems will be in place at the site to enable the investigator to check the form for clinical accuracy as soon as possible.

The minimum criteria required for reporting an SAE are the study number and date of birth, name of reporting investigator and sufficient information on the event to confirm seriousness. Any further information regarding the event that is unavailable at the time of the first report should be sent as soon as it becomes available.

The SAE form must be scanned and sent by email to the study team at CCTU on **cctu.hoci@ucl.ac.uk**

Where a related SAE occurs, participants must be followed up until clinical recovery is complete and laboratory results have returned to normal or baseline values, or until the event has stabilised. Follow-up should continue after completion of protocol treatment and/or study follow-up if necessary. Follow-up SAE forms (clearly marked as follow-up) should be completed and emailed to CCTU as further information becomes available. Additional information may be provided separately. The participant must be identified by study number, date of birth and initials only. The participant's name should not be used on any correspondence and should be redacted (blacked out) and replaced with study identifiers on any test results.

6.11.3.6.2 CCTU responsibilities

Medically qualified staff at CCTU and/or the Chief Investigator (CI or a medically qualified delegate) will review all SAE reports received. In the event of disagreement between the causality assessment given by the local investigator and the CI, both opinions and any justifications will be provided in subsequent reports.

A medically qualified member of staff will be appointed as the sponsor clinical reviewer (usually the Chief Investigator (CI) or a medically qualified delegate), and will perform a clinical review of all SAE reports received, and complete an expectedness assessment against the list in Section 6.11.3.2.3.

CCTU is undertaking the duties of study sponsor and is responsible only for the reporting of reports of Serious Adverse Events (SAEs) that are: related to the study (i.e. they resulted from administration of any of the research procedures) and unexpected (i.e. not listed in the protocol as an expected occurrence) to the EC. As per HRA guidance on this, reports will be emailed to the Research Ethics Committee (REC) within 15 of the Chief Investigator (or CCTU staff) become aware of the event.

CCTU will keep investigators informed of any safety issues that arise during the course of the study.

6.11.3.4 Potential for identifying HCWs transmitting COVID-19

As this study is being conducted, inter alia, to uncover occurrences of transmission of COVID-19 between HCWs and patients, and vice-versa, there are thought should be given to the potential for stigmatisation and adverse publicity from findings. Study staff may need to be able to adequately respond to (i) the concept of HCWs being identified as carrying, and transmitting COVID-19 within the ICU/ward setting at the host institution, and (ii) the idea of highly virulent organisms causing severe disease within the host institution. These potential findings will be handled in collaboration with the Occupational Health Department using procedures already in place for handling Infectious Healthcare

workers. Specifically, the HCW will be asked to self-isolate at home and not to return to work until it is deemed appropriate to do so (according to PHE COVID-19 guidance current at the time).

6.11.4 Quality Assurance and Control

6.11.4.1 Definitions

Quality Assurance (QA), defined as all the planned and systematic actions established to ensure the study is performed and data generated, documented and/or recorded and reported in compliance with the principles of ICH GCP and applicable regulatory requirements.

Quality Control (QC), defined as the operational techniques and activities performed within the Quality Management System (QMS) to verify that the requirements for quality of the study related activities are fulfilled.

6.11.4.2 Quality and Risk Management

Quality Assurance (QA) for the COG-UK HOCI study will implemented as described in CCTU Quality Management Policy and all SOPs and working instructions, which define the CCTU QMS that are applicable to the study's completion. The study proposal from the Chief Investigator is reviewed and developed in line with the processes required by the Study Adoption Group (TAG) and this protocol has been reviewed, updated and finalised passing through the Protocol Review Committee process. The study will be subject to a dynamic risk assessment process throughout its life cycle; the CCTU Quality Management Group reviews the risk assessment periodically. Study risks are defined in terms of their impact on: the rights and safety of participants, project concept including study design, reliability of results and institutional risk; project management; and other considerations.

All aspects of the HOCI study will be subject to the procedures followed by the CCTU QA function, this includes delivery of the CCTU Audit Programme and other due diligence procedures (vendor assessments). Aspects and entities that are subject to QA function procedures include, but are not limited to; outcome analysis laboratories, Contract Research Organisations (CROs), study sites and internal CCTU procedures which apply to the HOCI study.

6.11.4.3 Central Monitoring at CCTU

CCTU staff will review Case Report Form (CRF) data for errors and missing key data points. The study database will also be programmed to generate reports on errors and error rates. Essential study issues, events and outputs, including defined key data points, will be detailed in the COG-UK HOCI study Data Management Plan.

6.11.4.4 On-site Monitoring

The frequency, type and intensity of routine and triggered on-site monitoring will be detailed in the COG-UK HOCI Quality Management and Monitoring Plan (QMMP). The QMMP will also detail the procedures for review and sign-off of monitoring reports. In the event of a request for a study site inspection by any regulatory authority UCL CCTU must be notified as soon as possible.

6.11.4.5 Trial Oversight

Trial oversight is intended to preserve the integrity of the study by independently verifying a variety of processes and prompting corrective action where necessary. The processes reviewed relate to

participant enrolment and eligibility; adherence to study interventions; completeness, accuracy and timeliness of data collection; and will verify adherence to applicable policies detailed in the Compliance section of the protocol. Independent study oversight complies with the CCTU study oversight policy.

In multi-centre studies this oversight is considered and described both overall and for each recruiting centre by exploring the study dataset or performing site visits as described in the COG-UK HOCI QMMP.

6.11.4.5.1 Trial Team

The Trial Team (TT) will be set up to assist with developing the design, co-ordination and day to day operational issues in the management of the study, including budget management. The membership, frequency of meetings, activity (including study conduct and data review) and authority will be covered in the TT terms of reference.

6.11.4.5.2 Trial Management Group

A Trial Management Group (TMG) will be set up to assist with developing the design, co-ordination and strategic management of the study. The membership, frequency of meetings, activity (including study conduct and data review) and authority will be covered in the TMG terms of reference.

6.11.4.5.3 Independent Trial Steering Committee and Data Monitoring Committee

The Independent Trial Steering and Data Monitoring Committee (TSC-DMC) is the independent group responsible for oversight of the study in order to safeguard the interests of study participants. The TSC-DMC is also the only oversight body that has access to the accumulating comparative data, and can make determinations of whether the study should continue as planned. The TSC-DMC will consider data in accordance with the statistical analysis plan.

The TSC-DMC provides advice to the CI, CCTU, the funder and sponsor on all aspects of the study through its independent Chair. The membership, frequency of meetings, activity (including study conduct and data review) and authority will be covered in the TSC-DMC terms of reference.

It was decided that for the COG-UK HOCI study, it would be most appropriate to combine the TSC and IDMC roles into one committee in light of: the proposed high frequency of committee meetings, and that due to the nature of the intervention it would be disproportionate to have a separate committee solely for data monitoring activities.

6.11.4.5.4 Study Sponsor

The role of the sponsor is to take on responsibility for securing the arrangements to initiate, manage and finance the study. UCL is the study sponsor and has delegated the duties as sponsor to CCTU via a signed letter of delegation.

7 Ethics and Dissemination

7.1 Ethics Committee (EC) Approval

Before initiation of the study at any clinical site, the protocol will be submitted to the relevant EC for approval. Any subsequent amendments to these documents will be submitted for further approval.

Before initiation of the study at each additional clinical site, the same/amended documents will be submitted for local permissions.

After the participant has entered the study, the clinician remains free to give alternative treatment to that specified in the protocol, at any stage, if they feel it to be in the best interest of the participant. The reasons for doing so must be recorded.

7.2 Competent Authority (CA) Approvals

This protocol does not fall within the remit of the MHRA, and therefore will not be submitted to the United Kingdom CA for approval.

7.3 Other Approvals

The protocol will be submitted to the Health Research Authority (HRA) or equivalent organisation (if outside remit of NHS England) for approval.

The protocol has received formal approval and methodological, statistical, clinical and operational input from the CCTU Protocol Review Committee.

7.4 Protocol Amendments

The protocol and all agreed substantial amendments will be documented and submitted for ethical approval prior to implementation.

7.5 Consent or Assent

Consent for participant (both patient and healthcare worker) involvement will not be sought for COG-UK HOCI study. This approach relies on the Health Service (Control of Patient Information) Regulations 2002 (SI 1438).

In light of Regulation 3 (Communicable disease and other risks to public health), and given that COG-UK HOCI is (for the purposes of the legislation) engaged in monitoring and managing outbreaks of communicable disease and addressing incidents of exposure to communicable disease, the Trial Team (as persons employed or engaged for the purposes of the health service) will process confidential patient information for this purpose.

The Trial Team also rely on 2002 (SI 1438) Regulation 7, which allows for the processing of confidential information for medical research, following approval from the Secretary of State and a research ethics committee.

7.6 Confidentiality

Adequate measures will be in place to ensure all participant data collected are kept secure. Each participant on the study will be allocated the same pseudonymised identifier as used on the COG-UK project. CRFs will record the patient's initials and full date of birth but not the patient's name. The only links between the identifier and the patient's name will be on the COG-UK records and the study enrollment log kept at site and accessed only by the patient's direct clinical care team.

Data will be recorded on the CRFs and LRFs and entered onto COG-UK HOCI's custom-designed database under this identification number. The database will be password protected and only accessible to members of the COG-UK HOCI study team at CCTU, trained and authorised site staff, and external regulators if requested. The servers are protected by firewalls and are patched and

maintained according to best practice. The physical location of the servers is protected by CCTV and security door access.

7.7 Declaration of Interests

The investigators named on the protocol have no financial or other competing interests that impact on their responsibilities towards the scientific value or potential publishing activities associated with the study.

7.8 Indemnity

UCL holds insurance to cover participants for injury caused by their participation in the clinical study. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, as this clinical study is being carried out in a hospital, the hospital continues to have a duty of care to the participant in the clinical study. UCL does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or not. This does not affect the participant's right to seek compensation via the non-negligence route.

Participants may also be able to claim compensation for injury caused by participation in this clinical study without the need to prove negligence on the part of UCL or another party. Participants who sustain injury and wish to make a claim for compensation should do so in writing in the first instance to the Chief Investigator, who will pass the claim to UCL's insurers, via the Sponsor's office.

Hospitals selected to participate in this clinical study shall provide clinical negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary shall be provided to UCL, upon request.

7.9 Finance

COG-UK HOCI study is fully funded by an UKRI grant, number [TBC]. It is not expected that any further external funding will be sought.

7.10 Archiving

The investigators agree to archive and/or arrange for secure storage of COG-UK HOCI study materials and records for a minimum of 5 years after the close of the study unless otherwise advised by the CCTU.

7.11 Access to Data

Requests for access to study data will be considered, and approved in writing where appropriate, after formal application to the TSC. Considerations for approving access are documented in the TSC Terms of Reference.

7.12 Ancillary and Post-trial Care

There are no arrangements to provide additional care to participants post-trial.

7.13 Publication Policy

7.13.1 Study Results

Study results will be submitted for publication in a high-impact peer-reviewed academic publication.

Interim study results and data may be made available to Public Health England to facilitate the surveillance and combatting of the COVID-19 communicable disease outbreak.

As required in Health Service (Control of Patient Information) Regulations 2002 (SI 1438), information will be provided to the Secretary of State upon request under Regulation 3(5).

The results of the study will be disseminated regardless of the direction of effect.

7.13.2 Authorship

Authorship will be granted to individuals making a substantial contribution to the design, setup or conduct of the study and/or analysis and interpretation of the study data.

7.13.3 Reproducible Research

The latest version of the study protocol will be made available as Supplementary material upon publication of the final study report.

8 Ancillary Studies

8.1 Sub-study 1: Process Evaluation

Process evaluations will be conducted for the intervention based on MRC guidance[5]. We will explore the extent to which the intervention was delivered as intended (fidelity), uptake and engagement (reach), acceptability, and factors influencing intervention uptake and changes in practice (barriers/enablers, context, mechanisms of impact). We will conduct 10-15 in-depth semi-structured qualitative interviews with healthcare workers per site. Transcripts will be analysed using a combined deductive framework and inductive thematic analysis[6]. Interview topic guides and analysis will be structured around behavioural science frameworks related to intervention acceptability and barriers/enablers to behaviour change and implementation. The process evaluation will support interpretation of outcomes in the main study, and if successful, future implementation of viral sequencing as part of routine care.

9 Protocol Amendments

Protocol Version Number	Protocol Date	Summary of Changes
1.0	20-Apr-2020	N/A
2.0	19-May-2020	1. Clarification of study phase timelines, particularly to Section 2 and Section 5.3. 2. Minor administrative updates (typos and updates to institutional affiliations).

10 References

1. Roy, S. *et al.* Whole-genome Sequencing Provides Data for Stratifying Infection Prevention and Control Management of Nosocomial Influenza A. *Clin Infect Dis* **69**, 1649-1656, doi:10.1093/cid/ciz020 (2019).
2. Houldcroft, C. J. *et al.* Use of Whole-Genome Sequencing of Adenovirus in Immunocompromised Pediatric Patients to Identify Nosocomial Transmission and Mixed-Genotype Infection. *J Infect Dis* **218**, 1261-1271, doi:10.1093/infdis/jiy323 (2018).
3. Brown, J. R. *et al.* Norovirus Transmission Dynamics in a Pediatric Hospital Using Full Genome Sequences. *Clin Infect Dis* **68**, 222-228, doi:10.1093/cid/ciy438 (2019).
4. Bedford, T. *et al.*Phylodynamic estimation of incidence and prevalence of novel 362 coronavirus (nCoV) infections through time. *Virological*, accessed on 27/02/2020. http://virological.org/t/phylodynamic-estimation-of-incidence-and-prevalence-of-novel364 coronavirus-ncov-infections-through-time/391
5. https://mrc.ukri.org/documents/pdf/mrc-phsrn-process-evaluation-guidance-final/
6. Atkins L et al. A guide to using the Theoretical Domains Framework of behaviour change to investigate implementation problems. Implement Sci. [doi: 10.1186/s13012-017-0605-9]
7. Chan AW, Tetzlaff JM, Altman DG et Al. SPIRIT 2013 Statement: Defining Protocol Items for Clinical Trials. Ann Intern Med 2013; 158:200-207.
8. Chan AW, Tetzlaff, Gotzsche et Al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. BMJ 2013; 346: e7586.

11 Appendices

11.1 Compliance

The trial will be conducted in compliance with the approved protocol, the Declaration of Helsinki (2008), the principles of Good Clinical Practice (GCP) as laid down by the Commission Directive 2005/28/EC with implementation in national legislation in the UK by Statutory Instrument 2004/1031 and subsequent amendments, the Human Tissue (Quality and Safety for Human Application) Regulations 2007, the UK Data Protection Act, and the National Health Service (NHS) UK Policy Framework for Health and Social Care. International sites will comply with the principles of GCP as laid down by ICH topic E6 (Note for Guidance on GCP), Commission Directive 2005/28/EC, the European Directive 2001/20/EC (where applicable), the EU Tissue and Cells Directives 2004/23/EC, 2006/17/EC and 2006/86/EC, and other national and local applicable regulations. Agreements that include detailed roles and responsibilities will be in place between participating sites and CCTU.

Participating sites will inform CCTU as soon as they are aware of a possible serious breach of compliance, so that CCTU can fulfil its requirement to report the breach if necessary within the timelines specified in the UK Clinical Trials Regulations (currently 7 days). For the purposes of this regulation a 'serious breach' is one that is likely to affect to a significant degree:

- The safety or physical or mental integrity of the subjects in the trial, or
- The scientific value of the trial.

11.2 Protocol template and development

This document was constructed using the Comprehensive Clinical Trials Unit (CCTU) at UCL Protocol template Version 5. It has been modified by the CCTU Trial Team to fit an interventional cohort non-CTIMP trial with a public communicable disease surveillance aspect. It describes the COG-UK HOCI study, sponsored by UCL and co-ordinated by CCTU.

It provides information about procedures for entering participants into the study, and provides sufficient detail to enable: an understanding of the background, rationale, objectives, study population, intervention, methods, statistical analyses, ethical considerations, dissemination plans and administration of the study; replication of key aspects of study methods and conduct; and appraisal of the study's scientific and ethical rigour from the time of ethics approval through to dissemination of the results. The protocol should not be used as an aide-memoire or guide for the treatment of other patients. Every care has been taken in drafting this protocol, but corrections or amendments may be necessary. These will be circulated to registered investigators in the study. Sites entering participants for the first time should confirm they have the correct version through a member of the study team at CCTU.

CCTU supports the commitment that its trials adhere to the SPIRIT guidelines. As such, the protocol template is based on an adaptation of the Medical Research Council CTU protocol template (2012) and the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2012 Statement for protocols of clinical trials [7]. The SPIRIT Statement Explanation and Elaboration document [8] can be referred to, or a member of CCTU Protocol Review Committee can be contacted for further detail about specific items.