Study Title: Outcomes of Patients who survived Treatment on an Intensive Care unit for COVID-19 in England and Wales: a comparative retrospective cohort study

Internal Reference Number / Short title: OPTIC-19

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Chief Investigator Signature:

Statistician Signature:

The applicants have no relevant conflicts of interest to declare

Confidentiality Statement

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

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1. KEY CONTACTS

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Committees	Study management group. Chair: Peter Watkinson

2. LAY SUMMARY

Across England and Wales, over 10,000 patients have been treated for severe coronavirus disease 2019 (COVID-19) on an intensive care unit. Around 60% survived to leave hospital. We do not know how survivors' severe COVID-19 infection, or the treatment they received on the intensive care unit, will affect their long-term health. Understanding what happens to these patients can help us make sure they receive suitable care from their GP and other NHS services after they leave hospital.

This study will follow up survivors for 1 year after discharge from hospital. We will use data collected by the Intensive Care National Audit and Research Centre (ICNARC) to identify patients who were treated on an ICU for COVID-19. We will then use NHS data to see whether these patients were readmitted to hospital and why. Information from the Office of National Statistics will allow us to know whether these patients died. By linking different sources of patient data, we will be able to estimate the health risks faced by survivors of severe COVID-19. We will compare these risks to patients treated on an ICU for other conditions.

3. SYNOPSIS

Study Title	Outcomes of Patients who survived Treatment on an Intensive Care unit for COVID-19 in England and Wales: a comparative retrospective cohort study		
Internal ref. no. / short title	OPTIC-19		
Study registration	ClinicalTrials.gov:		
Sponsor	University of Oxford Clinical Trials & Research Governance, Boundary Brook House, Oxford, OX3 7GB, United Kingdom		
Funder	The study is funded by the University of Oxford's COVID-19 Research Response Fund (Ref: 0009471).		
Study Design	Retrospective cohort study		
Study Participants	Patients aged 16 or over admitted as an emergency to an intensive care unit in England or Wales and discharged alive from hospital, and treated for either COVID-19 or another acute condition.		
Sample Size	319,600		
Planned Study Period	Project length: 36 months Follow up period: 1 year after discharge from an intensive care unit		
Planned Recruitment period	January 2016 to July 2020		
	Objectives	Outcome Measures	Timepoint(s)
Primary	To estimate the risk of death for patients who	Mortality	1 year

	survived to hospital discharge after treatment on an ICU for COVID-19 and compare these risks to patients treated on ICU as an emergency for other conditions		
Secondary	To estimate the risk of adverse events for patients who survived to hospital discharge after treatment on an ICU for COVID-19 and compare these risks to patients treated on ICU as an emergency for other conditions	• Emergency hospital admission • Emergency hospital admission for respiratory infection • Emergency hospital admission for a major adverse cardiac event (myocardial infarction, stroke, heart failure) • Emergency hospital admission for a venous thrombotic event (deep vein thrombosis or pulmonary embolism) • Development of end stage renal failure treated by renal replacement therapy	1 year
Intervention(s)	Non-interventional study		

4. ABBREVIATIONS

CAG	Confidentiality Advisory Group
CCRG	Critical Care Research Group
CI	Chief Investigator
CMP	Case Mix Programme
COVID-19	COronaVIrus Disease 2019
CRF	Case Report Form
CTRG	Clinical Trials & Research Governance, University of Oxford
HES	Hospital Episode Statistics
GCP	Good Clinical Practice
GP	General Practitioner

HRA	Health Research Authority
ICF	Informed Consent Form
ICNARC	Intensive Care National Audit and Research Centre
ICU	Intensive Care Unit
NHS	National Health Service
NICOR	National Institute for Cardiovascular Outcomes Research
RES	Research Ethics Service
OXTREC	Oxford Tropical Research Ethics Committee
PEDW	Patient Episode Database for Wales
PI	Principal Investigator
PIL	Participant/ Patient Information Leaflet
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
SOP	Standard Operating Procedure
SSNAP	Stroke Sentinel National Audit Programme
UKOSS	UK Obstetric Surveillance System
UKRR	UK Renal Registry

5. BACKGROUND AND RATIONALE

Background

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in late 2019. By mid-July 2020 14 million people globally had been infected, of which over 600,000 died of coronavirus disease 2019 (COVID-19) (1). In the UK, nearly 20% of patients hospitalised with COVID-19 were transferred to an intensive care unit (ICU) or high dependency ward (2). In total, over 10,000 patients have been treated for COVID-19 on an ICU in England and Wales. On average, 50% of these patients survived to hospital discharge, although survival rates appear to be increasing (3,4). The long-term impact on the health of survivors is unknown.

Previous studies have shown that critically ill patients who survive ICU treatment are at greater risk of death and report lower health-related quality of life when compared with population norms (5–7). While pre-existing comorbidities partially account for these differences, organ damage caused by critical illness and the impact of intensive organ support given in the ICU likely also play a role (8). Analysis by the Intensive Care National Audit and Research Centre (ICNARC) suggests that patients admitted with COVID-19 receive higher intensity organ support and suffer more complications than observed in other viral respiratory infections (4). For example, nearly all COVID-19 patients required respiratory support, with nearly 60% receiving mechanical ventilation (compared to 43% with viral pneumonias) (4). Around one third of patients also required advanced cardiovascular or renal support (4,9). Cardiac (myocarditis, heart failure, arrhythmias, acute coronary syndrome) and venous thrombotic complications (e.g. pulmonary

embolism) were not uncommon (10–12). Although rare, some patients developed neurological complications such as stroke, encephalitis and Guillain-Barré syndrome (13).

Aim

This protocol describes a retrospective cohort study aiming to characterise outcomes for patients treated on an ICU with COVID-19 in England and Wales, one year after discharge from hospital. The study will use existing national audit data linked to routine healthcare datasets.

6. OBJECTIVES AND OUTCOME MEASURES

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure (if applicable)
Primary Objective To estimate the risk of death for patients who survived to hospital discharge after treatment on an ICU for COVID-19 and compare these risks to patients treated on ICU as an emergency for other conditions	**Primary outcome** • Death as recorded in the Civil Registration -- Deaths	1 year after discharge from ICU
Secondary Objectives To estimate the risk of adverse events for patients who survived to hospital discharge after treatment on an ICU for COVID-19 and compare these risks to patients treated on ICU as an emergency for other conditions	**Secondary outcomes** • Emergency hospital admission • Emergency hospital admission for respiratory infection • Emergency hospital admission for a major adverse cardiac event (myocardial infarction, stroke, heart failure) • Emergency hospital admission for a venous thrombotic event (deep	180 days after discharge from ICU AND 1 year after discharge from ICU

	vein thrombosis or pulmonary embolism) • Development of end stage renal failure treated by renal replacement therapy	
Exploratory Objectives To compare the risks in patients treated in ICU for COVID-19 to patients who survived to hospital discharge after treatment on an ICU for other bacterial or viral respiratory infections during the same period (January to June 2020) To compare the risks in pregnant patients treated in ICU for COVID-19 with an age-matched control group	**Primary outcome** • Death as recorded in the Civil Registration -- Deaths **Secondary outcomes** • Emergency hospital admission • Emergency hospital admission for respiratory infection • Emergency hospital admission for a major adverse cardiac event (myocardial infarction, stroke, heart failure) • Emergency hospital admission for a venous thrombotic event (deep vein thrombosis or pulmonary embolism) • Development of end stage renal failure treated by renal replacement therapy	180 days after discharge from ICU AND 1 year after discharge from ICU

7. STUDY DESIGN

7.1. Design

This is a retrospective cohort study of outcomes for patients treated on an ICU in England and Wales, one year after discharge from hospital. Our primary group will include patients admitted to ICU with confirmed COVID-19 between 1st January and 1st July 2020, who were discharged alive from hospital. We will use the ICNARC Case Mix Programme (CMP) to identify comparator groups of emergency ICU admissions, to which outcomes in the primary group can be compared. Once identified, each cohort will be linked to the national data sets to obtain information on subsequent hospitalisations, and longer-term mortality, cardiac and renal outcomes.

The study will be reported using the REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) (14).

7.2. Setting

This study will use data from patients admitted to general adult ICUs in England and Wales, collected as part of the CMP. The CMP is an audit of patients admitted to adult general (and some specialist) ICUs that covers England, Wales and Northern Ireland. This study will only use data from ICUs in England and Wales, all of which have participated in the CMP programme since 2015.

7.3. Data collection

Eligible participants identified from the CMP will be assigned a pseudonymous "study key". The study key will be sent to the other participating organisations for linkage alongside the following direct identifiers:

- Date of birth
- NHS number
- Postcode
- Sex/gender

Linkage will be performed by each participating organisation, following the principles of the NHS Digital matching algorithm. At no point will direct identifiers be sent to the co-ordinating site (Critical Care Research Group, University of Oxford).

Participating organisations performing linkage will be:

- NHS Digital
- Patient Episode Database for Wales (PEDW)
- UK Renal Registry (UKRR)
- National Institute for Cardiovascular Outcomes Research (NICOR)
- Stroke Sentinel National Audit Programme (SSNAP)

On a per patient level, the study will request 5 years of diagnostic coding data prior to ICU admission (to accurately assess prior medical co-morbidities) and 1 year post hospital discharge (to assess the outcomes of this study).

After linkage, only pseudonymous personal data will be securely transferred to the sponsor (Critical Care Research Group, University of Oxford), where it will be stored and accessed within a secure computing system that conforms to UK government Cyber Essentials Plus and NHS Digital Security Toolkit certifications. The study will also link data from the UK Obstetric Surveillance System (UKOSS) to identify patients who were pregnant at the time of ICU admission. As UKOSS does not collect direct identifiers, it will be linked to the pseudonymous data set using probabilistic matching.

Data will be combined into the final pseudonymised study dataset by researchers in the Critical Care Research Group at the University of Oxford for analysis. Analysis of the study dataset will be conducted by researchers at the University of Oxford and ICNARC, following the methods outlined in Section 11. The accompanying Data Flow Diagram outlines the exchange of confidential patient information within the study.

8. PARTICIPANT IDENTIFICATION

8.1. Study Participants

8.2. Inclusion Criteria

- Age ≥16 years
- Admitted to an adult, general ICU in England or Wales as an emergency (unplanned)
- Admitted to ICU for either:
    - confirmed COVID-19 between 1st January to 1st July 2020
    - without confirmed COVID-19 between 1st July 2016 and 1st July 2020

8.3. Exclusion Criteria

The participant may not enter the study if ANY of the following apply:

- Patients who died in hospital after treatment on an ICU

We chose to exclude ICU admissions after 1st July 2020 to account for a possible three-month delay in patient data being registered in HES and national audit databases. Linking data sources in March and October 2021 will maximise the chance that complete data will be available for outcomes at 180 and 365 days respectively.

9. PROTOCOL PROCEDURES

9.1. Recruitment

Participants will be recruited from general adult ICUs across England and Wales who participate in the ICNARC CMP audit. All ICUs in England and Wales have participated in the CMP audit since 2015.

9.2. Screening and Eligibility Assessment

Changes to inclusion and exclusion criteria will be made by ethical amendment only.

There will be no exceptions made regarding eligibility.

9.3. Informed Consent

We will apply for Health Research Approval (HRA), under advice from the Research Ethics Committee and the Confidentiality Advisory Group (CAG) to allow access to confidential medical records without informed or written consent (Section 251 support).

Patient Notification Strategy

As part of a similar study (the C3 study), we developed a patient notification strategy with input from the Oxford REC B ethics committee and members of the Oxford ICU Forum (a group of previous ICU patients, families, and lay members).

In common with C3, the current study:

- Uses retrospective patient data.
- At no point will any attempt be made to contact or otherwise influence the future care of any the participants.
- The data set compiled for analysis will be pseudonymised and therefore stripped of all direct identifiers.
- The study will fully implement the National Data Opt-out (DCB3058) and will therefore exclude any records related to patients who have notified the NHS of their wish for their data not to be used in research.

For the C3 study, we were advised by the ethics committee that placing posters in the relative rooms or waiting areas of the participating ICUs to notify patients of the study, "was not practical and should not therefore be used". All members of the PPI panel agreed with the ethics committee that displaying posters would not be appropriate. However, the PPI group advised that information should be available on a study website. The group advised that the website summary should be brief and accessible, with links to the detail (such as formal privacy policy) available.

Members of the Oxford ICU patient forum were also consulted for this study (OPTIC-19) and were supportive of its approach and aims.

Opt-out
The study will fully support and implement the NHS National Opt-out. We will utilise our link to NHS Digital asking them to inform us (by pseudonymous study ID) which patients have opted out and that will be a continuous process from enrolment until the study ends. Records that are already flagged within each site as meeting the opt-out will not be extracted.

If we are informed by NHS Digital of patients completing the Opt-out after data extraction, these data will be purged and future records relating to these patients will not be extracted.

We will also purge records from the study (in the same manner) if patients contact the study directly.

We will clearly display on the website links to register for the opt-out, as well as contact details for the study team.

Your data matters
The study will openly support the ICO "Your data matters campaign" (https://ico.org.uk/your-data-matters/). The aim is to increase the public's trust and confidence in how their data is used and made available. We will also support the NHS implementation of this campaign that has direct relevance to the study using data for patient benefit (https://digital.nhs.uk/services/national-data-opt-out/supporting-patients-information-and-resources).

9.4. Enrolment

This is a non-randomised observational study. Enrolment of participants will occur through their data being present within the ICNARC CMP.

9.5. Blinding and code-breaking

There is no blinding or code-breaking in this observational study.

9.6. Description of study intervention(s), comparators and study procedures (clinical)

This is a non-interventional study.

9.7. Baseline Assessments

Not applicable

9.8. Subsequent Visits

Not applicable

9.9. Sample Handling

No additional samples will be taken during this observational study.

9.10. Early Discontinuation/Withdrawal of Participants

This is an observational study. Participants can request their data to be deleted at any time in accordance with GPDR and the trial privacy policy.

9.11. Definition of End of Study

The end of the study will be 31st July 2023.

10. SAFETY REPORTING

This is an observational study using routinely-collected retrospective data, so safety reporting is not applicable

11. STATISTICS AND ANALYSIS

11.1. Statistical Analysis Plan (SAP)

The statistical aspects of the study are summarised here with details fully described in a statistical analysis plan that will be available from the time that the last participant is recruited. The SAP will be finalised before any analysis takes place.

11.2. Description of the Statistical Methods

Primary outcome
The primary outcome will be all-cause mortality at 1 year after discharge from ICU. For patients transferred between ICUs, this will be the time of discharge from the last ICU. Dates of death will be extracted from Civil Registration (deaths).

Secondary outcomes
Secondary outcomes will be:

- All-cause mortality at 30, 60, 90 and 180 days
- Any emergency (non-elective) hospital admission
- Emergency hospital admissions for respiratory infection
- Emergency hospital admission for a venous thrombotic event (deep vein thrombosis or pulmonary embolism)
- Emergency hospital admission for a major adverse cardiac event (myocardial infarction, stroke, heart failure)
- Development of end stage renal failure treated by renal replacement therapy

Reasons for hospital admission (i.e. primary diagnosis) will be identified using the International Classification of Diseases 10th Edition (ICD- 10) codes obtained by linkage to the HES/PEDW. Where required, ICD-10 codes will be assigned to broader diagnostic groups (e.g. respiratory infections) as per the UK Summary Hospital-level Mortality Indicator (SHMI) (16).

Statistical methods
For patients treated on ICU for COVID-19 and comparator groups, we will report the unadjusted proportions/incidence of primary and secondary outcomes, along with cumulative incidence function estimates over the 1 year follow-up period. When considering secondary outcomes (and where appropriate), the cumulative incidence estimates will account for the competing risk of death. For the COVID-19 group, we will also investigate the effect of ICU admission time (i.e. early epidemic, late epidemic) as this may impact their outcomes, as treatments changed over time.

We will compare the risk of the primary and secondary outcomes between the COVID-19 and comparator groups using survival models, such as Cox proportional hazards regression models or Fine and Gray models (when death is a competing risk). We will fit both univariable models (i.e. just including the COVID-19 vs comparator group variable) and multivariable models including potential confounders.

We will also analyse the data using propensity score matching as an alternative method to account for any potential confounding associated with the COVID-19 and comparator populations. A logistic propensity score will be used to create a matched population. The following variables will be considered for inclusion in the propensity score:

- Age at discharge from hospital
- Charlson/Elixhauser comorbidity index
- Ethnicity
- Illness severity (APACHE-II or ICNARC severity score) on admission to ICU
- Days of mechanical ventilation
- Week of the year of ICU admission (to account for potential increased survival over the course of the pandemic)

As an exploratory analysis, we will examine potential prognostic factors (such as patient or ICU treatment characteristics) for the primary and secondary outcomes. We will further investigate whether some of the secondary outcomes are time-varying predictors of mortality. Latent class analysis may also be used to identify any clustering of the secondary outcomes and their severity and/or timing.

Where common patient data items are available from multiple data sources (e.g. age, gender ethnicity), we will develop a standard protocol to resolve inconsistencies. Should substantial differences remain, we will explore any effect on our results through a sensitivity analysis.

11.3. Sample Size Determination

The study size will be determined by the number of ICU survivors available from the CMP. The CMP currently holds around 10,000 patients admitted with confirmed COVID-19, of which ≈5,000 survived to hospital discharge. Of the survivors, we expected 90% (4,600) to have been admitted to an ICU in England or Wales.

Prior to the COVID-19 pandemic, there were around 130,000 emergency ICU admissions per annum in the CMP. Of these, around 100,000 survived to hospital discharge. We expect ≈90,000 to have been admitted to an ICU in England or Wales.

Study participants will include around 3.5 years of pre-pandemic admissions (90,000 x 3.5 = 315,000) and 4,600 COVID admission during the pandemic giving a total sample size of 319,600.

11.4. Analysis populations

Primary group
Our primary group will be patients admitted with confirmed COVID-19 between 1st January to 1st July 2020.

Comparator groups
The primary comparator group will be patients admitted to ICU with viral or bacterial pneumonia between 1st July 2016 and 1st July 2019.

Secondary comparator groups will include:

- All emergency ICU admissions between 1st July 2016 and 1st July 2019
- All emergency ICU admissions between 1st July 2016 and 1st January 2020 where the primary diagnosis was not COVID-19
- All emergency ICU admissions between 1st January and 1st July 2020 where the primary diagnosis was not COVID-19

Pregnant patients
We will undertake a sub-group analysis in patients who were pregnant when treated for COVID-19 on ICU between 1st January and 1st July 2020.

11.5. Decision points

- March 2021: We will undertake data linkage and extraction from participating organisations. An interim analysis of outcomes at 180 days follow-up will be undertaken.
- October 2021: We will undertake data linkage and extraction from participating organisations. A final analysis of outcomes at 365 days follow-up will be undertaken.

11.6. Stopping rules

Not applicable

11.7. The Level of Statistical Significance

The level of statistical significance will be set at $p<0.05$.

11.8. Procedure for Accounting for Missing, Unused, and Spurious Data.

For multivariate models, we will impute missing covariates using fully conditional specification implemented using the Multivariate Imputation by Chained Equations (MICE) algorithm (17). The multiple imputation model will include all covariates, alongside the relevant outcome.

11.9. Procedures for Reporting any Deviation(s) from the Original Statistical Plan

Any deviation from the statistical analysis plan will be described and justified in all study publications.

12. DATA MANAGEMENT

The plan for the data management of the study are outlined below. There is not a separate Data Management document in use for the study.

12.1. Source Data

This study requires accessing and linking confidential health care records. Access to these data will be subject to approval from a REC and Section 251 support from the CAG.

Data linkage

Eligible participants will be identified by ICNARC from the CMP audit. Each eligible participant will be assigned a pseudonymous "study key". The study key will be sent to the other participating organisations for linkage alongside the following direct identifiers:

- Date of birth
- NHS number
- Postcode
- Sex/gender

Linkage will be performed by each participating organisation, following the principles of the NHS Digital matching algorithm, after which all direct identifiers will be removed. Only pseudonymised data (including the study key) will be securely transferred to the Sponsor (Critical Care Research Group, University of

Oxford), where researchers will assemble these data sources for analysis. At no point will direct identifiers be sent to the Sponsor.

Data sources
The following data sources will be linked to the CMP audit:

- NHS Digital
    - Hospital Episode Statistics (HES)
        - Admitted Patient Care
        - Outpatients
    - Maternity Services Data Set (MSDS)
    - Civil Registration (deaths)
    - Emergency Care Data Set (ECDS)
    - Hospital Episode Statistics Accident and Emergency
    - GPES Data for Pandemic Planning and Research (COVID-19)
- Patient Episode Database for Wales (PEDW)
- UK Renal Registry (UKRR)
- National Institute for Cardiovascular Outcomes Research (NICOR)
- Stroke Sentinel National Audit Programme (SSNAP)

The study will also link data from the UK Obstetric Surveillance System (UKOSS) to identify patients who were pregnant at the time of ICU admission. As UKOSS does not collect direct identifiers, it will be linked to the pseudonymous data set using probabilistic matching.

Data timeframes
On a per patient level, the study will request 5 years of diagnostic coding data prior to ICU admission (to accurately assess prior medical co-morbidities) and 1 year post hospital discharge (to assess the outcomes of this study). The use of a 5 year window of prior diagnostic coding data is based on previous literature that has shown this enhances data accuracy (14). This is preferable to relying solely on the diagnostic coding relating to the hospital admission, as complications cannot be differentiated from prior co-morbidities (15).

Data storage for analysis
The Sponsor will hold pseudonymised data within a secure “Data Safe Haven”, which is owned and maintained by the group. The “Data Safe Haven” is a computing environment which has been designed to store and analyse large datasets in a manner that is safe and secure. It conforms to NHS Digital Security Toolkit and Cyber Essentials Plus accreditation. The environment is designed to prevent patient level data leaving this environment.

ICNARC will hold data within a secure environment, which conforms to the NHS Digital Security Toolkit.

12.2. Access to Data

The final pseudonymised dataset will be accessed by authorised members of the study team at the University of Oxford and ICNARC for analysis purposes. At the University of Oxford, access will be via the Data Safe Haven subject to compliance with local information governance policies. Pseudonymised data will also be securely transferred to ICNARC and accessed via secure servers managed by ICNARC.

12.3. Data Recording and Record Keeping

All study records will be electronic -- their generation is detailed above. All records will be subject to quality assurance polices both at the University and research group level. These are designed to guarantee the accuracy and validity of the study data.

The participants will be identified by a unique study number (pseudonymous study key).

13. QUALITY ASSURANCE PROCEDURES

All research team members will be trained in Information Governance, data protection and confidentiality. The study may be monitored, or audited in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures.

13.1. Risk assessment

This is a retrospective observational study, where researchers will not interact directly with patients or intervene in their care.

This study requires access to confidential patient records. Eligible patient records will be identified by ICNARC from the CMP audit and linked with follow-up data held by NHS Digital and three national audit projects. Directly identifiable data is only required for record linkage and will not be available to the Sponsor.

To mitigate the risk of reidentification of participants and the risk of data loss we will undertake the following:

- All records will be accessed and de-identified at each participating site, using a dedicated computer that will conform to NHS information security standards.
- Only pseudonymous personal data will be transferred via secure/encrypted protocols to the coordinating centre (Critical Care Research Group (CCRG), Nuffield Department of Clinical Neurosciences, Oxford University).
- Only pseudonymous personal data will be held by the CCRG.
- Pseudonymous personal data will be held inside the Sponsors “Data Safe Haven” which conforms to the same NHS standards of information security and cyber security.

13.2. Study monitoring

All research team members will be fully trained in Information Governance, data protection and confidentiality. The study may be monitored, or audited in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures.

13.3. Study Committees

Study management group
The study management group will consist of the chief investigator and the named investigators listed under Key Contacts. The study management group will be primarily responsible for the running and conduct of the study. They will be responsible for ensuring that standard operating procedures are followed and that regulations are adhered to. Where appropriate public patient involvement will be gained in any changes or amendments that are needed during the study.

14. PROTOCOL DEVIATIONS

Any deviations from the protocol will be documented in a protocol deviation form and filed in the study master file.

15. SERIOUS BREACHES

A "serious breach" is a breach of the protocol or of the conditions or principles of Good Clinical Practice which is likely to affect to a significant degree –

(a) the safety or physical or mental integrity of the trial subjects; or

(b) the scientific value of the research.

In the event that a serious breach is suspected the Sponsor must be contacted within 1 working day. In collaboration with the C.I., the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the approving REC committee and the relevant NHS host organisation within seven calendar days.

16. ETHICAL AND REGULATORY CONSIDERATIONS

16.1. Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

16.2. Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

16.3. Approvals

Following Sponsor approval, the protocol, and any Privacy notification material will be submitted to an appropriate Research Ethics Committee (REC), CAG and HRA (where required) and host institutions for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

16.4. Other Ethical Considerations

16.5. Reporting

The CI shall submit once a year throughout the study, or on request, an Annual Progress report to the REC Committee, CAG, HRA (where required) host organisation, Sponsor and funder (where required). In addition, an End of Study notification and final report will be submitted to the same parties.

16.6. Transparency in Research

We will register the study on ClinicalTrails.gov.

16.7. Participant Confidentiality

The study will comply with the General Data Protection Regulation (GDPR) and Data Protection Act 2018, which require data to be de-identified as soon as it is practical to do so. The processing of the personal data of participants will be minimised by making use of a unique participant study number only on all study documents and any electronic database(sAll documents will be stored securely and only accessible by study staff and authorised personnel. The study staff will safeguard the privacy of participants' personal data.

16.8. Expenses and Benefits

No payments or any other benefits will be provided to participants.

17. FINANCE AND INSURANCE

17.1. Funding

The study is funded by the University of Oxford's COVID-19 Research Response Fund (Ref: 0009471).

17.2. Insurance

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London).

17.3. Contractual arrangements

Appropriate contractual arrangements will be put in place with all third parties.

18. PUBLICATION POLICY

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was funded by the University of Oxford's COVID-19 Research Response Fund (Ref: 0009471). Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

19. DEVELOPMENT OF A NEW PRODUCT/ PROCESS OR THE GENERATION OF INTELLECTUAL PROPERTY

Ownership of IP generated by employees of the University vests in the University. The University will ensure appropriate arrangements are in place as regards any new IP arising from the study.

19. ARCHIVING

The final linked anonymised study dataset will be stored securely within the CCRG data safe haven and ICNARC servers. Ethical approval will be sought for ongoing storage of study data as a research database. Study data will be available for future research/analysis and access will be governed by the Critical Care Research Group (CCRG) Data Access Committee (DAC). Any additional analyses will be restricted to the overall purpose of better understanding the epidemiology of and outcomes from, critical illness. All outputs will be restricted to aggregate data with small numbers supressed in line with the HES analysis guide.

20. REFERENCES

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21. APPENDIX A: DATA FLOW DIAGRAM

Please see attached Data Flow Diagram

22. APPENDIX C: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1	V3	02/08/2021	Oliver Redfern, Robert Hatch, Peter Watkinson	• Added 5 years of prior data for co-morbidity assessment (7.3) • Updated wording around data sources and the section this applies to (7.3, 12.1)
2	V4	02/12/2021	Oliver Redfern, Peter Watkinson	• Study end date changed to 31st July 2022
3	V5	17/06/2022	Peter Watkinson and study team	• Study end date changed to 31st July 2023. Study length updated accordingly

List details of all protocol amendments here whenever a new version of the protocol is produced.

Protocol amendments must be submitted to the Sponsor for approval prior to submission to the REC committee and HRA (where required).