CCP-CANCER UK

Clinical Characterisation Protocol for Severe Emerging Infections in the UK (CCP-UK) – a prospective companion study for patients with Cancer and COVID-19.

CCP-CANCER UK Protocol
Version 4.0 Dated: 21/04/2023

Study Sponsor(s):
Clatterbridge Cancer Centre NHS Foundation Trust
Clatterbridge Road,
Bebington,
Wirral,
CH63 4JY

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ISRCTN: ISRCTN15019599

Study funded by the UKRI-DHSC COVID-19 Rapid Response Rolling Call

Protocol Approval

I, the undersigned, hereby approve this clinical study protocol:

Authorised by Chief Investigator:

Signature: 

Date: 1 Jun 2023

Professor Carlo Palmieri
Chair of Translational Oncology
The University of Liverpool

Authorised on behalf of the Sponsor:

Signature: 

Date: Jun 1, 2023

Dr Gillian Heap
Director of Research and Innovation
Clatterbridge Cancer Centre NHS Foundation Trust

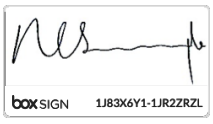
Authorised on behalf of the Lead Statistician:

Signature: 

Date: 5 Jul 2023

Dr Ashley Jones – Lead Statistician
Liverpool Clinical Trials Centre
University of Liverpool

Authorised on behalf of the Clinical Characterisation Protocol UK (Principal Study)

Signature: 

Date: 19 Jun 2023

Professor Calum Semple
Professor of Child Health and Outbreak Medicine
University of Liverpool

This document describes the CCP-CANCER UK companion study including detailed information about procedures and recruitment.

The purpose of CCP-CANCER UK is to obtain additional data from patients with cancer who are recruited into the Principal ISARIC CCP-UK study (UK CRN /CPMS ID 14152 IRAS ID126600, study registration ISRCTN66726260). The protocol described in this document is therefore designed to supplement, not replace, the Principal ISARIC CCP-UK protocol.

Every care was taken in the drafting of this protocol, but corrections or amendments may be necessary. Any amendments will be circulated to the investigators participating in the trial, but sites entering patients for the first time are advised to contact the coordinating centre (Liverpool Clinical Trials Centre, LCTC) to confirm they have the most up-to-date version. Clinical problems relating to this study should be referred to the relevant Chief Investigator, Professor Carlo Palmieri via the LCTC.

This protocol defines the participant characteristics required for study entry and the schedule of data collection. Participant recruitment will be undertaken in compliance with this document and applicable regulatory and governance requirements. Waivers to authorise non-compliance are not permitted.

Incidence of protocol non-compliance whether reported prospectively (e.g. where a treatment cannot be administered on a scheduled date as a result of public holidays) or retrospectively noted (e.g. as a result of central monitoring) are recorded as protocol deviations. These are monitored and reported to study oversight committees.

The LCTC brings together a wealth of expertise built on the experience of the Liverpool Trials Collaborative which has held full registration status with the UK Clinical Research Collaboration CTU network since its establishment in 2007 (www.ukcrc.org). The LCTC has a diverse trial portfolio underpinned by methodological rigour, a GCP compliant data management system, and quality management system.

Contact Details: Institutions

Sponsor:	**Trial Management and Monitoring:**	**Translational Laboratory:**
The Clatterbridge Cancer Centre NHS Foundation Trust Clatterbridge Road, Bebington CH63 4JY Tel: 00 44 (0) 151 482 7804 ext. 4740 Fax: 00 44 (0) 151 482 7673	Liverpool Clinical Trials Centre University of Liverpool 1st Floor Block C Waterhouse Building 3 Brownlow Street Liverpool L69 3GL Tel: 0151 794 8929 Email: ccpcanceruk@liverpool.ac.uk	Liverpool Good Clinical Laboratory Practice (GCLP) Facility GCPLab Facility 1st Floor William Henry Duncan Building University of Liverpool 6 West Derby Street Liverpool L7 8TX
Statistics:	**CCP UK Principal protocol**	**Data Management**
Liverpool Clinical Trials Centre University of Liverpool 1st Floor Block C Waterhouse Building 3 Brownlow Street Liverpool L69 3GL Tel: 0151 795 7730	Email: CCP@liverpool.ac.uk	Liverpool Clinical Trials Centre University of Liverpool 1st Floor Block C Waterhouse Building 3 Brownlow Street Liverpool L69 3GL Tel: 0151 795 7730 Email: ccpcanceruk@liverpool.ac.uk
Individual Authorised to Sign the Protocol and Protocol Amendments on behalf of the Sponsor:		
LCTC Trial Management Lead (Cancer) Liverpool Clinical Trials Centre University of Liverpool 1st Floor Block C Waterhouse Building 3 Brownlow Street Liverpool L69 3GL Tel: 0151 794 8167		

Contact Details: Individuals

Chief Investigator (CI):	Co-Chief Investigator	Translational Lead
Professor Carlo Palmieri Professor Translational Oncology & Honorary Consultant medical oncologist Molecular and Clinical Cancer Medicine University of Liverpool Email: C.Palmieri@liverpool.ac.uk	**Dr Lance Turtle** Senior Clinical Lecturer of Infectious Disease Clinical Infection, Microbiology and Immunological, University of Liverpool Email:Lance.Turtle@liverpool.ac.uk	**Professor William Greenhalf** GCPLab Facility 1st Floor William Henry Duncan Building University of Liverpool 6 West Derby Street Liverpool Email: Greenhaf@liverpool.ac.uk

In cases where the CI or Co-CI are unavailable to respond to urgent queries the following will act as cover:

Co-Investigator	Co- Investigator	Co- Investigator
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Trainee Representative Medical Oncology	**Trainee Representative Haemato-oncology**	**Trainee Representative Infectious diseases**
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Co-Investigator	**Patient representative**	
Dr Thomas M Drake Clinical Research Fellow Centre for Medical Informatics University of Edinburgh Email: t.drake@ed.ac.uk	**Mrs Hilary Stobart** Independent Cancer Patients Voice c/o CCP-Cancer UK Study Coordinator	
Key Collaborators		
ISARIC/WHO Clinical Characterisation Protocol for Severe Emerging Infections in the UK (CCP-UK) Group Cancer Research UK – Experimental Cancer Medicine Centres		
Additional Contacts: The contact details for any trial oversight committee members and participating centres are detailed in documents supplementary to the protocol and stored in the Trial Master File.		

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Glossary/Abbreviations

CAG	Confidentiality Advisory Group
CCP-UK	Clinical Characterisation Protocol UK
CI	Chief Investigator
Co-I	Co- Investigator
COPI	Control Of Patient Information
CRF	Case Report Form
CR-UK	Cancer Research UK
CTU	Clinical Trials Unit
ECMC	Experimental Cancer Medicine Centre
GCP	Good Clinical Practice
HRA	Health Research Authority
IDAMAC	Independent Data and Materials Access Committee
ISARIC	International Severe Acute Respiratory and Emerging Infection Consortium
LCTC	Liverpool Clinical Trials Centre
NHS	National Health Service
NIHR CRN	National Institute for Health Research Clinical Research Network
NRES	National Research Ethics Service
OID	Organisation Information Document
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
R&D	Research & Development
REC	Research Ethics Committee
RN	Research Nurse (Registered)
RSO	Research Support Office
SOP	Standard Operating Procedure
WHO	World Health Organisation

1 Study Overview

1.1.1 Study Overview - CCP-CANCER UK (Companion study)

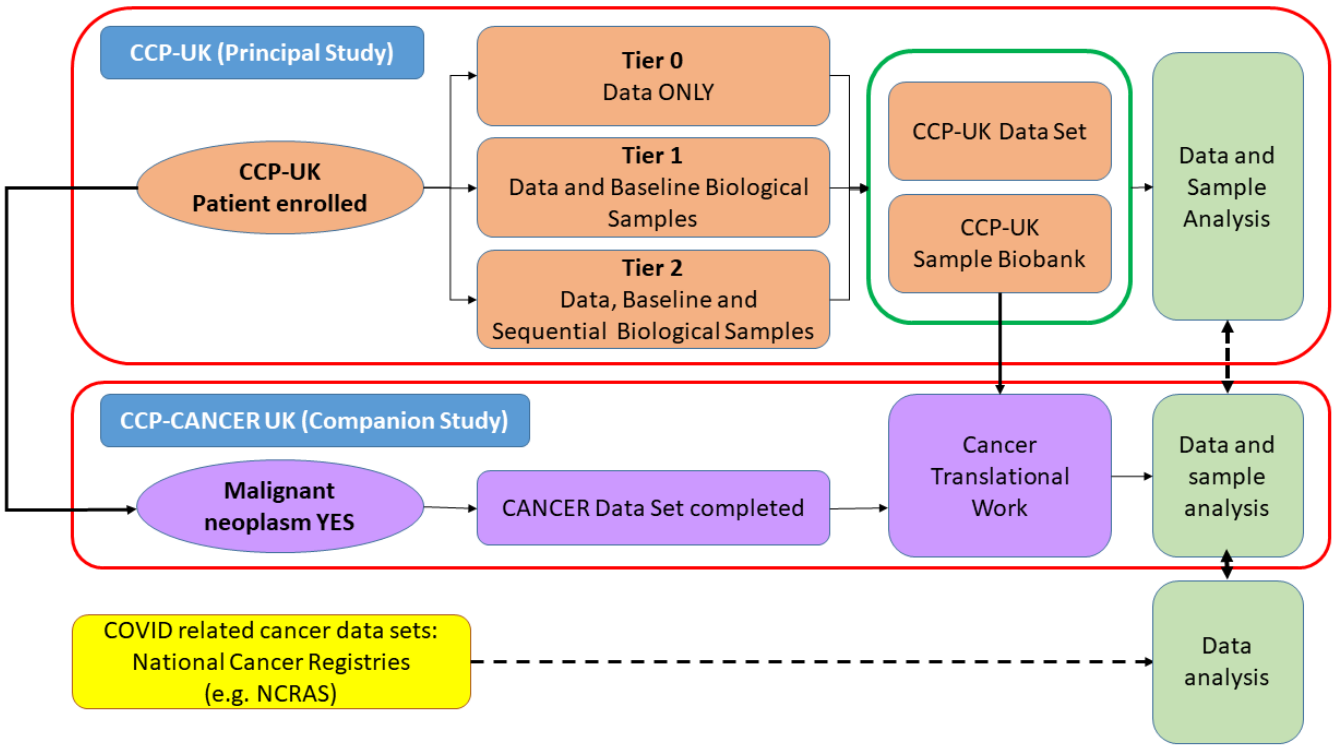
Full Title:	Clinical Characterisation Protocol for Severe Emerging Infections in the UK (CCP-UK) – A prospective companion study for patients with cancer and COVID-19.
Acronym:	CCP-CANCER UK
Phase:	Prospective observational cohort study, with routine healthcare data linkage.
Target Population:	Patients with COVID-19 who have with a diagnosis of a solid or haematological malignancy (D or C codes of ICD-10). The main population will be from patients who have been recruited to the UK Clinical Characterisation Protocol (CCP-UK) study.
Sample size:	5000 completed datasets
Inclusion Criteria:	Patients with proven COVID-19 and a diagnosis of cancer, as defined by either a past medical history recorded using the CCP-UK case report form, or who have a recorded diagnosis (C00-D49 ICD-10, or relevant equivalent i.e. ICD-9) in national cancer registries, who are enrolled into any Tier of the Principal CCP-UK protocol.
Exclusion Criteria:	None in addition to those specified in the Principal CCP-UK protocol.
Study Centres and Distribution:	Any healthcare facility in the UK who are participating in the CCP-UK study. To ascertain the number of cancer patients in the UK who have had SARS-CoV-2 infection, we will also request linked routine healthcare data for the UK, for all individuals with a cancer diagnosis, not just those in CCP-UK.
Nature and duration of patient participation:	The CCP-CANCER UK companion study involves the collection of additional data from patient case records. It does not require any additional patient visits, assessments or sample collections as these are all integral to the Principal CCP-UK protocol.
Study Duration	There will be three components of the study that run concurrently: **Additional data collection for patients in CCP-UK with cancer** The study will remain open for at least 2 years post first patient registration onto CCP-CANCER UK. All retrospective patient data collection will begin as soon as each site receives the greenlight to do so,

	and all prospectively enrolled patients (on to CCP UK) who meet inclusion criteria will have their data collected. **Co-enrolment of patients with COVID and cancer diagnosis** Patients who meet the eligibility criteria for the CCP-UK study and CCP-CANCER-UK can be co-enrolled prospectively into both studies. **Data linkage** Linkage to routine healthcare data (cancer registries, primary healthcare data, secondary healthcare data and testing data) will occur on one occasion only. Data will be retained for 15 years at the end of study.
Co-primary objectives:	To determine the mortality rate in patients with cancer and COVID-19, using data from the CCP-UK study and linked data. Identify factors associated with the poor outcomes in patients with cancer and COVID-19.
Secondary objectives:	The CCP-UK and CCP-CANCER-UK case report forms will be combined with linked data to: Describe the clinical features and severity of COVID-19 in different tumour types. Identify other clinical and laboratory variables that correlate with COVID-19 severity and mortality in different tumour types. Determine the influence of disease stage, treatment intent and treatment history on severity and COVID-19 fatality rate. Determine the potential influence of genomic variations on the severity and outcome of COVID-19 episode, where linked genomic data are available for example from ISARIC4C or GenoMICC. Describe the use of healthcare resources (including intensive care) in the treatment of COVID-19 in different tumour types. Undertake a matched cohort study using the cancer and non-cancer patients with COVID-19, using patients without cancer as controls from the CCP-UK dataset.
Exploratory/Translational objectives:	To investigate the biology of SARS-CoV-2 in the context of cancer-associated or iatrogenic immunosuppression. To investigate how COVID-19 interacts with cancer related immunosuppression.

1.1.2 Study Overview CCP-UK (Principal Study)

Full Title:	Clinical Characterisation Protocol for Severe Emerging Infections in the UK (CCP-UK)
Acronym:	CCP-UK
Sponsor and Data Controller	University of Oxford
Chief Investigator	Professor Calum Semple (University of Liverpool)
Target Population:	This study will enrol eligible patients with suspected or confirmed infection with a pathogen of public health interest (COVID-19)
Data collection:	Case Report Form Data - All patients
Sample Collection	No samples are collected or transferred for the CCP-CANCER UK Cancer UK Study. Translational data on the cancer cohort will be generated from the CCP-UK sample analysis and be used to answer translational endpoints once linked with the main study dataset.

1.1.3 Schematic of Study Design



There are no samples taken for the CCP Cancer UK study. There is only data collection.

2. Roles and Responsibilities

The Sponsor is Clatterbridge Cancer Centre NHS Foundation Trust is legally responsible for the study. The Sponsor will formally delegate specific Sponsoring roles to the Chief Investigator and Clinical Trials Centre.

The Data Controller(s) determines the purpose and means of the processing of personal data and is responsible for implementing appropriate technical and organisational measures to ensure processing is in compliance with the General Data Protection Regulation. Data controllers for the CCP Cancer UK Study are the University of Liverpool, Clatterbridge Cancer Centre and The University of Edinburgh.

Data Processor(s): The processor or data processor is a person or organization who deals with personal data as instructed by a controller for specific purposes and services offered to the controller that involve personal data processing. The Processer(s) are: Public Health Scotland.

Chief Investigator: Professor Carlo Palmieri and Dr Lance Turtle are the Chief Investigators (CI) for the trial and is responsible for overall design and conduct of the trial in collaboration with other members of the study team.

Co-Investigators: All Co-Investigators are listed in the table on page 5. They will work with the CI to design, write and deliver the research study.

Principal Investigator: In each participating centre a principal investigator (PI) will be identified for the CCP-CANCER UK study. He/she will be responsible for patient identification, recruitment, data collection and completion of Case Report Forms (CRFs), and adherence to the protocol.

Clinical Trials Unit: The Liverpool Clinical Trials Centre (LCTC) in collaboration with the CI will be responsible for all trial management activities including (but not limited to) study planning, budget administration, Trial Master File management, data management, randomisation, statistical analysis and participating site coordination.

Study Management Group (SMG): The CCP-CANCER UK SMG will convene at least monthly during the data collection and data analysis phases of the study. The group will include all co-investigators and representation from the Principal CCP-UK study group, the LCTC and the Sponsor (Clatterbridge Cancer Centre). The SMG will be accountable to the Sponsor. There is no Trial Steering Committee (TSC), nor Independent Safety Data Monitoring Committee (ISDMC), as there is no intervention and the study is only collecting data. The SMG is the overarching oversight body on CCP Cancer UK.

There are no safety data recorded or reported on the CCP CANCER UK study as there are no samples, assessments or interventions with study participants.

2.1. Organisational Relationships of CCP-CANCER UK

This CCP-CANCER UK study was conceived in the University of Liverpool, and developed with collaboration and intellectual input from investigators in University of Liverpool (UoL), University of Edinburgh (UoE), Imperial College London (ICL) and the University of Oxford (UoO), as well as representatives for patient and public involvement (PPI). The funding application was led from UoL and the study will be facilitated through the Liverpool Clinical Trials Centre (LCTC) within UoL. The study is based upon the CCP UK study which is sponsored by The University of Oxford and led from UoL (the CI is based at UoL). The University of Oxford hosts the REDCap database for the parent CCP UK study for which they are also the data controller.

Clatterbridge Cancer Centre NHS Foundation Trust (CCC) agreed to act as sponsor for CCP-CANCER UK because of their special interest in cancer research and how COVID-19 impacts their patients with cancer. In addition, several investigators hold substantive or honorary contracts with CCC. Data controllership for the study rests jointly with UoL, UoE and CCC. The organisations are considered CONTROLLERS under GDPR for the following reasons:

1. CCC as they will act as sponsor and will carry overall responsibility for the initiation, management and financing (or arranging the financing) of the research.
2. UoL as they conceived the project and decided the need to collect and process data alongside having overall responsible for the day to day running of the study and the data collection
3. UoE as they will have significant input into the identifying the research question, determining the dataset and developing and delivering the Statistical Analysis Plan. They will also determine on which patient's data will be collected from and make decisions on how data from the study will be processed and analysed in the National Safe Haven.

The 3 parties will enter in a tripartite joint data controller agreement with regard to the CCP-CANCER UK study.

The NHS Scotland National Safe Haven Hub located in Edinburgh will house the data but have no part in determining the analysis plan (data processor). For CCP-CANCER UK, Oxford will share NHS numbers with the tripartite (securely transmitted to UoE). This will be done via a CONTROLLER to CONTROLLER agreement.

Public Health Scotland (PHS) hosts, and has governance responsibility for the NHS Scotland National Safe Haven, a trusted research environment which is not connected to the internet in which personally identifiable data can be linked and processed. For the purposes of this protocol, an agreement will exist between the tripartite and PHS covering use of the National Safe Haven.

Once the data are analysed, manuscripts will be drafted and circulated among all the institutions and investigators that have been involved. This will follow the same principles as have applied to the parent ISARIC4C CCP UK study.

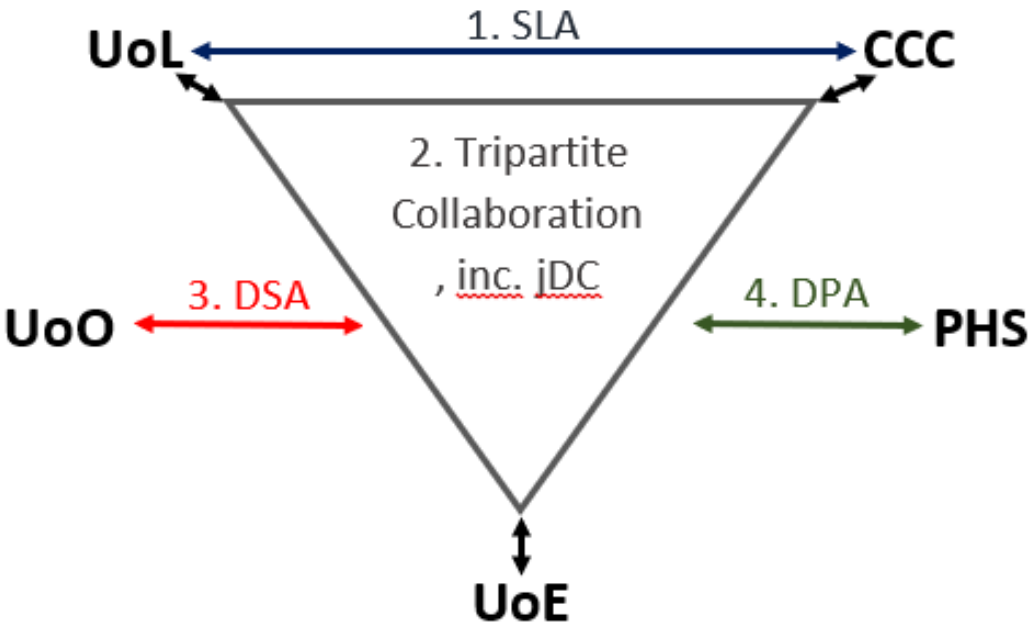
These relationships are summarised in the table and figures on the following page.

On behalf of the Data Controllers, named statistician(s) from LCTC will be granted access to the NHS Wales National Safe Haven, known as the Secure Anonymised Information Linkage (SAIL) Databank. Access is granted via an affiliation to the 'One-Wales' COVID project within SAIL, also known as 'Con-Cov' (SAIL reference 0911 – WMC_), therefore an agreement with NHS Wales is not required. Analysis of data for Welsh patients is described in the relevant statistical analysis plan.

Brief summary of agreements relating to the CCP cancer UK study

	Agreement	Parties	Brief summary of content
1.	Service Level Agreement	CCC and UoL	Delegates' responsibilities for day to day running of the study from CCC (Sponsor) to UoL (LCTC).
2.	Collaboration agreement	UoE, UoL and CCC	Defines academic ownership, publication policy, and finance for employment of data analyst in Edinburgh. Incorporates agreement of joint Data Controllership.
3.	Data Sharing Agreement	CCC, UoL and UoE, UoO	Defines the relationship between the three organisations ("The Tripartite"), roles & responsibilities with respect to data and data controllership. Includes the relationship between The Tripartite and University of Oxford (UoO) with respect to UoO providing data from the CCP-UK study. This will form a schedule to the contract described in point 3 below.
4.	Data processing agreement	UoE, CCC, UoL and PHS	Covers the hosting of data within the Scottish National Safe Haven. UoE to take on responsibility for liability for this relationship, as outlined in the Tripartite JDC.

Figure 1: Organisational relationships of agreements



3. Introduction

3.1. Background

In December 2019 the first pneumonia cases of unknown origin were identified in Wuhan, the capital city of Hubei province. High-throughput sequencing revealed the pathogen to be a novel enveloped RNA beta coronavirus. Initially named 2019 novel coronavirus (2019-nCoV) it was subsequently renamed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (2). Transmission of SARS-CoV-2 is via respiratory droplets and direct contact, and infection results in coronavirus disease (COVID-19). The World Health Organization (WHO) has recently declared the SARS-CoV-2 outbreak a public health emergency of international concern on 30th January 2020, and a global pandemic on 11th March 2020.

The clinical characteristics of COVID-19 are typically fever, dry cough and fatigue, sometimes accompanied by sore throat, chest discomfort and difficulty breathing. However, a wide range of other symptoms are possible, including gastrointestinal symptoms such as nausea, vomiting, loss of appetite, abdominal pain and diarrhoea. Loss of taste and smell have also been described.

Individuals with malignant disease are more prone to respiratory viruses than individuals without cancer as a result of immunosuppression caused by either the underlying disease process or systemic anti-cancer therapy. The death rate from influenza in patients with solid organ tumours is much higher than expected for the background population, even allowing for likely ascertainment bias. This is reflected in individuals with cancer being recommended to receive the seasonal flu vaccination. Certain groups of cancer patients are even more prone to infection. For example, patients with haematological malignancy undergoing bone marrow transplantation have significant mortality even with rhinovirus, which can double the transplant related mortality.

There is currently no prospective robust data regarding the presentation, management and outcome of patients with COVID-19 with cancer who are immunocompromised as result of either the disease or treatment. Furthermore, it is not clear if the immunosuppressive effects of systemic anti-cancer therapy such as chemotherapy are the same across all cancer types and the possible risks entailed by targeted therapies and immunotherapy. Currently, cancer patients on treatment are considered at high risk group of possible severe infection with SARS-CoV-2 and measures such as self-isolation are being recommended to mitigate the risks of such patients being infected. However, information to inform this decision, and whether any specific sub-groups of patients are at particular risk is lacking. These data are vital to inform policy on cancer treatments as patients may be potentially exposed to SARS-CoV-2 for a long time to come. Furthermore, given patients with cancer are often immunosuppressed and this may alter the clinical presentation as well as clinical course and outcomes. Different tumour types may also have implications for SARS-CoV-2 exposure, for example patients with lung cancer may be more susceptible, and require different pathways to ensure care can be delivered safely. This protocol aims to describe the presentation, management and outcomes of patients with solid and haematological malignancies with COVID-19 and compared to non-cancer patients. The CCP-CANCER UK will provide valuable information that would educate as well as help inform current practice and development of guidelines globally with regard to COVID19 infection in cancer patients. While samples collected within CCP-UK from cancer patients will enable an understanding of the biology of COVID-19 in the setting of cancer-related immunodeficiency both innate and iatrogenic.

3.2. Rationale

Currently, there is extremely limited information regarding the risks posed by SARS-CoV-2 to patients with cancer. This study aims to understand the presentation, management and outcomes of patients with cancer. The influence of cancer type and treatment will be explored as well, and the existence of a large dataset of COVID patients including both cancer patients and patients without cancer, allows a comparison between these two groups which can be

adjusted for other confounding variables such as age and co-morbidity. This dataset, on robust analysis, will provide valuable information that would educate as well as help inform practice for future possible outbreaks. The information may also inform the development of guidelines with regard to the care and management of cancer patients with viruses such as COVID19 and similar infectious diseases. Cancer is immunosuppressive, the nature of the immunosuppression seems to be influenced by the microbiota, and in addition pulmonary infections are also influenced by the host microbiota, therefore it is important to understand this impact in cancer patients.

The complexity and rapidly evolving nature of cancer therapies and in particular, molecularly targeted agents also may predispose patients to COVID-19. We propose to, where available in future, also take sequencing/genomic data through data linkages for patients recruited into CCP-CANCER UK will be used to outcomes to explore genetic susceptibility to COVID-19, the effects of molecularly targeted agents as well as predictors of severity and death from COVID-19.

Serial faecal samples and throat swabs are being collected from patients as part of the CCP-UK, and the ISARIC - Coronavirus Clinical Characterisation Consortium (ISARIC4C) is already carrying out extensive metagenomics sequencing including 16/18S sequencing and Illumina RNAseq. These data provides crucial detail on co-infection and also would allow an overview of microbiome diversity in patients with COVID-19 and how it changes during disease progression and treatment. This could be used as background to a more targeted and deeper analysis of the cancer patients in the cohort. Outcomes for patients with respiratory tract infections [1, 2] and various forms of cancer [3-6] have been shown to be influenced by respiratory and gastrointestinal microbiome diversity. Analysis of the microbiome can also help in directing therapy [7, 8], in particular the use of immunotherapy [9].

3.3. Objectives

The overall objective of the CCP-CANCER UK is to provide information that would educate as well as help inform current practice and development of guidelines globally with regard to COVID-19 infection in cancer patients, in both haematological and solid malignancies (ICD-10 C00x to D49x, all morphologies). We will use data linkages to supplement the CCP-CANCER UK dataset and details of data linkages can be found in the sections below.

Co-primary Objectives*

The co-primary objectives are:

- To determine the COVID-19 fatality rate overall in the cancer population using the most up to date dataset from the first wave
- To identify factors associated with poor outcomes from COVID-19 in patients with cancer.

Secondary Objective(s)*

The secondary objectives are:

- To describe the clinical features and severity of COVID-19 in different tumour types.
- To identify other clinical and laboratory variables that correlate with COVID-19 severity and mortality in different tumour types.
- To determine the influence of disease stage, treatment intent and treatment history on severity and COVID-19 fatality rate.
- To describe the use of healthcare resources (including intensive care) in the treatment of COVID-19 in different tumour types.
- To undertake a matched cohort study using the cancer and non-cancer patients with COVID-19.

Exploratory Objective(s):

The exploratory objectives* are:

- To investigate the biology of SARS-CoV-2 in the context of cancer-associated immunosuppression. (Iatrogenic or disease related).

- To investigate how COVID-19 interacts with cancer-related immunosuppression.

*All objectives within the cancer population will be compared to those same objectives within the non-cancer population as well as populations with co-morbid conditions as collected within the CCP-UK protocol.

4. Study Design and Setting

This is a prospective observational cohort study specifically for cancer patients which will be recruited alongside the Principal ISARIC CCP-UK protocol in the UK. It will therefore be run at multiple sites across the UK. It is appreciated that clinical infrastructure, resources and capacity will vary from site to site. ONLY those centres recruiting to the principal CCP-UK protocol *or* those cancer centres/units where patients on ISARIC CCP-UK received their cancer care will be permitted to open the CCP-CANCER UK companion study.

All centres opening for the CCP-CANCER UK study will have a named Principal Investigators to oversee the collection of cancer-specific data via the CCP-CANCER UK companion study.

The CCP-CANCER UK companion study has been reviewed and approved by the Independent Data and Materials Access Committee (IDAMAC) committee composed of representatives of research funders, academia, clinical medicine, public health and industry on behalf of the ISARIC consortium. The Principal study sponsor and data controller has agreed the fundamentals of data sharing to facilitate the companion study subject to executing a formal data sharing agreement prior to release of any data.

Each site opening to the CCP-CANCER UK study will be provided with the following documents prior to opening:

- CCP-CANCER UK Protocol;
- Organisation Information Document;
- Validated SoECAT form;
- Copies of all the related approvals;
- Paper copy of the electronic Case Report Form (eCRF) pages.

Sites will be asked to provide written confirmation of capacity and capability prior to collecting any data for patients.

The study will be registered as Urgent Public Health Research with the NIHR to allow access to NIHR research network resource.

5. Eligibility Criteria

The CCP-CANCER UK study aims to recruit all patients infected with SARS-CoV-2 and enrolled onto the Principal CCP-UK protocol and identified as having a neoplasm (Malignant, in situ, or benign haematological cancer or solid tumour). Recruitment will continue for up to 2 years.

The eligibility criteria are described below.

5.1. Inclusion Criteria

Patients with proven COVID-19 and a diagnosis of cancer who are enrolled into any Tier of the Principal CCP-UK protocol. Patients will be identified using two routes:

- Directly through the ISARIC CCP-UK CRF (either retrospectively or co-enrolled into the ISARIC CCP-UK and CCP-CANCER UK studies), using those marked as having cancer on their past medical history, those actively on therapy for cancer or those with cancer listed in free-text comorbidities.
- Identified through linkage to cancer registries
  Local investigators will not have to identify patients themselves, rather the identified patients will be automatically populated on the Liverpool REDCap system.

5.2. Exclusion Criteria

None.

5.3. Co-enrolment Guidelines

All patients MUST be recruited in the Principal CCP-UK protocol. There are no further restrictions in relation this data collection with regard to recruitment into any clinical trials or research studies.

6. Participant Identification, Assessments and Data Collection

6.1. Participant Identification and Screening

Where possible, a cancer co-investigator will be identified at each site prior to starting data collection for CCP-CANCER UK. They will be responsible for identifying a team to:

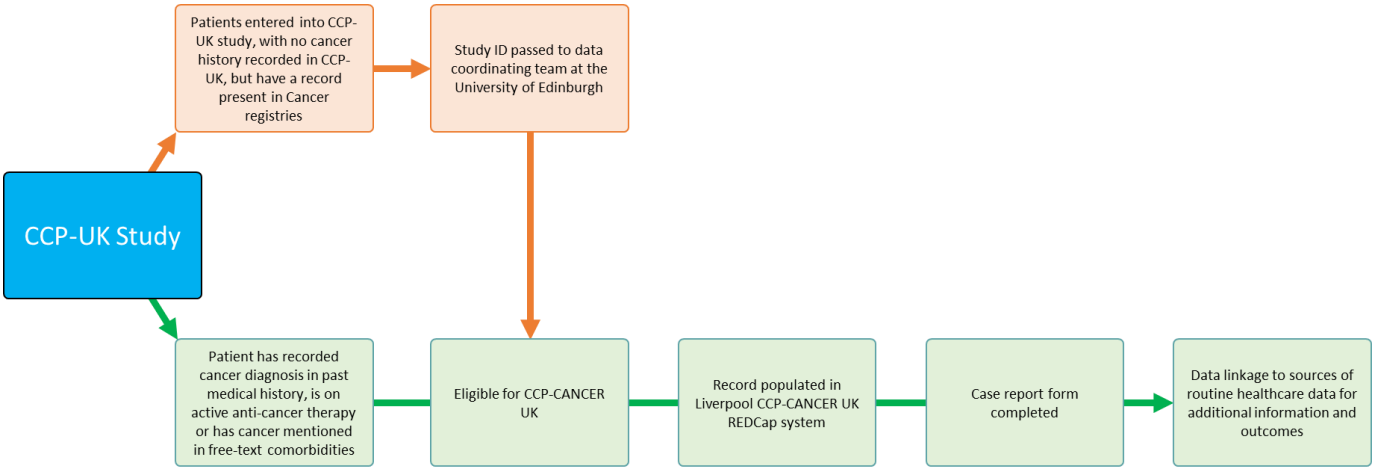
- Facilitate the completion of the CCP-CANCER UK REDCap Database (see section 9.3).
- Establish mechanisms to proactively identify patient admissions with SARS-CoV-2 infection and a current cancer diagnosis to allow prospective co-enrolment.

IDENTIFICATION of patients from the Principal CPP-UK study:

The Principal CCP-UK study team will alert the CCP-CANCER UK team, through an automated reporting system, within LCTC when a patient has been recruited and has been identified as also having a neoplasm. The CCP-UK team will securely prepopulate a database with patient National Health Service Number, Community Health Index (CHI) Number (Scotland), Northern Ireland Health and Care (H&C) Number or other identifier and the CCP-UK ID number to allow identification of the patients by the cancer staff at site. This will be in line with the current Control of Patient Information (COPI) notice and/or relevant national approval processes – See section 6.2 for further information.

The cancer team within LCTC will then notify the cancer contact(s) at the respective research sites to request the completion of the cancer dataset.

Figure 2: Patient Identification data flow



IDENTIFICATION of patients locally:

Sites may also establish local mechanisms to identify patients who have been admitted with SARS-CoV-2 infection with a current cancer diagnosis. Any patients identified locally need to be enrolled in the Principal CCP-UK Study and then the cancer data set should be completed.

It is recognised that local arrangements for both ISARIC CCP-UK and CCP-CANCER UK will vary. Where the principal CCP-UK study is open at a different centre to the CCP-CANCER UK study cross centre collaboration should be used to get both datasets completed. If the inclusion criteria of enrolment into any Tier of the Principal CCP-UK protocol cannot be met the patient should not be included on the CCP-CANCER-UK study

No screening data will be collected as part of the study.

6.2. Informed Consent

The CCP-CANCER UK study involves the collection of an additional Cancer Data Set ONLY. This is a limited clinical data set collected from routine health records. This study is observational and does not involve any deviation from the participant's standard care or conduct on the main CCP UK study. The consent process for the CCP-CANCER UK study will be aligned with the Principal CCP-UK protocol. This was a tiered approach, whereby patients could have clinical data collected only (tier 0), a single set of biological samples (tier 1) or longitudinal samples (tier 2). Consent was not sought for tier 0 data collection (see below).

Consent is not being sought from CCP-CANCER UK participants.

Under the General Data Protection Regulation (GDPR) and Data Protection Act 2018 (DPA2018), consent is not being used as the legal basis for data processing.

Under the common law duty of confidentiality, consent would normally be required for disclosure of confidential information outside of the usual treating team, however the following is in place meaning consent is not required from CCP-CANCER UK participants:

England & Wales:

- COPI Notice (Regulation 3(4)): an existing COPI Notice (Regulation 3(4)) has been served by the UK's Chief Medical Officer (CMO). At the time of writing this protocol, this COPI Notice is due to expire on 31st March 2021, however it may be renewed. This was the legal basis for data collection for the parent ISARIC CCP UK study.
- Section 251 (s251) approval: s251 approval will be sought by the CCP-CANCER UK study to replace the COPI Notice in advance of the COPI Notice expiration.

Scotland and Northern Ireland:

- Agreement will be obtained via applicable application routes (e.g. Public Benefit and Privacy Panel (PBPP) in Scotland) prior to any disclosure of confidential information for participants in Scotland or Northern Ireland.

No additional samples will be collected as part of the CCP-CANCER UK study. Translational samples provided as part of the CCP-UK (Tiers 1 and 2 only) study will be accessed by the CCP-CANCER UK study team. Consent for these samples collection and the translational work is covered in the consent process for the Principal CCP-UK study.

Please see section 4.2 Characterisation Protocol for Severe Emerging Infections in the UK (CCP-UK).

Dissent and Withdrawal

Inclusion on the main CCP-UK study is a prerequisite for enrolment on to the companion CCP-CANCER UK study. Should a patient wish for their involvement in the study to end, it will be communicated to the CCP-CANCER UK Study Management group so that their data is no longer used, or linked from the main study.

There will be a privacy notice for the CCP Cancer UK study published on the University of Liverpool and on the LCTC websites, should patients become aware of their involvement in this study and wish for their data and samples to be removed.

6.3. Cancer Data Set

CCP-CANCER UK dataset is a single Case Report Form completed post enrolment into Principal CCP-UK protocol. This dataset will take approximately 40mins to complete per patient. Please see section 6.4 for details of Data Collection method.

6.4. Data Collection Methods

6.4.1. Active data collection by NHS providers

The CCP-CANCER UK dataset will be held on a separate REDCap database (hosted by LCTC) to the Principal CCP-UK data.

Data will be collected at sites (which are all NHS facilities caring for patients) and stored online through a secure server located in the University of Liverpool running the Research Electronic Data Capture (REDCap) web application. REDCap allows collaborators to enter and store data in a secure, encrypted system. Designated collaborators at each participating site will be provided with REDCap project server login details, allowing them to securely submit data on to the REDCap system. Data are to be entered into the RECAP system directly by members of the research team at site. Training will be provided prior to any data entry via a short training module.

REDCAP cases will be created centrally at the LCTC using an automated system to receive NHS Numbers and CCP study ID numbers and allocate to a REDCap record, with the same record number that the patient has on the main study provided by the University of Edinburgh as outlined in section 6.1 This way there is no manual handling of these identifiers thus reducing the margin for error. REDCap records for CCP Cancer UK data entry should be ready within 24 hours of a REDCap record being completed for enrolment to the main study. There are no assessments, or interventions for the CCP CANCER study from which data are collected, data on this study are taken direct from the patient medical history. Site staff will be notified by email that entries exist on the REDCap database for them to complete. They will then log on, access the REDCap record, and identify the patient in order to enter data from local records (the NHS Number and ISARIC ID are stored on the database). In this way, the transfer of data pertaining to each patient is minimised, and the data are accessed only through the password protected REDCap database, which is stored securely.

Quality checks will be built into the data management system and there will be quality control checks of critical data points entered into the CRFs to ensure standardization and validity of the data collected. The UK GDPR and DPA2018 regulations will be adhered to. Patients' identities will be protected and their information held securely.

User names and passwords for the cancer data set will be assigned during the set-up of each centre onto the CCP-CANCER UK protocol.

Each site will maintain an investigator site file for this CCP-CANCER UK study including a protocol, any approval documentation, and a reference copy of the paper eCRF workbook. A participant list will be used in each study site to match identifier codes in the database to individual patients in order to record clinical outcomes and supply any missing data points. Each site’s Participant List is maintained locally and is not to be transferred to any other location. The enrolment log and study data will be kept separately.

6.4.2 Case validation and use of data linkage

In the UK, collection of NHS cancer data is managed individually by each of the nations. In England, the National Cancer Registration and Analysis Service; in Scotland, data is collected by the Public Health Scotland Information Service Division (PHSISD), the Welsh Cancer Intelligence and Surveillance Unit (WCISU) manages collection across Wales and in Northern Ireland, it is the responsibility of the Northern Irish Cancer Registry (NICR). Each registry operates a multi-source, event-based model to support complete case ascertainment of all patients suspected of or diagnosed with neoplasia (C00-D49). Data curated by the registries includes information about the patient (their NHS number (or other persistent identifier from the health record), name, address and date of birth), as well as detailed tumour level information from pathology reports and MDTs, and treatment information along their care pathway that includes administrative datasets such as cancer waiting times, PEDW or HES. This multi-source approach to data collection and data linkage also allows for:

(1) Complete case ascertainment of registerable events
(2) The entire process of a patient's diagnosis(es) of and treatment(s) for cancer

Consequently, the cancer registries provide a rich resource of patient, tumour and pathway data that will enhance the CRF data collection of the study in the following ways:

- Improve ascertainment of tumours across the cohort, through obtaining identifying diagnostic and treatment providers that can then be approached to complete the CRF
- Reduce the burden on NHS providers to report real time events in participants in CCP_UK
- Describe in detail, the clinical histories of cancer patients and the cumulative effect of their disease burden and treatment exposure
- Enrich data collection on chemotherapy-related toxicities (CRTs) are a complication of treatment in all cancer. In particularly, enabling the study to passively identify cytotoxic agents, immunotherapy, monoclonal antibodies, checkpoint inhibitors, cytokines, vaccines to treat cancer and adoptive cell transfer to develop drug and indication-specific measures of significant toxicity or immune-compromise based on time from event modelling.
- To identify cancer patient who may not have been picked up at time of presentation with COVID-19 by the main CCP UK study dataset.

This, in turn, will allow the study to:

- Inform national and international policy regarding cancer patient care in the era of COVID
- Enable clinicians to have informed discussions on the risk/benefit of various treatment in the era of COVID
- For patient to make informed decisions regarding their cancer care during the Sars-COV-2 pandemic

Data will be requested from each registry on:

- All registerable tumours (all primary diagnosis of a C00-D49x neoplasm, including both solid and haematological malignancy) known to the registry.
- The following prognostic factors which pertain to cancer outcomes as published in the literature, directly related to the tumour itself (site, morphology, extent of progression and other pathological factors, such as mutations to known tumour suppressor genes); these will be requested for analysis along with patient-specific cancer prognostic indicators such as stage at diagnosis to identify patients with a poor prognosis, such as those at most at risk for recurrence following treatment with curative intent.
- Using clinically relevant combinations of patient, tumour and treatment characteristics, specific sub-cohorts will be defined.

The temporal parameters of each registry will be requested from registry inception to present day however the study aims to have a comprehensive understanding of the diagnosis of all primary malignancies in the cohort and accepts

that over time, the quality and quantity of data recorded at a patient, tumour or treatment level may have changes to reflect clinical care and system need.

Retrospective data going back to the creation of the cancer registries will be obtained in order to distinguish between active and previous cancer diagnoses, as this is not captured in the ISARIC CCP-UK study. It is therefore important to understand which patients had cancer at any point in their lives, as patients who had cancer several years ago may not be at increased risk of mortality and may not need to shield. The risk associated with cancer may be from a more recent diagnosis, and we need to determine at what point in time from diagnosis that risk arises, so we can accurately inform patients and policy makers about what they need to do.

The national registries continue to seek ways to enrich their data collections. Where available, data will be sought from the registries to include specific molecular characteristics as covariates (for example, but not limited to overexpression of HER2, EGFR, ALK and K-RAS, which are accepted to modify the response of specific targeted therapies) and may have a role in the response to COVID.

6.4.3 Linkage process

The following linkages will be utilised, where indicated, this will be facilitated through existing study linkages for the CCP-UK study, in order to minimise the number of datasets required and prevent duplicate data being generated.

For each data source, the identifier numbers (i.e. NHS number or CHI number) for the whole ISARIC CCP-UK dataset will be provided to each body responsible for linkage. Additional direct identifiers may be warranted by data controllers to improve match rates. This will be agreed with each and always utilise the minimum data necessary.

England:

- National Cancer Registration and Analysis Service (NCRAS) data, through NHS Digital and subsequent bodies responsible for NCRAS. (through ISARIC CCP-UK linkage.)
- Hospital Episode Statistics (HES, NHS Digital, through the ISARIC CCP-UK linkage)
- General Practice Extraction Service (GPES, NHS Digital, through the ISARIC CCP-UK linkage)
- Office for National Statistics Registrations Data (Office for National Statistics, through the ISARIC CCP-UK linkage)
- SARS-CoV-2 testing data

Scotland:

- SMR06, Cancer Registrations (Public Health Scotland)
- SARS-CoV-2 testing data

Wales:

- Welsh cancer registry WCISU
- Patient Episode Database for Wales (Patient Episode Database Wales (PEDW), through ISARIC CCP-UK linkage)
- SARS-CoV-2 testing data
- Secure Anonymised Information Linkage (SAIL) Databank*
  *SAIL does not export data. Data collected by CCP-UK for Welsh patients will be exported to SAIL and analysed for the purposes of CCP-Cancer UK within the parameters of the databank.

Northern Ireland:

There are legislative challenges for linkage with routinely collected data in Northern Ireland. Although there are plans to develop solutions for this the project will not be able to access data for secondary uses at the start of the project. This will be monitored and if the data can be made available through ISARIC CCP-UK linkage then CCP-CANCER UK will be included for re-use of NI data.

In the ISARIC CCP-UK dataset, past medical history of cancer is missing in some patients and in other patients may be incorrectly recorded. To address this, we will use very limited data from the registries in order to collect data in the CCP-CANCER UK project that may have been missed otherwise. To facilitate this, there will be two linkage pathways with each data linkage provider. The first pathway (indicated in purple in the data flow diagram) is for patients who have been identified as having cancer in the ISARIC CCP-UK study. The University of Edinburgh will securely provide identifier data (i.e. NHS/ CHI) alongside the ISARIC CCP-UK subject ID (study number) to the linkage provider, either using a data transfer system, API or secure NHS/Government email. The data linkage provider will perform linkage as per the linkage specification (i.e. using deterministic matching), add the CCP-UK subject ID to each returned dataset and remove any identifiers. The linked clinical datasets containing the CCP-UK subject IDs will then be securely sent to the Scottish National Safe Haven (hosted by Public Health Scotland), where the CCP-UK subject ID's will be obfuscated, so data can still be linked, but those with access to the CCP-UK dataset cannot reverse identify individuals within the study. This will be done for all patients in CCP-UK.

This current data flow will be performed using the COPI notice as a legal instrument to do so. In the case this is revoked in future, we will implement an encryption step to transfer of identifiable information, where the identifiers will be encrypted using prespecified algorithm and shared cryptographic salt, which is used to encrypt the identifiers. These encrypted identifiers, along with their corresponding CCP-UK study IDs (study number) will then be transferred to the data linkage provider, who will perform the same process with the same algorithm and salt to generate a list of encrypted identifiers from the data they hold in their databases. Deterministic matching will then be used to match up encrypted IDs, the encrypted ID then will be removed leaving the clinical dataset and the corresponding ISARIC CCP-UK study identifier. Alternatively, where data will need to be reidentified for linkages (some linkage systems may not be able to one-way hash all the identifiers within a database due to size of data), data can be encrypted with a public key and a private key shared with or generated by the data linkage provider to allow decryption.

Data from sources of other non-cancer routine healthcare data (for example, SMR01, HES, GPES) are linked through separate requests for the entire ISARIC CCP-UK project. Amendments will be made to the applications for these data to allow for these linkages to be used in the CCP-CANCER UK study. No additional linkages will be performed for these data, but all data linkages will use the same ISARIC CCP-UK study identifiers, so all data can be linked up. We will use these sources of data, which include primary, secondary and civil registration data to determine prior comorbidities to account for patient level risk factors not captured by the ISARIC CCP-UK or CCP-CANCER UK studies. Similarly, these data will provide a means of collecting longer term outcome data such as mortality after discharge, readmission or the development of other conditions.

Once data from the CCP-CANCER UK, ISARIC CCP-UK and linked datasets are received into the Scottish National Safe Haven, they will be further processed by research coordinators to produce linked, anonymised datasets.

6.4.4 Data linkage to determine population level risks in UK cancer patients

In addition to taking data from the ISARIC CCP-UK study, which provides a focussed look at in-hospital treatment of patients with COVID-19, to be able to generalise our findings to a national population, we will need to establish how many cancer patients develop COVID-19 and their subsequent treatments and outcomes. To do this, we will use linked data that are not restricted to the ISARIC CCP-UK study and instead take all individuals with cancer registration data available and link these to SARS-CoV-2 testing data, primary care data, secondary care data and national statistics registrations.

Data will be requested according to the same specification provided to cancer registry linkage providers and will request additional data points held in testing data, primary care data, secondary care data and national statistics registrations. Data flow will be from the providers directly into the Scottish National Safe Haven, as no patient identifier lists will be required.

These data will allow us to determine which populations are at the highest risk of COVID-19, both in hospital and in the community and establish a baseline rate in these settings. This will allow us to establish whether there are

particular patient groups who are more likely to be admitted to hospital or who will go on to die while in hospital, compared to patients who do not die or who remain in the community with positive tests. We request data for all patients, both for those with negative and positive SARS-CoV-2 tests or diagnoses. These data will also enable us to determine whether changes in practice have led to improved or worsened cancer outcomes over the time of the SARS-CoV-2 pandemic.

The data will not contain any identifiers and will not be able to be linked with the ISARIC CCP-UK or CCP-CANCER UK datasets.

For data linkage, we will capture variables including lower super output area. This will be used to map individual region rates of SARS-CoV-2 and determine other geographical variables including deprivation, distance to healthcare facilities and other socioeconomic deprivation markers linked with geography. We will not capture information on hospital of treatment in the linkage requests, as this will provide too logistically challenging to match back to hospital for recruitment purposes.

6.4.5 Data minimisation

We will actively collect data from the eCRF, both retrospectively on patients who have been recruited to the CCP-UK study and prospectively for patients who will be co-enrolled into both ISARIC CCP-UK and CCP-CANCER-UK. The eCRF will obtain clinically specific treatment and stage data that are not available from sources of routine healthcare linkage. Details on existing comorbidities, tumour stage, treatments and clinical outcomes will be collected using linkages to sources of routine healthcare data. Data from these linkages will also give us data not available from the eCRF and allow efficient follow-up. There may be potential overlap between the two data sources. This is justified on the basis of ensuring the most complete coverage possible, in the fastest possible time, as linked data has a delay associated with it. Whilst it would be possible to collect these data in series instead of in parallel, this would take considerably longer, and would give rise to an unacceptable delay in providing our outputs for the benefit of patients, the public, policy makers and clinicians.

6.5. Data Management

For the CCP-CANCER UK study the responsibilities for Data Management and monitoring are delegated to the LCTC. A separate Data Management Plan (DMP) will be developed which provides details regarding the internal processes that will be conducted at the CTU throughout the study for data cleaning and monitoring data completion. All data will be managed as per local CTU processes and in line with all relevant regulatory, ethical and legal obligations. No formal study monitoring will be implemented for this study due to the nature of the study, i.e. prospective observational cohort.

The ISARIC CCP-UK data is held in a secure REDCap database at the University of Oxford (data controller for ISARIC CCP-UK data and ISARIC CCP Global data). All data from ISARIC CCP-UK will be securely transferred to the University of Edinburgh (data processor), where the data will be cleaned and NHS/CHI numbers validated using the modulus 11 algorithm. Patients with a cancer diagnosis in the ISARIC CCP-UK dataset, either recorded as a past medical condition or as being on active therapy, will be selected out of the main dataset. This subset will then have all data removed, except for NHS/CHI number, the ISARIC CCP-UK subject identifier number (study number), age and sex. These identifiers will then be securely transferred into the University of Liverpool CCP-CANCER UK study, on a site-specific basis, to allow investigators at each site to complete the data fields for each identified patient. Each site will only be able to see their own data. The University of Edinburgh will integrate data provided by cancer registries, as outlined in the above section, into the data that is uploaded into the Liverpool CCP-CANCER UK REDCap database.

Identifiers in the CCP-CANCER UK REDCap database, will be removed from any data download, leaving only the ISARIC CCP study identifier, which is shared between the ISARIC CCP-UK and CCP-CANCER UK studies. Identifiable data in the CCP-CANCER UK study is only for local investigators to aide recruitment. Once completed, the study data will be checked for accuracy and completeness by the coinvestigators and study management group, then sent securely to

the Scottish National Safe Haven. This will be performed every 3 months, to update the analysis which will be conducted in the Scottish National Safe Haven.

The patient health record will be considered the source document for the study data. No physical study data will exist for any participant – all data will be added to the eCRF directly from the source data for each patient. Data will be stored on the LCTC REDCAP server, data queries will be used to clean the dataset, the data entry/editing for this done by the teams at each site per the CCP Cancer UK study Data Management and Data Query plans.

Data will be transferred to the NHS Scotland National Safe Haven, which is an approved trusted research environment. Data analysts will then access the data through this platform. On this platform, the principal ISARIC CCP-UK study dataset and relevant linked datasets are also held. The National Safe Haven is a secure, firewalled platform that does not have access to the internet. It allows for the secure storage of datasets and analysis within a trusted environment. Access to the National Safe Haven is securely controlled and multifactor authentication steps are in place.

6.6. Data protection and Confidentiality

Data collection at sites for this study will be conducted by clinical staff and those involved in the study will ensure that each study participant's privacy and confidentiality is maintained. Participants will not be identified in any published reports of this study. All records will be kept confidential to the extent provided by international and local law. No information concerning the study, or the data will be released to any unauthorized third party.

Data from the CCP-UK study will be processed by the University of Edinburgh. For the purposes of study administration, this permission will be delegated to the University of Edinburgh by delegation from the University of Oxford (ISARIC CCP-UK study data controller). These data, as outlined above, will be processed to allow local investigators to complete additional data fields required by the CCP-CANCER UK study. The data controller for the CCP-CANCER UK study is the University of Liverpool.

For the CCP-CANCER UK study, minimal personal data will be entered into the database for analysis. The patient's identifying personal information (NHS/CHI/HSC number and dates of birth, as well as the ISARIC ID from the main study) will be logged and stored securely. These fields will be marked as identifiers and will not be able to be accessed or downloaded, except by local investigators or individuals with direct purpose for administration of the study. Individuals who are processing this data on behalf of the study will be mandated to complete a minimum level of information governance training, in line with the updated requirements of the GDPR 2018 legislation and amended UK-GDPR 2020 when available. Further research questions, subject to ethical approval, may be answered in retrospect in the future. Since the data generated by this work may be irreplaceable after an outbreak of infectious disease has passed, it is essential that future work is not impeded by unnecessary data loss. The stored research data are therefore likely to be of significant value in the future for other studies and therefore permission[1] is sought for this storing of the research data that does contain minimal patient identifiers such as age, sex and ethnicity.

Data from linkage providers will be provided directly to the Scottish National Safe Haven, which is a secure trusted research environment platform provided by the Edinburgh Parallel Computing Centre (EPCC). This is a secure facility, with full access logging and is only available for the use of pre-approved, bona fide researchers. Multifactor authentication is implemented. Data cannot be removed and there are no outward connections to the internet. Data cannot leave the National Safe Haven without prior review from Public Health Scotland to ensure there are no identifiable data released. This infrastructure is held in a secure facility, details of which cannot be disclosed for operational and security reasons.

- [1] Section 251 (s251) approval and/or applicable application routes in Scotland and Northern Ireland:

7. End of Study

The end of the study is defined to be the date on which data for all participants is frozen and data entry privileges are withdrawn from the trial database.

Once there is no need for data collection or cleaning, the identifiable information will be hidden so that no user can access both the study data and patient identifiers. The database will still be pseudo anonymised and possible to link back to the patient if needed.

8. Statistical Considerations

8.1. Introduction

Details are provided on the statistical methodology applied to the study design and an overview of the analysis approaches to be taken. Full details of all statistical analyses will be included in separate statistical analysis plans for data from Public Health Wales, and another for other sources.

8.2. Sample Size

As the study does not have a pre-defined hypothesis then no formal power calculations are set. Instead, the study is designed to demonstrate defined, precise set of key parameters used to evaluate the study data. It is anticipated, based on accumulating data from the principal CCP-UK study that a conservative estimate of 5000 cancer patients with COVID-19 will be available. With an estimated fatality rate of 10% then a 95% confidence interval will have an approximate length of 3% (e.g. 8.5% – 11.5%).

In terms of evaluating the difference between prognostic factors, conservative estimates of the precision about an odds ratio are considered for a single binary factor with a 70:30 split in prevalence. Here we would expect that a standard error about a log odds ratio of 0.17 to be observed meaning that an odds ratio <0.84 or >1.19 would be determined statistically significant.

Matched Cohort Study
Using the whole CCP-UK prospective observational cohort, we will perform a matched cohort study. We will match cancer patients and non-cancer patients within the main dataset by age, sex, race and comorbidities. We will determine which factors are associated with fatal outcomes for patients with cancer, particularly with respect to cancer type, stage, immune suppressive or immune modulating/immunotherapy treatment, treatment intent and time from diagnosis.

Data from the CCP-CANCER UK CRF will be supplemented by linked data. Where a data field is discussed that does not appear in the linked data specification, it will be present in the electronic CRF.

We will examine the effects of the following variables on mortality and severity of COVID-19 in cancer patients:

- Age, Sex, Co- morbidities
- Tumour type
- Solid versus haematological malignancy
- Bone marrow transplant
- Stage of malignancy at time of COVID-19 (from CCP-UK CRF) and stage at diagnosis from data linkage.
- *Diagnosis of malignancy in the last: 1-4 weeks, 1-6 months, 6 months -1 year, 1-5years, > 5 years
- *Surgery or Chemotherapy or radiotherapy treatment in the last: 1-4 weeks, 1-6 months, 6 months -1 year, > 1 year
- ¥Other systemic anticancer therapy in the last: 1-4 weeks, 1-6 months, 6 months -1 year, > 1 year
- Intent of treatment: Curative vs (neo)adjuvant vs palliative vs watch and wait
- Use of corticosteroids
- Use of Granulocyte colony-stimulating factor

*From COVID-19 episode
¥ Endocrine therapy, Immunotherapy, Small molecules, Monoclonal antibodies

8.3. Study Endpoints

8.3.1. Primary Endpoint

The primary endpoint is patient fatality measured as a binary endpoint.

8.3.2. Secondary Endpoint

Secondary endpoints include:

- Time to death measured as the time from COVID diagnosis to death by any cause.
- Time to recovery measured as the time from diagnosis to recovery.
- ITU admission measured as a binary endpoint.
- Describing the clinical features and degree of severity* of infection.
- Describing clinical and laboratory variables that correlate with COVID-19 severity and fatality rate.
- Describing the healthcare resource use.

*Currently, severity of infection is defined as:
Mild – no oxygen requirement, admission length < 7 days
Moderate – ward level oxygen administered
Severe – ITU admission, death, NIV, high flow oxygen administered

Severity definitions will be subject to change to keep them aligned with definitions used by the ISARIC4C consortium.

8.3.3. Exploratory Endpoints

Exploratory endpoints include:

- Baseline microbial diversity measured by microbial diversity index (16s rDNA) in cancer patients compared with non-cancer patients.
- Change in microbial diversity measured by microbial diversity index (16s rDNA) during transition from infection to convalescence in cancer patients compared with non-cancer patients.
- Baseline cancer related microbial species in cancer patients compared with non-cancer patients.
- Change in cancer related microbial species during transition from infection to convalescence in cancer patients compared with non-cancer patients.

8.4. Analytical Methods

8.4.1. Patient Groups for Analysis

Primary analysis will be performed on an ‘Intention to Treat’ (ITT) principles which will analyse all patients identified with cancer and a COVID-19 diagnosis unless there are sound reasons to remove them from the analysis. Various exploratory sub-group analyses may also be performed and these will be fully justified either in the statistical analysis plan or the final statistical report.

8.4.2. Missing Data

Analyses are planned on a complete case basis, however if data on any key covariate are missing at a rate >10% then multiple imputation techniques will be applied.

8.4.3. Levels of Significance

All analyses will be evaluated using the nominal p=0.05 level to determine statistical significance.

8.4.4. Analysis of the primary endpoint – patient fatality

The primary endpoint is patient fatality measured as the number of deaths as a ratio of the number of patients with a positive COVID-19 diagnosis. Fatality rates will be displayed overall and within different tumour types as a rate with associated 95% confidence intervals.

Further multivariable logistic regression models will be used to evaluate the risk attributable to key demographic/clinical covariates of interest whilst adjusting for possible confounding factors. Results will be presented in terms of an odds ratio and associated 95% confidence intervals.

9. Ethical Considerations

This study is to be conducted during a disease outbreak or presentation of cases of disease of public health interest. This is a challenging research situation because this falls in the area between clinical care, public health and clinical research. To limit the burden on patients during admissions we are mapping our procedures onto the Principal CCP-UK protocol.

The CCP-CANCER UK Protocol will be submitted to and approved by an appropriate Research Ethics Committee (REC), Health Research Authority (HRA), Confidentiality Advisory Group and host institution(s).

10. Publication Policy

In accordance with normal academic practice, all employees, students, agents or appointees of the Parties shall be permitted to publish results, jointly where applicable, obtained during the course of work undertaken as part of the Research.
Each Party shall endeavour to submit material intended for publication to the other in writing not less than fourteen (14) days in advance of the submission for publication.
There MUST be author representation from each of the parties included on any manuscript written in relation to the project. Each publication arising from the project will consider the relative contribution of each of the parties and ensure authorship and position and representative of that contribution
The Clatterbridge Cancer Centre NHS Foundation Trust as Sponsor must be acknowledged in all publications.
Any publication will follow the main ISARIC-4C publication policy, which requires inclusion of the consortium investigators list, CCP cancer UK investigators, and site PIs as authors.

Protocol Policy

The Study Management Group will form the basis of the Writing Committee and will advise on the nature and timing of publications. The ICMJE authorship guidelines will be followed when determining authorship alongside the quantity and quality of contributions from each individual. Headline authors will have their contribution identified using the Contributor Roles Taxonomy (CRedit*). Sponsor representative CI will be guarantor on all publications following advice from the Study Management Group.

As a minimum the authorship will include contributing authors from

- The University of Liverpool – Infection and Cancer
- The University of Edinburgh
- ISARIC 4C Investigator
- Liverpool Clinical Trials Centre
- The Clatterbridge Cancer Centre NHS Foundation Trust

All investigators in the ISARIC Coronavirus Clinical Characterisation Consortium (ISARIC 4C) and the CCP Cancer UK study who recruit patients will be named and acknowledged on all related publications.

11. References

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