CARDS

Cancer: Rapid Diagnostics and Immune assessment for SARS-CoV-2 (COVID-19)

Clinical Protocol Version 3.0, Dated 10th July 2020

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Confidentiality Notice

This document contains confidential information of the Gastrointestinal & Lymphoma Trials Unit of the Royal Marsden NHS Foundation Trust and The Institute of Cancer Research, London.

This document must not be disclosed to anyone other than the study staff and members of the Newcastle & North Tyneside 1 Research Ethics Committee.

The information in this document cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Gastrointestinal & Lymphoma Trials Unit of the Royal Marsden NHS Foundation Trust.

PROTOCOL SIGNATURE PAGE

Study title: Cancer: Rapid Diagnostics and Immune assessment for SARS-CoV-2

Acronym: CARDS
Protocol version number: 3.0
Version date: 10th July 2020

Approved by Chief Investigator:

_____

Name: Dr Sheela Rao

Date:

Investigator's Agreement

I have read the attached protocol entitled *CARDS (version 3.0, dated 10th July 2020)* and agree to abide by all provisions set forth therein.

I agree to comply with the principles of Good Clinical Practice (GCP), the EU and GCP Directives (2001/20/EC; 2005/28/EC) and The Medicines for Human Use (Clinical Trials) Regulations and Amendment Regulations 2006 (Statutory Instrument 2006 No. 1928).

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Gastrointestinal & Lymphoma Trials Unit of the Royal Marsden NHS Foundation Trust.

Signature	
Name of Principal Investigator	
Centre Name	
Date (DD/MM/YYYY)	

Co-investigators & Research Team

RMH denotes 'The Royal Marsden NHS Foundation Trust.'

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This protocol has yet to be reviewed and approved by the Committee for Clinical Research (CCR), Research and Ethics Committee (REC) and Health Research Authority (HRA).

Note: All queries about this trial should be addressed to the GI & Lymphoma Trials Unit, including clinical queries. Clinical queries will then be referred to the Trial Physician or Chief Investigator.

Contents

1. Protocol synopsis

Study title:	Cancer: Rapid Diagnostics and Immune assessment for SARS-CoV-2
Chief investigator:	Dr Sheela Rao
Study centres:	The Royal Marsden NHS Foundation Trust
Study period:	Approximately 1 year
Follow up duration:	Up to 84 days
Main objective:	This observational study will investigate how host cancer status and immune phenotype links to SARS-CoV-2 infection clinical presentation, seroconversion, and viral clearance. The study will also evaluate rapid antigen/antibody lateral flow tests.
Methodology:	Arm A: Suspected acute COVID-19 infection Throat/nose swabs, saliva and blood will be collected from patients undergoing investigation for suspected SARS-CoV-2 infection at the Royal Marsden NHS Foundation Trust on Day 0. Patients who are positive for SARS-CoV-2 by throat/nose RT-PCR or have a high clinical suspicion for acute COVID-19 will have further samples collected on D7 (if an inpatient), D14, D28, D42 and D56. Arm B: Asymptomatic patients with no clinical suspicion of COVID-19

Blood will be collected from patients who do not have symptoms of COVID-19. Repeat blood will be collected on D28, D56 and D84.

Research tests including serology and antigen/antibody lateral flow tests will be performed at St George's University NHS Trust. Exploratory analyses including, but not limited to HLA-KIR profiling, blood immune cell activation and transcriptome and lateral flow testing will be carried out. Viral and immunological data will be collated in a link-anonymised manner and correlated to clinical outcome data. Samples will also be used to develop more rapid SARS-CoV-2 testing and assist in the future planning of ongoing or delayed treatment in cancer patients.

Number of patients:

Arm A: Up to 60 patients with confirmed diagnosis of SARS-CoV-2 by RT-PCR over the study period.

Arm B: Up to 150 patients with no clinical suspicion of COVID-19

Main inclusion criteria:

1) Suspected COVID-19 infection undergoing diagnostic testing by SARS-CoV-2 RT-PCR or within 14 days of confirmed COVID-19 infection by SARS-CoV-2 RT-PCR (Arm A) OR
No symptoms of SARS-CoV-2 infection (Arm B)

2) Metastatic or advanced solid organ malignancy, including lymphoma
OR
Early stage solid organ malignancy having received or planning to commence radiotherapy, chemotherapy or targeted agents

3) Patient is ≥ 18 years of age.

	4) Patient can understand the patient information sheet and is able to provide written informed consent.
Exclusion criteria	There are no exclusion criteria for this study.
Primary endpoint:	Proportion of patients, at each sample timepoint, with a positive detection of IgM and IgG specific antibodies to SARS-CoV-2. (Arms A and B)
Secondary endpoints:	To describe the clinical course of SARS-CoV-2 infection in cancer patients. This will include duration and severity of clinical symptoms, supportive treatments given, cancer treatments received and outcome of SARS-CoV-2 infection. (Arm A) Proportion of patients, at each sample timepoint, with SARS-CoV-2 viral clearance by throat/nose swab by RT-PCR. (Arm A) Time from start of symptoms to Day 0 testing in the study. (Arm A) Feasibility of SARS-CoV-2 antigen testing with a throat/nose or saliva lateral flow assay (Arm A) Feasibility of SARS-CoV-2 antibody testing with a rapid lateral flow assay (Arms A & B)
Exploratory analyses:	Investigate antigen dynamics over time to compare with quantitative RT-PCR (Arm A) To examine HLA-KIR interactions that shape CD8 anti-viral responses (Arms A&B)

To explore the relationship between host immune genotype (e.g. HLA-KIR) and peripheral blood immune phenotype with viral clearance (Arms A&B)

To investigate blood immune cell activation and transcriptome in participants (Arms A&B)

2. Objectives

This observational study will investigate how host cancer status and immune phenotype links to SARS-CoV-2 infection clinical presentation, seroconversion, and viral clearance. The study will also evaluate rapid antigen/antibody lateral flow tests.

3. Background

On 12 January 2020, a novel coronavirus was identified as the cause of an outbreak of unexplained pneumonia in Wuhan City, Hubei Province, China. This coronavirus was later named SARS-CoV-2, and the disease it causes COVID-19 [1].

SARS-CoV-2 is a non-segmented, positive sense RNA virus and part of the family of coronaviruses. Similar to the Systemic Acute Respiratory Syndrome (SARS) virus, it binds to the angiotensin-converting enzyme 2 (ACE2) receptor located on type II alveolar cells and intestinal epithelia. SARS-CoV-2 can result in a severe Acute Respiratory Distress Syndrome (ARDS) which is characterised by diffuse alveolar damage and direct viral cytopathic effect on pneumocytes [2]. Some patients who develop COVID-19 may respond with a fulminant "cytokine storm" reaction. Co-morbidities such as hypertension, kidney disease and diabetes have been linked to poorer prognosis and clinical outcomes. However, a proportion of patients of younger age and without comorbidities also develop severe disease.

As of 23 March 2020, a total of 374,921 COVID-19 cases have been reported in 168 countries with a total of over 16,411 deaths (case fatality amongst confirmed cases of 4.4%) [3] (John Hopkins's Coronavirus Resource centre). Over 293,425 cases and 13,258 deaths have been reported from countries outside mainland China. The World Health Organisation (WHO) declared on the 12th of March 2020 the SARS-CoV-2 outbreak a pandemic in the context of a Public Health Emergency of

International Concern (PHEIC). Europe has rapidly become the epicentre of the pandemic and in the UK, cases are increasing daily.

Based upon small observational studies, cancer patients are thought to be more susceptible in infection during a viral pandemic. In a retrospective analysis of a 1524 patients with a diagnosis of COVID-19 at a tertiary care hospital in Wuhan, China, a history of cancer (n=18) were at a higher risk of SARS-CoV-2 infection (OR 2.31; 95% CI 1.89-3.02). [3] In a chart review of 355 fatal cases of SARS-CoV-2 infection in an Italian center, the median age of 79.5 years. The vast majority of patients had at least one medical co-morbidity. Strikingly, 20.8% patients had a history of cancer. [4] By contrast, an analysis of a UK-wide prospective database of cancer patients with COVID-19 infection (n=800) found the risk of death is driven mainly by age, gender and morbidities, rather than systemic anti-cancer therapy or radiotherapy. [5]

Amongst cancer patients at a French cancer centre, the rate of seroconversion 15 days after SARS-CoV-2 infection was 30% versus 71% when compared to healthcare workers. [6]

Little is known of the duration and severity of SARS-CoV-2 infection in cancer patients. Hence, SARS-CoV-2 pandemic poses of clinical dilemma in the provision of anti-cancer therapy. NICE guidance states the level of immunosuppression associated with treatments, capacity issues and the risk of cancer not being treated with the risk of immunosuppression and becoming seriously ill from SARS-CoV-2 infection. There is little data available which could inform clinicians on the timing of resumption of systemic anticancer treatment following recovery of SARS-CoV-2 infection. Similarly, the susceptibility of patients receiving immunotherapy to severe SARS-CoV-2 infection remains unclear.

Because of the lack of a validated serological test, the actual number, and therefore the proportion, of people that develop asymptomatic infections remains unknown. This means that an accurate case fatality estimate remains elusive. Due to the rise of the number of samples to diagnose, tests are taking longer than expected. Among the foremost priorities to facilitate public health interventions is a reliable laboratory diagnosis. Prompt case confirmation is necessary to ensure rapid and effective contact tracing, implementation of infection prevention and control measures according to WHO recommendations, and collection of relevant epidemiological and clinical information.

The SARS-CoV-2 antigen and antibody lateral flow assay (LFA) development has been led by Mologic, a company based in Bedford, England. We will use prototype LFA and ELISA that are ready for

preliminary evaluation, and subsequently use these tests on-site to evaluate the test at POC. LFA have been developed for SARS-CoV-2 antigen detection in throat/nose swabs and detection of IgG and IgM in blood/serum and SARS-CoV-2 antigen detection, IgG, IgM and IgA in saliva. Saliva is a convenient sample to use as it is far easier to use than blood or throat/nose swabs for potential self-testing.

The use of diagnostics developed within this study will improve the management of cases of COVID-19 in cancer patients. The LFA are rapid, easy to use and designed to be affordable globally. The rapid diagnosis of SARS-CoV-2 with antigen detection will allow cancer patients to be rapidly triaged in hospital and General practitioner (GP) surgeries. The use of antibody detection will allow both for diagnosis of immunological response to acute infections as well as after patients have recovered. To utilise these tests appropriately an understanding of dynamic immunopathological changes over time is necessary.

Characterisation of immune response and susceptibility and its association with viral clearance and disease progression in large cohorts with varied disease severity is important to assist clinical risk prediction outcomes and inform clinical decisions in relation to delaying cancer treatment. Immune response characteristics may have predictive and prognostic value, with early adaptive immune responses possibly correlated with improved clinical outcomes [7].

4. Rationale

This study is a collaboration between in the GI & Lymphoma Unit (RMH), the Infectious Diseases and Microbiology Units (St Georges Hospital) and our commercial partner Mologic Ltd who have been funded by DFID/Wellcome Trust to develop SARS-CoV-2 assays. This prospective study is intended to prospectively monitor cancer patients infected with SARS-CoV-2. This study will be valuable to understanding the clinical presentation and course of SARS-CoV-2 infection in this population as well as the virological parameters such as viral clearance by RT-PCR and IgM/IgG seroconversion. Serial measurement of SARS-CoV-2 antibody titres in asymptomatic individuals will provide insights into the longitudinal immune status of cancer patients.

This project will evaluate point-of-care/point-of-need (POC/PON) tests for the detection of the novel strain of coronavirus (2019 nCoV). We are working with Mologic Ltd, to develop a rapid, accurate and low cost, lateral flow assay (LFA) to detect viral circulating antigens and IgM/G against SARS-CoV-2 in less than 15 minutes. These POC/PON tests are intended for the rapid triage of patients

with fever and/or cough and to identify patients likely to be immune from previous infections. In addition, we will evaluate ELISA assays, also produced by Mologic to detect IgG and IgM (and possibly IgA) against SARS-CoV-2. Comparison of antibody and antigen dynamics over time will compare with ELISA and quantitative RT-PCR. Mologic have been instrumental in developing rapid tests for Ebola virus disease and dengue.

The ultimate diagnosis of SARS-Cov-2 is performed by laboratory testing as the clinical features are non-disease specific. Diagnostic testing of Covid-19 is currently undertaken using real-time reverse transcriptase PCR (RT-PCR) to detect the viral ribonucleic acid (RNA). These assays are sensitive but require transfer of samples to reference laboratories and thus results are obtained with a delay. In the UK, results are reported with a delay of 2-4 days, impeding the correct triage of patients, correct isolation measures and therefore putting the community and healthcare workers at risk.

A fast and reliable diagnostic assay that could be used at the POC is yet to be developed. Our collaborators have been working closely with Mologic Ltd in 2020 on the development of highly sensitive POC/PON tests to facilitate diagnosis at the point of need and to reduce the consequences of diagnostic delay. Dual antigen and antibody test development has been led by Mologic. We will use prototype lateral flow tests and ELISA that are ready for preliminary evaluation, and subsequently use the lateral flow tests at St Georges University of London to evaluate the test at the point of need. Left over and anonymised samples will be used to evaluate other diagnostics if appropriate, an amendment will be submitted if this is the case.

The information from our study will add significantly to the understanding of SARS-CoV-2 diagnostics and control and will improve the evidence-base for the management of cancer patients. Furthermore, data from this study could inform the timing and treatment for cancer patients who have recovered from SARS-CoV-2 infection.

This study may also serve as a valuable platform for assessing patients who may be at exceptional risk of a poor outcome with SARS-CoV-2 infection. Depending on the number of patients assessment for a biomarker of interest, exploratory analyses may be undertaken to assess the role of a prognostic or predictive role of these biomarkers in relation to the patients' clinical course and recovery.

SARS-CoV-2 can lead to acute respiratory distress syndrome (ARDS) and fulminant "cytokine storm". A recent case report of an immunocompetent patient diagnosed with a non-severe case of COVID-19

showed an increase in antibody-secreting cells (ASCs), immunoglobulin M (IgM), IgG antibodies follicular helper T cells (TFH cells), activated CD4+ T cells and CD8+ T cells. This patient did not experience ARDS or require supplemental oxygen and made a full recovery [7]. Evidence was provided of recruitment of immune cell populations (ASCs, TFH cells and activated CD4+ and CD8+ T cells), together with IgM and IgG SARS-CoV-2-binding antibodies, prior to resolution of symptoms.

These immunological changes appear to persist for at least 7 days following resolution of symptoms. The kinetics and immune responses associated with clinical resolution of COVID-19 were analysed, showing that ASCs and TFH were recruited as part of the immune response during the acute phase of COVID-19 illness and continued to be prominent during convalescence. ASCs appeared in the blood at the time of viral clearance (day 7; 1.48%) before peaking on day 8 (6.91%). TFH cells were shown to occur concurrently in blood at day 7 (1.98%) continuing to increase on day 8 (3.25%) and day 9 (4.46%) of illness. When compared to healthy control participants, the peak of both ASCs and cTFH cells was markedly higher in the patient with COVID-19 (0.61% ± 0.40% and 1.83% ± 0.77%, respectively (average ± s.d.); n = 5) [7]. Given their immunosuppressed state, cancer patients are likely to have different immunological responses to COVID-19.

Secondary haemophagocytic lymphohistiocytosis (sHLH) is a hyperinflammatory syndrome characterised by a fulminant and fatal hypercytokinaemia leading to multiorgan failure, most frequently triggered by viral infections [8]. Cardinal features of sHLH include unremitting fever, cytopenias, and hyperferritinaemia. In a prospective cohort study of 41 patients confirmed to have COVID-19 disease a cytokine profile resembling sHLH was associated with disease severity. This profile was characterised by increased interleukin (IL)-2, IL-7, monocyte chemoattractant protein 1, macrophage inflammatory protein 1-α, and tumour necrosis factor-α, granulocyte-colony stimulating factor, interferon-γ inducible protein 10.

In a retrospective multicenter study comparing 68 death cases (68/150, 45%) and 82 discharged cases (82/150, 55%) in patients with laboratory-confirmed infection of SARS-CoV-2, a significant difference was seen in C-reactive protein (CRP) and interleukin-6 (IL-6) between the two groups [9].

Further work needs to be done urgently to characterise immune parameters in cohorts of cancer patients with COVID-19 with varied clinical presentations and disease severities to identify predictive and prognostic biomarkers. It is vital to investigate how cancer patients with an impaired immune

system links to viral clearance and seroconversion and this forms one of the underlying aims of our study. The impact of systemic anti-cancer therapy on the host immunity status is unclear.

5. Hypothesis

Arm A: We hypothesise that cancer patients with SARS-CoV-2 infection will acquire immunity by seroconversion (IgG/IgM) which is measureable by an ELISA assay. Furthermore, we hypothesise the study cohort will clear SARS-CoV-2 virus by analysis of throat/nose swab RT-PCR.

Arm B: We hypothesise systemic cancer treatments will result in a lower level of SARS-CoV-2 antibodies.

Arms A & B: We also hypothesise that antigen/antibody point of care testing by saliva, throat/nose swabs and blood will be a feasible diagnostic tool for the detection and monitoring of SARS-CoV-2 infection.

6. Aims

Arm A: This is a prospective study which aims to define the clinical characteristics of SARS-CoV-2 infection in cancers patients. The aim is to collect clinical data, throat/nose swabs, saliva and blood longitudinally to investigate viral clearance and seroconversion.

Arm B: The arm of the study will investigate the prevalence of SARS-CoV-2 antibodies amongst patients with cancer. Clinical data and blood samples will be collected longitudinally to assess the impact of systemic therapy on SARS-CoV-2 antibody titres.

In parallel, the study will also evaluate an antigen (Arm A) and IgG/IgM antibody (Arms A & B): point of care test (lateral flow assay) for the development of rapid detection of SARS-CoV-2.

7. End Points

7.1 Primary endpoint

Proportion of patients, at each sample timepoint, with a positive detection of IgM and IgG specific antibodies to SARS-CoV-2. Both IgM and IgG seroconversion will be reported separately. (Arms A & B)

7.2 Secondary endpoints

The secondary endpoints are as follows:

- The primary endpoint is to describe the clinical course of SARS-CoV-2 infection in cancer patients. This will include duration and severity of clinical symptoms, supportive treatments given, cancer treatments received and outcome of SARS-CoV-2 infection. (Arm A)

- Proportion of patients, at each sample timepoint, with SARS-CoV-2 viral clearance by throat/nose swab by RT-PCR. (Arm A)

- Time from start of symptoms to Day 0 testing in the study. (Arm A)

- Feasibility of SARS-CoV-2 antigen testing with a throat/nose or saliva lateral flow assay (Arm A) will be assessed by the following

1) Proportion of samples successfully collected, processed and result obtained
2) Proportion of samples with a positive result by lateral flow by the gold standard (throat/nose RT-PCR)

If both of these are greater than 80% then the test would be considered successful and further research worthwhile.

- Feasibility of SARS-CoV-2 antibody testing with a rapid lateral flow assay will be assessed by the following (Arms A&B)
    - 1) Proportion of samples successfully collected, processed and result obtained
    - 2) Proportion of samples with a positive result by lateral flow by the gold standard (laboratory serology)

If both of these are greater than 80% then the test would be considered successful and further research worthwhile.

7.3 Exploratory endpoints:

The following endpoints and analyses are planned to be performed:

- Investigate antigen dynamics over time to compare with quantitative RT-PCR (Arm A)
- To examine HLA-KIR interactions that shape CD8 anti-viral responses (Arms A & B)
- To explore the relationship between host immune genotype (e.g. HLA-KIR) and peripheral blood (Arms A & B)immune cell phenotype with viral clearance (Arms A & B)
- To investigate blood immune cell activation and transcriptome in participants (Arms A & B)

As the pandemic evolves, the priority of these exploratory endpoints are subject to change. Any other exploratory analyses not specified in this protocol will be ratified by the TMG prior to analysis.

8. Inclusion/Exclusion Criteria

8.1 Number of patients

Arm A: Up to 60 patients with solid tumour malignancy or lymphoma with confirmed diagnosis of SARS-CoV-2 by RT-PCR will be recruited over the study period.

Arm B: Up to 150 patients with solid tumour malignancy or lymphoma with no clinical suspicion of COVID-19

Patients will be recruited from the Royal Marsden NHS Foundation Trust in both the inpatient and outpatient setting.

8.2 Inclusion criteria

1) Suspected COVID-19 infection undergoing diagnostic testing by SARS-CoV-2 RT-PCR or within 14 days of confirmed COVID-19 infection by SARS-CoV-2 RT-PCR (Arm A)

OR

No symptoms of SARS-CoV-2 infection (Arm B)

2) Metastatic or advanced solid organ malignancy, including lymphoma

OR

Early stage solid organ malignancy having received or planning to commence radiotherapy, chemotherapy or targeted agents

3) Patient is ≥ 18 years of age.

4) Patient can understand the patient information sheet and is able to provide written informed consent.

8.3 Exclusion criteria

There are no exclusion criteria for this study.

8.4 Subject withdrawal criteria

Patients have the right to withdraw fully or partially from the study at any time and for any reason without prejudice to his or her future medical care by the physician at the institution. Patients who are withdrawn from the study will be replaced.

Reasons for removal of patients from the study may include:

- withdrawal of consent (see above)
- administrative decision by the Investigator, Chief Investigator or Sponsor
- ineligibility
- patient non-compliance

Patients enrolled to the study who have tested negative for SARS-CoV-2 by RT-PCR and have a low clinical suspicion of COVID-19 will be withdrawn. No further follow-up will be conducted. Patients who have previously provided written consent who have previously tested negative for SARS-CoV-2

can have the D0 assessments repeated if there are new symptoms suggestive of SARS-CoV-2 infection.

9. Methodology

9.1 Informed consent

All patients will be consented by any health care professional with GCP training who has been delegated by the Principal investigator can obtain consent from eligible patients. All staff taking consent will have received training and be approved as competent in taking consent for this study by the chief investigator.

9.2 SARS-CoV-2 infection confirmation (Arm A)

Following a baseline throat/nose swab, if SARS-CoV-2 infection is confirmed, clinical data and additional samples are collected at the study time-points outlined in section 11. If SARS-CoV-2 infection is negative and deemed by the Investigator to have low clinical suspicion of SARS-CoV-2 infection no further samples or data will be collected and the patient will come off study. In the case the SARS-CoV-2 throat/nose swab is equivocal, the patient will remain on study and repeat testing will be performed as per local standard (Figure 1, Table 2). If a patient has a negative swab result but deemed by the Investigator to have a high clinical suspicion of SARS-CoV-2 infection, then the patient will remain on study. Patients who are within 14 days of a positive for SARS-CoV-2 by RT-PCR are eligible for entry into Arm A and the initial visit will be designated D0.

9.3 Asymptomatic patients with no clinical suspicion of COVID-19 (Arm B)

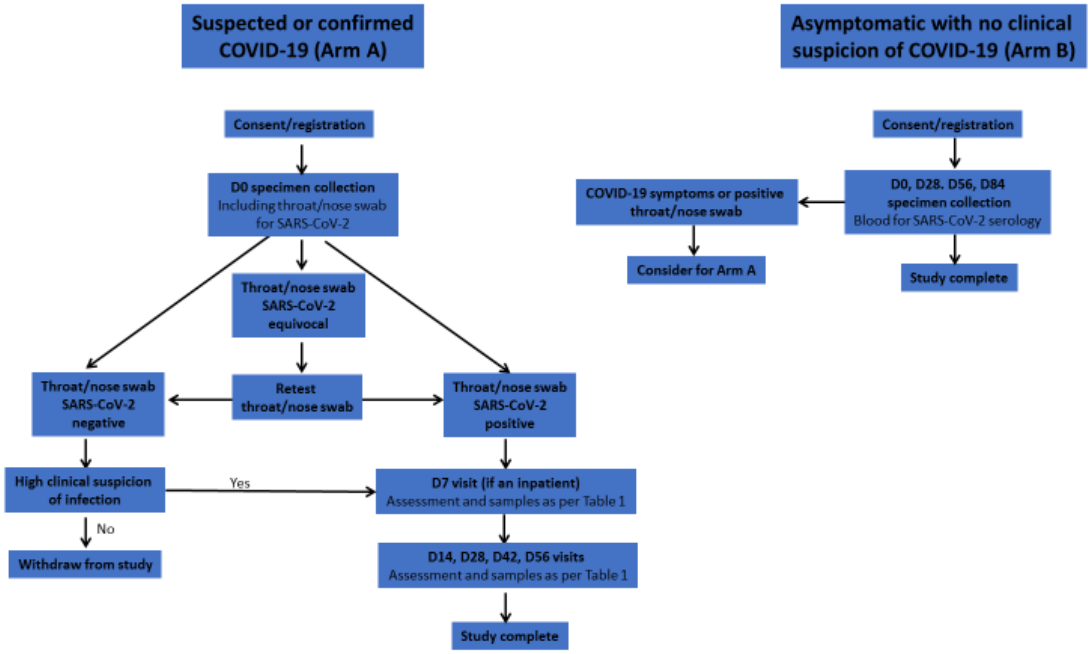
Patients with no current symptoms of COVID-19 will be eligible for inclusion in Arm B. Following written consent, samples (blood) will be collected from patients. Blood will be collected from patients on Day 0, 28, 56 and 84 (Figure 1, Table 3). Attempts will be made to ensure these blood collections will coincide with standard of care hospital visits.

Patients enrolled in Arm B develop COVID-19 symptoms or have confirmed COVID-19 can be invited to participate in Arm A. Patients will have to provide written consent for Arm A.

9.4 Personal protective equipment (PPE)

All staff performing study assessments including informed consent will require adequate personal protective equipment and adherence to infection control guidelines as per hospital guidance.

Figure 1 study schema (Arms A and B):



10. Data acquisition

Clinical data including demographics, medical history, medications, vital signs and symptom assessment will be collected as described in the schedule of assessments at the time of study visits. Additional information will be supplemented from the electronic patient records as appropriate. Standard investigations such as haematology, biochemistry and imaging assessments will only be performed if indicated by the treating unit. Results of such investigations will be recorded in the CRF.

11. Data analysis

11.1 Baseline assessments

Following initial eligibility checks and informed consent, the following baseline data will be collected.

For Arm A and B:

- Patient demographics
- Medical history (including history of malignancy and treatment)
- Concomitant medications
- SARS-CoV-2 symptom assessment

For Arm A only:

- Vital signsHaematology, biochemistry and imaging results (if performed as part of clinical management)

11.2 Specimen collection

The schedule of visits and specimen collection for Arm A and B is outlined in Tables 2 and 3 respectively. Each study visit has a window period to allow for flexibility of visits due to logistics and bank holidays. Refer to the lab manual for full details regarding the specimen collection and handling.

Throat/nose swabs

Throat/nose swabs will initially be collected at baseline (D0) as part of the diagnostic workup for SARS-CoV-2 infection. Subsequent throat/nose swabs will be taken at D7 (if an inpatient), D14, D28, D42 and D56. Two samples will be taken, one for standard of care testing and one for lateral flow assay and storage for further analysis later such as quantitative PCR.

Saliva

Saliva will be collected at each study visit, by asking the participant to provide a small amount of saliva (approximately 0.5mL) will be collected. Saliva will be tested by the lateral flow assay when available and excess material stored.

Blood

Approximately 30mL of blood will be taken at each study visit (Table 1).

Table 1 Blood specimens to be collected in CARDS study

Sample type	**Key analyte**
Serum (SST)	SARS-CoV-2 antibody testing ie IgG, IgM
Whole blood (EDTA)	Immune profiling

As the assays are currently under investigation, results of the research assays (i.e. LFA, IgG/IgM serology) will not be made known to clinical teams.

Table 2. Schedule of assessments (Arm A)

Assessment	D0	SARS-CoV-2 swab result check*	D7[a] +/- 3 days	D14 +/- 3 days	D28 +/- 3 days	D42 +/- 3 days	D56 +/- 3 days
Informed consent	X						
Registration	X						
Patient demographics	X						
Medical history[b]	X						
Concomitant medications	X		X	X	X	X	X
Symptom assessment	X		X	X	X	X	X
Vital signs[c]	X		X	X	X	X	X
Haematology[d]	X		X	X	X	X	X
Biochemistry[d]	X		X	X	X	X	X
Imaging assessment[d]	X		X	X	X	X	X
Throat/nose swab[e]	X		X	X	X	X	X
Blood (serum and EDTA whole blood)[f]	X		X	X	X	X	X
Saliva[g]	X		X	X	X	X	X

Schedule of Assessments Table Key

* Not applicable if patients have tested positive for SARS-CoV-2 prior to D0. If negative and has a low clinical suspicion of SARS-CoV-2 infection, the patient will be removed from the study.

a: Only if an inpatient. D7 visit will be omitted for patients in the outpatient setting.

b: Includes past medical history, oncological history

c: Includes temperature, blood pressure, heart rate, respiratory rate, oxygen saturations by pulse oximetry.

d: Results only to be recorded in CRF if performed as part of clinical management.

e: Two samples will be taken, one for diagnostic testing and one for research purposes and storage for further analysis.

f: For collection of serum and whole blood. See laboratory manual for full details

g: See laboratory manual for collection details.

Arm B:

Blood

Approximately 30mL of blood will be taken at each study visit (D0, D28, D56, D84). The blood samples taken are outlined in Table 3.

Table 3. Schedule of assessments (Arm B)

Assessment	D0	D28 +/- 10 days	D56 +/- 10 days	D84 +/- 10 days
Informed consent	X			
Registration	X			
Patient demographics	X			
Medical history [a]	X			
Concomitant medications	X			
Symptom assessment[b]	X	X	X	X
Blood (serum and EDTA whole blood)[b]	X	X	X	X

Schedule of Assessments Table Key

a: Includes past medical history, oncological history

b: See laboratory manual for full details

12. Study Organisation/ Trial Monitoring and Management Strategy

12.1 Responsibilities

The Chief Investigator is responsible for forwarding the following documents to the study sponsor for review before study initiation from the sponsor can occur:

- Signed and dated protocol signature page (see Investigator's Agreement on page 3)
- Copy of local research and development office and site specific assessment approvals, or equivalents thereof.

- Copy of approved patient information sheet and informed consent form on headed paper which will be used at the site
- Up-to-date *curricula vitae* of the Principal Investigator (hand-signed and hand-dated within 1 year)
- GCP training certificate (which must be within 3 years)
- Contact details for key study personnel and completed, signed site delegation log
- Signed study contract/ HRA statement of activities

Delegation logs will be kept which outline the allocation of responsibilities following adequate training: patients enrolment, monitoring study progress, the day-to-day running of the study, data collection, Case Report Forms, consent forms, data analysis, and data storage.

Specimen collection will be performed by staff trained/experienced in the collection as per standard of care. This will not necessarily be a member of the study team. The study team will ensure the samples are anonymised prior to being sent for analysis.

Transportation and storage will be arranged by a dedicated Translational team in the GI & Lymphoma Unit. Members of the team are GCP and IATA trained and certificates are available for review.

12.2 Start date

The study is reviewed and approved by the Committee for Clinical Research (CCR) only (as sponsor) prior to external regulatory review. Once REC/HRA review and approval is gained local R&D confirmation of capacity and capability is required before the study can start at a participating site.

12.3 Patient screening and enrolment

Patients will be considered as enrolled in the study after informed consent and registration has occurred. Any health care professional with GCP training who has been delegated by the Principal Investigator can obtain consent from eligible patients. At registration, each patient will be assigned a study subject identification number which will be used to identify the patient.

Before patients may be enrolled into the trial, the sponsor must receive proof that all required regulatory approval (both local and, if relevant, national) has been obtained for the site.

Before registration, each potential patient must be given a patient information sheet, and informed consent obtained according to the requirements of GCP. The registration case report forms (CRFs) must also be completed. Only patients fulfilling all inclusion criteria and not any exclusion criteria should be registered. Any queries about eligibility should be addressed directly with the clinical team.

A study subject identification number will be issued initially to the patient by the healthcare professional performing the patient registration – instructions will be provided separately. Once eligibility has been reviewed and the researcher is satisfied that the patient meets the criteria for study registration the subject identification number will be assigned to the patient. Completed registration CRFs must be sent to the GI & Lymphoma Trials Office at the Royal Marsden Hospital. The GI & Lymphoma Trials Office will check for completeness, complete the relevant CRF page and send back to the study personnel at the participating site responsible for recruitment of the patient.

12.4 Patient withdrawal

Withdrawal of full consent for a study means that the patient does not wish to or is unable to continue further study participation. Any patient may withdraw full consent to participate in the study at any time during the study. The investigator will discuss with the patient the most appropriate way to withdraw to maintain the patient's care. In this case, the patient's data already collected up to the point of withdrawal will still be included in the analysis of data, and the patient censored from that point onwards.

Withdrawal of partial consent means that the patient does not wish to undergo any further procedures (e.g. blood tests or swabs) but is still willing to collaborate in providing further data by continuing on study (e.g. permit further data collection from hospital records). Participants will have the opportunity to request for their samples to be discarded.

12.5 Study duration

The study is expected to take up to 6-9 months to complete accrual. If the recruitment target is reached before the predicted end date, then the trial will close early to any further recruitment. Conversely, if the target recruitment is not achieved by the estimated end date, the trial recruitment

period may be extended until the target number of patients is achieved depending on the overall status of the SARS-CoV-2 pandemic.

Individual participants whose throat/nose swab RT-PCR does not confirm SARS-CoV-2 infection and do not have a high clinical suspicion of SARS-CoV-2 infection at D0 will come off study at this time and no further clinical data or samples will be collected. Research samples will be destroyed. This only applies to Arm A.

12.6 End of study

The 'end of study' will be defined as the date that the last patient has had their last visit, or when adequate follow up has occurred for all the study end points to assessed and reported, whichever is sooner. At this point, the 'end of trial notification' will be submitted to the relevant regulatory authorities and ethics committees.

13. Safety reporting

The risks of an adverse event related to study specify procedures have been deemed to be minimal. Therefore, any AEs arising from the study procedures will not be recorded for the purposes of this study.

14. Evaluation of Outcome/Statistical Considerations

14.1 Sample size

Arm A

Based upon the current SARS-CoV-2 infection rates at the Royal Marsden NHS Foundation Trust, up to 60 patients (up to 50 patients with solid tumour or 10 with lymphoma) with confirmed SARS-CoV-2 infection by RT-PCR could be recruited in 6-9 months, assuming uptake of 40% (As per positivity rates in April 2020) in screening 150 patients.

For the primary endpoint, seroconversion, and the RT-PCR and LFA viral clearance secondary endpoints:

Arm A - Up to 60 SARS-CoV-2 positive patients are expected to be recruited in the study; the proportion of patients can be estimated with a 95% CI with a width of ± 12.7%. In the 50 patient solid tumour cohort then this will be estimated with a 95% CI with a width of ± 13.9%.

To account for lower recruitment rate of SARS-CoV-2 positive patients, the following table presents the maximum width of the 95% C.I.s, given a 50% observed proportion for the primary endpoint, according to different sample sizes (N).

An observed proportion of 50% has been selected, which is conservative and gives the widest possible 95% CI. (Table 4)

Table 4:

N	Proportion of patients, with a positive detection of IgM and IgG specific antibodies to SARS-CoV-2.	With of 95% CI
10	50%	± 31.0%
20	50%	± 21.9%
30	50%	± 17.9%
50	50%	± 13.9%
60	50%	± 12.7%

Arm B

For the primary endpoint up to 150 patients are expected to be recruited in Arm B. Considering a 10% antibody positivity rate [10], the proportion of patients can be estimated with a 95% CI with a width of ± 4.8%.

The clinical course of SARS-CoV-2 infection secondary endpoint is descriptive so no power calculation is required.

Due to the dynamic changes in the prevalence of SARS-CoV-2 infection during the pandemic, the study may be halted prematurely.

14.2 Analysis plan

The primary endpoint will be presented as the proportion of patients at each sample time-point with 95% confidence interval Arms A and B will be reported separately.

Continuous data will be summarised as n, mean, standard deviation, median, minimum value and maximum value. Categorical data will be presented as frequencies and percentages.

Arm A:

The secondary endpoint, viral clearance, will be presented as the proportion of patients at each sample time-point with 95% confidence interval.

The clinical course of SARS-CoV-2 infection described as patient characteristics, and cancer diagnosis, will be summarised, as well as duration and severity of clinical symptoms, supportive treatments given, cancer treatments received and outcome of SARS-CoV-2 infection.

Feasibility of SARS-CoV-2 antigen testing with a lateral flow assay will be assessed by the following

1 Proportion of samples successfully processed and result obtained, with 95% confidence interval

2 Proportion of samples processed with a positive result by lateral flow, by the gold standard (throat/nose RT-PCR)

Arm B:

Feasibility of SARS-CoV-2 antibody testing with a lateral flow assay will be assessed by the following

1 Proportion of samples successfully processed and result obtained, with 95% confidence interval

2 Proportion of samples processed with a positive result by lateral flow, by the gold standard (SARS-CoV-2 laboratory serology test)

The formal statistical analysis plan will be developed based on the size of the available cohort and the performance of the experiment assays. The analysis will be developed in a separate molecular and statistical analysis plan which will be drafted and approved by the Trial Management Group (TMG) with statistical input. However, the above gives a guide as to the planned analyses.

14.3 Study monitoring

The study will be centrally monitored using the following procedures:

Central Eligibility checking at registration

Registration eligibility criteria will be reviewed when CRFs are received by the GI & Lymphoma Trials Office. Registration will only take place once central checking of documents is complete and any queries addressed.

Statistical Monitoring

The trial statistician will regularly examine the data for anomalies and outliers, such as too few or too many events. Queries will be raised by the trial coordinators (or other appropriately delegated team member) in such situations and communication with the clinical teams will take place. In addition statistical monitoring of unusual dates and inconsistent data will take place. Again these will raise queries via the trial coordinators (or other appropriately delegated team members.)

RM GI Unit Research Meetings

Recruitment will be discussed in the Unit Research meetings.

Trial Management Group (TMG) meetings

The role of the Trial Management Group (TMG) is to monitor all the aspects of the conduct and progress of the study, ensuring that the protocol is adhered to. The TMG will develop and approve the molecular analysis plan. Any issues will be raised and addressed at the TMG meetings. The TMG will meet at minimum frequency of every 3 months. The minutes of the meeting will be documented in the Trial Master File (TMF) and copied to the Sponsor.

15. Regulatory & Ethics Committee Approval

15.1 Ethical considerations

Ethical considerations relating to this trial will carried out in accordance to the Declaration of Helsinki (1996).

A copy of the protocol, proposed informed consent form, other written patient information, and any proposed advertising material must be submitted to an independent ethics committee and any other relevant regulatory authorities, subject to the regulations of the country of each participating site, for written approval. A copy of the written approval of the protocol and informed consent form must be received by the sponsor before recruitment of patients into the study.

The investigator must submit and, where necessary, obtain approval from the independent ethics committee concerned and any other relevant regulatory authorities for all subsequent protocol amendments and changes to the informed consent document. The investigator should notify the same of deviations from the protocol.

15.2 Informed consent

Before a patient's participation in the clinical study, the investigator (or a member of the study team named in the site signature log and authorised by the site Principal Investigator) is responsible for obtaining written informed consent from the patient. This can only take place after the patient has been given adequate time to consider participation, and adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study, and must take place prior to any protocol-specific procedures.

The acquisition of informed consent should be documented in the patient's medical records, and the informed consent form should be signed and personally dated by the patient and by the authorised person who conducted the informed consent discussion. The original signed informed consent form should be retained in accordance with institutional policy and GCP, and a copy of the signed consent form should be provided to the patient or consultee.

If a potential patient is illiterate or visually impaired and does not have a consultee, the investigator must provide an impartial witness to read the informed consent form to the patient and must allow for questions. Thereafter, both the patient and the witness must sign the informed consent form to attest that informed consent was freely given and understood.

In the event a study participant loses capacity to provide ongoing consent (e.g. due to medical illness), ongoing participation will be discussed with the participant's consultee. The consultee will be provided with the Consultee information sheet and, if in agreement, provide written confirmation for continued study participation on the consultee declaration form. Withdrawal from the study will also be considered if ongoing participation is not believed to be in the patient's best interests.

15.3 Patient confidentiality

The investigator must ensure that the patient's confidentiality is maintained in compliance with the UK Data Protection Act of 2018 and the General Data Protection Regulation (GDPR). On the case report forms or other documents submitted to the sponsor, patients should be identified by their initials and a patient study subject identification number only. Documents that are not for

submission to the Sponsor (e.g., signed informed consent forms) should be kept in strict confidence by the Investigator.

16. Data Handling and Record Keeping

16.1 Investigator Signatory Obligations

Each clinical study report or case report form should be signed by the investigator or a member of the study team named in the site signature log and authorised by the site principal investigator.

Original copies of all completed case report forms should be retained by the site once they have been emailed to the GI & Lymphoma Trials Unit.

16.2 Data Handling

In compliance with GCP guidelines, it is required that the investigator and institution permit authorised representatives of the sponsor and of the regulatory agency(s) direct access to review the patient's original medical records for verification of study-related procedures and data. Direct access includes examining, analysing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform and obtain the consent of the patient to permit named representatives to have access to his/her study-related records without violating the confidentiality of the patient.

In this study anonymisation will be carried out by allocating a study subject identification number for samples which will be linked with a study subject identification number for patient outcome data, all patient identifiers will be removed. Tissue samples will be coded on entry to the study so that in all circumstances researchers carrying out the analysis will not have access to details that identify the patient and will see all data in an anonymised form.

Clinical data will be entered on to a MACRO database, which is held within a password protected environment with access controlled.

16.3 Study Documentation and Archive

The investigator should maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorised to make entries and/or corrections on case report forms will be included on the site signature log.

Source documents are original documents, data, and records from which the patient's Case Report Form data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, radiographs, and correspondence. The investigator and study staff are responsible for maintaining a comprehensive and centralised filing system of all study-related (essential) documentation, suitable for inspection at any time by representatives from the sponsor and/or applicable regulatory authorities. Elements should include:

- Patient files containing completed case report forms, informed consent forms, and patient identification list
- Study files containing the protocol with all amendments, copies of pre-study documentation, and all correspondence to and from the sponsor and institutional review board.

In addition, all original source documents supporting entries in the case report forms must be maintained and be readily available to permit trial related monitoring, audits, REC review and regulatory inspections where appropriate.

No study document should be destroyed without prior written agreement between the sponsor and the investigator. Should the investigator wish to assign the study records to another party or move them to another location, he/she must notify the sponsor in writing of the new responsible person and/or the new location.

Sponsor should ensure that all trial related documentation be retained for maximum period of time as specified in the UK clinical trials regulations.

16.4 Quality assurance/audit

Systems of quality assurance, including all elements described in this protocol will be implemented. Quality control is applied to each stage of data handling to ensure that data is accurate, reliable and processed correctly. All data and documentation related to this study will be available for GCP audit. All research staff will assist in all aspects of audit/inspection.

16.5 Annual reporting to REC

An Annual Progress Report will be submitted to the Research Committee.

16.6 Sample labelling, storage and destruction

In order to protect patient identity all samples will not be labelled with any information that may lead to the direct identification of the patient concerned, including patient name, date of birth, National Health Service (NHS) or hospital number. Instead, tissue and other specimens from each patient will be labelled with the study name, the study subject identification number (assigned at registration) and initials.

Samples will be stored indefinitely in secure facilities at St George's University Hospitals NHS Foundation Trust and offsite approved storage facilities (UK). However, the patient retains the right to have the sample material destroyed at any time.

The sponsor will be the exclusive owner of any data, discoveries, or derivative materials from the sample materials and is responsible, via the Chief Investigator, for the destruction of the sample(s) at the request of the research patient.

16.7 Use of information

All unpublished information relating to this study is considered confidential.

17. Financing, Indemnity & Insurance

The study sponsor is the Royal Marsden NHS Foundation Trust, Downs Road, Sutton, Surrey, SM2 5PT, United Kingdom. This study has been financed by the Royal Marsden Cancer Charity and the NIHR Biomedical Research Centre. Material Transfer Agreements (MTA) will be executed with St Georges Hospital.

No specific compensation arrangement exists for harmful events which might arise from participation in the study. However, the study is covered for negligent claims occurring with the NHS

by Crown indemnity. There is no pre-existing arrangement for non-negligent claims arising from the conduct of the study.

18. Publication Policy

The investigators will co-ordinate publication strategies, presentations and peer review publication. Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors, 2005), which states:

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3.
- When a large, multicentre group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

19. Abbreviations

ACE2	Angiotensin-Converting Enzyme 2
ARDS	Acute respiratory distress syndrome
ASCs	Antibody-Secreting Cells
CI	Confidence Interval
COVID-19	Coronavirus Disease 2019

CRF	Case Report Form
CRP	C-reactive Protein
D	Day number
DFID	Department for International Development
EDTA	Ethylenediaminetetraacetic Acid
ELISA	Enzyme-Linked Immunosorbent Assay
GCP	Good Clinical Practice
GP	General Practitioner
IL	interleukin
LFA	Lateral flow assay
OS	Overall Survival
HLA-KIR	Human leukocyte antigen, killer-cell immunoglobulin-like receptor
HRA	Health Research Authority
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
PHEIC	Public Health Emergency of International Concern
POC	Point of care
PON	Point of need
REC	Research Ethics Committee
RNA	Ribonucleic Acid
RT-PCR	Reverse Transcription-Polymerase Chain Reaction
SARS	Severe acute respiratory syndrome

sHLH	Secondary haemophagocytic lymphohistiocytosis
s.d.	standard deviation
TFH cells	follicular helper T cells
TMF	Trial Master file
TMG	Trial Management Group
WHO	World Health Organisation

20. Protocol Summary of Changes

Version	Summary of changes
v2.2 (first approved version)	Changes to accommodate R&D and HRA/REC recommendations
3.0	<u>Change of study title:</u> Cancer: Rapid Diagnostics and Immune assessment for SARS-CoV-2 (COVID-19) <u>Updated list of study personnel:</u> Investigators Dr Susana Banerjee (RMH) Dr Alison Reid (RMH) Professor Mary O'Brien (RMH) Dr Sophie McGrath (RMH) Research nurse(s) Ms Alexandra Diaz (RMH) <u>Updated eligibility criteria</u> Eligibility criteria: 1) Suspected COVID-19 infection undergoing diagnostic testing by SARS-CoV-2 RT-PCR or within 14 days of confirmed COVID-19 infection by SARS-CoV-2 RT-PCR (Arm A) OR No symptoms of SARS-CoV-2 infection (Arm B) 2) Metastatic or advanced solid organ malignancy, including lymphoma OR Early stage solid organ malignancy having

	received or planning to commence radiotherapy, chemotherapy or targeted agents Rationale: 1 To allow recruitment of patients with recently confirmed COVID-19 2 To facilitate Arm B of study 3 Amended to allow patients planned to commenced anti-cancer therapy <u>Addition of Arm B:</u> Asymptomatic patients with no clinical suspicion of COVID-19. Study procedures for Arm B and schedule of assessments outlined Existing study arm from v2.2 has been designated Arm A <u>Throat/nose SARS-CoV-2 results</u> For Arm A, patients with a SARS-CoV-2 negative nose/throat AND low clinical suspicion of COVID-19 will be removed from the study. <u>Number of patients:</u> Arm A: "Approximately 60 patients" – revised to "up to 60 patients" Arm B "Up to 150 patients"

21. References

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