A retrospective and prospective non interventional study to evaluate the role of immune and inflammatory response in recipients of allogeneic haematopoietic stem cell transplantation (SCT) affected by COVID19 infection (COVID19_BMT)

SHORT STUDY TITLE / ACRONYM

COVID19 infection in allogeneic stem cell recipient/COVID19 BMT

PROTOCOL VERSION NUMBER AND DATE

Version 4.0, 11th February 2021

RESEARCH REFERENCE NUMBERS

IRAS Number:	282229
SPONSORS Number:	20BO08
Clinical Trail Registration:	NCT 04349540

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:

Signature: Date: 17/04/20

Name (please print):

Stephanie De Sa Marques Basset

Chief Investigator:

Signature: Date: 18/05/20

Name: Giovanna Lucchini

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STUDY SUMMARY

Sponsor	Great Ormond Street Hospital
Chief Investigator	Persis Amrolia Great Ormond Street Hospital Persis.Amrolia@gosh.nhs.uk
Study title	**A retrospective and prospective non interventional study to evaluate the role of immune and inflammatory response in recipients of allogeneic haematopoietic stem cell transplantation (SCT) affected by COVID19 infection**
Short title	COVID19 post HSCT
Protocol version	Version 4.0, 11th February 2021
Study registration	R&D 20BO08 IRAS 282229
Study design	Multicentre, prospective and retrospective, non interventional.
Background and rationale	COVID19 pandemic currently represents a public health emergency. Based on current data, 15% of the affected individuals will develop a severe form of the disease requiring admission to hospital and respiratory support. Data show that age and cardiovascular pre-existing comorbidities predict a poorer outcome. Some evidence suggests that a subset of patients with poorer outcome present with a cytokine mediated inflammatory response and with a secondary HLH like clinical phenotype. Few data are so far available with regard to the risk of severe COVID19 disease in the post stem

	cell transplantation setting. Recipients of allogeneic stem cell transplantation are by definition immunologically dysregulated and could potentially present with a unique immune-inflammatory response to COVID 19 infection. Moreover, the immunosuppression used to prevent/treat GVHD may also impact clinical progression and it is possible that because of their immunological defects, SCT patients could potentially have prolonged carriage of the virus and hence act as "super spreaders". The present study aims at documenting clinical and biological characteristics, including immunological profiling, of allogeneic stem cell transplant recipients presenting with COVID 19 infection and its impact on patients survival. **This work may provide the scientific basis for targeted therapy with biological agents in this patient group.**
Primary hypothesis	Allogeneic stem cell transplant recipients represent a subset of patients with unique immunological characteristics and may present with a different response/risk profile to COVID19 infection as compared to the general population.
Objectives	**Primary objective:** 1. To describe the clinical, immune and inflammatory characteristics in recipients of allogeneic SCT presenting with COVID19 infection and determine the percentage of viral related mortality in this group of patients. **Secondary objectives:** 1. To determine whether immunosuppression at the time of development of COVID19 infection is associated with outcome

	2. To characterize the natural history of COVID19 infection in allogeneic SCT recipients in particular the proportion requiring mechanical ventilation and the frequency of secondary HLH 3. To determine the proportion of allogeneic SCT with COVID19 infection who clear the virus by 30 days
Inclusion criteria	**For both prospective and retrospective cohorts:** 1. Adult and paediatric patients (any age) who have received allogeneic stem cell transplantation 2. Proven COVID19 infection as documented by PCR testing of nasal/ throat swab or NPA NB: Both patients who develop COVID19 infection during their inpatient admission and those who are ambulated with confirmed COVID19 infection are eligible.
Exclusion criteria	**For the prospective cohort:** 1. Patients beyond the first 72 hours from COVID19 positive result **2.** Patients who have received cytokine targeting treatment before blood sampling
Endpoints	**All end points are exploratory** 1. Death rate at day 30 and day 100 days post diagnosis of COVID19 2. Requirement of mechanical ventilation 3. Incidence of secondary HLH (as defined by HS score)

	4. Incidence of COVID19 still detectable at 30 days post COVID19 diagnosis. 5. Inflammatory, biomarkers (CRP, clotting including fibrinogen and D-dimers, ferritin, albumin, cardiac troponin) and immunological profile (lymphocyte subsets, immunoglobulins + serum IL 2, 4, 6, 8, 10, 12, IFN-γ and TNFα levels) early (<72 hours) after development of oxygen requirement for severe COVID19 infection

Methods	The transplant teams in each participating site will be identifying and approaching eligible patients. Adult and paediatric patients with a history of allogeneic stem cell transplantation who are diagnosed with a PCR proven COVID19 infection will be eligible for the study. **For the retrospective cohort:** Clinical characteristics, blood results, and outcomes of the patients diagnosed with COVID19 infection will be recorded. **For the prospective cohort:** Within 72 hrs of COVID19 diagnosis, a 10 ml clotted blood (5 mls for pts below 15 kg weight) will be collected and serum frozen at -80^0 C. This sample will be sent with a 10ml blood sample (5 mls for pts below 15 kg weight) in EDTA to the Immunology Laboratories at Great Ormond Street Hospital (GOSH) in London for centralized cytokine and lymphocyte subset analysis. The sample will be divided into aliquots, one being analyzed directly, the second one being frozen for further assays as developed. Other immunological and biochemical parameters will be tested locally and results with local reference ranges will be collected for the purpose of the current study. In case the patient deteriorates from a respiratory perspective requiring oxygen, a second 5 ml serum sample

	will be collected, frozen at -80^0 C and sent to GOSH for repeated cytokine analysis. HScore will be calculated as per published data but bone marrow aspiration will be optional in calculating the scoring given the expected acute clinical situation of the patient. *(Fardet et al, Arthritis Rheumatol 2014).* Transplant research team members will collect demographic and clinical characteristics at the time samples are sent to GOSH. Blood results, data on clinical course, therapy (including biological agents) and outcome data will be collected with a follow up survey 30 and 100 days after COVID19 confirmed diagnosis **Statistical analysis:** All analysis of retrospective and prospective cohorts will be conducted separately. 1. Death rates will be presented as a proportion of patients who have died from any cause at each time point out of the total number of patients in the relevant cohort of the study. Proportions will be presented alongside 95% CI. Given sufficient patient numbers, logistic regression models will be used to assess the effects of baseline characteristics on this outcome. Death rates will also be analyzed within the subgroup of patients who are vs are not on ongoing immunosuppression. Additional analysis assessing death rates by IL-6 and CRP levels may be conducted if appropriate.

	2. Requirement for mechanical ventilation, incidence of secondary HLH and incidence of COVID presence post day 30 will be presented as a proportion of patients with the event of interest out of the total number of patients in the relevant cohort of the study. Proportions will be presented alongside 95% CI. Given sufficient patient numbers, logistic regression models will be used to assess the effects of baseline characteristics on this outcome. Time to COVID negativity will be assessed using Kaplan Meier curves and given sufficient numbers Cox model will be used to assess the effects of baseline characteristics on the outcome. 3. Inflammatory, biomarker and Immunoglobulin profiles post oxygen requirement will be plotted (if appropriate) and presented descriptively using medians and interquartile ranges 4. Multivariable models including multiple biomarkers and other factors such as age, co-morbidities and immunosuppression may be created as appropriate.
Enrolment timeframe	April 2020 to June 2021
Estimated number of participant	Up to 100 patients (retrospective and prospective) based on cases reported to EBMT Inborn Errors Working Party to date. It is anticipated that around 50 patients will be recruited retrospectively. The true incidence of COVID 19 infection in SCT patients is unknown, as are the outcomes for this group and therefore it is not possible to perform a reliable sample

	size calculation. Instead we aim to collect data for all patients within this time period.

FUNDING AND SUPPORT IN KIND

ABBREVIATIONS:

CRP: C reactive protein

GVHD: graft versus host disease

HLH: haemophagocytic lymphohistocytosis

HS: haemophagocytic score

HSCT: haematopoietic stem cell transplantation

IL-2,4,6,10,12: Interleukin -2,4,6,10,12

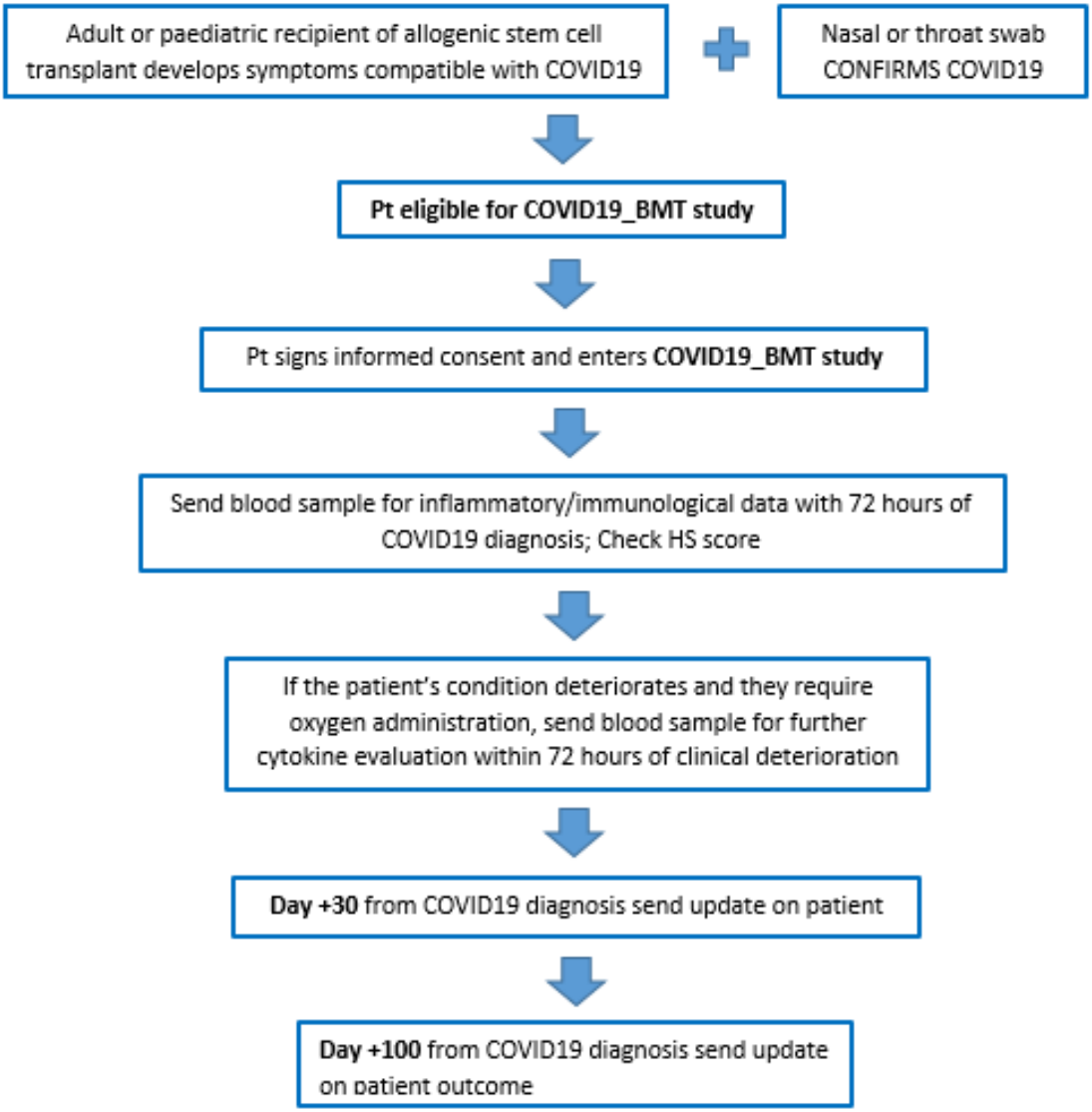
IFN: interferon

PHE: Publich Health England

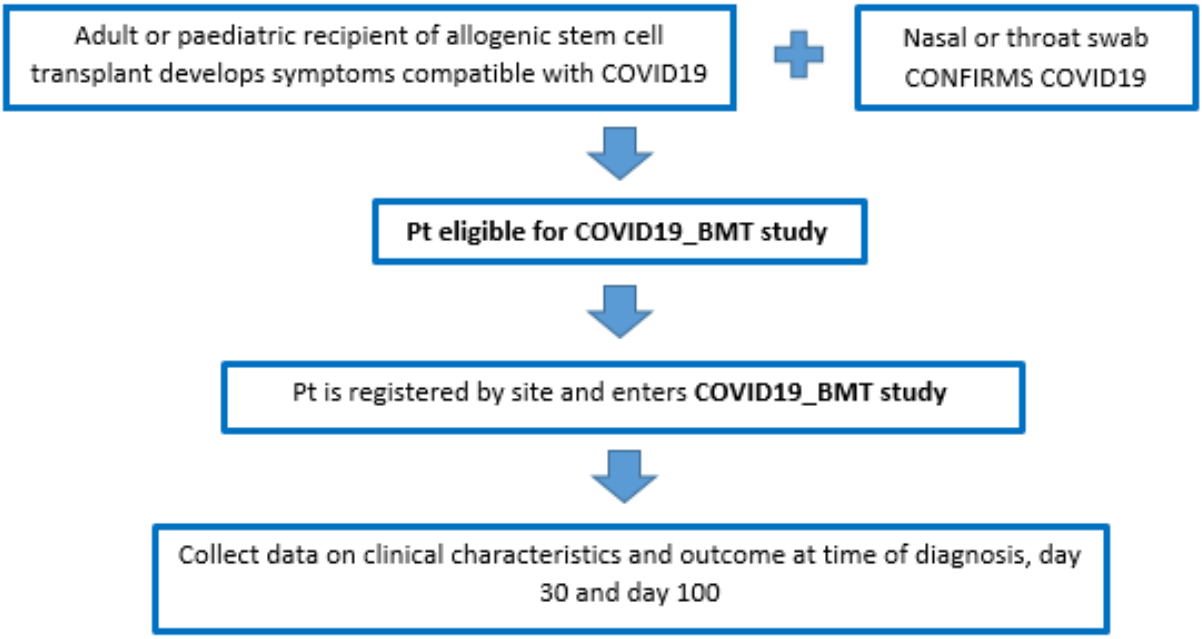
TNF: Tumor Necrosis Factor

STUDY FLOW CHART

Prospective cohort:



Retrospective cohort:



Transplant research teams at each site will be responsible for identifying eligible patients, approaching them for consent, shipping research related blood samples (if necessary), and collecting demographic and clinical data and data related to the patient follow up on day +30 and +100.

The standard of care related procedures during the admission of the patients will rest with the treating team, which can vary according to Trust organization, COVID19 sensitive practices and severity of the clinical picture.

STUDY PROTOCOL

A retrospective and prospective non interventional study to evaluate the role of immune and inflammatory response in recipients of allogeneic haematopoietic stem cell transplantation (SCT) affected by COVID19 infection.

1 BACKGROUND AND RATIONALE

In December 2019 Chinese authorities reported a cluster of cases of pneumonia of unknown origin in the Hubei province(1). China Center for Disease Control identified the pathogen responsible for those cases to be a new strain of Coronavirus on 9th January 2020 (SARS-CoV-2) (2). Inter human transmission of the virus/disease was confirmed again in China on the 11th January 2020, and the infection related to this virus has come to be known as COVID19 (3). The virus has quickly become the reason of the first pandemic of the 21st century and has spread with unprecedented relevance.

As of August 18th 2020, WHO confirms that cases of infection related to SAR-CoV19 have been reported as a total number of affected people >21,763,000 and >771,0000 viral related deaths (4).

The virus seems to be responsible for minor flu like symptoms in the majority of the general population, but around 15% of the proven positive patients develop a severe form of lower airways infection and up to 10% of the affected individuals require admission to intensive care for ventilatory support. Overall mortality from COVID19 disease seems to be around 2-3% of the affected individuals, but those figures are not final given substantial differences in mass population screening in different countries (5-6).

It has been recognized that age plays an important role in determining the risk of developing severe disease, with children below the age of 9 years representing only 1% of the known infected population with very rare reports of severe disease (7). On the opposite end of the spectrum, elderly people have by far the highest risk for severe disease

As of now it has reported a median age of all confirmed cases of 63 years and 78 years (range 30-103) in fatal cases (8). Importantly, according to both Chinese and Italian data >90% of the deceased patients became affected while already suffering from one or more chronic comorbidities. Specifically >70% of the deceased suffered from hypertension, 50% of cardiac problems, 30% of diabetes and 18% had had a cancer in 5 years preceding COVID 9 infection (9).

While most of the patients developing severe disease seem to have a frank pneumonitic evolution, with myocarditis in a minority of cases (11), there have been reports of cases where a severe inflammatory component might be responsible of a clinical picture similar to secondary HLH (12). A number of reports have hinted at an increased cytokine response in such cases, with elevation of IL-2R, IL-6, IL-8, IL-10, ferritin and TNFα being associated to worse disease course and prognosis (13, 14). Few data are so far available for the role of cytokine targeting agents in this context, but it has been recommended that COVID19 affected patients should be screened for signs and symptoms of secondary HLH (12).

Data on the risk of patients with primary or secondary immunosuppression are scanty and to some extent contradictory. Indeed some authors have reported previous cancer as one of the risk factors for severe COVID19 disease in adults (9), while limited data on paediatric patients with secondary immunosuppression due to organ transplant seem reassuring (10). The paucity of data in these groups and the lack of lack of a clear denominator with regard to the real extent of the population affected makes it difficult to draw conclusions at this stage.

At present there is virtually no data on the natural history of COVID19 after stem cell transplantation. It is possible that, by virtue of their poor immune reconstitution, SCT recipients may be more prone to severe COVID19 infection and could potentially have prolonged carriage of the virus, acting as "super-spreaders". Conversely, the immune paresis in these patients could paradoxically be protective in terms of secondary HLH/Cytokine Release Syndrome.

The present study aims to document the clinical and biological characteristics, including immunological profiling, of allogeneic stem cell transplant recipients presenting with COVID 19 infection and its impact on survival. This work may provide the scientific basis for targeted therapy with biological agents in this patient group.

2. PRIMARY HYPOTHESIS

Our hypothesis is that allogeneic stem cell transplant recipients represent a subset of patients with unique immunological characteristics and may present with a different response/risk profile to COVID19 infection as compared to the general population. The aim of this study is to investigate the inflammatory and immune response of patients developing COVID19 infection after allogeneic stem cell transplantation and to understand if a specific early inflammatory response impact on the severity of the COVID19 and ultimately on the patients outcome.

3. OBJECTIVES

Primary objective:

To describe the clinical, immune and inflammatory characteristics in recipients of allogeneic SCT presenting with COVID19 infection and determine the percentage of viral related mortality in this group of patients.

Secondary objectives:

- To determine whether immunosuppression at the time of development of COVID19 infection is associated with outcome;

- To characterise the natural history of COVID19 infection in allogeneic SCT recipients in particular the proportion requiring mechanical ventilation and the frequency of secondary HLH;

- To determine the proportion of allogeneic SCT with COVID19 infection who clear the virus by 30 days.

4. STUDY ENDPOINTS

1. Death rate from any cause at day 30 and day 100 post COVID-19 diagnosis.
2. Requirement of mechanical ventilation recorded for patients at any time post COVID19 diagnosis.
3. Incidence of secondary HLH as defined by HS score.
4. Incidence of COVID19 still detectable at 30 days post COVID19 diagnosis.
5. Inflammatory, biomarkers (CRP, clotting including fibrinogen and D-dimers, ferritin, albumin, cardiac troponin) and immunological profile (lymphocyte subsets, immunoglobulins + serum IL 2, 4, 6, 8, 10, 12, IFN-γ and TNFα levels) early (<72 hours) after development of oxygen requirement for any patient who presents with severe COVID19 infection or develops sever COVID19 infection.

5. STUDY SETTING

The study will involve adult and paediatric stem cell transplant centres in the UK and is supported through the IMPACT Clinical Trials Network.

Transplant physicians at each site will be responsible for identifying and screening for eligibility of potential patients.

For the retrospective cohort of the study, the BMT team (primary care team) at involved centres will review cases of COVID19 infection in allogeneic stem cell transplanted patients. For those identified, they will contact the patient to ask for consent for clinical data review and transfer. In case of patient death, as no identifiable data will be collected, and it will only be relevant staff at site dealing with this data, consent will not be collected.

For the prospective cohort of the study, it is predicted that most of the eligible patients will be admitted as inpatients at enrolment, either on the transplant/haematology ward or in intensive care. Regardless of the setting, the BMT research team will be responsible for the study related data and sample collection, for the sample shipping and for the follow up to day +100. As the patients will have different clinical severity of symptoms, their standard of care procedures will be different and only directed by their clinical needs.

Given the population of patients for this study will be COVID+, the patient facing study related activities will have to comply with the PHE and Trust guidelines for personnel protection while facing COVID19 positive patients.

All the participating sites will be involved in identifying and recruiting patients, sending samples for centralized analysis to Great Ormond Street Hospital (GOSH) and following up the patients until day +100.

GOSH will be responsible for sample analysis and storage.

6. SELECTION OF SITES/SITE INVESTIGATORS

In this protocol, trial 'site' refers to a hospital where study-related activities are conducted.

Sites must be able to comply with:

- Study sampling and follow up schedules and all requirements of the study protocol.
- Data collection requirements, including adherence to CRF submission
- Sample collection, processing and shipping requirements

Sites must have an appropriate Principal Investigator (PI), i.e. a health care professional authorised by the site, ethics committee and regulatory authority, to lead and coordinate the work of the trial on behalf of the site. Other investigators at site wishing to participate in the trial must be trained and approved by the PI. All investigators must be medical doctors and have experience of treating stem cell transplanted patients.

All site staff must be appropriately qualified by education, training and experience to perform the trial related duties allocated to them, which must be recorded on the site delegation log.

CVs for all staff must be kept up-to-date, signed and dated and copies held in the Investigator Site File (ISF).

Good Clinical Practice (GCP) training is required for all staff responsible for trial activities. The frequency of repeat training may be dictated by the requirements of their employing institution, or 2 yearly where the institution has no policy, and more frequently when there have been updates to the legal or regulatory requirements for the conduct of clinical trials.

Before a site is activated, the Sponsor and CI will arrange on-line training for study related procedures.

7. ELIGIBILITY CRITERIA

Inclusion criteria

Prospective and retrospective cohorts:

1. Adult and paediatric patents (any age) who have received allogeneic stem cell transplantation
2. Proven COVID19 infection as documented by PCR testing of nasal/ throat swab or NPA

Exclusion criteria

Prospective cohort:

1. Patients beyond the first 72 hours of positive COVID19 diagnosis or
2. Patients who have received cytokine targeting treatment before blood sampling

8. STUDY DESIGN AND DURATION

This is a non interventional, retrospective and prospective, multicentre study.

It is anticipated the first patient will be enrolled in April 2020 and the last patient in June 2021.

With a follow up of 100 days from study start we envisage last patient last visit to be in September 2021.

Data analysis will be carried out between October and December 2021.

9. STUDY RELATED PROCEDURES

9.1. Patient identification/enrolment

Prospective cohort:

Patients who have received stem cell transplantation are in close contact with their transplant centres as this remains their point of reference in case of clinical complications and therefore the transplant team will be alerted when a previously transplanted patient is being admitted at the site.

Post stem cell transplant patients who present with symptoms compatible with COVID19 infection will be assessed for COVID19 infection with a throat and/or nasal swab/NPA as per standard of care by the treating team on admission.

The transplant research team should approach the patient at this stage with study related information to allow the patient adequate time to consider entering the study if eligibility confirmed.

If the patient is confirmed to be COVID19 positive the patient will be eligible for the study and the transplant research team will perform consent related procedures. Informed consent will be obtained from the patients (if age ≥ 16 years) or parent/legal guardian if age < 16 years. If the patient is not capable of giving informed consent due to his/her clinical condition, the site PI or delegate will contact the next of kin/consultee to obtain consent if appropriate.

Once consent is obtained, the transplant research team will notify the sponsor and CI via email (see details on eCRF) and send the Registration Form eCRF. A study number will be issued for the patient and will be communicated via email to the site research team. All data/sample collected following this communication should refer to the patient with his study number, month and year of birth only.

Patients will be treated with medical therapy and supportive care as per local institutional policy, independent of the study.

Retrospective cohort:

Patients who have received stem cell transplantation and who have been diagnosed with COVID19 may be eligible for the retrospective cohort.

The transplant research team should identify any patients they believe to be eligible and approach the patient at this stage with study related information to allow the patient adequate time to consider entering the study while eligibility is confirmed.

At this time if the patient is deemed to be eligible the transplant team will perform consent related procedures. Informed consent will be obtained from the patients (if age ≥ 16 years) or parent/legal guardian if age < 16 years. Once consent is obtained, the transplant research team will notify the sponsor and CI via email (see details on eCRF) and send the Registration Form eCRF. A study number will be issued for the patient and will be communicated via email to the site research team. All data collected following this communication should refer to the patient with his study number, month and year of birth only.

In the case of deceased patients, consent will not need to be obtained as no identifiable information is being collected. However, once they have confirmed eligibility, the transplant research team will still need to notify the sponsor and CI via email (see details on eCRF) and send the Registration Form eCRF. A study number will be issued for the patient and will be communicated via email to the site research team. All data collected following this communication should refer to the patient with his study number, month and year of birth only.

Remote consenting:

If due to local policies and procedures it is not advised for the patient to attend the site, consent may be collected remotely. In this instance the PIS and consent forms should be sent to the patient (emailed or posted), and a call should be made to speak to the participant and/or guardian. The patient should sign the consent form and send it back to the site. It should be documented that the patient and/or guardian has read and understood the PIS version xx date xxxx and has agreed to take part in this study. Once the signed consent form is received, the PI or delegate who spoke to the patient should sign the consent form and send a copy to the patient. Additionally, the medical team who spoke to the patient should record this in the medical notes.

9.2. Time point 1

Prospective cohort only:

Within 72 hrs from diagnosis of COVID19 infection the following study related procedures/assessments will take place

(a) Blood draw of 10 ml in EDTA (5 mls if weight<15 kg) for centralized lymphocyte subset assessment, blood sample will be taken together with standard of care bloods to minimize patient discomfort (this sample can be taken either by the treating team or by the transplant research team members depending on where the patient is admitted);

(b) Blood draw of 10 ml clotted blood (5 mls if weight<15 kg) for centralized cytokine assessment which will include IL2,4,6,10,12 TNFα and IFN-γ (this sample can be taken either by the treating team or by the transplant research team members depending on where the patient is admitted). The sample will be centrifuged by the site laboratory and serum cryopreserved.

The transplant research team will be responsible for organizing the shipment of the blood samples to Great Ormond Street Hospital Immunology Laboratory accompanied by the lab sheet (see Appendix 1). Please note samples should be sent with only trial number, month and year of birth at shipping.

(c) The transplant research team on sites will assess the patient modified HS score (see Appendix 2). The score is based on published data by *Fardet et al* (15) but modified as in our setting NO bone marrow aspirate evaluation will take place given the severity of the patient clinical situation and the practicalities of invasive procedures in a COVID19 positive patient and report them via eCRF within 15 days from data collection;

(d) The transplant research team will collect the following transplant related information: underlying condition, disease status at SCT, type of donor, HLA matching, source of stem cells, conditioning regimen and GVHD prophylaxis, date of SCT, history of acute or chronic GVHD and report them via eCRF within 15 days from data collection;

(e) The transplant research team will collect the following clinical history information: hypertension, diabetes, previous cardiac disease, smoking habit and report them via eCRF within 15 days from data collection;

(f) The transplant research team will collect clinical data on the following at study entry and report them via eCRF within 15 days from data collection:

- Lansky/Karnofsky
- Ventilatory support
- Signs of acute myocarditis
- Need for vasopressor
- Need for renal support

(g) The transplant research team will collect data on medication regarding immunosuppression and COVID19 directed therapy and report them via eCRF within 15 days from data collection;

9.3. Time point 2

Prospective cohort only:

If the patient deteriorates significantly to the point of requiring oxygen support it is mandatory that the site take a second 5 ml sample of clotted blood and send serum for centralized cytokine measurement in order to assess the profile at the time of clinical deterioration.

The ample must be collected within 72 hrs from patient deterioration and cryopreserved serum promptly shipped to GOSH for analysis via courier (see Lab Manual for details).

The sample will again be sent with trial number, month and year of birth and accompanied by lab shipping sheet.

Clinical data with regard to timepoint 2 will be reported on a dedicated CRF within 15 days from blood sampling.

The following clinical data will be collected:

- Lansky/Karnofsky
- Ventilatory support
- Signs of acute myocarditis
- Need for vasopressor
- Need for renal support
- HS score
- Ongoing immunosuppression/GVHD

If the patient does not require supplemental oxygen at any point during the trial, time point 2 will not need to be completed.

9.4. Time points 3 (day +30) and 4 (day +100)

Prospective and retrospective cohorts:

The transplant team will re assess patient data remotely on day +30 and +100 from COVID19 diagnosis and report them via eCRF within 15 days from data collection. The study is designed in such a way that no face to face contact with the patient will be required on day +30 and +100.

The following clinical data will be collected at day +30 and +100

- Patient outcome
- Maximum degree of ventilator support
- Maximum degree of cardiovascular support
- Maximum degree of renal support

- Clinical features of secondary HLH at any point
- Time to negative PCR for COVID19 in nasal and/or throat swab/NPA
- Data on immunosuppressive and COVID19 related treatment

10. SCHEDULE OF ASSESSMENTS

Prospective cohort:

Timepoints	**Enrolment**	**1.** **Within 72 hrs** **from COVID19 positive test**	**2.** **Within 72 hrs of pt requiring oxygen administration**	**3.** **Day +30** **from COVID19 diagnosis**	**4.** **Day+100** **from COVID19 diagnosis**
				(± 2 days)	(± 7 days)
Administrative procedures					
Informed consent/child assent/parental permission	x				
Confirm eligibility	x				
Demographics	x				
Comorbidities		x			
Transplant history		x			
Infection surveillance		x			
Physical assessment					
Karnofsky/Lansky score		x	x	x	x
Respiratory support assessment		x	x	x	x
Ongoing Subject assessments					
HS score		x	x		
Immunosuppression history		x	x	x	

GVHD history		x	x	x	x
Patient outcome				x	x
Clinical course of COVID19		x	x	x	x
COVID19 related pharmacological treatment		x	x	x	x
Laboratory assessment done at each centre					
Full blood count		x	x		
Immunoglobulins		x			
CRP		x	x		
Clotting (including fibrinogen and D-dimers)		x	x		
Ferritin		x	x		
Albumin		x	x		
Cardiac troponin		x	x		
AST, ALT		x	x		
Creatinine		x	x		
Triglycerides		x	x		
Blood withdrawal **To be sent to GOSH immunology lab (see lab manual for details)**					
10 mls EDTA (5 mls if pt <15 kg)		x			
10 mls clotted blood (5 mls if pt<15 kg)		x			
5 mls clotted blood for all patients			x		

Retrospective cohort:

Timepoints	**Enrolment**	**1.** **Within 72 hrs** **from COVID19 positive test**	**2.** **Within 72 hrs of pt requiring oxygen administration**	**3.** **Day +30** **from COVID19 diagnosis**	**4.** **Day+100** **from COVID19 diagnosis**
				(± 2 days)	(± 7 days)
Administrative procedures					

Informed consent/child assent/parental permission	X[1]				
Confirm eligibility	x				
Demographics	x				
Comorbidities	x				
Transplant history	x				
Infection surveillance	x				
Physical assessment					
Karnofsky/Lansky score	x			x	x
Respiratory support assessment	x			x	x
Ongoing Subject assessments					
HS score	x				
Immunosuppression history	x			x	
GVHD history	x			x	x
Patient outcome	x			x	x
Clinical course of COVID19	x			x	x
COVID19 related pharmacological treatment	x			x	x
Laboratory assessment done at each centre					
Full blood count		x	x		
Immunoglobulins		x			
CRP		x	x		
Clotting (including fibrinogen and D-dimers)		x	x		
Ferritin		x	x		
Albumin		x	x		
Cardiac troponin		x	x		
AST, ALT		x	x		
Creatinine		x	x		
Triglycerides		x	x		

[1]If patient is deceased, this is not applicable

11. BLOOD SAMPLING

Prospective cohort:

The current study mandates the following blood sampling:

Within 72 hrs from confirmed diagnosis of COVID19 (Time point 1):

1) EDTA blood (10 mls if >15 kg weight and 5 mls if below) to be collected for lymphocyte subsets centralized analysis
2) Clotted blood (10 mls if >15 kg weight and 5 mls if below) to be collected for cytokine analysis. This sample should be kept in ice until spun to collect serum should be frozen at -80C and sent with courier to the Immunology Laboratory of Great Ormond Street Hospital*

*Sample should be sent accompanied by the lab sheet (Appendix 1) and labelled with month and year of birth and study number.

A second sample of clotted blood (5 mls only for all pts) is required for further cytokine analysis if the patient deteriorates to the point of requiring any level of oxygen support (time point 2). We recommend this sample to be sent within 72hrs form the clinical deterioration. This sample should be kept in ice until spun to collect serum should be frozen at -80C and sent with courier to the Immunology Laboratory of Great Ormond Street Hospital. Sample should be sent accompanied by the lab sheet and labelled with study number, month and year of birth.

Blood will be withdrawn at the same time point as standard of care bloods to limit the patients discomfort.

Excess peripheral blood mononuclear cells and serum will be cryopreserved at Great Ormond Street Hospital Immunology lab for future study-related assays as developed. Stored samples will be discarded according to GOSH standard operating procedure and HTA regulation at the end of the study period.

Please ensure that standard of care bloods as outlined in schedule of assessment are taken at time point 1 and 2

**Please see Lab Manual and Lab shipping sheet for details of samples preparation and shipment*

12. CENTRALIZED BLOOD RESULTS

The Sponsor and Chief Investigator will communicate the results of serum cytokine profiling (including IL-2,IL-4, IL-6, IL-10, IFN-γ and TNFα levels) within 48-72 hrs from having received the blood sample to the PI at the transplant site.

However, it should be noted that these data are provided for information only and are not intended to guide clinical management. At the time of protocol writing THERE IS NO CLINICAL EVIDENCE that treatment based on biomarkers of disease improves outcomes. While HLH like activation and hyperinflammatory reactions have been described to be more common in patients with COVID19 infection with poor prognosis, there is as yet no clear evidence that targeting any of the biochemical markers of hyperinflammation is of proven benefit to patients.

A Chinese study reported of 21 patients with severe/critical COVID infection being treated with Tocilizumab (Il-6 Ab) after failing antivirals and steroids with a significant response in terms of fevers and oxygen requirement in all treated patients and full recovery in 19/21 (16). While these data are encouraging, they are based on a very limited number of patients with no control arm. Based on this report Roche launched a phase 2 study for the use of Tocilizumab in COVID19-related pneumonia (NCT04317092). Recruitment is completed but results are currently not available. Similarly, data targeting other cytokines in COVID-19 infection is also very limited. Given the lack of solid data with regard to potential cytokine targeted treatment, the potential of limited drug availability and the rapid clinical deterioration that some of the COVID19 affected patients experience, we strongly believe treatment of patients should for now be based on clinical evaluation and that patients should be treated on therapeutic clinical trials where possible. The results of cytokine data will be provided to sites because we recognise this may provide clinicians with useful diagnostic information and that this may become increasingly relevant as new data emerge.

13. SAMPLE SIZE AND STATISTICAL CONSIDERATION

The true incidence of COVID 19 infection in SCT patients is unknown, as are the outcomes for this group and therefore it is not possible to perform a reliable sample size calculation, instead we aim to collect data for all patients within this time period. Based on estimates drawn from non published data we aim at recruiting up to 100 patients to this study (including retrospective patients). It is anticipated that roughly 50 patients will be recruited to the retrospective cohort.

All analysis will be conducted on an intention to treat basis regardless of if a patient is found to be ineligible. Analysis of retrospective and prospective cohorts will be conducted separately and will be descriptive and exploratory in nature.

With relation to our endpoints, these are the analysis that will be carried out on the data:

1. Death rate at day 30 and day 100:
    - Death rates will be presented as the number of patient deaths from any cause at each time point out of the total number of patients in the relevant cohort of the study. Proportion will be presented alongside 95% CI.
    - Analysis within the subgroup of patients who are vs are not on ongoing immunosuppression will also be conducted.
    - Additional analysis assessing death rates by IL-6 and CRP levels may be conducted if appropriate using logistic regression.
2. Requirement for mechanical ventilation, incidence of secondary HLH and incidence of COVID presence post day 30:
    - These categorical outcomes will be presented as a proportion of patients with the event of interest out of the total number of patients in the relevant cohort of the study. Proportions will be presented alongside 95% CI.
    - Given sufficient patient numbers, logistic regression models will be used to assess the effects of baseline characteristics on this outcome.
    - Time to COVID negativity will be assessed using Kapaln Meier curves and given sufficient numbers Cox model will be used to assess the effects of baseline characteristics on the outcome.
3. Inflammatory, biomarker and Immunoglobulin profiles post oxygen requirement:
    - These outcomes will be presented descriptively using medians and interquartile ranges.
    - Plots of levels over time will also be presented if appropriate

4. Multivariable models including multiple biomarkers and other factors such as age, co-morbidities and immunosuppression may be created as appropriate.

14. INFORMED CONSENT

The study team at each site will be responsible in undertaking informed consent from each participant prior to participation in the study, following adequate explanation of the aims, methods, anticipated benefits and potential hazards of the study. For children under the age of 16 years old an informed assent will be obtained.

Age appropriate patient information leaflets have been created as part of this study to assist the investigators in seeking consent for eligible patients and to offer eligible patients of different age ranges a clear explanation of the study. The person undertaking consent will be suitably qualified and experienced and will have been delegated this duty by the CI/ PI on the Staff Signature and Delegation of Tasks.

Sites must assess a patient's (and/or parent/guardian's) ability to understand verbal and written information in English and whether or not an interpreter would be required to ensure fully informed consent. If a patient (and/or parent/guardian) requires an interpreter and none is available, the patient should not be considered for the sites. We envisage most of the eligible patients will be identified at the onset of clinical symptoms compatible with COVID19. They should be approached at this stage to discuss the details of the study, while PCR confirmation of COVID19 infection is pending. This will give the patient a period of 24 hrs (usually the turn around time of COVID19 PCR screening) to consider the study content and related procedure and ask questions if necessary.

Each participant can withdraw consent at any time point during the study, data that were collected up to the point of withdrawal will be kept as part of the study, as specified in the informed consent.

Some of the adult patients who are eligible for the study will be clinically unwell to the point of not being able to consent for the study.

The PI will have to assess capability before approaching consent procedures. To do so he will rely on his clinical experience, on his GCP training and on the principle of the Mental Capacity Act 2005 and its associated Code of Practice.

Provisions for seeking consent from a consultee have been made and adequate forms to that regard are found in the patient facing information file. The inclusion of these patients in the study should be attempted if the local Principal Investigators regards it as appropriate.

If yes, the PI should :

1) Make sure of whether it has been documented in the clinical notes that the patient has expressed personal views on entering research studies either in present or past times and take his/her views into account

If such a search retrieve evidence of the patient expressing negative feelings/beliefs or thoughts about research studies, the patient should not be included in the study.

If no such evidence is documented the PI should:

2) Make sure of whether it has been documented in the clinical notes that the patient has indicated a preferred relative or friend to be involved in decision making in case of the patient becoming unable to take those decisions

If that is the case the PI can contact the designated personal consultee and have an extensive discussion about views/thoughts and beliefs of the potential participant with regard to scientific research and potentially taking part in clinical research. If anything would hint at the patient views being against taking part in clinical research the patient should not be considered for the study.

3) If 2) is not true, than the PI can decide to contact family members and ask for consent to take part to the study in England and Wales, whereas in Scotland the PI should identify a Legal representative for the same purpose. Given the current epidemic risk, contact with relevant family member is encouraged to be over the phone

The PI will have to consider the emotional implication of having a telephone conversation with regard to the potential participation of a critically ill individual in a clinical research study over the phone with a friend or family member that had not been previously acknowledged of his/her potential role a consultee.

The PI will make the final call with regard to whether he feels appropriate to engage in such conversation to try and achieve consent on behalf of the patient. The PI is encouraged to consider identifying a nominated consultee instead of a personal consultee where the latter was not available/appropriate to approach. The PI should make provision within its site to identify a nominated Consultee according to local arrangement.

If at any point a patient who has entered the study via consultee consent because of being non-capable regains capability to consent, the PI will hold responsibility of repeating the consenting process with the patient itself and withdrawing him/her form the study should his/her opinion about entering the study be not favourable.

Data collected up to the point of withdrawal will be stored in the research database.

No trial procedures will be conducted prior to the participant signing the consent form. A copy of the signed consent/ Assent form will be give to the participant. The original signed form will be retained in the trial file at site and a copy placed in the medical notes. The procedure of consent taking MUST be recorded in the patient notes.

Site staff will be responsible for:

- checking that the correct (current approved) versions of the patient information sheets and consent form are used;
- checking that information on the consent form is complete and legible;
- checking that the patient (and/or parent/guardian) has completed/initialled all relevant sections and signed and dated the form;
- checking that an appropriate member of staff has countersigned and dated the consent form to confirm that they provided information to the patient;
- checking that an appropriate member of staff has made dated entries in the patient's medical notes relating to the informed consent process (i.e. information given, consent signed etc.);
- following registration: adding the patient trial number to all copies of the consent form, which should be filed in the patient's medical notes and investigator site file;
- giving the patient (and/or parent/guardian) a copy of their signed consent form, patient information sheet.

Remote Consenting:

If due to local policies and procedures it is not advised for the patient to attend the site, consent may be collected remotely. In this instance the PIS and consent forms should be sent to the patient (emailed or posted), and a call should be made to speak to the participant and/or guardian. The patient should sign the consent form and send it back to the site. It should be documented that the patient and/or guardian has read and understood the PIS version xx date xxxx and has agreed to take part in this study. Once the signed consent form is received, the PI or delegate who spoke to the patient should sign the consent form and send a copy to the patient. Additionally, the medical team who spoke to the patient should record this in the medical notes.

For the retrospective cohort (deceased patients):

In the case of deceased patients entering the retrospective cohort of the study, as no identifiable data will be collected, and only the relevant site staff will be accessing this information, informed consent is not required. Informed consent will be required and carried out per the details specified above for retrospective patients that are alive upon entering the study.

15. STUDY SAFETY

This study will enrol patients with confirmed COVID19 infection.

As such it is our intention to limit the burden on both patients and healthcare operators imposed by study related procedures.

All clinical personnel approaching the patients per study purpose should be trained in infection control and personal protection specifically relating to COVID19 infection. General guidance with regard to this is available from Public Health England at https://www.england.nhs.uk/coronavirus/secondary-care/ and specific Trust related guidance must be followed.

Patients admitted for COVID19 infection post allogeneic stem cell transplantation will have a venous access in place in most cases for standard of care procedures and the mandatory study bloods will be taken during standard of care access to available venous access wherever possible. Venepuncture will be required for patients with no venous access in place and study bloods will be coupled with standard of care monitoring bloods when possible.

Healthcare professionals performing study related blood withdrawal will be appropriately trained in infection control, aseptic technique, blood sampling.

This study poses minimal risk to the patient but we recognize the possibility of the following safety issues to the patients:

1) Increased risk of line related infection due to accessing the central venous line if in place
2) Risk of local pain, bruising and patient distress if venepuncture required

The appropriate training of the site staff as well as the effort in limiting the study related blood sampling to a time where standard of care bloods will already be taken will minimize those risks.

16. ETHICAL AND REGULATORY CONSIDERATIONS

In conducting the trial, the Sponsor and sites shall comply with all laws and statutes, as amended from time to time, applicable to the performance of clinical trials including, but not limited to:

- the principles of ICH Harmonised Tripartite Guideline for Good Clinical Practice (CPMP/ICH/135/95) as set out in Schedule 1 (Conditions and Principles of Good Clinical Practice and for the Protection of Clinical Trial Subjects) of the Medicines for Human Use (Clinical Trials) Regulations 2004 and the GCP Directive 2005/28/EC, as set out in SI 2006/1928

- the Human Rights Act 1998

- the Data Protection Act 1998

- the Freedom of Information Act 2000

- the Human Tissue Act 2004

- the Medicines Act 1968

- the Medicines for Human Use (Clinical Trials) UK Regulations SI 2004/1031, and subsequent amendments

- the Research Governance Framework for Health and Social Care, issued by the UK Department of Health (Second Edition 2005) or the Scottish Health Department Research Governance Framework for Health and Community Care (Second Edition 2006)

The study will be conducted in accordance with the World Medical Association Declaration of Helsinki entitled 'Ethical Principles for Medical Research Involving Human Subjects' (1996 version), ICH Good Clinical Practice Guidelines and in accordance with the terms and conditions of the ethical approval given to the trial. The trial has received a favourable opinion from the Research Ethics Committee. CI will submit Annual Progress Reports to the REC, which will commence one year from the date of ethical approval for the trial.

17. DATA MANAGEMENT

Study related data will be collected at the participating centres by health care professionals within the BMT teams. Data will be filed in an eCRF and electronically sent to the IMPACT hub where it will kept on password controlled computers and analysed once the study is finished.

Source documents are original documents, data, and records from which participants' CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRFs), clinical and office charts, laboratory and pharmacy records, diaries. This personal data will only be accessed by the medical team directly looking after the patient.
Following registration to the study, the pt will only be referred to with study number, month and year of birth.
The participant study ID will be entered on the participant's medical notes, this may be housed on a Hospital Electronic Patient Record. This is so that hospital staff can link the participant to the study.

CRFs will only report those details as well as blood samples mandated by the study.
CRF will be shared electronically within NHS password protected computers and data will be collected within the IMPACT Hub for research, which operates in line with National data on Data protection and Governance.

At the end of the study, data will be fully anonymized, summarized in a database and kept within IMPACT for analysis. Anonymised electronic data are retained indefinitely.

All data will be handled in accordance to the Data Protection Act 2018 and GDPR regulations.

18. DIRECT ACCESS TO DATA SOURCE

Only members of the trial research team and the trial monitor will have direct access to the source data and trial documentation. All source data and trial documentation will also be available to external auditors if and when required, and inspectors in the event of regulatory inspection. Access to the final data set will remain with the chief investigator.

19. FINANCIAL INFORMATION AND INSURANCE

No financial provisions are made within the study for patients reimbursement.
The individual NHS Trusts have a duty of care to patients and indemnity for participating hospitals will be provided through the usual NHS indemnity arrangements

20. PUBLICATION POLICY

All individuals who have made substantial intellectual, scientific and practical contributions to the trial and the manuscript should, where possible, be credited as authors; all individuals credited as authors should deserve that designation. It is the responsibility of the Chief Investigator and co-PI and, ultimately, the Sponsors to ensure that these principles are upheld. The status of manuscripts in preparation will be reviewed by the chief Investigator and sponsor if requires. In all cases where journal policies permit, all investigators who contribute patients to the trial will be acknowledged.
The results of the study will be reported and disseminated as follows;

- Peer reviewed scientific journals;
- Internal report, plus possible article on Institute web pages (publicly accessible) ;
- Conference presentation(s)
- Written feedback to patient support groups.

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APPENDIX 1: Lab sheet

A retrospective and prospective non interventional study to evaluate the role of immune and inflammatory response in recipients of allogeneic haematopoietic stem cell transplantation (SCT) affected by COVID19 infection

<table>
<tr><td colspan="3">BIOLOGICAL SAMPLES</td></tr>
<tr><td colspan="3">Please complete the following details and forward to GOSH IMMUNOLOGY lab along with each samples</td></tr>
<tr><td colspan="3">Please remember to use patient study number: DO NOT USE THE PT FULL NAME TO IDENTIFY A PATIENT</td></tr>
<tr><td colspan="3">STUDY: COVID19_BMT</td></tr>
<tr><td>Site :

Patient study number:</td><td>Sex:
☐ Male
☐ Female</td><td>Month and year of birth
(mm/yyyy):</td></tr>
<tr><td>Type of sample
Tick all that applies</td><td colspan="2">☐ Peripheral blood EDTA

☐ Clotted blood (keep on ice until serum obtained and then promptly freeze at -80; ship on dry ice)</td></tr>
<tr><td></td><td>Date sample collected:</td><td></td></tr>
<tr><td>Sample sent by staff member name:</td><td>Contact tel:</td><td>Contact email</td></tr>
<tr><td>Study time point
(tick as appropriate, ONE box only)</td><td>☐ Initial sample 72 hrs from diagnosis of COVID19

☐ Second sample as pt deteriorated and</td><td></td></tr>
</table>

	Requires oxygen support	
Send samples with courier: Overnight delivery (to arrive by noon the day after the sample was taken)	**Immunology Laboratory** Dr. Kimberly Gilmour Level 4, Camelia Botnar Laboratories Great Ormond Street Hospital For Children NHS Trust Great ormond Street London WC1N 3JH	
Sample	**Peripheral blood in EDTA for lymphocyte subsets analysis**	**10 mls fro pts >15 kg, 5 mls fro pts < 15 kg within 72 hrs from O_2requirement start** **NO SECOND SAMPLE REQUIRED FOR ANY PATIENT**
	Clotted blood **Use a white top S-Monovette tube** **For serum cytokine analysis, keep on ice until serum is frozen at -80C**	**10 mls fro pts >15 kg, 5 mls fro pts < 15 kg within 72 hrs from O_2requirement start** **Second sample OPTIONAL and ONLY if the patient becomes CPAP OR mechanical ventilation dependant**

For laboratory use only	**MRN:**	**AFFIX LAB NUMBER:**	
Sample received/sufficient quantity	☐ **YES** ☐ **NO**	If no, please specify:	
Date sample received		Time sample received	
Checked by			
Processed by			

Date Processed			

APPENDIX 2: MODIFIED HS score

	Number of points
Temperature max	
<38,4℃	0
38,4-39,4 ℃	33
>39,4 ℃	49
Organomegaly	
None	0
Hepatomegaly or splenomegaly	23
Hepatomegaly and splenomegaly	38
Number of cytopenias[#]	
One lineage	0
Two lineages	24
Three lineages	34
Triglycerides (mmol/l)	
<1,5 mmol/l	0
1,5-4 mmol/l	44
>4 mmol/l	64
Fibrinogen (g/L)	
>2,5 g/L	0
≤2,5 g/L	30
Ferritin (ng/ml)	
<2000 ng/ml	0
2000-6000 ng/ml	35
>6000 ng/ml	50
Serum aspartate aminotransferase	
< 30 IU/L	0
≥ 30 IU/L	19

Known immunosuppression†	
No	0
Yes	18

Defined as either haemoglobin concentration of 9,2 g/dL or less (≤5,71 mmol/L), a white blood cell count of 5000 white blood cells per mm³ or less, or platelet count of 110 000 platelets per mm³ or less, or all of these criteria combined.

†HIV positive or receiving long-term immunosuppressive therapy (ie, glucocorticoids, cyclosporine, azathioprine).

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