

BSBMTCT recommendations for the management of adult patients and allogeneic donors during the COVID-19 (causative agent the SARS-CoV-2 virus) outbreak.

Version 9; 27th March 2022

Current status of SARS-CoV-2 in the UK.

The waves of the SARS-CoV-2 pandemic have been characterised by Variants of Concern (VOC), most recently dominated by the omicron variant, the precise impact of which remains uncertain in HSCT, haemato-oncology and other immunocompromised patients, despite being associated with milder illness in the general population.

Highly effective vaccines against SARS-CoV-2 are widely available with the vast majority of the adult UK population having received at least a two dose primary course of vaccination, with 66% of the population over the age of 11 now also receiving a third booster dose of a SARS-CoV-2 vaccine. The current SARS-CoV-2 vaccines are significantly less immunogenic in patients who have undergone allogeneic and autologous stem cell transplantation leading to continued vulnerability to serious life-threatening complications following SARS-CoV-2 infection even after vaccination. A range of factors can affect response to vaccination, including disease type, time from transplant and immunosuppressive therapy, especially previous treatment with targeted lympho-depleting therapy. Data in CAR-T cell recipients are more limited, but similar principles are expected to apply. The current position of BSBMTCT is regularly updated by the Vaccination Sub-Committee in our vaccination guidelines available at <https://bsbmtct.org/bsbmtct-and-covid>.

The efficient rollout of the SARS-CoV-2 vaccination programme in the wider population was hoped to be the key factor that would finally control the pandemic and convert the virus into an endemic state but the emergence of the new VOC has significantly challenged this outlook. The enhanced immune-evasive properties of the omicron variant further reduces the effectiveness of the current generation of anti-spike SARS-CoV-2 vaccines even in immunocompetent individuals, though a booster vaccine dose helps to restore most, but not all of their effectiveness.

Transplant teams must continue to remind patients that they remain at risk, even after receiving a full course of vaccination. Transplant teams must also continue to advise patients and their families on social distancing behaviour to minimise exposure to the virus*.

While hospitals are much better prepared when compared to the start of the pandemic, most healthcare facilities continue to struggle with accommodating emergency and elective activity alongside the care of patients admitted with COVID-19. Many transplant programmes remain under pressure with staff reallocation, staff illness or isolation due to contact with COVID-19 cases. The impact on transplant activity through the waves of COVID-19 has been varied, with some centres being able to deliver near-normal activity and others more affected. All centres and staff have experienced increased levels of stress related to workload, staffing and different ways of working, and it is unlikely that this situation will return to normal for the present.

However, considerable progress has been made with the development and delivery of therapeutics for COVID-19. The optimisation of the management of patients with COVID-19 has led to major improvements in patient outcomes with COVID-19 when compared to the first wave of the pandemic. SARS-CoV-2 antivirals and SARS-CoV-2 neutralising monoclonal antibody therapies have particular potential for improving outcomes of transplant patients who develop COVID-19. Both classes of agents are currently undergoing rollout for a defined group of immunocompromised individuals for hospitalised and non-hospitalised patients (including transplant patients).

The recommendation to reduce transplant activity at the onset of the pandemic was based on two concerns;

- 1) **Capacity:** The capacity within transplant centres to manage patients, bed capacity in the units, Critical Care (ITU/HDU) bed availability and staffing reduction due to illness, self-isolation and transfer to non-transplant activities.
- 2) **COVID-19 risk:** The risk of COVID-19 in this vulnerable patient group.

Whilst there has been a significant impact on activity across BSBMTCT centres, following each of the previous pandemic waves, most transplant centres worked towards restoring to relatively normal transplant activity

depending on local bed capacity and staffing levels, supported in principle by regional 'mutual aid' with other centres and NHS commissioners.

Despite widespread vaccination, COVID-19 remains widely prevalent, with the increasingly dominant BA.2 omicron lineage potentially more transmissible than the BA.1 lineage responsible for the initial omicron wave in the UK. With statutory infection control measures within the wider population being removed at pace, transplant teams need to continuously address ongoing risks while maintaining necessary transplant activity through prioritisation and quality measures. As previously, for the current omicron and any future waves transplant teams will need to maintain reassessments of their programmes urgently and frequently to safeguard transplant patients and staff, as well as maintaining the quality of transplant outcomes. Maintaining or resuming connections with regional centres and NHS commissioners is recommended during this present wave, in case 'mutual aid' is required.

These BSBMTCT recommendations have been produced and updated to provide support to BMT teams in the UK. Advice may change as COVID-19 prevalence changes in the UK. They are closely linked with current NICE Guideline NG164, which links in updates on the BSBMTCT COVID-19 website, and other organisations (below). The recommendations are also linked with guidance from several sources including the EBMT, ASTCT, WMDA, Anthony Nolan and NHSBT but with interpretations for the situation in the UK. They aim to represent a consensus from UK transplant teams, with input from other specialist groups, to support individual centres and regional networks according to the local circumstances. Individual centres should use these recommendations for general guidance only, as such circumstances will vary between centres and localities over time, and institutional and regional pathways procedures should be followed.

The latest guidance from NICE, EBMT and other specific groups, and for donor issues, the Anthony Nolan, NHSBT and WMDA, is available on their websites.

NICE Guideline NG164, updated 22nd July 2021 - COVID-19 rapid guideline: haematopoietic stem cell transplantation
<https://www.nice.org.uk/guidance/ng164>

NICE Guideline NG191, updated 16th December 2021 - COVID-19 rapid guideline: managing COVID-19
<https://www.nice.org.uk/guidance/ng191/chapter/Recommendations>

BSBMTCT COVID-19 website
<https://bsbmtct.org/bsbmtct-and-covid/>

EBMT guidance (regularly updated):
<https://www.ebmt.org/sites/default/files/2021-06/EBMT%20COVID-19%20guidelines%20v.%2016.03.pdf>

ASTCT guidance (regularly updated):
<https://www.astct.org/communities/community-home/librarydocuments?communitykey=d3949d84-3440-45f4-8142-90ea05adb0e5&tab=librarydocuments&LibraryFolderKey=&DefaultView=>

WMDA:
<https://share.wmda.info/pages/viewpage.action?pageId=344866320>

Anthony Nolan COVID-19 information for patients (regularly updated):
<https://www.anthonynolan.org/patients-and-families/understanding-stem-cell-transplants/coronavirus-and-your-stem-cell-transplant>

NHSBT:
<https://www.nhsbt.nhs.uk/news/coronavirus-update/>

UK Myeloma Forum COVID-19 Guidelines:
<https://www.ukmf.org.uk/guidelines/covid-19-guidance/>

BSBMTCT Collaborative Group advice

Changes since the last set of recommendations:

- 1) Update of recommendations for maintaining transplant activity.
- 2) Updated links to other HSCT organisations.
- 3) Updated advice on cryopreservation of donor cells.
- 4) SARS-CoV-2 vaccination.
- 5) SARS-CoV-2 therapeutics.

Maintaining transplant activity:

The NHS is now generally better prepared for dealing with the fluctuating incidence of infection in the population but as the omicron wave continues, transplant teams may experience periods of staff shortages, reduced capacity and heightened levels of anxiety in their patients and staff. It is expected that transplant programmes continue to follow the NICE Rapid Guideline NG164 which provides advice on establishing and maintaining 'COVID-19 safe' treatment pathways. As the incidence of infection is rising rapidly and pressure on capacity and staff increases, teams must now address prioritisation of transplant activity.

The main patient groups that have been affected by the deferral of transplantation in previous waves of the pandemic are those requiring autologous HSCT for myeloma and lymphoma. The BSBMTCT have previously worked closely with the UK Myeloma Forum in preparing recovery recommendations. In some centres, temporary expansion of in-patient capacity may need to be negotiated with management in order to facilitate reduction of the back-log of patients.

Capacity

- It is essential that centres are able to confirm sufficient capacity to manage planned activity. This includes:
 - Bed capacity in the transplant unit and ICU.
 - Staffing on BMT unit.
 - Stem cell laboratory capacity to manage donor cells for cryopreservation.
 - Associated services – pharmacy, renal support, physiotherapy.
 - Laboratory testing for SARS-CoV-2 in patients and staff.
 - Safe access to critical investigations such as endoscopy, bronchoscopy and radiology.
- Maintain 'COVID-19 safe' patient treatment pathways, from clinics, during in-patient stay and post-transplant care.
- Reduce out-patient visits by establishing telephone or video-clinics.
- Continue to minimise visitors to hospital. Utilise Lateral Flow Device (LFD) testing for every visitor into the inpatient and outpatient facility.
- Continued review of ambulatory transplant operations; the decision should be patient-focussed and ratified by the relevant MDT. Prevailing levels of SARS-CoV-2 in the catchment area of the centre should be considered; if rising, then safe ambulatory pathways may not be possible.

Case selection and prioritisation

Where transplant selection requires prioritisation, the priorities table (page 4 of this document) remains a useful tool. Case-by-case decision making will be essential to safe re-starting of transplant activity. Discussions will need to take place within the transplant teams and the regional referrers regarding the potential for deferring some transplants. The priorities table may serve as a useful guide for this.

- Continue to follow NICE Rapid Guideline NG164 for COVID-19 in HSCT for guidance with prioritisation for patients with high risk disease based on disease characteristics and period of deferral.
- Refer to disease specific professional groups for guidance.
- Case-by-case decisions based on MDT discussions.
- Consult disease specific organisations which may provide guidelines to inform MDT decisions.
- Patients should be informed of the potential risks from SARS-CoV-2 infection as this may influence their decision regarding proceeding to transplant.

The following table may help in determining transplant prioritisation:

Priority level	Categorisation based on treatment intent and risk:benefit ratio of treatment
1	Urgent HSCT procedures where delaying the procedure presents a high risk of disease progression, morbidity or mortality. This group will include consideration of: <ul style="list-style-type: none"> high cure fraction or other clinical and long term effectiveness.
2	HSCT procedures where there is risk of disease progression or clinical complications if delayed significantly (as determined by the relevant multidisciplinary team): <ul style="list-style-type: none"> intermediate cure fraction or effectiveness.
3	HSCT procedures where the risk of disease progression or clinical complications if significantly delayed is low (as determined by the relevant multidisciplinary team), including: <ul style="list-style-type: none"> procedures where the risks associated with undertaking an HSCT procedure within the current environment are deemed to be higher than the benefits of the procedure procedures that are not of curative intent or limited long-term effectiveness.

In addition the use of transplant outcome predictive tools such as the refined disease risk index¹ and HCT-CI² (link to online calculator at [HCT-CI](#)) is advised to inform decision-making for patients.

SARS-CoV-2 surveillance:

It will be important to continue to maintain robust policies and procedures to protect HSCT patients from SARS-CoV-2. These should be incorporated into existing Quality Management plans and become routine practice. The virus will remain within the community and will continue to be a major risk to patients. Programmes must work with their local infectious diseases, virology and infection control teams to create safe operational environments for patients. How this will be achieved will have to be determined at a local level but policies that include regular staff screening by symptom awareness and viral swab tests, will be required. The emergence of more infectious variants underlines the need to maintain 'COVID-19 safe' pathways, such as:

- Screening protocols – symptoms, naso-pharyngeal and throat swabs.
- The role of serological testing is unclear but may be available in some centres.
- Screening of asymptomatic BMT unit staff (including non-medical staff) and in-patients with viral swabs on a weekly basis at a minimum.
- Pre-admission screening by symptoms checks and viral swabs, ideally within 72hrs of planned admission prior to the start of conditioning.
- Patient triage and quarantine policies in clinics, in hospital, in ambulatory treatment pathways.
- EBMT continue to recommend a nucleic acid based test such as PCR rather than the antigen rapid test due to the relatively lower sensitivity of the latter (EBMT COVID-19 guidelines, version 16, 27th May 2021).

Prophylaxis and treatment:

Transplant units will be familiar with the prevention and spread of respiratory viruses within their programs. It is vital that programs continue to review their existing respiratory pathogen management procedures, policies and, for the current outbreak, align with local hospital and national policies and procedures. Patients at any time during their transplant pathway should be screened for possible upper respiratory tract infections (URTI) by careful history taking, particularly paying attention to respiratory symptoms, fevers, cough, shortness of breath. The original Wuhan SARS-CoV-2 appears to mainly cause fever, dry cough, temperature and a loss of smell and/or taste with sore throat and coryza occurring in only a minority of cases but it has been reported that the recent VOC may also commonly cause general coryzal symptoms. It is important to be aware that many infections are entirely asymptomatic and there is also a presymptomatic phase where individuals may be highly infectious to others. Any patient pre, peri or post-transplant with respiratory symptoms should be isolated and tested for respiratory viral pathogens *including but not limited to* SARS-CoV-2 by nasal and throat swabs for PCR. Local guidelines must be followed for any patients identified as positive

for SARS-CoV-2. Note that other respiratory viral pathogens are already known to be a serious risk to transplant recipients, and, if identified during screening, appropriate measures should be taken including deferral of transplantation.

It is very important that staff responsible for taking viral swabs, including self-swabbing, follow correct procedures to avoid false negative results. Staff should undertake formal training and document evidence of correct technique, ideally as part of the JACIE quality management system within the transplant program.

Due to the higher infectivity of the new variants, BMT teams should liaise with their Infection Control teams on the use of enhanced respiratory PPE rather than simple surgical masks when working with transplant patients.

Pre-SCT

- As a preventive measure, patients should be advised to avoid crowded places, public transport, use good hand hygiene measures and remain in self-isolation for 14 days prior to the start of conditioning.
- Wearing face masks to provide protection when outside of their home.
- Careful history taking to determine whether the patient has had a recent contact with an individual proven to have COVID-19 or symptoms suggestive of COVID-19 (as per government guidance)

All patients should be tested for SARS-CoV-2 by nasal and throat swabs by PCR before starting conditioning, as there is an asymptomatic period. Testing should be repeated at least twice, ideally 1 week apart or as a minimum >24hrs apart, but practice and availability of testing may vary between institutions. However, it is vital to test transplant patients prior to the start of conditioning if they have a history of recent contact with individuals with any symptoms that may be due to a respiratory viral infection. It is strongly advised to use PCR rather than an antigen based testing method.

Psychological and emotional support

Patients will be under considerable additional psychological and emotional stress due to the risks associated with COVID-19. Ensure that sufficient support processes and staff are available to provide support for patients and their families. Staff are also experiencing increasing levels of stress and may need support.

SARS-CoV-2 positive patients pre-transplant

There are two considerations regarding the decision to proceed to transplant in patients who develop SARS-CoV-2 infections prior to the start of transplant conditioning:

- 1) The risk from the underlying haematological condition
- 2) The severity of the SARS-CoV-2 infection

In patients with high risk disease, HSCT should be deferred until the patient is asymptomatic and has achieved three virus PCR negative tests at least one week apart (deferral of 14 days minimum). This differs from the EBMT guidance but in practice assumes that after two negative tests patients would start pre-transplant assessments including organ function with a final test immediately prior to the start of conditioning. There is growing evidence that some patients may remain PCR positive for many weeks following infection with SARS-CoV-2, possibly because of a limited immune response due to their treatment or disease. Patients that remain PCR positive for SARS-CoV-2 but who are otherwise well will need to be carefully assessed on the risk vs benefit of proceeding to transplant or for any transplant related procedure such as autologous stem cell harvest and they will need to be counselled appropriately.

Patients that experienced moderate to severe COVID-19 symptoms should have sufficient time to allow recovery of critical organ function and general performance status to those similar to pre-COVID-19 infection levels.

In patients with low risk haematological disease, a three-month HSCT deferral is recommended if they experienced moderate to severe COVID-19 symptoms, with negative SARS-CoV-2 PCR tests and critical organ function tests and performance status similar to pre-COVID-19 levels.

In cases of asymptomatic or mildly symptomatic infection, a deferral of a minimum of 14 days, preferably 21 days, with three negative swab test results is recommended, similar to the EBMT guidance. There tends to be a higher incidence of asymptomatic SARS-CoV-2 infection in the paediatric population with haematological malignancies and many of these patients remain SARS-CoV-2 PCR positive for some time. In those paediatric patients with high risk disease indications for CAR T cell therapy or HSCT, consideration should be given to proceeding to HSCT or CAR T without the recommended

interval for PCR clearance of virus based on a risk assessment and so long as mitigation strategies are put in place in the event that patients develop symptomatic infection post conditioning/lymphodepletion.

SARS-CoV-2 positive patients detected in the pre-transplant period may be eligible for the SARS-CoV-2 neutralising monoclonal antibody therapy or anti-viral drugs (see below section on therapeutics). Each such positive case should be discussed with the hospital infectious disease/virology team for further advice on management and referred to the local COVID-19 Medicines Delivery Unit (CMDU) without delay if eligible for treatment.

Autologous transplant recipients

- Programs should review all cases and consider carefully the risk from COVID-19 in their area and the pressures on resources within their hospital.
- Advice will continue to be produced by the disease specific specialist groups, UK Myeloma Forum and Lymphoma Specialist Interest Group.
- Decisions on which patients to prioritise should be based on clinical risk assessments, decided in MDT settings.
- Patients should be advised to practice strict self-protective measures and if at all possible self-isolate for 14 days prior to admission.
- Asymptomatic recipients should be screened for respiratory viruses and SARS-CoV-2 at least once, ideally 24-72 hrs prior to the start of conditioning. Some units may require a negative swab prior to admission to the transplant unit and a repeat sample prior to the start of conditioning.
- If clinically appropriate, GCSF alone mobilisation should be used.
- If chemotherapy priming or GCSF alone, test by SARS-CoV-2 swabs *prior* to start of treatment.
- Autologous donors *do not* require repeated SARS-CoV-2 testing on the day of stem cell harvest unless required to maintain 'COVID-19 safe' patient pathways.
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- Where relevant, the provision of ambulatory care services should be risk assessed carefully on a local basis according to means of delivery and patient pathway in respect to both COVID-19 and other factors. Patients should be managed according to updated standard operating procedures approved within the relevant MDT and broader organisation, including unhindered direct rapid in-patient admission to the transplant unit when necessary and other safeguards. Outcomes (including any SARS-CoV-2 infections) should be regularly audited and services subject to review if conditions change.

Allogeneic transplant recipients

- Careful planning is required for the preparative regimen, especially when cryopreserving donor cells prior to starting patient conditioning. Patients should have completed pre-transplant assessments and be deemed fit to proceed to transplant before the donor commences GCSF (see donor section).
- Patients should be advised to practice strict self-protective measures and if at all possible self-isolate for 14 days prior to admission.
- Asymptomatic recipients should be screened for respiratory viruses and SARS-CoV-2 at least once 72 hrs prior to the start of conditioning.
- Patients and relatives should receive instructions regarding isolation and preventative measures, this should be repeated and supported with written information.
- If close contact with a COVID-19 individual has occurred immediately prior to transplant, defer transplant for 14 days if possible (EBMT guidelines), test if symptomatic, following local infection control guidelines.
- Patients who test positive for SARS-CoV-2 pre-SCT should be managed as detailed in the section 'SARS-CoV-2 positive patients pre-transplant'.

Allogeneic donors

- Advise all donors to avoid crowded public places, practise good hygiene and avoid large group gatherings for 10 days prior to donation. Screen by viral swabs donors if symptomatic (asymptomatic screening indicated below).
- The situation regarding the cryopreservation of allogeneic donor HSC grafts, either prior to or after transport to the receiving transplant centre, is complex and changing. There is concern that cryopreservation may reduce the number of viable stem cells following thawing and infusion. However, whether cryopreservation of allogeneic HSC grafts has any significant effect on patient outcomes remains under careful review and there are ongoing BSMBMTCT-CTC/UK registry analyses to provide further data in this field.

- The BSBMTCT strongly encourages transplant centres to return data on transplant outcomes following the use of cryopreserved allogeneic donor stem cells to the Anthony Nolan and BSBMTCT survey.
- The decision on whether to use fresh or cryopreserved HSC from allogeneic donors **must** be made on a case-by-case basis as several factors need to be considered. These include disease indication for transplant (some indications have higher risk of graft failure), donor age, stem cells source (BM may be at greater risk of stem cell attrition), country of origin (incidence of SARS-CoV-2, risk of late donation failure, time from cell collection to cryopreservation, possible disruption to local/international transport networks). Also, when cryopreserved, HSC grafts may be prepared in many separate cryobags which may complicate cell infusion.
- The rise in incidence of the omicron variant of SARS-CoV-2 in UK and Europe in late 2021 swung the balance of risk in favour of cryopreservation for donor cell from countries with high COVID-19 cases. Routine collection, transportation and cryopreservation of allogeneic stem cells is still recommended to avoid serious disruption and prevent late failure of cell donation after commencing patient conditioning (e.g. donor testing positive for SARS-CoV-2 late in donation pathway and/or needing to isolate due to close/household contact with omicron variant of SARS-CoV-2). If the incidence of infection were to fall, this advice is likely to change.
- In individual cases where there is a clinical requirement for fresh stem cell or bone marrow infusion this should be carefully discussed at the local BMT MDT before proceeding. **If fresh cells are to be used, it is strongly advised that 'back-up' donors including alternative unrelated donors, haplo-identical donors or cord blood units are identified ahead of the start of conditioning and are worked up to a point where they could be activated very rapidly.** Anthony Nolan can support with identification and work up of back up donors.
- Internationally, registries have varying policies surrounding both testing and backup donor workups. The situation is extremely dynamic and advice may change and some national registries will check whether cryopreservation is planned. Check on the WMDA website which is frequently updated: <https://share.wmda.info/display/LP/COVID-19+--+Impact+on+Registry+Operations> for the recommendations in specific countries. Where possible, we recommend identifying a UK backup donor or cord blood unit. Anthony Nolan, DKMS UK, NHSBT and the Welsh Bone Marrow Donor Registry can each bring a backup donor to medical and clearance if requested.
- Transplant centres should liaise closely with their local stem cell processing laboratories to warn them of each donation and whether to cryopreserve or not. Anthony Nolan and NHSBT can help identify cryopreservation facilities if local cryopreservation capacity is limited.

Other allogeneic donor issues

- Anthony Nolan and some other registries will arrange SARS-CoV-2 testing of unrelated donors at medical, prior to starting GCSF (for cryopreserved products), prior to patient starting conditioning (for fresh products), and prior to attending for apheresis. Results should be available by the time product is cryopreserved. If not, the processing laboratory may need to quarantine cryopreserved cells until results are available.
- Donors should be screened twice for SARS-CoV-2 testing prior to donation; once at the medical (or within 72 hours) and prior to starting GCSF (for cryopreserved products) or prior to the patient starting conditioning therapy (for fresh products). Donors may also be screened prior to attending the local apheresis centre although timings may vary. Transplant centres should liaise with their local units.
- Donors with confirmed or suspected COVID-19 should be excluded from donation for 28 days, from:
 - a) The *resolution of symptoms* if they had confirmed COVID-19 by PCR for SARS-CoV-2 **and** history of one or more symptoms of COVID-19 infection.
 - b) The *date of positive diagnostic test* if they had confirmed SARS-CoV-2 by PCR **but no history of symptoms of COVID-19 infection.**
 - c) The *resolution of symptoms* if they had *suspected* COVID-19 due to one or more symptoms of COVID-19 **but had not been tested for SARS-CoV-2.**

- If less than 28 days, no suitable alternative donors and the HSCT is urgent, perform risk assessment and liaise with registry for unrelated donors. In this situation, the recipient should be involved in the discussion and be informed of the donor situation.
- Donors should be deferred for 10 days if in close contact with COVID-19 case and have at least 2 negative swabs prior to starting harvest procedure.
- The latest information of donor eligibility criteria due to SARS-CoV-2 infection can be found on JPAC guidelines (<https://www.transfusionguidelines.org/dsg/bm/guidelines/coronavirus-infection>).
- Donors who have received a COVID-19 vaccine under the UK vaccination programme must not donate if
 - a) Less than 14 days after the last immunisation if the vaccine given was nucleic acid (mRNA) vaccine.
 - b) Less than 28 days after the last immunisation if the vaccine given was virus-vector-based (non-replicating virus) vaccine.
 - c) Donor felt unwell due to unexpected complications (other than common side effects) after any vaccination. Refer to donor medical team for individual risk assessment.
- Donors who have received a COVID-19 vaccine outside the UK vaccination programme, including participants in clinical trials of donors vaccinated outside of UK, should be referred to donor medical team for individual risk assessment.
- The latest information of donor eligibility criteria due to *SARS-CoV-2 vaccination* can be found on JPAC guidelines (<https://www.transfusionguidelines.org/dsg/bm/guidelines/coronavirus-vaccination>).
- There have been concerns that SARS-CoV-2 may be passed via blood products. Although viral RNA has been detected in blood samples of patients with COVID-19 there have been no reports of transmission of infection by blood products.
- Advise avoiding bone marrow as the stem cell source as access to theatres may be limited and prone to sudden cancellation depending on local circumstances.
- Donors should be contacted approximately 14 days post-harvest to determine if they have experienced any symptoms suggestive of COVID-19.

Peri and post-transplant

- Minimise the number of family members that visit patients, ideally none except in exceptional circumstances.
- Educate all family members on hand hygiene, and how to avoid potential contact risk behaviour.
- Patients should be managed in strict protective isolation; risk assess the need for any investigations and procedures that remove the patient from their isolation room, there may be a greater risk from exposure to SARS-CoV-2 than from not having the investigation.
- Patients who are known to be SARS-CoV-2 positive should be isolated in negative pressure cubicles wherever possible, failing this in a neutral pressure cubicle. When seeing such patients, healthcare professionals should wear full PPE including gowns, FFP3 masks, gloves and visors.
- There is evidence of prolonged viral PCR positivity in patients post-transplant. It is possible that these patients may be shedding viable virus. Such patients may remain relatively well but should be managed in ways to minimise transfer of virus to other patients and staff with strict viral isolation policies.
- Management of COVID-19 cases should involve a multidisciplinary team.
- In order to establish COVID-19 free environments and the evidence of asymptomatic carriage and possible transmission it is necessary to screen ward staff routinely in contact with patients. Regular screening of in-patients is also strongly recommended if not already in use. Programs should work with their Infection Control and Infectious Disease teams to develop routine procedures.

After discharge

- **This will be the time of greatest risk to transplant recipients.**
- Evidence from several retrospective studies confirms the concern that HSCT recipients are at increased risk of severe COVID-19 and have a higher mortality rate than non-transplant individuals.
- At discharge reinforce the need for strict self-isolation of the transplant recipient and if possible the immediate carer(s). During periods of high SARS-CoV-2 incidence in the community advice similar to that given by PHE (now UKHSA) at the onset of the first wave should apply:
 - o These apply to autologous SCT recipients who have received an auto SCT *within* the previous 6 months.
 - o These apply to allogeneic SCT recipients who have received an allo-SCT *within* the previous 12 months or for patients with continuing immunosuppressive therapy; with chronic GvHD or ongoing evidence of immunodeficiency based on insufficient CD4 count and/or hypogammaglobulinaemia.
 - o The risk of severe COVID-19 appear to be greatest in older patients, those with co-morbid conditions or with poor performance status irrespective of transplant type ^{3,4}.
 - o For newly transplanted patients, the period of rigorous self-isolation starts *from the time of discharge* for 12 weeks.

After the period of rigorous self-isolation patients should follow social distancing behaviour to minimise the risks of viral infections*.

- Minimise clinic visits, review how patients travel to the centre and try to reduce risks from public transport. Hospital transport may become limited.
- Set up telephone or video follow-up clinics, explore ways for patients to have blood tests away from busy areas in hospitals or in community settings closer to home, explore medicines home delivery.
- As some patients will still require face-to-face visits for review centres must develop strategies to minimise risks to patients attending the hospital.
- There is some evidence that individuals with low vitamin D3 levels may develop more severe COVID-19 disease. It is recommended that patients receive vitamin D3 supplementation (EBMT recommendations), with regular checks on serum levels of the vitamin.

Staff

- Healthcare professionals with cough/SOB/fever/sore throat/other coryzal symptoms or loss of taste or smell should not come to work without discussion with local Occupational Health services. They should follow local pathways and/or specialist advice for staff on HSCT programmes, including obtaining a SARS-CoV-2 swab test for PCR or Lateral Flow Device Testing.
- Be aware of the less frequent symptoms that have been associated with SARS-CoV-2 infection, staff education and self-reporting procedures must be in place to increase awareness of these symptoms.
- HCP with symptoms consistent with SARS-CoV-2 infection should consult local policies which could include testing to exclude SARS-CoV-2 before caring for immunocompromised patients. They should be screened for respiratory viruses (if local arrangements allow) and SARS-CoV-2. These recommendations need to be discussed with your local Infection Control Team.
- There is evidence that healthy individuals can continue to shed virus for up to 12 days from the onset of symptoms. It is recognised that a positive PCR test beyond 10 days from the start of symptoms in an individual recovered from symptoms may not correlate with infectiousness and return to work should be based as per local policies. This recognises that some people continue to have cough and taste/smell disturbance for several weeks.
- SARS-CoV-2 household contact of staff or other exposure should follow current government guidelines, which are linked with vaccination status and other criteria, plus individual risk assessment of staff depending on their role within the organisation and HSCT programme. Impact of staffing on units/departments is a consideration at a local level to maintain services and staff can be instructed to work from home, be deployed or directly support the service depending on individual and local factors.
- Switch meetings/MDTs to telecons as much as possible and if possible splitting workforce to mitigate risk of large proportion of team being affected at same time.
- Avoid work related international travel/ large meetings.
- Avoid teams de-masking at the same time, e.g. lunch breaks should be split
- Be aware of the additional psychological and emotional stress that staff will experience and identify measures to provide support.

CAR-T therapy:

Depending on the degree of immune reconstitution and time from lymphodepletion/CAR-T infusion, patients may have a similar degree of increased risk as allo-HSCT recipients. Delays in patients awaiting collection of MNCs or for immune-depletion therapy prior to infusion of CAR-Ts results in a risk of progression of their underlying disease⁷. This must be balanced against the risks from either acquiring SARS-CoV-2 and the potential high risk of severe COVID-19 if a patient with SARS-CoV-2 proceeds to treatment.

There are additional risks from interruptions in the manufacturing chain. The pharmaceutical companies involved in the manufacture of CAR-T should be contacted directly for up to date information.

Vaccination against SARS-CoV-2:

The vaccination sub-committee of the BSBMTCT has produced detailed guidance relating to vaccination of transplant patients against SARS-CoV-2: https://bsbmtct.org/wp-content/uploads/2021/11/BSBMTCT-SARS-CoV-2-vaccination-statement_30Nov2021_FINAL.pdf.

COVID-19 therapeutics:

General management

(1) Patients hospitalised for COVID-19

A number of therapeutics in the management of COVID-19 have now been developed and are now in routine use in the UK. **The NICE COVID-19 rapid guideline: managing COVID-19 (NG191)** provides a comprehensive summary with a very recent update. Transplant teams are strongly recommended to work with multidisciplinary teams including specialists from infectious disease, virology, infection control, respiratory medicine and intensive care when managing transplant patients who develop COVID-19. When possible COVID-19 patients should be entered into clinical trials.

Dexamethasone and tocilizumab used in the appropriate clinical settings are associated with improved survival in COVID-19 patients. Low dose dexamethasone is indicated for hospitalised patients requiring oxygen and/or ventilator support. Tocilizumab (or sarilumab if tocilizumab unavailable) should be considered for patients for COVID-19 patients who are within 48 hours of starting high-flow nasal oxygen, continuous positive airway pressure, non-invasive ventilation or invasive mechanical ventilation with a CRP>75, and are receiving or recently completed a course of low dose dexamethasone. Tocilizumab may be contraindicated in the presence of another active bacterial or viral infection and treatment should be discussed with the local infection team. Remdesivir can be considered for up to 5 days for COVID-19 pneumonia in adults in hospital and needing only low-flow supplemental oxygen. Results from the RECOVERY trial have recently shown a reduction in mortality from Baricitinib in patients with COVID-19 already on low dose Dexamethasone, but how this will be deployed in the UK alongside the existing COVID-19 therapeutics is currently unclear.

(2) Non-hospitalised patients with symptomatic SARS-COV-2 infection

Eligible patients in the 'highest' risk groups in England who receive a positive SARS-CoV-2 test will be assessed over the phone by an expert clinician from an **NHS COVID Medicines Delivery Unit (CMDU)**, who will review and discuss with the patient the most appropriate anti-SARS-CoV-2 therapeutic. Those being prescribed the monoclonal antibody or remdesivir will be invited to attend the CMDU which may be located at an NHS site outside the transplant centre depending on regional arrangements. The directory of CMDUs (including contact details) is available at: <https://www.england.nhs.uk/coronavirus/publication/covid-medicine-delivery-unit-directory/>. Patients allocated oral therapies will have the appropriate anti-viral drug sent to their home.

'Highest' risk group eligibility criteria relevant to haematological disorders

More targeted therapies are also available for patients who are classified as being part of the 'highest' risk group as defined by NHS-England. The 'highest' risk group eligibility criteria relevant to haematological disorders is defined below:

- Allogeneic haematopoietic stem cell transplant (HSCT) recipients in the last 12 months or active graft vs host disease (GVHD) regardless of time from transplant
- Autologous HSCT recipients in the last 12 months
- Individuals with haematological malignancies who have
 - received chimaeric antigen receptor (CAR)-T cell therapy in the last 24 months, or

- anti-CD20 monoclonal antibody therapy in the last 12 months
- Individuals with chronic B-cell lymphoproliferative disorders receiving systemic treatment or radiotherapy within the last 3 months
- Individuals with chronic B-cell lymphoproliferative disorders with hypogammaglobulinaemia or reduced peripheral B cell counts
- Individuals with acute leukaemias and clinically aggressive lymphomas who are receiving chemotherapy or within 3 months of completion at the time of vaccination
- Individuals with haematological malignancies who have received anti-CD38 monoclonal antibody or Bcell maturation agent (BCMA) targeted therapy in the last 6 months
- Individuals with chronic B-cell lymphoproliferative disorders not otherwise described above
- All patients with a diagnosis of sickle cell disease

This list may be updated as further data emerges.

Targetted therapies against SARS-CoV-2:

Monoclonal antibody therapies

A number of neutralising monoclonal antibody therapies directed specifically against SARS-CoV-2 are effective in the treatment of infected patients. The efficacy of each monoclonal antibody is VOC specific. Ronapreve is active against all SARS-CoV-2 variants with the exception of omicron and has been used in the treatment of hospitalised patients with COVID-19 who are seronegative for SARS-CoV-2. Sotrovimab is the only neutralising monoclonal antibody therapy currently approved and in use in the UK that has activity against the omicron variant.

Antiviral therapies

The antiviral drug nirmatrelvir/ritonavir known by the tradename Paxlovid has high activity against all known SARS-CoV-2 variants. Trial data suggests that Paxlovid is almost 90% effective in preventing hospitalisations in symptomatic, non-hospitalised patients infected with SARS-CoV-2⁹. Paxlovid has a long list of drug interactions including tacrolimus and ciclosporin which should be considered carefully before use in transplant patients. Molnupiravir⁶ is another antiviral available for community use, though much less effective at preventing hospitalisations than Paxlovid. Both Paxlovid and molnupiravir are available in tablet form prescribed by the local CMDU and the patient can either have the drug collected or have it delivered to their home.

Remdesivir infusion is also extremely effective at preventing hospitalisation in symptomatic, non-hospitalised patients as shown in the PINETREE trial⁸. Remdesevir requires daily intravenous administration over 3 days in the ambulatory setting.

(3) Patients with symptomatic hospital-onset COVID-19

This is a group of patients for which there is a commissioned therapeutic pathway. Access to this clinical pathway should be considered in patients hospitalised for indications other than for the management of acute symptoms of COVID-19. Onset of symptoms of COVID-19 should be within the last 5 days (for nirmatrelvir/ritonavir¹ and sotrovimab) or 7 days (for remdesivir), remains symptomatic and with no signs of clinical recovery. The patient is should be a member of a highest risk group as defined above. The patient is not requiring new supplemental oxygen specifically for the management of COVID-19 symptoms.

Sequential use of therapeutics in patients infected with SARS-CoV-2

The sequential use of the therapeutic agents in patients infected with SARS-CoV-2 is dependent on whether patients acquire the infection in the community and not requiring hospitalisation or acquire the infection in the hospital setting. The algorithm for each of these scenarios are detailed in the following documents. It is of note that the algorithms are frequently updated depending on the available anti-viral and monoclonals and the circulating VOCs.

<https://www.cas.mhra.gov.uk/ViewandAcknowledgment/ViewAlert.aspx?AlertID=103197>

<https://www.cas.mhra.gov.uk/ViewandAcknowledgment/ViewAlert.aspx?AlertID=103196>

<https://www.cas.mhra.gov.uk/ViewandAcknowledgment/ViewAlert.aspx?AlertID=103191>

It is essential that transplant centres and haematology units clearly identify all eligible patients for neutralising monoclonal antibodies and antivirals to their [local CMDU](#) to avoid unnecessary delays in accessing treatment for patients if testing positive for SARS-CoV-2.

Ongoing developments

Other agents active against SARS-CoV-2 will likely be developed in the near future. The treatment and prophylaxis of SARS-COV-2 infection is a rapidly moving field and transplant teams are advised to keep up to date with new NHS guidance as they are issued. Patients should be enrolled on clinical trials, where available.

Continue to check the most up to date guidelines from the donor registries, disease specific groups and EBMT.

Note: The updated BSBMTCT Vaccination Sub-Committee guidelines on COVID-19 vaccination is posted on the BSBMTCT website as a separate document.

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***Social distancing behaviour examples:**

- Avoid contact with anyone displaying symptoms of coronavirus (COVID-19). These symptoms include high temperature, new and continuous cough, shortness of breath, loss of taste and smell.
- Work from home where possible.
- Avoid non-essential use of public transport, varying your travel times to avoid rush hour, when possible.
- Avoid large gatherings, and gatherings in smaller public spaces such as pubs, cinemas, restaurants, theatres, bars, clubs.
- Avoid gatherings with friends and family. If they do need to visit, request that they take lateral flow tests prior to meeting and be extra cautious about hygiene, touching and hand-washing. Ventilate indoor spaces. Protective masks should be worn. Keep in contact using remote technology such as phone, internet, and social media.
- Wear protective masks when in public spaces.