MANAGEMENT IN CONFIDENCE

CLINICAL PRIORITIES ADVISORY GROUP
10 May 2021

Agenda Item No	4.1
National Programme	Internal Medicine
Clinical Reference Group	Specialised Respiratory
URN	1803

Title
Extracorporeal membrane oxygenation (ECMO) as a bridge to lung transplant (all ages)

Actions Requested	1. Support the adoption of the policy proposition
	2. Recommend its approval as an IYSD.

Proposition
For routine commissioning. Lung transplantation is routinely performed for selected patients with respiratory failure in whom there are no other options for treatment. Approximately 25% of patients on the waiting list die from respiratory failure before a suitable donor becomes available. Some of these patients can be given ECMO as respiratory support to keep them alive until a transplant organ becomes available. This is known as Bridge to Transplant (BTT). Use of ECMO as a bridge to transplant for this indication is not routinely commissioned but some centres have offered it, so this policy is to clarify the commissioning position and obtain the associated investment, if supported. Clinical Panel requested that a specific report is provided to give additional information on the lung allocation scheme, the patients in the super-urgent group and their outcomes. This is included in the CPAG Evaluation pack.

Clinical Panel recommendation
The Clinical Panel recommended that the policy progress as a routine commissioning policy.

The committee is asked to receive the following assurance:	
1.	The Head of Clinical Effectiveness confirms the proposal has completed the appropriate sequence of governance steps and includes an: Evidence Review; Clinical Panel Report.
2.	The Head of Acute Programmes confirms the proposition is supported by an: Impact Assessment; Engagement Report; Consultation Report, Equality and Health Inequalities Impact Assessment; Clinical Policy Proposition. The relevant National Programme of Care has approved these reports.
3.	The Director of Finance (Specialised Commissioning) confirms that the impact assessment has reasonably estimated a) the incremental cost and b) the budget impact of the proposal.
4.	The Clinical Programmes Director (Specialised Commissioning) confirms that the service and operational impacts have been completed.

The following documents are included (others available on request):	
1.	Clinical Policy Proposition
2.	Consultation Report
3.	Evidence Summary plus Public Health Evidence Report
4.	Clinical Panel Reports (3)
5.	Equality and Health Inequalities Impact Assessment plus additional paper

No	*Metric*	*Summary from evidence review*
1.	Survival	**Survival at 1 year and 3 years** This outcome reports the likelihood of a patient being alive at 1 year and 3 years post-transplant and is generally reported as the proportion (percentage) of patients alive at that time. All studies included in this review contained post-transplant survival as an outcome, all report this at 1-year post-transplant and two include survival at 3-years, and three report it at 5-years. Although there was some variation in the exact rates of survival at each of these time points, there was very high agreement that survival after transplant is no worse in critically ill patients requiring ECMO BTT compared with less ill patients who survive to transplant without ECMO bridging support. The two best studies (Schechter et al 2016 and Ius et al 2018) both report survival at 1-year post-transplant. Schechter et al 2016 report cumulative survival at 1 year in ECMO BTT and non-bridged patients as 70.4% and 84.2% respectively, and additionally report 3-year survival as 64.5% and 67% respectively. Survival for ECMO BTT was

		not significantly different from those requiring no bridging support (P = 0.16). Ius et al 2018 report slightly higher rates of survival at 1-year: 79% in ECMO BTT patients compared with 90% in non-bridged patients. This difference was not statistically significant. They also report survival at 1-year conditioned to hospital discharge and this shows an even smaller difference between the groups with ECMO BTT patients at 93% and non-bridged patients at 95%. This suggests that if patients bridged with ECMO remain alive in the early days post-transplant until discharge they have virtually the same rate of survival at 1 year. This was a recent, high quality study with a relatively large number of patients. Given the large body of evidence supporting this outcome, including several good-sized, high quality studies, there is a high degree of certainty that survival for ECMO BTT is no different from patients not requiring bridging. **Survival at 5 years** This outcome reports the likelihood of a patient being alive at 5 years post-transplant and is generally reported as the proportion (percentage) of patients alive at this time. One of the two best studies included data on survival at 5 years. Ius et al 2018 report the percentage of patients who are still alive at 5 years post-transplant as 65% of patients on ECMO BTT and 71% of patients non-bridged. This difference in survival was not statistically significant suggesting that there is no difference in 5-year survival of patients on ECMO BTT and those not requiring bridging support. This outcome has a relatively high degree of certainty as the outcome is very objective and it is reported by several studies with a good level of consistency. The evidence therefore suggests that two thirds of patients who receive ECMO BTT survive until at least 5 years and that this survival is no different to those not receiving bridging support.
2.	Progression free survival	
3.	Mobility	
4.	Self-care	
5.	Usual activities	This outcome refers to an individual's ability to perform normal daily activities required to meet basic needs, fulfil usual roles, and maintain health and well-being. Neither of the two best studies in this review reported this outcome, but it was included in one other study. Todd et al 2017 included assessment of functional status with the

		Karnofsky scale index which is an assessment tool for functional impairment. A score of 50-70 on the Karnofsy Performance Status (KPS) Scale signifies inability to work but living at home and able to care for most personal needs. Score of 80-100 signifies ability to carry out normal activity and work with no assistance needed. Post-transplant Karnofsky scale functional status scores for each of the 12 patients undergoing ECMO BTT reported as between 70 and 100 (median=90, mean=87.5). The 1-year functional status in ECMO BTT group was not significantly different from the non-ECMO group (p=0.74) It was concluded that 1-year functional status was excellent in both groups. However, they highlight that this is in a select group of patients (under 65 years old, ambulatory before deterioration, no other organ dysfunction and good rehabilitation potential). These results suggest that there is no difference between the functional status of patients on ECMO BTT as those who do not receive bridging support, however there is a moderate degree of uncertainty around this. Although the study is of high quality and used a recognised and validated measure of functional status, the findings were based on relatively few patients in the ECMO group who have been selected for ECMO on the basis of being of good functional status before deterioration, therefore the extent to which these results would be generalisable to patients who were less well functioning or older is questionable.
6.	Pain	
7.	Anxiety / Depression	
8.	Replacement of more toxic treatment	
9.	Dependency on care giver / supporting independence	
10.	Safety	**Death on ECMO while awaiting transplant** This outcome refers to the deaths that occur in patients who are on ECMO while they are on the waiting list for a suitable donor for lung transplant. It is usually reported as a number or proportion of the patients who are in the ECMO BTT group who die before transplant. The two best studies both include rates of death while on ECMO pre-transplant. Ius et al 2018 reported that 19/87 (22%)

		patients required ECMO BTT but died before transplantation after a median support time of 9 (4-14) days. Death was due to bleeding (cerebral n=4, other n=2), acute haemodynamic decompensation (cardiopulmonary resuscitation n=2, right heart failure n=6), sepsis (n=4), massive haemolysis (n=1). Schechter et al 2016 reported that of the 32 patients on ECMO at time of listing, 22 (68.8%) were transplanted, whereas 6 (18.8%) either died or their condition deteriorated such that they were removed from the list. However, these data are limited by reporting only deaths for those on ECMO at the time of listing so it is unclear how they relate to all patients who received ECMO BTT. There is a high degree of uncertainty as to the exact rate of mortality to expect in patients on ECMO BTT while awaiting transplant as varying rates have been reported in the studies, but it is likely to be around 20-30%. This is likely to be due to small sample sizes in several studies and differences in the level of sickness and comorbidities of the patients put on ECMO, and advances in ECMO technology and safety which will affect survival. A lack of a control group for comparison also makes it difficult to interpret this data, however it should be noted that without ECMO 100% of the patients who need it would have died. **Post-operative complications** Post-operative complications refer to any adverse consequences of having the lung transplant operation. This gives an indication of the impacts of ECMO on the safety of the subsequent lung transplant. The two best studies in this review both report post-operative complications. The most comprehensive list of the post-operative complications seen in ECMO BTT patients compared with non-bridged patients is provided by Ius et al 2018. The majority (57/68) of the patients in the ECMO BTT group were on an awake ECMO strategy and so did not receive concurrent MV. Several post-operative complications were more likely in ECMO BTT patients including bleeding (indicated by need for blood products and re-thoracotomy for bleeding), renal failure (indicated by need for dialysis), vascular complications, need pulsed steroid therapy, tracheostomy, longer ventilation times, and higher in hospital mortality. Schechter et al 2016 included only two measures of post-operative complications; episode of acute rejection before discharge and new onset of dialysis. The incidence of new-onset dialysis in ECMO BTT patients was higher than in non-

		bridged patients (13.9% vs 10.3%) although this difference was due to chance. This is a high-quality study with a relatively large cohort of patients on ECMO, however it obtained data from a national organ sharing database so is likely to have been limited in the complications it reports due to only being able to include information recorded on the database. Three other studies report post-operative complications. Overall, there is evidence that ECMO BTT is associated with some increased post-operative complications. There is relatively high certainly that the risk of bleeding is higher in ECMO BTT patients as this has been found in all the studies that report this outcome. Higher risk of renal failure is a little less consistently reported with one of the three studies including this outcome finding it to be more common in ECMO BTT and two studies finding this not to be the case. There is therefore quite a high degree of uncertainty about this outcome. It is, however, difficult to give precise estimates of risk for each of these complications in ECMO BTT as the studies all use slightly different, indirect measures of the complications (e.g. blood transfusion vs re-thoracotomy for bleeding). Although there is some degree uncertainty due to small sample size in the single study that reports it (Todd et al 2017), there is clear suggestion that ECMO BTT is associated with far higher risk of delirium and myopathy with around 50% and 80% of patients experiencing each of these respectively. There is slightly more certainty that thrombotic and vascular events may be an increased risk int his procedure as this was also found by a larger, more robust study (Ius et al), albeit at a far lower rate (10% compared with 50% of ECMO BTT patients in Todd et al 2017.
11.	Delivery of intervention	

No	Metric	Other health outcome measures determined by the evidence review
1	Quality of life	This outcome refers to an individual's perceived physical and mental health over time. Patients who undergo lung transplantation and ECMO are critically ill and both procedures are high-risk and associated with complications and potentially long hospital stays and can therefore impact on an individual's perceived physical and mental health.

		Neither of the two best studies in this review reported this outcome, but it was included in one other study. Kolaitis et al 2018 reported changes in scores on 5 different measures of Health-related Quality of Life (HRQL) from pre-transplant to 6 months post-transplant in patients on ECMO BTT and non-bridged patients. Before transplantation, HRQL and depressive symptoms were similar among the groups, although non-bridged patients reported better baseline HRQL on two of the surveys (SF12-MCS and EQ5D). After transplantation, HRQL and depressive symptoms generally improved across both groups. Overall, peak improvement in HRQL and depressive symptoms was seen in the early period, within 6 months post-transplantation, and remained stable through to 12 months post-transplantation. The magnitude of these early improvements at 6 months varied by instrument. Estimates for change in the 5 HRQL measures over time from before transplant through to 6 months post-transplant include 17 (11-22) versus 21 (19 – 23) for ECMO BTT versus the non-bridged group on the SF12 physical component score; 11(9 – 13) versus 10 (9 – 11) on the Airways Questionnaire revised; 0.31 (0.20 – 0.42) versus 0.17 (0.13 – 0.21) on the EQ5D; and 4.8 (3.2 – 6.5) versus 3.5 (3.0 to 4.1) on the Geriatric Depression Scale. The greatest improvement was seen in respiratory-specific HRQL, but there were also substantial improvements in health utility and depressive symptoms, and some improvement in generic mental HRQL. In summary, patients ill enough to require ECMO BTT achieve similar improvements in HRQL and depressive symptoms as those who do not require ECMO. These improvements are greatest in the 6 months post-transplant and then remain stable to 12 months. There is a low to moderate uncertainty with these conclusions, the study was high quality and used several different measures of HRQL which make the results reliable and valid, but only one study with relatively small sample size included measures of HRQL as an outcome. It is also not clear what duration of ECMO or level of sedation was experienced by patients which may affect generalisability. This is based on only one study with relatively small sample size that included measures of HRQL as an outcome.
2	Length of ITU and hospital stay	**Length of ITU stay** This outcome measure refers to the length of time that patients stay in ITU and hospital post-transplant. A shorter length of stay indicates a quicker recovery after the operation.

		One of the two best studies identified by this review report data on ITU stay post-transplant. Ius et al 2018 found that the length of ITU stay in patients on ECMO BTT was a median of 11 days (IQR 4-23) compared with 2 days (IQR 1-4) in those without bridging support. This difference was statistically significant (p=<0.001). There is reasonable certainty that the length of post-transplant ITU stays are longer in patients who receive ECMO BTT than those who do not require bridging support. As only one recent study reports length of ITU stay the exact duration of ITU stay to be expected for an ECMO BTT patent remains unclear as it may vary centre to centre. **Length of hospital stay** This outcome measure refers to the length of time that patients stay in hospital post-transplant. A shorter length of stay indicates a quicker recovery after the operation. The two best studies identified in this review both report length of hospital stay (LOS). Schechter et al 2016 report median length of stays of 15 days (IQR 10-24) for non-bridged patients, compared with 25 days (IQR 19-39.5) for those receiving ECMO BTT. The difference between the length of stay for these groups was not statistically significant. Ius et al 2018 report slightly longer median length of hospital stays for all transplanted patients; 23 days (IQR 21-28 days) for non-bridged patients and 42 days (IQR 26 – 67 days) for those on ECMO BTT. This difference was statistically significant (P<0.001). This outcome has a moderate level of uncertainty. It is objectively measured and has been reported in several studies with a similar pattern of outcome (longer LOS in ECMO BTT than in non-bridged patents). However, the exact LOS stay is not consistently reported and there is no consensus on whether differences in LOS are statistically significant between ECMO BTT and non-bridged patients.
3	Graft survival	This outcome measure refers to the duration of time after the operation that the lung transplant remains functional, or the time from transplantation to the time when the lung transplant has irreversible failure and is no longer functioning. At this point, respiratory support is needed, and a re-transplant may be required. This outcome is reported in the studies in the short term as rates of acute rejection (proportion of transplants that have been rejected), or in the longer-term as graft survival (the proportion of patients who have a surviving graft at various time points) or graft dysfunction (the proportion of patients with transplants that are no longer functioning at various time points).

		One of the two best studies in this review, reports measures of both acute rejection and longer-term graft survival. Ius et al 2018 found higher rates of acute rejection (PGD score Grade 2-3) of the graft in ECMO BTT patients than in non-bridged patients at 24 hr (37% vs 15% respectively), 48 hrs (46% vs 14%) and 72hrs (42% vs 11%), all differences significant at p=<0.001. They also followed up graft survival at 1 and 5 years. They found that 90% of non-bridged and 79% of ECMO BTT patients had grafts that survived at 1 year, and 68% of non-bridged and 61% of ECMO BTT patients with grafts surviving at 5 years. These differences were not statistically significant (p=0.13) suggesting that graft survival is no worse in ECMO BTT patients. This relatively large and high-quality study suggests that acute rejection of the graft in the days immediately after transplantation is far more likely in ECMO BTT, but that in the long-term graft survival does not differ from non-bridged patients. The second of the two best studies in this review, Schechter et al 2016, reported the proportion of patients experiencing an episode of acute rejection before discharge only. This occurred in 8.7% of non-bridged patients and 10.8% in those receiving ECMO BTT. However, these differences were not statistically significant. Other studies have not found any difference in rates of acute rejection immediately post-transplant but include major limitations (and none included a long-term follow up of graft survival). Although all studies report a trend towards higher rates of acute rejection in ECMO BTT patients in the short-term immediately post-transplant, there is some disagreement over whether this difference is statistically significant. There are no clear methodological or clinical reasons why this might be the case. Long-term follow up of graft survival is only reported by one study but clearly shows that there is no difference between ECMO BTT and non-bridged patients at 1- and 5-years.
4	Post-operative ventilation	This outcome refers to whether or not patients required either mechanical ventilation (MV) or ECMO post-operatively, and in the case of MV the duration of time they needed it for before they could be taken off the ventilator to breathe for themselves. A shorter time on MV, or not requiring MV or

		ECMO at all indicates a faster recovery after the lung transplant. This outcome was reported by one of the two best studies included in this review. Ius et al 2018 looked at secondary ECMO requirements in patients who were on ECMO BTT and report no difference in the rate of secondary ECMO in patients compared with non-bridged patients (4% vs 2%, p=0.18). All patients on ECMO BTT in this study were on an 'awake' ECMO strategy which did not include concurrent MV. This study did not include data on requirement for MV post-operatively. Overall, there is some disagreement about whether ECMO BTT results in a greater likelihood of needing ECMO post-operatively. The different findings of the two recent large studies (Hayanga et al 2018 and Ius et al 2018) may be due to the different ECMO BTT procedure used, i.e. with or without concurrent MV.
5	Duration of pre-transplant ECMO	This outcome refers to the duration of time patients spend on ECMO before having a lung transplant. One of the two best studies included in this review report the duration of pre-transplant ECMO. Ius et al 2018 report the median support time of ECMO BTT in patients surviving to transplant as 9 days (range 5-16 days). The majority (57/68) of these patients were awake on ECMO therefore had no MV. There is little certainty about the exact duration of pre-transplant ECMO in these patients, probably due to the different indications for ECMO at different centres and slightly different management of transplant waiting lists. However, it certainly seems to be the case that durations do not tend to exceed around 16 days in the majority of patients. This is likely to be due to the fact that once on ECMO, a patient becomes a high priority for available donor lungs.
6	Awake versus sedated ECMO	This outcome refers to a variation in the ECMO BTT procedure. ECMO can either be delivered to patients who are sedated and bedbound, either for their comfort, success of ECMO application or because they are receiving concurrent MV, or it can be delivered to patients who are awake and able to walk and potentially take part in exercise. As described above, the studies included in this review differed in the ECMO BTT procedure received by patients both within and between studies. Schechter et al 2016 includes additional data for groups of patients who received MV + ECMO and MV alone (all sedated) which can be compared to outcomes for patients in the ECMO BTT group who received ECMO alone (awake). Survival at 3 years for patients on ECMO alone was not significantly different from those not requiring support (P =

		0.16), however patients requiring either MV alone or ECMO + MV had significantly worse survival compared with patients not requiring support ($P < 0.0001$ for both). These results suggest that awake ECMO is associated with better survival than sedated ECMO which requires MV and supports the survival outcome data (above) which demonstrates that survival for ECMO BTT is comparable to non-bridged patients. There is moderate to high level of certainty from the large, recent, high quality study by Schechter et al 2016 that awake ECMO confers a survival advantage over sedated ECMO that requires MV. However, the comparison of awake versus sedated ECMO is an indirect one as it is limited to a comparison of outcomes in subgroups of patients receiving the intervention as no cross-group comparison can be made as this is not a procedural variation in the non-bridged patients.

Patient Impact Summary

The condition has the following impacts on the patient's everyday life:

- **mobility:** Patients have severe problems in walking about or are unable to walk about
- **ability to provide self-care:** Patients have severe problems in washing or dressing or are unable to wash or dress
- **undertaking usual activities:** Patients have severe problems in doing their usual activities or are unable to do their daily activities
- **experience of pain/discomfort:** Patients have severe /extreme pain or discomfort
- **experience of anxiety/depression:** Patients are severely/extremely anxious or depressed

Further details of impact upon patients: Lung disease can result in respiratory failure where a person's lungs can no longer get enough oxygen into their blood and clear enough carbon dioxide out. Symptoms of respiratory failure include worsening shortness of breath, rapid breathing, fatigue, anxiety, confusion and then death.

Further details of impact upon carers: The impact on carers can be overlooked in the immediate desire to treat the patient. The constant strain attached to an undefined transplant waiting period can place significant physical and emotional pressures on the carers and their families, especially if children are involved. Additionally, financial pressures can ensue which may be particularly acute for the self-employed with potential significant travel costs. In the event, that death comes without the opportunity for a life-saving transplant, the impact on the carer/their

families may have far reaching consequences to their mental well-being long after the patient has died.

Considerations from review by Rare Disease Advisory Group

RDAG supported the policy proposition which was considered at the October 2020 meeting.

Pharmaceutical considerations

N/A

Considerations from review by National Programme of Care

1) The proposition was emailed for comment and then received the support of the National Internal Medicine Programme of Care Assurance Group on 20 October 2020 subject to the following comments:

The NPoC discussed the equality impact statement and the responses to the public consultation and made the following points:

- It was noted that NHS Blood and Transplant had instituted the "Super Urgent" listing. Prior to this, patients with obstructive airway disease were slightly more likely to receive a transplant over other groups on the waiting list.
- The NPoC reviewed the additional equality report requested by Clinical Panel on the lung allocation scheme, the patients in the super-urgent group and their outcomes. It was noted the Super Urgent Lung Allocation Scheme (SULAS) waiting list prioritised patients by clinical need. Hence the NPoC having considered the equalities issues support the proposition for use of ECMO to support patients identified through "SULAS" was appropriate and did not create concerns about equality of access. The NPoC fully supported that the existing monitoring of organ allocation should include monitoring of organ allocation for all patients on any of the lung transplant lists.