Conventional Ventilation or
ECMO for
Severe
Adult
Respiratory Failure

Frequently Asked Questions

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What is the trial about?

The CESAR trial is comparing conventional ventilation methods with ECMO for the treatment of adults with severe acute respiratory failure.

Who is taking part?

It is a nationwide trial, involving many of the ICUs in the UK. Please see the website www.cesar-trial.org for an updated list of participating centres who have already been given LREC approval.

Who is funding the trial?

The trial is funded by the NHS Health Technology Assessment Programme and also sponsored by the National Specialist Commissioning Advisory Group (NSCAG), who are funding the treatment.

What are the criteria for entry to the trial?

All adult patients aged 18-65 years with severe, but potentially reversible respiratory failure are eligible for the trial. Severe respiratory failure will be defined as a Murray Score =3.0, or uncompensated hypercapnoea with a pH < 7.20. The Murray Score* of = 3.0 is a MINIMUM entry criterion. Those excluded from the trial will be patients who have received high pressure (> 30 cmH_2O) and/or high FIO_2 (> 0.8) ventilation for more than 7 days, intra-cranial bleeding and any other contra-indication to limited heparinisation. Also excluded are those patients who are moribund and have any contra-indication to continuation of active treatment.

Why is the Murray Score set at 3.0?

The Murray Score will be calculated by a member of the Clinical Advisory Team (CAT) in Glenfield using all 4 parameters (PaO_2/FIO_2, PEEP, Lung compliance and Chest X-ray appearance), and with an FIO_2 = 1**.** The Murray Score of 3.0 is based on the average score of pre-trial patients FROM Glenfield that have been referred to ECMO in the past, which is 3.4. It is usually considered that at a Murray Score of =2.5, patients have significant lung injury. While we accept that many units have good results treating patients conventionally with a Murray Score of 2.5, we recognise that patients can deteriorate rapidly and this is why we recommend that intensivists refer earlier rather than later. We are encouraging intensive care staff to calculate the Murray Score themselves and they may wish to use the Murray Score calculator on the website at www.cesar-trial.org

What are you defining as high inspiratory pressures and high FiO_2?

High inspiratory pressure is defined as peak or plateau airway pressure more than 30 cm of water. High FiO2 is defined as more than 80 % of oxygen.

Do you recommend any ventilation strategy while managing patients with ARDS?

We recommend that intensivists adopt the low volume ventilation strategy. Adherence to this strategy is defined for the purposes of CESAR as a plateau pressure <30 cm H_2O (or if plateau pressure is not measured the peak inspiratory pressure). This will usually mean a tidal volume of

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* Murray score = Average score (all 4 parameters must be used):

PaO_2/FIO_2 : On 100% Oxygen, ≥300=0, 225-299=1, 175-224=2, 100-174=3, <100=4

CXR: normal=0, 1 point per quadrant infiltrated.

PEEP: ≤5=0, 6-8=1, 9-11=2, 12-14=3, ≥15=4.

Compliance (ml/cmH_2O): ≥80=0, 60-79=1, 40-59=2, 20-39=3, and ≤19=4

4-8ml/kg body weight as defined in the low tidal volume ventilation strategy according to the ARDS Network group (1). This has been made explicit in the protocol (approved February 2003).

Why do you use the peak pressure and not the plateau pressure as defined by the NIH ARDS Network publication?

Although the NIH ARDS network used the plateau pressure, many find it difficult to measure this, and therefore, it is not reproducible. The peak inspiratory pressure, however, is much easier to determine, and also allows us to calculate the dynamic lung compliance for the purposes of the Murray Score.

What if they have more than one organ failure?

Single organ failure has never been the criterion for an ECMO referral. We recognise that many patients will have more than one organ failure as a consequence of the underlying disease process. However, all organ failure must be potentially reversible. We will be recording the number of organs failed at the time of trial entry using the SOFA criteria. We will also be recording the severity of illness using the APACHE II score.

How can we speed up the entry process?

It will be helpful for relatives if you make sure that an ECMO and ICU bed is available before you approach them to discuss the trial and obtain assent. Since patients may deteriorate quickly and conventional treatment must be optimised prior to referral into the trial, intensivists will also have the option to discuss registration of the patient for the trial with the CAT as soon as the Murray Score exceeds 2.5. If the patient then continues to deteriorate, prior identification of available beds, and discussion of the trial with the relatives will allow rapid randomisation and trial entry. This procedure for registration before proceeding to trial entry and random allocation is modelled on the highly successful neonatal ECMO Trial.

Can someone other than the consultant register the patient into the trial?

Yes! A member of the nursing staff or junior medical staff can register the patient into the trial if so directed by the patient's consultant. The person referring the patient must be familiar with the trial procedures and have the registration form with them when they make the enquiry. The decision about eligibility must be made by the consultant. A doctor of reasonable experience must obtain assent from the patient's relatives. This would normally mean the consultant or an experienced SpR. The CESAR nurse can also play an important role in screening potentially eligible patients and alerting the medical staff.

What if there is no next of kin or relatives, can I still register the patient into the trial?

Since ECMO will only be available through the trial, this raises important ethical issues such as should patients without relatives or a next of kin be denied the chance of receiving potentially life-saving treatment? In 2002 we had discussed approaching MREC about the inclusion of patients where no relative was present. Although we still consider this as an important point of principle, in practice very few patients are missed in this way. As we had other priorities, we are **not** now planning to include such patients. The assent form **must be signed** by the patient's relative before entering the patient into the trial.

I am unhappy about obtaining assent for a procedure that I know little about such as ECMO.

You are not required to gain assent for ECMO or for transport. The transport team will be gaining assent for this when they arrive. You are asked to gain assent for entry into the trial. When the patient is registered the CAT team will ask you to discuss the trial with the patient's relatives and then to give the information pack for patient's relatives. This pack contains

introductory information and more detailed information on the two forms of treatment following allocation.

What about relatives, what do you provide for them?

We provide free accommodation for the immediate next of kin of patients who are treated at Glenfield Hospital during the trial. For recuperation of transport costs, we will put them in touch with our social services department, who are very used to dealing with relatives of patients on ECMO. However, this is means tested. Some hospitals have agreed to pay relatives' travel costs to Leicester.

Which hospitals can participate in the trial?

For CESAR trial purposes, there are two classifications of hospitals: Conventional Treatment Centres (CTC); and Referring Hospitals (RH).

All patients with severe acute respiratory failure who meet the eligibility criteria can be registered for the trial regardless of the classification of hospital where they are currently being treated. The intensivist looking after the patient will decide whether they approach the relatives in order to enter the patient into the trial. If the patient is already currently being treated in a **CTC** and is then randomised to conventional treatment, then they will simply remain where they are and continue with the treatment they are already receiving. If they are randomised to ECMO then our specialised transport team will arrange to come and transfer the patient to Leicester. If they are in an **RH**, then the patient will be transferred by the specialist transport team based in Leicester to either the nearest conventional treatment centre with a bed available or to Leicester for consideration of ECMO, depending upon the allocation.

How are hospitals classified?

1. We have approached the critical care networks within England that are currently "up and running" and asked them to classify the hospitals within their network. They obviously know the hospitals, and their abilities for treatment of severe acute respiratory distress syndrome. They also know what facilities each hospital can provide in terms of multi-organ failure support (e.g. haemofiltration).

2. Initially, in areas where networks were not fully developed, we classified hospitals according to our protocol. That is CTCs are those able to provide low pressure/volume ventilation, CVVH and have >350 ICU admissions/year. We will review the classification from time to time.

3. For Scotland, Wales, and Northern Ireland, we are approaching each of the hospitals individually to discuss with them.

What about transport?

We will provide/arrange all the transport of the patients within the trial following allocation and a specialist team will carry this out. Because this is a clinical trial, the transfers are permitted under the framework of "transfer for clinical reasons" and they do not come under the same scrutiny that other transfers between hospitals will come under (i.e. non-clinical transfers). All transfers within the remit of this trial are seen as clinical transfers, and so will not be included in the transfer audits directed by the government. All the costs for transferring the patients within the trial immediately following random allocation are being met by the Department of Health. It will not cost your hospital anything. In fact the cost to your hospital of treating trial patients will be lower because half of them (or all of them if you are an RH) will be transferred out.

I am concerned about the risks of transferring patients to Leicester

A specialist team with expert knowledge and experience in managing these types of patients will carry out the transfer of patients in the trial. This team is based in Glenfield and we view the transfer of patients as part of the evaluation of ECMO. ECMO is clearly a specialist treatment currently only funded to be carried out by Glenfield Hospital during this trial. As such we must be able to transfer patients safely to Leicester in order that we can manage patients with ECMO. The transport team will discuss the risks of transfer with the relatives and is responsible for gaining assent for transfer as separate from assent for the trial. If the transport team or the relatives are not happy for the patient to be transferred, then the patient will remain where he/she is. The analysis will be by intention to treat i.e. the outcome will be recorded in the arm of the trial to which the patient has been allocated.

What if we are a CTC and have no beds?

If you are a CTC and are approached for a bed for purposes of the trial and you feel compromised in any way, then you simply state that you have no beds available. We will keep in contact in order that should the situation change, we can then enter the patient into the trial. We can only enter the patient into the trial if they meet the criteria and if there is a bed available in a nearby CTC (or CTC within the network frame) and the ECMO centre. Because most hospitals are being classified as CTCs, there will be very few patients that will be transferred to another hospital for conventional treatment. At the most, it is likely that your hospital will be asked to treat one extra patient/year from an RH but this potential increase is expected to be counteracted by the number of patients transferred to Leicester from your unit for ECMO.

Are you determining how we treat these patients conventionally?

We are not dictating how intensivists treat their patients. We accept that there are many ways of treating ARDS e.g. prone, steroids, nitric oxide and oscillation. We will be recording how each patient is treated during the course of the trial. We do however, strongly advise that you follow the ARDS network recommendations i.e. low volume and pressure ventilation. (If you require a copy of this, we can send it out to you). This strategy is the only ventilator protocol ***proven*** to increase survival in ARDS. The CESAR trial is pragmatic in its aim to compare ECMO with conventional treatments currently available.

How did you derive your estimate of mortality for the sample size?

We have estimated the mortality for severe ARDS as 60-70% from a combination of our own experience, a retrospective study of patients referred for ECMO but not transferred for purely logistic reasons, the published literature, the NIH ARDS network database and the ICNARC database. We believe it to be a very good estimate. Indeed, it is similar to survival figures given in two published articles in *The New England Journal of Medicine*, both in May 2000 (see below for references). However, it is possible that recent changes in conventional management may have altered the expected survival in the conventional arm that would obviously have important implications in terms of sample size. If the outcomes in either group differ markedly from our estimates then the sample size can be adjusted by the independent data monitoring committee. The statistical power calculation grid given in the protocol allows for this.

Why have you reduced the sample size ?

The sample size was reviewed in June 2003 when the Principal Investigators made an application for an extension of funding to the HTA. In the original application, they provided a grid showing the implications of different estimates for the primary outcome in the control group and for the size of difference. This showed, for instance, that with a sample size of about 240 if the primary outcome rate in the control group was about 57% or more they would be able to detect a reduction by a third OR if the primary outcome rate in the control group was about 73% or more, they would be able to detect a reduction by a quarter. If the primary outcome rate in the control group was around 65% or more, a sample size of about 180 would allow them to detect a

reduction by a third (all estimates based on 5% statistical significance (2-sided test) and 80% power). The HTA agreed an extension of recruitment to the end of November 2005 by which time CESAR is likely to recruit about 180 patients.

Could a patient with SARS be considered eligible for CESAR

A position statement on SARS is posted on our website. Our experience of treating other forms of atypical pneumonia suggest that ECMO may be a useful adjunct in the management of this new condition.

Could a patient receiving Xigris (drotrecogin alfa (activated)) be considered eligible for CESAR trial?

Patients receiving Xigris are eligible for the trial. However if the patient is randomised to ECMO, we have to stop Xigris when we start ECMO treatment. This is in view of the increased risk of bleeding when heparin and Xigris are used together.

I have been approached to take part in another trial dealing with ARDS, does this matter?

Because we are not dictating how patients are treated in the conventional arm, there should not be a problem as far as our trial is concerned, with your participation in another trial. However, there may be a problem with your ethics committee if your patients have to be randomised for both our trial and for any other trial. We would be grateful if you could inform us of any developments in this other trial and also supply us with a copy of the protocol.

What about other trials e.g. Tracheostomy Management in Critical Care - TracMan

Again, we have no problems with your patients being recruited into other trials, but you need to let your ethics committee know. Patients who already have a tracheostomy inserted whether recruited to TracMan or not may be considered for CESAR.

Will the trial cost me anything?

As costs for transfer and treatment on ECMO are provided by NSCAG, ECMO and all transfers following allocation will cost your health trust/board nothing! ECMO is free!

When can my hospital start recruiting into the trial?

When you have obtained R&D and LREC approval for the participation of your hospital and have sent a copy of the LREC approval letter to the Data Co-ordinating Centre (DCC). The DCC will put you 'on-line' by informing the randomisation service and send you a copy of the trial folder as soon as possible thereafter.

What if I want to refer a patient for ECMO?

ECMO is only available within the context of the trial. If you wish to enter a patient into the trial before your LREC approval is through, it is possible to enter your patient into the trial through the Emergency Inclusion Protocol. However the patient would need to be treated at a conventional treatment centre that has LREC approval if they are randomised to conventional treatment. This will mean that the patient will be transferred either to the ECMO Centre or a CTC within the trial. This procedure will only be used in exceptional circumstances, as you await LREC approval.

Are other centres offering ECMO?

Yes, but the Glenfield Hospital adult ECMO programme is the only programme in the UK that has an acceptable level of experience of adult ECMO. The standard of care for an adult ECMO centre is a caseload of more than 20 patients per year, with a full time ECMO co-ordinator, properly qualified nursing, medical and technical staff and survival figures of around 50 to 70%.

I do not see many ECMO eligible patients. Is it worth my joining the trial?

Yes! It is unlikely that any hospital will have many such patients, but each one will be an important addition to being able to answer the important question about the place of ECMO for this condition. A recent paper (3) calls for a randomised controlled trial. You will be at the cutting edge of research if you take part.

What will the workload be to us as a unit if we are involved?

We have tried to keep the paperwork to a minimum as we recognise that doctors and nurses have enough paperwork already. The initial paperwork involves the registration form, which is really very easy and straightforward to use and is similar to a referral form. The data collection forms are also straightforward and are similar to other data collection forms already in use. In addition to the usual referral time required for ECMO, we estimate that you may require to spend an extra 20 minutes to register a patient into the trial and another 20 minutes to gain assent. The time required to fill in the data collection forms will be approximately 2-3 hours/patient/month. In addition, we recognise that most units will not be able to spare vital staff in order to transfer patients for the trial and this is partly why the transport team at Glenfield is responsible for all transfers of patients. Hospital costs will also be collected by Clare Hibbert from the Economics Team who will write to the finance directors of each trust that has cared for a patient allocated to remain on conventional care.

References:

1. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute respiratory distress syndrome. New England Journal of Medicine May 2000; 342(18): 1301-1308.

2. The Acute Respiratory Distress Syndrome. New England Journal of Medicine May 2000; 342(18): 1334-1348.

3. Extracorporeal Life Support for Severe Acute Respiratory Distress Syndrome in Adults. Annals of Surgery October 2004; 240(4):595-607.

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