Repair of Acute Respiratory Distress Syndrome by Stromal Cell Administration (REALIST)

Covering statement, information leaflet and consent form for Professional Legal Representative (Pro LR)
IRAS ID: 227090

A study to determine the effect of a single intravenous infusion of Mesenchymal Stem Cells (MSCs) in patients with Acute Respiratory Distress Syndrome (ARDS).

We would like your patient to take part in a research study while they are in this Intensive Care Unit. Unfortunately, your patient is not well enough to be able to decide for themselves whether or not to participate and we are unable to contact any relatives or partners. Therefore as the clinician with overall responsibility for this patient we ask if you would read the patient information sheet carefully and give your opinion as to whether or not you think your patient should participate in this medical research.

When your patient has regained consciousness and has the ability to understand the purpose of this study, we will explain the study to them and seek their permission to continue in the research. Your patient's decision to continue in the study or withdraw will override the consent you have given.

If you have any further questions either now or at any time subsequently, please feel free to contact a member of the research team (details at the end of the Information Sheet).

Thank you for your time in considering this request.

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What is the purpose of the study?

For reasons that are unclear when people are critically ill, their lungs often fail which is termed the Acute Respiratory Distress Syndrome (ARDS). ARDS is characterised by widespread inflammation in the lungs which impairs lung function. Patients need to be admitted to the Intensive Care Unit (ICU) and often need to have a breathing machine, or ventilator, to help them breathe and ensure that enough oxygen gets into their blood. Currently, there are no specific drugs or interventions that can be used to treat patients with ARDS.

What are Mesenchymal Stromal Cells (MSCs)?

Mesenchymal Stromal Cells (MSCs) are cells which originate in the human body and can help the body to repair. When MSCs are extracted and used as a treatment, they have been shown to reduce the body's immune response when it is overactive and causing damage.

These MSCs can be found in almost every part of our body, including bone marrow (the tissue inside some of your bones) and umbilical cord tissue (the tube that connects an unborn baby to its mother, through which it receives oxygen and food) after a baby is born. Adults have similar cells present throughout their life but with age are less potent.

Studies have shown that MSCs may be helpful when given to patients with other diseases. These studies to date show that treatment with MSCs is generally well tolerated by patients. The purpose of this study is to investigate if MSCs can improve outcomes in patients with ARDS. We plan to use MSCs obtained from umbilical cords which will be collected from mothers with their consent after childbirth. Records will be kept allowing traceability between the MSC donor and the patient.

Although these cells are from a source other than your patient there is no clear evidence that they will be rejected or cause any genetic mutations.

We will determine the safety and ability of MSCs to improve lung function in patients with ARDS. We will also take samples of blood, urine and may also take samples of fluid in the lung to allow us to determine the ways in which ARDS develops and how MSCs might work to improve the condition.

Why has your patient been invited?

As the treating physician you have diagnosed your patient with ARDS. It is unknown whether MSCs will help your patient recover more quickly. Therefore, we are inviting you to give consent for your patient to take part in this study to help us find out if MSCs are beneficial for patients with ARDS. We plan to recruit up to 78 patients to join the study. Patients from several ICUs will take part.

Does my patient have to take part?

No. It is up to you to decide whether or not that your patient takes part. If you do decide that they can take part you will be given this information sheet to keep and will be asked to sign a study consent form. You are free to withdraw your patient from the study at any time and without giving a reason. If you decide that your patient should not take part the standard of care they will receive will not be affected.

What will happen to my patient if they take part?

The study will be carried out in 2 parts.

Part 1 of the trial is to determine the best dose to use for the second part of the trial. Part 1 will involve 3 groups of patients, consisting of 3-6 patients in each group. The first group will receive a low dose of MSCs. If the dose is well tolerated, the following group will receive a higher dose of MSCs and if this dose is well tolerated, then the final group will receive the highest dose, which is the dose we aim to use in part 2 of the trial.

Patients who are enrolled in part 2 of the trial will be put into one of two groups. It is not possible to know beforehand which group they will be in; this will be decided by

chance. One group will receive the MSCs once only and one group will receive a dummy infusion (placebo). Both the MSCs and placebo will have a similar appearance and it will not be possible to determine which treatment the patient is receiving. Patients will have a 1:1 chance of receiving MSCs or placebo; 30 patients will receive MSCs and 30 will receive the placebo, totalling 60 patients to complete the study. When they receive the study treatment, neither you, nor the doctors and nurses will know which group your patient is in, although the doctors can find out if they need to. This type of study is called a randomized, double-blind, placebo-controlled trial and it ensures that the treatment is tested fairly.

For both parts of the study, the intervention will be administered as an infusion into a vein (blood vessel). Your patient will already have a cannula (plastic tube) inserted into a vein for drug administration in ICU. The infusion will last about 60 minutes. There is a small risk of an allergic reaction to the MSCs and to prevent this we will treat everyone with an anti-histamine injection before the MSCs are given. This will be given through the cannula already in place in a vein for drug administration in ICU. All other treatment will be the same as is provided to other patients with ARDS.

Patients who participate in part 1 of the study do not participate in part 2 of the study.

The medical notes will be reviewed by the doctors and nurses, to find out if the treatment that your patient has received has had any effect. The study team will review your patient's progress on a daily basis while in ICU.

Samples will also be taken while your patient remains in ICU to allow the study team to determine the ways in which ARDS develops and by which MSCs might work to improve their condition. Blood and urine samples will be taken from the catheters they already have and so will not cause them any pain or discomfort. We may share these samples, which will be anonymised, with investigators in the UK or internationally for more specialised tests to help us understand ARDS.

A procedure called a bronchoalveolar lavage (BAL) may be performed at the start of the study and on the fourth day of the study. If so, it will only be performed on those patients who are stable and will not interfere or delay any investigations or treatments. This involves the passage of a flexible tube (bronchoscope) with a light and video camera, which sends pictures to a television screen in the room. The bronchoscope is passed through the tube already in their throat and down into a lung. Some salty water is flushed into a small part of the lung and drawn back up again then the bronchoscope is removed. The entire procedure should take no more than 30 minutes. This is a well-recognised safe procedure often undertaken often in ICU to look at lung inflammation. The patient will already be sedated but extra sedation may be used if needed and some local anaesthetic may be used to make the procedure comfortable for them. This can rarely be associated with a fall in oxygen levels. Prior to inserting the bronchoscope the amount of oxygen will be increased and we will closely monitor these levels during the test. The test will be stopped if the oxygen level falls significantly. This will not be performed if the consultant in charge of the ICU has any concerns whatsoever.

We will contact the GP of your patient to let them know of their participation in the study. After discharge from hospital we will follow-up the medical status of your patient either by telephone, contact with the GP or review of their health care record to 2 years following treatment. We may also use NHS Digital if available in your region to confirm contact details and medical status. Where possible patients will have blood samples taken at 1 and 2 years following treatment. Patients will be contacted by a member of the trial team and if it is possible to do so, arrangements will be made for attendance at a suitable healthcare facility to have samples taken.

Storage of Samples

The samples will be stored in anonymised format in Queen's University Belfast. Samples are always stored according to appropriate regulations. We would like to store the samples indefinitely, however if you do not believe your patient would want this it does not affect their participation in the study and any samples will be disposed of when the study analyses are completed. The reason we want to store

samples is that if new information or techniques are discovered in the future this will allow us to use the samples stored to investigate if this new information is important for patients who have ARDS. Future tests may involve genetic analysis. We may share samples with other investigators or commercial organisations in the UK or internationally, to help further understanding of ARDS. If this is happens, the samples shared would be anonymous and external investigators or organisations would not be able to identify your patient. The anonymised data collected as part of the study may also be used to understand the sample analyses. If future studies are to be carried out on the stored samples the investigators will first obtain an Ethics Committee approval, if additional to the analyses planned as part of this trial.

What are the possible benefits and disadvantages of taking part?

Taking part in this study may contribute to improved treatment of patients with ARDS in the future.

MSCs have the potential, as with any drug administered, to cause allergic reaction. Should this occur the treatment will be stopped and the appropriate clinical care given. Although the MSCs are prepared in a sterile environment, there is a possibility of infection risk.

Infusion of the MSCs may cause a decrease in blood pressure, increase in heart rate or decrease in oxygen levels. Patients in ICU are continuously monitored and if these changes are identified, they will be treated.

The treatment may have side effects that no one knows about yet and this is the reason for a follow up medical visit over 2 years. Many patients have been treated with MSCs for a variety of conditions and to date no long-term harms including cancer have been reported. In fact, MSCs are being studied as a potential treatment for cancer.The researchers will let you know if they learn anything that might make you change your mind about your patient participating in the study.

What if something goes wrong?

If you have any concerns about any aspect of this study, you should contact the local Principal Investigator (contact details below), who will do their best to answer your questions. If you remain unhappy and wish to complain formally, you can do this through the normal NHS Complaints Procedure.

If something does go wrong and your patient is harmed due to someone's negligence, then they may have grounds for a legal action against their NHS Trust, but they may have to pay their legal costs.

Would your patient taking part in this study be kept confidential?

Any information which is collected about your patient during the course of the study will be kept strictly confidential and will only be seen by staff involved in the study from the NHS Trust, Trial Co-ordinating Centre, Belfast Health and Social Care Trust, Queen's University of Belfast and people from regulatory authorities who ensure that studies such as this are carried out correctly. All of them will have a duty of confidentiality to your patient as a research participant.

In addition, information held and maintained by central UK NHS bodies, and organisations contracted to provide services to the NHS, may be used to access data collected routinely during your patient's stay in hospital and to ascertain their long term health status. In this instance only their NHS number/hospital number and date of birth will be used and held by the Trial Co-ordinating Centre, all other personal data will remain anonymised. This information will be used only for this study and will not be given to anyone else.

Because we may need to contact your patient after they leave hospital, the Trial Co-ordinating Centre will need to keep records of their name, address and other contact details.

Your patient has the right to see their personal health information related to the research study, but they will not be able to review some parts of the information until

after the study has finished. When any information from the study is published it will contain no personal information and it will not be possible to identify any individual.

The data from this study will be kept for at least thirty years after its conclusion and may be used in other research studies and data may be retained by Belfast Health and Social Care Trust and Queens University of Belfast. If it is used in this way all personal identifiers will be removed and it will not be possible to identify any individual.

What will happen to the results of the research study?

The study is expected to take 2-3 years, commencing in March 2018. It is envisaged that publication of the results will follow shortly after this, through medical publications, websites and press releases. At this point we will be happy to forward a summarised version of the principle findings of the results of the study at your patient's request. This can be requested through the Northern Ireland Clinical Trial Unit (NICTU), contact details can be found at the end of this leaflet.

Who is organising and funding the study?

REALIST is being organised by a group of doctors and scientists led by Professor Danny McAuley, who is a consultant in Intensive Care Medicine at the Royal Hospitals, Belfast, Northern Ireland. It is funded by the Wellcome Trust Health Innovation Challenge Fund. The sponsor of the study is the Belfast Health and Social Care Trust.

Who has reviewed the study?

This research has been reviewed and given a favourable opinion by an independent group of people, called a Research Ethics Committee (REC), to protect your patients safety, rights, wellbeing and dignity. The Ethics Committee is completely independent from the trial. The study has also been reviewed by the regulatory body, the Medicines and Healthcare Products Regulatory Agency (MHRA).

What happens if I have any questions, concerns or complaints about the study?

If you have any questions about your patients participation in this study or concerns about the way it has been carried out, you should contact the local Principal Investigator, member of the research team or for independent advice [insert local name] (contact details below).

What happens if I don't want my patient to carry on with the study?

You are free to withdraw your consent for your patient to participate at any time and without giving a reason. This will not affect the standard of care they receive. You have the right to request samples collected as part of this study to be destroyed and no further laboratory analysis to be performed. You can take them out of the study at any time if in your opinion it is in their best medical interests to stop their participation.

If you have any questions that remain unanswered, a member of the research team will be happy to answer these for you. If you require any further information you may contact the local Principal Investigator or the co-ordinating centre as below. For any updates on the progress of your patient during the trial please speak to a member of the research team.

How long do I have to think about entering my patient in the trial?

We are examining the effect of MSCs early in the course of ARDS. To do this we need to recruit your patient within 48 hours of their diagnosis of ARDS.

Thank you for taking the time to read this Information Sheet.

Contact details:

Chief Investigator:

Name: Prof Danny McAuley

Address: Regional Intensive Care Unit
Royal Hospitals
Grosvenor Road
Belfast, BT12 6BA

Telephone: 028 961 50690

Principal Investigator:

Name: «name»

Address: «address»

Telephone: «telephone»

REALIST Co-ordinating Centre:

Address: NI Clinical Trials Unit
1st Floor Elliott Dynes Building
Royal Hospitals
Grosvenor Road
Belfast, BT12 6BA

Telephone: 028 96151447

Complaints/concerns:

Name: «name»

Address: «address»

Telephone: «telephone»

Belfast Health and Social Care Trust is the sponsor for this study.

How will we use information about your patient?

We will need to use information from your patient, from your patient's medical records, your patient's GP, NHS Digital, national clinical audit databases, central UK NHS bodies and organisations contracted to provide services for the NHS for this research project.

This information will include your patient's initials/ NHS number/ Hospital number/ name/ contact details and national clinical audit database number. People will use this information to do the research or to check your patient records to make sure that the research is being done properly.

People who do not need to know who your patient is will not be able to see your patient's name or contact details. Your patient's data will have a code number instead.

We will keep all information about your patient safe and secure.

Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that your patient took part in the study.

What are your choices about how your information is used?

- Your patient can stop being part of the study at any time, without giving a reason, but we will keep information about your patient that we already have.
- If your patient chooses to stop taking part in the study, we would like to continue collecting information about your patient's health from central NHS records/ your patient's hospital/ your patient's GP. If you or your patient do not want this to happen, tell us and we will stop.
- We need to manage your patient's records in specific ways for the research to be reliable. This means that we won't be able to let your patient see or change the data we hold about them. We can provide a list of the type of information we are collecting, if requested.

- If you agree for your patient to take part in this study, your patient will have the option to take part in future research using their data saved from this study.

Where can you find out more about how your patient's information is used?

You can find out more about how we use your patient's information

- at www.hra.nhs.uk/information-about-patients/
- our leaflet available from www.belfasttrust.hscni.net/about/DataProtection.htm

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Regarding patient (patients name):_____

This form should be completed by a doctor who is unconnected with this research study only in situations where the patient is temporarily unable to provide informed consent for themselves, and if there is no relative/friend/partner willing and capable to act as the Personal Legal Representative. The doctor primarily responsible for the medical treatment of the patient, or a person nominated by the relevant health care provider, can act as a professional legal representative for the patient, providing that they are not connected with the conduct of this study.

I, _____, as the clinician with responsibility for this patient declare by signing this form that I have read the patient information sheet and have no objection for this patient to be entered into this research study. I also understand that should the patient regain consciousness they will be informed of the decision to enter them into this research study and consent will be sought from them for their continued participation. I agree that the patients consent will override my consent when the patient is able to give informed consent.

Name of Professional Legal Representative	**Signature**	**Date (dd/mm/yy)**