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

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

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

We are inviting your relative/friend/partner to take part in a research study while they are a patient in this Intensive Care Unit. Unfortunately, your relative/friend/partner is not well enough to be able to decide for themselves whether or not to participate. Therefore we ask if you would read the information sheet carefully and give your opinion as to whether or not you think your relative/friend/partner would be willing to participate in this medical research.

When your relative/friend/partner 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 relative/friend/partner'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 relative/partner/friend 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 relative/friend/partner been invited?

The intensive care doctors have found that your relative/friend/partner is suffering from ARDS. Neither the researchers nor the intensive care doctors know whether MSCs will help your relative/friend/partner recover more quickly. Therefore, we are inviting you to give consent for your relative/friend/partner 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 ICUs across the UK will take part.

Does my relative/friend/partner have to take part?

No. It is up to you to decide whether or not that your relative/friend/partner 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 still free to withdraw at any time and without giving a reason. If you decide that your relative/friend/partner should not take part the standard of care they will receive will not be affected.

What will happen to my relative/friend/partner 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 your relative/friend/partner nor the doctors and nurses will know which group they are in, although the doctors can find out if they need to. This type of study is called a randomised, 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 relative 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 will 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 relative/friend/partner has received has had any effect. The study team will review your relative/friend/partner's progress on a daily basis while in ICU.

Samples will also be taken while your relative/friend/partner 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 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 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 friend/relative/partner to let them know of their participation in the study. After discharge from hospital we will follow-up the medical status of your relative/friend/partner 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 relative/friend/partner 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 relative/friend/partner. 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 follow up 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. The researchers will let you know if they learn anything that might make you change your mind about your relative/friend/partner 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 relative/friend/partner 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 relative/friend/partner taking part in this study be kept confidential?

Any information which is collected about your relative/friend/partner 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 relative/friend/partner 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 relative/friend/partner'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 relative/friend/partner after they leave hospital, the Trial Co-ordinating Centre will need to keep records of their name, address and other contact details.

Your relative/friend/partner 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 relative/friend/partner'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 relative/friend/partner's 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 relative/friend/partner's 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 relative/friend/partner to carry on with the study?

You are free to withdraw your consent for your relative /friend/partner 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. Your study doctor can take them out of the study at any time if it is in their best medical interests to stop their participation.

If you have any questions that remain unanswered, the study doctor or research nurse 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 relative/friend/partner during the trial please speak to a treating physician or 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 relative/friend/partner 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/relative/friend/partner?

We will need to use information from your relative/friend/partner, your relative/friend/partner's medical records, your relative/friend/partner'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 relative/friend/partner'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 relative/friend/partner's records to make sure that the research is being done properly.

People who do not need to know who you are will not be able to see your relative/friend/partner's name or contact details. Your relative/friend/partner's data will have a code number instead.

We will keep all information about your relative/friend/partner 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 relative/friend/partner took part in the study.

What are your choices about how your information is used?

- Your relative/friend/partner can stop being part of the study at any time, without giving a reason, but we will keep information about them that we already have.
- If your relative/friend/partner chooses to stop taking part in the study, we would like to continue collecting information about their health from central NHS records/ their hospital/ their GP. If you or your relative/friend/partner do not want this to happen, tell us and we will stop.
- We need to manage your relative/friend/partner's records in specific ways for the research to be reliable. This means that we won't be able to let your relative/friend/partner 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 relative/friend/partner to take part in this study, your relative/friend/partner will have the option to take part in future research using the data saved from this study.

Where can you find out more about how your relative/friend/partner's information is used?

You can find out more about how we use your relative/friend/partner 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 (please write patients name here): _____

Please initial each box

1. I confirm that I have read and understood the information sheet for the above study and have had the opportunity to ask questions and discuss the study. ☐

2. I understand that I am giving this consent based on what I believe would be my relative/friend/partner's wishes. In my opinion, they would be willing to participate in this study. ☐

3. I understand that my relative/friend/partner's participation is voluntary and that I am free to withdraw my consent at any time, without giving any reason and without their medical care or legal rights being affected. ☐

4. I understand that sections of my relative/friend/partner's medical notes may be inspected by responsible individuals from the NHS Trust, Trial Co-ordinating centre, Belfast Health and Social Care Trust, or regulatory authorities, where it is relevant to their taking part in this research. I give permission for these individuals to have access to my relative/friend/partner's records. I agree to information related to this research being retained at the NHS Trust, Trial Co-ordinating Centre, Belfast Health and Social Care Trust and the Queen's University of Belfast. ☐

5. I understand that the Trial Co-ordinating Centre will keep records of my relative/friend/partner's name and contact details and may access information held by other central UK NHS bodies and organisations contracted to provide services to the NHS to access data collected routinely ☐

during their hospital stay, to facilitate follow up and to ascertain their long term health status.

6. I agree to my relative/friend/partner taking part in this study. ☐

7. I agree to my relative/friend/partner having a bronchoscopy and bronchoalveolar lavage (BAL) performed at baseline and day 4. ☐

8. I understand that my relative/friend/partner will have blood and urine samples taken as part of this research study. ☐

9. I agree to my relative/friend/partner's blood, urine and BAL samples being stored indefinitely so they can be used in future research in the event of new scientific research or techniques becoming available with regards to ARDS. ☐

10. I agree to my relative/friend/partner's anonymised data being kept for at least 30 years after the study conclusion and it being used in other research studies, and I understand that they will not be personally identified. ☐

11. I agree to my relative/friend/partner's GP being contacted by the research team to advise of their participation in the study ☐

12. I agree to my relative/ friend/partner being followed-up by the research team to assess their medical status ☐

13. I understand that my relative/friend/partner's data will be shared in an anonymised format in publications, at conferences, and in research data-sharing repositories, and I understand that they will not be personally identified. ☐

14. I understand that samples taken during this study may be shared with external non-NHS organisations to undertake the planned and future ☐

analyses, including genetic analysis, transfer abroad and commercial research.

15. I agree that my relative/friend/partner's consent will override my consent, when they are able to give informed consent. ☐

I am the patient's:

_____

(please write your relationship to the patient here, e.g. wife/brother/partner etc)

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

Name of person taking consent	**Signature**	**Date (dd/mm/yy)**