Subject information for participation in medical research

Restrictive versus Liberal Thresholds for Red Blood Cell Transfusion in ExtraCorporeal Membrane Oxygenation – the TREC study

Official title (in Dutch): Restrictieve versus liberale grenzen voor rode bloedcel transfusie in patiënten aan de extracorporale membraan oxygenatie

Introduction

Dear Sir/Madam,

You are receiving this letter because your family member or relative (hereafter referred to as your relative) has either been supported or is currently receiving support with extracorporeal membrane oxygenation (ECMO), commonly known as the heart-lung machine. We are currently conducting research on blood transfusion policies during ECMO treatment and are comparing two different approaches. During your relative's ECMO support, the transfusion policy was randomly assigned as part of this study, meaning your relative is participating in the research. This study has been approved by the Medical Research Ethics Committee of Amsterdam UMC. Since your relative is not fully responsive at this time, we are providing you with information about the study. Once your relative regains responsiveness and is able to make decisions, the details of the study will be discussed with them as well.

Here, you will find details about the nature of the research, its implications for your relative, and the potential benefits and drawbacks. Please read this information carefully, and if you have any questions, do not hesitate to ask the researcher for clarification. You can also seek additional information from the independent expert. Additionally, feel free to discuss this decision with your partner, family, and/or friends before deciding whether to give consent.

If, after reviewing the information, you agree to your relative's continued participation in the study, please fill out the form located in Appendix D.

Ask your questions

We would like to encourage you to base your decision on the information provided in this document. Additionally, we recommend that you take the opportunity to:

- Ask your questions to the investigator who gave you this information.
- Talk to your partner, family or friends about this study.
- Ask questions to the independent expert, Prof. Dr. Janneke Horn.
- Read the information on www.rijksoverheid.nl/mensenonderzoek.

1. General information

This study has been established by Amsterdam UMC, location AMC. The Amsterdam UMC, location AMC will be referred as the *'sponsor'* throughout this document. Investigators, including doctors, or research nurses, conduct the study in many different hospitals. The study aims to recruit 526 participants from different countries. The Medical Research Ethics Committee of the Amsterdam UMC has granted approval for this study.

2. What is the purpose of the study?

In this study, we are examining whether it is safe to adopt a more restrictive approach to administering red blood cells ("blood transfusion") to patients undergoing extracorporeal membrane oxygenation, also known as ECMO. ECMO is used in the intensive care unit (ICU) to support critically ill patients. In this study, we are comparing two thresholds for blood transfusion: a higher hemoglobin level versus a lower hemoglobin level.

3. What is the background of the study?

Blood transfusion has traditionally been regarded as a life-saving procedure. However, in recent years it has become increasingly clear that blood transfusions can lead to severe side effects and are therefore not risk-free. Almost all patients supported with ECMO develop anemia due to blood loss and their underlying illness. Currently, the standard approach to correcting this anemia is by administering a blood transfusion.

Patients are supported with ECMO due to severe heart and/or lung failure. It was long believed that correcting anemia in these patients would be beneficial. However, recent studies in ICU patients with anemia, who are **not supported** with ECMO, have shown that a restrictive approach to blood transfusions is safe and can even lead to better outcomes. Since ECMO partially takes over the function of the heart and/or lungs, anemia may be well tolerated. We believe that by using a lower hemoglobin threshold and delaying blood transfusions, we can reduce the number of unnecessary transfusions. This approach also helps prevent potential side effects from transfusions, reduces the demand on volunteer blood donors, and lowers overall healthcare costs.

4. What happens during the study?

Step 1: are you eligible to take part?
On the day your relative began receiving ECMO support, doctors and researchers assessed whether he/she was eligible for this study. No additional tests or blood samples were needed for this evaluation.

It is likely that, on this day, your relative was unable to discuss participation in the study. Therefore, we are informing you, as the legal representative, about the study and seeking your (preliminary) consent. With your approval, as long as ECMO support continues, the treatment will follow the protocol of the randomly assigned plan.

Step 2: The limits for blood transfusion
During the time your relative is supported with ECMO, a target value for blood transfusion based on the hemoglobin level in your blood will be investigated.

For this study, we will compare **two** groups:

- Group 1. The participants in this group receive a blood transfusion at a low-normal hemoglobin value (“restrictive strategy ”);
- Group 2. The participants in this group receive a blood transfusion at the current, high hemoglobin value (“liberal strategy”).

A random selection process will determine the transfusion strategy assigned to your relative. Both you, as the legal representative, and the doctor will be informed of the specific transfusion strategy allocated to your relative.

Step 3: study and measurements
No additional measurements are conducted for this study. In the ICU, it is common practice to monitor various blood values daily to assess the condition of your relative. One such value is the hemoglobin level, which indicates the degree of anemia. If the hemoglobin level, determined from the blood, is equal to or lower than the value associated with the transfusion strategy, a blood transfusion is administered. After the transfusion, it's assessed whether the desired outcome (a higher hemoglobin level) has been achieved. This blood draw is a routine procedure. Apart from this, your relative undergoes all procedures as he/she would have undergone if not participating in this study.

How long will the study take?
If your relative participates in the research, we will collect data during the ECMO support period. Additional data will be collected three months after ECMO support, and contact will be made with your relative twelve months later to check on their well-being (referred to as "quality of life"). Your relative's consent will be obtained for this:

- After 3 months, researchers will collect medical data related to their status. This will be done via the electronic patient record, through the general practitioner, or in the case of death, through the Central Agency for Statistics. The Central Agency for Statistics will be asked for the cause of death. This is necessary to investigate any potential relation with the study. If the outlined options are insufficient, it's possible that the researcher may contact your relative.

- Your relative will be contacted by the researcher at 3, 6, 9, and 12 months, either by email or phone. During these follow-ups, they will be asked about their well-being and any difficulties they may be experiencing in their daily activities. Each conversation or completion of the questionnaire will take approximately 20 minutes. In total, there will be four follow-ups. If your relative is able to respond, their permission will be requested beforehand. Should they choose not to complete the questionnaires, they can still participate in the study but they will not receive follow-up questionnaires.

What is the difference with standard care?
In this study, most aspects reflect standard care. Your relative received all the treatments and measurements that are typically performed during ECMO support, regardless of their participation in the study. The only difference is the potential use of a different blood transfusion threshold based on hemoglobin levels: depending on the thresholds established by the hospital outside of this study, transfusions may have been administered either earlier or later.

5. What agreements do we make with you?

Your relative does not need to alter their daily activities; there are no restrictions or specific rules to follow. They may continue with their usual routine. However, we kindly ask that your relative contacts the researcher in the following situations:

- Your relative no longer wish to participate in the study.
- Your relative's telephone number, address or e-mail address changes.

6. What side effects, adverse effects or discomforts could you experience?

Transfusing red blood cells carries the risk of certain side effects, including 1) an allergic reaction, 2) lung injury (*transfusion-related acute lung injury*), and 3) a high volume load in the vascular system leading an excessive amount of fluid in the lungs (*transfusion-associated circulatory overload*), although these are the most serious side effects. By adopting a restrictive transfusion strategy, we anticipate a lower need for blood transfusion and subsequently a reduced risk of experiencing these side effects. However, red blood cells play a crucial role in transporting oxygen to tissues. As a consequence, a more restrictive transfusion strategy may lead to symptoms of anemia, resulting in reduced physical capacity. Being more conservative in administering red blood cells could result in experiencing symptoms of anemia.

7. What are the pros and cons if you take part in the study?

Participating in the research can have both benefits and potential drawbacks. We have listed them below. Please consider these carefully and discuss them with others. If your relative participates in this study, it does not imply that their illness will be cured or that they will experience less discomfort from it.

Potential benefits of participating in the research:

- By participating, your relative is supporting researchers in understanding the safety of adopting a more restrictive approach for blood transfusions.
- A restrictive transfusion strategy might be beneficial in preventing potential side effects of blood transfusion.
- During ECMO support, your relative may need fewer blood transfusions, but this is not a guarantee. Their participation contributes to the search for a more effective approach to treating anemia during ECMO: transfusing only when necessary and avoiding unnecessary ones.

Potential drawbacks of participating in the research:

- Your relative might experience side effects or adverse effects of anemia, as described in paragraph 6.
- Three, six, nine and twelve months after ICU admission, your relative will be asked to complete a questionnaire about your current health status over the phone or by email.

8. You do not wish to participate in the study?

Participation in this research is entirely voluntary. If you decide that your relative should not participate, they will continue to receive standard treatment from that point forward. Even if you initially agree for your relative to participate, you can change your mind or withdraw them from the study at any time. In that case, they will resume receiving standard treatment. You are not required to provide a reason for discontinuing participation, but you must inform the researcher of your decision.

9. When does the study end?

The study will be discontinued in the following situations:

- Once all the data has been collected according to the schedule, the study will continue for 12 months after the ICU admission if your relative consents to complete the questionnaires.
- You or your relative decide to withdraw from the study voluntarily. You or your relative may withdraw at any time by notifying the investigator immediately. It is not obligated to provide a reason for the withdrawal. In such cases, your relative will receive standard ECMO support.

- The investigator deems it necessary for your relative to withdraw.
- The study is required to stop by one of the following authorities:
  - Amsterdam UMC, location AMC,
  - the government, or
  - the Medical Research Ethics Committee of the Amsterdam UMC.

The research team will ensure that you and your relative are informed of any significant updates to the study that may have an impact. If any noteworthy developments arise, they will ask whether you or your relative wish to continue participating in the study.

What happens if you stop participating in the study?
The researchers will make use of the data gathered until the point of withdrawal. The study will be concluded once all participants have provided the necessary data.

10. What happens after the study has ended?

Will you get the results of the study?
Approximately one to four years after your participation, the researchers will have information on the key outcomes of the study. If you are interested in learning about these outcomes, please let the researcher know your preference.

11. What will be done with your data

For this study, personal data about your relative will be collected, used, and stored.

What data do we store?
We store the following data:

- name
- sex
- age
- information about health
- (medical) information that we collect during the study

Why do we collect, use and store data?
We collect, utilize, and store the data in order to address the research questions of this study. Furthermore, it is essential to have this data to enable publication of the study's results.

How do we protect privacy?
To ensure privacy protection, we assign a research number ("code") to the data. Only this code is used on all data records. The key to decipher the code is securely stored in the hospital. When processing the data, we exclusively use the assigned code. In reports and

publications related to the research, it is impossible for anyone to identify the information to your relative.

Who can see your data?
Certain authorized individuals may have access to your relative's name and other personal information without the use of a code. This access may include information collected specifically for this study, as well as data from your relative's medical records. These individuals are responsible for ensuring the proper and reliable conduct of the study. The following persons can access your relative's data:

- Members of the committee that keeps an eye on the safety of the study.
- An auditor who is hired by the Amsterdam UMC, location AMC.
- National and international supervisory authorities. For example, the Health and Youth Care Inspectorate (IGJ, Inspectie Gezondheidszorg en Jeugd in Dutch).

These individuals will keep your relative's information confidential. We kindly ask for your permission to grant them access to their data. The Health and Youth Inspectorate can access the personal information without permission.

For how long do we store your relative's data?
We store your relative's data in the hospital for a maximum of 15 years.

Can we use your relative's data for other research?
The data collected in this research may also be valuable for other scientific studies related to anemia during ECMO support. Therefore, the data will be stored at the hospital for a period of 15 years. Once your relative has recovered, they will have the option to decide whether their data can be used for these additional studies.

What happens if there are coincidental findings?
During the course of the study, there is a possibility of incidentally discovering something important related to your relative's health. In such cases, the researcher will contact the attending physician. By completing the form, you give consent for the researcher to inform your relative's primary care physician or specialist about any relevant findings.

Can you withdraw your relative's consent for the use of your data?
You have the right to withdraw your consent for the use of your relative's data at any time. This applies to the use of their data in this research study as well as for any other research purposes. However, please note that if you withdraw your consent and researchers have already collected data for a specific study, they may still use that data as permitted by the applicable regulations and ethical guidelines.

Do you want to know more about privacy?

- Do you want to know more about your relative's rights when processing personal data? Visit www.autoriteitpersoonsgegevens.nl/en

- Do you have questions about your relative's rights? Or do you have a complaint about the processing of your relative's personal data? Please contact the person who is responsible for processing your personal data. Currently, this is:
    - Amsterdam UMC, location AMC. See Appendix A for contact details, and website.
- If you have any complaints about the processing of your relative's personal data, we recommend that you first discuss them with the research team. You can also contact the Data Protection Officer of the Amsterdam UMC, location AMC. Or you can submit a complaint to the Dutch Data Protection Authority.

Where can you find more information about the study?
You can find more information about the study on the following website(s): www.ClinicalTrials.gov and/or www.clinicaltrialsregister.eu. After the study, the website may show a summary of the results of this study. You can find the study by searching for name: TREC.

12. Will your relative receive compensation if he/she participate in the study?

Participation in the research does not incur any costs for you or your relative. There is also no compensation provided for participating in this study.

13. Is your relative insured during the study?

A separate insurance policy has been obtained for all participants in this research study. The insurance will provide coverage for potential damages resulting from the study, although it may not cover all types of damages. In **Appendix B**, you will find more information about the insurance and the exceptions. It also specifies whom your relative should report any damages to.

14. We will inform your relative's doctor

The researcher will inform the treating specialist to ensure that your relative's participation in the research study is known. This is done for safety purposes.

15. Do you have any questions?

If you have any questions about the study, you can reach out to the research team. If you prefer to seek advice from someone who is not directly involved in the study, you can consult Prof. Dr. Janneke Horn. She has extensive knowledge about the research but is not directly involved in this particular study.

If you have any complaints, please discuss them with the researcher or the physician overseeing your treatment. If you would rather not do so, you can contact the complaints officer at Amsterdam UMC, location AMC. **Appendix A** provides information on how to reach the complaints officer.

16. How do you give consent for the study?

Please take your time to consider whether your relative should continue participating in the study. You are encouraged to discuss this decision with others. Once you have made a decision, please inform the attending physician and/or the researcher. If you agree to proceed with the randomized treatment strategy, kindly complete the consent form attached to this information sheet. Both you and the research team will receive a signed copy of the consent form.

Thank you for your attention.

16. Appendices to this information

A. Contact details Amsterdam UMC, location AMC
B. Information about the insurance
C. Schedule of study interventions/description of study interventions or overview of measurements
D. Consent form(s) Representative

Appendix A: contact details for Amsterdam UMC, location AMC

If you have any questions or comments about the research, please contact the principal investigator.

Principal Investigator:
Prof. Dr. A.P.J. Vlaar, internist-intensivist AMC
Department of Intensive Care, Amsterdam UMC, location AMC
E-mail: a.p.vlaar@amsterdamumc.nl
Telephone number: +31(0)20 5669111: Contact possible via nurse on duty

Executive researchers:

- C.M. Schaap, medical doctor/researcher
  Department of Intensive Care, Amsterdam UMC, location AMC
  E-mail: c.m.schaap@amsterdamumc.nl, telephone number: +31(0)20 7328696
- S.F. van Wonderen, medical doctor/researcher
  Department of Intensive Care, Amsterdam UMC, location AMC
  E-mail: s.vanwonderen@amsterdamumc.nl, telephone number: +31(0)20 7328696

Independent expert:
Prof. Dr. J. Horn, Neurologist-Intensivist
Department of Intensive Care, Amsterdam UMC, location AMC
E-mail: j.horn@amsterdamumc.nl
Telephone number: +31(0)20 5669111: Contact possible via nurse on duty

Data Protection Officer of the institution:
Data Protection Officer Amsterdam UMC, location AMC
E-mail: privacy@amsterdamumc.nl
Weekdays, 09:00 – 17:00

Complaints:
Klachtenfunctionaris Amsterdam UMC, location AMC
E-mail: klachtenfunctionaris@amc.nl / klachten@amsterdamumc.nl
Telephone number: 020-5663355
Weekdays, 9:00-12:30 and 13.00 - 15.30

Personal Data Authority (Autoriteit Persoonsgegevens in Dutch):
https://autoriteitpersoonsgegevens.nl/

For more information about your rights:
https://www.amsterdamumc.nl/nl/locatie-amc/rechten-en-plichten.htm

Appendix B: information about the insurance

The Amsterdam UMC, location AMC has taken out insurance for everyone who takes part in the study. The insurance pays for the damage you have suffered because you participated in the study. This concerns damage you suffer during the study or within 4 years after you participated in the study. You must report damage to the insurer within 4 years.

Have you suffered damage as a result of the study? Please report this to this insurer:

The insurer of the study is:	
Name insurer:	Centramed B.A.
Address:	Postbus 7374
	2701 AJ Zoetermeer
Telephone number:	070 301 70 70
Email:	info@centramed.nl
Policy number:	624.100.044

The insurance pays a maximum of €650,000 per person and a maximum of €5,000,000 for the entire study and a maximum of € 7,500,000 per year for all studies by the same sponsor.

Please note that the insurance does **not** cover the following damage:

- Damage due to a risk about which we have given you information in this sheet. But this does not apply if the risk turned out to be greater than we previously thought. Or if the risk was very unlikely.
- Damage to your health that would also have happened if you had not taken part in the study.
- Damage that happens because you did not follow directions or instructions or did not follow them properly.
- Damage to the health of your children or grandchildren.
- Damage caused by a treatment method that already exists. Or by research into a treatment method that already exists.

These provisions can be found in the 'Besluit verplichte verzekering bij medisch-wetenschappelijk onderzoek met mensen 2015' ('Medical Research (Human Subjects) Compulsory Insurance Decree 2015'). This decision can be found in the Government Law Gazette (https://wetten.overheid.nl).

Appendix C: Diagram of study interventions and/or overview of measurements/description of study interventions

During the ICU admission

During your relative's ECMO support, they will receive standard care. No additional procedures or measurements will be conducted specifically for the research. If their hemoglobin level in the blood is lower or equal to the threshold corresponding to their assigned strategy, a blood transfusion will be administered. After the transfusion, the effectiveness (increase in hemoglobin level) will be evaluated, which involves a routine blood draw. It is possible that the blood draw may occur earlier than the usual hospital practice, for example, within 4 hours instead of 6 hours. Your relative will have a standard intravenous line in their wrist for blood sample collection, which should not cause any discomfort.

Once the ECMO support is discontinued, the transfusion strategy will no longer be applicable. One day after stopping ECMO, no further data will be collected regarding the course of their hemoglobin level, and no additional measurements will be conducted.

After 3 months

Approximately 3 months after participating in the study, the researcher will collect data regarding their current status. The necessary information will be obtained through the electronic patient record or by contacting their general practitioner. If the available information through these channels is limited, the researcher may contact them for a phone conversation. Prior consent will be sought for this phone conversation.

After 12 months

Approximately 3, 6, 9, and 12 months after participation in the study, the researchers will contact your relative by phone or email to complete a questionnaire. The questionnaire will ask about his/her well-being and any ongoing issues with reduced (physical) functioning, such as whether he/she is able to care for him/herself independently or need assistance. It will also inquire about the use of medical care and any loss of productivity in daily life. Completing the questionnaire will take about 20 minutes. We will ask for your relative's consent to contact him/her for this purpose. After completing the final questionnaire, the email address will be removed from our system. If he/she does not consent to be contacted, he/she can still participate in the study.

Appendix D: Informed consent form - Representative

Belonging to “Restrictive versus Liberal Thresholds for Red Blood Cell Transfusion in ExtraCorporeal Membrane Oxygenation – the TREC study”

I have been asked to give consent for the following person to take part in this medical study:

Subject’s name: ……. Date of birth: ____ / ____ / ____

- I have read the information sheet for the participant/representative. I also had the opportunity to ask questions, and my questions have been adequately answered. I had enough time to decide whether I want this person to participate or their data to be used for this research.
- I understand that participation is voluntary, and I can decide at any time that this person will not participate. I do not need to provide a reason for this decision.
- I give the researcher permission to inform the general practitioner and/or treating specialist that this person is participating in this research.
- I give the researcher permission to provide the general practitioner and/or specialist with information about any unexpected research outcomes that are relevant to this person's health.
- I give consent for the retrieval of information from this person's general practitioner and, if necessary, the specialist.
- I give the researchers permission to collect and use this person's data. The researchers will only use the data to answer the research question in this study.
- I give permission to access official cause of death data from the Central Agency for Statistics in the event of this person's death during the study (if necessary).
- I understand that certain individuals mentioned in this information sheet will have access to all of this person's data for the purpose of study monitoring. I give these individuals permission to access this person's data for study monitoring purposes.
- I understand that the researchers will approach my relative to request permission for the use of the data collected during the study.
- I consent to the continued participation in the study.

Name of legal representative: …….

Relationship to the subject: …….

Signature: ……. Date: ____ / ____ / ____

I declare that I have fully informed the person(s) mentioned above about the said study. If any information becomes known during the study that could influence the representative's consent, I will let them know in good time.

Investigator name (or their representative): …….

Signature: ……. Date: ____ / ____ / ____

The representative will receive a complete information sheet, together with a signed version of the consent form.