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,

Some time ago, you received extracorporeal membrane oxygenation (ECMO) support, also known as the heart-lung machine, in the intensive care unit. We are currently researching blood transfusion policies during ECMO support by comparing two treatment approaches. While you were on ECMO, the transfusion policy you received was randomly assigned with the approval of the Medical Research Ethics Committee of Amsterdam UMC. Since you were unable to give consent at the time, we sought consent from your legal representative (a family member or relative). Now that you are able to respond, we kindly ask for your permission to use your data for this research.

Here, you can find details about the nature of this research, its potential implications for you, as well as the associated benefits and drawbacks. We understand it's a significant amount of information. Please take the time to review it carefully and consider granting us permission to use your data. If you agree, kindly fill out the form provided in **Appendix D**.

Ask your questions
We encourage you to make your decision based on the information provided in this document. Additionally, we recommend that you

- Ask any questions you may have to the investigator who presented this information to you.
- 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, location AMC 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 you were supported with ECMO, the doctors and researchers assessed your eligibility for this study. No additional measurements or blood samples were taken for this assessment.

When you were admitted, you were randomly assigned to a specific treatment group. After randomization, your treating physicians followed the assigned transfusion threshold. Your participation in the study did not alter the other aspects of your treatment. While various

medical data were collected during your stay, no extra tests or hospital visits were required compared to those not involved in the study.

Everyone involved in your treatment was aware of your participation in the study. It is likely that you were unable to discuss the study on that day, so your legal representative was informed about the study and asked for preliminary consent on your behalf.

Step 2: The limits for blood transfusion
During ECMO support, the decision to administer a blood transfusion was based on your blood hemoglobin levels and the assigned threshold.

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

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

The transfusion strategy you received was determined by randomization. You, your legal representative, and your doctor were informed of the assigned strategy.

Step 3: study and measurements
No additional measurements were taken for this study. In the ICU, it is standard practice to monitor various blood values to assess your condition. If your hemoglobin level, as determined by a blood test, was at or below the threshold specified by the transfusion strategy assigned to you, a blood transfusion was given. After the transfusion, your hemoglobin level was rechecked to ensure that the desired increase had been achieved. This blood test is part of routine care. Additionally, you underwent all the procedures that you would have received even if you weren't participating in this study.

How long will the study take?
If you participate in the study, we will use your data from the period during ECMO support. Three months after ECMO support, additional data will be collected. We will complete a follow-up at 3, 6, 9, and 12 months to assess your status, including aspects such as "quality of life," "productivity loss," and "use of healthcare services":

- After 3 months, the researchers will collect medical data regarding your current status. This will be done through the electronic patient record, your general practitioner, or, in the case of death, the Central Agency for Statistics will be contacted to inquire about the cause of death. This is necessary to examine the relationship with the study. If the mentioned options are incomplete, the researcher may contact you by phone or email.
- After 3, 6, 9, and 12 months, the researcher will either call you or send you an email requesting you to complete a questionnaire. You will be asked about your well-being,

any difficulties you experience in daily functioning (i.e., your "quality of life"), and how often you need medical care. The conversation or completion of the questionnaire will take approximately 20 minutes. You will be contacted a total of four times. We will ask for your consent to contact you. After you complete the final questionnaire, your email address will be removed from our system. You can still participate in the study even if you do not consent to be contacted.

What is the difference with standard care?
In this study, most aspects reflect standard care. You received all the treatments and measurements that are typically performed during ECMO support, regardless of your 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?

You do not have to adjust your activities in daily life: there are no restrictions or rules. You may continue your daily activities as usual. We would, however, like to ask you to contact the researcher in the following situations:

- You no longer wish to participate in the study.
- Your telephone number 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 this research may offer both benefits and potential drawbacks. These are outlined below for your careful consideration, and we encourage you to discuss them with

others. Please be aware that taking part in this study does not guarantee that your condition will be cured or that your discomfort will be alleviated.

The possible advantages of participating in this study include:

- By participating, you are 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 your ECMO support, you may need fewer blood transfusions, but this is not a guarantee. Your participation contributes to the search for a more effective approach to treating anemia during ECMO: transfusing only when necessary and avoiding unnecessary ones.

Potential disadvantages of participating in the study are:

- You might experience side effects or adverse effects related to anemia, as outlined in paragraph 6.
- Three, six, nine and twelve months after ICU admission, you 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 or you would like to withdraw?

Participation in this research and the sharing of your data with the research team is entirely up to you. If you choose not to participate or not to share your data, all collected information will be promptly deleted. Furthermore, if you initially agree to participate but later decide to withdraw, you have the right to do so. If you withdraw while still receiving ECMO support, you will return to the standard anemia treatment.

9. When does the study end?

The study will be discontinued for you in the following situations:

- If you consent to completing the questionnaires, the study will continue for an additional 12 months after your ICU admission, once all data has been collected according to the schedule.
- You decide to withdraw from the study voluntarily. You may withdraw at any time by notifying the investigator immediately. You are not obligated to provide a reason for your withdrawal. If you decide to withdraw from the study or no longer participate, you will resume receiving the standard treatment for your anemia while still undergoing ECMO support.
- The investigator deems it necessary for you 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 keep you updated on any important changes or developments related to the study. In the event of any new information becoming available, they will share this with you and ask whether you would like to continue your participation in the research, if applicable.

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

By participating in the study, you are providing your consent for the collection, utilization, and storage of your data.

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

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

Why do we collect, use and store your data?
We collect, utilize, and store your data to address the research questions and facilitate the publication of the study's findings.

How do we protect your privacy?
To protect your privacy, we assign a research number ("code") to your data. Only this code is used on your data. The key to this code is securely stored at the hospital. When processing your data, we use only the code. Additionally, in reports and publications about the study, it is not possible to identify you.

Who can see your data?

Certain authorized individuals may have access to your 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 medical records. These individuals are responsible for ensuring the proper and reliable conduct of the study. The following individuals can access your 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 (in Dutch: “Inspectie Gezondheidszorg en Jeugd”).

These individuals will keep your data confidential. We kindly request your permission to grant them access to your information. The Health and Youth Inspectorate can access your personal information without your permission.

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

Can we use your data for other research?
The data collected may also be relevant for other scientific research in the field of anemia during ECMO support, even after the completion of this study. Therefore, the data will be stored in the hospital for a period of 15 years. In the consent form, you can indicate whether you agree to this. If you do not provide consent for the usage of your data in other scientific research, your data will only be used for the purposes of this specific study and will not be utilized for any other research.

What happens if there are coincidental findings?
Throughout the study, there is a chance that significant health-related information may arise. In such instances, the researcher will contact your attending physician, and you will subsequently discuss the required steps with your general practitioner or specialist. By completing the form, you grant consent to inform your general practitioner or specialist about any pertinent findings.

Can you withdraw your consent for the use of your data?
You have the right to withdraw your consent for the use of your data at any time, both for this specific study and for any other research purposes. However, please note that if you withdraw your consent after researchers have already collected data for the study, they are still be permitted to use that data by the regulations and ethical guidelines

Do you want to know more about your privacy?

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

- Do you have questions about your rights? Or do you have a complaint about the processing of your 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 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 you receive compensation if you participate in the study?

Participating in the research does not incur any costs for you. Additionally, there is no compensation provided for participating in this study.

13. Are you insured during the study?

Insurance coverage has been arranged 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. Detailed information regarding the insurance policy and its exceptions can be found in **Appendix B**. This section also specifies the appropriate contact person to report any damages.

14. We will inform your doctor

For your safety, the researcher will inform your treating specialist about your participation in the study.

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 carefully review the information about this research. Once you have considered it, you can inform the researcher whether you understand the details and whether you wish to participate or allow your data to be used. If you decide to participate or share your data, please complete the consent form provided with this information sheet. Both you and the researcher will receive a signed copy of the consent form.

Thank you for your time.

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) Patient

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 IC admission

During your ECMO support, you received standard care. No additional procedures or measurements were performed for the purpose of the research. If your hemoglobin level in your blood was lower or equal to the value corresponding to the assigned strategy, a blood transfusion was administered. After the transfusion, the desired effect (an increase in hemoglobin level) was monitored. This involved a routine blood draw. However, it is possible that the timing of the blood draw was adjusted compared to the usual hospital practice, such as within 4 hours instead of 6 hours. During your ECMO support, you had an arterial catheter in your wrist from which the blood samples were taken. You should not experience any discomfort from this.

When the ECMO support was discontinued, the transfusion strategy was also discontinued. One day after stopping ECMO support, no data were subsequently collected regarding the course of your hemoglobin level, and no additional measurements were performed.

After 3 months

Approximately 3 months after your participation in the study, the researcher will collect data regarding your current status. The necessary information will be gathered through the electronic patient record or your general practitioner. If the available information through these channels is limited, the researcher may contact you.

Questionnaire after 3, 6, 9 and 12 months

Approximately 3, 6, 9, and 12 months after your participation in the study, we will contact you by phone or email to complete a questionnaire. The questionnaire will ask about your well-being and any ongoing issues with reduced (physical) functioning, such as whether you are able to care for yourself independently or need assistance. It will also inquire about your 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 consent to contact you for this purpose. After you complete the final questionnaire, your email address will be removed from our system. If you do not consent to be contacted, you can still participate in the study.

Appendix D: Informed consent form – Subject

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

- I have read the information sheet and had the opportunity to ask questions. My questions have been adequately answered, and I had sufficient time to decide whether or not to participate/share my data for this research.
- I understand that participation is voluntary, and I can decide at any time to withdraw from the study or stop participating without having to provide a reason.
- I grant the researcher permission to inform my treating general practitioner/specialist(s) about my participation in this study.
- I give consent to the researcher to provide my general practitioner or specialist with information regarding any unexpected findings from the study that are relevant to my health.
- I authorize the retrieval of information from my general practitioner and, if necessary, the specialist treating me.
- I provide consent for the researchers to collect and use my data solely for the purpose of answering the research question of this study.
- In the event of my death during the study, I understand that the official cause of death data may be obtained from the Central Agency for Statistics.
- I am aware that certain individuals listed in this information sheet may have access to all of my data for the purpose of study monitoring. I grant these individuals permission to access my data for this monitoring.

- Please mark "yes" or "no" in the table below:

I give permission for my data to be stored and used for other research purposes, as stated in the information sheet.	Yes ☐	No ☐
I consent to be approached for potential participation in future studies after the completion of this research.	Yes ☐	No ☐
I consent to further participation in the study, which involves up to four instances of completing a questionnaire (either by phone or email).	Yes ☐	No ☐

My name is (subject): ……..

Telephone number: ……..

Email address: ……..

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

I declare that I have fully informed this subject about the study mentioned. If any information becomes known during the study that could influence the subject's consent, I will let this subject know in good time.

Investigator name (or their representative): ……..

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

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