Title: Functional and genetic characterization of Danish patients suspected of hereditary anemia (DAHEAN)

We will ask if you would like to participate in a scientific trial.

Participation in the trial is voluntary. You can withdraw your consent at any time and without giving a reason.

The trial is a national collaboration coordinated by Rigshospitalet, Blegdamsvej 9, DK-2100 Copenhagen.

The trial is led by:
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The purpose of the trial is to:

- Improve the diagnosis of hereditary red blood cell deficiency (anemia)
- Establish national cooperation in rare anemias
- Create scientific basis for targeted treatment of rare anemias.

Plan for the experiment:

- Results of diagnostic tests performed for participants are collected in a secure electronic database.
- In collaboration with the attending physician, the need for additional diagnostics, including comprehensive genetic analyzes, is evaluated
- If the studies give rise to doubt, they are discussed by a national panel of Danish experts in the field of anemias to ensure the best possible diagnosis.
- Accurate diagnosis will ultimately lead to more qualified guidance and better treatment options for the individual patient

Participation in the trial may give rise to several diagnostic tests, which may result in additional blood sampling.

In the attached participant information, you can read more about what the trial is about, what will happen to you, and your rights if you say yes.

1 PARTICIPANT INFORMATION ABOUT PARTICIPATING IN A SCIENTIFIC TRIAL

Trial title: Functional and genetic characterization of Danish patients suspected of hereditary anemia (DAHEAN)

We would like to ask if you would like to take part in a national scientific trial coordinated by the Dr. Andreas Glenthøj.

Before you decide whether you want to participate in the experiment, you must fully understand what the trial is about and why we are conducting it. We would therefore ask you to read this participant information carefully.

You will be invited to a conversation about the trial, where this participant information will be elaborated and where you can ask the questions you have about the trial. Feel free to bring a family member, friend or acquaintance to the interview.

If you decide to participate in the trial, we will ask you to sign an informed consent form. Remember that you are entitled to a reflection period before you decide whether you want to sign the consent form.

Participation in the trial is voluntary. You can withdraw your consent at any time and without giving a reason. This will not have consequences for your further treatment.

2 PURPOSE OF THE TRIAL

Anemia is a term for a lack of red blood cells. In some patients, it is due to congenital genetic defects that either hinder the formation or shorten the life of red blood cells. In some, the symptoms are mild, e.g. fatigue and reduced physical capacity. In severe cases, patients need blood transfusions to survive.

An accurate diagnosis is essential to guide and treat the individual patient. Often, the diseases are rare and the diagnosis difficult. This experiment aims to:

1) Collect diagnostic information about Danish patients suspected of having an inherited deficiency of red blood cells (anemia)
2) Improve diagnostics of anemias and improve the foundation for choosing the best treatment
3) Establish national cooperation in rare anemias
4) Create scientific basis for targeted treatment of rare anemias

3 BIOLOGICAL MATERIAL

Participation in the trial results in the registration of diagnostic tests relevant to the deficiency of red blood cells. In addition, advanced analyzes are offered, leading to the donation of extra blood (0.1 ml - 50 ml depending on age and purpose).

The material will be analyzed continuously and mostly within 2 months. Material is stored securely until the end of the trial in 2037. The purpose of storage is to ensure easy access to additional tests that would otherwise require new donation of blood or bone marrow.
Any excess material will after 2037 be stored in a biobank for future research for use in the current project as well as any use in future research projects. The material may not be used in new projects without prior approval from the Ethics Committee and without obtaining renewed consent from you. However, the committee may in certain cases dispense with this and allow the project without your consent has been attempted to be obtained. Material sent to the Netherlands is destroyed after analysis.

Subjects can have donated material destroyed at any time by contacting the trial management.

There are no serious risks associated with donating material to the trial (see section on side effects).

4 PLAN FOR THE TRIAL

Participation in the trial involves:

1) Registration of existing diagnostic data concerning deficiencies in red blood cells.
2) If it makes sense in diagnosing the individual patient, extensive genetic testing is offered. ***Extensive genetic testing requires separate consent:*** ***https://ngc.dk/blanketter-og-vejledninger***
3) Optional additional blood tests for examinations that increase diagnostic certainty and characterize anemia.
4) Discussion of test results among experts in the field of hereditary anemias to ensure the best possible diagnosis.

Blood is drawn from a vein using standard donor cannula. The bottling takes a few minutes by authorized healthcare professionals. In some cases, special test can only be performed at external laboratories in Denmark or at the University Medical Center Utrecht in the Netherlands.

Bone marrow and skin biopsies *are not performed* as part of trial participation*. If* either of these are performed in the routine diagnostics, they will be included in the trial and the results registered in the trial database.

Not all studies are done at once. Blood is therefore stored in a secured biobank for later analyzes. Genomic material (DNA) is purified for the purpose of mapping gene variations and gene expressions that may be important for defective blood cell formation. Genetic testing by the National Genome Center requires separate consent (https://ngc.dk/blanketter-og-vejledninger).

The genetic analyzes are performed by so-called whole genome sequencing via the national genome center (www.ngc.dk). The analyzes target genes related to defective red blood cell formation.

Findings of genetic variants related to defective red blood cell formation will increase the diagnostic certainty of the individual patient and in some cases guide the right treatment choice.

Although the genetic studies are targeting genetic changes related to inadequate red blood cell formation, there is a risk of random findings that are not related to it. Sometimes these changes can take effect many years later. In these cases, the patient will be offered genetic counseling. You can refuse to receive information about random genetic findings, but in that case you must choose this when you fill in the consent for comprehensive genetic analysis.

Genome data are stored after the experiment in accordance with the Data Protection Regulation and the Data Protection Act.

The person responsible for the trial will access the patient record to find diagnostic tests performed and the treating doctor's assessment of the patient's condition.

If the donated material can later be used for projects not mentioned above, an application for approval will be submitted before use for these projects.

5 USEFULNESS OF THE TRIAL

The trial aims to improve the diagnosis of hereditary deficiencies of red blood cells. This increase both the diagnostic accuracy of the individual patient and our overall understanding of these diseases. Overall, a better and more secure basis for treatment offers is formed. The importance of an accurate diagnosis gradually increases as more targeted treatments become available.

6 SIDE EFFECTS, RISKS, COMPLICATIONS AND DISADVANTAGES

There are no significant risks associated with blood donation. To the greatest extent possible, we will seek to take samples in connection with already planned blood samples. Bone marrow examination is not performed due to participation in the trial.

In general, blood sampling can cause local bleeding after the insertion, which in rare cases can give rise to discomfort and discoloration for a few days. In rare cases, a vasovagal shock can be triggered which leads to short-term fainting. However, this is prevented by donors being tapped sitting / lying down.

Skin biopsies are associated with brief pain while the local anesthesia is given. Local bleeding can occur. A small wound (typically 3 mm in diameter) is formed and heals over time.

Bone marrow examination is routinely performed in hematology departments. The procedure is performed by health personnel with routine in performing the procedure. This procedure is associated with discomfort partly in the form of a short-term pain in connection with the application of the local anesthetic, and partly an unpleasant sensation while the bone marrow is drawn. This takes approximately 30 seconds. In the last 30 years, in connection with the many daily bone marrow examinations carried out at the department of hematological at Rigshospitalet, complications have never arisen apart from minor blood collection. In addition to the immediate discomfort associated with the procedure, transient local tenderness may occur when the effect of the local anesthetic ceases. This is most often handled effectively by paracetamol.

	Frequent and not serious	Rare and serious	Permanent
Side Effects	None	None	None
Risks	None	None	None
Complications	Local bleeding at the incision site.	None	None
Disadvantages	Discomfort/pain	None	None

There may be risks in the experiment that we do not yet know. We therefore ask you to tell us if you experience problems with your health while the trial is on. If we discover side effects that we have not already told you about, you will of course be informed immediately, and you will have to decide whether you want to continue the trial.

7 STANDARD TREATMENT OUTSIDE THE TRIAL

If you do not participate in the trial, you will receive a standard assessment and treatment. Most of the studies registered as part of the trial are also part of a normal investigation outside the trial. Participation in the trial does not in itself include any treatment. The trial simply aims to improve the diagnosis of hereditary anemias and thereby form an optimal basis for choosing treatment.

8 JOURNAL INFORMATION

By participating in the study, the investigator and his/her representatives are given access to certain information in the medical record in order to be able to carry out and control the study. Data is registered in a secure database in the Capital Region of Denmark, which has been approved for the purpose by the Danish Data Protection Agency.

Journal information is obtained for the purpose of:

1) To be able to present the individual patient's information at the highly specialized national anemia conference, where new examinations can be proposed, a diagnosis determined, and treatment proposals prepared
2) To generally map and describe patients with hereditary anemias in Denmark and thereby determine the presumed benefit of the specialized and comprehensive diagnostics in the project

The following information will be registered in the secured database:

- Identification information: Name, birthday, CPR number, contact information
- Genetic Data: The result of genetic analyzes relevant to anemia
- Health information: Tests results (e.g. blood tests), symptoms, treatment
- Ethnic Origin: Relevant as hereditary anemias are primarily seen in specific geographical areas
- Biological material: Overview of any available biological material available for further relevant analyzes

9 PROCESSING OF PERSONAL INFORMATION

Personal data will be processed in compliance with the Data Protection Act and the Data Protection Regulation. The Data Protection Act and the Data Protection Ordinance are also complied with for data / material analyzed in the Netherlands.

10 EXCLUSION FROM AND INTERRUPTION OF TRIAL

All patients who are suspected or have confirmed a diagnosis of hereditary anemia are welcome to participate in the trial. There are no circumstances in which patients will be excluded from participation against their wishes.

The study can be stopped if patients are not included or if patients do not seem to benefit.

11 FINANCIAL INFORMATION

Principal investigator and initiator of the study is Andreas Glenthøj, chief physician, PhD, associate professor, at the Department of Hematology at Rigshospitalet.

Andreas Glenthøj has done consulting work for and has research collaborations with pharmaceutical companies that work with the diagnosis and treatment of rare anemias. A list of these activities is updated

regularly at www.laegemiddelstyrelsen.dk. These companies may have an interest in improved diagnosis of rare anemias that the trial aims for.

Direct support for the project will be applied for from private and public foundations and grants will be reported to the National Science Ethics Committee. Trial participants will also be informed and will always be able to see updated information about this via www.anemia.dk.

Patients do not receive compensation for participating in the project.

12 ACCESS TO EXPERIMENTAL RESULTS

Both positive, negative and inconclusive research results will be published in international journals. The results will also be presented at national and international meetings and congresses. A report will be generated on an ongoing basis, presumably on annual basis, with overview data of the register, its activities and benefits (e.g. number of patients included, their overall diagnoses and whether the diagnostics were helped by the study). This report will be shared with health authorities and may be shared with commercial and non-commercial donors.

The trial is expected to be completed in 2037.

We hope that with this information you have gained sufficient insight into what it means to participate in the trial and that you feel equipped to make the decision about your possible participation. We also ask you to read the attached material "The subject's rights in a health science research project".

If you want to know more about the trial, you are very welcome to contact the investigator Andreas Glenthøj using the contact details below.

Sincerely,

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Informed consent to participate in a health research project.

Title of research project: Functional and genetic characterization of Danish patients suspected of hereditary anemia (DAHEAN)

Statement from the subject:

I have received written and oral information and I know enough about the purpose, method, advantages and disadvantages of saying yes to participating.

I know that participation is voluntary and that I can always withdraw my consent without losing my current or future rights to treatment.

I give my consent to participate in the research project and to have my biological material taken out for storage in a research biobank. I have received a copy of this consent form as well as a copy of the written information about the project for my own use.

Name of subject: _____

Date: _____ Signature: _____

Do you want to be informed about the result of the research project and any consequences for you?

Yes _____ (set x) No _____ (set x)

Statement from the person providing the information:

I declare that the subject has received oral and written information about the experiment.

In my opinion, sufficient information has been provided to enable a decision to be taken on participation in the trial.

The name of the person providing the information: _____

Date: _____ Signature: _____

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