

**Patient consent form UPSIDE study, version 2.0****Information for patients on participating in medical research****Autologous stem cell transplantation in diffuse cutaneous systemic sclerosis: early onset or only after failure of other treatments?**

**Official title: Upfront autologous hematopoietic stem cell transplantation versus immunosuppressive medication in early diffuse cutaneous systemic sclerosis (UPSIDE): an international multicenter, open-label, randomized, controlled trial**

Dear Madam/Sir,

We are asking you to participate in a medical scientific study. Participation is voluntary, however your written permission is required in order to participate. You are receiving this letter because you have been diagnosed with diffuse cutaneous systemic sclerosis (dcSSc).

DcSSc is treated with immunosuppressive drugs, chemotherapy or autologous stem cell transplantation (ASCT). The choice for a specific treatment depends on the preference of patient and physician. With this study, we want to investigate which treatment strategy is best. Before you decide whether you want to participate in this study, you will receive information about what the study entails. Please read this information carefully and contact the researcher if you have any questions.

**1. General information**

This study has been initiated by the Utrecht University Medical Centre in the Netherlands, and is being carried out by rheumatologists in various expert centres for systemic sclerosis in Europe. The study will enrol 120 patients from different countries. In the Netherlands, 50 patients are expected to participate. The Utrecht Medical Ethics Committee has approved this study.

**2. Aim of the study**

The aim of this study is to determine the best treatment strategy for dcSSc. We will compare the efficacy and safety of ASCT with cyclophosphamide therapy followed by mycophenolate mofetil (MMF) and possibly ASCT if this treatment fails. Both treatment strategies are already used in current health care in dcSSc.

**3. Background of the study**

ASCT, cyclophosphamide and MMF are both treatments used to slow down disease progression. Two previous studies have shown that ASCT has a higher chance of survival compared to cyclophosphamide. However, ASCT also carries a higher risk of serious side effects is greater. The optimal treatment strategy in dcSSc is therefore not clear. Especially the question whether ASCT should be given directly or only for patients who do not respond to other treatments like methotrexate,

MMF or cyclophosphamide. Given the risks associated with ASCT, it may be preferable to evaluate the response to other immune suppressive drugs before proceeding with ASCT. However, the use of ASCT in the event of failure of other drugs may lead to more disease damage and possibly a higher risk of complications during ASCT because the disease is more advanced.

#### **4. What it means to participate**

In this study all patients will be followed for five years. You will be randomly assigned to either 1. Direct ASCT or 2. Cyclophosphamide infusion therapy followed by MMF and possibly ASCT if this treatment fails. This random assignment means that your doctors cannot influence which treatment you receive.

##### *Eligibility assessment*

Before you can participate in this study, we will determine whether the treatments given in the study can be administered safely. This screening is done according to usual clinical care and consists of blood and urine tests, lung function tests, an ultrasound of the heart, a right heart catheterisation (to measure the pressure in the right heart side) and a 24-hour cardiac holter.

##### *Treatments*

We will not treat you with experimental treatments in this study, the therapies we investigate have been used in systemic sclerosis for some time. Half of the participants will be treated by treatment strategy A: ASCT, the other half by treatment strategy B: monthly infusion therapy with cyclophosphamide followed by MMF tablets, and possibly ASCT if this treatment fails.

##### Treatment strategy A: ASCT

Transplantation consists of the following steps:

##### *Step 1. Pre-treatment and stem cell harvesting*

This treatment will take place in the hospital's day care unit, or at the haematology department, depending on local practice of your hospital. Cyclophosphamide is administered via an infusion. Side effects are nausea and sometimes hair loss. To prevent cyclophosphamide from irritating the bladder, we give you plenty of fluids and medication. Sometimes the white blood cell count may drop in the weeks following the cyclophosphamide treatment, and if you develop a fever, antibiotic treatment may be necessary.

From the fifth day after the cyclophosphamide infusion, you will receive daily subcutaneous injections with G-CSF (filgrastim), which causes the bone marrow to make more cells. G-CSF can cause flu-like symptoms and muscle and joint pain. Cyclophosphamide and G-CSF make stem cells move from the bone marrow into the blood. Blood tests will be done to see if there are enough stem cells in the blood. If there are, they will be harvested through a leukapheresis machine. This involves one infusion in each arm. The leukapheresis machine is a bit like a kidney dialysis machine: the blood comes out of the infusion and into the machine, the machine removes the stem cells and the rest of the blood is returned. You will be hooked up to this machine for one to two consecutive days for about 4 hours (this can vary depending on the number of stem cells in your blood). The harvested cells are frozen until needed. Then you will go home to recover.

##### **Cardiac monitoring**

Two to three weeks after the stem cell harvest, you will visit the haematologist and rheumatologist for a check-up. Blood test, an ultrasound of the heart will also be done.

### **Step 2. Stem cell transplantation**

The next step takes place within 6 weeks after leukapheresis. For this, you will be admitted to the haematology department and stay in hospital for approximately 3-4 weeks. An infusion will be placed to take blood samples and to administer medication including chemotherapy.

You will receive a high dose of chemotherapy (cyclophosphamide), corticosteroids and ATG) with generous fluid infusion. You will be given medication to prevent nausea and to protect the bladder. You will also receive antibiotics to prevent infections. Cyclophosphamide often causes nausea, hair loss and mouth ulcers. There is a very small risk of heart damage caused by the chemotherapy. Due to the large amount of fluids, you may retain fluids, which will be closely monitored. Bone marrow cells (red and white blood cells and platelets) will drop sharply as a result of the treatment. Sometimes a transfusion is needed. The white blood cells will remain very low for about 10-14 days and during this period you are at risk of serious infections.

On the 3rd day that you receive cyclophosphamide, treatment with (r-ATG) a protein obtained from rabbit blood is also started. This drug will also be administered via infusion and can cause flu-like symptoms and fever. After these treatments, you will receive your own stem cells back; this procedure is similar to a blood transfusion.

There is a small risk of damage to the heart, kidneys and lungs with these treatments. The risk is greater in patients with existing heart or lung problems. Therefore, you will have extensive screening test before to assess whether we can give the treatments safely.

### **Treatment strategy B: Infusion therapy with cyclophosphamide followed by MMF tablets**

Cyclophosphamide is given at the day care unit of the rheumatology department. You will receive an infusion once a month during 12 months. A common side-effects are nausea, which usually lasts a few days after the infusion and sometimes temporarily hair loss. Sometimes the white blood cell count may drop in the weeks following the cyclophosphamide treatment, if you develop a fever, antibiotic treatment may be necessary.

After 12 months the treatment is switched to mycophenolate mofetil (MMF). MMF tablets should be taken twice a day. This treatment can cause gastrointestinal complaints such as diarrhoea or nausea. Sometimes the white blood cell levels in the blood may drop, therefore blood tests are done every month.

If you do not respond well to the treatment you received, it is possible to switch from treatment strategy. This means that if you have received the treatment in arm A (ASCT), you will receive immunosuppressive treatment and ASCT may be started in arm B.

### **Monitoring after the treatment**

All patients are closely monitored for 5 years, regardless the treatment assigned. We will ensure that appointments are combined with your usual care appointments. Hospital visits will take place 3, 6, 9, 12, 15, 18, 21 and 24 months and every year thereafter. The frequency of follow-up visits is the same as usual care. To evaluate the safety and effectiveness of both treatments, the following tests will be done. This is done according to usual clinical care.

*During all visits:*

- blood count: liver tests, kidney function, sedimentation rate
- skin score (assessment of skin thickening)

*Annually:*

- Lung function test
- CT scan of the lungs
- Cardiogram (ECG)
- Echo of the heart
- MRI of the heart (only 1 year after treatment)
- Urine spot test

**Other than for usual care**

For research purposes, we will do nailfold microscopy and a hand mobility test during the follow-up.

This will be done on the same day as your follow-up appointments in hospital.

In addition, you will receive an invitation by mail for online questionnaires at the start of the study, after 6, 12, 18 and 24 months and annually thereafter, to assess quality of life, daily functioning, fatigue, gastrointestinal complaints and sexual functioning. In addition, every three months you will be asked to score your skin thickness using an online questionnaire. We understand that questions on certain topics may be perceived as difficult or personal. You can therefore fill in the questionnaires when and where it suits you. Your answers will of course be treated with strict confidentiality.

*Nailfold capillaroscopy*

We will examine changes in the small blood vessels (capillaries) of the nail bed before and after treatment, and we will examine whether there are differences between treatments. The appointment for the nailfold capillaroscopy will be scheduled in combination with a routine hospital visit, so no additional hospital visits are necessary. Examination will be done at the start of the study and 6, 12, 24 months and annually up to 5 years after the treatment.

The examination will be done by a rheumatologist or nurse. You will sit at an examination table and position your hands flat on the table. The doctor will apply a drop of oil to your cuticles. Then he will gently place the capillaroscope, a cylindrical instrument, on your nail. The capillaroscope makes the small blood vessels in your nail bed visible on a computer screen. They are magnified 200 times. A photograph is then taken. The doctor examines all fingers, except for the thumbs. The examination takes about 30 minutes and is completely painless. The analysis of this data takes place at Ghent University Hospital, at the end of the study.

*Hand mobility test*

We will investigate which changes occur in hand mobility before and after treatment, and we will investigate if there are differences between treatments. This examination will be done at the start of the study and 6, 12, 24 months and annually up to 5 years after the start of the study. The examination will be done by a rheumatologist or nurse. You will sit at an examination table and a doctor or nurse will test your hand function in four ways. The examination takes about 15 minutes and is completely painless. The analysis of the results will take place at the University Hospital in Lund at the end of the study.

**5. What is expected of you?**

When you are going to participate in this study, it is important to read the following agreements.

We expect you will:

1. take the medication according to the instructions.
2. do not take part in any other medical scientific research.
3. attend to hospital and study appointments

You will receive a research participant's card, we recommend to carry this with you. This card states that you are participating in this study. It will also tell you who to notify in case of an emergency. Show this card when you visit a doctor.

For the nailfold capillaroscopy, it is important that your fingers are at room temperature. We therefore ask you to be arrive at the clinics 15 minutes prior your appointment so that your hands can get used to this temperature. You should not wear nail polish or have a manicure just before the examination. You should also not smoke for at least 1 hour before the examination.

It is important that you contact the researcher:

- before taking any other medicine. Even if these are homeopathic medicines, natural medicines, vitamins and/or over-the-counter medicines.
- if you are hospitalised or treated in a hospital.
- if you suddenly experience health problems.
- If you no longer wish to participate in the study.
- if your contact details change.

### **Pregnancy and fertility**

Women who are pregnant or breastfeeding cannot take part in this study. Women should also not become pregnant during the treatment. Only after at least 3 months after the last administration of medication pregnancy is regarded as safe. For men, their partner may not become pregnant during the entire study period. Please inform your partner about this. The treatments may have consequences for an unborn child. The researcher will talk to you about suitable contraceptives. Should you become pregnant during the study? Please inform the medical examiner immediately. If your partner becomes pregnant during the study, please ask her permission to tell the medical examiner. The pregnancy can then be monitored more closely.

Both men and women can become less fertile as a result of the treatment. We will discuss family planning with you and, if desired, the possibilities of freezing sperm and egg cells before the treatment starts.

### **6. Possible side effects**

The treatments given in this study may cause side effects. Please contact the investigator if you experience any health problems. The main side effects for the study medication are listed below:

#### *Side effects of cyclophosphamide*

- nausea, mouth ulcers, hair loss

- in- or subfertility, irritation of the bladder
- serious infections, severe bleeding
- increased long-term risk of leukaemia, lymphoma or bladder cancer

#### *Side effects of G-CSF*

- flu-like symptoms

#### *Side effects of ATG (Anti-thymocyte Globulin):*

- muscle and joint pain
- fever, flu-like symptoms
- rarely serum sickness (allergic reaction to foreign proteins, manifested by fever, rash and joint pain).

#### *Side effects of MMF*

- nausea, diarrhoea
- infections

At each visit, we will monitor for any side effects. If you experience any problems in between visits, you should inform the study doctor immediately. The regular study visits and blood tests are there for your safety.

## **7. Possible advantages and disadvantages**

It is important that you balance the possible advantages and disadvantages before you decide to participate. ASCT, cyclophosphamide and MMF are all used in routine care in dcSSc. However, in this study we will use ASCT earlier in the disease course. The advantages of participating in this study may be that the disease progression is slowed down early and there will be fewer side effects. In addition, if there is a serious deterioration and the first treatment has insufficient effect, it may be possible to change treatment.

Disadvantages of participating in the study may be possible side effects of one of the above mentioned treatment strategies. Participation in the study also means that it takes extra time to fill in the questionnaires.

## **8. If you do not want to take part or want to stop the study**

The decision to participate in the study is yours. Participation is voluntary. If you do not wish to take part, you will be treated for your condition as usual. You and your doctor will then decide on the treatment (immunosuppressive drugs, chemotherapy or ASCT). The researcher can tell you more about the treatment options available and their pros and cons.

If you do take part, you can always change your mind and stop, even during the study. You will then be treated according to usual care. You do not have to say why you want to stop. However, you must tell the researcher immediately. Discontinue your participation will not have any negative consequences for you, but stopping the treatment you have been assigned to may have negative consequences, such as worsening the disease. It is therefore important to discuss this with your doctor. The data collected up to this point will be used for the study.

If there is new information about the study that is important to you, the researcher will let you know. You will then be asked if you wish to continue to take part.

## 9. End of the study

Your participation in the study will end when:

- all visits have been completed
- you decide to stop
- you become pregnant
- the end of the study has been reached
- the researcher feels it would be better for you to stop
- UMC Utrecht, the government or the reviewing medical ethics committee decide to stop the study.

The whole study ends when all participants have finished the follow-up period. After all data have been processed, the researcher will inform you of the main results of the study. The researcher will discuss how to continue your medical care.

## 10. Use and storage of your data

For this study, your personal data will be collected, used and stored. This includes data such as your name, age and data concerning your health. The collection, use and storage of your data is necessary to answer the questions posed in this study and to publish the results. We ask you for your permission to use your data.

### *Confidentiality of your data*

In order to protect your privacy, your data will be coded. Your name and other data that can directly identify you are omitted. Only the key to the code can be used to trace the data back to you. The key to the code remains safely stored at the local research institute. The data sent to the principal investigator and other researchers will only contain the code, but not your name or any other data that could identify you. Also, reports and publications about the study do not contain any data that can be traced back to you.

### *Access to your data for control purposes*

Some people at the research location may have access to your data. Also to the data without a code. This is necessary in order to check whether the research has been carried out properly and reliably. Persons who will have access to your data for control purposes are: the committee supervising the safety of the research, a monitor working for UMC Utrecht, national and international regulatory bodies, e.g. the Health Care Inspectorate. They will keep your data confidential. We ask your permission for this access.

### *Data retention period*

By law, your data must be stored for 15 years at the research location and 15 years at the client's location. It will be stored to carry out new assessments in the course of this study, related to this study.

### *Retention and use of data for other research*

Your data may still be of interest to other scientific research in the field of systemic sclerosis and stem cell transplantation after this research has ended. For this purpose your data will be stored for 15 years. You can indicate on the consent form whether you agree with this or not. If you do not agree, you can only participate in the current study.

#### *Information about unexpected findings*

During the study, something unexpectedly may be found that is not important for the study but for you. If this is important for your health, you will be informed by your treating rheumatologist. You can then discuss with your specialist what needs to be done. We will ask your permission for this.

#### *Withdrawing consent*

You can always withdraw your permission for the use of your personal data. This applies to this study as well as to its storage and use in future studies. The research data that has been collected up until the moment you withdraw your permission will still be used in the research.

#### *Transfer to countries outside the European Union (EU)*

Your encrypted data will not be transferred to countries outside the EU.

#### *More information on your rights regarding data processing*

For general information about your rights regarding the processing of your personal data, please visit the website of the Dutch Data Protection Authority.

If you have any questions about your rights, please contact the person responsible for processing your personal data. If you have any questions or complaints about the processing of your personal data, we recommend that you first contact the research site. You can also contact the data protection officer of the institution or the Dutch Data Protection Authority.

#### *Registration of the study*

Information about this study can also be found on [www.upsidetrial.com](http://www.upsidetrial.com). This site does not contain any data that can be traced back to you. After the study, the website may show a summary of the study results.

### **11. Insurance for test subjects**

Insurance has been taken out for everyone who participates in this study. The insurance covers any damage caused by the study.

### **12. Informing your GP**

We will always send a letter to your GP and the specialist treating you to let them know you are taking part in the study. This is for your own safety.

### **13. Reimbursement for participation.**

The treatment strategies investigated in the study will not cost you anything, as these are part of usual care and covered by your health insurance. You will not be paid for participating in this study. We will reimburse you for additional travel and parking costs.

### **14. Do you have any questions?**

If you have any questions, please contact the researcher. For independent advice on participation in this study, you can contact our independent expert. He/she knows a lot about the study, but is not involved in it.

If you have any complaints about the study, you can discuss them with the researcher or your doctor, you can also contact the complaints officer.



**15. Signing the consent form**

When you have had enough time to think, you will be asked to decide whether you wish to take part in this study. If you give your consent, we will ask you to confirm this in writing on the accompanying consent form. Your written consent indicates that you have understood the information and agree to participate in the study.

Both you and the researcher will receive a signed copy of this consent form.

Thank you for your interest and attention.

**The UPSIDE study team**

**Consent form**

- I have read the information letter. I have also been able to ask questions. My questions have been answered sufficiently. I had enough time to make a decision.
- I know that participation is voluntary. I also know that I can decide at any time not to participate or to stop. I do not have to give a reason for this.
- I consent to inform my GP that I am participating in this study.
- I consent to the collection and use of my data for answering the research question as described in the information letter.
- I consent to forward my data/ in the context of this study as described in the information letter. The data will only be transferred in coded form, without my name and other personal details that can directly identify me.
- I consent to any random findings being discussed with me.
- I know that for the purpose of monitoring the study some people may have access to all my data. These people are mentioned in this information letter. I give permission for these people to have access to my data.
- I give permission for my GP and/or treating specialist to be informed of any unexpected findings that may be relevant to my health.
- I know that I am not allowed to become pregnant during the study until 3 months after the last administration of medication.
- The investigator has discussed the most suitable contraception for me.

- I give  
 I give not

permission for my personal data to be stored for a longer period (up to 15 years) and used for future research in the field of systemic sclerosis.

- I give  
 I give not

permission that they may contact me again for a follow-up study after this study.

I would like to participate in this study.

Name of participant: .....

Signature: ..... Date: .... /.... /.....

I declare that I have fully informed this patient about the research in question.

If, during the study, information becomes known that could influence the patient's consent, I will inform him/her in a timely manner.

Name researcher (or his representative): .....

Signature: ..... Date: .... /.... /.....