Subject information for participation in medical scientific research

A study on the effect of carotid artery stenting during endovascular treatment of acute ischemic stroke

Official English title: CASES: Stenting a carotid stenosis during endovascular thrombectomy compared to an endovascular thrombectomy with delayed treatment of a carotid stenosis in patients with an acute ischemic stroke caused by a proximal intracranial occlusion.

Introduction

Dear Sir/Madam,

We ask for your consent for your partner/family member to participate in a medical research. Participation is voluntary. Your written permission is required to participate. You are receiving this letter because your partner/family member has suffered an acute ischemic stroke. You have now been informed about this condition by his/her treating physician. Because it was in your partner/family member's interest to be treated as soon as possible, the medical ethics review committee has been asked to postpone your consent to participate in the study until after the treatment. Because the risks of this research are low, the medical ethics review committee has agreed to this. This means that your partner/family member has already undergone the treatment to be examined or the standard treatment. This has been determined by lottery. At the moment, the medical condition of your partner/family member is not good enough to give permission themselves. Before you decide whether you want your partner/family member to continue participating in this study, you will receive an explanation of what the study entails via this information letter. Please read this information carefully and ask the researcher for an explanation if you have any questions. You can also ask the independent expert, mentioned at the end of this letter, for additional information. And you can also talk about it with friends or family. If you give your consent, you can fill in the form found in Appendix D.

Ask your questions

You can make your decision with the information you will find in this information letter. In addition, we recommend that you do this:

- Ask questions to the researcher who gave you this information.
- Talk to your partner, family or friends about this research.
- Ask questions to the independent expert. For contact details see Appendix A
- Read the information on www.rijksoverheid.nl/mensenonderzoek.

1. General information

Participants in a medical-scientific study are often referred to as test subjects. Both patients and people who are healthy can be test subjects.

This study was set up by the University Medical Center Groningen (UMCG) and is being done by doctors in various hospitals in Belgium and the Netherlands. The medical ethics review committee of Erasmus MC Rotterdam has approved this study. General information about the review of research can be found on the website of the Dutch government; www.rijksoverheid.nl/mensenonderzoek.

2. What is the purpose of the study?

The aim of this study is to find out whether stenting of severe carotid artery stenosis during endovascular thrombectomy for acute ischemic stroke is as effective as deferred treatment of carotid artery stenosis after endovascular thrombectomy.

3. What is the background to the research?

Your partner/family member has been admitted to hospital because he/she has had an acute ischemic stroke. A ischemic stroke occurs when a blood vessel in the brain is blocked by a clot and a part of the brain therefore does not receive blood and is damaged. The symptoms that can arise from this condition include paralysis, sensory disturbances, language problems and/or partial blindness. To increase the chances of recovery, patients are treated with endovascular treatment through the groin (endovascular thrombectomy) if possible. This is a procedure in which the doctor inserts a very thin tube (catheter) through the groin through the blood vessels to remove the clot from the cerebral artery. For this treatment, the sooner the procedure starts, the greater the chance of recovery.
About 1 in 3 treated people are able to function independently after a recovery period of 3 months. In 1 in 5 treated people, the clot is caused by a severe stenosis in the carotid artery. A severe stenosis of the carotid artery gives increases the risk of a new ischemic stroke in the first few weeks. Therefore, people with severe carotid artery stenosis are often operated on within 2 weeks after the ischemic stroke to prevent another ischemic stroke. The carotid artery stenosis can also be relieved immediately during endovascular treatment of an acute ischemic stroke by placing a stent. A stent is a small tube with a mesh structure that can be placed in a blood vessel to correct a narrowing in a blood vessel. The advantages of stenting directly during endovascular treatment is that a patient only has to undergo one procedure and that the risk of a new ischemic stroke is immediately reduced. A possible disadvantage is that people use two blood thinners for a longer period of time after stenting than when there is no stenting. That is why we want to use this research to study whether the immediate stenting of a carotid artery stenosis at the time of endovascular treatment of an acute ischemic stroke works at least as well as delayed treatment of carotid artery stenosis.

4. How does the research work?

How long does the study take?
Is your partner/family member participating in the study? Then it takes about 3 months in total, from treatment to final (telephone) check-up.

Step 1: His/her suitability for the study

In order to participate in this study, the investigator checked whether your partner/family member is suitable. The criteria are described below;

- Age above 18 years
- Degree of neurological complaints
- On imaging, a clot that occludes one of the cerebral arteries
- A severe stenosis or occlusion in the carotid artery on the same side as the clot
- No cerebral hemorrhage on imaging (within 6 weeks)
- No recent ischemic stroke or brain trauma (within 6 weeks)
- No recent other gastrointestinal or bladder bleeding (within 6 weeks)
- No allergy to anticoagulant medication
- No longer-standing neurological deficit that interferes with daily activity
- No pregnancy
- (Deferred) written consent for participation

Justification of deferred consent

First, the treatment of ischemic stroke is carried out as soon as possible. For every hour of delay, the chance of recovery and being able to carry out daily activities independently (ADL) decreases by 6%. In previous acute stroke studies, it has been found that waiting for treatment consent led to an (unacceptable) delay in the start of treatment.
Secondly, during the acute phase of a ischemic stroke, a patient is often unable to make an informed decision whether or not to participate in a study, for example due to disabilities such as language disorders, inability to communicate or reduced insight into the disease. Obtaining consent from the patient's proxy may also lead to unacceptable delays in acute treatment.
In summary, due to the emergency situation and the potential lack of decision-making ability, the process cannot be carried out without deferred consent. This approach has been successfully used in recent studies on ischemic strokes in the Netherlands.

Step 2: the treatment

Because the treatment had to take place urgently, your partner/family member has already been assigned to one of the following two groups.

Group 1: has immediately undergone a stenting of the carotid artery at the time of endovascular treatment for the acute ischemic stroke.
Group 2: has not undergone carotid artery stenting at the time of endovascular treatment for the acute ischemic stroke (control group, standard of care).

The division into treatment groups and undergoing the treatment was done with the agreement of a medical ethics committee prior to requesting permission. It is important to inform you and your partner/family member extensively about the study. Since it is important to treat ischemic

strokes as soon as possible in order to save as much brain tissue as possible, this is not possible prior to treatment.
In order to keep the distribution over both groups as equal as possible, a draw has been used to determine in which group your partner/family member has ended up. More information about drawing lots can be found on the website of the Dutch government.
If your partner/family member has been drawn for group 1, a stent has been placed in his/her carotid artery at the time of endovascular treatment. This treatment means that he/she is transported to a treatment room almost immediately after the scan that has been made of the head. Once in the treatment room, a catheter was inserted into the artery of his/her groin under local anesthesia, a sedation or general anesthesia. Under X-ray, this catheter was advanced to the blocked blood vessel in their head. There, an attempt was made to remove the clot by means of catheter techniques (with a removable stent and/or a small suction tube). The procedure took about 1 hour. During this procedure, the carotid artery stenosis was also treated at the same time with a permanent stent that was also placed through the blood vessels in your carotid artery via catheters.
If your partner/family member has drawn lots for group 2, the control group, then your partner/relative has undergone the endovascular treatment without the placement of a stent in the carotid artery. However, it is possible that the stenosis has been treated with angioplasty (carefully inflating a balloon in the narrowing) in order to be able to get past this narrowing to remove the blood clot in the brain. However, angioplasty alone does not give sufficient results in the long term. This means that if your partner/family member recovers well in the coming weeks, additional surgery may follow to remove the carotid artery stenosis.

Step 3: Surveys and measurements
Your partner/family member has already undergone the following measurements/tests during the hospitalization:

- Physical examination in the emergency department before the endovascular treatment and immediately after the endovascular treatment at the stroke unit by the treating physician.
- CT scan with and without contrast in the emergency department
- Endovascular treatment with or without stent placement in the carotid artery

During the hospitalization, the following measurements/tests may still take place:

- We will perform a CT scan with and without contrast of your partner/family member's neck and brain approximately 24 hours after treatment.
- We will perform a physical examination approximately 5-7 days after treatment or before discharge from the hospital (if discharge is earlier than 5-7 days)

After discharge from the hospital, you or your partner/family member will be called 1 time by the study team. This phone call will take place approximately 3 months after the treatment. You or your partner/family member will then be asked questions about his/her state of health. This appointment will take about 15 to 30 minutes and will be scheduled with a member of the

research team from the UMC Groningen. There will also be an ultrasound examination of the carotid artery after 3 months. Finally, your partner/family member will receive a questionnaire at home with questions about how he/she experiences his/her own health, whether your partner/family member has been able to resume work and whether your partner/family member has been treated by other doctors.

What is different from regular care?
In group 1, the carotid artery is treated earlier by means of stent placement during acute endovascular treatment. Group 2 will receive standard treatment, in which the carotid artery will be treated at a later date by medication, a stent, or surgery.
Some of the examinations are part of the usual care. Additional examinations in the context of this study are the CT scan with and without contrast approximately 24 hours after the endovascular treatment and an ultrasound examination of the carotid artery after 90 days.
A schematic overview of these operations can be found in Appendix C.

5. What agreements do we make with your partner/family member?

To ensure that the examination runs smoothly, it is important that your partner/family member adheres to the following agreements:

- He/she will not participate in any other medical-scientific study during this study.
- He/she comes to every appointment.
- He/she will contact the investigator in these situations:
    - If he/she is admitted to a hospital or treated.
    - If he/she suddenly develops health problems.
    - If he/she no longer wants to participate in the study.
    - His/her phone number, address or email address changes.

6. What side effects, adverse effects or discomforts can your partner/family member suffer from?

It is known that blood thinners that are necessary for the placement of a stent increase the risk of bleeding in patients with ischemic stroke. Not stenting the carotid artery stenosis immediately during endovascular treatment, the standard treatment, increases the risk of a new ischemic stroke. In addition, it is possible that in the coming weeks your partner/family member will still have to be operated on his/her carotid artery.

Radiation exposure
During a CT scan, we use X-rays. The total radiation exposure in this study is 4 mSv in the CT scan with and without contrast. By way of comparison: the background radiation that every inhabitant in the Netherlands receives is ~2.5 mSv per year. The radiation used during the examination can lead to damage to the health of your partner/family member. However, this risk is very small.

7. What are the advantages and disadvantages of your partner/family member participating in the study?

Participating in the study can have advantages and disadvantages. We list them below. Talk about this with others and if you have any questions, please contact the investigator or the independent physician (contact details can be found in Appendix A)
It is important that you have a good understanding of the potential benefits and drawbacks. Stoning the carotid artery directly can have a positive effect on recovery after the ischemic stroke and reduce the risk of a new ischemic stroke, but this is not certain. No study has yet been done to draw firm conclusions about the effect of the treatment. However, based on previous studies, patients who have undergone carotid artery stenting during endovascular treatment seem to have the same treatment effect as patients who have not undergone stenting. Furthermore, we think that fewer new ischemic strokes occur in the stenting group. Finally, if your partner/family member recovers well, your partner/family member will no longer need surgery on his/her carotid artery in the coming weeks.

Disadvantages of participating in the study can be:

- Possible adverse effects/discomforts of the examinations and scans in the study. And possibly slightly higher chance of cerebral hemorrhage for patients in group 1.A possibly slightly higher chance of a new ischemic stroke for patients in group 2. Any additional surgery on the carotid artery in group 2.

If you do not want your partner/family member to participate or if you want to stop your partner/relative from the study
You decide for your partner/family member whether he/she participates in the study. Participation is voluntary.

If you decide that he/she will participate, you or your partner/family member can always change your mind and stop anyway, even during the study. He/she will then be treated in the usual way. You or your partner/family member do not have to say why he/she is quitting. However, this must be reported immediately to the researcher.

If there is new information about the study that is important to you or your partner/family member, the investigator will let you or your partner/family member know, if his/her medical condition has recovered sufficiently. They will then be asked if they will continue to participate.

8. When does the study end?

The investigator will let you know if there is new information about the study that is important to your partner/family member. The researcher will then ask you whether your partner/family member will continue to participate.

Your partner/family member's participation in the study will stop if;

- The phone call with the investigator took place after approximately 3 months;
- You or your partner/family member choose to stop;
- The UMCG, the government or the assessing medical ethics review committee decides to stop the research.

The entire study is over when all participants are finished.

What happens if your partner/family member stops the study?
The data collected up to that point will only be used if you do not object to its use in encrypted form that cannot be directly traced back to your partner/family member. If you do object, the collected data will be destroyed. You can indicate this on the information form "Use clinical data in case of no consent", attached to this letter. Your treating physician will be able to tell you more about the treatment options available and the pros and cons of them.

9. What happens after the study?

Will you get the results of the study?
After processing all the data, the investigator will inform your partner/family member about the main outcomes of the study. This will be done no later than 4 years after his/her participation.

10. What do we do with his/her data?

Is your partner/family member participating in the study? Then you also give permission for his/her data to be collected, used and stored.

What data do we store?
We store this data:
- His/her name
- His/her gender
- His/her address
- His/her date of birth
- information about his/her health, neurological complaints and degree of disability
- imaging of the brain and blood vessels
- information from the ambulance service about the transport to the hospital

What body material do we store?
No bodily materials of your partner/family member will be kept.

Why do we collect, use and store the data?
We collect, use and store the data of your partner/family member in order to be able to answer the questions of this study. And to be able to publish the results. Data may be used by the sponsor and companies that assist the sponsor in conducting the study and analyzing research data. We also need this data to be able to market the drug under investigation.

How do we protect the privacy of your partner/family member?

Each subject will be given a code that will appear on the data. The name of your partner/family member and other personal data will be omitted.

All his/her data will remain confidential. Only the researchers in your partner/family member's hospital and the coordinating research team from the UMCG know which code he/she has. The data of your partner/family member will only be used for the telephone check-up after 3 months. The key to the code remains with the research team. Only that code is also used in reports about the investigation.

Who can see the data?

Some people will be able to see their name and other personal information without a code. This can be data collected specifically for this study, but also data from the medical file of your partner/family member.
These are people who check whether the researchers are conducting the research properly and reliably. These people can access your data:

- The coordinating research team.
- Members of the committee that monitors the security of the investigation.
- An independent auditor.
- National and international regulatory authorities, such as the Food and Drug Administration (FDA).

These people keep your information confidential. We ask you to give permission for access by these persons. The Health and Youth Care Inspectorate can view your data without your permission.

How long do we keep the data?

We keep the data in the hospital for 15 years.

What happens in the event of unexpected discoveries?

During the investigation, we may find something that is not directly relevant to the study, but is important to your partners/family members, health or other family members. The investigator will then contact the general practitioner or specialist of your partner/family member. Your partner/family member will then discuss with your GP or specialist what needs to be done. The costs of this are covered by your own health insurance. With the form, you give permission to inform the general practitioner or specialist of your partner/family member.

Can you withdraw your consent to the use of his/her data?

You can withdraw your consent to the use of his/her data at any time. Your partner/family member can also withdraw the use of his/her data at any time. Then tell the researcher. This applies to use in this study and to use in other studies. But beware: do you withdraw your consent, and have researchers already collected data for a study? In that case, they are still allowed to use this data.

Would you like to know more about the privacy of your partner/family member?

- Would you like to know more about his/her rights with regard to the processing of personal data? Then take a look at www.autoriteitpersoonsgegevens.nl.
- Do you have questions about his/her rights? Or do you have a complaint about the processing of personal data? Please contact the person responsible for processing your personal data. For your research, that is:
    - See Appendix A for contact details, and website.
- If you have any complaints about the processing of the personal data, we recommend that you first discuss them with the investigation team. You can also go to the Data Protection Officer of the UMCG. Or you can file a complaint with 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).

- ISRCTN registry, www.isrctn.com/; You can find the study by searching for 'carotid artery stent' or by searching by number: 14956654.
- CONTRAST consortium; www.contrast-consortium.nl/cases/

After the study, the website may show a summary of the results of this study.

11. Will your partner/family member be compensated if you participate in the study?

Participating in the study does not cost your partner/family member anything. He/she will not be paid for participating in this study. However, he/she will be reimbursed for any additional travel expenses.

12. Is your partner/family member insured during the examination?

Insurance has been taken out for everyone who participates in this study. The insurance covers damage caused by the examination. Not all damage is covered. You can find more information about the insurance in Appendix B. It will also tell you to whom you can report damage.

13. We inform the GP of your partner/family member

We will always send a letter to your partner/family member's GP to let them know that he/she is participating in the study. This is for his/her own safety. If you do not approve of this, your partner/family member will not be able to participate in this study.
Even if you decide not to participate in the study, we will inform your GP about the treatment you may have received as part of the study.

14. Do you have any questions?

If you have any questions about the study, please contact the research team. Do you want advice from someone who has no interest in it? Then go to the independent expert, for contact details see Appendix A. He knows a lot about the investigation, but does not cooperate with this investigation.

Do you have a complaint? Discuss this with the researcher or doctor who is treating you. Would you rather not do this? Then go to the complaints officer/complaints committee. Appendix A tells you where to find them.

15. How do you give permission for the study?

When you have had sufficient time to reflect, you will be asked to decide whether your partner/family member will participate in this study. If you give your consent, we will ask you to confirm by signing the consent form. By giving your written consent, you indicate that you have understood the information and agree to both the participation of your partner/family member in the study and the use/access to his/her data.
The consent form will be kept by the research team. You will be given a copy or a second copy of this consent form.
If you do not give your consent, we will ask you to sign the form 'Use clinical data in case of no consent'. You can object to the use of the data collected up to that point (in an encrypted, non-personally identifiable form).

Thank you for your time.

Appendices to this information

A. Contact Details
B. Information about the insurance
C. Schedule of investigative actions
D. Legal Representative Consent Form
E. Use of clinical data in case of non-consent

Appendix A: contact details for Elisabeth-TweeSteden Hospital

Local Principal Investigators:

Dr. J.H. van Tuijl, neurologist, Elisabeth-TweeSteden Hospital Tilburg

Dr. G.J. Kortman, interventional radiologist, Elisabeth-TweeSteden Hospital Tilburg

Independent Physician:

Dr. B. Jacobs, neurologist UMC Groningen

Can be reached via: 050 - 3612400

Complaints:

Complaints information##

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Appendix B: Insurance Information

The UMCG has taken out insurance for everyone who participates in the study. The insurance pays for the damage that your partner/family member has as a result of he/she participating in the study. It concerns damage that he/she receives during the study, or within 4 years after the end of his/her participation in the study. The damage must be reported to the insurer within 4 years.

Has your partner/family member been harmed by the research? Then report this to this insurer:

The insurer of the study is: Name of insurer: Centramed Address: P.O. Box 7374, 2701 AJ Zoetermeer, The Netherlands Telephone number: 070 301 7070 Email: ... (Policy number: 624.529.102

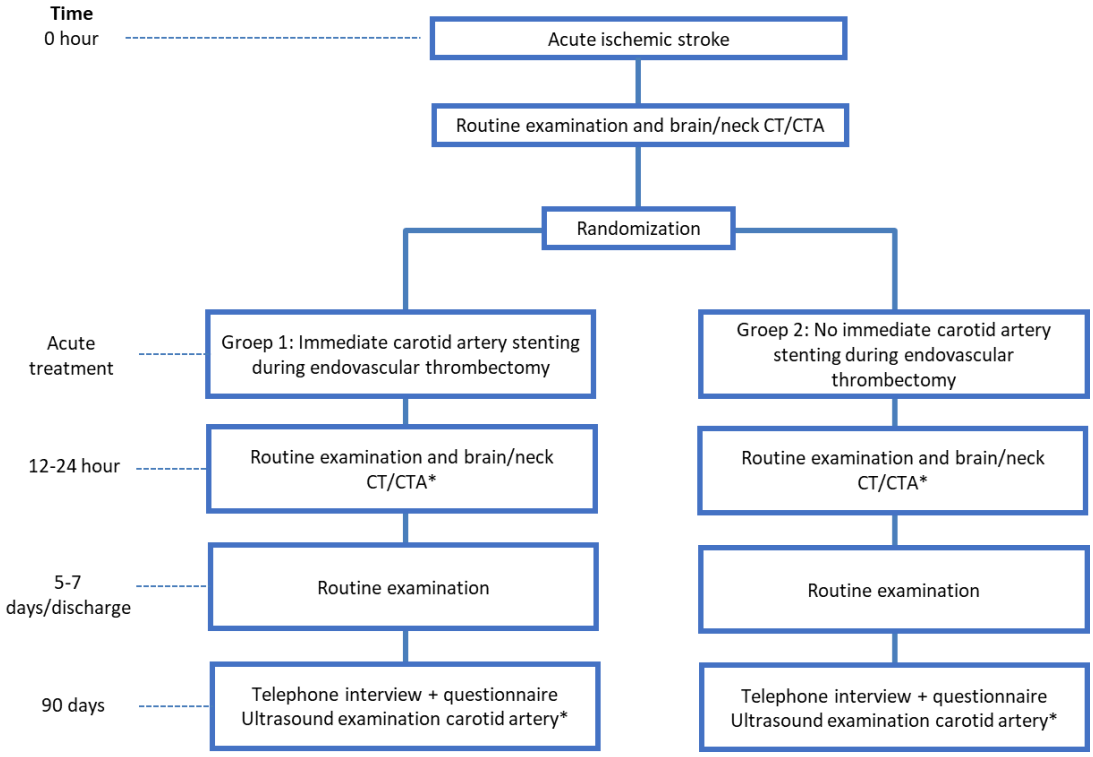
The insurance pays a maximum *of €650,000 per person* and €5,000,000 for the entire study and *€7,500,000* per year for all studies of the same client.

Please note that the insurance does not cover the following damages:

- Damage due to a risk that we have provided you and your partner/family member with information about in this letter. But this does not apply if the risk turned out to be greater than we thought beforehand. Or if the risk was very unlikely.
- Damage to the health of your partner/family member that would have occurred even if he/she had not participated in the study.
- Damage that occurs because he/she did not follow directions or instructions or did not follow them properly.
- Damage to the health of your partner's/relative's children or grandchildren.
- Damage caused by a treatment method that already exists. Or by researching a treatment method that already exists.

These provisions are set out in the 'Decree on Compulsory Insurance for Medical Research Involving Human Subjects 2015'. This decision is published in the Government Bench of Laws (https://wetten.overheid.nl).

Appendix C: Schedule of investigative acts



A schematic representation of the examinations and treatments during participation in the CASES study
* means that these examinations are extra on top of the regular care.

Appendix D: Legal Representative Consent Form

A study on the effect of stenting carotid stenosis during endovascular treatment of acute ischemic stroke.

I have been asked to give permission for the following person to participate in this medical scientific study:

Subject's name: Date of birth: / /

- ○ I have read the information letter for the representative. I was also able to ask questions. My questions have been adequately answered. I had plenty of time to decide if this person is going to join.
- ○ I know that participation is voluntary. I also know that at any time I will can decide that this person will not participate after all. I do not need to give a reason for that.
- ○ I give permission for the GP to be informed that this person is participating in this study. The GP is also informed of unexpected findings.
- ○ I give permission for some people to view this person's data. These persons are listed in this information letter.
- ○ I give permission for information to be requested from the ambulance service about the transport to the hospital.
- ○ I consent to the collection and use of this person's data, in the manner and for the purposes stated in the information letter.
- ○ I give permission that the research data from this study may be used by the funder of this study (BeNeFIT call, being KCE in Belgium and ZonMw in the Netherlands) or similar public health institutions in Europe for additional analyses such as determining which treatment is the most cost-effective. The investigators who carry out these analyses will not have access to your identifying data and are bound by professional secrecy.
- ○ I give permission for this person's research data to be kept at the study site for at least 15 years after this study. This could possibly be used for new research.

- I □ **give**
  - ○ **Do not give** permission to approach me or this person again after this investigation for a follow-up investigation.

Name of legal representative:
Relation to the subject:
Signature: Date: //
Time: :

I hereby declare that I have fully informed this person(s) about the said investigation. If any information becomes known during the investigation that could affect the consent of the legal representative, I will inform him/her in a timely manner.
Name of investigator (or his/her representative):
Function: □ Attending physician
□ Researcher

Signature: Date://

The legal representative will receive a full information letter, together with a copy of the signed consent form.

Appendix E: Use of Clinical Data in the Event of Non-Consent

A study on the effect of stenting carotid stenosis during endovascular treatment of acute ischemic stroke.

Subject's name: Date of birth://

- I have read the information letter. I was also able to ask questions. My questions have been adequately answered. I had enough time to decide whether my partner/family member would participate in the study.
- I **do not** consent to participate in the study, no blood samples, examinations and interviews may be carried out that are not necessary for the treatment of my partner/family member.
- I □ **Do**
  - **Do not** object to the use of the research data already collected in coded (not directly traceable) form.
- I □ **Do**
  - **Do not** object to the use of the yet to be recorded clinical data from the first 3 months after treatment that will be obtained in the context of regular care, in coded (not directly traceable to the person) form.

Name of legal representative:
Relation to subject:
Signature: Date: / /
Time:

I declare that I have fully informed this legal representative of the said investigation.
If information becomes known during the study that could influence the consent of the subject, I will inform him/her in a timely manner.

Name of investigator (or his/her representative):
Investigator function: □Treating physician
□ Researcher

Signature: Date: / /

The subject will be provided with a full information letter, along with a copy of the signed consent form.