Subject information for participation in medical research

nCLE in lung tumors

Official tittle: nCLE-guided bronchoscopy for peripheral lung cancer diagnosis; a randomized controlled trial

Introduction

Dear Sir/Madam,

With this letter, we would like to ask you to take part in a medical study. Participation is voluntary. You have received this letter because a scan showed an abnormality in the lung. You are scheduled for an examination of the lungs (bronchoscopy) to establish a diagnosis. You can read about the medical study in this information sheet, what it means for you, and what the pros and cons are. It is a lot of information. Can you please read the information and decide if you want to take part? If you want to take part, complete the form in Appendix D.

Ask your questions

You can take your decision based on the information in this information sheet. We also suggest that you do this:
- Put your questions to the investigator who gave you this information.
- Talk to your partner, family or friends about this study.

1. General information

The Amsterdam University Medical Center (Amsterdam UMC), location AMC in The Netherlands has set up this study and is funded by Mauna Kea Technologies, a company specialized in making instruments used during bronchoscopy. Below, we always call the Amsterdam UMC the 'sponsor'.
Investigators, these can be doctors/research nurses, conduct the study in different hospitals.

Participants in medical research are often referred to as subjects.

This study needs 208 subjects from different countries. In [country], it is expected that 30 - 40 subjects will take part.
The Medical Ethics Review Committee Amsterdam UMC has initially approved this study in The Netherlands. The Medical Ethics Review Committee [X] has also approved the start of this study in [country].

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2. What is the purpose of the study?

With this study we investigate the addition of confocal laser endomicroscopy (CLE) to the regular bronchoscopic examination. We investigate whether the addition of CLE contributes to the accurate diagnosis of suspected lung abnormalities compared to normal diagnostic bronchoscopy without the addition of CLE.

3. What is the background of the study?

Abnormalities in the lungs can be a results of many different conditions. With current techniques used to visualize these abnormalities (PET-CT scan, CT scan and ultrasound) it is not always possible to say with certainty what causes the abnormality. Therefore, it is often decided to perform a bronchoscopy. During the examination, the suspected lung abnormality is localized in the lungs and some tissue is extracted with a thin needle of for further examination. The current tissue examination has limitations because tissue is not always obtained from the optimal site. As a result, the cause of the abnormality cannot always be diagnosed with certainty.

The newly available technique confocal laser endomicroscopy (CLE) offers possibilities to potentially establish a diagnosis with more certainty. The CLE technique works like a microscope where individual cells can be imaged with safe laser light. The CLE laser beam can be emitted into the tissue via the thin needle used for the standard bronchoscopy exam. By using CLE imaging at the tip of the needle, we expect to be able to extract tissue at the right place in more cases. We also call this the 'smart needle'.

The advantage of this technique is that a lung abnormality can be accurately imaged inside the body. However, it is not yet sufficiently known how and to what extent we can establish a better diagnosis if we use the 'smart needle'. That is why we are investigating whether adding the CLE technique to the existing standard examination leads to a better diagnosis.

4. What happens during the study?

How long will the study take?

Are you taking part in the study? The bronchoscopy will approximately take 10 minutes longer than usual. Because of the sedative that we administer during the bronchoscopy, you will not notice the extended duration of the procedure.

Step 1: are you eligible to take part?

First, we want to know if you are eligible to take part. The investigator will assess whether you are eligible based on your scans (PET-CT or CT scan). Your physician will discuss your potential participation with you.

Step 2: the bronchoscopy

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As part of standard care, you will undergo a bronchoscopy exam via the trachea. A sedative will be administered through an IV in your arm to ensure you don't notice anything during the examination.
For the study, we will use the CLE-technique as an addition to the bronchoscopy exam in 50% of participants.

For this study, we will have 2 groups:

- Group 1. The participants in this group undergo the regular bronchoscopy exam without the addition of the CLE technique.
- Group 2. The participants in this group undergo the regular bronchoscopy exam with the addition of the CLE technique.

A draw will decide in which group you are in. Before the start of the bronchoscopy, you will not know which group you were assigned to.

First the bronchoscopy will start. The lungs will be inspected and we will search for the lung abnormality located deeper in the lungs. As part of the standard procedure, a needle will be used to puncture the suspected lung lesion to extract tissue samples for diagnosis.
In case you were assigned to group 2 (i.e., implementation of the CLE technique), CLE images will be acquired at the tip of the needle used for tissue sampling. Administration of a contrast dye (fluorescein) is needed for CLE imaging. This dye will be administered via an IV which is also used to administer sedatives.

What is the difference with standard care?
This study is not very different from standard care. Due to participation in the study, the bronchoscopy may approximately take 10 minutes longer. You will not notice this because of the sedative. No additional body material is collected for this study. If you are placed in the group in which CLE is done in addition to the normal procedure, the safe dye fluorescein will also be administered.
After the bronchoscopy, you will stay in the recovery room for approximately 1.5 hours, which is standard protocol after a normal bronchoscopic exam. You do not have to come to the hospital for an extra visit if you participate in this study.

5. What agreements do we make with you?

If you participate in this study, you have to follow the instructions your doctor gave you for the regular bronchosopy. In total, the bronchoscopy will be extended by a maximum of 10 minutes due to the extra study measurements.
To obtain good images with the CLE method, it is essential that the fluorescein dye is administered via the IV. Fluorescein is a commonly used and safe drug. A small proportion of people (1.1%) may experience side effects such as nausea. In case you have a known sensitivity to fluorescein, you should not participate in this study. Consult your doctor if this applies to you.

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Is it OK for you to get pregnant during the study?
Women who are pregnant or breastfeeding cannot take part in this study. This is because it is not known what the effects of fluorescein are during pregnancy or breastfeeding.

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

Few risks are associated with the CLE technique. Extensive research has been done and the CLE technique has been assessed as safe.
To obtain good image quality with the CLE method, it is essential that fluorescein dye is administered via your IV. Fluorescein is a widely used and safe contrast dye and side effects are rarely reported. About one in hundred people develop side effects of which nausea, vomiting and a rash are most commonly seen. Please let the doctor or researcher know if you experience any of these side effects.

You can find more information about fluorescein in the information leaflet, see Appendix C.

What are the possible discomforts you may experience with checks or measurements during the study?
Due acquisition of the CLE images, the bronchoscopy can take about 10 minutes longer than usual. You will be given sedatives as part of the standard bronchoscopy protocol and will therefore hardly notice the additional 10 minutes during the exam. After administration of fluorescein, you urine can be more yellow than usual for a day, this is normal.

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

Taking part in the study can have pros and cons, listed below. Think about this carefully and talk to other people about it.
If you participate in this research you will not have a direct benefit. In case you are assigned to group B in which CLE is used in addition to the normal bronchoscopy, there might be a higher chance of a diagnosis. However, the purpose of this research is to investigate if that is the case. If you take part you will help with the search for better diagnostics of lung abnormalities.

Taking part in the study can have these cons:
- You may experience side effects or adverse events from the fluorescein drug.
- The bronchoscopy will be 10 minutes longer than usual.

You do not wish to participate in the study?
It is up to you to decide if you wish to participate in the study. You do not wish to participate? Then the regular bronchoscopy exam will be done.

8. When does the study end?

The investigator will let you know if there is any new information about the study that is important to you. The investigator will then ask you if you want to continue to take part.

In these situations, the study will stop for you:

- All checks are finished and you are discharged from the hospital.
- You want to stop participating in the study yourself. You can stop at any time. Report this to the investigator immediately. You do not have to explain why you want to stop. You will then get the standard bronchoscopy exam.
- The investigator thinks it is better for you to stop.
- One of the following authorities decides that the study should stop:
    - The government, or
    - The Medical Ethics Review Committee assessing the study, or
    - The Sponsor,

What happens if you stop participating in the study?
The investigators use the data that have been collected up to the moment that you decide to stop participating in the study.

9. What happens after the study has ended?

Will you get the results of the study?
If there is new information about the study that is important for you , the investigator will let you know what the main findings are. The researcher can also tell you which group you were in. Do you prefer not to know? Please tell the invesitagor. He/she will not tell you in that case.

10. What will be done with your data?

Are you taking part in the study? Then you also give your consent to collect, use and store your data.

What data do we store?
We store these data:
- your gender
- your date of birth
- information about your health
- (medical) information we collect during the study
- CLE videos

Why do we collect, use and store you data?
We collect, use and store your data to answer the questions of this study. And to be able to publish the results. Data can be used by the sponsor to perform analysis of the data. The company that support this research (Mauna Kea Technologies) will receive anonymized CLE videos upon reasonable request. This data will only be shared anonymously and cannot be traced back to you.

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How do we protect your privacy?
To protect your privacy, we give a code to your data. We only put this code on your data. We keep the key to the code in a safe place in the hospital. When we process your data we always use only that code. Even in reports and publications about the study, nobody will be able to see that it was about you.

Who can see your data?
Some people can see your name and other personal information without a code. This could include data specifically collected for this study, but also data from your medical file. These are people checking whether the investigators are carrying out the study properly and reliably. These persons can access your data:

- An auditor who works for the investigator or sponsor
- National and international supervisory authorities.
- [other]

These people will keep your information confidential. We ask you to give permission for this access.

For how long do we store your data?
We store your data in the hospital for […] years. And for 15 years with the sponsor.

Can we use your data for other research?
Your collected data may also be important for other medical research on suspected lung lesions and diagnostics. For this purpose , your data will be stored in the hospital for X years. Please indicate in the consent form whether you agree with this. Do you not want to give your consent? Then you can still take part in this study. You will get the same healthcare.

Can you take back your consent for the use of your data?
You can take back your consent for the use of your data at any time. Please tell the investigator if you wish to do so. But please note: if you take back your consent, and the investigators have already collected data for research, they are still allowed to use this information.

Do you want to know more about your privacy?

- Do you want to know more about your rights when processing personal data? Visit [URL]
- 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. For the present, this is:
    - The Amsterdam UMC and [institution] See Appendix A for contact details and website(s).
- 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 institution]. 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. After the study, the website may show a summary of the results of this study. You can find the study by searching for *"Confocal Laser Endomicroscopy VERification"* (number: NCT06079970).

11. Will you receive compensation if you participate in the study?

Participation in the study will not cost you anything. Neither will you get any compensation if you take part in this study. Because no additional travel expenses are made for participation, you will not be reimbursed for travel expenses.

12. Are you insured during the study?

Insurance has been taken out for everyone who takes part in this study. The insurance pays for damage caused by the study. But not for all damage. You can find more information about this insurance and any exceptions in **Appendix B**. It also says who you can report damage to.

13. Informing other physicians

The pulmonologist who performs the bronchoscopy knows that you are participating in the study. We do not inform your general practitioner or other treating specialists that you are participating, given that the study does not have any complications or additional risks that your general practitioner or other treating physician should be aware of.

14. Do you have any questions?

You can ask questions about the study to the research team.
Do you have a complaint? Discuss it with the investigator or the doctor who is treating you. If you prefer not to do so, please visit [complaints officer/complaints committee of your hospital/institute/other]. Appendix A tells you where to find this.

15. How do you give consent for the study?

You can first think carefully about this study. Then you tell the investigator if you understand the information and if you want to take part or not. If you want to take part, fill in the consent form that you can find with this information sheet. You and the investigator will both get a signed version of this consent form.

Thank you for your attention.

Subject information

16. Appendices tot his information

A. Contact details
B. Information about the insurance
C. Information leaflet fluorescein for patients
D. Consent form

Subject information

Bijlage A: contact details for [name of participating centre]

Principal investigator:
[for principal investigator of centre: name, contact details and accessibility]

< *if applicable*>
Co-investigator:

< *if applicable*>
[Study nurse/study doctor/nurse specialist]:

<if applicable> **Independent expert:**
[name, type of doctor/expert, contact details and accessibility]

Complaints: [service or person with contact details and accessibility]

Data Protection Officer:
Data protection officer of the institution: [contact details]
Data Protection Officer of the Sponsor: privacy@amsterdamumc.nl

For more information about your rights visit: [Contact details [including website]

Subject information

Appendix B: information about the insurance

The [Institution] 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: *<also indicate here how subject should act/report in the event of damage: telephone/mail/post, other instructions?*

The insurer of the study is: Name insurer: … Address: … Telephone number: … Email: … (Policy number: …)

< include only if there is a claims representative – this is compulsory if the insurer is established outside the Netherlands> The claims representative of the study is: Name: … Address: … Email: Telephone number: …

The insurance pays a maximum of *<amount to be copied from policy, this must be at least €650,000 >* per person and *<amount to be copied from policy, this must be at least €5,000,000>* for the entire study (and *<amount to be copied from policy, this must be at least € 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 caused by a treatment method that already exists. Or by research into a treatment method that already exists.

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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).

van Heumen S, *et al. BMJ Open* 2024; 14:e081148. doi: 10.1136/bmjopen-2023-081148

Subject information

Appendix C – Information leaflet fluorescein for patients

The name of this medicine is Fluorescein Sodium 100mg/ml Solution for Injection, which will be referred to as Fluorescein Sodium Injection throughout this leaflet.

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

IN THIS LEAFLET

1. What Fluorescein Sodium Injection is and what it is used for
2. What you need to know before you are given Fluorescein Sodium Injection
3. How to use Fluorescein Sodium Injection
4. Possible side effects
5. How to store Fluorescein Sodium Injection

1. What Fluorescein Sodium Injection is and what it is used for

Fluorescein Sodium Injection contains the active ingredient fluorescein sodium which works as a diagnostic stain. It is used in a hospital-based procedure on for example the eye called fluorescein angiography of the ocular fundus (part of the eye). This medicinal product is for diagnostic use only.

2. What you need to know before you are given Fluorescein Sodium Injectio

Do not use Fluorescein Sodium Injection if:

- you are allergic (hypersensitive) to fluorescein sodium or any of the other ingredients of this medicine.

If the above applies to you or you are in any doubt you should ask your doctor or pharmacist for advice before being given this medicine.

Warning and Precautions:

Your doctor or other healthcare professional will give you this medicine through an injection into one of your veins. Fluorescein Sodium Injection is for intravenous injection only and MUST NOT be injected into the arteries (arterial route) or into the spinal column (intrathecal route).

You must tell your doctor if:

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- You have previously undergone a hospital procedure on the eye called fluorescein angiography of the ocular fundus (a part of the eye)
- You have a history of allergy
- You have a history of heart or pulmonary disease
- You are taking drugs known as Beta-blockers including those applied in eye drops.
- You have kidney disease

Taking other medicines

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines including medicines obtained without a prescription. Fluorescein sodium can sometimes interact with other medicines that you could be taking causing unwanted side effects.

Preferably do not add anything. Fluorescein disodium is incompatible with acids, salts of acids and salts of heavy metals. Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines. This also applies to medicines that you can obtain without a prescription.

If you are due to have other diagnostic tests including blood, urine, and X-Ray investigations

Fluorescein Sodium Injection may interfere with the results of some blood and urine tests within 3 days of having the procedure. If you are having any blood or urine tests taken, you should tell the doctor or nurse that you have been given Fluorescein Sodium Injection.

If an X-ray procedure is conducted within 36 hours of injection, the resulting high visibility of some organs such as the kidneys may lead to misinterpretation of the results.

Pregnancy, breastfeeding and fertility

If you are pregnant or think you may be pregnant prior to using Fluorescein Sodium Injection, tell your doctor who will decide whether to give you this medicine or not.

Fluorescein disodium should not be used during breast-feeding. Ask your doctor or pharmacist for advice before taking any medicine.

Driving or operating machinery

The use of Fluorescein Sodium during certain procedures, your vision may be temporarily impaired. Patients must abstain from driving a vehicle or operating machinery until the eyesight returns to normal.

3. How to use Fluorescein Sodium 100mg/ml?

Fluorescein disodium is injected directly into the bloodstream.

Dosage:

Subject information

The exact dose, to be determined by the doctor, is up to a maximum dose of Fluorescein sodium 500mg (equivalent to one 5ml ampoule 100 mg/ml) administered by intravenous injection.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. If you have undergone a similar examination, please tell your doctor if you have experienced an intolerance reaction regardless of how severe it may or may not have been.

The following side effects may occur during administration:

- nausea and vomiting,
- allergic reactions such as skin rash with intense itching and lump formation (urticaria), increased salivation (hypersalivation), runny nose (rhinorrhoea) and fever
- decreased number of blood platelets (thrombocytopenia)
- the appearance of fluid in the lungs (pulmonary oedema)
- temporary discoloration (yellowing) of the skin and urine
- anaphylactic reaction – anaphylactic shock

If you notice any side effects not listed in this leaflet or which you consider to be serious, please inform your doctor or pharmacist.

5. How to store Fluorescein Sodium 100 mg/ml

Keep this medicine out of reach and sight of children. Keep ampoules in a cardboard box in order to protect from light

Use by date: Do not use this medicine after the expiry date which is stated on the carton and ampoule label after EXP. The expiry date refers to the last day of that month.
Do not use Fluorescein disodium if you notice that the solution is no longer completely clear or the ampoule is damaged.
For single use only. Once opened the ampoule must be used immediately.

Any unused product or waste material should be disposed of in accordance with local requirements.

Subject information

Appendix D: Informed consent form – subject

Belonging to nCLE in lung tumors

- I have read the information sheet. I was able to ask questions. My questions have been answered well enough. I had enough time to decide if I wanted to take part.
- I know that taking part is voluntary. I also know that at any time I can decide not to take part in the study. Or to stop taking part. I do not have to explain why.
- I give consent to collect and use my date. The investigators only do this to answer the question of this study.
- I know that some people will be able to see all of my data to review the study. These people are mentioned in this information sheet. I give consent to let them see my data for this review.
- I know that I cannot be pregnant during the study.
- Please tick yes or no in the table below.

I give consent to store my data to use for other research, as stated in the information sheet.	Yes ☐	No☐
I give consent to ask me after this study if I want to participate in a follow-up study.	Yes ☐	No☐
I give consent to let me know after the study which treatment I received/in which group I was.	Yes ☐	No☐

- I want to take part in this study.

My name is (subject): ……..
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.