Cliniques universitaires SAINT-LUC UCLouvain BRUXELLES

BELGICA

achieving a BEtter outcome through Limiting the GIIoblastoma Clinical tArget volume

ClinicalTrials.gov identifier: NCT06719440

Study coordinator: Pr. Dario Di Perri

Information and Informed Consent Form Version 1.1, dated 20/03/2025

Title of the study: Impact of reducing the irradiation volume on survival, toxicity, and quality of life in patients with glioblastoma treated with radiochemoradiotherapy: a prospective multicenter randomised study.

Short Title: *achieving a BEtter outcome through Limiting the GIloblastoma Clinical tArget volume (BELGICA)*

Study sponsor: *Cliniques universitaires Saint-Luc, avenue Hippocrate 10, 1200 Woluwe-Saint-Lambert*

Research organization: *n/a*

Medical Ethics Committee:*: Comité d'éthique hospitalo-facultaire des Cliniques universitaires Saint-Luc*

Local investigator physicians: Name, First name, function

I Essential Information for Your Decision to Participate

Introduction

You have recently been diagnosed with glioblastoma, a type of brain cancer. The standard treatment for glioblastoma involves several steps. The first step is an operation to confirm the diagnosis and, when possible, to remove as much of the tumor as possible. The surgery is followed by a treatment combining radiotherapy and chemotherapy (radiochemotherapy). Radiotherapy uses rays to destroy tumor cells. These rays are directed towards the area affected by the tumor. At the same time, a treatment in the form of tablets, called oral chemotherapy, is prescribed to enhance the effect of radiotherapy. After radiotherapy, chemotherapy continues on its own for several months.

You are invited to participate in a clinical study aimed at evaluating whether radiotherapy could be administered more precisely to patients with glioblastoma who are treated with radiochemotherapy. The goal is to demonstrate that delivering radiotherapy to a reduced volume, compared to the standard treatment does not compromise, and to assess whether this approach can reduce side effects and improve quality of life of patients.

Participation in this study may or may not seem beneficial to you. However, there is no guarantee that you will benefit from participating in this study.

Before you agree to participate, we invite you to understand its implications in terms of organization, potential benefits, and risks, so that you can make an informed decision. This is called giving "informed consent."

We invite you to carefully read these few pages of information and ask any questions you may have to the investigator (also called "investigator") or their representative. This document includes three parts : essential information for your decision-making, your written consent, and additional information (appendices) that detail certain parts of the basic information.

If you participate in this clinical study, you should know that:

- This clinical study is implemented after evaluation by one or more ethics committees.
- Your participation is voluntary and must remain free from any constraint. It requires the signing of a document expressing your consent. Even after signing it, you can stop participating by informing the investigator. Your decision not to participate or to stop participating in the study will not affect the quality of your care or your relationship with the investigator.
- The data collected on this occasion is confidential, and your anonymity is guaranteed when the results are published.
- No-fault insurance has been taken out in case you suffer harm related to your participation in this clinical study.
- You will not be charged for visits/consultations, examinations, or treatments specific to this study.
- You can always contact the investigator or a member of their team if you need additional information.

Additional information on your "Rights as a participant in a clinical study" is provided in Appendix 2.

Objectives and Study Protocol Description

You are invited to participate in a national multicenter clinical study on radiotherapy in the treatment of glioblastoma. This study aims to recruit 347 participants across Belgium.

Radiotherapy is a treatment that uses ionizing radiation to destroy cancer cells. In the case of glioblastoma, radiotherapy targets the tumor (or the tumor bed, the area of the brain where the tumor was prior to surgery that might contain microscopic cancer cells) with a safety margin around it (the "clinical target volume" or CTV) to account for the potential microscopic spread of the tumor. In the standard setting, the safety margin is set at 15mm around the tumor location. The downside of this is that a non-négligible amount of brain tissue is irradiated, which can lead to side effects.

The main objective of the study is to demonstrate that reducing the margin of the clinical target volume from 15mm to 10mm maintains the effectiveness of the treatment, and thus the patients' survival, compared to the standard margin. The secondary objective is to analyze whether this reduction in irradiation volume can decrease adverse effects in patients, particularly cognitive disorders (such as memory, concentration or reasoning disorders), and/or improve their quality of life.

Patients who can participate in this study:

- Aged at least 18 years and able to give their consent;
- In sufficient physical condition, possibly requiring occasional assistance but generally able to take care of themselves, bedridden less than 50% of the time;
- Diagnosed with glioblastoma confirmed by surgery;
- For whom radiochemotherapy is indicated.

Patients who cannot participate in this study:

- Included in another concurrent clinical study;
- Presenting a contraindication to undergoing MRI (e.g., metal fragments or metal implants, neurostimulators or other active implants, claustrophobia, …).

This study is a non-inferiority study, meaning it aims to prove that the experimental treatment has the same effectiveness as the standard treatment. This study is single-blind, meaning your doctor will know which treatment you will receive, but you won’t. This is necessary to avoid influencing your perception of the treatment and to prevent bias. A total of 347 people will be included in this study in Belgium.

The study will have two treatment arms: the experimental arm and the control arm. The experimental arm will include patients who receive radiotherapy with a reduced target volume margin (10 mm), while the control arm will include patients who receive radiotherapy with a standard target volume margin (15 mm). Your assignment to one of the two arms will be done by random draw: 50% of participants will be in the experimental arm and 50% in the control arm.

After being assigned to one of the study arms, you will begin your radiotherapy treatment, and at the end of it, you will enter the follow-up phase. In total, radiotherapy will last between 3 and 6 weeks (depending on your age), and the follow-up period will continue for 2 years. During this follow-up phase, you will regularly return to the hospital for medical visits. During some of these visits, you will be asked to undergo neurocognitive tests or complete quality of life questionnaires.

Study Procedure

Your participation in the study will last approximately 24 months and will involve 10 visits (see summary table – Appendix 1). The number of visits is similar to those of patients not participating in the study.

As part of your participation in the study, the initial visit will allow the investigator to verify if you can participate in the study. The information to be collected during this visit (for example, the medications you are taking, the results of your blood tests or your pre- and post-operative MRIs) does not require additional imaging or sampling compared to what you would have had outside of the study. During the

initial assessment, you will be asked to complete a cognitive evaluation (3 exercises/tests lasting a total of up to 45 minutes) as well as quality of life questionnaires.

After signing the consent form, and provided you are eligible to participate in the study, you will be assigned to one of the two treatment arms. You will begin your radiotherapy, which will last between 3 and 6 weeks, depending on your age. You will come to the hospital for radiotherapy every day (usually Monday to Friday) during this period. During radiotherapy, you will also receive oral chemotherapy (temozolomide), which is the standard treatment for your condition. You will take temozolomide every day during radiotherapy. Once radiotherapy is completed, chemotherapy will be paused for 4 weeks. Chemotherapy then will resume at a rate of 5 days every 4 weeks, and this cycle will be repeated 6 times (adjuvant chemotherapy).

The visits during which data is collected for the study occur at the same frequency as for patients not participating in the study. The imaging and samples taken are also considered standard care outside the study. In practice, the difference is that during some of these visits, you will be asked to:

- Undergo neurocognitive tests 3 times: before radiotherapy, 1 month after radiotherapy and during the 1-year assessment.
- Complete quality of life questionnaires: before radiotherapy, at the end of radiotherapy, 1 month after radiotherapy, then every 3 months during the first year and every 6 months during the second year (see Appendix 1).

Risks and Inconveniences

Radiochemotherapy is the standard adjuvant treatment for glioblastoma. Your doctor will explain the expected side effects and benefits. In this study, the only difference is that in the experimental arm, radiotherapy will be delivered to a more limited area around the tumor/tumor bed. The theoretical risk associated with this intervention is an faster return of the tumor (recurrence) in the case that the experimental intervention was less efficient.

However, available data in the scientific literature suggest that treating a smaller area around the tumor (a 10 mm margin instead of a larger one) provides similar results in terms of disease control and survival, without increasing the risk of recurrence.

At the same time, it is well established that radiotherapy can affect memory and other cognitive functions. Reducing the radiation dose received by the healthy parts of the brain may help limit these side effects, improve quality of life, and reduce fatigue.

It is also possible that other risks or inconveniences may arise that are currently unknown. Therefore, it is very important that any new health problem is communicated to the investigator, regardless of the likelihood of its relation to the study in your opinion.

Notification of New Information

During the course of a clinical study, important new information about the treatment being studied may become available. You will be informed of any new elements that may affect your decision to continue participating in this study.

In such cases, you will be asked to sign either an addendum to the consent form or a new information and consent document. If, in light of the new information, you decide to end your participation in the study, your investigator will ensure that you continue to receive the best possible treatment.

Benefits

If you agree to participate in this study and are assigned the experimental treatment, the reduction in irradiation volume may or may not prove beneficial for you. The information obtained from this study can contribute to a better understanding of radiotherapy for the treatment of glioblastoma in future patients.

Withdrawal from the Study

Your participation is voluntary, and you have the right to withdraw from the study at any time, for any reason, without having to justify your decision. However, it may be helpful for the investigator and the

study sponsor to know if you are withdrawing because the testing and examination requirements are too burdensome.

It is also possible that the investigator may withdraw you from the study if they believe it is in your best interest or if they find that you are not following the instructions given to participants.

Finally, it sometimes happens that the ethics committees that initially approved the study or the sponsor may stop the study for medical reasons.

Treatment After Study Withdrawal

In all these situations of study withdrawal, as well as when the planned participation period is over, your investigator will assess your health and prescribe the best available treatment.

If you participate in this study, we ask you to:

- Fully cooperate with the proper conduct of this research.
- Not withhold any information regarding your health status, the medications you are taking, or the symptoms you are experiencing.
- Contact the investigator if you wish to participate in another clinical study.

You should also know that:

Your general practitioner or other specialist doctors responsible for your health will be informed of your participation in this study.
The KCE, the Belgian Healthcare Knowledge Centre, funds this study. KCE Trials is a funding programme for non-commercial clinical trials financed by the Belgian public authorities. More information can be found on their website : https://kce.fgov.be/en/research-programmes/what-is-the-kce-trials-programme
If the study shows that one treatment works as well as another, the KCE, may request a coded copy of certain study data to evaluate which treatment should, for example, be reimbursed or recommended and if its cost is justified. Your identity will never be known to the KCE. This data processing is necessary in the public interest to improve public health policy. The KCE is responsible for the data processed in this additional research and must comply with data protection rules.

Costs Associated with Your Participation

The sponsor has planned to compensate the hospital for the time spent on the study by the investigator and their team, for the time in consultations specific to the study, and for all examinations scheduled as part of this study.

If you decide to participate in this study, there will be no additional costs for you or your insurer. Only the costs corresponding to routine medical care in your clinical situation may be billed to you.

You will receive compensation for the time spent undergoing neurocognitive tests that would not have been performed if you were not included in the study. A gift card will be credited with €25 at the end of visits No. 3 and No. 6 (see summary table in Appendix 2), for a total of €50.

The vouchers will be provided via a payment card managed by the company Monizze. The activation of this card can be done in two ways: either by yourself (or one of your relatives) or by the study staff.

By choosing to activate your card yourself, you will be asked to provide an email address or a phone number to receive the activation code for your card. Your personal data will be processed and protected according to Monizze's privacy policy and in compliance with the GDPR. Your data will never be shared with a third party.

As the card's expiration date approaches, you will be notified through the channel used for its activation regarding its expiry date.

If you do not wish to share your contact details with Monizze, the study staff can activate the card upon request to the Monizze administrator without requiring your contact information. In this case, the card remains completely anonymous.

The study staff will give you more information about the activation of utilisation of the gift card during visits No.3 and No.6.

Contact

If you need additional information, or if you have any problems or concerns, you can contact the investigator (Name, First name) or a member of their research team (Name, First name) at the following phone number (+32 xxx-xx-xx).

If you have questions about your rights as a participant in a clinical study, you can contact the participant rights mediator at your institution via the phone number: phone contact details or by email (email address). If necessary, they can put you in touch with the ethics committee.

For the management of complaints not resolved by the investigator, you can contact the comité d'éthique hospitalo-facultaire Saint-Luc UCLouvain.
Email : commission.ethique-saintluc@uclouvain.be

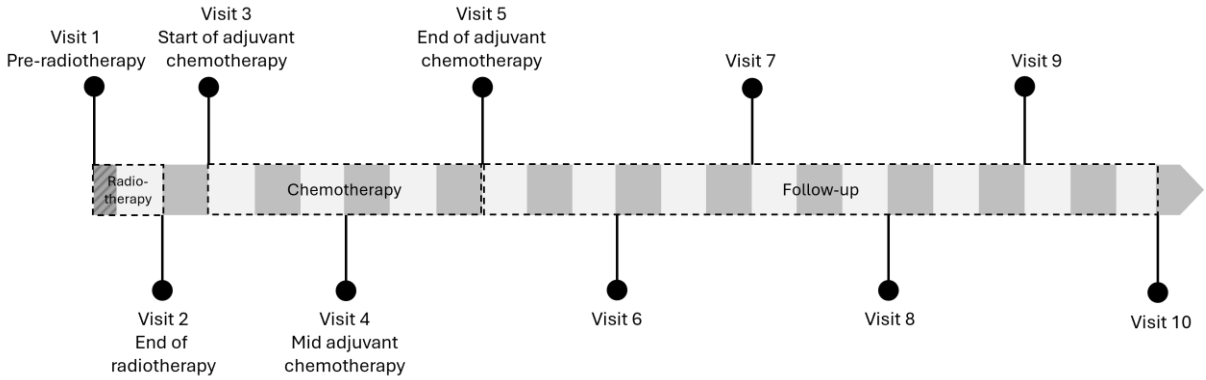
In case of emergency, you can contact XX at the following phone number XX.

Outside consultation hours, go to your hospital's emergency department and inform them that you are participating in a clinical study. Your file will contain useful information for the on-call doctor regarding this clinical study.

II Additional Information

Appendix 1: Additional Information on the Organization of the Study

Overview of the study visits :



Each greyed-out area corresponds to a one-month period. The duration of radiochemotherapy varies according to the patient's age, ranging from 4 to 6 weeks. This difference is standard in the treatment setup and will be applied to both patients in the standard treatment group and those in the interventional treatment group of the study.

Table of trial procedures :

	Radiotherapy (RT)		**Adjuvant Chemotherapy (adj. CT)**			**Follow-up (3-monthly)**				
Approximative number of months from the start of RT	0	1-1.5	2-2.5	5-5.5	8-8.5	11-11.5	14-14.5	17-17.5	20-20.5	23-23.5
Description	Pre RT	End RT	Start adj. CT	Mid adj. CT	End adj. CT	FollowUp 1year	FollowUp 1y 3m	FollowUp 1y 6m	FollowUp 1y 9m	FollowUp 2 year
Visit nb	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Medical visit*	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*
Blood draw*	X*	X*	X*	X*	X*					
Magnetic Resonance Imaging (MRI)*	X*		X*	X*	X*	X*	X*	X*	X*	X*
Quality-of-Life questionnaires (approx. 15min)	X	X	X	X	X	X		X		X
Neurocognitive assessment (approx. 45min)	X		X			X				

*Standard of care procedures

Appendix 2: Additional Information on the Protection and Rights of Participants in a Clinical Study

Ethics Committee

This study has been evaluated by an independent central Ethics Committee (the Hospital-Faculty Ethics Committee of Cliniques universitaires Saint-Luc) and local Ethics Committees of participating centres. The central and locals committees have issued a favorable opinion for this study. The Ethics Committees are responsible for protecting individuals participating in a clinical trial. They ensure that your rights as a clinical study participant are respected, that the balance between risks and benefits remains favorable to participants based on current knowledge, and that the study is scientifically relevant and ethical. The Ethics Committees issue their opinions in accordance with the Belgian law of May 7, 2004. Under no circumstances should you take the favorable opinion of the Ethics Committee as an encouragement to participate in this study.

Voluntary Participation

Before signing, do not hesitate to ask any questions you deem useful. Take the time to discuss it with a trusted person if you wish. Your participation in the study is voluntary and must remain free from any constraint: this means that you have the right not to participate or to withdraw without justification even if you had previously agreed to participate. Your decision will not affect your relationship with the investigator or the quality of your future therapeutic care. If you agree to participate in this study, you will sign the informed consent form. The investigator will also sign this form, confirming that they have provided you with the necessary information about the study. You will receive your copy. For your safety, it is advisable to inform the investigator if you decide to stop your participation in the study.

Confidentiality Guarantee

Your participation in the study means that the investigator collects data about you and the study sponsor uses it for research purposes and in scientific and medical publications.

The processing of your personal data during this study is authorized because it is necessary for scientific purposes and that your provided consent.

Your data will be processed in accordance with the General Data Protection Regulation (GDPR) and Belgian legislation on the protection of individuals with regard to the processing of personal data. Cliniques universitaires Saint-Luc will be responsible for processing your data.

As part of this study, we are working with a subcontractor, AQUILAB, for data management and storage. AQUILAB will be responsible for the following tasks:

I. Managing the pseudonymized patient data entered into the Onco Place platform of AQUILAB, in accordance with the study protocol.
II. Managing the registered users of the Onco Place platform within the scope of this project.
III. Storing the pseudonymized patient data entered into the Onco Place platform of AQUILAB, as well as storing user data from the database.

AQUILAB commits to processing your data in compliance with the General Data Protection Regulation (GDPR) and Belgian legislation on the protection of individuals regarding the processing of personal data. Your data will be pseudonymized (your identity will be replaced with an identification code in the study to avoid using any identifiable information) before being transferred to AQUILAB, ensuring the confidentiality and security of your personal information.

You have the right to ask the investigator what data is collected about you and how it is used in the study. This data concerns your current clinical situation as well as some of your medical history, the results of examinations carried out as part of your standard health care, and of course the results of the examinations required by the protocol. You have the right to review this data and to make corrections if it is incorrect[1].

[1] These rights are guaranteed to you by the General Data Protection Regulation (GDPR), by the Belgian legislation of July 30, 2018, on the protection of individuals with regard to the processing of personal data, and by the law of August 22, 2002, on patient rights.

The investigator has a duty of confidentiality regarding the collected data. This means that they commit not only to never disclose your name in a publication or conference but also to pseudonymize your data before transmitting it to the database manager. The investigator and their team will therefore be the only ones able to link the transmitted data to your medical record throughout the study[2].
The personal data transmitted will not contain any combination of elements that would allow you to be identified[3].

For the research data manager designated by the sponsor, the transmitted data does not allow you to be identified. The manager is responsible for collecting the data gathered by all investigators participating in the research, processing it, and protecting it in accordance with the requirements of Belgian privacy protection law.

To verify the quality of the study, it is possible that your medical record will be reviewed by individuals bound by professional secrecy and designated by the ethics committee, the study sponsor, or an independent audit organization. In any case, this review of your medical record can only take place under the responsibility of the investigator and under the supervision of one of their designated collaborators.

The research data (pseudonymized) may be transmitted to Belgian or other regulatory authorities, the relevant ethics committees, other investigators, and/or organizations working in collaboration with the sponsor.

They may also be transmitted to other sponsor sites in Belgium and other countries where personal data protection standards may be different or less stringent. As explained above, the transmitted data is pseudonymized[4].

Your consent to participate in this study also implies the use of your pseudonymized medical data for the purposes described in this information document and their transmission to the aforementioned persons and entities.

The sponsor undertakes to use the collected data only within the framework of the study in which you are participating. The sponsor will use the data collected in the study in which you are participating but also wishes to be able to use it in other research concerning the same disease as yours. Any use of your data outside the context described in this document can only be carried out after approval by the ethics committee.

If you withdraw your consent to participate in the study, to ensure the validity of the research, the pseudonymized data up to the point of your withdrawal will be retained. No new data can be transmitted to the sponsor.

If you have questions about the processing of your data, you can contact your investigator. The data protection officer of your hospital is also available to you. Their contact details are as follows: (contact details).

Finally, if you have a complaint about the processing of your data, you can contact the Belgian supervisory authority responsible for ensuring compliance with the fundamental principles of personal data protection:
The Belgian supervisory authority is called:
The Data Protection Authority (APD)
Rue de la Presse 35,
1000 Brussels
Tel. +32 2 274 48 00
Email: contact@apd-gba.be
Website: https://www.autoriteprotectiondonnees.be

[2] For clinical trials, the law requires maintaining this link with your medical record for 25 years.

[3] The database containing the study results will therefore not include any combination of elements such as your initials, gender, and full date of birth (dd/mm/yyyy).

[4] The sponsor then undertakes to comply with the requirements of the General Data Protection Regulation (GDPR) and Belgian legislation on the protection of individuals with regard to the processing of personal data.

What happens in case of incidental findings?

If by chance and in addition to the trial objectives a result is discovered during the trial that may be important to your health or the health of your blood relatives (called ”incidental findings”), the sponsor will inform the investigator. With your consent the investigator will notify you and your treating physician about your results and potential consequences. If necessary, the investigator and/or the treating physician will advise you on the next steps.

Insurance

Any participation in a clinical study involves a risk, however small it is. Even if there is no fault, the sponsor accepts responsibility for damage caused to the participant (or in the event of death, his/her dependants) and directly or indirectly linked to his/her participation in the study. The sponsor has taken out insurance for this responsibility[5].
[Where applicable] You are therefore asked to report any new health problem to the investigator. He/she will be able to provide you with additional information concerning possible treatments.

If the investigator believes that a link with the study is possible (the insurance does not cover the natural progression of your disease or the known side effects of your normal treatment), he/she will inform the study sponsor, which will initiate the declaration procedure to the insurance company. The latter will appoint an expert - if it considers it necessary - to assess whether there is a link between your new health problems and the study.
In the event of disagreement either with the investigator or with the expert appointed by the insurance company and also whenever you feel it is appropriate, you or - in case of death - your dependants may bring proceedings against the insurer directly in Belgium (MS Amlin Insurance SE, policy number: LXX002596, King Albert II lane, 37 – 1030 Brussels).
The law provides that the insurer may be summoned to appear either before the judge of the location where the event giving rise to the damage occurred, or before the judge of your domicile, or before the judge of the insurer’s registered offices.

[5] In accordance with Article 29 of the Belgian Law related to experiments on humans (7 May 2004)

Appendix 3: Who can I contact in case of questions?

Name	Function	In case of	Contact details
Surname, First name of the investigator	Principal Investigator of the site	Information, problems or concerns	Phone N°, E-mail
	The trial staff	Information, problems, concerns	Phone N°
	Emergency contact	Emergency	Phone N°
	Patient rights ombudsman	Concerns relating to your rights as a participant in a trial	Phone N°
MS Amlin Insurance SE, MS Amlin Insurance SE, King Albert II-lane, 37 – 1030 Brussels	Insurance Company of the sponsor	In case of disagreement or complaint on a damage claim	Policy N° LXX002596
	Data protection officer of the **site**	Questions relating to the confidentiality of your data	Phone N° E-mail: e-mail
	Belgian Data Protection Authority	Complaints relating to the confidentiality of your data	E-mail : contact@apd-gba.be

Title of the study: Impact of reducing the irradiation volume on survival, toxicity, and quality of life in patients with glioblastoma treated with radiochemoradiotherapy: a prospective multicenter randomised study (BELGICA)

III Informed consent

Participant

I declare that I have been informed about the nature of the study, its purpose, duration, potential benefits and risks, and what is expected of me. I have read the information document and its appendices.

I have had enough time to think about it and discuss it with a person of my choice, such as my general practitioner or a family member.

I have had the opportunity to ask all the questions that came to mind and received satisfactory answers to my questions.

I understand that my participation in this study is voluntary and that I am free to end my participation at any time without affecting my relationship with the healthcare team responsible for my health.

I understand that data concerning me will be collected throughout my participation in this study and that the investigator and the study sponsor guarantee the confidentiality of this data in accordance with applicable European and Belgian legislation.

I have been informed that an insurance has been contracted for this study.

I consent to the processing of my personal data as described in the section on confidentiality guarantees (Appendix 2). I also agree to the transfer and processing of this pseudonimized data (your identity will be replaced with an identification code in the study to avoid using any identifiable information) in countries other than Belgium.

I accept / do not accept (strike out as appropriate) that the research data collected for the purposes of this study may be processed later, provided that this processing is limited to the context of this study for a better understanding of the disease and its treatment.

I accept that my general practitioner or other specialist doctors responsible for my health are informed of my participation in this clinical study.

I accept / do not accept (strike out as appropriate) that, in case of incidental findings, the investigator keeps me informed (directly or through my treating physician) of this result.

I accept / do not accept (strike out as appropriate) that my personal data be transmitted to Monizze for the purpose of obtaining compensation vouchers.

If I refuse to share my data with Monizze, I will receive an anonymous card that allows me to receive the financial compensation.

I have received a copy of the participant information and informed consent.

Last name and first name of the participant	
Date and Signature of the participant	

Witness / Interpreter

I was present throughout the entire process of informing the participant and I confirm that the information on the study's objectives and procedures was provided adequately, that the participant (or their legal representative) apparently understood the study, and that consent to participate in the study was given freely.

Last name, First name, and qualifications of witness / interpreter	
Date and signature of witness / interpreter	

Investigator

I, the undersigned, (name, first name) …… investigator, confirm that I have orally provided the necessary information about the study and have given a copy of the information document to the participant.

I confirm that no pressure was exerted for the participant to agree to participate in the study and that I am ready to answer any additional questions, if necessary.

I confirm that I work in accordance with the ethical principles set out in the latest version of the "Declaration of Helsinki," "Good Clinical Practices," and the Belgian law of May 7, 2004, relating to experiments on the human person.

Last Name and first name of representative of investigator	
Date and signature of representative of investigator	

Last Name and first name of investigator	
Date and signature of investigator	