Informed consent 2: to participate in screening visit 2 and the rest of the Flu Air-shedding & Immunity Monitoring (FLAIM) Study

This follows informed consent 1 & screening visit 1

Official title of the study: ***FLAIM study: an open-label, single center influenza H3N2 controlled human infection model study of viral shedding, mucosal and systemic immunity***

Study number: CHIMFLU-M-001

Sponsor(s) of the study: Centre for the Evaluation of Vaccination (CEV) / Vaccinopolis, University of Antwerp

Contract Research organisation: Harmony Clinical Research BV, Brusselsesteenweg 159, 9090 Melle, Belgium.

Site name: Ccntre for the Evaluation of Vaccination (CEV), University of Antwerp

Address of site: Drie Eikenstraat 663, 2650 Edegem, Belgium

Document Revision History

Version	Date	Change
1	12 May 2025	NA
2	03 Jul 2025	Resolved inconsistency in wording eligibility criteria between protocol and ICF
3	24 Jul 2025	Addition of continuous monitoring of participants and an optional intravenous catheter during quarantine, adjustments to the schedule of study activities to support safety and scientific questioning, recalculation of blood volume, textual clarifications of among others eligibility criteria

Who can I contact in case of questions?

Name	Function	In case of	Contact details
Joren Raymenants	Principal Investigator of the site	Information, problems or concerns	+3232652652 vaccinopolis@uantwerpen.be
	The study staff	Information, problems, concerns	+3232652652 vaccinopolis@uantwerpen.be
	Emergency contact	Emergency	+32496230712
Amlin Insurance SE, Koning Albert II laan 37, 1030 Brussels, Belgium	Insurance Company of the sponsor	In case of disagreement or complaint on a damage claim	Policy N°: 199.535.692
	Patient rights ombudsman	Concerns relating to your rights as a participant in a study	+32 3 821 31 60, ombudsdienst@uza.be
	Data protection officer of the **site**	Questions relating to the confidentiality of your data	+3232655263 koen.pepermans@uantwerpen.be
	Belgian Data Protection Authority	Complaints relating to the confidentiality of your data	+32(0)2274 48 00 contact@apd-gba.be

- *To manage complaints not resolved by the investigator, you can contact the study centre ombudsman at the above address.*
- *According to the GDPR, you have the right to access the processing of your data. For questions about this, you can contact the Study Centre's Data Protection Officer at the above address.*
- *You also have the right to lodge a complaint about the way your data are processed with the Belgian supervisory authority responsible for compliance with data protection legislation: Data Protection Authority (GBA), above.*

University of Antwerp Vaccinopolis

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Dear Sir, Madam,

With this informed consent form 2, we would like to inform you about the second screening visit and the remainder of the FLAIM study. Informed consent form 1, which pertains only to screening visit 1, precedes what is explained in this form.

The FLAIM study is a controlled human infection study. If you have been found eligible to participate during screening visit 1, and are still happy to participate, you will undergo more extensive screening during screening visit 2. Then, you may be invited for a 13-day in-patient stay in a quarantine unit ("Vaccinopolis"), where you may be given a known quantity of a well-characterized Influenza virus under very controlled conditions to induce flu. We ask you to watch the video ICF version of this brochure, in addition to reading the document, via https://www.uantwerpen.be/flaim.

Participation in this study is entirely voluntary, so you have the choice whether or not to participate.

This study was approved by an independent central ethics committee, the ethics committee of the University Hospital of Antwerp (UZA, Belgian Registration number: B3002023000030) on 26 May 2025. The study is conducted in accordance with Good Clinical Practice (ICH-GCP) and the 2013 Declaration of Helsinki regarding the protection of participants in clinical studies. Ethics committees are responsible for protecting participants in clinical studies according to Belgian law of May 7, 2004 (amended by the law of May 7, 2017) concerning studies involving humans. The approval of this study by the ethics committee should not influence your decision to participate in this study or not. Before you agree to participate in this study, we ask you to become aware of what this study will entail in terms of organization, possible risks and benefits, so that you can make an informed decision. This is called 'informed consent'. We ask you to read the information brochure carefully. For any questions, please contact the physician-researcher or their representative. This brochure consists of two parts: (1) the essential information you need to make your decision, (2) your written consent when you decide to participate.

THE STUDY AT A GLANCE

The influenza virus or "flu" still has an important health impact worldwide. Better interventions are needed for influenza control.

Human challenge studies (also known as controlled human infection models) involve deliberately exposing healthy volunteers to infectious organisms in a controlled manner. These studies allow better understanding of the impact of the organism on the exposed person (e.g. signs and symptoms), the body's response to infection (e.g. the development of immunity) and the risk of onward transmission.

This study plans to expose healthy, nonsmoking volunteers of 18–55 years old with low antibody levels influenza in the blood to a measured amount of influenza A(H3N2) virus via nasal spray. This exact virus has been used before in similar studies.

We aim to reestablish the percentage of persons that become infected and which symptoms they develop. Also, we will study how many respiratory (viral) particles participants exhale before, during and after infection and the immune response they develop in airways and blood.

We are asking you to participate in this clinical study because you are a healthy adult aged 18 to 55. You may meet the health criteria for this study.

Before you agree to take part in this study, we want to fully inform you about the study and its implications in terms of organisation, and its possible risks and benefits, so you can decide for yourself if you want to take part. This process is known as giving "informed consent".

This chapter will already give you an idea of what will happen during this study, but we nevertheless ask you to read all the pages and to look at the video version of this form via https://www.uantwerpen.be/flaim. It is important that you read and understand all the information. The aim is to avoid you taking part in the study without knowing what you're signing up for. Ask the study team all your questions before signing. After signing this form you will be asked to complete a short comprehension test, and to discuss your answers with the study physician.

The total study duration is maximum around 120 days but will usually be shorter. If you decide to join our study:

- You will be screened for inclusion during two study visits.
    - During a first visit, which you should have attended at this point, we assess your eligibility based on the pre-screening checklist you filled out and test your level of immunity against the administered Influenza virus.
    - During a second visit, we further assess your eligibility and therefore take a thorough history, perform a clinical examination and safety testing: bloods, urine, ECG (test of the heart), spirometry (a type of lung function testing) and measure the amount of exhaled respiratory particles. If you fit the criteria, you will also undergo a more comprehensive lung function test at University Hospital Antwerp.
- During a 13 day quarantine, you would
    - undergo more safety testing
    - be exposed to a well characterized amount of influenza virus via nasal spray
        - You could get flu infection
        - There is a very small risk that you develop complications, including myocarditis and post-viral fatigue.

        - We may offer you antiviral medication (oseltamivir) or other medical interventions if your infection is concerning to us.

          Note, this is for additional safety only and we do not anticipate therapy to be required.
    - remain in our quarantine unit under Biosafety Level 2 conditions. This means you will have your own private room with en-suite bathroom. You can use common areas during the day while wearing a mask and observing hygiene measures. You will not be able to receive outside visitors, but you can interact with other study participants and staff while following safety protocols. You can bring in personal devices such as phones, laptops and tablets to watch films, study, work, etc and to call friends and family.
    - be monitored closely and have medical assistance available at all times.
    - undergo regular tests that focus on the amount of virus you spread, the signs and symptoms you develop, the immune response you mount in the airways and blood and a number of safety tests (bloods, ECG, spirometry).
    - We ask your agreement to collect stool samples (maximum once daily), but this is optional.
- You would come for an ambulatory follow up visit 28±2 days after we give you the study virus with more clinical assessments, safety tests, breath sampling and immune tests.

You will not benefit directly from participation in this study. You will be compensated approximately €4657 for your time, travel and efforts.

There is a no fault insurance cover in case something goes wrong within the study.

Participants are not allowed to become pregnant during the study. The study team will discuss with you the appropriate method of contraception.

All treatments and examinations that you will undergo or receive in the context of the study will be free of charge for you.

Data collected within this study are treated confidentially and in accordance with applicable laws. Biological samples (e.g. blood, nasal swabs) taken during this study may be stored for up to 25 years and used for research. The study staff will give you clear information about this.

You will be free to withdraw from the study at any time you wish. We will fully understand your decision and will continue to take care of you as before. You will, however, be strongly encouraged to remain in quarantine until you are no longer infectious.

This clinical study has been reviewed and approved by the Ethics Committee of UZA/Uantwerpen.

If you decide to participate, you agree:

- to sign the informed consent form. The study investigator will also sign the form and thereby confirm that you have received the necessary information about the study. You will receive a signed and dated copy of the form.
- to not take part in any other clinical trial at the same time
- to communicate the relevant information related to the state of health, other medication taken or the symptoms experienced

Now that you have some idea what this study is about, please take your time to read the other pages of this document. You do not have to do that all at once. It is important that you understand what you are reading. Feel free to discuss the study with a trusted person (for example a friend, relatives, your family doctor).

The study staff is also available to help you if there is anything that is not clear. It is our job to make sure that you understand all the information.

For more information, you can contact

the study team: +3232652652, vaccinopolis@uantwerpen.be

the principal investigator (Joren Raymenants): +3232652652, vaccinopolis@uantwerpen.be

CHAPTER I – DESCRIPTION OF THE STUDY AND YOUR RIGHTS WHEN PARTICIPATING

1. Why are we doing this study

Infections with the influenza virus, or "flu", still cause important health and economic costs for which we need better vaccines, treatments and other interventions (e.g. ventilation and masking).

In this clinical study, we will experimentally expose healthy adults to the influenza A virus under strictly controlled conditions, aiming to induce an influenza infection and cause "flu". The key aims of this study are to better understand

- the impact of the organism on the exposed person (e.g. signs and symptoms)
- the body's response to infection (e.g. the development of immunity)
- the risk of onward transmission.

2. Why am I being asked to take part?

You are being asked to take part in this study because you:

- Are aged between 18 and 55 years old at screening 1
- Are in good health with no significant medical conditions (including lung problems and psychiatric problems)
- Are not a current smoker (including vaping) since ≥ 3 months at screening 1 and haven't smoked more than 1 pack of cigarettes per day on average for a total of 5 years
- Are not a heavy drinker (at least 80% of days or >15 units per week)
- Don't have a substantial history of drug abuse as judged by the investigator
- Are not pregnant or breastfeeding
- Have no household contacts who are at high risk of severe flu, which are the following individuals:
    - 65+ years
    - Persons >6 months of age with chronic lung/heart/liver/kidney conditions, metabolic disorders, neuromuscular disorders or~~,~~ immune disorders.
    - Pregnant women (any stage)
    - Children 6 months-18 years on long-term aspirin
    - Children < 6 months of age whose mother did not receive a flu vaccine during pregnancy.
- Don't have seasonal allergies during summer or fall, any significant food allergies, or allergy to egg products

During screening visit 1, we test your blood to check your level of immunity against the challenge virus used in this study. We will only include people with low levels of existing immunity. See ICF 1 for details on that study visit.

The investigator or study staff will discuss with you the requirements to be allowed to enter the study. This happens both during screening visit 1 (based on a pre-screening checklist) and more thoroughly at the start of screening visit 2.

3. Do I have to take part in a study?

Your participation in a study is voluntary and must remain free of any coercion. This means that you have the right not to take part in the study or to withdraw at any time without giving a reason, even if you previously agreed to take part. Your decision will not affect your relationship with the investigator or your treating physician nor will it affect the quality of your future medical care.

4. What will happen during the study?

The study will enrol up to approximately 180 persons, of which up to 24 persons will be experimentally infected with the challenge virus. Reserve participants are invited for quarantine, but can be sent home after two days (before inoculation). The study runs in Belgium only and takes place between June and November 2025.

This is a single-group study, which means all participants receive the same dose of the challenge virus and there is no placebo group or randomization. The study is also "open-label", meaning both you and the study team will know whether you received the challenge virus. You will, however, not know whether or not you are infected until day 7 after virus administration, to avoid influencing your reporting of symptoms.

Your participation will last a maximum of 120 days but will usually be shorter. It involves two screening visits, a 13 day quarantine stay and one follow-up visit at D28±2.

1. Screening Phase - Two screening visits will entail the following:

First visit (approximately 1 hour, 90–5 days before possible virus administration):

- Signing of informed consent form 1, that pertains only to that first screening visit.
- Assessment and recording of your answers to the pre-screening checklist, to see if they are in line with eligibility criteria. Possible uncertainties will be flagged and assessed in depth at screening visit 2.
- Blood test to check your level of immunity against the influenza virus.

Second visit (approximately 6 hours, 60-2 days before possible virus administration, yet always after or in combination with the First visit):

- Medial history and physical examination.
- Height and weight measurement.
- Vital signs (blood pressure, heart rate, temperature, blood oxygen saturation).
- Heart test (ECG). This exam looks at the electricity in your heart muscle.
- Mental health questionnaires to exclude current psychological difficulties.
- Breathing test to measure exhaled particles. During this test, you breathe into a machine that measures the number and size of exhaled respiratory particles.
- Blood test for safety. This test checks the correct functioning of several of your organs and excludes pregnancy (if applicable).
- Urine test to assess the functioning of your kidney’s and exclude drug use.
- Alcohol test to exclude that you are under the influence of alcohol.
- Lung function test (spirometry) in Vaccinopolis: breathing test to measure the exhaled volumes.

- Lung function test (at Universitair Ziekenhuis Antwerpen): breathing test to measure the exhaled volumes and other parameters. This may take place on the same or a separate day.

2. Quarantine Phase (13 days in-patient stay).

A few notes:

- More individuals will be admitted than will be inoculated. This accounts for possible last-minute exclusion/withdrawal. They will be discharged and reimbursed pro-rata. They are 'reserve participants'. Reserve participants stay on the quarantine unit for a maximum from D-2 up to D0.

Day -2 and -1 (Admission)
You will check into the quarantine unit two days before being exposed to the virus and stay under Biosafety Level 2 conditions.

- You have a private room with en-suite bathroom, with WiFi and meals provided.
- You can use common areas during the day while wearing a mask and observing hygiene measures.
- You cannot receive outside visitors, but you can interact with other study participants and staff while following safety protocols.
- You can bring in personal devices such as phones, laptops and tablets to watch films, study, work, etc and to call friends and family.
- You will be monitored closely and have medical assistance available at all times.
- Moderate physical activity is encouraged throughout the study and the quarantine period. Vigorous physical activity is not allowed due to the risk of exercise induced muscle soreness.
- You will receive a quarantine information sheet before admission.

On the day of admission and the following day, you will undergo:

- An alcohol breath test .
- A screening test for respiratory infections. A nose swab is tested for the presence of several respiratory pathogens. We want to avoid administering the influenza virus to someone who currently has a respiratory infection.
- Vital signs testing (blood pressure, heart rate, temperature, blood oxygen saturation).
- A physical examination.
- A heart test (electrocardiogram or ECG).
- A breathing test (Spirometry) to measure the exhaled volume.
- A urine test including a drug and pregnancy screen (if applicable).
- A breathing test to measure the number and size of exhaled particles.

- Blood sampling to make sure your organs function normally and to assess your baseline immunity against the influenza virus.
- A 'nasosorption test', a type of swab to assess the immunity in the front of your nose.
- Deep nose swabs to assess the immunity in the back of your nose.
- Saliva sampling to check the immunity in your saliva.
- Stool sampling (optional) to check the immunity in your gut.
- Complete questionnaires about mental health to exclude current psychological problems.
- Complete the FLU PRO symptom questionnaire, to see whether you already experience symptoms at baseline that we might otherwise contribute to flu after administration of the virus.
- A specifically designed device will be attached to your upper arm and continuously monitor your heart rate, skin temperature and the oxygen saturation in your blood. It also records when you fall and allows you to activate an emergency button. These data can be consulted by the study team during the entire study period and help to detect any abnormalities earlier.

Day 0 (Challenge Day). The following activities take place:

- Vital parameters (daily at a specific timepoint and continuously) and physical examination, if necessary.
- Administration of influenza virus via nasal spray
- Symptom recording using the FLU-PRO questionnaire (twice daily)

Days 1-10 Daily activities:

- Vital signs (daily at a specific timepoint and continuously)
- Record symptoms via FLU-PRO questionnaire (twice daily). They may continue past discharge until resolution if ongoing symptoms at discharge.
- Nose and throat swabs (once daily)
- Deep nose swabs (once daily, but varying number of samples)
- 'Nasosorption test' (once daily but varying number of samples)
- Wear mask with special strips inside for 60 minutes to collect exhaled virus. This may be stopped from day 7 onwards if you remain uninfected
- Breathing test to measure exhaled particles
- Breathing test to measure exhaled virus.
- Sampling of your room (ambient air and surface swabs – once daily) for the presence of virus. This may be stopped from day 7 onwards if you remain uninfected
- Completion of FLU PRO questionnaire (twice daily)
- Saliva samples (every day)

Regular activities:

- Blood test (around every 2 days)
- Breathing test (spirometry, around every 2 days)
- Urine test (around every 2 days)
- Optional stool samples (once daily)
- Heart tests (ECG, every few days)
- Mental health questionnaires (day 7)
- Physical examination, if necesaary

From discharge to follow-up visit

- Completion of FLU PRO questionnaire (daily) as long as symptoms persist.

Follow-up Visit (Day 28 ± 2 days)

- Vital signs and physical examination, if necessary
- Record symptoms via FLU-PRO questionnaire
- Blood test
- Heart test (electrocardiogram or ECG)
- Spirometry
- Pregnancy test on urine (if applicable)
- Breathing test to measure exhaled particles
- Deep nose swabs
- 'Nasosorption test'
- Saliva sample
- Optional stool sample

Notes:

- Some tests may be repeated if needed for safety
- Additional tests may be done if you experience side effects
- The use of tobacco, recreational drugs are prohibited during the study. During quarantine, only moderate caffeine consumption is allowed (<400mg caffeine or about 1L of coffee per day). Alcohol use is prohibited during quarantine.
- Donations of blood products are prohibited from 30 days before screening visit 1 until 30 days after study completion.

A flowchart of the study is shown in Figure 1. An overview of all planned assessments can be found in table 1 below. The total blood collected throughout the study will not supersede around 305ml. All examinations, including those as UZA, are specific to the study and will be paid for by the sponsor. You can find more details about which costs are covered by the sponsor in Section 11 of this document.

If you meet all the conditions required to be enrolled in the study and agree to take part in the study, you will undergo the above-mentioned tests and examinations (note that the stool samples are optional). If you have any important side effects, the investigator might determine that it is necessary to perform additional tests.

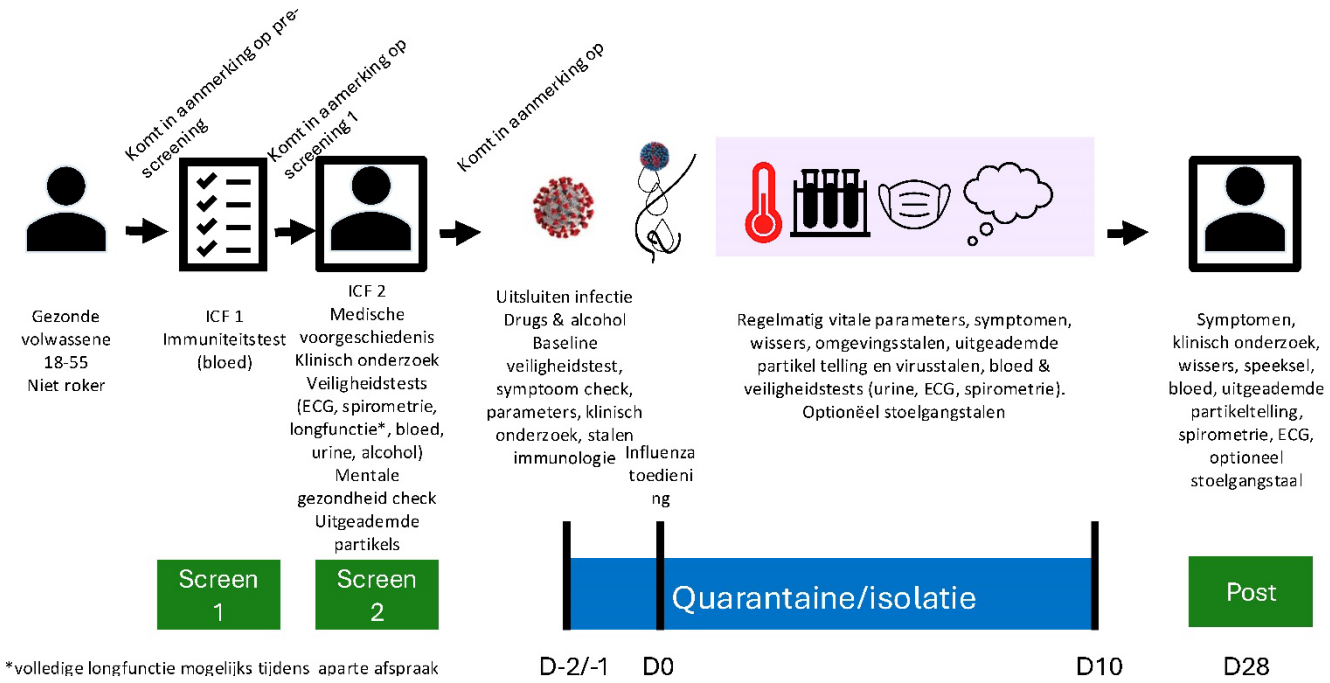

Figure 1. Proposed study setup

	Screening 1	Screening 2	D -2	D -1	D0	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D 28
Informed consent	ICF 1 (for screening 1)	ICF 2 (for rest of study)														
Eligibility criteria	x	x	x	x	x											
Medical & medication history		x	x													
Demographics		x														
Physical exam	x[f]	x	x[c]	x[f]	x	x[f]	x[f]	x[f]	x[f]	x[f]	x[f]	x[f]	x[f]	x[f]	x[f]	x[f]
Vital signs	x[f]	x	x[c]	x[f]	x	x	x	x	x	x	x	x	x	x	x	x[f]
ECG		x		x[c]		x[f]	x	x[f]	x[f]	x[f]	x[f]	x	x[f]	x[f]	x[f]	x
Spirometry		x		x[c]		x	x	x[f]	x[f]	x	x[f]	x	x[f]	x	x[f]	x
Lung function test (UZA)		x														
Mental health questionnaires		x		x								x				
Virus administration					x											
FLU PRO symptom Questionnaire				2	2[x]	2[x]	2[x]	2[x]	2[x]	2[x]	2[x]	2[x]	2[x]	2[x]	x[e]	x[e]
Recording adverse events & medication use	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Continuous monitoring			x													
Urine Drug Screen		x	x													
Alcohol Breath Test		x	x													
Pregnancy test		blood	urine													U
Urine test		x	x				x			x				x		
Bloods for safety		x	x				x			x				x		
Bloods for immunology	x		x	x		x	x		x	x	x	x		x		x
Respiratory pathogen screen			x													
Nose swab						x	x	x	x	x	x	x	x	x		
Throat swab						x	x	x	x	x	x	x	x	x		
Deep nose swabs			2	2		2	3		1	1	2	2		1		3
Mask sampling						x	x	x	x	x	x	x[i]	x[i]	x[i]		
Exhaled breath particle counting		x		x		x	x	x	x	x	x	x	x	x		x
Exhaled breath virus sample						x	x	x	x	x	x	x	x	x		
Ambient air virus sample						x	x	x	x	x	x	x[i]	x[i]	x[i]		
Environmental surface virus sample						x	x	x	x	x	x	x[i]	x[i]	x[i]		
Nasosorption samples			2	2		2	2			2		2		2		2
Saliva sample				x		x	x	x	x	x	x	x	x	x		x
Optional stool sample				±[c]		±	±	±	±	±	±	±	±	±		±

Table 1. Schedule of Study activities. [c] = assessments can take place on day –2 or day –1, [f] optional (investigator or symptom driven), 2[x] = twice daily, [i] = only if at least 1 pcr on nose or throat swab positive up to this point, [e] if ongoing symptoms at discharge, twice daily symptom scoring continue until symptom resolution.

5. Will I benefit from the study?

The information obtained during a study may contribute to a better understanding of infections with the H3N2 influenza virus, or to the development of new medicinal products. Study procedures may also benefit you by allowing you to learn about your own health.

6. What are the possible risks and discomforts of taking part?

6.1 What are the possible side effects of exposure to Influenza?

Participation in a study involves some risk. There are known discomforts and risks of side effects that can happen with experimental infections with the H3N2 Influenza virus. The study staff are trained to take the right measures to reduce risks and limit any discomforts you may experience.

There are **physical risks and discomforts** related to influenza virus exposure. All virus exposed individuals will be at risk of become infected with influenza virus and developing flu symptoms. It is anticipated that the exposure will induce a mild to moderate illness. Potential symptoms include high body temperature, sore throat, cough, headache, aching body, feeling tired or exhausted, difficulty sleeping, loss of appetite, stomach or tummy pain and diarrhea. Most people will recover after a few days, but complications are possible. Severe illness is unlikely due to rigorous screening for inclusion and existing immunity (all individuals have previously been infected with Influenza virus). Flu can, however, cause serious infections and complications including post-viral fatigue. Possible complications, which are more frequent in persons with underlying risk factors (e.g. old age, medical conditions, etc), are lung infection, sinus or ear infection, inflammation of the heart muscle, inflammation of the brain, inflammation of the muscles, 'blood poisoning' (known as sepsis in medical terminology) and organ failure. Such complications could result in death.

Participating in a clinical study and being deliberately exposed to a virus may cause **emotional stress** (e.g. anxiety, despondency etc) for some individuals. This may be further aggravated by extended isolation (up to 13 days), which may lead to feelings of loneliness or boredom.

It is very important that you report any new or worsened health problems immediately to the investigator, regardless of whether or not you think it has to do with the study and even when it is already described in this document.

If, for any reason, you consult another treating physician during the study, you must inform them that you are taking part in a study. This could be important in determining a diagnosis and giving you the correct treatment if needed. You will be provided with a participant ID card.

All participants will be screened for underlying psychological problems before and during a possible quarantine.
If you experience any psychological symptoms or discomfort, let the study staff know. We do everything possible to minimize discomfort and psychological distress during quarantine and monitor your general and psychological well-being throughout the quarantine period. Any symptoms or complications will be addressed promptly with access to treatment as needed.

6.2 What are the possible risks or discomforts of the examinations during the study?

The examinations of the study may cause the following discomforts and risks:

- The taking of blood (up to around 305ml over the course of the study) is necessary to ensure study safety by evaluation the functioning of your organs and to evaluate pre-existing and developing immunity to influenza. This may cause pain, bleeding, bruising or infection localised around the injection site. Similarly, some participants may feel dizzy or even faint during the procedure. The staff who take the blood will do all they can to minimize these discomforts.
- Discomfort and bleeding from nasal, deep nasal and throat swabs performed frequently throughout the study.
- Mild dizziness or nausea may occur during breathing tests to measure the exhaled volume, the number and size of exhaled particles or the amount of exhaled virus.
- No side-effects or complications are expected from the heart test (electrocardiogram or ECG) or other assessments.

6.3 Can I take other medicines during the study?

Participants in this clinical study are generally required to avoid taking other medications during the study unless explicitly approved by the study team. This is to prevent interactions between the medication and the study procedures, including the controlled exposure to the virus, which could affect the study outcomes or your safety. Of particular note is that we try to avoid administering medication that influences flu symptoms (e.g. paracetamol or anti-inflammatory agents) as this could change the patient-reported symptom scores.

If you take any medications, including over-the-counter drugs, supplements, or herbal remedies, you must disclose these during the screening phase. The study team will evaluate whether the medication is compatible with the study. If medication is needed for a new condition that arises during the study, you should inform the study team, who will determine the appropriate course of action.

Allowed Medications:
You may only take medications that are approved by the study team after a thorough review. These typically include:

- Contraceptives: Highly effective birth control methods are required if you are of childbearing potential.
- Essential prescription medications: For stable, chronic conditions, provided they do not interfere with the study outcomes (e.g., thyroid medications).
- Over-the-counter pain relievers and anti-inflammatory agents such as paracetamol and acetaminophen should be avoided but can be considered in consultation with the study team.

Prohibited Medications:
To ensure safety and avoid interference with study results, the following medications are not allowed:

- Immunosuppressive drugs: Such as corticosteroids or chemotherapy medications.
- Vaccines: Certain vaccines are not allowed during the study. Discuss with the investigator any vaccines you plan or wish to receive during the study.
- Experimental treatments: Participation in other clinical trials or investigational drug use is not permitted.
- Antiviral medications: These are restricted unless needed as part of emergency care related to the study.

- Recreational drugs or substances: Including smoking or vaping products. Alcohol use is strictly prohibited during the quarantine period.

- Herbal supplements starting from 7 days prior to inoculation or planned during the study.

Do not hesitate to ask your investigator for more explanation about the use of other medicines and food supplements.

Participants should disclose all medications, supplements, or herbal remedies during the screening process, and any new medication needs should be discussed with the study team during the study.

6.4 Will my participation to the study have an impact on my daily activities?

Participation in this study will have a temporary impact on your daily activities, especially during the quarantine phase. Here's how it may affect your routine:

Quarantine Period (Days -2 to 10):

- You will need to stay in a designated quarantine unit for 13 days.
- During this time, you will be isolated from friends, family, and your usual activities.
- all meals, entertainment options, and support services will be provided. You may bring snacks and drinks after prior approved by the study team.
- You can interact with other participants in common rooms while observing hygiene measures. Participants are, however, not allowed to enter other participants' rooms.

Medical Assessments and Monitoring:

- Frequent medical assessments, including blood tests and other samples, may interrupt your routine. We do every effort, however, to inform you of the sampling times beforehand and to facilitate any planned activities such as online meetings.
- Two screening visits, a visit for a lung function test at UZA (which may be separate) and a follow-up visit on Day 28±2 will require time for clinic appointments.

Work or Study Impact:

- You may need to take time off from work, studies, or personal responsibilities during the quarantine and follow-up phases. We note that you are welcome to work or study during your stay in the unit, and we will do our very best to plan proceedings around your schedule. You are happy to bring electronic devices such as phones, tablets and laptops. Physical books and documents may need to be placed in quarantine before your returning them home. These aspects will be outlined in a quarantine information sheet prior to your admission to the unit.

Travel Requirements:

- You may need to travel to and from the trial site (Vaccinopolis) for screening, follow-up visits, and other study-related activities.

Exercise: Moderate physical activity is encouraged throughout the study and the quarantine period. Vigorous physical activity is not allowed due to the risk of exercise induced muscle soreness.

While the study involves temporary disruptions, every effort will be made to minimize inconvenience and support participants throughout the study

6.5 Can my partner or I get pregnant or can I breastfeed during the study?

Please share the following information with your partner and talk to your GP or the study staff to decide the best method of birth control.

Female participant
Volunteers who are not of childbearing potential are those who have had a complete absence of menstrual periods for at least 12 months (and this is not due to the use of hormonal contraception or a medical condition) or practise same sex intercourse only, or provide documented proof of surgical sterilisation or hysterectomy (uterus removal).

If you are able to have a baby, you must be using acceptable birth control or practice abstinence (if this is the preferred and usual lifestyle of the participant) from 2 months before possible administration of the influenza virus until after discharge from the quarantine unit.

Acceptable forms of contraception include:

- male partner who is sterile (vasectomised) prior to the female participants' entry into the study, and they are the sole sexual partner for the female participant;
- hormonal (oral, intravaginal, transdermal, implantable or injectable);
- an intrauterine hormone-releasing system (IUS);
- an intrauterine device (IUD) with a documented failure rate of < 1%;
- bilateral tubal occlusion.

Please discuss this point with your investigator if this applies to you. Please inform the investigator in case you would decide during the study to change your method of contraception.

You must notify the study doctor if you become pregnant during the study. If you become pregnant, your study participation will be stopped and your pregnancy will be monitored.

You will be required to have a pregnancy test during inclusion visit 2 (blood), before virus exposure and at the follow-up visit on Day 28±2 (both urine).

Male participant:

Male participants do not need to take any contraceptive measure to avoid their partner becoming pregnant.

7. What If something goes wrong within the study?

Even if there is no fault, the sponsor is liable for harm caused to you whether directly or indirectly related to your participation in the study. The sponsor has taken an appropriate insurance (a so called "NO FAULT INSURANCE") for this liability (Ref. 1). A copy of the insurance certificate can be obtained from the investigator or study staff.

If you (or in the event of death, your rightful claimants) seek compensation for a harm to your health as a direct or indirect result of participating in the study, you must inform your investigator or study staff promptly.

If the investigator believes that a link between the new or worsened health problem(s) and the study is possible, they will inform the study sponsor. The sponsor will then immediately initiate the declaration procedure to its insurance company. If the company considers it necessary, it will appoint an expert to assess whether there is a link between your reported health problem(s) and the study.

Whenever you feel it is appropriate or if you or your rightful claimants disagree either with the investigator or with the expert appointed by the insurance company, you may contact the insurance company or proceedings may be brought against the insurance company. You will find the contact details on the front page of this form.

8. What if new information becomes available during the course of the study?

During the course of the study, important new information might become available, possibly affecting your decision to (further) participate. For example, important new information on influenza challenge studies or this particular challenge virus may become available. It is the duty of the investigator to discuss this new information with you and to give you the opportunity to re-consider your participation in the study.

If you decide to stop taking part in the study or if you are no longer able to participate, your investigator will see to it that you continue to receive the best possible medical care.

9. Can my participation in the study end prematurely?

As explained in detail below, your study participation may end prematurely when

- you decide to withdraw your consent,
- the investigator decides to end your study participation, or
- other entities interrupt or end the study.

In any case, if your study participation ends prematurely, the investigator will discuss your future medical care with you. The sponsor can continue to retain and use any data that have already been collected before the end of your participation. This is to avoid skewing / biasing results of the study (as described in I. § 11).

Depending on your situation, the investigator will discuss with you whether follow-up visits or procedures are needed.

If you experience a side effect at the moment of premature study interruption, the investigator may contact you in the future to see if it has resolved or not after the end of the study participation.

If you experience a new side effect after the end of your study participation you may contact the investigator to ask for a follow-up.

9.1 You decide to withdraw your consent

You are entitled to withdraw your consent for any reason, at any time, without having to justify your decision. However, for your safety, you should inform the investigator of your decision. Although it is not mandatory, it may be useful for the investigator and for the sponsor to know the reason of your decision (for example side effects, frequency of clinical visits,…).

If you withdraw your consent, this means you decide to stop all study-related visits and examinations.

No new data will be collected and passed on to the sponsor.

Please discuss with the investigators to evaluate the practical modalities of your withdrawal (in light of your situation), including any follow up-visits or procedures.

Please note that once you have received the flu virus, stopping your participation will not undo the exposure, but we can still provide appropriate medical care and follow-up.

If you withdraw during the quarantine period while potentially infectious:

- We strongly encourage you to stay until you are no longer infectious
- If you decide to leave, we will advise you on how to prevent spreading an infection (using masks, distancing, ventilation, hand hygiene)
- We may offer you antiviral medication (oseltamivir)
- We will ask you to complete safety assessments on your last day
- No new data will be sent to the sponsor

- We will invite you to return for the Day 28±2 safety follow-up visit

If your biological samples (e.g. blood samples, urine samples) have already been used or analysed before the withdrawal of your consent, the sponsor still has the right to use the results from those tests.

The biological samples that have been collected (but not tested) before the withdrawal of your consent and the data obtained from it, can also still be used by the sponsor. You may ask for a destruction of those samples. If this impacts the validity of the study, the destruction may be postponed till the end of the study.

9.2 The investigator decides to end your study participation

The investigator may end your study participation because

- you become pregnant during the study,
- it is better for your health,
- he/she determines that you are not following the instructions given to participants, or
- any other reason that will be explained.

The same practical arrangements will be made if your study participation ends while you may be infectious (see Section 9.1 above).

9.3 Other entities may interrupt or end the study

The sponsor and the competent Belgian health authorities may interrupt or end the study because

- the challenge agent causes more (serious) side effects than anticipated, or
- any other reason that will be duly motivated by such party.

10. Will my participation in the study involve extra costs for me?

10.1 Examinations and treatments paid by the sponsor

The sponsor has arranged to cover

- the time devoted to the study by the investigator and the study staff,
- the visits/consultations and all scheduled examinations specific to the study,
- the challenge virus and any other medication and material specifically used for the study.

None of the assessments are considered standard of care. None will therefore be charged to you as a participant or your mutual insurance fund (Belgian social security).

You will receive compensation for certain expenses related to your participation in the study. The reimbursement received by Belgian participants as part of this study are not subjected to income tax in Belgium. You will find the reimbursement scheme for your study participation in the table below.

Study visit / day	**Reimbursement**
Screening visit 1	€ 43,68
Screening visit 2 (other assessments)	€ 43,68
Screening visit 2 (lung function)	€ 71,5
Quarantine Day -2	€ 349,18
Quarantine Day -1	€ 349,18
Quarantine Day 0	€ 349,18
Quarantine Day 1	€ 349,18

Quarantine Day 2	€ 349,18
Quarantine Day 3	€ 349,18
Quarantine Day 4	€ 349,18
Quarantine Day 5	€ 349,18
Quarantine Day 6	€ 349,18
Quarantine Day 7	€ 349,18
Quarantine Day 8	€ 349,18
Quarantine Day 9	€ 349,18
Quarantine Day 10	€ 193,18
Follow up visit Day 28	€ 115,18
Total	€ 4657

You will be paid pro rata for the study visits you completed.

The visits and treatments which are a consequence of a side effect are also considered as study specific.

All reimbursement as part of this study will be made by bank transfer on a quarterly base.

In case you encounter any problems in receiving your compensation or have additional questions, do not hesitate to contact the study staff. If you withdraw or are ineligible for the study, we will pay you up to the timepoint at which you withdrew/became ineligible.

10.2 Other expenses paid by the sponsor

Other expenses you incur in relation to your participation in the study, such as mandatory contraception, travel costs, fuel, parking, public transport, meals, time investment and effort and possible hotel costs are considered part of the above reimbursement. You will receive a compensation for the following expenses based on the receipts: medication needed to treat possible remaining side effects after discharge from the quarantine phase. The study staff shall contact you for the practical arrangements.

11. Which data are collected about me during the study and what will happen with them?

11.1 Which data are collected and processed during the study?

The collected and processed personal data concern information about your health and medical condition. This includes your medical history, some of your background information (for example your age, sex, and race) and the results of examinations required by the study.

11.2 How will the investigator treat my personal data?

The investigator (and study team) is bound by professional secrecy about the data collected.

This means that they will never reveal your identity, including in a scientific publication or a lecture and that they will encode your data (Ref 3) (*that is* by replacing your identity by an identification code in the study).

Therefore, the investigator and the study staff under the responsibility of the investigator, will be the only ones able to establish a link between your identity and the data collected during the study, with the exceptions listed under section 11.6.

The investigator and the sponsor can only use the encoded personal data for research purposes in connection with scientific publications within the context of the study that you participate in, or for a broader use of the encoded data if described below.

In addition, the sponsor may provide access to the encoded data to external researchers (that are not involved in this study). In the event an external researcher wants to use the data in a project not yet described in this document, this project will have to be approved by an Ethics Committee. If your encoded study data are sold, you will not benefit from this.

11.3 How will my data be handled?

Your study data will be processed in accordance with the current European and Belgian Data Protection legislation (Ref 2). The sponsor is responsible for this processing.
Processing your personal data in this study is allowed because we are conducting scientific research and

- You have given your **consent.**
- we must perform a task carried out in the **public interest**, namely advancing of science.

11.4 Do I have access to my data collected and processed during the study and can I rectify them ?

You are entitled to ask the investigator what data are being collected about you and how those data will be used in connection with the study.

You have the right

- to inspect and access these data
- to receive the personal data that are collected
- to ask for correction if they are incorrect
- to withdraw your consent for the processing of personal data. However personal data collected before withdrawal will be kept to avoid skewing of results in the study.

It is not possible

- to have all your data erased
- to restrict the processing of your data
- to object to the processing of your personal data

to avoid skewing of results in the study and to preserve the integrity of the study.

11.5 Who, other than the Investigator and his staff, has access to my personal data?

To verify the quality of the study, it is possible that your personal **un**coded data or information in your medical records relevant for the study, will be examined by people outside the study staff but under the responsibility of the investigator. These persons must be subject to professional secrecy or a confidentiality agreement. The following might be considered:

- the personnel designated by the sponsor of the study (MONITORS and AUDITORS), and people or organisations providing services for or collaborating with the sponsor. They will however never transfer your name and contact details to the sponsor.
- inspectors of competent health authorities worldwide
- an independent audit group
- people designated by the Ethics Committee

Limited uncoded data will be shared with UZA to schedule your appointment for the lung function test at UZA.

For the needs of the study, the encoded study data may be sent to other EU and non-EU countries and may be reviewed by

- personnel (other than the inspectors) of competent health authorities of Belgium (Federal agency for medicines and health products, FAMHP) and other EU and non-EU countries,
- the evaluating Belgian Ethics Committee(s),
- external researchers,
- the sponsor of the study, personnel designated by the sponsor, and people or organisations providing services for or collaborating with the sponsor
- the providers of the continuous monitoring device, for proper functioning of the device

The European regulation and the Belgian legislation on data protection have requirements for transferring data to non-EU countries. The sponsor must ensure equivalent guarantees regarding personal data protection standards before transferring the encoded data to non-EU countries. If for this purpose, there is a data protection agreement, a copy of this agreement may be obtained via the investigator. You can always contact your investigator to obtain more information about any such transfers.

11.6 What will happen to the results of the study?

After study closure, a description and the results of this clinical study will be published in specialised medical journals. A copy of the scientific publication or a summary for laypersons can be obtained from the investigator or the study staff.

These publications will not include information that can identify you.

11.7 Will my data be used for other purposes than for the study in which I take part?

The results of the study will be used to answer the scientific questions of the study. In addition, the sponsor would like to use your data obtained from this study, in connection with other research and development activities (and the associated scientific publications). These activities may concern

- Further research on infectious diseases and immunology.

Any additional research outside of the study, must be approved by a Belgian recognized Ethics Committee.

11.8 How long will my data be kept?

After the end of the study your encoded data will be retained for at least 25 years (Ref. 2) to ensure the validity of the research. This will also be the case if you stopped study participation prematurely.

12. Which biological samples are collected from me during the study and what will happen with them?

12.1 Which biological samples are collected from me during the study?

Biological samples are samples of human body material (for example blood, tissue, urine, faecal stool, ….).
See *figure 1* for the study schema and *table 1* for the schedule of assessments of this study.
In this study, the following biological sample(s) will be taken:

<u>Nose swabs</u>
Nose swabs will be obtained by placing a swab into your nostrils. Swabs may be taken from the middle or back of the nose. Because we will be asking you to record any symptoms on the electronic diary we will not tell you the swab results until day 7 at the earliest. This is to avoid any unintentional differences in the way you might experience or report symptoms knowing you are, or are not,

infected. If you need rescue therapy or any other changes to study procedures (e.g. because you become unwell), we will tell you the results then.

The deep nose swabs are inserted between 5 and 10 cm into a nasal passage and rotated gently for a few seconds, for research purposes other than monitoring whether you are infected or not. These swabs will be collected regularly during the quarantine period and at the follow-up visit after quarantine.

Nasosorption
In addition to the nose swabs, we will perform a nasosorption test regularly whilst in quarantine and then at the follow up visit. This involves the placement of a short soft sterile strip into one or both nostrils. We will then ask you to pinch your nose or put on a nose clip for 1-2 minutes, before removing the strip(s). This allows us to collect samples from the fluid in your nostrils.

Throat swabs
We will ask you to tilt your head back and open your mouth while a swab is rubbed along the back of your throat. You will need to resist gagging and closing your mouth.

Mask wearing samples
We want to capture and analyse the droplets coming from your airways. To do this you will be asked to wear an adapted facemask containing strips that capture droplets as you breathe out. You will do this daily starting on Day 1, once a day for 60 minutes on each occasion.

Saliva samples
You will be asked to provide a saliva sample each day of approximately 2mls.

Blood sampling
We will take your blood samples for safety and/or research at pre-specified timepoints. The amount of blood samples taken each time would be variable. Overall, we will not take more than around 305ml of blood over the course of the study.

Environmental sampling
During quarantine, we will enter your room daily to take samples from the air and surfaces to see if the virus stays in the environment (zie tabel 1).

Breath test for exhaled particle counting and virus sampling
You will be asked to breathe into a purpose built setup which has tubing attached to a machine that can count the number of expired particles and capture the airborne virus you expire.
This will take no more than 15 minutes and you may be asked to sing and/or exhale deeply during this test.

Urine samples
Urine samples will be mandatory at certain time points to monitor your health and, in case you are able to bear children, to rule out pregnancy.

Optional stool samples
You may be asked to collect a stool sample using a collection device (cotton-headed swab or small spoon or similar) after opening your bowels during the quarantine stay and on D28±2.

Additional study procedures may be performed to monitor your safety.

The procedure to encode your biological samples is the same as that used for your personal data (see I § 11, Ref 3). Samples sent to organisations working in collaboration with the sponsor, will only be labelled with your study identification code.

As part of the study, the sponsor might transfer (a part of) your samples to a laboratory that is working with them. This laboratory may only use your samples as specified in this document. The tracking of your samples will be ensured by the sponsor.

Your biological samples are deemed to be a "donation". You will not receive any financial benefit associated with the development of new therapies derived from the use of your biological samples, and which may have commercial value.

12.2 What will happen to the collected biological samples?

These biological samples will be analysed for the objectives of the study.

Since scientific progress in this area is constant, the sponsor would like to, with your consent retain the remainders of your biological samples for 25 years. The sponsor will use them for additional research that remains within the context of the current clinical trial and is thus further research into infectious diseases and immunology.With your consent, the sponsor would also like to invite you to take part in additional research intended to better understand the disease, the influenza pathogen, its transmission, and the development of immunity. Your participation in this additional research is optional and will involve donating additional biological samples. The additional biological samples will be retained for 25 years. It concerns the following samples:

Stool samples, which we will use to assess the shedding if virus and the development of a response in the gut.

You agree or disagree to donate additional biological samples and participate in the described research by ticking the appropriate checkbox in Chapter II.

13 What happens in case of incidental findings?

If by chance and in addition to the study objectives a result is discovered during the study 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.

You agree or disagree to being informed of it by ticking the appropriate check-box in Chapter II. The researcher/your treating physician will inform you about this information in any case where not being informed may cause serious harm to your health or that of third parties.

14 Who has reviewed and approved the study documents?

The documents of the study have been reviewed by an independent Belgian Ethics Committee.

It is the task of the Ethics Committees to protect people who take part in a study. The Ethics Committee will ensure that the study is conducted in accordance with the applicable legislation.

You should not under any circumstances take their approval as an incentive to take part in the study.

CHAPTER II - INFORMED CONSENT

FLAIM study: an open-label, single center influenza H3N2 controlled human infection model study of viral shedding, mucosal and systemic immunity

PARTICIPANT

PREREQUISITES FOR YOUR PARTICIPATION IN THE STUDY

- I declare that I have read this form, seen the corresponding video version of this form and understood its information.
- I declare that I have been informed of and that I understand the purpose of the clinical study, its duration, possible risks and discomforts, the precautions that I have to take and what is expected of me. My rights have been explained to me and I have understood those rights.
- I have had enough time to think about taking part in study study and to discuss it with a trusted person (for example friends, relatives, treating physician, …).
- I have had the opportunity to ask any questions that came to mind and have obtained a satisfactory response to my questions.
- I understand that my participation in this study is voluntarily and free from any coercion and that I am free to stop at any time my study participation.
- I understand that data about me will be collected and that they will be treated confidentially.
- I agree to my personal data being processed as described in this document.
- I understand that the sponsor has taken out an insurance in case I should suffer any damage in connection with my participation in this study.
- I understand that when participating in this study, I will not have any costs.
- I will voice my wish to the investigators to inform my general practitioner of my participation in this study.
- I agree not to take part in any other trial at the same time without first informing the investigator or the trial staff, who might not permit me to participate for a good reason.
- I understand that I need to cooperate and follow the investigator's and study staff's instructions regarding the study.
- I understand that participation to the study might end for me without my consent if I need other treatment, do not follow the study plan, have a study-related injury, or for any other justified reason.
- I certify that all the information I have given about my medical history is correct. I understand that my failure to inform the investigator or designee about any exclusion criteria may harm myself.

OPTIONAL CONSENTS WHICH ARE NO PREREQUISITE FOR YOUR PARTICIPATION IN THIS STUDY.

1. As specified in Chapter I, § 12, the sponsor would like to invite you to take part in additional research intended to gain a better understanding of the disease, the influenza virus, and the development of immunity. Your participation in this additional research is optional and will involve donating additional biological samples.

   Do you agree donating additional biological material (Stool samples) and participating in this additional research?

   (Tick as appropriate If you leave this question open, we assume the answer is 'I do not agree'.)

Stool samples	
☐ **I agree**	☐ **I do not agree**

2. As described in Chapter I, § 12, and § 14, it may happen that incidental findings are discovered that may be important to your health or the health of your blood relatives.

   If this happens: do you want the investigator to inform you (directly or via your treating physician) of this result?

   (Tick as appropriate. If you leave this question open, we assume the answer is 'yes, I want to be informed'.)

☐ **No, I do not want to be informed**	☐ **Yes, I want to be informed**

I consent to take part in the study, with the above restrictions and I have received a signed and dated copy of all pages of this document.

Participant's surname and first name:

Date (DD/MMM/YYYY):

Participant's signature:

INVESTIGATOR

I, the undersigned investigator, confirm that

- the participant has been provided with the necessary information about the study via a paper ICF, a video ICF and verbal clarifications. They have been explained the content and have been given an original signed document.
- I have verified that the participant has understood the study. I have given the participant sufficient time to agree to take part and to ask any questions.
- no pressure was applied to persuade the participant to agree to take part in the study.
- I operate in accordance with the ethical principles set out in the latest version of the "Helsinki Declaration", the "Good Clinical Practices" and the Belgian Law (Ref 3)

Investigator's delegate/investigator, surname and first name:

Investigator's delegate/ investigator, qualification:

Date (DD/MMM/YYYY):

Investigator's delegate/ investigator signature:

GLOSSARY

DPA: The Data Protection Authority ensures that personal data are handled with care and thoroughly protected, and that your future privacy also remains guaranteed.

FAMHP: Federal agency for medicines and health products

NO FAULT INSURANCE:

The sponsor is liable for any injury or any damage that the participant has suffered, and which is directly or indirectly related to the clinical study. You do not have to prove any mistake in this respect.

MONITOR and AUDITOR

Both the monitor and auditor work for the sponsor.
The monitor takes care of a continuous quality check during the course of a study. The auditor performs a quality check after the study. They verify if the study is being/was conducted according to the protocol, if the reported data are liable and if the clinical study was conducted according the applicable rules.

REFERENCES

[1] This is in accordance with Article 29 of the Belgian Law of 7 May 2004 related to experiments on humans.

[2] General Data Protection Regulation No 2016/679 of the European Parliament and of the council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC.

The Belgian Law of 30 July 2018 on the protection of natural persons with regard to the processing of personal data.

[3] Throughout the document, the term “encoding” is used as a synonym of the term “pseudonymising”, the term used in General Data Protection Regulation No. 2016/679.

[4] In accordance with article 58 of the Clinical trial regulation No 536/2014 of the European Parliament and of the council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC.

[5] Belgian Law of 19 December 2008 on the acquisition and use of human body material with a view to medical application to humans or scientific research, and the applicable royal decrees.

[6] Belgian Law of 7 May 2004 related to experiments on humans, and the applicable royal decrees.