CLINICAL INVESTIGATION PLAN

A single centre, controlled, investigation to evaluate the performance of the hyperspectral camera for retinal non-invasive examination through the observation of retinal oxygenation

CIV-22-05-039512

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Investigation site	Sundets Ögonläkare
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Revision history

Document version	Date of Issue	Summary of Change	Autor
1.0	29/06/2022	Basic document outline	J. Hantson
E	03/08/2022	$6.1: scrap Mantis Photonics as test site Updated wording of test summary and inclusion/exclusion criteria	J. Alexander J. Hantson
F	10/08/2022	Implementation of remarks Ingegred Dalfelt	J. Alexander

Signatures

Sponsor

I am responsible for ensuring that this CIP includes all essential information to be able to conduct this clinical investigation. I will submit the CIP and all other important clinical investigation-related information to the responsible Principal Investigator so that she can conduct the clinical investigation correctly. I am aware that it is my responsibility to hold the staff members who work with this clinical investigation informed and trained.

Sponsor's signature Date

Name: Denis Hellebuyck, CEO Mantis Photonics

Principal Investigator

I have read this CIP and agree that it includes all essential information to be able to conduct the clinical investigation. By signing my name below, I agree to conduct the clinical investigation in compliance with this Clinical Investigation Plan, the Declaration of Helsinki, EN-ISO 14155:2020 (Good Clinical Practice), and the current national and international regulations governing the conduct of this clinical investigation.

I will submit this CIP and all other important clinical investigation-related information to the staff members who participate in this clinical investigation, so that they can conduct the clinical investigation correctly. I am aware of my responsibility to continuously keep the staff members who work with this clinical investigation informed and trained.

I am aware that quality control of this clinical investigation will be performed in the form of monitoring, audit, and possibly inspection.

Principal Investigator's signature Date

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List of used acronyms and abbreviations

Abbreviation	Term/Explanation
AD	Alzheimer's Disease
ADE	Adverse Device Effect
AE	Adverse Event
CIP	Clinical Investigation Plan
CRF	Case Report Form
DD	Device Deficiency
GCP	Good Clinical Practice
IFU	Instructions for Use
EN-ISO	European standard International Organization for Standardization
ITT	Intention-to-treat = including all data from all subjects who have participated in the clinical investigation
MDCG	Medical Device Coordination Group
PMCF	Post-Market Clinical Follow Up
PP	Per Protocol analysis = including only data from subjects who have completed the clinical investigation completely in accordance with the CIP, with no deviations from the CIP
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
USADE	Unanticipated Serious Adverse Device Effect

1. Synopsis

Background and rationale:	In the retina, light is captured and then transported via the optic nerve to the brain. Common diseases in the retina are glaucoma, diabetes and age-related changes in the macular area. Diagnostics of these diseases are important in order to be able to treat them in time. Currently, it is possible to image the retina with, for example, a regular camera or with ultrasound. Similarly, with optical coherence tomography, OCT, you can get a deep view of the layers of the retina. To get an idea of the oxygenation level of the retina is more difficult. With intravenous injection followed by photography, images can be collected of the retina that shows areas of non-perfusion. However, injecting a drug is not always possible and also associated with a risk. Mantis Photonics AB has developed a new diagnostic camera that uses an ordinary camera's light flash and capture the light that bounces back from the retina in a way than an ordinary camera does, but in a new patented new technology splits the light into different wavelengths; hyperspectral imaging (HI). With HI it is possible to capture and see changes that are not visible with a normal camera such as the oxygenation level of the vessels in the retina thereby assess the metabolic status of the retina. The oxygenation level is affected in several retinal disease such as diabetes and glaucoma. Initial reports have shown that the technology could be valuable for early detection of, for example, diabetic retinopathy. Furthermore, hyperspectral imaging can be used to detect molecular changes seen in age-related macular degeneration. Since the retina is an extension of the brain, it has been discovered that some diseases that affect the brain can also be detected in the retina. The deposition of beta amyloid associated with Alzheimer's disease (AD) has also been found in the post mortem retinas of AD patients. With the new hyperspectral camera technology, it has been possible to differentiate between beta amyloid positive and negative subjects. As this is a new technology, there are only sparse reports (Haddoux2019, Lemmens2020). We believe that the hyperspectral technology can provide detailed information about various disease states in the retina,

	such as hemorrhages, ischemia, diabetes, glaucoma, but also provide early diagnosis of neurological diseases that cause changes in the retina, such as Alzheimer's disease. Our project aims to investigate and refine the hyperspectral camera technology by photographing healthy retinas. Furthermore, we intend to also examine people with diseases that affect the retina such as glaucoma and age-related macular changes, diabetes, retinal detachment and compare diagnostic accuracy with other available techniques. With improved examination technology, it is possible to sharpen treatment and in some cases perhaps also advance adequate treatment.
Investigational device:	Mantis Photonics' hyperspectral camera for non-invasive retinal examination (i.e., hardware device): CB200-10nm-160x160-2
Inclusion criteria:	For inclusion in the investigation, the patient-subjects must fulfill all of the below criteria prior to enrollment: 1. Age > 18 years. 2. Ophthalmological disease, disorder, illness or problem involving the retina 3. Provision of informed consent i.e., subject must be able to understand and sign the patient information and consent form. For inclusion in the investigation, the healthy subjects must fulfill all of the below criteria prior to enrollment: 1. Age >18 years. 2. Without known eye disease. 3. Provision of informed consent i.e., subject must be able to understand and sign the patient information and consent form.
Exclusion criteria:	Patients-subjects who meet any of the below criteria will be excluded from the investigation: 1. Patients with narrow angle glaucoma 2. Inclusion in other ongoing investigations at present that would preclude the subject from participating in this investigation as judged by the Principal Investigator. Healthy subjects who meet any of the below criteria will be excluded from the investigation: 1. Presence of eye disease, eye trauma, diabetes or pregnancy.

	3. Inclusion in other ongoing investigations at present that would preclude the subject from participating in this investigation as judged by the Principal Investigator.
Study objectives:	Primary objective: To evaluate the performance of the hyperspectral camera for non-invasive retinal examination in order to improve the diagnosis of diseases affecting the retina or central nervous system. Secondary objective: To investigate the possibilities of the use of a hyperspectral camera for non-invasive retinal examination. Safety objective(s): To evaluate the safety of the hyperspectral camera for non-invasive retinal examination by assessment of device deficiencies and adverse events, non-serious and serious, rated for causality.
Study endpoints:	Primary endpoints: To evaluate the effectiveness of the hyperspectral imaging of retinal changes by detecting structures and conditions in the retina and to compare the hyperspectral imaging with other diagnostic techniques. More specifically, can the hyperspectral camera detect the different structures of the retina based on spectral distribution? Can the hyperspectral camera detect differences in oxygenation levels between arteries and veins in healthy retina and retina with disease? Secondary endpoint: To investigate if additional signs of reduced oxygenation can be seen in retinal disease. More specifically, can optic nerve thinning be detected by hyperspectral camera? Can hyperspectral imaging detect changes that are not measurable with other examination modalities and do these differ from normal retinal changes? Safety endpoint(s): 1. Incidence of AE/ADE/SAE/SADE/DD. 2. Incidence of AE/ADE/SAEE/SADE/DD leading to withdrawal of a subject. The experience of having a temporary, benign after-image of the flash lamp for a brief period is common. The mydriatic eye drops can be temporary unpleasant (pain and discomfort, redness, itching and/or blurriness). Those effects are expected and explained during the informed consent phase before including the subject in the trial. Those effects should not be qualified as unacceptable risks of harm to the subject, and therefore those effects are no reason to stop the clinical investigation, unless the subject wants to withdrawal from the clinical investigation.
Planned duration of the clinical investigation:	Estimated date of first subject enrolled: Q3 2022.

	Estimated date of last subject completed: Q2 2023. Estimated date of end of clinical investigation (database lock) is Q4 2023.

2. Identification and description of the investigational device

The investigational device shall be used only in this investigation and according to the Clinical Investigation Plan. The investigational device must be used according to Instructions for Use. For more information regarding the investigational device, see the Instructions for Use and precautions.

This device is identified by the identification label on the camera stating the identification code (CB200-10nm-160x160-2) the production date and the Sponsor's / Manufacturers information.

2.1. Description of the investigational device

The Mantis Photonics hyperspectral camera (investigational device) is a prototype that can be applied to an existing fundus camera. Light with wavelengths in the visible light spectrum is used and multiple images are generated with different wavelengths. The Mantis Photonics retinal scan set-up is thus based on a commercial mydriatic retinoscopy camera set-up (Topcon). In this set-up, Mantis Photonics builds in the patented Mantis Photonics hyperspectral camera. Apart from the camera, the commercial camera set-up of Topcon is not changed.

A trained operator of a common commercial retinoscopy camera can learn to work with the Mantis Photonics solution in a short time.

1. DESCRIPTION OF THE COMPONENTS OF THE MANTIS PHOTONICS HYPERSPECTRAL CAMERA:

The unique camera identification for the research prototype used for the retinal oxygenation trial is CB200-10nm-160x160-2.

Camera set-up ID	**MANTIS ID**	**Component name**	**Producer**	**Component type**
004	CB200-10nm-160x160-2	Fundus camera	Topcon	TRC50 IX
		CMOS sensor	Ximea	CB200MG-CM
		microlens array	Okotech	APO-Q-P148-F1.75
		Grating	Thorlabs	GT25-03 or GT25-06
		Optical orifice	Thorlabs	
		TTL trigger box	REDLAKE	MegaPlus II camera controller
		TTL connection cable	Kjell & Company (Goobay)	BNC coaxial cable

2. DESCRIPTION OF THE REQUIREMENTS OF THE MANTIS PHOTONICS HYPERSPECTRAL CAMERA:

ref : GEN_THW_20_A Design Justification Document.

ID	Description
REQ-HW-1	The Mantis Photonics camera must be mountable with either a female c-mount thread or a Nikon F mount.
REQ-HW-2	The Mantis Photonics hyperspectral camera must be mounted in the commercial retinal scan rig.
REQ-HW-3	The Mantis Photonics hyperspectral camera functions following the principle illustrated in Figure 1 and in patents WO 2020/263161. and patent under application P436042SE00.
REQ-HW-4	The camera sensor must be powered according to constructor requirement.
REQ-HW-5	The camera sensor must have a secure control and data connection to the software, to allow communication of data and instructions between both.
REQ-HW-6	The camera exposure must be synchronized with the flash lamp when operated in hardware trigger mode.
REQ-HW-7	It must be possible to operate the camera in software trigger mode to allow validation and debugging of the set-up.
REQ-HW-8	The flash lamp must illuminate the retina with light between 400 nm and 700 nm.
REQ-HW-9	The flash lamp spectrum must be known and must be stable because the software requires this information to calculate the relative reflectance of the retina.

The Mantis Photonics hyperspectral camera is based on a patented solution where the incoming light is collected so that only parallel beams are passed through a collimator, then the light is diffracted and reaches a micro lens array and is then captured in the camera. Figure 1 shows the conceptual design of the Mantis Photonics hyperspectral camera - Imaging principle.

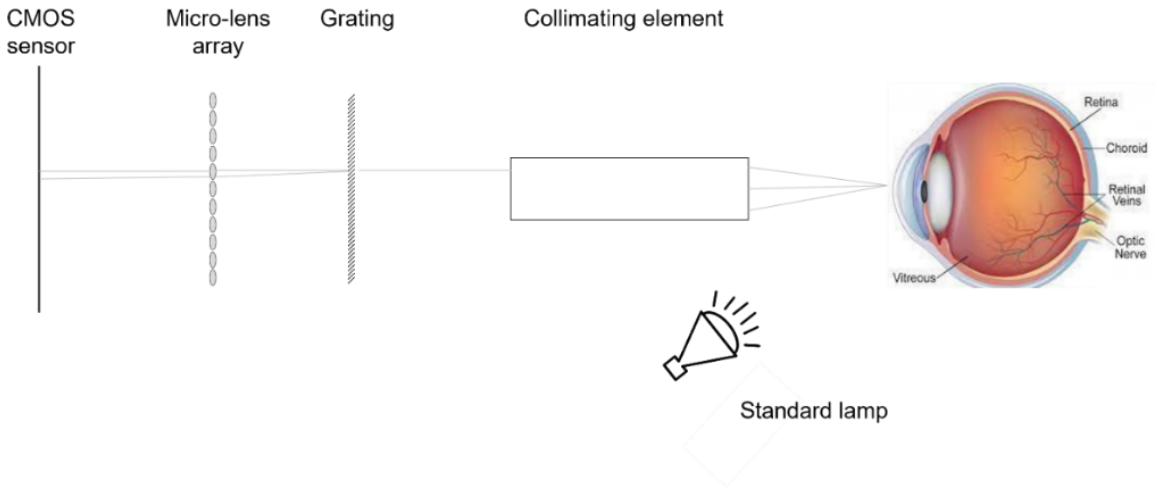

Figure 1

Figure 2 and figure 3 illustrate the electric circuit for powering the Mantis Photonics hyperspectral camera and synchronizing it with the flash lamp trigger box - Electrical circuit to power the camera and connect the camera to the triggerbox.

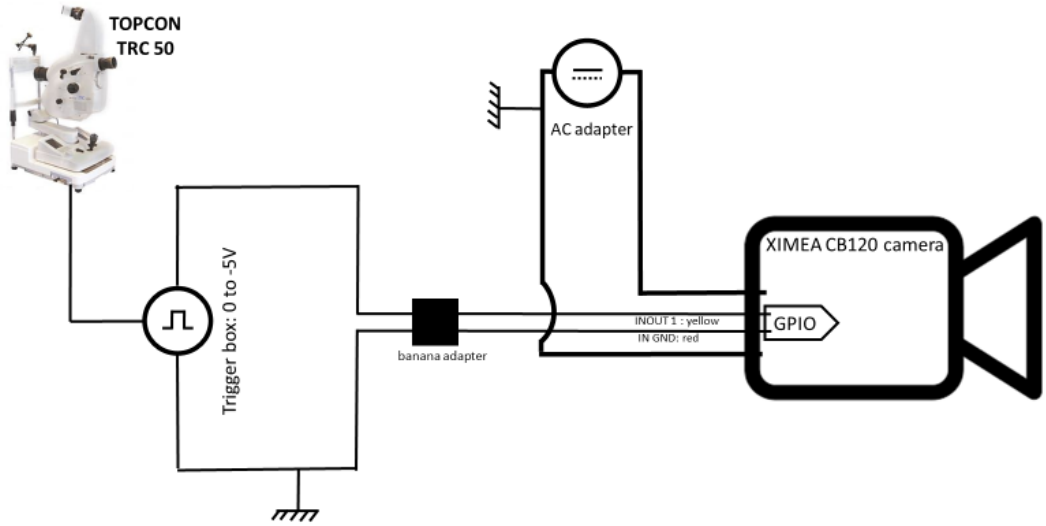

Figure 2

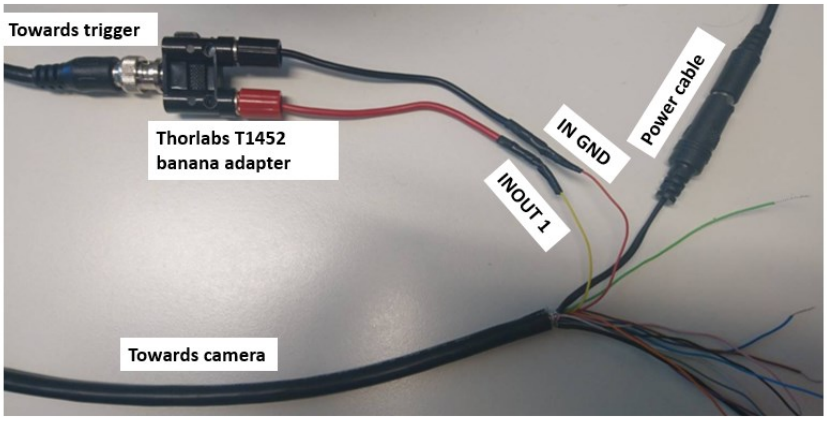

Figure 3

3. DESCRIPTION OF THE REQUIREMENTS OF THE MANTIS PHOTONICS SOFTWARE LINKED TO THE CAMERA:

ID	Description
REQ-SW-3	The software must allow to control the camera in software trigger mode (see REQ-HW-7).
REQ-SW-4	The software must allow to control the camera in hardware trigger mode, initiating the camera to wait for the TTL signal from the flash lamp (see REQ-HW-6).
REQ-SW-5	The software must show the most the frequency slices at 450 nm to 700 nm in steps of 50 nm to the operator for revision of the retinal scan quality (see REQ-MED-7). This conversion should be under 30 seconds to allow the operator to take corrective action if needed.

4. MEDICAL REQUIREMENTS OF THE MANTIS PHOTONICS SET-UP:

ID	Description
REQ-MED-1	The test set-up must be safe for medical use, both for the patient and for the operator.
REQ-MED-2	The flash lamp must be safe for medical use, both for the patient and for the operator.
REQ-MED-3	The flash lamp settings, including light intensity and flash duration, must be safe for medical use.
REQ-MED-4	The set-up operation must be comparable or identical to the use of other retinoscopy cameras used by trained ophthalmologists and optometrists.
REQ-MED-5	The patient experience must be comparable or identical to the use of other retinoscopy cameras used by trained ophthalmologists and optometrists.
REQ-MED-6	The set-up must allow a 15° angle view of the retina to allow taking retinal scans with sufficient view of the retinal to identify ischemia and/or contain the required regions of interest for the Alzheimer's disease classification algorithm.

2.2. Intended purpose

The Mantis Photonics hyperspectral camera for non-invasive retinal examination is built to capture retinal ischemia and amyloid-β accumulation in the retina using a hyperspectral retinal scan, based on its wavelength-dependent effect on light scattering. The intended purpose of the investigational device in the light of this clinical investigation is to evaluate the performance of the hyperspectral camera for non-invasive retinal examination in order to improve the diagnosis of diseases affecting the retina or central nervous system.

2.3. Target population

A healthy population and a patient-population with an ophthalmological disease affecting the retina.

2.4. Detailed description of the investigational device and materials coming into contact with the human body

None of the components of the investigational device will be in contact with tissues or body fluids of the subjects.

2.5. Medical procedures

The Principal Investigator will make sure that the medical history of the subjects is evaluated before the performance of the hyperspectral retinal scan. The Principal Investigator will make sure that the status of the eye and the surrounded tissue (e.g., pain and discomfort, redness, itching, blurriness and/or pupil dilating) of all the subjects is recorded before and after performing the hyperspectral retinal scan.

The Principal Investigator is responsible for ensuring that procedures and expertise are available to cope with medical emergencies during the investigation.

2.6. Summary of required training/experience needed

The Principal Investigator will ensure that appropriate training relevant to the investigation is given to the medical, nursing and other staff members at the site involved and that new information of relevance to the performance of this investigation is forwarded to the staff members involved.

Before the first subject is entered into the investigation, the Principal Investigator will ensure that the medical, nursing and other staff members at the investigation site undergo a training including, but not limited to the following items:

1. The Clinical Investigation Plan and the execution thereof.
2. Use of the investigational device.
3. Use of a record system.

The staff members at the investigational site will sign a confirmation document that they are trained in how to use the investigational device. Only trained staff members will be allowed to perform a hyperspectral retinal scan with the investigational device for a given subject.

Detailed instructions can be found in *5A. LU_LR_37_B_Investigator's Brochure* and *GEN_THW_34_A Mantis Photonics camera technical manual*.

3. Background and justification for the design of the clinical investigation

3.1. Background

1. BENEFITS OF DETECTION OF LOW OXYGENATION REGIONS IN THE RETINA

The Western population is getting older. This is of course a positive development, but more and more people are also suffering from age-related diseases such as glaucoma and yellow spot changes that reduce vision and quality of life (Flaxman, et al. 2017). Diabetes is another disease whose complications affecting the retina are increasing in prevalence (Zimmet, et al. 2016).

The diagnosis of retinal diseases has improved in recent years with the advent of refined imaging techniques such as OCT and Ultrasound and functional tests such as automated perimetry. However, there is still a need to improve our understanding of the pathogenesis of several eye-related diseases. In the development of diabetic retinopathy, a disturbed oxygenation of the tissues with elements of hypoxia plays a role (Hardarson en Stefánsson 2012). In the development of glaucoma, there is also a discussion of an element of ischemia as an etiology (Lee, et al. 2021). To measure the degree of perfusion in the retina, angiography can be performed. However, this is time-consuming and invasive, also associated with certain risks for patients. Therefore, there is a need to improve and simplify the diagnosis and to measure the oxygenation of retinal tissues in a more convenient way.

Through shared ontogeny, the retina shares similar functions to the brain and spinal cord in terms of anatomy, functionality and immunology (De Groef en Cordeiro 2018) (London, Benhar en Schwartz 2013). There are several ocular markers for stroke and MS (London, Benhar en Schwartz 2013). There are also several similarities between disease markers for Alzheimer's disease, age-related macular disease and glaucoma (Sivak 2013). In Alzheimer's disease, which primarily affects the brain, increased beta amyloid deposition is also seen in the retina and in patients with glaucoma and age-related macular disease, increased deposition of beta amyloid and tau protein, for example, is seen in the tissues (Sivak 2013). Good retinal imaging and functional testing is therefore important to detect diseases affecting the retina but also as a means of detecting diseases that do not primarily affect visual function. The retina is therefore opening up as a structure suitable for non-invasive detection not only of retinal diseases but also an opportunity for early diagnosis and monitoring of, for example, Alzheimer's disease.

Hyperspectral imaging is a new technique that can capture spatially distributed spectral information from the retina non-invasively. The technique is the result of a research project at Lund University. Conventional fundus photography detects either monochromatic light or light in the bands, red, green and blue reflected by retinal structures, providing spatial detail but limited spectral information from the retina (Bernardes, Serranho en Lobo 2011).

Hyperspectral imaging appropriates a three-dimensional dataset with two spatial dimensions and one spectral dimension. This provides information on tissue physiology, morphology and composition (Lu en Fei 2014). In biological tissue, this is interesting as it contains chromophores, i.e. substances that absorb light. Two important chromophores for visible light are melanin and haemoglobin (Lu en Fei 2014).

In ophthalmology, interest has begun to be shown in using the technique to measure the degree of oxygenation in the retina. Johnson et al reported how by comparing the spectral distribution of oxygenated and deoxygenated haemoglobin it was possible to visualize the degree of oxygenation in the retina (Johnson, et al. 2007). Similar type of maps have also been made by Geirsdottir et al using two wavelengths and not a whole wavelength spectrum to calculate retinal oxygenation. In several of

the reported studies, the investigations were made on healthy individuals but the hyperspectral imaging of the retina in patients with eye disease is still relatively unexplored. Retinal oximetry has been shown to distinguish healthy from early stage diabetic retinopathy patients (Safi, et al. 2018). Furthermore, Mordant et al found that for patients with open-angle glaucoma, the venous oxygenation rate was higher compared to the venous oxygenation rate in healthy individuals. For AS patients, it has been reported that machine learning was able to distinguish between individuals with clinical AD/biomarker-determined AD and healthy individuals using hyperspectral camera imaging (Lemmens 2020).

3.2. Justification

The justification for the chosen design of the investigational device and the clinical investigation is based on the question how is it possible to detect retinal ischemia and amyloid-β accumulation in the retina as quickly as possible in a non-invasive, pain-free, manner at the lowest possible cost for the benefit of a large population. When answering this question, the above-mentioned benefits under section 3.1 were taken into account.

The Mantis Photonics hyperspectral camera for non-invasive retinal examination is built to detect retinal ischemia and amyloid-β accumulation in the retina using a hyperspectral retinal scan, based on its wavelength-dependent effect on light scattering, in a quick non-invasive pain-free manner. Considering the intended use and the functioning of the investigational device, the choice of the target population for the clinical investigation is consequently justified: healthy persons and patients with an ophthalmological disease affecting the retina.

The set-up of the Mantis Photonics hyperspectral camera for non-invasive retinal examination is based on the provided requirements definition. In the design of the investigational device, as well in the context of the clinical investigation, several design choices were made to comply to the above requirements mentioned under section 2.1. Those justifications are described in the table below:

Component	Description	Justification	Requirement references
Commercial retinal camera	TopCon TRC 50 IX	Commercial camera with top-mounted external camera. Allows to comply to because this assures the operation is comparable to or equal to the operation of a commercial retinal scan camera.	REQ-MED-1 REQ-MED-4 REQ-MED-5 REQ-MED-6
Flash lamp	Flash lamp build into TopCon TRC 50 IX	Flash lamp is part of a certified retinal scan device and has been tested in clinical practice. The flash lamp has a known spectrum between 400 nm and 700 nm.	REQ-MED-1 REQ-MED-2 REQ-MED-3 REQ-HW-8 REQ-HW-9
CMOS camera sensor	Ximea MC124MG-SY-UB 3,0M NW3	Camera sensor for scientific purposes with API available to control camera from custom software. The sensor has an form factor that allows it to be built into the retinal camera set-up The sensor has a GPIO input that can register a TTL signal.	REQ-HW-1 REQ-HW-5 REQ-HW-6

Component	Description	Justification	Requirement references
Optical orifice	visible transmission grating, 600 lines per mm, 25x25mm	Required for the Mantis Photonics hyperspectral camera function as illustrated in Figure 1 and required in	REQ-HW-3
Microlens array	orthogonal (square) array, 148um pitch, 1.75mm focal length		
Optical grating			
Camera AC adaptor	MeanWell GSM60B24	Power the camera	REQ-HW-4
TTL connection cable		Allows to synchronize the camera exposure with the flash lamp	REQ-HW-6
Camera connection to laptop	USB cable		REQ-SW-3
Trigger box		Allows to synchronize the camera exposure with the flash lamp	REQ-SW-3
Banana adaptor		Allows to synchronize the camera exposure with the flash lamp while still allowing for debugging and adaptation work.	REQ-SW-3

3.3. Evaluation of clinical data

The collected clinical data can be grouped into several data sets based on their different data type (identification data and raw data on the photos) and the data quality.

3.4. Description of the clinical development stage

The clinical development stage of the Investigational device during the clinical investigation is the pilot stage. In this pilot stage, the limitations and advantages of the investigational device are evaluated. This stage includes first-in-human studies and feasibility studies.

4. Risks and clinical benefits of the investigational device and clinical investigation

4.1. Expected clinical benefits

The project of Mantis Photonics aims to investigate and refine the technique of hyperspectral imaging by photographing healthy retinas. Furthermore, Mantis Photonics also intends to examine people with diseases affecting the retina such as glaucoma, age-related yellow spot changes, diabetes as well as patients who have undergone retinal detachment surgery where the retina has been detached and compare diagnostic accuracy with other available techniques. Mantis Photonics believes that the current hyperspectral technique can provide detailed information about various disease-related conditions in the retina such as hemorrhages, ischemia, deposits but also provide early diagnosis of neurological diseases that cause changes in the retina, such as Alzheimer's disease. Improved diagnosis of these diseases may lead to better treatment options if they are detected at an earlier stage than today.

The clinical benefit of the investigational device for an individual is thus the early detection of a disease. An early detection of the presence of retina modification associated with a disease (e.g., Alzheimer's disease, dementia, diabetic retinopathy, glaucoma) may lead to an early diagnosis of (the risks of getting) the disease. An early diagnosis of (the risks of getting) a disease may result in prevention efforts and the reduction of potentially modifiable risk factors. Eventually, this means a positive impact on patient management or public health.

4.2. Anticipated adverse device effects

Mantis Photonics performed a risk analysis concerning the anticipated adverse investigation device effects. Some small anticipated adverse events resulting from insufficient or inadequate instructions for use, deployment, installation, operation or any malfunction of the investigational medical device are identified and described in the risk analysis report of Mantis Photonics. The severity and occurrence ranking of those identified and described adverse events are no unacceptable risks of harm to the subject, the administering investigator, nor third party involved in this investigational device when used under normal conditions and for its intended use.

4.3. Risks associated with participation in the clinical investigation

Mydriatic retinal scans are common procedures in ophthalmological practice. It can be considered a low-risk intervention due to its non-invasive nature. Subjects can experience some inconvenience by the flash light (e.g., pain and discomfort, redness, itching and/or blurriness), but this is not dangerous. Mantis Photonics consciously makes use of a commercial retinal camera set-up in which only the camera is replaced. This means that the subjects experiences, including the flash lamp are identical to the experience of tested and verified retinal scan devices.

A known risk of the mydriatic retinal scan procedure is the effect of the pupil dilating eye-drops. The glare effect causes the patient to be unfit to drive a vehicle for a period of about 4 hours. The effect ends after about 4 hours without lasting consequences.

Based on a risk assessment that Mantis Photonics performed, it can be concluded that for the investigational device (incl. the administration of the fluid eye drops of tropicamide 1% and phenylephrine hydrochloride 10%), there are no unacceptable risks of harm to the subject, the administering investigator, nor third party involved in this investigational device when used under normal conditions and for its intended use.

4.4. Possible interactions with concomitant medical treatments

There are no possible interactions with concomitant medical treatments identified in the risk analysis report performed by Mantis Photonics AB.

4.5. Steps to be taken to control or mitigate risks

The medical, nursing and other staff members of the investigation site will be trained on how to use the investigational device (incl. the administration of the fluid eye drops of tropicamide 1% and phenylephrine hydrochloride 10%) and subjects will be closely monitored during the clinical investigation.

AE's, ADE's, SAE's and DD's will be registered throughout the clinical investigation.

5. Objectives and hypotheses of the clinical investigation

5.1. The purpose of the clinical investigation

The clinical investigation is undertaken to investigate the performance of the hyperspectral camera for retinal non-invasive examination through the observation of retinal oxygenation.

5.2. Objectives

The primary objective and outcome variable are shown in the table below:

Primary objective	Primary outcome variable
To evaluate the performance of the hyperspectral camera for non-invasive retinal examination in order to improve the diagnosis of diseases affecting the retina or central nervous system.	Effectiveness of the hyperspectral imaging of retinal changes and retinal structures in terms of detecting: - Different structures of the retina based on spectral distribution. - Ability to measure the blood oxygenation with an acceptable repeatability - Demonstrate differences in blood oxygenation levels for healthy retinas; above 95% in arteries and below 70% in veins.

The secondary objective and outcome variable are shown in the table below:

Secondary objective	Secondary outcome variable
To investigate if additional signs of reduced oxygenation can be seen in retinal disease. More specifically, can optic nerve thinning be detected by hyperspectral camera? Can hyperspectral imaging detect changes that are not measurable with other examination modalities and do these differ from normal retinal changes?	Effectiveness of the hyperspectral imaging in terms of detecting: - Signs of reduced oxygenation be seen in retinal disease Ischemia detection in the retina. - Optic nerve thinning. - Changes that are not measurable with other examination modalities.

The safety objective and outcome variables are shown in the table below:

Safety objective	Safety outcome variable
To evaluate the safety of the hyperspectral camera for non-invasive retinal examination by assessment of device deficiencies and adverse events, non-serious and serious, rated for causality.	- Incidence of AE/ADE/SAE/SADE/DD. - Incidence of AE/ADE/SAEE/SADE/DD leading to withdrawal of a subject.

6. Design of the clinical investigation

6.1. General information

This single centre, open, controlled investigation will be conducted at the clinic of Sundets Ögonläkare, Helsingborg (patients and healthy subjects).

In this study, patients with known retinal oxygenation problems and volunteers without known or suspected retinal pathologies will be subjected to retinal scanning. The trial's aim is not to demonstrate any treatment effect between the treatment group and the control group. Thus, no control group is defined. The study objective is the demonstration of the feasibility and applicability of the technique.

6.2. Endpoints

All endpoints (i.e., outcomes) are summarized as above mentioned under section 5.1 and by visit.

6.3. Subjects

Inclusion criteria

For inclusion in the clinical investigation, the subject must fulfill all of the below criteria prior to enrollment and after enrollment (*i.e.,* screening phase and enrollment phase).

For inclusion in the investigation of patient-subjects:

1. Age > 18 years.
2. Ophthalmological disease, disorder, illness or problem.
3. Provision of informed consent i.e., subject must be able to understand and sign the patient information and consent form.

For inclusion in the investigation, the healthy subjects:

1. Age > 18 years.
2. Without known eye disease.
3. Provision of informed consent i.e., subject must be able to understand and sign the patient information and consent form.

Exclusion criteria

Subjects who meet any of the below criteria, during screening phase and/or enrollment phase) will be excluded from the investigation.

For the exclusion of patients-subjects:

1. Patients with narrow-angle glaucoma.
2. Inclusion in other ongoing investigations at present that would preclude the subject from participating in this investigation as judged by the Principal Investigator.

For the exclusion of healthy subjects:

1. Presence of eye disease, eye trauma, diabetes or pregnancy.
2. Inclusion in other ongoing investigations at present that would preclude the subject from participating in this investigation as judged by the Principal Investigator.

Subject eligibility

Once written informed consent has been obtained, the Case Report Form and Subject prescreening and screening log will be completed to document adherence to the inclusion and exclusion criteria.

Where a subject fails to fulfil any element of the inclusion and exclusion criteria, this will be documented and the signed consent form and completed inclusion/exclusion criteria retained by the Principal Investigator. The subject will not be advanced any further into this clinical investigation.

Subject identification

When a subject is identified and considered eligible for entry to this clinical investigation, the subject will be allocated the next available investigation number (i.e. enrolment number) and the enrolment of the patient must be recorded in the Subject Enrolment Identification log.

For subjects enrolled, this number will consist of 01 for the first subject, 02 for the second subject and so on. This number will be the unique identifier of the subject (*i.e.* enrolment number) and written on each page of the paper/electronic Case Report Form booklet and all other documentation relating to that subject.

Each subject that is enrolled into the study will have their study participation recorded in their medical records, a copy of their signed and dated consent form and a patient information sheet should also be placed on his patient files to identify the subject as participating in a clinical investigation.

Investigation population

The investigation population are healthy persons and patients (120 subjects in total).

Approximately 100 male or female subjects, 18 years or older, with an ophthalmological disease, disorder, illness or problem will be recruited in this investigation.

Approximately 20 healthy male or female subjects, 18 years or older, will be recruited in this investigation.

The investigation population is not a *vulnerable population* as described by GCP.

Criteria and procedures for subject withdrawal or discontinuation

Subjects are free to discontinue participation in the clinical investigation at any time, and without prejudice to further treatment. Subjects who discontinue the clinical investigation should always be asked about the reason(s) for their discontinuation and about the presence of any AE/ADE or DD and, if possible, be assessed by an investigator. AE/ADE should be followed up. Subjects will be informed clearly they have no obligation to give a reason for discontinuation or to answer other questions.

Subjects may be withdrawn from clinical investigation at any time, at the discretion of the investigator.

Incorrectly enrolled subjects will be withdrawn from further clinical investigation. A subject may, however, continue the investigation under special circumstances (i.e., if continuation of investigation or follow-up actions are necessary for the subject's safety and well-being, and the continuation of the investigation is not expected to be associated with any risk or discomfort for the subject).

When a subject redraws or is discontinued from the research, the subject recruitment continues until the defined number of both patient and healthy subjects are maintained in the study dataset.

6.4. Description of the clinical procedures and methods relating to the clinical investigation

Recruitment of healthy subjects is done through local advertising. Recruitment of patient-subjects with eye disease is done at the clinic Sundets Öganläkare.

Coordinated registration and allocation of participant trial numbers will be required to enroll all participants (see section 6.3). The Principal Investigator ensures through the Informed Consent Form that the trial objective, process and all trial subject rights are clear to the subject.

All participants (healthy subjects and patient-subjects) are considered to be enrolled into the clinical trial following the informed consent is signed, the evaluation of the medical history and the inclusion criteria, confirmation of eligibility, completion of the registration, allocation of the participant trial number and the investigation performance phase.

The overall purpose is to investigate if the investigational device can produce clear hyperspectral imaging of retinal changes by detecting structures and conditions in the retina and to compare the hyperspectral imaging with the expert diagnosis, as well as to investigate if additional signs of reduced oxygenation can be seen in retinal disease.

The admission visit (visit 1) is carried out as planned with visual acuity, refraction, pressure, field of view (if applicable), OCT and corneal microscope examination. Records of age and sex, other diseases and treatment are obtained. The subject will be administered pupil dilating drops of tropicamide 1% and phenylephrine hydrochloride 10% are instilled in each eye at the time of the examination. Images of the retina of the subject will be taken with the use of the Mantis Photonics hyperspectral camera by the medical staff members at the investigational site. The subjects are usually sent home after the image is taken when there are no inconveniences for the subjects.

The overview of the clinical investigation provides a review of each visit describing clinical investigation-related procedure(s) the subject undergoes during each visit:

Procedure	Visit 1 - part 1 Admission & screening phase	Visit 1 - part 2 Application of the investigation device phase	Visit 1 - part 3 End phase
Informed consent	x		
Inclusion/exclusion criteria	x		
Medical history review	x		
Eligibility	x		
Administration of eye drops and flashlight taking image		x	
Adverse Events review		x	x
Clinical investigation end			x

After the phases above, the retinal images are taken and analyzed. Researchers such as (Meinke 2007) have demonstrated how one can estimate the blood oxygenation at a given location (image pixel) based on the frequency absorbance spectrum. The reference frequency absorbance spectrum of fully oxygenated blood (100% oxygenation) and fully oxygen-depleted blood (0% oxygenation) are known and tabulated by comparing the pixel's frequency spectrum to the frequency absorbance spectrum of two reference curves allows us to estimate the oxygenation of the blood at the respective location.

We will compare oxygenation between arteries and veins. The largest artery and vein at the superior and the inferior temporal vascular tree will be marked for each eye. We will analyze 10 to 20 consecutive points from the papillary edge along the vascular tree to measure the mean vessel oxygenation level and the evolution of the oxygenation level. The initial image analysis can be followed by machine learning to distinguish between a normal retina and a retina affected by a disease (the ophthalmologist's diagnosis can be taken as ground truth).

6.5. Timeline of the clinical investigation

The prefixed time schedule for the Investigation is as follows:

- August 2022: putting equipment in place.
- October-November2022: recruiting healthy subjects.
- December 2022-February 2023: analyse the data from healthy subjects.
- October-December 2022: recruiting patients with eye disease.
- January-March 2023: analysing all data.

- April 2023 - February 2024: compiling and evaluating results.
- March 2024- July 2024: writing, submitting and revising a scientific article.

The Sponsor and Principal Investigator will notify the Swedish Medical Products Agency (Läkemedelsverket) within 15 days after end of the clinical investigation and the Sponsor will send the clinical investigation report within 1 year after the end of the clinical investigation including an easily understandable summary.

6.6. Monitoring plan

The clinical investigation will be monitored by a Sponsor representative before the clinical investigation begins, during the clinical investigation conduct, and after the clinical investigation has been completed, so as to ensure that the clinical investigation is carried out according to the CIP, the relevant laws and regulations and the rules of Good Clinical Practice (GCP) and that data is collected, documented, and reported according to EN-ISO 14155:2020 and applicable ethical and regulatory requirements. The document LU_LR_56_A Trial Monitoring Plan describes this.

The Sponsor will schedule the monitoring visits with advance notice and confirm the scheduling of the visit with the investigation site. The Sponsor representative should meet with the Principal Investigator at each monitoring visit.

The Principal Investigator and its representative staff members and the institution site will permit investigation-related monitoring, audits, and regulatory inspection(s), providing direct access to source data/documents to the Monitor. The subjects are informed of this during the informed consent discussion. The Monitor will sign a confidentiality agreement before receiving access to the medical records of the study subjects.

The monitoring is intended to ensure that the subject's rights, safety, and well-being are met as well as data in the CRF are complete, correct, and consistent with the source data.

At the conclusion of the monitoring visit, the Sponsor representative shall write a monitoring report detailing the activities performed during the visit with recommendations for action items and study site action. A follow-up letter to the study site detailing these recommendations and actions will be sent to the Principal Investigator.

The monitoring is intended to ensure that the subject's rights, safety, and well-being are met as well as data in the CRF are complete, correct, and consistent with the source data.

7. Statistical Considerations

7.1. Presentation of the data

The results from this open, controlled clinical investigation will be presented with descriptive statistics. No hypothesis testing is planned for this investigation.

Data listings will be prepared for all data. Certain data will be collated into summary tables and figures. Those summary tables and figures will be integrated into investigation reports.

7.2. Population for analysis

Safety Population

The population for the assessment of safety will include all enrolled subjects who provide at least the investigation performance phase (visit 1 - part2).

PP population

The Per Protocol (PP) population will include all subjects without significant protocol violations. Subjects identified as protocol violators will be documented and agreed upon before declaration of clean-file.

Population size

An estimated 120 people will be recruited for the study:

- Approximately 100 male or female subjects, 18 years or older, with an ophthalmological disease, disorder, illness or problem will be recruited in this investigation.
- Approximately 20 healthy male or female subjects, 18 years or older, will be recruited in this investigation.

7.3. Baseline characteristics

All variables measured at baseline will be summarized for the PP population using appropriate summary statistics.

7.4. Performance and safety measurement

All endpoints will be summarized as above and by visit. The result from the CRF will be summarized appropriately for all evaluable subjects. The number of subjects reporting one or more adverse events during the course of the investigation will be summarized using frequency counts.

7.1 Determination of sample size - sample size calculation

This is a descriptive investigation and the number of subjects has been chosen to be able to find explorative trends.

8 Data management

The data management includes all activities related to data handling regarding:

Set-up of CRF and database.

If necessary, specification of online checks.

Data entry / data editing.

Export of data.

Creation of post-entry checks and listings.

Reconciliation of SAE, SADE, ADE and DD.

Measures implemented to ensure confidentiality of the records and personal data of subjects.

Measures implemented in case of data security breach.

All data will be registered, managed, and stored in a manner that enables correct reporting, interpretation, and verification.

Subjects who participate in the clinical investigation are coded with a specific clinical investigation identification number (i.e., subject ID). All subjects are registered in a subject identification list (subject enrolment and identification list) that connects the subject's name and personal number with a clinical investigation identification number.

8.1 Case Report Form

The handling of all data on the CRFs will be the responsibility of the Principal Investigator.

It will be the responsibility of the Principal Investigator to ensure the accuracy of all data entered in the CRFs. The delegation log will identify all those staff members with responsibilities for data collection and handling, including those who have access to the trial database.

The Principal Investigator will be responsible for timely data entry, accuracy and completeness of a CRF for each individual subject. The personal data recorded on all documents will be regarded as confidential.

The Principal Investigator must record the subject's participation in this clinical investigation in the subject's patient files. In addition, the Principal Investigator must keep a separate list of all subjects entered into the clinical investigation showing each subject's name, date of birth and assigned subject number (for identification purposes).

Photos are marked with the subject ID. The photos shall not contain any information that can reveal the identity of the subject.

The CRFs will not bear the subject's name or other personal identifiable data. The subject's initials, date of birth and trial identification number, will be used for identification.

The Principal Investigator will make the original CRF's available to the Sponsor's designated monitor at each visit. At the conclusion of the clinical investigation, completed CFR's will be signed by the Principal Investigator and the original CFR's will be left with the Principal Investigator.

8.2 Archiving

The Principal Investigator and the Sponsor will maintain the essential clinical investigation documents in the investigation site files archive and sponsor files archive, respectively. The Sponsor shall keep all documentation and data for at least 10 years after the clinical investigation has ended. The Principal Investigator will archive all local investigation documentation for at least 10 years or as long as stipulated by the law.

8.3 Data protection

If any part of the data is handled by any other organization, inside or outside the European Union, appropriate agreements and/or other documentation will be established, to ensure that the data processing is performed in accordance with the provisions of the General Data Protection Regulation (EU ordinance 2016/679, GDPR) and other relevant legislation, before any data transfer takes place.

The content of the informed consent form shall comply with relevant integrity and data protection legislation. In the subject information and the informed consent form, the subject will be given complete information about how collection, use and publication of their clinical investigation data will take place.

All information processed by the Sponsor will be anonymized. As stated in 8.1, the images and metadata will be labelled only with the subject ID, which cannot be traced back to the subject identity.

The informed consent form will also explain that for verification of the data, authorized representatives of the Sponsor, as well as relevant authority, may require access to parts of medical records or study records that are relevant to the clinical investigation, including the subject's medical history.

9 Amendments to the CIP

Amendments to the CIP will be agreed upon between the Principal Investigator and the Sponsor. Substantial modifications must be approved by the Swedish Ethical Review Authority and/or Swedish Medical Products Agency (Läkemedelsverket) before implementation.

10 Deviations from the CIP

The Principal Investigator and their staff members are not allowed to deviate from the CIP except if it is for the protection of the subject´s rights, safety, or well-being under emergency circumstances.

All such deviations shall be logged and documented in the protocol deviation log and reported to the Sponsor, Swedish Medical Products Agency (Läkemedelsverket) and/or the Swedish Ethical Review Authority as soon as possible (with a maximal delay of 2 weeks).

All deviations shall be documented with an explanation and reported to the Sponsor. Deviations will be reviewed by the Sponsor and reported to the appropriate regulatory bodies as required. When repeated deviations from the CIP are reported, the Sponsor will discuss corrective actions with the Principal Investigator.

11 Device traceability and accountability

The investigational device(s) will only be used in the clinical investigation and according to the Clinical investigation Plan. All investigational device(s) will be labelled *«For clinical investigation use only»* on the packaging as well as on the device. The Sponsor provides the site with written instructions and technical support.

The Principal Investigator will keep records to document the physical location of the investigational device from shipment to return/disposal. This record should include: name(s) of clinical investigation personnel who received, used, returned, or disposed the device, the date of receipt, identification and quantity of each investigational device (batch number/serial number or unique code), the date or dates of use, subject study-ID, malfunctioning investigational device.

11.1 Compliance to the investigational plan, good clinical practice, and regulations

The clinical investigation will be conducted in accordance with the Clinical Investigation Plan, the ethical principles of the Declaration of Helsinki, the principles of EN-ISO 14155:2020 and current national and international regulations governing this clinical investigation. This is to ensure the safety and integrity of the subjects as well as the quality of the data collected.

11.2 Ethical review of the clinical investigation

The clinical investigation will commence when written approval/favorable opinion from the Swedish Ethical Review Authority (Läkemedelsverket) and the Ethical Review Authority (Etikprövningsmyndigheten) has been received and confirmation of validity has been received from the Swedish Medical Products Agency.

The Swedish Ethical Review Authority and the Swedish Medical Products Agency must be informed of any changes in the CIP in accordance with the current requirements.

11.3 Insurance

Sponsor has an applicable insurance to cover the clinical investigation in compliance with local legal requirements.

Underwriters: Lloyd’s Insurance Company S.A.

Policy No:MCIEEA22003

Type: No Fault Compensation Insurance For Clinical Trials And/Or Human Volunteers Studies

12 Informed consent process

12.1 General process for informed consent

The Principal Investigator shall ensure that the subject is given full and adequate oral and written information about the clinical investigation, its purpose, any risks and benefits as well as inclusion and exclusion criteria. Subjects must also be informed that they are free to discontinue their participation in the clinical investigation at any time without having to provide a reason. Subjects shall be given the opportunity to ask questions and be allowed time to consider the provided information and participation in the clinical investigation. If the person chooses to participate, both the subject and the Investigator shall sign the informed consent form. A copy of the subject information as well as a copy of the informed consent form shall be provided to the subject. The subject's signed and d informed consent must be obtained before performing any activity specific to the clinical investigation.

The process shall be documented in the subject's source documents and the signed informed consents shall be maintained with the essential documents. If new information becomes available that can significantly affect a subject's future health and medical care, that information shall be provided to the affected subject(s) in written form. If new information is added to the clinical investigation, the subject has the right to reconsider whether he/she will continue their participation.

13 Adverse events, adverse device effects and device deficiencies

13.1 Definitions

13.1.1 Adverse Event

An Adverse Event (AE) is untoward medical occurrence, unintended disease or injury or any untoward clinical signs, including an abnormal laboratory finding, in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the investigational device.

This definition includes events that are anticipated as well as unanticipated events.

This definition includes events occurring in the context of a clinical investigation related to the investigational device or the procedures involved.

13.1.2 Adverse Device Effect

An Adverse Device Effect (ADE) is any AE related to the use of an investigational medical device.

This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.

This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

13.1.3 Serious Adverse Event

A Serious Adverse Event (SAE) is any AE that led to any of the following:

a) death;

b) serious deterioration in the health of the subject, that resulted in any of the following:

i. life-threatening illness or injury,

ii. permanent impairment of a body structure or a body function,

iii. hospitalization or prolongation of patient hospitalization,

iv. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,

v. chronic disease,

c) fetal distress, fetal death or a congenital physical or mental impairment or birth defect.

13.1.4 Serious Adverse Device Effect

A Serious Adverse Device Effect (SADE) is an ADE that has resulted in any of the consequences characteristic of a serious adverse event.

SAE's related to procedures imposed by the Clinical Investigation Plan but not with the use of the device shall not be considered Serious Adverse Device Effects.

13.1.5 Unanticipated Serious Adverse Device Effect

An unanticipated SADE is an effect which by its nature, incidence, severity or outcome has not been identified in the current risk assessment. Procedures associated with the use of a device shall be addressed in the risk assessment, which makes it possible to determine whether the procedure related SAE's are Unanticipated Serious Adverse Device Effect or not. SAE's related to procedures imposed by the Clinical Investigation Plan but not with the use of the device shall not be considered Serious Adverse Device Effects.

For the anticipated adverse device effects, see above.

13.1.6 Device Deficiency

A Device Deficiency (DD) is any inadequacy in the identity, quality, durability, reliability, safety or performance of an investigational device, including malfunction, use errors or inadequacy in information supplied by the manufacturer.

Analysis of potential Device Deficiencies was done through document LU_LR_49_A_Final FMEA.

13.2 Recording and Reporting

13.2.1 Recording

The Principal Investigator or an authorized designee will record:

- All AE's.
- all SAE's.
- all DD's.
- any new finding in relation to any of the above-mentioned events.

13.2.2 Reporting

The Principal Investigator will report all SAE's and DD's to the Sponsor, immediately but not later than 3 calendar days after investigation site study personnel's awareness of the event.

The Sponsor will report to the Swedish Medical Products Agency all of the following reportable events:

any SAE that has a causal relationship with the investigational device, or the investigation procedure, or where such causal relationship is reasonably possible;

any DD that might have led to a SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate; and

any new findings in relation to any event referred to above.

Reporting by the Sponsor will be done by filling out the "Summary Reporting Form" (MDCG 2020-10/2). The form will be filled in/updated for each reportable event or for new findings/updates to already reported events. The form will be transmitted to the Swedish Medical Products Agency. For events that indicate an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients/subjects, users or other persons or a new finding to it will be reported immediately, but not later than 2 calendar days after awareness by the Sponsor of a new reportable event or of new information in relation with an already reported event. Any other reportable events or a new finding/update to it will be reported immediately, but not later than 7 calendar days following the date of awareness by the Sponsor of the new reportable event or of new information in relation with an already reported event.

13.2.3 Assessment of Causality

The relationship between each adverse event and the investigational device and the investigation procedure will be assessed and recorded by the Principal Investigator and the Sponsor. For assessment of causality, the risk analysis report will be consulted. The Sponsor and the Principal Investigator will distinguish between SAE's related to the investigational device and those related to the procedures, relatedness to both is possible.

Each AE and SAE will be classified according to four different levels of causality:

1. Not related

   Relationship to the device or procedures can be excluded when:

   the event has no temporal relationship with the use of the investigational device, or the procedures related to application of the investigational device;

   the SAE does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;

   the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible - and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious adverse event;

the event involves a body-site or an organ that cannot be affected by the device or procedure;

the SAE can be attributed to another cause (e.g., an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);
the event does not depend on a false result given by the investigational device used for diagnosis, when applicable;

In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the SAE.

2. Possibly related to the investigation
The relationship with the use of the investigational device or the relationship with procedures, is weak but cannot be ruled out completely. Alternative causes are also possible (e.g., an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed, or no information has been obtained shall also be classified as possible.

3. Probably related to the investigation
The relationship with the use of the investigational device or the relationship with procedures, seems relevant and/or the event cannot be reasonably explained by another cause.

4. Causal relationship with the investigation
The AE or SAE is associated with the investigational device or with procedures beyond reasonable doubt when:
the event is a known side effect of the product category the device belongs to or of similar devices and procedures;

the event has a temporal relationship with investigational device use/application or procedures;

the event involves a body-site or organ that:

   - the investigational device or procedures are applied to;
   - the investigational device or procedures have an effect on;

- the serious adverse event follows a known response pattern to the medical device (if the response pattern is previously known);

- the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the SAE (when clinically feasible);

- other possible causes (e.g., an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
- harm to the subject is due to error in use.

In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the SAE.

14 Premature termination of the clinical investigation

The Sponsor may suspend or prematurely terminate either the clinical investigation at an individual investigation site or the entire clinical investigation for significant and documented reasons. The Läkemedelsverket (Swedish Medical Products Agency) may suspend or prematurely terminate the clinical investigation at the applicable investigation sites.

If suspicion of an unacceptable risk to subjects arises during the clinical investigation, or when so instructed by the Swedish Medical Products Agency, the Sponsor will suspend the clinical investigation while the risk is assessed. The Sponsor will terminate the clinical investigation if an unacceptable risk is confirmed. The Sponsor will inform the Principal Investigator.

The Sponsor shall consider terminating or suspending the participation of a particular investigation site or the Principal Investigator in the clinical investigation if monitoring or auditing identifies serious or repeated deviations on the part of an Investigator. If the suspension or premature termination was in the interest of safety, the Sponsor shall inform all other Investigators.

If, in the opinion of the Principal Investigator, the clinical observations in the clinical investigation suggest that it may be unsafe to continue the investigation at the site, the Principal Investigator may terminate participation in the investigation after consultation with the Sponsor. A written statement fully documenting the reasons for such termination will be provided to the Sponsor. If the clinical investigation is prematurely terminated, the Principal Investigator shall promptly inform the subjects and take necessary steps to finalize their engagement in the clinical investigation. All relevant investigation material must be collected, and accountability completed.

If the clinical investigation is interrupted or terminated prematurely the Sponsor will report to the Swedish Medical Products Agency within 15 days together with a justification. If the Sponsor has temporarily halted or prematurely terminated the clinical investigation on safety grounds, the Swedish Medical Products Agency will be informed within 24 hours. A clinical investigation report will be prepared within three months of the early termination or temporary halt, irrespective of the results. In the event that the clinical investigation is restarted within three months of the temporary halt, the Sponsor does not have to submit a clinical investigation report until the clinical investigation has been completed.

15 Publication policy

The clinical investigation will be registered in a publicly accessible database (https://trialsearch.who.int) before the start of recruitment activities and the content will be updated throughout the conduct of the clinical investigation and the results entered at completion of the clinical investigation.

The contractual obligations between Sponsor and Principal Investigator and/or investigation site are described in a detailed manner in the clinical investigation agreement.

The Principal Investigator and the Sponsor will distribute the results of the investigation through academic publication.

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Appendix 1: Financial conditions

Parties agreed on the following responsibilities:

Mantis Photonics AB is responsible for designing, building, installing and maintaining the research prototype. The device will be moved to the main location of Sundets Ögonläkere by Mantis Photonics and installed in location. Mantis Photonics will not invoice any costs to the other parties for these actions and responsibilities.

As described in the CIP, the Subject is guided by Sundets Ögonläkare ophthalmologist Madeleine Selvander. The Subject will be introduced to and explained the informed consent document. After obtaining consent form to perform the retinal eye exam after being guided for the Subject, ophthalmologist Madeleine Selvander will perform the retinal scan with the research prototype provided by Mantis Photonics AB. Sundets Ögonläkare will invoice 50 SEK per patient for these actions and responsibilities additional to demonstratable costs such as patient transportation reimbursement and costs for communication and patient recruitment. Madeleine Selvander makes her time and expertise available to Mantis Photonics as part of her involvement with Mantis Photonics as a board member and shareholder.

Parties agree the listed compensations are fair and reasonable compensation.

1. The Parties declare that the agreement is in reasonable proportion to the services provided and have agreed no other financial compensation from the Sponsor other than the agreements referred to in this Agreement.

2. If any increase in compensation due for the conduct of the study is necessary or appropriate, the Parties shall negotiate further remuneration, and the Sponsor shall provide a written notice in the form of a budget increase letter. This includes an increase in the amount of Subjects to be enrolled, and if amendments are made to the CIP which result in increased cost for the Institution/Site.