Clinical Investigation Plan (CIP)

Investigation of retinal pathology in Eye Diseases using High Resolution Optical Coherence Tomography (High-Res-SD-OCT)

Type of investigation:	Clinical investigation concerning medical devices (MD).
Categorisation:	Clinical trial with medical devices (according to ClinO-MD), Category A, Subcategory A1
Registration:	Swiss National Clinical Trials Portal (SNCTP) 2021-D0038
Identifier:	HighResOCT
Principal Investigator and Sponsor, or Sponsor-Investigator:	Prof. Dr. Dr. Martin Zinkernagel Universitätsklinik für Augenheilkunde Inselspital CH-3010 Bern Telefon 031 632 25 01
Sponsor representative (if the Sponsor is not located in Switzerland)	Not applicable
Medical Device:	SPECTRALIS® High-Res OCT- DMR001
CIP Version and Date:	Version 1.2, 07. October 2021

Signature Page(s)

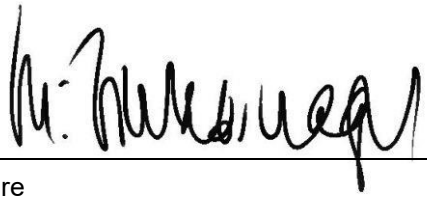
Complete the signature pages with name and title of the person(s) authorised to sign the CIP and the CIP amendment(s): Sponsor, medical expert, Principal Investigator responsible for conducting the investigation, Statistician.

Add more lines, functions and pages as needed.

ID number of the investigation:	HighResOCT Registry and registration number (to be filled in once available, in any case before the start of the investigation).
Title:	Investigation of retinal pathology in Eye Diseases using High Resolution Optical Coherence Tomography (High-Res-SD-OCT)

The Sponsor, the Principal Investigator and the Statistician have approved the CIP version 1.2, 07.10.2021, and confirm hereby to conduct the investigation according to the CIP, the current version of the World Medical Association Declaration of Helsinki, ISO14155 norm, ICH-GCP as far as applicable, and the local legally applicable requirements.

Sponsor-Investigator:



Bern07. October 2021	
Place/Date	Signature

Statistician

Bern, 07. October 2021	
Place/Date	Signature

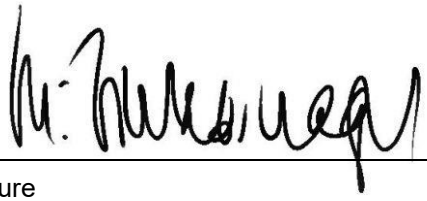
Principal Investigator at the local investigational site*:

I have read and understood this CIP version 1.2, 07.10.2021, and agree to conduct the investigation according to the CIP, the current version of the World Medical Association Declaration of Helsinki, ISO14155 norm, ICH-GCP as far as applicable, and the local legally applicable requirements.

Site:	Universitätsklinik für Augenheilkunde, Inselspital, Bern
Principal investigator at the local investigational site:	Prof. Dr. Dr. Martin Zinkernagel

Bern, 01. October 2021

Place/Date



Signature

*Note: In multicentre investigations, this page must be individually signed by all participating Local Principal Investigators.

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SYNOPSIS

Sponsor / Sponsor-Investigator	Professor Martin Zinkernagel, MD, PHD
Title:	Investigation of Retinal Pathology in Eye Diseases using High Resolution Optical Coherence Tomography (High-Res-OCT)
Short title / Investigation ID:	HighResOCT
Clinical Investigation Plan, version and date:	Version 1.2, 07. October 2021
Registration:	The clinical trial is registered in the Swiss National Clinical Trial Portal (2021-D0038) and will be registered on the platform clinicaltrial.gov
Category and its rationale:	Clinical trial with a CE certified medical devices (according to ClinO-MD), Category A, Subcategory A1
Name of the MD, Unique Device Identification (UDI), name of the manufacturer	SPECTRALIS® High-Res OCT- DMR001 Software Version SP-X1904, Article No. 230346-003 INT.AE21 © Heidelberg Engineering GmbH
Stage of development:	Post market stage. The clinical investigation is not conducted for a conformity assessment purpose.
Background and rationale:	The high resolution optical coherence tomography (High-Res-OCT) is an improvement of a non-invasive routinely used imaging technique, the optical coherence tomography (OCT), with a light-source capable of providing an increased axial resolution. The routinely used Spectral-Domain OCT has a center wavelength of 880 nm and a spectral bandwidth of 40 nm, resulting in an axial resolution of approximately 7 µm in the eye and is used routinely worldwide [14],[15]. The High-Res OCT works with a central wavelength of 840 nm and an increased bandwidth of 130 nm, making it possible to improve the optical axial resolution in tissue from 7 to 3 µm, without increasing the maximum laser exposure limit. The improved axial resolution of the High-Res OCT results in clearer and more detailed images. At present, level 1 evidence of the technology's clinical applications doesn't exist, however the technique is routinely used in clinical practice and the device used for High-Res-OCT (Heidelberg, SPECTRALIS® High-Res OCT- DMR001) has received CE mark approval in March 2021. We plan to compare High-Res-OCT as an imaging modality to conventional imaging modalities used in clinical routine, such as the Spectral-Domain-OCT (SD-OCT)
Objective(s):	Comparison of High-Res-OCT to conventional imaging modalities for the diagnosis of eye diseases

Outcome(s):	The primary objective of this observational study is to evaluate the sensitivity and specificity to diagnose retinal pathologies and vascular abnormalities with High-Res- OCT compared to conventional imaging methods. The main parameters, which will be assessed are the presence of morphological abnormalities (such as but not limited to intraretinal or subretinal fluid, epiretinal membrane, substance defect, drusen, hyperreflective foci, atrophy, neovascularization, choroid abnormalities, scars, ischemia) within the macula and optic nerve head. The incidence (binary) and diagnostic accuracy of these morphological abnormalities will be assessed in High-Res-OCT and compared to conventional imaging methods such as SD-OCT. Secondary endpoints: -Evaluation whether pathological changes seen in SD-OCT or color fundus photography correlate with changes seen in High-Res-OCT - Subgroup analysis will be performed with patients suffering from diabetic retinopathy, artery and vein occlusion, retinal detachment, glaucoma, optic nerve neuropathy, hereditary retinal diseases, age related macular degeneration, retinal changes from arterial hypertension and uveitis. -Evaluation of the intra-and inter-reader reproducibility in the diagnosis (binary) using High-Res-OCT and investigation for age dependent changes in High-Res-OCT - Evaluation of the inter-reader reproducibility in healthy subjects with High-Res-OCT
Design:	Prospective clinical trial with a CE certified medical device
Inclusion / exclusion criteria:	Inclusion criteria: Patients from the Department of Ophthalmology, University Hospital Bern requiring conventional imaging for eye disease and willing to sign informed consent Patients of 18 years or older **<u>Exclusion criteria:</u>** Patients not willing or able to sign informed consent Patients younger than 18 years Patients with epilepsy
Measurements and procedures:	Acquisition of retinal images with a CE certified high resolution optical coherence tomography (High-Res-OCT)
Intervention:	The acquisition of retinal images will be performed according to the routine indications for performing an OCT and provided by a senior clinician in patients who have previously given their consent. The acquisition time and procedure does not differ from the standard SD-OCT.
Control intervention (if applicable):	Conventional ophthalmic imaging including optical coherence tomography, fluorescein angiography and color fundus photography.

Number of subjects with rationale:	550 subjects Healthy subjects: 100 Subgroup analysis will be performed with patients suffering from the following eye diseases: Diabetic retinopathy; approximately 50 patients Artery and vein occlusion; approximately 50 patients Glaucoma; approximately 50 patients Optic nerve neuropathy; approximately 50 patients Hereditary retinal diseases; approximately 50 patients Retinal detachment; approximately 50 patients Age related macular degeneration; approximately 50 patients Retinal changes from arterial hypertension; approximately 50 patients Uveitis ; approximately 50 patients The primary variable for this assessment is the ability to detect the presence of retinal structural abnormalities with High-Res-OCT in comparison to conventional ophthalmic imaging methods, mainly SD-OCT. This will result in a binary outcome. Assuming that the accuracy of each of these conventional imaging modalities separately is 90%, and there is truly no difference between the conventional imaging and High-Res-OCT (null hypothesis), then 550 patients are required to be 90% sure that the upper limit of a one-sided 95% confidence interval (or equivalently a 90% two-sided confidence interval) will exclude a difference in favour of the conventional imaging of more than 10% [16]. The results will be displayed using a receiver operating characteristic (ROC), or ROC curve. The curve is created by plotting the true positive rate (TPR) against the false positive rate (FPR) at various threshold settings. Here the required total sample size for estimating sensitivity (presence of the pathological changes within the scans) with respect to marginal error (0.03), sensitivity (90%) and the prevalence (0.9) of disease in target population would be approximately 550 subjects [17]. Subgroup analysis will be performed with patients suffering from diabetic retinopathy, artery and vein occlusion, glaucoma, optic nerve neuropathy, hereditary retinal diseases, retinal detachment, age related macular degeneration, retinal changes from arterial hypertension and uveitis. In order to compare these groups with conventional imaging and controlling for some degree of variation due to age, we estimate a group size of approximately 50 patients and 100 healthy subjects.
Duration of the investigation:	Last participant processed and finishing the study : 30.11.2023
Investigation schedule:	31.October 2021 30. November 2023

Investigator(s):	Prof. Dr. Dr. Sebastian Wolf Prof. Dr. Dr. Martin Zinkernagel Prof. Dr. Marion Munk Dr. Lieselotte Berger PhD. Dr. Chantal Dysli Dr. Souska Sophie Zandi Oussama Habra Virgilia Henchoz Universitätsklinik für Augenheilkunde Inselspital CH-3010 Bern Telefon 031 632 25 01
Investigational Site(s):	Single center study at Universitätsklinik für Augenheilkunde Inselspital, Bern
Statistical considerations:	The primary variable for this assessment is the ability to detect retinal morphological changes with High-Res-OCT in comparison to conventional ophthalmic imaging methods such as OCT, color fundus photography and fluorescein angiography. This will result in a binary outcome. Assuming that the accuracy of each of these conventional imaging modalities separately is 90%, and there is truly no difference between the conventional imaging and High-Res-OCT, then 550 patients are required to be 90% sure that the upper limit of a one-sided 95% confidence interval (or equivalently a 90% two-sided confidence interval) will exclude a difference in favour of the conventional imaging of more than 10% [16,17]. Subgroup analysis will be performed to differentiate different disease entities using non-parametric test with a significance level of 0.05. Descriptive analyses will evaluate demographic data as well as visual acuity data separately for each group of patients. Subgroup analysis will be performed with patients suffering from diabetic retinopathy, artery and vein occlusion, optic nerve neuropathy, glaucoma, retinal detachment, age related macular degeneration, retinal changes from arterial hypertension and uveitis. In order to compare these groups with conventional imaging and controlling for some degree of variation due to age, we estimate a group size of approximately 50 patients and 100 healthy subjects.
Compliance statement:	This investigation will be conducted in compliance with the CIP, the current version of the Declaration of Helsinki, ISO14155, ICH-GCP (as far as applicable) as well as all national legal and regulatory requirements.

ABBREVIATIONS

Provide a list of abbreviations used in the CIP – to be completed/adapted

AE	Adverse Event
ADE	Adverse Device Effect
ASADE	Anticipated Serious Adverse Device Effect
ASR	Annual Safety Report
CEC	Competent Ethics Committee
CIP	Clinical investigation plan
ClinO	Ordinance on Clinical Trials in Human Research *(in German KlinV, in French Oclin, in Italian OSRUm)*
ClinO-MD	Ordinance on Clinical Trials with Medical Devices *(in German: KlinV-Mep, in French: Oclin-Dim, in Italian: OSRUm-Dmed)*
CRF	Case Report Form (pCRF paper CRF; eCRF electronic CRF)
DD	Device Deficiency
DMC / DSMC	Data Monitoring Committee, Data Safety Monitoring Committee
FPR	false positive rate
Ho	Null hypothesis
H1	Alternative hypothesis
High-Res-OCT	High-Resolution Optical Coherence Tomography
HRA	Federal Act on Research involving Human Beings *(in German: HFG, in French: LRH, in Italian: LRUm)*
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH-GCP	International Council for Harmonisation – guidelines of Good Clinical Practice
IFU	Instruction For Use
ISF	Investigator Site File
ISO	International Organisation for Standardisation
ITT	Intention to treat
MedDO	Medical Devices Ordinance *(in German: MepV, in French: Odim, in Italian: Odmed)*
MD	Medical Device
MDR	Medical Device Regulation (EU) 2017/745 of 5 April 2017
OCT	Optical Coherence Tomography
PI	Principal Investigator
ROC	receiver operating characteristic
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SDV	Source Data Verification
SD-OCT	Spectral-Domain Optical Coherence Tomography
SNCTP	Swiss National Clinical Trials Portal
SOP	Standard Operating Procedure
TPR	true positive rate
USADE	Unanticipated Serious Adverse Device Effect

SUMMARY OF THE REVISION HISTORY IN CASE OF AMENDMENTS

Version Nr, Version Date	Chapter	Description of change	Reason for the change

INVESTIGATION SCHEDULE

Study with a CE certified medical device. First patient in anticipated in October 2021, last patient in anticipated in November 2023.

1. INVESTIGATION ADMINISTRATIVE STRUCTURE

1.1 Sponsor-Investigator

Professor Dr. med. Martin Zinkernagel, Universitätsklinik für Augenheilkunde, Inselspital Bern, Freiburgstrasse, 3010 Bern

1.2 Principal Investigator(s)

Professor Dr. med. Martin Zinkernagel, Universitätsklinik für Augenheilkunde, Inselspital Bern, Freiburgstrasse, 3010 Bern

1.3 Statistician ("Biostatistician")

Oussama Habra, Universitätsklinik für Augenheilkunde, Inselspital Bern, Freiburgstrasse, 3010 Bern

1.4 Laboratory

Not applicable.

1.5 Monitoring institution

Pia Steinger, Study Coordinator DAS, Universitätsklinik für Augenheilkunde, Inselspital Bern, 3010 Bern

1.6 Data Safety Monitoring Committee

Not applicable.

1.7 Any other relevant Committee, Person, Organisation, Institution

Not applicable.

2. ETHICAL AND REGULATORY ASPECTS

2.1 Registration of the investigation

This study ist registered on the Swiss National Clinical Trials Portal (ID 2021-D0038) and will be registered on theClinicalTrials.gov Protocol Registration and Results System (PRS). The results will be published in a peer-reviewed medical journal.

2.2 Categorisation of the investigation

This clinical trials of a medical devices comes under Category A, subcategory A1, as the medical device bears a conformity marking; and is used in accordance with the instructions. The OCT has been used in our clinic for years and the High-Resolution-OCT represent an improvement of the previous imaging technique. However, as there is at present no systematic comparison of findings to conventional imaging methods such as fluorescein angiography and spectral-domain optical coherence tomography we plan to compare the High-Res-OCT with these imaging methods. The examinations serving as comparator (retinal fundus photography, fluorescein angiography and OCT) performed in this study are routinely used in daily clinic and are standard for the diagnosis of vascular diseases in ophthalmology. High Resolution Optical Coherence Tomography is a safe procedure and is used in daily routine. , The SPECTRALIS® High-Res OCT- DMR001 has received CE mark in March 2021 and is used in clinical practice.

2.3 Competent Ethics Committee (CEC)

The Sponsor-Investigator will submit the investigation to the CEC and obtain ethical committee approval before the start of the investigation. The PI ensures that approval from the CEC is obtained and filed in the Investigator site file before the investigation starts.

2.3.1 Reporting duties to the Competent Ethics Committee

Amendments are reported according to Art. 15 ClinO-MD (see also 2.10).

The regular or premature end of the investigation as well as the interruption of the investigation is reported to the CEC within 15 days (within 24 hours if it is due to security reasons) (Art. 36 ClinO-MD). The reasons for a premature end or an interruption have to be explained.

A final report shall be submitted within one year after the regular end of the investigation and within 3 months after a premature end of the investigation (Art. 37 ClinO-MD).

2.4 Ethical Conduct of the Investigation

The investigation will be carried out according to the CIP and with principles enunciated in the current version of the Declaration of Helsinki, the European Regulation on medical devices 2017/745 (MDR), the Norms ISO14155 and ISO14971, the ICH-guidelines of Good Clinical Practice (GCP) as applicable, the Swiss Human Research Act (HRA) and its Ordinances and Swiss regulatory authority's requirements. The CEC and the CA will receive the Annual Safety Report (ASR) and interim reports and be notified about investigation stop/end in agreement with local requirements.

2.5 Declaration of interests

There is no conflict of interest on the content of this study.

2.6 Patient Information and Informed Consent

The PI explains to each subject the nature of the investigation, its purpose, the procedures involved, the expected duration, the potential risks and benefits and any discomfort it may entail. Each subject is informed that the participation in the investigation is voluntary and that he/she may withdraw from the investigation at any time and that withdrawal of consent will not affect his/her subsequent medical assistance and treatment. The subjects are informed that he/she can ask any question, and consult with family members, friends, their treating physicians or other experts before deciding about their

participation in the investigation. Enough time is given to the subjects.

The subjects are informed that authorised individuals other than their treating physician may examine his/her medical records.

All subjects a given a subject information sheet and a consent form describing the investigation and providing sufficient information for the subjects to make an informed decision about their participation in the investigation.

The formal consent of a subject, using the approved consent form, is obtained before the subject is submitted to any investigation procedure.

The subject should read, understand, and voluntarily agree before signing and dating the informed consent form, and is given a copy of the signed document. The consent form is signed and dated by the subject and the PI (or her/his designee). The signed consent form it is retained as part of the investigation records.

2.7 Subject privacy and confidentiality

The Sponsor and the PI affirm and uphold the principle of the subjects' right to privacy and that they shall comply with applicable privacy laws. Especially, anonymity of the subjects shall be guaranteed when presenting the data at scientific meetings or publishing them in scientific journals.

Individual subject medical information obtained as a result of this investigation is considered confidential and disclosure to third parties is prohibited.

The assignment to each subject of a unique subject identification number ensures subject confidentiality. The unique identification number will contain the year of birth with a combination of letter/number that have no relation with the trial subject.

For data verification purposes, authorised representatives of the Sponsor, the CA or a CEC may require direct access to parts of the medical records relevant to the investigation, including subjects' medical history.

2.8 Early termination of the investigation

The Sponsor may terminate the investigation prematurely according to certain circumstances, for example:

- ethical concerns,
- insufficient subject recruitment,
- when the safety of the subjects is doubtful or at risk, respectively,
- alterations in accepted clinical practice that make the continuation of the investigation unwise,
- early evidence of benefit or harm of the experimental intervention.

2.9 Clinical investigation plan amendments

Substantial amendments are only implemented after approval by the CEC (Art. 15 ClinO-MD) and, for category C investigations, after approval by the CA also (Art. 20 ClinO-MD). The use of waivers from the CIP is prohibited (Annex XV, Chapter 2, Art. 3.10 MDR).

Under emergency circumstances, deviations from the CIP to protect the rights, safety and well-being of the subjects may proceed without prior approval by the Sponsor and the CEC (and for category C investigations without prior approval by the CA). Such deviations shall be documented and reported to the Sponsor and the CEC (and to the CA for category C investigations) within 2 days (Art. 34 ClinO-MD).

All non-substantial amendments are communicated to the CEC together with the Annual Safety Report (ASR) (Art. 15 ClinO-MD). The ASR shall include any deviations from the CIP that may have affected the rights, safety or well-being of the subject or the scientific integrity of the investigation (ISO14155).

2.10 Deviation from the Clinical Investigation Plan

The use of waivers from the CIP is prohibited (Annex XV, Chapter 2, Art. 3.10 MDR).

The investigator is not allowed to deviate from the CIP, except as specified in 2.10. Important modifications will be reported to the CEC by one of the investigators. Substantial amendments are only implemented after approval of the CEC respectively.

3. BACKGROUND AND RATIONALE

3.1 Background and Rationale for the clinical investigation

Optical Coherence Tomography (OCT) is a non-invasive, non-contact 3D imaging technique based on low coherence interferometry [18], who has changed the clinical practice of ophthalmology most notably in the diagnosis and management of sight-threatening retinal diseases such as age-related macular degeneration (AMD) and diabetic retinopathy (DR). This imaging tool allows ophthalmologists to noninvasively visualize retinal structures at micrometer resolution thereby enhancing their ability to examine the retina and its sub-layers in order to (1) diagnose and monitor progression of diseases, (2) aid in treatment planning and (3) monitor a patient's response to therapy. The first commercially available OCT was a time-domaine OCT (TD-OCT), which requires acquisition of a depth scan for every location and subsequently offers very slow imaging speed and poor image quality. Usability and the impact of the noisy images on clinical diagnosis limited adaption of this technology [14]. The introduction of spectral domain OCT (SD-OCT) was able to overcome the limitations of TD-OCT. Image quality and imaging speed were significantly improved by SD-OCT, where the point detector is replaced by a spectrometer, which is able to capture the whole depth information simultaneously [19].

The SPECTRALIS device was introduced by Heidelberg Engineering in 2006 based on the Heidelberg Retina Angiograph 2 (HRA2) [20,21]. It incorporates two complementary imaging techniques: confocal scanning laser ophthalmoscopy (cSLO) and optical coherence tomography (OCT). The Superluminescent Diodes (SLD) has a center wavelength of 880 nm and a spectral bandwidth of 40 nm (full-width-half-maximum, FWHM), resulting in an axial resolution of approximately 7 µm in the eye. The spectral resolution of the spectrometer determines the characteristic roll-off in sensitivity with imaging depth. Compared to the first generation OCT device (40 kHz A-scan rate), the roll-off of SPECTRALIS with OCT Module has been improved considerably to less than 5 dB over an imaging depth of 1.9 mm. There is a tradeoff between acquisition speed and sensitivity: The higher the line rate, the faster the image acquisition but the less that photons can be detected. Acquisition speed therefore is inherently coupled to the sensitivity of the system. For retinal imaging, the maximum laser power is set by the exposure limit according to the laser safety guidelines. Therefore, to compensate for shorter integration time, the power can only be increased up to a limit (1.2 mW). At the same time, eye motion, heart beat and any motion in general requires accelerated acquisition.

Recently a new improvement of the OCT has been developed, the high resolution OCT, with a light-source capable of providing an increased axial resolution. The High-Res OCT works with a central wavelength of 840 nm and an increased bandwidth (130 nm), making it possible to improve the optical axial resolution in tissue from 7 to 3 µm, without increasing the maximum laser exposure limit. The improved axial resolution of the High-Res OCT results in clearer and more detailed images resolving even minuscule vessels in the retinal layers and the choriocapillaris.

The overall study aim is whether High-Res OCT can reliably diagnose retinopathies thereby making more invasive investigations such as fluorescein angiography futile and to investigate the diagnostic accuracy of the High-Res OCT in comparison with conventional imaging methods. The main goal is to facilitate diagnosis of eye diseases for individual patients.

3.2 Identification and description of the Investigational Medical Device

The SPECTRALIS © HighRes-OCT is a Spectral-Domain OCT, which has received CE mark in March 2021 and is used in clinical practice (within the research framework) and is manufactured by © Heidelberg Engineering GmbH.

The SPECTRALIS © HighRes-OCT, is a non-contact, high resolution, wide field-of-view tomographic and biomicroscopic imaging device intended for in-vivo viewing, axial cross-sectional and three-dimensional imaging of posterior ocular structures. The device is indicated for visualizing posterior ocular structures including, but not limited to, retina, retinal nerve fiber layer, ganglion cell plus inner plexiform layer, macula, optic nerve head, vitreous and choroid. The SPECTRALIS © HighRes-OCT is indicated as a diagnostic device to aid in the detection and management of ocular diseases including, but not limited to, macular holes, cystoid macular edema, diabetic retinopathy, age-related macular degeneration and glaucoma.

The Optical Safety of this device conforms to EN 14971 :2012 (ISO 14971 :2007), EN 60601-1 : 2006/A1 :2013 (IEC 60601-1:2005 + Cor. :2006 + Cor. :2007 + Al :2012), EN 60601-1-2:2016-05 (IEC 60601-1-2:2015), EN 10993-1:2018 (ISO 10993-1 :2018), EN 60825-1 :2Ù14 (IEC 60825-1:2014). The

device is classified as a group 1 instrument per EN ISO 15004–2 (Group 1 instruments are ophthalmic instruments for which no potential light hazard exists).

No cases have been identified in which the product's failure to perform its intended clinical functions would result.

Operators of this device are adults with professional training or experience in the use of ophthalmic imaging equipment. Specific assumptions regarding the qualifications of individuals operating the instrument are given below:

• Ophthalmologist or other Medical Doctor

• Optometrist or equivalent

• Nurse

• Certified Medical Technician

• Ophthalmic Photographer

3.3 Preclinical Evidence

Not applicable.

3.4 Clinical Evidence to Date

A High-resolution OCT system uses broadband light sources to achieve axial resolutions below the 7-µm range of standard commercial OCT instruments [22]. Former High resolution OCTs (Spectral/Fourier Domain) often used light-sources of 840-nm center wavelength and previous studies have shown that the visualization of photoreceptor impairment, retinal pigment epithelium (RPE) disruption, drusen, which are important markers of age-related macular degeneration (AMD) progression, have been drastically improved [22-24].

The limited imaging range of High-Resolution OCTs at 840 nm has been a substantial barrier to its clinical adoption. To achieve fine axial resolution, the OCT spectrometer should be designed to cover a broad wavelength range by compromising the spectral resolution—the wavelength difference between adjacent line-scan camera pixels. Former High-Resolution OCTs had a limited axial image range because imaging range is inversely related to spectral resolution. Thus, a High-Resolution OCT imaging requires finer transverse spatial sampling of the retina, mandating higher acquisition speeds. Complex SD-OCT have been designed to resolve this issue by using for example multiple line-scan cameras [25], however, sufficient depth range for reliable clinical application has not been made possible until now. To create a sufficient depth range and high spatial resolution the High-Resolution OCT uses an infrared Laser of 730 nm wavelength.

3.5 Justification for the design of the clinical investigation

The SPECTRALIS © HighRes-OCT is indicated as an aid in the visualization of structures of the retina and choroid. The SPECTRALIS © HighRes-OCT is indicated as a device to aid in the detection and management of ocular diseases including, but not limited to, macular holes, cystoid macular edema, diabetic retinopathy, hypertensive retinopathy, age-related macular degeneration, optic nerve neuropathy and glaucoma.

3.6 Explanation for choice of comparator

The comparator in this study is conventional imaging of the retina with fluorescein angiography and standard SD-OCT. The fluorescein angiography allows to image the retinal vasculature using a dye and is routinely performed in clinical routine for diagnosis of retinal vasculopathies. Fluorescein angiography (FA) and indocyanine green angiography (ICGA) are both invasive test that require intravenous administration of dye and imaging up to 10–30 minutes [26]. The SD-OCT is used in the clinical routine and allows to image the retinal structure with an axial resolution of approximately 7 µm.

3.7 Risk evaluation (Risk-to-Benefits rationale)

This ophthalmological examination is non-invasive and is routinely performed to diagnose and monitor pathologies in eye diseases. High Resolution OCT is used in clinics (within research framework) and no adverse events have been reported. All instruments used in this study, are certified with a CE mark. The light intensities in the High-Resolution OCT are below the light levels used for a standard fluorescein angiography or autofluorescence imaging and the Optical Safety of this device conforms to IEC 60825-1, EN ISO 15004-2 and is classified as a group 1 instrument per EN ISO 15004–2 (Group 1 instruments are ophthalmic instruments for which no potential light hazard exists).

Study data will be collected in REDCap, a secure, and validated web application for building and managing online surveys and databases, in order to provide a maximum on data security. With this background, we consider from a clinical point of view that the benefits by far outweigh the risks and the study procedures (i.e. standard, routine clinical examinations) per se represent a low risk to the study participants.

3.8 Justification of the choice of the investigation population

The study population will consist of adult patients > 18 years of age with retinal diseases. The rationale for the age cut off is based on the large incidence of retinal diseases such as type I and type II diabetes mellitus or arterial hypertension. In order to validate the High-Res-OCT method we plan to analyze a subgroup of healthy subjects. Minors, participants incapable of judgment or participants under tutelage will not be included in this study.

4. CLINICAL INVESTIGATION OBJECTIVES

4.1 Overall Objective

The study aim is to investigate the diagnostic accuracy of the High-Resolution OCT in comparison with conventional imaging methods and whether High-Resolution OCT can reliably diagnose retinopathies thereby making more invasive investigations such as fluorescein angiography or conventional imaging methods futile. The main goal is to facilitate diagnosis of eye diseases for individual patients.

4.2 Primary Objective

The primary objective of this study is to evaluate the sensitivity and specificity to diagnose retinal morphological abnormalities with High-Resolution OCT compared to conventional imaging methods, such as SD-OCT, fluorescein angiography. The main parameters, which will be assessed are the presence of morphological abnormalities (such as but not limited to intraretinal or subretinal fluid, epiretinal membrane, substance defect, drusen, hyperreflective foci, atrophy, neovascularization, optic nerve, swelling, choroid abnormalities, scars, ischemia) within the macula and optic nerve head. The incidence (binary) and diagnostic accuracy of these morphological abnormalities will be assessed in High-Res-OCT and compared to conventional imaging methods such as SD-OCT.

4.3 Secondary Objectives

- Evaluation of the inter-reader reproducibility in healthy subjects with High-Res-OCT
- Evaluation whether pathological changes seen in SD-OCT or color fundus photography correlate with changes seen in High-Res-OCT. Here, a binary readout, i.e pathology present (yes/no) will be used.
- Subgroup analysis will be performed with patients suffering from diabetic retinopathy, artery and vein occlusion, retinal detachment, glaucoma, optic nerve neuropathy, hereditary retinal diseases, age related macular degeneration, retinal changes from arterial hypertension and uveitis.
- Evaluation of the intra-and inter-reader reproducibility in the diagnosis (binary) using High-Res-OCT
- Evaluation of the segmentation quality of the retinal layers using High-Res-OCT

4.4 Safety Objectives

As this is a CE certified device with minimal safety concerns no safety objectives are planned.

5. CLINICAL INVESTIGATION OUTCOMES

5.1 Primary Outcome

The primary outcome as measured on the individual patient-level is whether High-Resolution OCT has a similar or higher specificity and sensitivity to detect pathological changes in the retina/optic nerve as conventional imaging methods, such as SD-OCT, color fundus photography and fluorescein angiography. This will result in a binary outcome. Pathological morphological changes includes but are not limited to, intraretinal or subretinal fluid, epiretinal membrane, substance defect, drusen, hyperreflective foci, atrophy, neovascularization, optic nerve swelling, choroid abnormalities, scars, ischemia. Additionally, study participants will be asked to consent to prospective collection of clinical and demographic data, to correlate findings of High-Resolution OCT imaging to subsequent clinical course.

Ophthalmic diseases include, but are not limited to:

- Retinal vascular diseases
- Retinal detachment
- Hereditary retinal diseases/dystrophies
- Glaucoma
- Optic nerve neuropathy
- Inflammatory/infectious retinal diseases

5.2 Secondary Outcomes

- Evaluation of the inter-reader reproducibility in healthy subjects with High-Res-OCT
- Evaluation whether pathological changes seen in SD-OCT or color fundus photography correlate with changes seen in High-Res-OCT. Here, a binary readout, i.e pathology present (yes/no) will be used.
- Subgroup analysis will be performed with patients suffering from diabetic retinopathy, artery and vein occlusion, retinal detachment, glaucoma, optic nerve neuropathy, hereditary retinal diseases, age related macular degeneration, retinal changes from arterial hypertension and uveitis
- Evaluation of the intra-and inter-reader reproducibility in the diagnosis (binary) using High-Res-OCT
- Evaluation of the segmentation quality of the retinal layers using High-Res-OCT. For this purpose the discrimination capacity between the different retinal layers will be assessed, especially in the healthy group. For this purpose, a binary outcome will also result.

5.3 Other Outcomes of Interest

Exploratory outcome include:

- Usefulness of colored infrared images using the Mutlicolorimaging software compared to color fundus photography

5.4 Safety Outcomes

As this is a CE certified device with minimal safety concerns we do not plan to study safety outcomes with this device.

6. CLINICAL INVESTIGATION DESIGN

6.1 General clinical investigation design and justification of design

This trial is a prospective clinical study. Patients, who fulfilled the inclusion criteria will be recruited at the Inselspital Bern. Study data will be collected in REDCap®, a secure, and validated web application for building and managing online surveys and databases. Study participants will undergo imaging of one or both eyes in accordance with the clinical indication, which will last approximately 30-60 seconds per eye. The imaging process is without any contact and pharmacologic dilatation of the pupils will not be used for the purposes of this study.

We plan to include approximately 550 participants in the study, including 100 healthy participants and 450 patients with diagnosed ocular disorders, including diabetic retinopathy (50 patients), artery and vein occlusion (50 patients), glaucoma (50 patients), optic nerve neuropathy (50 patients), hereditary retinal diseases/dystrophies (50 patients), retinal detachment (50 patients), age related macular degeneration (50 patients), retinal changes from arterial hypertension (50 patients), uveitis (50 patients).

Study participants will undergo imaging with High-Resolution OCT only within a single imaging session on a single day. Additionally, study participants will be asked to consent to prospective collection of clinical and demographic data, to correlate findings of High-Resolution OCT imaging to subsequent clinical course. Data from the clinical records are to be used for the study up to the time of the visit.

6.2 Methods for minimising bias

This study is a non-randomized and open label observational study.

6.2.1 Randomisation

No randomization is planned.

6.2.2 Blinding procedures

Not applicable.

6.2.3 Other methods for minimising bias

Not applicable.

6.3 Unblinding Procedures (Code break)

Not applicable.

7. CLINICAL INVESTIGATION POPULATION

7.1 Eligibility criteria

Subjects fulfilling all of the following inclusion criteria are eligible for the investigation:

- Informed Consent signed by the subject
  - Patients and healthy subjects from the Department of Ophthalmology, University Hospital Bern requiring conventional imaging for eye disease
  - Patients of 18 years or older

The presence of any one of the following exclusion criteria will lead to the exclusion of the subject

- Patients not willing or able to sign informed consent
- Patients younger than 18 years
- Contraindication and limitation of the MD as described in the instructions for use: Patients with epilepsy.
- Vulnerable subjects (except the objectives of the investigation concern vulnerable subjects specifically),
- Inability to follow the procedures of the investigation, e.g. due to language problems, psychological disorders, dementia, etc. of the subject
- Participation in another investigation with an investigational drug or another MD within the 30 days preceding and during the present investigation
- Enrolment of the PI, his/her family members, employees and other dependent persons

7.2 Recruitment and screening

There will be a consecutive ongoing recruitment of patients and healthy subjects attending routine follow-ups through the involved investigators in daily clinical practice at Department of Ophthalmology, Inselspital, Bern. Recruitment will last from October 2021 to November 2023. Subjects will be given enough time (hours to days) to consider and to council with relatives and experts. No screening requirements is necessary (laboratory or other diagnostic tests). There will be no payment or compensation given to subjects.

7.3 Assignment to investigation groups

The recruited participants will be assigned to the diagnostic categories mentioned at 6.1. or categorized as healthy. No randomization is planned.

7.4 Criteria for withdrawal / discontinuation of subjects

Patients are allowed to withdraw their participation at any point of time without communicating their reason. Investigators as well are allowed to exclude enrolled participants from the ongoing study if participants are non-compliant or if they see potentially harming constellations.

Data from patients who withdrew their participation will be made completely anonymous.

8. CLINICAL INVESTIGATION INTERVENTION

8.1 Identity of the medical device under investigation

Optical coherence tomography is a safe, non-invasive and worldwide spread imaging technique, using light in the near-infrared spectral range to produce a cross-sectional tissue images. The OCT is used in daily routine and an established diagnostic tool for detecting and diagnosing retinal and optic nerve diseases. The assessment of OCT images of both eyes takes about 5 minutes

8.1.1 Experimental Intervention (medical device)

The SPECTRALIS HighRes-OCT ® is a non-contact ophthalmic imaging device for the eye to investigate anatomy and has received CE mark. SPECTRALIS HighRes-OCT® has a confocal laser scanning and an optical coherence tomography. The device is indicated for visualizing posterior ocular structures including, but not limited to, retina, retinal nerve fiber layer, ganglion cell plus inner plexiform layer, macula, optic nerve head, vitreous and choroid.

To produce an image a laser beam is focused on the retina. The intensity of the reflected light or of the emitted fluorescent light at each point is measured with a light sensitive detector. Light reflected or emitted outside of the adjusted focal plane is suppressed in a confocal optical system, resulting in high contrast images. The latter acquires furthermore a layer-by-layer three dimensional image. This system allows to image patients with non-dilated pupils, which is especially important in a daily routine. The laser sources of the device emit laser light with four different wavelengths:

- A blue laser diode with a wavelength of 486 nm is used to excite the fluorescein or the intrinsic autofluorescence. A barrier filter at 500 nm separates excitation and fluorescence light. The same wavelength without the barrier filter is used to create red-free images.
- A diode laser at 730 nm wavelength produces infrared reflectance images.
- A diode laser at 518 nm wavelength.

The SPECTRALIS ® uses spectral domain optical coherence tomography (SD-OCT) technology, also referred to as Fourier domain OCT (FD-OCT). The beam of a super luminescence diode (SLD) scans across the retina to produce a cross sectional B-scan image. To create high spatial resolution three dimensional images of the retina, B-scans as close as 11 microns to each other can be acquired.

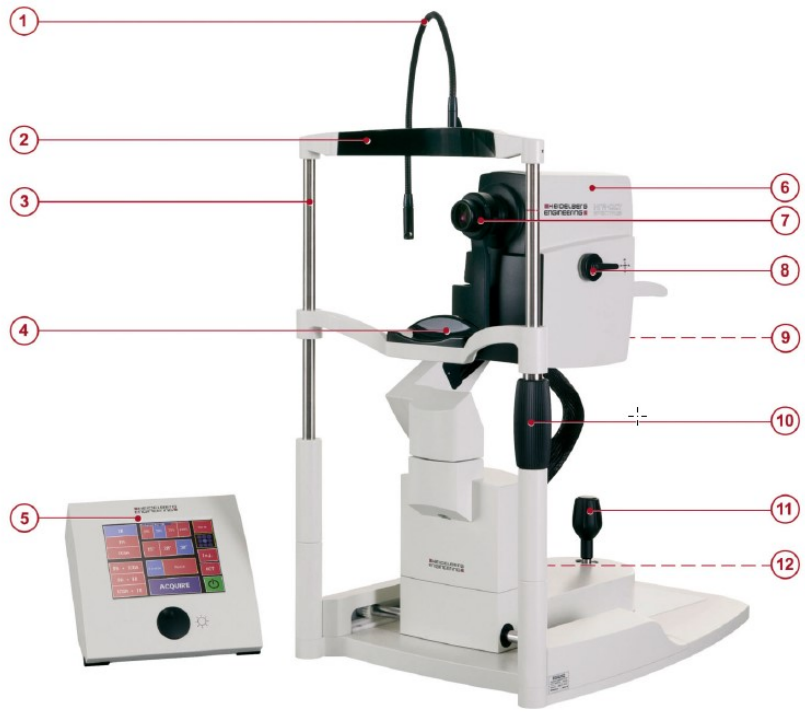

Fig. 1: SPECTRALIS HighRes-OCT

① External fixation light
② Forehead rest
③ Head rest column with red canthus marks
④ Chin rest
⑤ Touch panel with ART/Sensitivity knob
⑥ Camera head
⑦ SPECTRALIS HighRes-OCT standard objective lens
⑧ Filter wheel
⑨ Focus knob; not shown
⑩ Screw for adjusting the chin rest
⑪ Joystick
⑫ Set screw; not shown

The infrared beam of the SLD has a central wavelength of 850 nm. The SPECTRALIS utilizes two separate beams of light to capture two images simultaneously. One beam constantly tracks and images the fundus. It also acts as a reference, guiding the OCT beam. Active eye tracking "locks" the OCT to the fundus, providing precise alignment of blood vessels and fundus image. Active eye tracking is of critical importance in 3D volume scans which are susceptible to eye motion artifact.

The SPECTRALIS HighRes-OCT ® is a retinal imaging device intended to be used as a non-contact, imaging instrument for in vivo viewing, axial cross-sectional imaging, and three-dimensional imaging of ocular structures. No cases have been identified in which the product's failure to perform its intended clinical functions would result in unacceptable risk. The subject will be imaged according to the SOP set forth in the user manual of the device. No dye is necessary when performing

8.1.2 Control Intervention (standard/routine/comparator)

The routine (standard) examinations to investigate retinal pathologies are spectral-domain optical coherence tomography (SD-OCT), color fundus imaging and fluorescein angiography. These investigations are routinely performed in daily clinical practice. SD-OCT and color fundus imaging are noncontact and dye free imaging methods. Intravenous Fluorescein angiography (IVFA) is a technique for examining the circulation of the retina and choroid using a fluorescent dye and a specialized camera. The nurse will ensure intravenous access with a venflon intravenous cannulation device. Just prior to obtaining images 500 mg (1 ampoule of 5 mL) of fluorescein (Fluoresceine 10% Faure, Novartis Pharma AG, Basel, Switzerland) will be injected intravenously. Then an angiogram is obtained by photographing the fluorescence emitted after illumination of the retina with blue light at a wavelength of 490 nanometers. This test uses the dye tracing method. In daily routine patient consent is obtained to perform fluorescein angiography. If there is known hypersensitivity or allergy to fluorescein no fluorescein angiography is performed.

The fluorescein dye also reappears in the patient urine, causing the urine to appear darker, and sometimes orange. It can also cause discoloration of the saliva. Fluorescein angiography is one of several health care applications of this dye, all of which have a risk of severe adverse effects, such as allergic responses.

8.1.3 Labelling and Supply (re-supply)

Not applicable.

8.1.4 Storage Conditions

Not applicable.

8.2 Discontinuation or modifications of the intervention

Since the procedure consists of a simple image capture on a single visit, lasting approximately 230-60 seconds and since the procedure is not related to a risk for the participants, the point 8.2 is not applicable for this study. If a participant wants to stop the process at any time, their decision will be respected.

8.3 Compliance with clinical investigation intervention

As the examinations will be performed only once in this study there are no concerns with patient compliance.

8.4 Data Collection and Follow-up for withdrawn subjects

As this is a clinical study where most participants are imaged only once, there are no concerns with data collection from withdrawn subjects. Data from withdrawn subjects will be anonymized and evaluated as far possible according to Art. 3 Abs. b ClinO-MD. If a subject withdraws from the investigation, the reason of withdrawal will be asked and recorded. If such withdrawal is related to the SPECTRALIS HighRes-OCT ®, the PI will ask for the subject's permission to follow his/her condition outside the investigation, using routine (standard) examinations. The medical follow-up of withdrawn subjects, or of subjects that drop out from the investigation prematurely is described in chapter 9.2.5 and chapter 9.2.6.

8.5 Clinical investigation specific preventive measures

Not applicable.

8.6 Concomitant Interventions (treatments)

Not applicable.

8.7 Medical Device Accountability

The SPECTRALIS HighRes-OCT ® has been provisioned by Heidelberg Engineering GmbH, 69115 Heidelberg/Germany to the department of Ophthalmology at the university hospital Bern, Inselspita. Maintenance and support is provided by Heidelberg Engineering GmbH - 8105 Regensdorf – Switzerland.

8.8 Return, Analysis or Destruction of the Medical Device

Return of this device is according to standard procedures of the Inselspital Bern.

9. CLINICAL INVESTIGATION ASSESSMENTS

9.1 Clinical investigation flow chart(s) / table of clinical investigation procedures and assessments

There will be a consecutive ongoing recruitment of patients and healthy subjects attending routine follow-ups through the involved investigators in daily clinical practice at Department of Ophthalmology, Inselspital, Bern. Recruitment will last from October 2021 to November 2023. Patients, who fulfilled the indication of either SD-OCT or fluorescein angiography imaging for diagnosis of retinal/optic nerve disease will be included and additional imaging will be performed with the High-Res-OCT.

Subject	Initial imaging with High-Res-OCT
Healthy volunteers	X_1
Patients with retinal/optic nerve disease	X_1
X =mandatory imaging session. [1] routine imaging with either SD-OCT, fundus photography or fluorescein angiography according to clinical routine	

9.2 Assessments of outcomes

Fig. 2: Switching the device on and off

① Isolating transformer
② Power supply
③ PC
④ Monitor

The high-quality images of the retinal structures acquired with the SPECTRALIS HighRes-OCT ® will be obtained as follow:

- Power on the unit and log on
- Enter, find, and modify patient identifying data
- Clean surfaces that contact patient
- Position patient with the device, including moving the patient, the device, the table height, and the patient's chair
- Select and acquire scan
- Review and save scan or try again
- Generate reports using available reporting protocols
- Review reports for completeness
- Output reports
- Archive data
- Turn off the unit

The operators will be trained Heidelberg Engineering GmbH - 8105 Regensdorf – Switzerland, which will also calibrate the medical device and offers maintenance and support.

The data analysis will be performed by the investigator with the appropriate professional training or experience in the use of ophthalmic imaging equipment.

9.2.1 Assessment of primary outcome

The sensitivity and specificity of the High-Resolution OCT to diagnose the presence/absence of pathological changes in the retina/optic nerve in comparison to conventional imaging modalities will be assessed as a primary outcome. The following pathological changes will be assessed: intraretinal or subretinal fluid, pigment epithelial detachment, epiretinal membrane, substance defect, drusen, hyperreflective foci, atrophy, neovascularization, choroid abnormalities, scars, optic nerve swelling and ischemia. For each of these pathological changes a binary outcome will result. Additionally, study participants will be asked to consent to prospective collection of clinical and demographic data, to correlate findings of High-Res-OCT imaging to subsequent clinical course.

There is no need to be in a particular posture before the examination in order to obtain high quality images. The participants will be in a sitting position during the examination during approximately 30-60 seconds per eye. In case the measurement needs to be repeated, no waiting period will be necessary. A repeated measurement needs to be recorded in the CRF.

9.2.2 Assessment of secondary outcomes

- To evaluate whether pathological changes seen in SD-OCT or color fundus photography correlate with changes seen in High-Res-OCT, a binary readout will be used, i.e. pathology present yes/no.
- Subgroup analysis will be performed with patients suffering from diabetic retinopathy, artery and vein occlusion, retinal detachment, glaucoma, optic nerve neuropathy, hereditary retinal diseases, age related macular degeneration, retinal changes from arterial hypertension and uveitis. For this purpose a quantification and classification of the pathological changes in relation to each disease will be performed, among them; Drusen classification according to Age-Related Eye Disease Study (AREDS) [27], neovascularization, bleeding, ischemia, atrophy, exudate, retinal thickness, intra-subretinal fluid, pigment epithelial detachment (PED) and epiretinal membrane [28,29] In order to compare these groups with conventional imaging and controlling for some degree of variation due to age, patients included in subgroup analysis will be compared to a pool of healthy subjects.
- Evaluation of the intra-and inter-reader reproducibility in the diagnosis using High-Res-OCT. This will result in a binary outcome (diagnosis present or absent). The evaluation of the inter-reader reproducibility in healthy subjects with High-Res-OCT will be assessed. For this purpose a senior physician, a resident and an expert physician will subsequently analyze the images.
- Furthermore the quality of the segmentation of the retinal layers, i.e. the discrimination capacity between the different layers (internal limiting membrane, retinal nerve fibre layer, ganglion cell layer, inner plexiform layer, inner nuclear layer, outer plexiform layer, outer nuclear layer, external limiting membrane, photoreceptor layer, retinal pigment epithelium, Bruch's membrane, choriocapillaris and choroidal stroma) will be assessed, especially in the healthy group. For this purpose, a binary outcome will also result, i.e. discrimination between each layer possible, yes or no.

9.2.3 Assessment of other outcomes of interest

Exploratory outcome:

- Usefulness of colored infrared images using the Mutlicolorimaging software compared to color fundus photography. For this purpose the images will be recomposed using the Mutlicolorimaging software and compared with color fundus photography. A binary outcome will be assessed, i.e. presence/absence of every pathological changes.

9.2.4 Assessment of safety outcomes

9.2.4.1 Adverse events

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient is entered into the study and until 4 weeks after the patient has stopped study participation will be reported to the Ethics Commission of the Canton of Bern within 24 hours of learning of its occurrence. Recurrent episodes, complications, or progression of the initial SAE will be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should

be reported separately as a new event.

Information about all SAEs is collected and recorded on a Serious Adverse Event Report Form, including following details: time of onset, duration, resolution, action to be taken/ or already taken, assessment of intensity, relationship with the MD and with the procedures of the investigation, expectedness, seriousness. The investigator will assess the relationship to the medical device, complete the SAE Report Form, and send the completed, signed form via BASEC within 24 hours to the Ethics Commission of the Canton of Bern.

9.2.4.2 Laboratory parameters

Not applicable.

9.2.4.3 Vital signs

Not applicable.

9.2.5 Assessments in subjects who prematurely stop the clinical investigation

In order to compare High-Resolution OCT with conventional imaging, only one imaging session is necessary. Data from patients who withdrew their participation will be made completely anonymous.

9.2.6 Follow-up of the subjects after the regular termination of the clinical investigation

After the regular termination of the clinical investigation, the subjects will be assessed and the follow up visits will be done according to clinical routine. The need for follow up will be dictated by clinical routine.

9.3 Procedures at each visit

All patients will be imaged only once in this study. Therefore screening, baseline visit and imaging will be performed on the same day.Data from the clinical records are to be used for the study up to the time of the visit.

9.3.1 Split into subtitles by type of visit

Screening visit: Informed consent, routine ophthalmological testing including ophthalmic imaging as required by clinical routine, imaging with High-Res-OCT.

9.3.2 Split into subtitles by type of visit

Not applicable as all patients will be imaged only once.

10. SAFETY

10.1 Definition and Assessment of (Serious) Adverse Events and other safety related events

Adverse Event (AE) (Art. 2 Abs 57 MDR)

Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the MD.

Serious Adverse Event (SAE) (Art. 2 Abs 58 MDR)

Any adverse event 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) hospitalisation or prolongation of patient hospitalisation,
  (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) foetal distress, foetal death or a congenital physical or mental impairment or birth defect.

Note: planned hospitalization for pre-existing condition, or a procedure required by the CIP, without a serious deterioration of the health status of the subject, is not considered an SAE

Device deficiency (Art. 2 Abs 59 MDR)

Inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, of an investigational device, including malfunction, user errors and inadequate information supplied by the manufacturer.

Malfunction (ISO14155)

Failure of an investigational device to perform in accordance with its intended purpose when used in accordance with the instructions for use or the CIP.

Device deficiency with Serious Adverse Device Effect (SADE) potential (Art. 80 Abs 1 letter c MDR; ISO14155)

Any device deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.

Adverse Device Effect (ADE) (ISO14155)

Adverse event possibly, probably or causally related to the use of an investigational device or procedures.

This includes any adverse event resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, operation, or any malfunction of the MD under investigation. This includes any event that is a result of a use error or intentional misuse.

Serious Adverse Device Effect (SADE) (ISO14155)

Adverse device effect (ADE) that has resulted in any of the consequences characteristic of a serious adverse event.

Unanticipated Serious Adverse Device Effect (USADE) (ISO14155)

Serious adverse device effect (SADE) which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

Note: Anticipated SADE (ASADE) is an effect which by its nature, incidence, severity or outcome has

been previously identified in the risk analysis report.

Causal Relationship of SAE (MDCG 2020-10/1)

A causal relationship towards the medical device or the procedure of the investigation should be rated by the PI and the Sponsor as follows:

- **Not related:** The relationship to the device or procedures can be excluded.
- **Possible:** The relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible.
- **Probable:** The relationship with the use of the investigational device seems relevant and/or the event cannot reasonably be explained by another cause.
- **Causal relationship:** The serious event is associated with the investigational device or with procedures beyond reasonable doubt.

10.2 Adverse events categorization

The adverse events are categorized by the PI and the Sponsor using the following algorithm:

Does the AE meet the seriousness criteria?

- No, it is not serious
  - Is the relationship to the device or the procedure possible, probable or causal?
    - No: non-related AE
    - Yes: ADE
- Yes, it is serious: SAE
  - Is the relationship to the device or the procedure possible, probable or causal?
    - No: non-related SAE
    - Yes: SADE
- Is it anticipated (within expected type, severity and frequency of the complications)?
    - No: unanticipated SADE (USADE)
    - Yes: anticipated SADE (ASADE)

10.3 Documentation and reporting in Medical Device Category A clinical investigations

Device deficiencies (DD) and all **adverse events (AE)** including all **serious adverse events (SAE)** are collected, fully investigated and documented in the source document and appropriate case report form (CRF) during the entire investigation period, i.e. from patient's informed consent until the last CIP-specific procedure, including a safety follow-up period.

- Documentation of AEs (including SAEs) by the PI includes diagnosis or symptoms, start and stop dates of event, event treatment, event resolution, assessment of seriousness and causal relationship to MD and/or investigation procedure (Art. 32 ClinO-MD, ISO14155).
- Documentation of DDs by the PI includes description of event, start date, investigational device information, action taken with regard to the investigational device, and whether the DD led to an AE. The Sponsor shall review all DDs and determine and document in writing whether they could have led to a SAE (DD with SADE potential) (Art 32. ClinO-MD, ISO14155).

At the end of each visit, the information on possible AEs will be systematically collected with the help of a safety assessment and will be systematically asked at every regular visits.

10.3.1 Foreseeable adverse events and anticipated adverse device effects

Photophobic symptoms could rarely occurred after performing any types of OCT, which includes mild and transitory migraine-like-symptoms (light headache, nausea, blurry vision, changed color perception). This symptoms typically resolved on their own without treatment, within a few minutes. If such symptoms appears, the participant will be observed till resolution of the symptomatic.

10.3.2 Reporting of Safety related events

Reporting to the Sponsor:

All SAEs, device deficiencies and health hazards that require measures are reported to the Sponsor by the PI (or authorized designee) within 24 hours after becoming aware of the event. Device deficiencies are assessed regarding their potential to lead to an SAE. DD are assessed regarding their potential to lead to an SAE.

Reporting to the Competent Ethics Committee:

The Sponsor reports to the CEC promptly any serious adverse event which has a causal relation with the MD, comparator or procedure/test method or where a causal relation appears to be possible (Art. 33 ClinO-MD).

In order to ensure prompt notification, the Sponsor may initially submit an incomplete notification.

If safety and health hazards that require measures must be taken immediately during the conduct of the investigation, the Sponsor notifies the CEC within 2 days of these measures and the circumstances which made them necessary (Art. 34 ClinO-MD).

Periodic safety reporting (Art. 35 ClinO-MD):

An Annual Safety Report (ASR) is submitted by the Sponsor to the CEC, yearly. The ASR contains a list of all SADEs and DDs and a report on their degree of seriousness, causal relationship with the MD and procedure and on subjects' safety.

Other reporting is done according to provisions of MD vigilance as per Art. 87-90 MDR (Art. 33 abs 4.b ClinO-MD) and Art. 67 MedDO.

10.4 Assessment, notification and reporting on the use of radiation sources

Not applicable.

11. STATISTICAL METHODS

11.1 Hypothesis

The primary variable in this study is the ability to detect pathological changes in the retina/optic nerve in comparison to conventional imaging modalities such as SD-OCT, color fundus photography and fluorescein angiography.

Null hypothesis: there is no difference in detecting pathological changes in the retina/optic nerve between conventional imaging and High-Resolution OCT

Alternative hypothesis: there is a difference in detecting pathological changes in the retina/optic nerve between conventional imaging and High-Resolution OCT

11.2 Determination of Sample Size

The primary variable for this assessment is the ability to detect the presence of retinal structural abnormalities with High-Res-OCT in comparison to conventional ophthalmic imaging methods, mainly SD-OCT. This will result in a binary outcome. Assuming that the accuracy of each of these conventional imaging modalities separately is 90%, and there is truly no difference between the conventional imaging and High-Res-OCT (null hypothesis), then 550 patients are required to be 90% certain that the upper limit of a one-sided 95% confidence interval (or equivalently a 90% two-sided confidence interval) will exclude a difference in favor of the conventional imaging of more than 10% [16].

11.3 Statistical criteria of termination of the investigation

Due to the nature of the study, statistical criteria of termination of the investigation are not planned.

11.4 Planned Analyses

The primary variable for this assessment is the ability to detect retinal morphological changes with High-Res-OCT in comparison to conventional ophthalmic imaging methods such as OCT, color fundus photography and fluorescein angiography.

To prove the null hypothesis, hypothesis testing will be done with a one-sided 95% confidence interval to exclude a difference in favour of conventional imaging. The results will be displayed using a receiver operating characteristic (ROC) curve and a Precision-Recall (PR) curve. The ROC curve is created by plotting the true positive rate (TPR) against the false positive rate (FPR) at various threshold settings, the PR curve by plotting precision against recall.

Moreover, subgroup analysis will be performed to differentiate different disease entities using non-parametric test with a significance level of 0.05.

Descriptive analyses will evaluate demographic data as well as visual acuity data separately for each group of patients.

11.4.1 Datasets to be analysed, analysis populations

Descriptive analyses will evaluate demographic data, such as age, gender, as well as visual acuity data separately for each group of patients. No additional analyses will be performed. However, if the data are significant, a longitudinal study will be planned and submitted.

11.4.2 Primary Analysis

The results will be displayed using a receiver operating characteristic (ROC), or ROC curve. The curve is created by plotting the true positive rate (TPR) against the false positive rate (FPR) at various threshold settings. Here the required total sample size for estimating sensitivity (presence of the pathological changes within the scans) with respect to marginal error (0.03), sensitivity (90%) and the prevalence (0.9) of disease in target population would be approximately 550 subjects [17]. Depending on the results, precision and recall (PR) curves are also going to be computed, which are useful in case of distribution imbalance between two classes of a binary model, specifically if the true negative values are high, the latter not being taken into account in the calculation [30]. Precision (Y-axis) is referred as the positive predictive value and recall (X-axis) as sensitivity. A high precision value means that the tested classifier/device provides accurate results, while high recall indicates that the majority of all positive samples were detected. The possible AUC value ranges from 0.5 (discriminative performance equal to chance) to 1.00 (perfect discriminative performance). The primary analysis will be done using

Python 3 and its open-source package Scikit-learn v0.20.3.

11.4.3 Secondary Analyses

Subgroup analysis will be performed to differentiate different disease entities using non-parametric test with a significance level of 0.05, with patients suffering from diabetic retinopathy, glaucoma, optic nerve neuropathy, hereditary retinal diseases, retinal detachment, artery and vein occlusion, age related macular degeneration, retinal changes from arterial hypertension and uveitis. In order to compare these groups with conventional imaging and controlling for some degree of variation due to age, we estimate a group size of approximately 50 patients and 100 healthy subjects [16].

11.4.4 Interim analyses

Interim analysis is not planned.

11.4.5 Deviation(s) from the original statistical plan

Planned statistical analysis will be adapted if further interesting questions arise while analyzing the study. Any deviation from the original statistical plan will be described and justified in the CIP and in the final report.

11.5 Handling of missing data and drop-outs

All data from all participants included in the study will be analyzed.

12. QUALITY ASSURANCE AND CONTROL

All personnel/investigators involved are trained and are qualified to conduct this study. The Sponsor-investigator is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs and Working Instructions. The project leader is responsible for proper training of all involved study personnel.

12.1 Data handling and record keeping / archiving

Acquired data are stored save and archived at the investigation site (department of ophthalmology, University Hospital Bern, Inselspital).

12.1.1 Case Report Forms

Study data are recorded on the CRFs “demographics” and “clinical examination”. CRFs are kept current to reflect subject status at each phase during the course of study. Participants can be identified in the CRF by the study number but not by name or initials and birth date. The assignment to each subject of a unique subject identification number ensures subject confidentiality. The unique identification number will contain the year of birth with a combination of letter/number that have no relation with the trial subject.

All investigators are authorized for entering data in CRF “demographics” and “clinical examination”. The investigator/examiner is protocolled on the CRF. Data will be entered electronically in REDcap.

12.1.2 Specification of source data and source documents

Source data will be available at the site to document the existence of the investigation subjects. Source data will include the original documents relating to the investigation, as well as the medical treatment and medical history of the subject.

The source documents include:

-Demographic form: Study ID, study eye, personal information (year of birth, age, sex), eye anamnesis (diagnosis, date of diagnosis, recurrences). Data will be entered electronically in REDcap.

-Examination form (data from both eyes): visit date and if applicable, visual acuity, SD-OCT; FA, ICG, FAF plus additional information if required (correction). Data will be entered electronically in REDcap.

-Informed consent form; stored in a locked cupboard.

12.1.3 Archiving of essential clinical investigation documents

All study data must be archived for a minimum of 10 years after study termination or premature termination of the pilot study. They are stored in the Research Electronic Data Capture System "REDCap". Informed consents will be stored in a locked cupboard at the department of ophthalmology. Regular examination data will be resided in the normal patients' charts.

12.2 Data management

Project data will be handled with uttermost discretion and is only accessible to authorized personnel who require the data to fulfil their duties within the scope of the research project. On the CRFs and other project specific documents, participants are only identified by a unique participant number. All investigators are authorized for entering data in the source documents.

An identification code will be assigned for each patient using continuous numbering according to electronic CRF. Only the coded identifier list will contain respective patient's identification number and their names. This coded identification list will be stored on a password locked computer and only the authorized personnel will have access to this list.

12.2.1 Data Management System

REDcap DMS, hosted by server infrastructure of the Dept. Head Organs and Neurology.

12.2.2 Data security, access and back-up

Access is granted to study team using dedicated user accounts. The server hosting the REDCap system and the database is kept in a looked server room of the CTU. Only the system administrators have direct access to the server and back-up tapes. All data entered into the eCRFs are transferred to the database using Secure Sockets Layer (SSL) encryption. Each data point has attributes attached to it identifying the user who entered it with the exact time and date. Retrospective alterations of data in the database are recorded in an audit table. Time table, data field and altered value, and the person are recorded. A multi-level back-up system is implemented. Back-ups of the whole system including the database are run internally several times per day and on external tapes once a day. The back-up tapes are stored in a secure place in a different building. Direct access to source documents will be permitted for purposes of monitoring, audits or inspections.

12.2.3 Analysis and archiving

At final analyses, data files will be extracted from the database into statistical packages to be analyzed. The status of the database at this time is recorded in special archive tables. CTU Bern will securely store the final study database with all archive tables for at least 10 years.

If requested, data can be archived in electronic vaults provided by the Dept. Head Organs and Neurology.

12.2.4 Electronic and central data validation

Data can be entered into the database only after a check of completeness and plausibility. Furthermore, selected data points are cross-checked for plausibility with previously entered data for that participant. In addition, central data reviews will be performed on a regular basis to ensure completeness of the data collected and accuracy of the primary outcome data.

12.3 Monitoring

The monitoring of this open label observational, category A and subcategory A1 study is carried out by an in-clinic, study-independent monitor. An initiation visit in presence of the Sponsor-Investigator and the study team will be conducted. A full review of the essential documents will be undergone (included but not limited to signed protocol and amendments, if any, case report form (CRF), curriculum vitae, GCP certificates and other relevant documents evidencing qualifications of sponsor-investigator and sub-investigators, list of collaborators and their roles in the study team, completed and signed by the study team members and signed by the sponsor-investigator, manual user and certification of the medical device and comparator, study specific sources documents, all other documentation approved by the CEC, information given to trial subjects and informed consent form). The informed consent

process, safety, processing of subjects data, access regulation to the study database and preservation of subjects confidentiality will be assessed. Furthermore an evaluation of the facilities/premises where the medical device is located and of the technical procedures will be performed. The first visit will be done as soon as possible after the inclusion of the first few trial subjects. Any modification/revision to the above mentioned essential documents or any additional study-related document will be assessed. The signed informed consent forms, the source documents, the signed, dated and completed CRFs, the SAE forms, the subject identification code list, enrolment log, anonymization and encrypting procedure, data acquisition, reporting to CEC, and compliance with the study protocol will be verified. Additional monitoring visits will be performed at three month intervals. A close out visit will be planned at the end of the clinical trial. If a corrective action is needed, the monitor will immediately contact the sponsor-investigator and a corrective action will be performed. The source data/documents are accessible to monitor and questions are answered during monitoring by the sponsor-investigator and the site staff.

The monitoring of this observational study category A, subcategory A1 is carried out by :

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12.4 Audits and Inspections

The documentation of the investigation and the source data/documents are accessible to auditors/inspectors (also CEC) and questions are answered during inspections. All involved parties must keep the subject data strictly confidential.

12.5 Confidentiality, Data Protection

Project data will be handled with uttermost discretion and only by authorized personnel. Direct access to source documents will be permitted for purposes of monitoring (chapter 12.3), audits and inspections (chapter 12.4). Access to protocols, dataset, statistical code, etc. during and after the investigation will only be permitted to mentioned investigators. The Investigator ensures encryption of the patient's data; patients will not be identified by names in any documents. Signed informed consent forms and patient enrollment log will be kept strictly confidential to enable patient identification.

12.6 Storage of biological material and related health data

The collected data should be further used for future research.

13. THE COLLECTED DATA SHOULD BE FURTHER USED FOR FUTURE RESEARCH.PUBLICATION AND DISSEMINATION POLICY

Results of the study are planned to be presented in a peer-reviewed journal and via scientific presentations.

If gender effects are observed, they will be published in the final study report. If an analysis is performed but no gender effects are observed, this should also be published.

14. FUNDING AND SUPPORT

14.1 Funding

The study is funding by the department of ophthalmology, Inselspital, Bern.

14.2 Other Support

There is no other support.

15. INSURANCE

Insurance will be provided by Inselspital Bern (Trial Category A with minimal risk). A copy of the certificate is filed in each investigation site file and the sponsor file.

16. REFERENCES

Provide a list of the references pertaining and cited in the CIP.

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17. APPENDICES

NOTE: Further relevant information can be found in the ISO14155, Annex A Clinical Investigation Plan (CIP)

Documents that do frequently change during the course of the investigation can be mentioned as ‘documents provided separately’ and listed here.

The section headings can be renamed accordingly.

1. Medical Devices: manual user of the High-Res-OCT
2. Medical Devices: manual user of the SD-OCT
3. Case Report Form (e.g. CRF)
4. Study information and informed consent
5. SAE form