RESEARCH PROTOCOL

Final Version 1.0_30th November 2021
Final Version 1.1_10th December 2021
Final Version 1.2_20th December 2021
Final Version 1.3_19th January 2022
Final Version 1.4_3rd March 2022
Final Version 1.5_22nd. March 2022

Title

Validation of Bulbicam for use on patient suffering from Diabetic retinopathy (DR) and Age-related macular degeneration (AMD)

EudraCT number: 2021-006258-30
ClinicalTrial.gov: NCT
Protocol number: V1_OTH /DR; AMD– I/2022

Sponsor

BulbiTech A/S, Dybdahls veg 5, Trondheim, Norway

Administration

Project Manager: Prof Stig Larsen
Responsible Ophthalmologist: Prof Goran Petrovski
Project Coordinator: Bård Dalhøi

0: Steering committee

The study will be administered by a steering committee headed by Prof Stig Larsen. The members of the committee are:

Project manager:	Professor Emeritus Stig Larsen; Norwegian University of Life Sciences / Meddoc AS, Hvamstubben 14 2013 Skjetten
Project coordinator:	Bård Dalhøi. MSc Osteopathy Chief Executive Officer (CEO) BulbiTech AS Trondheim
Responsible Ophthalmology:	Professor Goran Petrovski Dr Med, MD, Ophthalmologist Department of Ophthalmology, Oslo University Hospitals / Ullevål Hospital, Oslo
PhD-fellow:	Dr Bjørn Helland Hansen MD, Ophthalmologist Department of Ophthalmology, Oslo University Hospitals / Ullevål Hospital, Oslo
PhD-supervisors:	Prof Goran Petrovski and Prof Emeritus Stig Larsen

The steering committee is responsible of:

1) The communication between the investigational sites
2) Supplementing study material to the sites
3) Continues data clarification
4) Corrections and amendments to the protocol
5) Publication of the results

Other central participants in this study are:

Investigators:	-Dr Alexander Sverstad MD, Ophthalmologist Department of Ophthalmology, Oslo University Hospitals / Ullevål Hospital, Oslo -Dr Eivind Hovden Augustsen MD, Ophthalmologist Department of Ophthalmology Helgeland Sykehus -Dr Henrik Skaret, Ophthalmologist Department of Ophthalmology Helgeland Sykehus
Responsible statistician:	Hans E Fagertun; MS Mathematical Statistics with specialty in Biostatistics Meddoc A/S, Hvamstubben 14, 2013 Skjetten
Data Manager:	Vivy Liang Larsen; MS, Data Manager Meddoc A/S, Hvamstubben 14, 2013 Skjetten
Clinical Monitor:	Sakaoduean Phonphimai; BS, CRA Meddoc A/S Hvamstubben 14 2013 Skjetten

The study will follow the ethical guidelines for health-related research involving humans prepared by CIOMS and conducted in compliance with the protocol.[1]
Prof Stig Larsen has written the trial protocol and is responsible for writing the clinical study report (CSR) with supports and corrections from the steering committee and the participating investigators. Hans E Fagertun is responsible for the statistical analysis supported by Stig Larsen. The data management and the clinical monitoring will be headed by Vivy Liang Larsen supported by members from the clinical- and the DM-group.

The result shall be published in an international medical journal and the manuscript prepared by the steering committee and the investigator. All participating centers shall be represented in the list of authors.

0.1: Signature Sheet

Protocol Authorized:

Stig Larsen[1], Goran Petrovski [2], Bjørn Helland Hansen[3] and Bård Dalhøi[4]

Qualifications:

1. Project Manager, Professor; Controlled Clinical Trials Research Methodology and Biostatistics
2. Professor; Ophthalmology
3. PhD-fellow; Ophthalmology
4. Project Coordinator, CEO BulbiTech A/S

Signature 1…… Date……

Signature 2……. Date……

Signature 3……. Date……

Signature 4…….....Date……

0.2: Contact names and addresses

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0.3: List of Abbreviations

Abbreviation	Explanation
AE	Adverse Event
AMD	Age related macular degeneration
BCAM	Bulbicam
BSC	Bachelor of Science
EMP	Eye Movement Perimeter
CIOMS	Council for International Organizations of Medical Sciences
CSR	Clinical Study Report
CRD	Clinically Relevant Difference
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CV	Curriculum Vita
DA	Dark adaptation
DR	Diabetes retropathy
DM	Data Management
DME	Diabetic macular edema
EQ-5D-5L	QoL questionnaire
GCP	Good Clinical Practice
HC	Healthy Control
ITT	Intention to treat
LOCS	Lens Opacification classification system
LOCF	Last Observation Carried Forward
MSC	Master of Science
NPDR	non-proliferative stage
NSD	Norwegian Centre for Research data
OTH	Ophthalmology
OR	Odds Ratio
PCIOL	Posterior Chamber Artificial Ocular Lens
PDR	proliferative stage
PP	Per Protocol
PhNR	Photonic negative response
PDR	Proliferative DR
PIPR	Post-illumination pupil response
PSC	Posterior Sub Capsular
QoL	Quality of Life Questionnaire
RAPD	Relative Afferent Pupil Defect
REK	Regional Ethical Committee
SAE	Serious Adverse Event
SAS	Statistical Analysis System
SD	Standard Deviation
SFT	Swinging flashlight test
ST	Standard Method
SOC	System Organ Class
SURSAR	Suspected Unexpected Serious Adverse Reactions
VAS	Visual Analogue Scale

0.4: Distribution of Clinical trial Protocols

Complete Version	Date	Writer	Receivers	Internal review	Date released
Version 0.1	*28.10.2021*	*SL*	*BD, GP, BHH, HF, VL, EL*	*Yes*	*No*
Version 0.2	*02.11.2021*	*SL*	*BD, GP, BHH, HF, VL, EL*	*Yes*	*No*
Version 0.3	*15.11.2021*	*SL*	*BD, GP, BHH, HF, VL, EL, AS, HS*	*Yes*	*No*
Final Version 1.0	*30.11.2021*	*SL*	*BD, GP, BHH, HF, VL, EL, AS, HS*	*No*	*30.11.2021*
Final Version 1.1	*10.12.2021*	*SL*	*BD, GP, BHH, HF, VL, EL, AS, HS*	*No*	*30.11.2021*
Final Version 1.2	*20.12.2021*	*SL*	*BD, GP, BHH, HF, VL, EL, AS, HS*	*No*	*30.11.2021*
Final Version 1.3	*19.01.2022*	*SL*	*BD, GP, BHH, HF, VL, EL, AS, HS*	*No*	*30.11.2021*
Final Version 1.4	*03.03.2022*	*SL*	*BD, GP, BHH, HF, VL, EL, AS, HS*	*No*	*03.03.2022*
Final Version 1.5	*22.03.2022*	*SL/BHH*	*BD, GP, HF, VL, EL, AS, HS*	*No*	*03.03.2022*

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BD: Bård Dalhøi
GP: Goran Petrovski
BHH: Bjørn Helland Hansen
HF: Hans Fagertun
VL: Vivy Larsen
EL: Einar Lundberg
AS: Alexander Sverstad
HS: Henrik Skaret

0.5: Participating Institutions

The study will be performed as a multicenter study at Oslo University Hospitals/Ullevål and Helgeland Hospital.

Content

I: Protocol Synopsis

1.1: Title.

Validation of Bulbicam for use on patient suffering from Diabetic retinopathy ((DR) and Age-related macular degeneration (AMD)

1.2: Protocol number

Protocol number: V1_OTH/DR; AMD - I/2022

1.3: Aim

- To investigate repeatability and stability of the six OTH-related Bulbicam tests in patients suffering from a) Diabetic retinopathy (DR), b) Age related macular degeneration (AMD) and matched healthy controls (HC).
- To compare Bulbicam and the Standard Method on measurements of Visual Field and Pupil
- To contribute to the establishment of normal range for DR and AMD patients with different degree in the disease development related to the Bulbicam tests.
- To contribute to the establishment of normal range for a normal population without eye-disease related to the Bulbicam tests.

1.4: Study population

The study consists of the following three study populations: 1) Patients suffering from DR of both genders above 18 years of age with different disease degree; 2) Patients suffering from AMD of both genders above 18 years of age with different disease degree; 3) Gender- and age-matched HC without any eye diseases.

1.5: Trial equipment

Bulbicam will be used in the study and the following six tests will be performed at each investigation: “Neurofield 64”, “Ptosis”, “Dynamic Acuity”, “Dynamic Contrast “, “Dark Adoption” and Pupil. The Standard Method will be used initially for measurements of “Neurofield64”, “Visual Field” and “pupil”.

1.6: Design

The study will be performed as a controlled, open, and non-randomized, stratified observational multicenter study. The stratification factors are the pathology of DR and AMD and the degree of disease. Within each of the four strata, healthy matched controls related to gender- and age (1:1) will be included. The degree of DR is defined as follows:

1) Mild retinopathy: Mild nonproliferative diabetic retinopathy
2) Moderate retinopathy: Moderate nonproliferative diabetic retinopathy

The degree of AMD is defined as follows:

1) Early AMD
2) Intermediate

For each included patient, a gender- and age-matched HC will be included. All included participants will perform Bulbicam eye-investigation twice at three flowing days with a rest period of at least one hour. Each investigation includes same six Bulbicam tests. The Standard method will only be performed once as the first investigation at day 1 for measurements of "Visual Field" and Pupil"

1.7: Variables

1.7.1 Main Variables

The main variables will be the variables recorded at the six Bulbicam tests described in the table below:

TEST	VARIABLE	UNIT	FORMAT
Visual Field	Seen/unseen (0)	0= unseen target	xml.
	Saccadic Reaction Time	Ms - 4 digits, 0 decimals	xml.
	Angular deviation	Degree - 3 digits, 0 decimals	xml.
	X-coordinate	Degree - 2 digits, 0 decimals	
	Y-coordinate	Degree - 2 digits, 0 decimals	
Ptosis	MDR1	mm - 2 digits, 2 decimals	xml.
	MDR2	mm - 2 digits, 2 decimals	xml.
Dynamic Acuity	Visual acuity	LogMAR 1 digit, 2 decimals	xml.
Dynamic Contrast	Contrast sensitivity	ConRatio 1 digit, 2 decimals	xml.
Dark Adaptation	Fixed contrast	Hz 1 digit, 1 decimal	xml.
	Fixed frequency	ConRatio 1 digit, 2 decimals	xml.
Pupil	Diameter (mm)	mm - 1 digit, 2 decimals	xml.
	Peak velocity	mm/s - 1 digit, 2 decimals	xml.
	Latency	Ms - 3 digits, 0 decimals	xml.
	RAPDlog	1 digit, 2 decimals	xml.

LogCon defined as -log10 (contrast ratio), EG if the low brightness part of the stimulus is 2 nits, the high brightness part 255 nits, the LogCon would be -log10 (2/255) =2, 1.

1.7.2 Supporting Variables

The supporting variables will be recorded by the Standard (ST) investigation for DR and AMD.

Test	No of instances	Variable	Unit	Unit description
GAT	1	Pressure	mmHg	2 digits, 1 decimal
iCare	1	Pressure	mmHg	2 digits, 1 decimal
Acuity chart	1	Visual acuity	logMAR	1 digit, 1 decimal
Contrast chart	1	Contrast acuity	Pelli-Robson score	1 digit, 2 decimals
Visual field	1	Nasal step	Present	Boolean (true / false)
	1	Temporal wedge		
	1	Partial arcuate (sup)		
	1	Partial arcuate (inf)		
	1	Arcuate (sup)		
	1	Arcuate (inf)		
	1	Altitudinal (inf)		
	1	Altitudinal (sup)		
	1	Paracentral		
	54	MD	dB	2 digits, 2 decimals
		X coordinate	Degrees	3 digits, 1 decimal
		Y coordinate	Degrees	3 digits, 1 decimal
	1	Threshold sensitivity	dB	2 digits, 2 decimals
	1	Percentile degree	Score 1-5	1 digit
	1	Defuse defect	dB	2 digits, 1 decimal
	1	Local defect	dB	2 digits, 1 decimal
	1	sLV	dB	2 digits, 1 decimal
	1	False positive	Percent (Reliability)	2 digits
	1	False negative	Percent (Reliability)	2 digits
	1	Reliability factor	Percent (Reliability)	2digits, 1 decimal
	1	Mean Sensitivity	dB	2 digits, 1 decimal
OCT RNFL	1	Average thickness	µm	3 decimals
OCT GCL	1	Volume	mm^3	3 decimals
Pupil	1	Diameter change (max-min)	mm	1 digit, 2 decimals

The central variables related to DR and AMD will be “RAPD NDF”, “Seen /unseen “,” Time until the given point is recorded as seen”, “the light in decibel when the point is seen”, X- and Y-coordinates and “Pupil diameter in mm” and “OCT RNFL “.

1.8: Study procedure

Participants, who fulfil the inclusion criteria; do not meet any of the exclusion criteria and willing to give informed consent to participate will receive an appointment for starting the study. The Bulbicam examination will be performed twice a day with a rest period of one hour between each registration. This procedure will be repeated the following two days. All demographic data, social factors and history of disease will be recorded at screening. Additionally, the quality of life (QoL) questionnaires EQ-5D-5L developed by EuroQol will be recorded initially as individual baseline values.

The Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be used for measuring and classifying the tolerability and toxicity at the end of each day of investigation.

1.9: Sample size

Sixteen DR patients and 16 AMD patients from each of the two categories will be recruited from the two participating hospitals. All together a total of 16x2=32 patients will be included. For each included patient, one gender- and age-matched HC will be recruited. In total 32 HC.

1.10: Time schedule

The study duration for each participant will be 3 days including six measurements using Bulbicam and one using the Standard method. The recruitment period is nine months. The total duration of the study will be as follows:

Inclusion of the first patient with control	01-05-2022
End of trial; last patient with control	15-01-2023
Closing database	15-02-2023
Finalized Clinical Study Report	01-03-2023

1.11: Flow chart

	Screening	Day 1; Repeatability	Day 2; Stability-1	Day 3; Stability-2
Inclusion and Exclusion criteria	x			
Oral & written informed consent	x			
Patient factors	x			
History of disease	x			
Eye-examination.	x			
Concom. Medicine	x	x	x	x
Quality of Life	x			
Bulbicam tests				
Visual Field		x	x	x
Ptosis		x	x	x
Dynamic Acuity		x	x	x
Dynamic Contrast		x	x	x
Dark Adaption		x	x	x
Pupil		x	x	x
Standard Method				
GAT		x		
ICare		x		
Visual Field		x		
Pupil		x		
OCT RNFL		x		
OCT GCL		x		
Adverse Events [CTCAE]	x	x	x	x
End of study				x

II: Introduction

2.1: Background

2.1.1:Diabetic Retinopathy (DR) remains a common complication of diabetes mellitus and is a leading cause of vision loss elderly population globally.[2] Among those with diabetes, global prevalence was 22.27% (95% confidence interval, 19.73-25.03%) for Diabetic retinopathy, 6.17% (95% CI 5.43-6.98%) for vision-threatening DR and 4.07% (95% CI 3.42-4.82%) for clinically significant macular edema.[3] The prevalence of DR in Indian population with DM was 19% (95% CI 16-20.1%).[4] DR prevalence was highest in Africa (35.90%), and North American and Caribbean regions (33.30%); and lowest in South and Central America region (13.37%). In meta-regression models adjusting for habitation type, response rate, study year and DR diagnostic method, Hispanics (odds ratio [OR], 2.92; 95% CI, 1.22-6.98) and Middle Easterners (OR, 2.44; 95% CI, 1.51-3.94) with diabetes were more likely to have DR, compared to Asians.[2] The major risk factors of DR include disease duration, poor glycaemic control, presence of hypertension, higher body mass index, puberty, pregnancy, and cataract surgery. Early detection and treatment can prevent any diabetic-related visual impairment. To reduce the impact of DR-related visual loss, it is important to look for innovative ways of managing and preventing diabetes and optimize cost-effective screening programs within the community.

Diabetic Retinopathy can be clinically characterised into a non-proliferative (NPDR) stage and proliferative (PDR) stage depending on the retinal vascular lesions. It can also lead to fluid accumulation in the retina called diabetic macular edema (DME). Visual functions are affected in the early and late stage of the disease. Current research shows that contrast sensitivity is a more sensitive tool to detect early retinal changes than visual acuity. In a recent study contrast sensitivity score was noted to be significantly lower in diabetic patients with no retinopathy and mild nonproliferative retinopathy.[5] Cone photoreceptor light sensitivity is responsible for light adaptation and rod light sensitivity for dark adaptation and performance. Studies on retinal neurodegeneration in DM have reported abnormalities of inner-retina structure and function. These include reduced retinal ganglion cell thickness, abnormal ERG patterns i.e., reduced photonic and scotopic response.[6]Delay in high-frequency flicker ERG and reduced cone sensitivity have been reported in early cases that can serve as a screening tool. Reduction in pattern ERG, photonic negative response (PhNR) and the post-illumination pupil response (PIPR) have been reported in diabetic patients with and without NPDR.[7] Light and dark adapted steady state pupil size and melanosis mediated pupil light reflex are reduced in diabetes and all stages of DR.[8,9] These proof-of-concept studies demonstrate that chromatic pupilometer methods can serve as a screening and early detection tool to assess the damage to photoreceptors of retinal/optic nerve diseases. Dark adaptation is being reported to be affected in retinal dysfunction conditions such as ARMD, Diabetic Retinopathy and Retinitis Pigmentosa. In addition to the effect of early DR on cone-mediated light sensitivity, the second most impaired visual function was rod-mediated visual sensitivity. These indicate diabetes exerts early impact on the inner and outer retinal function.[10] Dark adaptation was measured in NPDR using AdaptDx dark adaptometer (MacuLogix, IncHummelstown, PA, USA) and the results suggested that RPE and photoreceptor cell dysfunction was noted to be progressed with worsening DR and rod recovery dysfunction occurred earlier than cone dysfunction.[11]

2.1.2: Age-related macular degeneration (AMD) is the main cause of adult blindness in the Western world. The prevalence of advanced AMD in two studies were 1,6% and 1,5% respectively, and the incidence of AMD in the population of >75 years of age is significantly

growing, which is becoming a big public health problem as the population of elderly is expected to increase by 54% between 2005 and 2025 in a Western population [12,13].
In developing countries there is little data on the prevalence of the disease[3].
In a study from India, there is evidence that AMD may exist to the same extent as it does in developed countries. The prevalence of early (dry form) and late (wet form) stages of AMD is like that observed in Western populations. The prevalence in the age of >80 years seems to be underestimated [14]. In countries with growing elderly populations, it is important for society to plan for low-vision services and rehabilitation, which implies the need for early detection of AMD.
Research states subjects in the early stages of dry AMD have delayed dark adaptation (DA), which indicates a delay of light sensitivity by the photoreceptors (cones and rods), which have been exposed to bright light[15-21]. The photoreceptors of cones and rods are slowly increasing their sensitivity to light in a dim environment. Cones adapt faster, so the first few minutes of adaptation is related to the cone moderated vision. Rods adapt slower, but can adapt to dimmer illuminations, and they replace the cone mediated period. The method of functionally assessing DA in early detection of dry AMD is described in multiple studies. Patients with dry AMD have problems with their vision under low light conditions. Therefore, the functional sign of early AMD is the lack of the subject's ability to adapt in the dark after being exposed to light. The rod photoreceptor cells are extremely sensitive and can be triggered by a single photon [22-23]. Cone photoreceptor cells improve sensitivity quickly and recover their total function after 5 to 10 minutes. There is a transition from cone to rod function in dark adaptation, and the rod responses to changes in light level is thought to be slow as the rods take 20 to 40 min to fully recover after the offset of a bright light [24]. Although rod recovery is affected in early AMD, cone sensitivity is investigated also to be an effective index of early AMD detection[25-26]. To clinically investigate the rod adaptation is time consuming for the patient and may last up to 20 to 40 minutes, whereas cone adaptation should not take longer than 1-2 minutes, as cones take up to 2 min to recover in the dark. As both cones and rods are affected in early AMD, it is more time saving to investigate the cone DA effort.
When bleaching the retinal photo pigments exposed to lower light levels, there is an adaptation in the retinal neurons fed by the cones. The approximate time for recovery in the dark after moderate light adaptation is said to be ± 15 sec in the blue/yellow pathway[27] and ± 20 s in the red/green pathway for the recovery[28]. It is even shown that there is a very rapid adaptation that takes less than 0.6 sec[29]. AMD usually classifies as "Early" and "Intermediate".

2.2: BulbiCam

BulbiTech AS has developed a hardware/software product combination to simplify neuro-ophthalmic examinations. The multi-test device, BulbiCam (BCAM), is a combined eye tracking; pupil metric; video graphic dual device which include the following 10 tests under development and ready for validation:

1. 26 grids glaucoma screening perimetry
2. 64 grids full perimetry (NeuroField64)
3. Pupil and Relative Afferent Pupil Defect (RAPD) assessment
4. Semi-automatic ptosis (droopy eyelid) grading
5. Video-based nystagmus test
6. Dynamic acuity and contrast sensitivity test
7. Dark adaptation test
8. Smooth pursuit eye movements
9. Saccade movements

10. Eye fixation stability

BCAM is connected to the BulbiHub software where measured data is stored and presented in numbers, diagrams, and graphs.

2.3: Standard Method

Standard Method (ST) is the notation used for the golden eye-examination standard today. The supporting variables will be recorded by the Standard (ST) investigation for DR and AMD.

Table 1: Standard examination

Test	No of instances	Variable	Unit	Unit description
GAT	1	Pressure	mmHg	2 digits, 1 decimal
iCare	1	Pressure	mmHg	2 digits, 1 decimal
Acuity chart	1	Visual acuity	logMAR	1 digit, 1 decimal
Contrast chart	1	Contrast acuity	Pelli-Robson score	1 digit, 2 decimals
Visual field	1	Nasal step	Present	Boolean (true / false)
	1	Temporal wedge		
	1	Partial arcuate (sup)		
	1	Partial arcuate (inf)		
	1	Arcuate (sup)		
	1	Arcuate (inf)		
	1	Altitudinal (inf)		
	1	Altitudinal (sup)		
	1	Paracentral		
	54	MD	dB	2 digits, 2 decimals
		X coordinate	Degrees	3 digits, 1 decimal
		Y coordinate	Degrees	3 digits, 1 decimal
	1	Threshold sensitivity	dB	2 digits, 2 decimals
	1	Percentile degree	Score 1-5	1 digit
	1	Defuse defect	dB	2 digits, 1 decimal
	1	Local defect	dB	2 digits, 1 decimal
	1	sLV	dB	2 digits, 1 decimal
	1	False positive	Percent (Reliability)	2 digits
	1	False negative	Percent (Reliability)	2 digits
	1	Reliability factor	Percent (Reliability)	2digits, 1 decimal
	1	Mean Sensitivity	dB	2 digits, 1 decimal
OCT RNFL	1	Average thickness	µm	3 decimals
OCT GCL	1	Volume	mm^3	3 decimals
Pupil	1	Diameter change (max-min)	mm	1 digit, 2 decimals

2.4: Objective

The objective in this study is to validate the six of the BCAM tests to be used in examination of patients suffering from DR or AMD. The specific aims of the study are:

- To investigate repeatability and stability of the six OTH-related BCAM tests in patients suffering from a) DR, b) AMD and c) gender- and age-matched HC.
- To compare BCAM and the Standard Method on measurements of Visual Field and Pupil to ensure that BCAM measures what is assumed to measure.
- To contribute to the establishment of normal range for DR and AMD patients with different degree in the disease development related to the BCAM tests.

- To contribute to the establishment of normal range for a normal population without eye-disease related to the BCAM tests.

III: Population and sampling

3.1: Reference population

The reference population consists of patients either suffering from DR or AMD without other eye diseases.

3.2: Study populations

3.2.1: Inclusion criteria; study population 1 (DR)

Consists of patients diagnosed with DR of both gender; passed the age of 18 years; without any other eye disease; suffering from other know serious disease but have a health situation in accordance with expectations related to the age.

3.2.2: Exclusion criteria; study population 1 (DR)

Patients fulfil at least one of the following criteria will be excluded from participation in the study:

- Other visual disturbances and blindness
- Posterior Chamber Intra Ocular Lens (PCIOL)
- Physical or psychiatric disease, which may disturb the measuring procedure
- Patients who are not able to perform eye movements, so no full paresis of any ocular muscles.
- Patients whose visual acuity is less more than 1 logMAR in any eye, as these will not be able to focus on the test stimuli.
- Patients whose visible part of the eye is abnormal, such as subconjunctival hemorrhages or deformed pupils.
- Patients whose pupils are not able to respond normally to dilation or contraction due to damaged nerves, mechanical damage of the pupil etc.
- Participating in another clinical trial with pharmaceuticals the last six weeks before start of this trial treatment.
- With known alcoholic and drug dependency
- Not able to understand information.
- Not willing to give written consent to participate in the study.

3.2.3: Inclusion criteria; study population 2 (AMD)

Consists of patients diagnosed with AMD of both gender; passed the age of 18 years; without any other eye disease; suffering from other know serious disease but have a health situation in accordance with expectations related to the age.

3.2.4: Exclusion criteria; study population 2 (AMD)

Patients fulfilling at least one of the following criteria will be excluded from participation in the study:

- Other visual disturbances and blindness
- Posterior Chamber Artificial Ocular Lens (PCIOL)
- Physical or psychiatric disease, which may disturb the measuring procedure

- Patients who are not able to perform eye movements, e.g., full paresis of any ocular muscles
- Patients with visual acuity more than 1 logMAR, as they will not be able to focus on the test stimuli
- Patients whose visible part of the eye is abnormal, such as subconjunctival haemorrhages or deformed pupils.
- Patients whose pupils are not able to respond normally to dilation or contraction due to damaged nerves, mechanical damage of the pupil etc.
- With known alcoholic and drug dependency
- Not able to understand information.
- Not willing to give written consent to participate in the study.

3.2.5: Inclusion criteria; study population 3 (HC)

The study population 3 consists of gender- and age-matched controls to patients in study population 1 or 2; passed the age of 18 years without any eye diseases; not suffering from other know serious disease and have a health situation in accordance with expectations related to the age.

3.2.6: Exclusion criteria; study population 3 (HC)

Patients fulfilling at least one of the exclusion criteria listed under either paragraph 3.2.2 or 3.2.4 will be excluded from participation in the study

3.3: Recruitment of patients

The patients will be recruited from Oslo University hospital, Ullevål and Helgeland hospital. If necessary, private Ophthalmology clinics in Oslo will be asked for recruitment. All the investigations in the study will be performed by the same Ophthalmologist at the given hospital. The investigator informs the patients about the study, handing and collecting the written informed consent form. In case the patient fulfils the inclusion/exclusion criteria and willing to sign the consent form, the patient is included in the study. No data from possible participants included in the screening phase but not fulfils the inclusion/exclusion criteria will be recorded in the database. The included patient will be asked if he/she know any person with same gender and age; in good health condition without any eye disease which may participate as a control in the study. The potential controls will be contacted by the responsible investigator, obtain information about the study, and expected tasks. Controls willing to sign the consent form is included in the study. In case of lack in controls, requests among the hospital staff will be performed.

3.4: Benefit and risk assessment

BulbiCam is new equipment specially developed for clinical investigation of eye. It will simplify neuro-ophthalmic examinations; increase the quality- and benefit of the examinations; detecting earlier correct diagnoses and increase the knowledge of the disease development under treatment. BCAM do not harm neither to the patients nor to the investigator.

IV: Design

4.1: Study design

The study will be performed as a controlled, open and non-randomized, stratified observational multicenter. The two stratification factors will be ophthalmological diagnose and the severity of the disease.

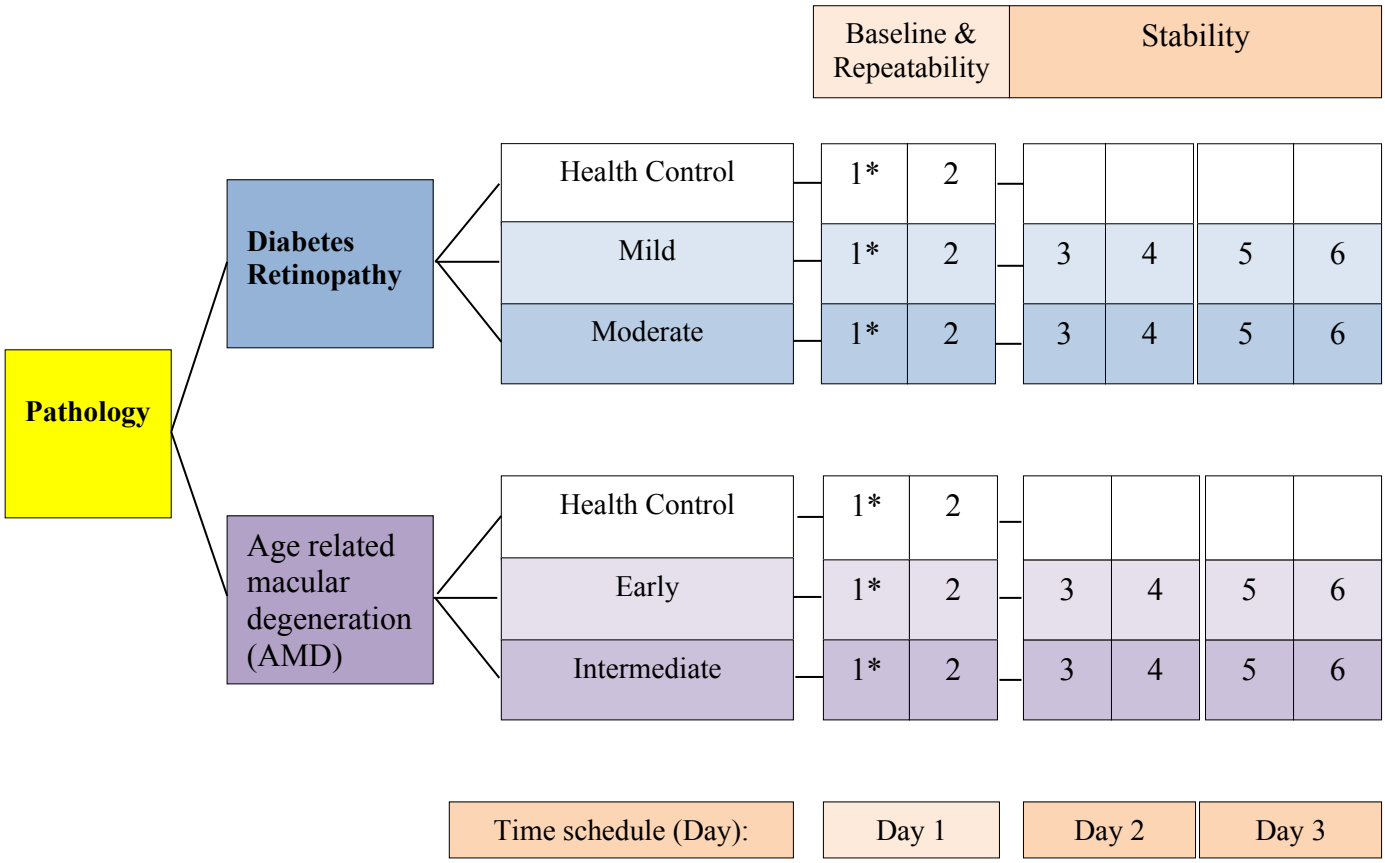


Figure 1: The overall study design. The numbers 1 to 6 indicate the sequence of Bulbicam measurements and *) the measurements using the Standard Method

4.2: Stratification

The two main strata are DR and AMD. The patients within each of these two strata will be divided in two sub-strata depending on the disease severity. Within each of the main strata, a third stratum will consist of gender- and age-matched HCs to the patients included in the two other sub-strata.
The three sub-strata within DR will be:

1. Healthy gender- and age-matched controls
2. Mild retinopathy: Mild nonproliferative retinopathy
3. Moderate retinopathy: Moderate nonproliferative retinopathy

The three sub-strata within AMD will be:

1. Healthy gender- and age-matched controls
2. Early AMD
3. Intermediate AMD

4.3: Identification of patients

All information in the database will be anonymized and the activation key is stored by the clinically responsible ophthalmologist. The patients will be given one study identification number of six digits. The Id-number is divided in two parts in which the first part consists of four digits based on; country; site; disease and degree of the disease. Within these four-digit groups, two digits running number will be created by the DB-system.

Digit 1:	Indicate the country [1=Norway; 2=India i.e.]
Digit 2:	Indicate hospital site [1 = Site 1/Ullevål; 2= Site 2/Helgeland i.e.]
Digit 3:	Disease [0= Control; 1=Gla; 2=Cat; 3=DR; 4=AMD; 5=MS, i.e.].
Digit 4:	Degree of disease [0= none; 1= Mild/Early; 2=Moderate/Intermediate; 3=Severe].
Digit 5&6:	Running number within group [01= Patient 1; 02=Patient 2 i.e.]

V: Evaluation

5.1: Main variables

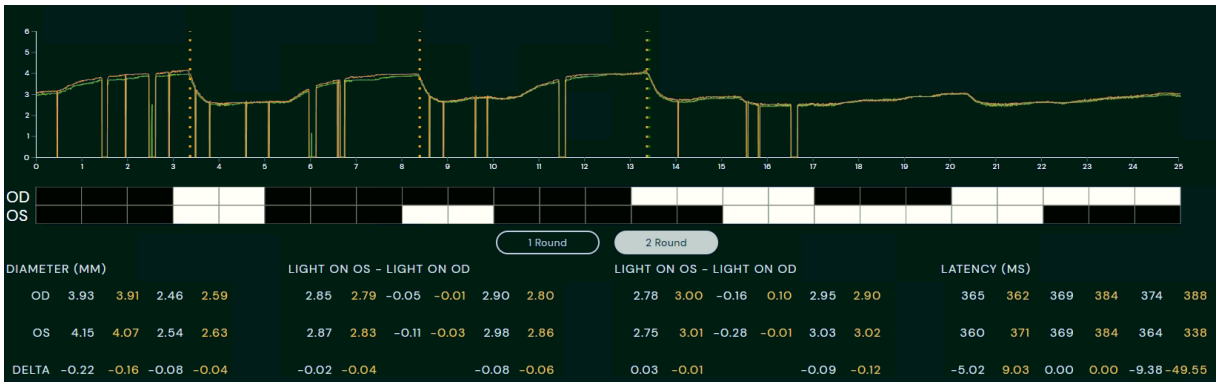
5.1.1: BulbiCam investigation

The main variables will be the variables recorded at the six Bulbicam tests described in the table below:

Table 2: The main variables with unit of the six Bulbicam test included in the study

TEST	VARIABLE	UNIT	FORMAT
NeuroField64	Seen/unseen (0)	0= unseen target	xml.
	Saccadic Reaction Time	Ms - 4 digits, 0 decimals	xml.
	Angular deviation	degree - 3 digits, 0 decimals	xml.
Ptosis	MDR1	mm - 2 digits, 2 decimals	xml.
	MDR2	mm - 2 digits, 2 decimals	xml.
Dynamic Acuity	Visual acuity	LogMAR 1 digit, 2 decimals	xml.
Dynamic Contrast	Contrast sensitivity	ConRatio 1 digit, 2 decimals	xml.
Dark Adaptation	Fixed contrast	Hz 1 digit, 1 decimal	xml.
	Fixed frequency	ConRatio 1 digit, 2 decimals	xml.
Pupil	Diameter (mm)	mm - 1 digit, 2 decimals	xml.
	Peak velocity	mm/s - 1 digit, 2 decimals	xml.
	Latency	Ms - 3 digits, 0 decimals	xml.
	RAPDlog	1 digit, 2 decimals	xml.

For Pupil module, a typical continuous recording of the pupil size and parameters is shown below:



LogCon defined as -log10 (contrast ratio), EG if the low brightness part of the stimulus is 2 nits, the high brightness part 255 nits, the LogCon would be -log10 (2/255) =2, 1.

5.1.2: Standard investigation

The supporting variables will be recorded by the Standard (ST) investigation for DR and AMD.

Table 3: The supporting variables with unit of the standard eye investigation

Test	No of instances	Variable	Unit	Unit description
GAT	1	Pressure	mmHg	2 digits, 1 decimal
iCare	1	Pressure	mmHg	2 digits, 1 decimal
Acuity chart	1	Visual acuity	logMAR	1 digit, 1 decimal
Contrast chart	1	Contrast acuity	Pelli-Robson score	1 digit, 2 decimals
Visual field	1	Nasal step	Present	Boolean (true / false)
	1	Temporal wedge		
	1	Partial arcuate (sup)		
	1	Partial arcuate (inf)		
	1	Arcuate (sup)		
	1	Arcuate (inf)		
	1	Altitudinal (inf)		
	1	Altitudinal (sup)		
	1	Paracentral		
	54	MD	dB	2 digits, 2 decimals
		X coordinate	Degrees	3 digits, 1 decimal
		Y coordinate	Degrees	3 digits, 1 decimal
	1	Threshold sensitivity	dB	2 digits, 2 decimals
	1	Percentile degree	Score 1-5	1 digit
	1	Defuse defect	dB	2 digits, 1 decimal
	1	Local defect	dB	2 digits, 1 decimal
	1	sLV	dB	2 digits, 1 decimal
	1	False positive	Percent (Reliability)	2 digits
	1	False negative	Percent (Reliability)	2 digits
	1	Mean Sensitivity	dB	2 digits, 1 decimal
	1	Reliability factor	Percent (Reliability)	2digits, 1 decimal
OCT RNFL	1	Average thickness	µm	3 decimals
OCT GCL	1	Volume	mm^3	3 decimals
Pupil	1	Diameter change (max-min)	mm	1 digit, 2 decimals

The central variables related to DR and AMD will be “RAPD NDF”, “Seen /unseen “,” Time until the given point is recorded as seen”, “the light in decibel when the point is seen”, X- and Y-coordinates and “Pupil diameter in mm” and “OCT RNFL “.

5.2: Secondary variables

5.2.1: Quality-of- Life questionnaires[30]

The Quality-of-Life (QoL) questionnaires EQ-5D-5L developed by EuroQol will be recorded the same day as the first BCAM registration.
The QoL questionnaire EQ-5D-5L consists of 5 dimensions; “Mobility”, “Self-care”, “Usual activities”, “Pain / Discomfort” and “Anxiety / Depression”[30, 31, 32]. Each of these five dimensions has 5 levels. Additionally, the patient scores the daily health situation on a 20 cm subdivided Visual Analogue Scale (VAS) with defined endpoints. The questionnaire is administrated by the investigators and will be given in patient’s mother tongue language.

Under each heading or dimension, the patient is asked to describe the health situation today:

MOBILITY
I have no problems in walking about □ (1)
I have slight problems in walking about □ (2)

I have moderate problems in walking about □ (3)
I have severe problems in walking about □ (4)
I am unable to walk about □ (5)

SELF-CARE
I have no problems washing or dressing myself □ (1)
I have slight problems washing or dressing myself □ (2)
I have moderate problems washing or dressing myself □ (3)
I have severe problems washing or dressing myself □ (4)
I am unable to wash or dress myself □ (5)

USUAL ACTIVITIES (e.g., work, study, housework, family or leisure activities)
I have no problems doing my usual activities □ (1)
I have slight problems doing my usual activities □ (2)
I have moderate problems doing my usual activities □ (3)
I have severe problems doing my usual activities □ (4)
I am unable to do my usual activities □ (5)

PAIN / DISCOMFORT
I have no pain or discomfort □ (1)
I have slight pain or discomfort □ (2)
I have moderate pain or discomfort □ (3)
I have severe pain or discomfort □ (4)
I have extreme pain or discomfort □ (5)

ANXIETY / DEPRESSION
I am not anxious or depressed □ (1)
I am slightly anxious or depressed □ (2)
I am moderately anxious or depressed □ (3)
I am severely anxious or depressed □ (4)
I am extremely anxious or depressed □ (5)

In addition, the patient will describe his /her daily health situation on a 100mm VAS (Figure 2)

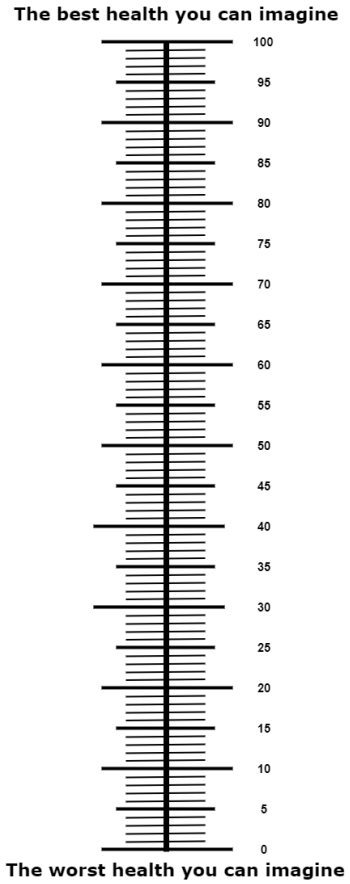


Figure 2: EQ-Visual Analogue Scale

5.2.2: Common Terminology Criteria for Adverse Events version 4.0

The tolerability variables will be evaluated by using CTCAE version 4.0.[33]
The CTCAE is divided in 26 System Organ Class (SOC) in accordance with the MedDRA hierarch. Within each SOC, adverse events (AE) are listed and accompanied by descriptions of severity or grade:

- Blood and lymphatic system disorders (11 Items)
- Cardiac disorders (36 Items)
- Congenital, familial, and genetic disorders (1 Items)
- Ear and labyrinth disorders (9 Items)
- Endocrine disorders (11 Items)
- Eye disorders (25 Items)
- Gastrointestinal disorders (117 Items)
- General disorders and administration site conditions (24 Items)
- Hepatobiliary disorder (16 Items)
- Immune system disorders (6 Items)
- Infections and infestations (76 Items)
- Injury, poisoning and procedural complications (77 Items)

- Investigations (38 Items)
- Metabolism and nutrition disorders (24 Items)
- Musculoskeletal and connective disorders (41 Items)
- Neoplasms benign, malignant, and unspecified incl. cysts and polyps (5 Items)
- Nervous system disorders (63 Items)
- Pregnancy, puerperium, and perinatal conditions (5 Items)
- Psychiatric disorders (20 Items)
- Renal and urinary disorders (20 Items)
- Reproductive system and breast disorders (51 Items)
- Respiratory, thoracic, and mediastinal disorders (59 Items)
- Skin and subcutaneous tissue disorders (34 Items)
- Social circumstances (2 Items)
- Surgical and medical procedures (1 Item)
- Vascular disorders (17 Items)

5.2.2.1: Grading and classification of Items

Grade refers to the severity of the AE. The CTCAE displays Grade 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 0 =	None
Grade 1 =	Mild: asymptomatic or mild symptoms; clinical or diagnostic Observations only; intervention not indicated
Grade 2 =	Moderate: minimal, local or non-invasive intervention indicated. Limiting age-appropriate instrumental Activity of Daily Living (ADL)
Grade 3 =	Severe or medically significant, but not immediately life-threatening: Hospitalization or prolongation of hospitalization indicated disabling. Limiting self-care ADL
Grade 4 =	Life-threatening consequences; urgent intervention indicated
Grade 5 =	Death related to AE.

Relationship to trial medication as: “Unrelated”, “Possibly”, “Probably” or “Definitely”

Action taken as:	“None”,” Interruption”, “Modified” or “Discontinued”
AE treatment as:	“None”, “Continue Medication”, “Procedure” or “Hospitalization”
Outcome at last visit as:	“Resolved”, “Ongoing” or “Fatal”

Definitions of relationship to study medication are as follows:

Unrelated:	bears no relation to timing of medication, like symptoms or signs expected in the disease process, does not recur on re-challenge.
Possibly:	bears relation to timing of medication, like symptoms or signs expected in the disease process, does not recur on re-challenge.
Probably:	bears clear relation to timing of medication, distinct from symptoms or signs expected in the disease process, does not recur on re-challenge.

Definitely: bears clear relation to timing of medication, distinct from symptoms or signs expected in the disease process, recurs on re-challenge.

5.2.2.2: Outcome variables

The CTCAE results in two response variables. The main one is the sum of CTCAE score obtained by summarization of all the score obtained at a given visit. This is shown as Sum CTCAE. The second is the maximum) recorded score (Max CTCAE) given as the highest observed CTCAE score at a given visit. This is the most common way of reporting AE but has low statistical power to detect changes in toxicity during treatment. However, it is usable in classification of change in tolerability of treatment.

5.2.2.3: Serious Adverse Event (SAE)

An adverse event is any untoward symptom or sign befalling a patient in a clinical trial regardless of its relationship to the study medications. All adverse events must be described in detail and their severity and putative relationship to the study medication noted.
Adverse events may be considered seriously (SAE). The definition of this is as follows:

- Death
- Life threatening
- Leads to or prolongs hospitalization
- Results in persistent of significant disability
- Congenital anomaly

All adverse events will be recorded on relevant forms and their attribution to study medication will be evaluated. The severity of the reactions will be recorded along with a brief description of the event.
SAEs will be reported to sponsor and to the local sponsor representative via e-mail as soon as possible, but in any case, within 24 hours of the PI's knowledge of the event. It is the responsibility of the Principal Investigator to notify the Ethics Committee. It is the responsibility of the sponsor to report any Suspected Unexpected Serious Adverse Reactions (SUSAR) to the Regulatory Authority.
In case of SAE or SUSAR occurs, this will be handled in accordance with the hospital routines.

5.3: Patient factors

The patient factors recorded in the study will be age in days from birth to the screening visit calculated in the database and gender. The disease degree and previous and ongoing treatments of the disease will be recorded. Additionally, concomitant disease and treatments will be recorded.

Age and gender will be used to recruit controls to the included patients. Concomitant diseases and medication together with history of disease will be used to demonstrate the health condition of the participants at the time of inclusion in the study. Additionally, quality of life of the participants will be recorded at screening. This will also be a part of the health

evaluation but also gives the possibility of comparing the patients with the age- and gender matched controls.

VI: Study procedure

6.1: Trial equipment and clinical procedure

In this study only Bulbicam (BCAM) version 1.7 will be used. Additionally, ST will be performed as the starting examination
The study will be performed according to European GCP regulation. All the participants have to perform BCAM registration twice per day in three consecutive days. Each registration will have duration of 15 minutes with one hour rest between the two observations. In case AE of grade 3 or 4 according to CTCAE occurs during the study, the participants will contact the responsible investigator. The BCAM registration will be stopped for at least 2 days or until the disappearance of the symptoms. The responsible investigator decides if the participant will continue or withdraw from the study.

6.2: Inclusion visit and Screening phase

Both patients and the age- and gender matched controls must have a health situation in accordance with expectations related to the age and not suffering from other know serious disease. Participants, who fulfil the inclusion criteria; do not meet any of the exclusion criteria and willing to give informed consent to participate will be invited to participate and receive an appointment for starting the study (CRF III). No data from possible participants included in the screening phase but not fulfils the inclusion/exclusion criteria will be recorded in the database. During this initial inclusion visit, all demographic data and medical history will be recorded (CRF I & CRF II). Additionally, the QoL questionnaires EQ-5D-5L developed by EuroQol will be recorded initially as individual baseline values (CRF IV). The Common Terminology Criteria for AE (CTCAE) will be used for measuring the baseline AE situation (CRF V). The results from the initial measurements of the visual field and pupil obtained by ST will be recorded on CRF VI.

6.3: Study procedure

The clinical part of the study consists of two parts.

6.3.1: Part one (Repeatability)

This part will be performed the first day in the study; starting with the initial ST measurement and followed by two BCAM measurements (Fig 1). Each measurement includes the following six BCAM tests: Visual Field, Ptosis, Dynamic Acuity, Dynamic Contrast, Dark Adoption, and Pupil. Between the two measurements, a one-hour rest period will be included. ST includes Visual Field and Pupil. At the end of the last measurement a new CTCAE registration will be performed.

6.3.2: Part 2 (Stability)

This part will be performed during two following days and consists of two BCAM measurements each day (Fig 1). Each measurement includes the same six BCAM tests as described in part 1 with one-hour rest period between the two registrations. At the end of each day in this stability part a new CTCAE registration will be performed.

6.4: End of the study

As soon as possible after the last BCAM registration is done, the responsible investigator has to finalize the “End-of-Trial” CRF (CRF VI)

6.5: Stopping rule

If AE of grade 3 or 4 according to CTCAE occur, the participant will contact the responsible investigator. The BCAM registration will be stopped for at least 2 days or until disappearance of the symptoms. The responsible investigator decides if the participant will continue or withdraw from the study.
In case of life-threatening AE, SAE or SUSAR occurs, the BCAM registration has to stop until the disappearance of the symptoms. If possible, treatment of the symptoms will be given in accordance with the hospitals' routines. In case of life-threatening AE, SAE or SUSAR occurs at one of the sites, the other participating site will be informed at once by the study manager.

6.6: Report of serious adverse effect (SAE)

The patient will be advised to contact the investigator if she/he suffers from severe AE or any other annoying conditions.
In case of SAE or SUSAR, the investigator has to complete the SAE form and send it to the health authorities. All AE's will be recorded on relevant forms and their attribution to study intervention will be evaluated. The severity of the reactions will be recorded along with a brief description of the event.
SAEs and SUSAR will be reported to health authorities with copy to BulbiTech A/S and the project manager Prof. Stig Larsen by e-mail as soon as possible, but in any case, within 24 hours of the PI's knowledge of the event. It is the responsibility of the sponsor to report any SAE and SUSAR to the Regulatory Authority. In case of SAE or SUSAR occurs, this will be handled in accordance with the hospital routines.

Prof Stig Larsen
Meddoc AS,
Hvamstubben 14B 2013 Skjetten
Phone: +47 41 32 63 25
E-mail**: sl@meddoc.no**

6.7: Study duration

The study duration for each participant will be 3 days. The recruitment period is nine months. The time schedule of the study will be as follows:

Inclusion of the first patient with control	01-05-2022
End of trial; last patient with control	15-01-2023
Closing database	15-02-2023
Finalized Clinical Study Report	01-03-2023

VII: Project management and Monitoring

7.1: Project management

Prof Stig Larsen supported by Bård Dalhøi will administer the study. Vivy L Larsen (MSC) will oversee Data Management and clinical monitoring supported by the clinical staff at Meddoc. Hans E Fagertun (MSC) and Prof Larsen will oversee the statistical analysis. Prof Goran Petrovski will evaluate the ophthalmological part of the results.

7.2: Publication of the results

The results will be published in an international medical journal. In principle, all the participating centers will be represented in the list of authors. The rules stated in the Vancouver recommendation will be followed.

7.3: Quality assurance demands

The hospital sites will be monitored at regular intervals at site and electronically during the study. It is the duty of the investigator to provide open access to the monitor to all study related records at previously agreed times and locations.

In conducting the trial, the investigator accepts that the Sponsor, the regional Ethics Committee, the regulatory body, and monitor may, at any time, by appointment, conduct an audit of the study site.

In conducting the trial, the Sponsor accepts that the Ethics Committee or the regulatory body may, at any time, by appointment, conduct an audit of the study site, the laboratories conducting any clinical testing or the Good Manufacturing Practice (GMP) manufacturing facilities.

7.4: Start-up and closing visit

The project manager and the clinical monitor will perform the start-up visit. The visit will consist of a site inspection, information, instruction and handing over the needed study materials as e-CRFs. A training program in use of the electronical data catching system InCRF will be given.
The project manager will perform the closing visit within one month after the last patient on the given site has finalized the study. All the trial material including CRFs will be removed from the site, but copies of the CRFs from the included patients will be stored at the site.

7.5: Monitoring procedure

Essential demographic data will be documented both within the patients' hospital record notes as source data and within the trial e-CRFs. This has to be available for inspection by the clinical trial monitor. Source data will also include the date of written consent. The times and dates of any other investigations must also be recorded.

It is the responsibility of the investigator to maintain accurate and up to date records of all clinical trial related activities, which should be legibly entered onto the e-CRFs provided. The e-CRFs should be made available to the monitor on request, and in the event of a formal investigator site audit.

On completion of the study, one copy of the e-CRFs will be retained at the hospital site for the duration stipulated by International Conference on Harmonization Good Clinical Practice (ICH/CGP), which currently is 5 years.
The eCRFs can be accessed online via web-based database InCRF. The contents of eCRFs should be approved by the investigators.
Monitoring at site will be performed at least three times at each participating hospital during the study. Monitoring report will be sent to the project manager latest one week after each site inspection.

7.6: Curriculum vitae

The investigators have to submit an updated CV documenting their expertise in the relevant clinical field. The CV has to be signed and dated by the physician and a copy has to be attached to the protocol if required according to international rules. Another copy must be kept in the Trial Master File and a third copy in the Site File.

7.7: Site file

On behalf of the Sponsor, Meddoc AS will supply the investigators with a Site File. The Site File should contain all relevant documents for the study. The investigator is responsible for keeping the Site File updated and secure that all required documents are present in the Site File. The Site File will be inspected during the monitor visits.

VIII: Data Management

8.1. Case Record Forms (CRF)

In this study the electronical database and data catching system InCRF will be used. The identity of the participants in the database will be anonymized. The activation key is stored and only to be used by the clinically responsible ophthalmologist. Each study participants are given a study identification number which will be stored in the database. The data manager (DM) and the DM-staff at Meddoc will perform the secondary monitoring on the e-CRFs. Prior to study start, a data entry instruction document will be made. Source data consist of printouts from the laboratory examinations; baseline characteristics; clinical examination collected by the investigator and entered by site. In case of missing data or need of clarification, the responsible monitor will contact the site.

8.2. Study Database

The validated data management system InCRF will be used for collecting the CRF data. The system selected is compliant with GCP guidelines and subject to 21 CFR (Code of federal regulations) FDA part 11 requirements. The final database will be stored in the Statistical Analysis system (SAS ver. 9.4 or later).

8.3: Data handling

A data entry person at site will enter the e-CRF data in InCRF and the DM will perform the initial data validation. In case of missing data, logical errors or interpretation problems, a query will be generated directly in InCRF. Investigator can review the query status via either InCRF function of “Study reports” /” Query report” or patient’s e-Form dashboard. When all the needed participants have finalized the clinical part, and the investigator has electronically signed the e-CRFs, the DM will do the final verification checks and perform final database hard-lock when all errors are corrected.
Screening analysis for logical errors will be evenly performed on this database and errors will be corrected after new information is collected from the site. When all the detected errors are corrected, the main basic database will be locked. The database will be transformed to a labeled SAS database, which also will be locked up to prevent all possible changes or additions. In this copy, the responsible statistician can make derivations but no corrections of the data. If corrections are needed, the main basic study database has to be re-opened and corrected. The international procedure for such changes will be followed.

IX: Discontinuation

A patient may discontinue the study at any time if, in the view of the investigator, it is in the participant's best interests. Alternatively, the participant has the right to discontinue her/his consent and exit the study without prejudice concerning her/his future treatment or care.
If a participant does not show up to an agreed visit, the investigator should try to motivate her/him to continue. However, if the participant has decided not to continue, she/he should be asked to attend a control visit as described for the end of the study (CRF VI).

9.1: Discontinuation not related to the study question

A participant who discontinues the study for administrative reasons or reasons documented not related to the trial equipment classifies as "Drop out" and has to be replaced by a new participant. Such participants will not be included in the statistical analysis.

9.2: Discontinuation related to the study question

Participants discontinue the study for the reasons are related to or might be related to the trial equipment will be classified as "Patient Withdrawal". These participants will not be replaced. They will be included in the Per-Protocol (PP) and the ITT analysis using the "Last-observation-carried-forward" (LOCF) procedure.

X: Ethical consideration

10.1: Consideration of steering committee

The study will be conducted in compliance with the protocol and according to the Helsinki declaration with latest amendments and Good Clinical Practice (GCP).
Participants will only be included in this clinical trial after approval of the trial by the regional Ethical Committee (REK). The patients will receive oral and written information and have to give signed informed consent for participation.
All participants invited to participate in a clinical trial are entitled to make their decision based on the fullest amount of information available at that time. In order to make the choice, they will be given a written document expressed in a clear concise language of their native tongue to consider.
The document will tell potential participants about the nature of the measurements and the equipment. No interventions; only twice BCAM registration per day consecutively in three days. It will outline the numbers of participants in the trial, the steps of the protocol and type of measurements. This will give the participants a clear picture of the risks, inconveniences, and benefits that may accrue from the trial. The participants will be informed that she/he may decline the offer to join the trial or may withdraw at any time without prejudicing further medical care and is covered by the Sponsor's indemnity insurance in the event of mishap. Individuals must also know that their personal hospital records may be reviewed in confidence by the trial appointed research staff and that all personal information will be held on a confidential database. All information in the database will be anonymized and the activation key is stored by the clinically responsible ophthalmologist. Consent must always be given in writing after the participant has had time to reflect on the information and had an opportunity to ask further questions.

BCAM is new equipment, but certificated for clinical use [ISO 13485:2016] and sale in Norway (Appendix 15.2)
BCAM may increase the possibility for the investigator to give a safe diagnose at an early stage; give the final diagnose earlier and follow-up the patients more closely during treatment. However, before using such equipment in clinical practice the validity of the measurements must be documented.

Summary: No results from previous studies with this new equipment indicate any negative effect on the participants and AE has so far never been reported. All participants will be given oral and written information and have to give their written consent to participate in the study. To the best of our knowledge, this study fulfils the entire international requirement to an ethical controlled clinical trial.

10.2: Approval of the project

This study will be performed in Norway and the study protocol together and other requested information will be sent for approval by REK. Inclusion of patients will not be started before the approval is received.

The database and storage will be in Norway and must be approved by the Norwegian center for research data (NSD)

10.3: Informed consent

Before the start of the trial, the investigator will explain the confidentiality of participation in this research project; the objectives of the trial; the specific requirements for the participating patients; the trial design and the consequences of participation. Additionally, the investigators have to obtain written informed consent from the participants before inclusion in the study.

10.4: Protection of personal data

The monitor may know the identity of the patients during verification of the source data. However, the monitor has unconditional professional secrecy.
All patient-related material leaving the department will be anonymous so that the patient only can be identified by date of birth, initials, and study number.
The investigator is responsible for keeping a list with the full names of the patients, their citizens' number, and corresponding study numbers according to the demands in GCP.

XI: Statistical model

11.1: Handling of discontinuation

All patients fulfilling the inclusion and exclusion criteria, given informed consent to participate and started BCAM registration are classified as included in the study.
In the ITT analysis, all these patients will be included and if necessary, the LOCF procedure will be used. The patients classified as Drop-out will be excluded from the statistical analysis.

11.2: Presentation of the result

Assumed continuously distributed variables will be expressed by mean values with 95% confidence intervals. [34] As an index of dispersion Standard Deviation (SD) will be used.
The agreement index AI defined as AI=1 – [SD (X_1-X_2)/Mean (X_1-X_2)] will be used for estimation of agreement in continuously variables and expressed by Blend &Altman plot.[35]
Analysis of variance (ANOVA) with repeated measurements will be used in the analysis of stability. [36] In case of skewed distribution, the variable will be tried logarithmic transformed, and the analyses performed on the transformed data. The results will be retransformed for presentation. ANOVA will be used for comparison between patient groups and HC.[37]
Categorized and discrete distributed variables will be expressed in contingency tables .[38]
κ-analysis will be performed for estimation of agreement in these variables .[39]
Additionally, important prevalence will be expressed in percentage with 95% confidence intervals constructed by using the theory of Simple Binomial Sequences.[38]
Assumed continuously distributed variables will be expressed by mean values with 95% confidence intervals [34]. As an index of dispersion Standard Deviation (SD) will be used.
In case of skewed distribution, the variable will be tried logarithmic transformed, and the analyses performed on the transformed data. The results will be retransformed for presentation.
Categorized and discrete distributed variables will be expressed in contingency tables .[35]
Additionally, important prevalence will be expressed in percentage with 95% confidence intervals constructed by using the theory of Simple Binomial Sequences[35].

11.3: Sample size

With a significance level of 5%; a power of 90% and a Clinically Relevant Difference (CRD) of 1xSD between patient groups and HC, at least 16 HC and 16 patients in each diagnose have to be included.

XII: Operational matters

12.1: Investigator's agreement

Before start, the investigators will confirm their agreements to participate in the trial by signing the Investigator's Agreement Form with the Sponsor.

12.2: Instructions

The project manager, supported by the clinical monitor, will instruct the investigators at the start-up visit and during the study.

12.3: Amendments to the protocol

Changes in the protocol can be required by REK, investigators, project manager or Sponsor. Changes must be given in written amendments and numbered in the original protocol. It is forbidden to add new parameters consisting of measurements on the patients in the study unless they are covered as amendments in the protocol or taken due to the health and safety of the patient.

12.4: Protocol deviations

Deviations from the protocol should be restricted as much as possible and will be fully recorded and justified. The project manager will be informed as soon as possible of all protocol deviations.

12.5: Compliance monitoring

The project manager and the investigators will ensure that the site is suitable for the trial and that the participants are well informed of the particular trial. They shall check protocol compliance, handling of the test articles and recording of data during the critical stages of the trial. A report is prepared of each visit and kept in the trial master file (TMF).

12.6: Responsibilities

The investigators will acknowledge their responsibilities and their agreement to participate in the trial by dating and signing the agreement form. The project manager will verify that adequate arrangements have been made for the observations, measurements and recording of the data.

12.7: Confidentiality

This clinical trial is a precondition for further studies in order to obtain permission to market the product worldwide. The Sponsor will therefore use the obtained data and results for the registration of the product. The main study database will be stored in the product database of the Sponsor.
The project manager and the investigators may demand and have the right to have the results published in an international medical journal. The draft of the manuscript has to be presented to the Sponsor for comments, discussion and final approval. The Sponsor cannot stop the

publication unless it is proved that publication of the results may damage the marketing of the product.
The project manager or the investigators cannot present the results in any meeting or congresses without approval by the Sponsor. The data obtained in this study has to be handled confidentially until the first registration of the product is performed.

12.8: Investigator and Sponsor withdrawals

An investigator can finalize his or her participation in the study if BulbiTech A/S does not fulfill its duties according to the protocol or the Sponsor-investigator agreement.
BulbiTech A/S has the right to terminate the study at any time. The investigators will be paid according to the agreements in the Sponsor-investigator agreement. A written explanation will be sent to all investigators and REK according to present rules.

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XIV: Amendments

14.1: Study identification

The Study identification has been changed from OTH /Dr; Amd; con – BCAM/ST – IM/1_22 to V1_OTH/DR; AMD – I/2022

14.2: Study administration

The steering committee is specified page 1, point 0 to:

Project Manager:	Professor Emeritus Stig Larsen; Norwegian University of Life Sciences / Meddoc AS, Hvamstubben 14 2013 Skjetten
Project Coordinator:	Bård Dalhøi. MSc Osteopathy Chief Executive Officer (CEO) BulbiTech AS Trondheim
Responsible Ophthalmology:	Professor Goran Petrovski Dr Med, MD, Ophthalmologist Department of Ophthalmology, Oslo University Hospitals / Ullevål Hospital, Oslo
PhD-fellow:	Dr Bjørn Helland Hansen MD, Ophthalmologist Department of Ophthalmology, Oslo University Hospitals / Ullevål Hospital, Oslo
PhD supervisors:	Prof Goran Petrovski and Prof Emeritus Stig Larsen

14.2: Specification of Standard examination

The specification of Standard examination is included in Chapter 1.7, 1.11, 2.3, and 5.2:
The supporting variables will be recorded by the Standard (ST) investigation for DR and AMD.

Test	No of instances	Variable	Unit	Unit description
GAT	1	Pressure	mmHg	2 digits, 1 decimal
iCare	1	Pressure	mmHg	2 digits, 1 decimal
Acuity chart	1	Visual acuity	logMAR	1 digit, 1 decimal
Contrast chart	1	Contrast acuity	Pelli-Robson score	1 digit, 2 decimals
Visual field	1	Nasal step	Present	Boolean (true / false)
	1	Temporal wedge		
	1	Partial arcuate (sup)		
	1	Partial arcuate (inf)		
	1	Arcuate (sup)		
	1	Arcuate (inf)		
	1	Altitudinal (inf)		
	1	Altitudinal (sup)		
	1	Paracentral		
		MD	dB	2 digits, 2 decimals
	54	X coordinate	Degrees	3 digits, 1 decimal
		Y coordinate	Degrees	3 digits, 1 decimal
	1	Threshold sensitivity	dB	2 digits, 2 decimals
	1	Percentile degree	Score 1-5	1 digit
	1	Defuse defect	dB	2 digits, 1 decimal
	1	Local defect	dB	2 digits, 1 decimal
	1	sLV	dB	2 digits, 1 decimal

	1	False positive	Percent (Reliability)	2 digits
	1	False negative	Percent (Reliability)	2 digits
	1	Mean Sensitivity	dB	2 digits, 1 decimal
	1	Reliability factor	Percent (Reliability)	2digits, 1 decimal
OCT RNFL	1	Average thickness	µm	3 decimals
OCT GCL	1	Volume	mm^3	3 decimals
Pupil	1	Diameter change (max-min)	mm	1 digit, 2 decimals

The central variables related to DR and AMD will be “RAPD NDF”, “Seen /unseen “,” Time until the given point is recorded as seen”, “the light in decibel when the point is seen”, X- and Y-coordinates and “Pupil diameter in mm” and “OCT RNFL “.

14.3: Study population

Chapter 3.2.1 is specified as: The study population 1 consists of patients diagnosed with DR of both gender; passed the age of 18 years; without any other eye disease; suffering from other know serious disease but have a health situation in accordance with expectations related to the age.

Chapter 3.2.2 is specified as: The study population 2 consists of patients diagnosed with AMD of both gender; passed the age of 18 years; without any other eye disease; suffering from other know serious disease but have a health situation in accordance with expectations related to the age.

Chapter 3.2.5 is specified as: The study population 3 consists of gender- and age-matched controls to patients in study population 1 or 2; passed the age of 18 years without any eye diseases; not suffering from other know serious disease and have a health situation in accordance with expectations related to the age.

Chapter 3.3 is specified as: No data from possible participants included in the screening phase but not fulfils the inclusion/exclusion criteria will be recorded in the database

Chapter 6.2 is specified with the following new introduction: Both patients and the age- and gender matched controls must have a health situation in accordance with expectations related to the age and not suffering from other know serious disease.
The following additional specification is done in *Chapter 6.2*: No data from possible participants included in the screening phase but not fulfils the inclusion/exclusion criteria will be recorded in the study database.

Chapter 5.2. The following information is added under 5.2.1: The Quality-of-Life (QoL) questionnaires EQ-5D-5L developed by EuroQol will be recorded once in the study and at the same day as the first BCAM registration. This will be performing as additional health verification and the possibility of comparing QoL of patients and controls.

14.4: Recruitment of patients

Chapter 3.3 is rewritten and no given as follows:

The patients will be recruited from Oslo University hospital, Ullevål and Helgeland hospital. If necessary, private Ophthalmology clinics in Oslo will be asked for recruitment. All the investigations in the study will be performed by the same Ophthalmologist at the given hospital. The investigator informs the patients about the study, handing and collecting the written informed consent form. In case the patient fulfils the inclusion/exclusion criteria and willing to sign the consent form, the patient is included in the study. No data from possible participants included in the screening phase but not fulfils the inclusion/exclusion criteria will be recorded in the database. The included patient will be asked if he/she know any person with same gender and age; in good health condition without any eye disease which may participate as a control in the study. The potential controls will be contacted by the responsible investigator, obtain information about the study, and expected tasks. Controls willing to sign the consent form is included in the study. In case of lack in controls, requests among the hospital staff will be performed.

14.5: Patient factor

The following paragraph are added to *chapter 5.5*: Age and gender will be used to recruit controls to the included patients. Concomitant diseases and medication together with history of disease will be used to demonstrate the health condition of the participants at the time of inclusion in the study. Additionally, quality of life of the participants will be recorded at screening. This will also be a part of the health evaluation but also gives the possibility of comparing the patients with the age- and gender matched controls.

14.6: Data Management

Additions to *Chapter 4.3.* All information in the database will be anonymized and the activation key is stored by the clinically responsible ophthalmologist.

Addition to *Chapter 8.1.* The identity of the participants in the database will be anonymized. The activation key is stored and only to be used by the clinically responsible ophthalmologist. Each study participants are given a study identification number which will be stored in the database

14.7: Ethical consideration

The previous statement under C*hapter 10.1*, page 34*:" No results from previous studies with this new equipment indicate any negative effect on the participants and AE has so far never been reported"* has been removed and replaced by "Despite that BulbiCam not previously has been used in any clinical study, it is nothing that may indicate that BulbiCam causes any adverse events.
The following specification is made in *Chapter 10.1*. All information in the database will be anonymized and the activation key is stored by the clinically responsible ophthalmologist

XV: Appendix

15.1: Set of CRF's

15.1.1: CRF I; Inclusion and exclusion

Case Record Form I (A=DR)

(Inclusion and Exclusion criteria)

Study Id: V1_OTH /DR; AMD – I/2022; *Participant Initials:* _____

Participant category. DR patient ☐; AMD patient ☐; Healthy Control without any ophthalmological or neurological disease

Inclusion criteria

A	Diagnosed with DR	☐ Yes ☐ No
B	At least age of 18 years	☐ Yes ☐ No
C	Without any other eye disease	☐ Yes ☐ No

Exclusion criteria

1	Other visual disturbances and blindness	☐ Yes ☐ No
2	Posterior Chamber Artificial Ocular Lens (PCIOL)	☐ Yes ☐ No
3	Physical or psychiatric disease disturbing the measuring procedure	☐ Yes ☐ No
4	Not able to perform full eye movements	☐ Yes ☐ No
5	Visual acuity is less than 1 logMAR in any eye	☐ Yes ☐ No
6	Visible part of the eye is abnormal. Haemorrhages/deformed pupils	☐ Yes ☐ No
7	Pupils not able to respond normally to dilation or contraction	☐ Yes ☐ No
8	Participating another clinical trial with pharmaceuticals	☐ Yes ☐ No
9	Not able to understand information	☐ Yes ☐ No
10	With known alcoholic and drug dependency	☐ Yes ☐ No
11	Not willing to give written consent to participate in the study	☐ Yes ☐ No

.

Has the participant given written consent to participate? ☐ Yes ☐ No; Date: ☐☐ ☐☐ ☐☐

_____

Investigator (Sign)

Date: ☐☐ ☐☐ ☐☐

Case Record Form I (B=AMD)
(Inclusion and Exclusion criteria)

Study Id: V1_OTH /DR; AMD – I/2022; *Participant Initials:* _____

Participant category. DR patient ☐; AMD patient ☐; Healthy Control without any ophthalmological or neurological disease

Inclusion criteria

A	Diagnosed with AMD	☐ Yes ☐ No
B	At least age of 18 years	☐ Yes ☐ No
C	Without any other eye disease	☐ Yes ☐ No

Exclusion criteria

1	Other visual disturbances and blindness	☐ Yes ☐ No
2	Posterior Chamber Artificial Ocular Lens (PCIOL)	☐ Yes ☐ No
3	Physical or psychiatric disease disturbing the measuring procedure	☐ Yes ☐ No
4	Not able to perform full eye movements	☐ Yes ☐ No
5	Visual acuity is less than 1 logMAR in any eye	☐ Yes ☐ No
6	Visible part of the eye is abnormal. Haemorrhages/deformed pupils	☐ Yes ☐ No
7	Pupils not able to respond normally to dilation or contraction	☐ Yes ☐ No
8	Participating another clinical trial with pharmaceuticals	☐ Yes ☐ No
9	Not able to understand information	☐ Yes ☐ No
10	With known alcoholic and drug dependency	☐ Yes ☐ No
11	Not willing to give written consent to participate in the study	☐ Yes ☐ No

.

Has the participant given written consent to participate? ☐ Yes ☐ No; Date: ☐☐ ☐☐ ☐☐

_____

Investigator (Sign)

Date: ☐☐ ☐☐ ☐☐

15.1.2: CRF II; Demographic factors

Case Record Form II
(Demographic factors)

Study Id: V1_OTH/DR; AMD-I/2022 [Transferred from the system]

Country:☐ (Norway=1; India=2 etc); Site:☐ (First site =1 Second=2 etc); Disease☐ (None =0; Glaucoma=1; Cataract=2; DR =3 etc); Disease degree ☐ (None=0; Mild =1; Moderate =2; Severe=3);

Running number: ☐☐*[Created from the system within the group defined by information above]*

Participant Id-number: ☐☐☐☐ _☐☐ *[Created from the system by using information above]*

Patient initials_____; Date of inclusion: ☐☐ ☐☐ ☐☐

Demographic factors

Date of birth: ☐☐ ☐☐ ☐☐ Age: ☐☐ (years), Gender: ☐(Male=M; Female=F)

Comment:

_____
Investigator (Sign)

Date: ☐☐ ☐☐ ☐☐

15.1.3: CRF III; Medical history

Case Record Form III (A=DR)
(Medical history**)**

Study Id: V1_OTH/DR; AMD-I/2022*[Transferred from the system]*

Participant Id-number: ☐☐☐☐_☐☐ *[Transferred from CRF I]*

Actual disease

Specification: DR; Date first time diagnosed: ☐☐ ☐☐ ☐☐
Degree (classification) of disease: ☐ [specification for each study]
Ongoing treatment
…… Date of start: ☐☐ ☐☐☐☐
…… Date of start: ☐☐ ☐☐☐☐
…… Date of start: ☐☐ ☐☐☐☐
…… Date of start: ☐☐ ☐☐☐☐

Ongoing concomitant disease

Medical area: ☐Cardiac, ☐Congenital, ☐Ear and Labyrinth, ☐Endocrine, ☐Eye, ☐Gastrointestinal, ☐General disorders, ☐Hepatobiliary, ☐Immune system disorder ☐Infections, ☐Injury and procedural, ☐Investigations, ☐Metabolism and nutrition, ☐Musculoskeletal, ☐Neoplasm, ☐Neurology, ☐Ophthalmology, ☐Pregnancy and perinatal, ☐Psychiatric, ☐Renal and urinary, ☐Reproductive, ☐Respiratory, ☐Rheumatic, ☐Skin, ☐Social circumstances, ☐Surgical and Medical, ☐Vascular

Ongoing concomitant diagnoses

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Ongoing concomitant treatment

…… Date of start: ☐☐ ☐☐☐☐
…… Date of start: ☐☐ ☐☐☐☐
…… Date of start: ☐☐ ☐☐☐☐
…… Date of start: ☐☐ ☐☐☐☐
…… Date of start: ☐☐ ☐☐☐☐
…… Date of start: ☐☐ ☐☐☐☐

_____ Date: ☐☐ ☐☐ ☐☐
Investigator (Sign)

Case Record Form III (B=AMD)

(Medical history)

Study Id: V1_OTH /DR; AMD – I/2022 *[Transferred from the system]*

Participant Id-number: ☐☐☐☐_☐☐ *[Transferred from CRF I]*

Actual disease

Specification: AMD; Date first time diagnosed: ☐☐ ☐☐ ☐☐

Degree (classification) of disease: ☐ [specification for each study]

Ongoing treatment

…… Date of start: ☐☐ ☐☐☐☐
…… Date of start: ☐☐ ☐☐☐☐
…… Date of start: ☐☐ ☐☐☐☐
…… Date of start: ☐☐ ☐☐☐☐

Ongoing concomitant disease

Medical area: ☐Cardiac, ☐Congenital, ☐Ear and Labyrinth, ☐Endocrine, ☐Eye, ☐Gastrointestinal, ☐General disorders, ☐Hepatobiliary, ☐Immune system disorder ☐Infections, ☐Injury and procedural, ☐Investigations, ☐Metabolism and nutrition, ☐Musculoskeletal, ☐Neoplasm, ☐Neurology, ☐Ophthalmology, ☐Pregnancy and perinatal, ☐Psychiatric, ☐Renal and urinary, ☐Reproductive, ☐Respiratory, ☐Rheumatic, ☐Skin, ☐Social circumstances, ☐Surgical and Medical, ☐Vascular

Ongoing concomitant diagnoses

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Ongoing concomitant treatment

…… Date of start: ☐☐ ☐☐☐☐
…… Date of start: ☐☐ ☐☐☐☐
…… Date of start: ☐☐ ☐☐☐☐
…… Date of start: ☐☐ ☐☐☐☐
…… Date of start: ☐☐ ☐☐☐☐
…… Date of start: ☐☐ ☐☐☐☐

_____ Date: ☐☐ ☐☐ ☐☐

Investigator (Sign)

15.1.4: CRF IV; Quality of life

Case Record Form IV
(Quality of Life)

Study Id: V1_OTH /DR; AMD – IM/1_22 *[Transferred from the system]*

Participant Id-number: ☐☐☐☐_☐☐ *[Transferred from CRF I]*

EQ-5D-5L

BEVEGELSE

Jeg har ingen problemer med å gå rundt	☐ (1)
Jeg har noen problemer med å gå rundt	☐ (2)
Jeg har moderate problemer med å gå rundt	☐ (3)
Jeg har store problemer med å gå rundt	☐ (4)
Jeg klarer ikke å gå rundt	☐ (5)

SELVPLEIE

Jeg har ingen problemer med å vaske eller kle på meg	☐ (1)
Jeg har noen problemer med å vaske eller kle på meg	☐ (2)
Jeg har moderate problemer med å vaske eller kle på meg	☐ (3)
Jeg har store problemer med å vaske eller kle på meg	☐ (4)
Jeg klarer ikke å vaske eller kle på meg	☐ (5)

VANLIGE AKTIVITETER (f.eks. arbeid, studier, husarbeid og familie- eller fritidsaktiviteter)

Jeg har ingen problemer med å gjøre de vanlige aktivitetene mine	☐ (1)
Jeg har noen problemer med å gjøre de vanlige aktivitetene mine	☐ (2)
Jeg har moderate problemer med å gjøre de vanlige aktivitetene mine	☐ (3)
Jeg har store problemer med å gjøre de vanlige aktivitetene mine	☐ (4)
Jeg klarer ikke å gjøre de vanlige aktivitetene mine	☐ (5)

SMERTER / UBEHAG

Jeg har ingen smerter eller ubehag	☐ (1)
Jeg har noen smerter eller ubehag	☐ (2)
Jeg har moderate smerter eller ubehag	☐ (3)
Jeg har store smerter eller ubehag	☐ (4)
Jeg har ekstrem smerte eller ubehag	☐ (5)

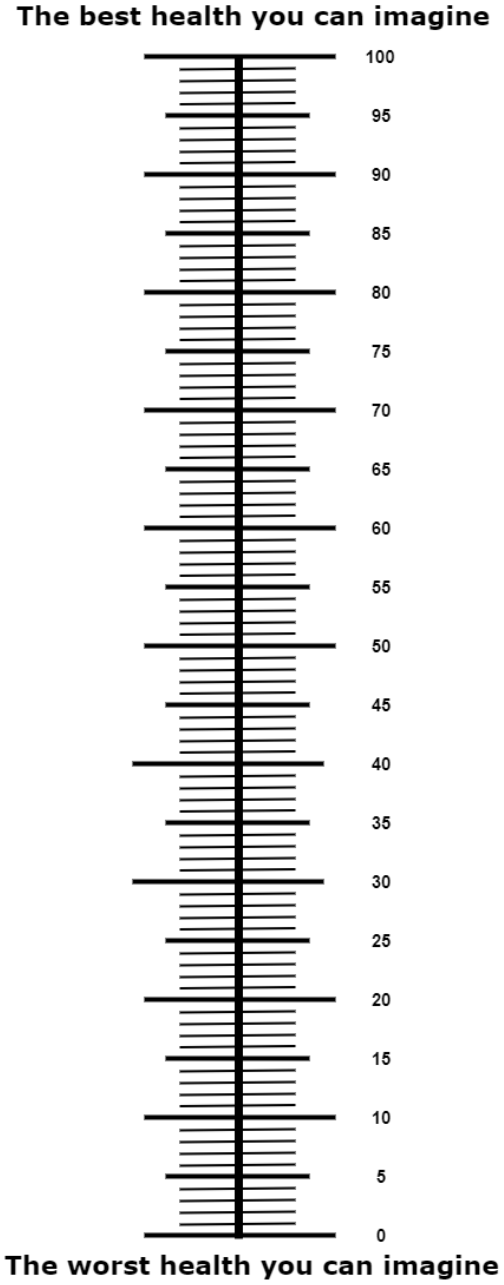
ANGST / DEPRESSJON

Jeg er ikke engstelig eller deprimert	☐ (1)
Jeg er noe engstelig eller deprimert	☐ (2)
Jeg er engstelig eller deprimert	☐ (3)
Jeg er veldig engstelig eller deprimert	☐ (4)
Jeg er ekstremt engstelig eller deprimert	☐ (5)

EQ-Visual Analogue Scale (VAS)

Pasienten skal beskrive sin daglige helsesituasjon på en 100mm VAS ved å avsette en horisontal strek på skalaen nedenfor hvorav «0» angir «Den verste helsen du kan forestille deg» og «100» angir «Den beste helsen du kan forestille deg»

Angi resultatet i mm fra bunnen og opp til merket på skalaen nedenfor: □□□mm



15.1.5: CRF V; Adverse Events

Case Record Form V

(Adverse Event**)**

Study Id: V1_OTH /DR; AMD – I/2022 *[Transferred from the system]*

Participant Id-number: ☐☐☐☐_☐☐ *[Transferred from CRF I]*

Adverse Event (specify …)	**Severity** (1 - 5)	**SAE** (N/Y)	**Relationship to medical device** (1-4)	**Action taken** (1-4)	**AE treatment** (1-4)	**Date Started** (ddmmyy)	**Date Stopped** (ddmmyy)	**Outcome** (1-3)

Classifications					
Severity of AE	**SAE**	**Relationship to IP**	**Action Taken**	**AE Treatment**	**Outcome**
1 = Mild **2** = Moderate **3** = Severe **4** = Life threatening **5** = Death	**N** = No **Y** = Yes	**1** = Unrelated **2** = Possibly **3** = Probably **4** = Definitely	**1** = None **2** = Interruption **3** = Modified **4** = Discontinued	**1** = None **2** = Continue Medication **3** = Procedure **4** =Hospitalization	**1** = Resolved **2** = Ongoing **3** = Fatal

15.1.6: CRF VI; Adverse Events

Case Record Form VI

(Initial registration by ST)

Study Id: V1_OTH /DR; AMD–I/2022 *[Transferred from the system]*

Participant Id-number: ☐☐☐☐_☐☐ *[Transferred from CRF I]*

The Standard method

GAT-pressure:	☐☐,☐ mmHg
iCare-*pressure:*	☐☐,☐ mmHg
Acuity chart:	☐,☐ mmHg
Contrast chart:	☐,☐☐ mmHg

Visible Field

Point seen:	☐Yes	☐No
Nasal step:	☐Yes	☐No
Temporal wedge:	☐Yes	☐No
Partial arcuate (sup):	☐Yes	☐No
Partial arcuate (inf):	☐Yes	☐No
Arcuate (sup):	☐Yes	☐No
Arcuate (inf):	☐Yes	☐No
Altitudinal (inf):	☐Yes	☐No
Altitudinal (sup):	☐Yes	☐No
Paracentral:	☐Yes	☐No

MD:	☐☐☐,☐ dB
X-coordinate	☐☐,☐☐ degree
Y-coordinate	☐☐,☐☐ degree
Threshold sensitivity	☐☐,☐ dB
Percentile degree	☐ Score (1 – 5)
Defuse defect	☐☐,☐dB
Local defect	☐☐,☐dB
sLV	☐☐,☐dB
False positive	☐☐ % (Reliability)
False negative	☐☐ % (Reliability)
Mean Sensitivity	☐☐,☐dB

OCT RNFL:	☐☐☐ µm	
OCT GCL:	☐☐☐ m^3	
Pupil diameter size:	Min ☐☐☐ mm	Max ☐☐☐ mm

Date: _____ **Investigator's signature:** _____

15.1.7: CRF VII; End of Trial

Case Record Form VII
(End of Trial)

Study Id: V1_OTH /DR; AMD–I/2022 *[Transferred from the system]*

Participant Id-number: ☐☐☐☐_☐☐ *[Transferred from CRF I]*

Please state the trial end reason:

☐ **Completion of trial**

☐ **Withdrawal:** patient withdrew consent.

Date withdrawal (dd-mm-yyyy): _____

Reason withdrawal:

☐ Adverse experience – please specify: _____

☐ Inter-current illness (must be reported as an AE)

☐ Protocol Violation- please specify:_____

☐ **Drop-out:** patient request.

Date drop-out (dd-mm-yyyy): _____

☐ **Patient lost to follow up.**

Date last contact (dd-mm-yyyy): _____

☐ **Death** – must be reported as a SAE.

Date of death (dd-mm-yyyy): _____

☐ **Other,** please specify: _____

Date of discontinuation (dd-mm-yyyy): _____

I hereby certify that the entries on all pages of this Case Report Form accurately and completely represent the results of the examinations, tests, and evaluations performed on the dates specified.

Date: _____ **Investigator's signature:** _____

15.2: Bulbicam Certificate

15.2.1: ISO-Certificate

SIQ

Certifikat / Certificate

for
Management System

BULBITECH AS

Dybdahls veg 5, 7051 Trondheim

Research, design and development, production, sales, distribution and servicing of ophthalmic medical devices and software for ophthalmic medical devices
List of locations at the addendum to the certificate:
BulbiTech AS, Dybdahls veg 5, 7051 Trondheim, Norway
HEADS Stockholm AB, Gustavslundsvägen 143, 16751 Bromma Stockholm, Sweden

adequately operates and maintains a management system which meets the requirements of the standard

ISO 13485:2016

Certificate No. / Certification date
M-139 / 2018-10-30

Issue **07 / 2021-12-07** *Valid until:* **2024-10-30**

Director of SIQ Ljubljana
Gregor Schoss

SIQ je partner IQNet IAF SLOVENSKA AKREDITACIJA CS-001

SIQ Ljubljana, Mašera-Spasićeva ulica 10, 1000 Ljubljana, Slovenija

15.2.2: Certificate of free Sales

Norwegian Medicines Agency

To Whom it May Concern

NO-20/11005

Date: 08.02.2021

Certificate of Free Sales

The Norwegian Medicines Agency as Competent Authority for medical devices hereby certifies that the products listed below are manufactured by:

Bulbitech AS
Krambugata 2
7011 Trondheim
Norway

We have been notified that the following medical devices are sold as CE-marked products:

Cat. Number	*Product Name*
65177	**BulbiCAM - Vision physiology / eye movement analysis system**

The precondition for medical devices to be CE-marked in compliance with directive 90/385/EEC, directive 93/42/EEC or directive 98/79 EC is to meet the essential requirements for safety. A CE-marked medical device may therefore be placed on the market in Norway without any approval from the Medicines Agency and may be exported without any restrictions.

This certificate is valid until 05. February 2023

Raymond Ludvigsen
Senior Adviser

Jørgen Bryn
Consultant

NORWEGIAN MEDICINES AGENCY

Norwegian Medicines Agency (NoMA)
Postboks 240 Skøyen, 0213 Oslo, Norway
Visit address: Grensesvingen 26, 0663 Oslo, Norway
post@noma.no or mesder-no@noma.no
noma.no

Letters should be adressed to the Norwegian Medicines Agency
Please state our reference
Tlf: +47 22 89 77 00
IBAN.: NO 71 7694 05 00803
SWIFT: DNBANOKK

15.3: CV; Primary investigator & Steering Committee

15.3.1: Bård Dalhøi CEO BulbiTech AS

Curriculum vitae

*** PERSONAL INFORMATION**

*Family name, First name:	Dalhøi, Bård		
*Date of birth:	18.06.64	*Sex:	Male
*Nationality:	Norwegian		

*** HIGHER EDUCATION/OTHER TRAINING**

	Subjects/degree/	***Name of institution, country***
1987-1989	Physical Therapy	REHA-Zentrum Berlin
1990-1995	Diploma degree in Osteopathy	Norwegian Academy of Osteopathy
2007-2008	Medical PhD studies in Medical Research Methodologies	NMBU – Norwegian University of Life Sciences
2008	Medical PhD studies in Experimental design in clinical studies	Faculty of Life Sciences, University of Copenhagen

*** POSITIONS** (academic, business, industry, public sector, national or international organisations)

Current Position

Job title/name of employer/country	
2021-	Chief Executive Officer, Bulbitech AS
2015 -	Chief Scientific Officer, BulbiTech AS, Norway
2013-2015	Chief Executive Officer, Bulbitech AS, former Heads AS, Norway from 2013-2019

Previous positions held (list)

Job title/name of employer/country	
1995-2013	Private Practice and co-founder, Osteopatiklinikken Midt-Norge AS, Norway

2010-2012	Senior lecturer, Program Osteopathy, Høyskolen Kristiania, Norway
1997-2010	Co-founder of Academy of Osteopathy, board member and lecturer in Program for Osteopathy Nordic Academic of Osteopathy, Norway
1990-1997	Private Practice, Fjordgata Fysioterapi & Osteopati, Norway
1993-1995	Clinical lecture, Physical therapy, University NTNU, Norway
1989-1990	Clinical practice, Physical Therapy department, St. Olav Hospital, Norway

PROJECT MANAGEMENT EXPERIENCE

Project/topic/role in project/funding from	
2021-	Project leader BulbiEYE. Project was approved in Norwegian Research Council June 2021. Budget 20 mNOK.
2015-2020	Development of the first version of hardware (BulbiCAM) and software (BulbiHUB) – patent BulbiCAM, public funding application and project leader: 3 major projects supported by Innovation Norway 2015-2018 LASFIN, 2016-2017 HASFIN, 2019-2020 Project BulbiCAM and SkatteFunn LASFIN and HASFIN

EXPERIENCE FROM RELEVANT RESEARCH & INNOVATION ACTIVITIES (if applicable)

Project/type of R&I activity and R&I content /role and tasks/funding from	
2018- 2019	**Publications:** 1. Randomized two dimensional between patient response surface pathway design with two interventional and one response variable in estimating minimum efficacy dose, International Journal of Clinical Trials 2. Osteopathic manual Therapy (OMT) in treatment of gastroesophageal reflux disease (GERD), Larsen S et al. Int J Clin Trials. 2019 Aug;6(3):75-83, Clinical Practice.
2017	Chennai, India Sankara Nethralaya Glaucoma Meet (SANGAM) September 2017 Binocular pupillometry: Quantification of pupillary responses using eye tracking technology
2017	Hyderabad, India World Congress of Optometry (WCO) 2017Clinical applicability of an eye tracker based pupillometry system
2017	VISION conference June 2017 An approach to quantify the pupil response using an eye tracker-based pupilometer

EXPERIENCE FROM NATIONAL/INTERNATIONAL COLLABORATION/NETWORKING (if applicable)

Activity or project / tasks and responsibilities / context/programme/framework of the collaboration and names of key partners (companies, institutions)

2021-2023	Project leader of BulbiEYE, granted from Norwegian Research Council. Project partners: Collaborating partners; Oslo University Hospital (Ullevål Eye Dept and Rikshospitalet Nero Dept), Helgelandssykehuset Eye Dept., Meddoc AS
2021-	Clinical validation of Eye Movement based Acuity, Contrast and Dark Adaptation test. Pupil RAPD test, Vergence test, Nystagmus test.
2020	Study measuring the reliability, and stability of Video Oculography Device in BulbiCAM in Eye Movement Perimetry and Pupillometry. Coordinator and study leader of the overall study's progress in collaboration with the Medical Research Foundation at Sankara Nethralaya Eye Hospital (India) and Prof. Emeritus Stig Larsen at Meddoc AS (Norway).
2019-2020	Clinical validation of eye tracking, pupillometry and nystagmography (Pupil, Visual Field, Saccades, Ptosis, Worth 4 dot, Amsler test); coordinator and study leader of the overall study's progress; collaboration with the Medical Research Foundation/Sankara Nethralaya Eye Hospital (India), Ass Prof Johan Pel, Department of Neuroscience, Erasmus MC, The Netherlands, and Prof. Stig Larsen, Norwegian University of Life Science.
2015-2018	Project leader, LASFIN project partners: Neuroscience department at Erasmus MC, NL, EyeSeeTech Gmbh, Munich, Germany, Lameris Ootech BV, NL, Medical Research Foundation, Sankara Nethralaya Eye Hospital, Chennai, India

OTHER MERITS RELEVANT TO THE PROJECT

- Project manager of BulbiEYE project, which is a 2 mill. Euro industrial and clinical projects financial supported by the Norwegian Research Council
- Project manager of 3 Innovation Norway financial supported projects
- Publications, technical reports, peer-review assignments, etc.
- Presentations at workshops or conferences (national/international level)
- Positions in professional associations/networks

Bård is the CEO and CSO at BulbiTech AS with a working experience within the biotechnology industry and has experience in clinical research, including the development and participation in studies concerning the osteopathic clinical research and clinical research in medical technology development. Bård is skilled in clinical research, pain management, healthcare, rehabilitation, and sports medicine. His work has brought him in contact with several research institutions, enabling him to increase its network for national and international collaborations. His experience within the medical field and clinical care goes back to 1989, when Bård started his professional practice as a Physical Therapist in both public and private hospitals and clinics, and from 1995 as an Osteopath at private healthcare institutions. Co-founder and chairman Norwegian Association of Osteopathy founded 09.06.1997, which was public registered 15.07.1997. Cofounders and board member of the Norwegian Academy of Osteopath. Today the education is approved as a health care education with a BSc degree, and the profession is to get their official authorisation in Norway 2021. Since 2013, Bård was the co-founder of Bulbitech AS (former Heads AS) and served as a CEO in Heads from 2013 until 2015. Re-engaged as a CEO in Bulbitech in 2021 and holds both the position as a CEO and CSO (Chief Science Officer).

15.3.2: Professor Goran Petrovski; Ophthalmology

Role in the project Project manager ☒ Project partner ☐

Personal information

First name, Surname:	Goran Petrovski		
Date of birth:	13.02.1975	Sex:	M
Nationality:	Hungarian		
Researcher unique identifier(s) (ORCID, ResearcherID, etc.):	0000-0003-2905-9252		
URL for personal website:	https://www.med.uio.no/klinmed/personer/vit/goranpe/index.html		

Education

Year	Faculty/department - University/institution - Country
2007 (dissertation defended)	Ph.D. University of Debrecen, Medical and Health Science Center (UDMHSC), Dept. of Biochemistry and Molecular Biology , Hungary
2003	Medical Doctor UDMHSC, Hungary

Positions - current and previous

Year	Job title – Employer - Country
2016-	Professor and Head of the Center of Eye Research, Department of Ophthalmology, Oslo University Hospital and UiO, Oslo, Norway
2013-2016	Associate Professor of Ophthalmology and Head, Stem Cells and Eye Research Laboratory, Department of Ophthalmology, University of Szeged, Hungary

Project management experience

Year	Project owner - Project - Role - Funder
2020-2023	Principal investigator/project leader – "Optimization of stem cell-laden smart biomaterials for 3D bioprinting of human cornea" – Norway-India collaborative project – Funder: Norwegian Research Council
2021-2024	Principal investigator/project leader – "Development of standardized culture, transplantation and banking of RPE cells for treatment of age-related macular degeneration (AMD)" – Norway-Czechia collaborative project – Funder: EEA Norway grants

15.3.3: Professor Stig Larsen

Curriculum vitae (CV) with track record

Role in the project Manager ☐ Partner ☒

Personal information

First name, Surname:	Stig Larsen		
Date of birth:	26.March 1947	Sex:	Male
Nationality:	Norwegian		
Researcher unique identifier(s) (ORCID, Researcher ID, etc.):	0000-0001-9591-9324		
URL for personal website:			

Education

Year	Faculty/department - University/institution - Country
1982	PhD: Dept. of Gastroenterology/Ullevål Hospital- Oslo University -Norway
1975	Cand. Real: Dept. of Mathematics/Master- Oslo University -Norway

Positions - current and previous

Year	Job title – Employer - Country
2017-	- Prof Emeritus- Norwegian University of Life Sciences (NMBU)- Norway - Research Director- Meddoc-Norway
2000-2017 1990-2000 1990-2000	-Professor I; Controlled clinical Research Methodology- NMBU- Norway -Professor II: Norwegian School of Veterinary Medicine-Norway -Research Director: Medstat/Parexel- Europe

Project management experience
(*Academic sector/research institutes/industrial sector/public sector/other. Please list the most relevant.)*

Year	Project owner - Project - Role - Funder
2018-2020 2020- 2022	Tine SA- The effect of optimized daily intake of Jarlsberg cheese on s-Osteocalcin and Vitamin K2- Project manager. [Publication 10; reference list]. Tine SA- Comparison of Jarlsberg® cheese and cheese without content of vitamin K2 on s-Osteocalcin- Project manager. [NFR-IPN project; Additionally, 3 manuscripts under preparation for international publication]

Supervision of students

Master's students	Ph.D. students	University/institution - Country
1	16	NMBU/Faculty of Veterinary Medicine -Norway
0	12	Oslo University/ Faculty of Medicine-Gastroenterology-Norway
1	1	Bergen University/ Faculty of Medicine- Rheumatology-Norway
0	2	Oslo University/ Faculty of Medicine- Radiology-Norway
2	3	Norwegian School of Sport Science-Norway
5	0	Norwegian School of Osteopathy

Other relevant professional experiences

Year	Description - Role
1992 - 2000	Research Manager; Development of PTW-design: An Adaptive design approach. [Publication 1-3; Additionally 4 international papers are published + 1 PhD]
2000 - 2020	Research Manager; Development of Response Surface Pathway (RSP) design. [Publication 4-6; Additionally, 11 paper are internationally published + 2 PhD]
2003	Research Manager; The effect of an Ergonomic Intervention on Musculoskeletal, Psychosocial and Visual Strain of VDT Entry Work: Organization and Methodology of International Study. [Publication 7; Additionally, 4 papers are internationally published]
2010 – 2020	Research Manager; Clinical documentation of a new immune modulating chemotherapeutic drug (BP-C1) in treatment of breast cancer and gastric cancer. [Publication 5,8 and 9; Additionally 8 papers are internationally published]
2018 - 2022	Project Manager; The effect of daily Jarlsberg cheese intake on the Osteocalcin level and vitamin K2 status to healthy premenopausal women. [Publication 10; Additionally 3 more manuscripts ready for evaluation in international journals] _

Track record

A: 342 scientific publications in international peer-reviewed journals; 10 related publications given

1) Reiertsen O, Larsen S, Størkson R, Trondsen E, Løvig T, Andersen OK, Lund H & Mowinckel P. Safety of enoxaparin and dextran 70 in the prevention of venous thromboembolism in digestive surgery. A Play-the-Winner designed study. Scand.J.Gastroenterol. 1993; 28:1015-1020.
2) Larsen S, Reiertsen O, Mowinckel P, Lund H & Osnes M. Play The Winner: a step-by-step process design to compare and control the efficacy and safety of treatments. Pharm. Med. 1994; 8: 11-23.

3) Bjerkeset O, Larsen S & Reiertsen O. Evaluation of enoxaparin given before and after operation to prevent venous thrombo-embolism during digestive surgery: Play-the-Winner designed study. World J Surg 1997; 21: 584-589.
4) Dewi S; Aune T, Buanæs JAAa; Smith A; Lasen S. The development of response surface pathway design to reduce animal number in toxicity studies. BMC Pharmacology and Toxicology, 2014; 15: 18-28
5) Dewi S; Kristiansen V; Lindkær-Jensen S & Larsen S. Between Patient, n-level Response Surface Pathway Design in dose-finding studies. Open Access Journal of Clinical Trials, 2014; 6: 1-12.
6) Larsen S, Holand T, Bjørnæs KE, Glomsrød E, Kaufmann J, Garberg TH, Elvbakken G, Dalhøi B, Reiertsen O & Dewi S. Randomized two-dimensional between-patient Response Surface Pathway design with two interventional- and one response variable in estimating Minimum Efficacy dose. Int J Clin Trials. 2019 Aug; 6(3):75-83.
7) Dainoff M, Aarås A, Horgen G, Konarska M, Larsen S, Thoresen M, Cohen BGF. The Effect of an Ergomic Intervention on Musculoskeletal, Psychosocial and Visual Strain of VDT Data Entry Work: Organization and methodology of the international study. JOSE 2005; 11 (1): 9-23.
8) Larsen S; Butthongkomvong K; Manikhas A; Trishkina E; Poddubuskaya E; Matrosova M; Srimuninnimit V; Lindkær-Jensen S. BP-C1 in the treatment of patients with stage IV breast cancer: a randomized, double-blind, placebo-controlled multicentre study and an additional open-label treatment phase. Breast Cancer: Targets and Therapy 2014:6 179–189
9) Ibrahim T; Larsen S; Hashish S, Harling H. Metronomic Chemotherapy for Pre-Treated Metastatic Pancreatic Cancer. Br J Cancer Res 2019;3: 286 - 91
10) Lundberg HE, Holand T, Holo H, Larsen S. Increased serum osteocalcin levels and vitamin K status by daily cheese intake. Int J Clin Trials. 2020 May;7(2):55-65.

B: Lecturing experience

1) Every year since 1987, I have lectured PhD/DSc candidates in “Controlled clinical research methodology”; “Medical Statistics” and “Scientific writing”
2) Written 9 compendiums in these three fields
3) Arranged and headed 12 seminars in medical science

C: Distinction

- Astra Meditec research Award 1991
- Glaxo Research Award 1994
- IEA/JOSE_ Best Paper Award 2003 – 2005
- Pegasus research Award 2005
- Norecopas 3R-Award 2015

D: Memberships

- Norwegian Statistical Society Since 1975
- Norwegian Society Since 1979
- International Society of Clinical Biostatistics Since 1984
- American Society of Clinical Oncology (ASCO) Since 2000

E: First publication in different field

- Design of Controlled Clinical Trial (first publication 1979)
- Clinical Trial Methodology (first publication 1978)
- Medical Statistics
    - Estimation and predication (first publication 1978)
    - Discriminate analysis (first publication 1985)
    - Sequential Analysis (first publication 1987)
    - Maximum probability estimation (first publication 1978)

Signature: …… Initials: SEL
Date prepared: February 2021.