CLINICAL INVESTIGATION PLAN (CIP)

Analysis of Diabetic Retinopathy, Glaucoma and Macular Degeneration Diagnosis via Digital Fundus Images with Artificial Intelligence

CLINICAL INVESTIGATION PLAN (CIP) NUMBER	**TF.01.CIP.01**
DEVICE NAME	**Cloud-Based Retinow AI Software for Diagnosing Retinal Disorders**
[redacted]	[redacted]

Sponsor

Name	**Retinow Sağlık Teknolojileri ve ARGE Sanayi A.Ş.**
Address	Bahçelievler mah. 319.cad Ankara Üni Teknokent No:35-8 /B46
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Sponsor Representative

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Coordinator Information

Name and surname	[redacted]
Profession	[redacted]
Institution	Ankara Şehir Hastanesi
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In the clinical investigation plan file (CIP), the objectives of the clinical investigation are clearly stated. The proposed design is justified based on scientific and ethical principles. The objectives of the study are an exploratory or confirmatory design to determine whether the goals of the clinical investigation can be achieved.

This clinical trial plan was prepared in accordance with EN ISO 14155 Good Clinical Practice and EU 2017/745 MDR ANNEX XV.

CONTENTS

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SIGNATURES

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ABBREVIATIONS

AI	Artificial Intelligence	SVM	Support Vector Machine
DR	Diabetic Retinopathy	ANN	Artificial Neural Network
CIP	Clinical Investigation Report	C/D	Cup /Disk Ratio
TİTCK	Turkish Medicines and Medical Devices Agency	FFA	Fundus fluoresein anjiografisi
ICF	Informed Consent Form	ACC	Accuracy
AMD	Age-Related Macular Degeneration	GDPR	General Data Protection Regulation
TP	True Positive	ICDR	International Clinical Diabetic Retinopathy
TN	True Negative	PACS	Picture Archiving and Communication System
FP	False Positive	ICF	Informed Consent Form
FN	False Negative	PP	Per Protocol
AE	Adverse Event	PI	Principal Investigator
ADE	Adverse Device Effect	IB	Investigator Brochure
SAE	Serious Adverse Events	DD	Device Deficiencies
MDR	Medical Device Regulation	SADE	Serious Adverse Device Event
CRF	Case Report Form		
API	Application Programming Interface		
SGD	Stochastic Gradient Descent		
CT	Computer Vision		
OCT	Optic Coherence Tomography		
DL	Deep Learning		
Arias	Automated DR imaging and assessment systems		
IOP	Intraocular pressure		
RNFL	Retinal Nerve Fiber Layer		
OCTA	OCT angiography		
CNN	Convolutional Neural Network		

1. Sponsor Identification

Name:	Retinow Sağlık Teknolojileri ve ARGE Sanayi A.Ş.
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1.1. Sponsor's Contact Person

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2. Principal Investigator, Coordinating Investigator and Research Area

2.1. Coordinator/Principal Researchers

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Name and surname:	Tuğba Haklı
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2.3. Research Center Information

Name of research center	Address
Ankara Bilkent City Hospital	Üniversiteler, 1604. Cd. No:9 D:No:9, 06800 Çankaya/Ankara

Note: No service is received from outside the center regarding the research.

3. General Summary of the Clinical Trial

Background	Eye diseases stand out as a major public health problem worldwide and constitute one of the leading causes of vision loss. Diseases such as diabetic retinopathy, glaucoma and macular degeneration are among the problems that can seriously affect the quality of life and lead to vision loss. Therefore, early diagnosis of these diseases is vital for determining effective treatment methods and protecting and improving the quality of life of patients. In recent years, artificial intelligence (AI) technologies in the field of medicine have offered great potential in disease diagnosis and management. Artificial intelligence algorithms, especially those used for retinal image analysis, play an important role in the early diagnosis of eye diseases and the determination of treatment methods. The use of artificial intelligence in the field of ophthalmological clinical research is mostly related to the prediction and diagnosis, treatment and interventions, and prevention and management of ophthalmic diseases. In this context, ophthalmic imaging and early screening systems supported by artificial intelligence technology play an effective role in the diagnosis of diseases such as diabetic retinopathy, glaucoma and macular degeneration. Diabetes is a major global health problem with an estimated 463 million people living with diabetes worldwide. This number is expected to increase to 700 million by 2045 [1]. Diabetic retinopathy (DR), a common complication of diabetes, is considered the leading cause of new-onset blindness among adults aged 20–74 years [2]. As the prevalence of diabetes continues to increase, the global DR patient population is projected to increase to 160 million by 2045 [1]. Early diagnosis and timely treatment of DR can reduce 95% of blindness from this cause [3]. Therefore, DR screening programs are recommended for patients with diabetes by the World Health Organization [4]. Glaucoma is characterized by optic disc cupping and visual field distortion, and is the most common cause of irreversible blindness, affecting more than 70 million people worldwide [5,7].

	The number of patients with glaucoma is expected to increase due to population growth and aging worldwide; it is projected to reach 112 million by 2040 [6]. Most vision loss from glaucoma can be prevented with early diagnosis and timely treatment [8]. However, glaucoma is diagnosed by a glaucoma specialist via ophthalmoscopy or fundus images [9,10]. Such manual optic disc assessment is time-consuming and labor-intensive, and is not applicable to large populations. Therefore, improvements in glaucoma screening methods are needed. Artificial intelligence may pave the way for cost-effective glaucoma screening programs, such as automatic detection of glaucoma from fundus images. Macular degeneration, a disease affecting the macula region of the retina, usually causes progressive vision loss [11]. Age is the strongest risk factor for macular degeneration, with almost all cases occurring in people over the age of 60 [11]. With the aging population, macular degeneration will continue to be a major cause of visual impairment worldwide. The number of patients with macular degeneration is projected to reach 288 million by 2040 [12]. This is an important indicator of the global burden of macular degeneration. Consequently, screening patients with macular degeneration and providing appropriate medical interventions in a timely manner can reduce vision loss and improve patients' vision [13]. AI has the potential to facilitate automatic detection of macular degeneration and prediction of disease progression.
Study Rationale	Diabetes is a chronic disease that affects millions of people worldwide. As the prevalence of diabetes increases, the incidence of eye diseases such as diabetic retinopathy (DR), glaucoma and macular degeneration also increases. An estimated 93 million people worldwide are known to have diabetic retinopathy, and approximately 28 million of these people have severe forms that threaten their vision [14]. Glaucoma has become one of the leading causes of vision loss, affecting 76 million people worldwide, and this number is expected to increase to 111.8 million by 2040 [15]. Macular degeneration affects 196 million people worldwide, and this number is predicted to reach 288 million by 2040 [16]. Early diagnosis of these diseases is of great importance to preserve the quality of life of patients. A similar situation is observed in Turkey. As the prevalence of diabetes increases, eye problems related to this disease are also seen more frequently. According to studies conducted in Turkey, diabetic retinopathy rates range from 15% to 45% [17]. Glaucoma and macular degeneration are other serious eye diseases that are especially common among the elderly population. The prevalence of age-related macular degeneration in Turkey varies between 2% and 8% [18]. Early diagnosis and regular screening are critical to preventing vision loss. However, as is the case worldwide, the number of patients in Turkey who have regular eye screenings for diabetic retinopathy, glaucoma and macular degeneration is not at the desired level. Therefore, technological solutions for the early detection of these diseases are becoming increasingly important. The Retinow AI device is an image interpretation device that automatically performs diabetic retinopathy, glaucoma and macular degeneration screenings. It aims to increase access to screening for these diseases by healthcare providers and to reduce screening costs. This clinical study was designed to evaluate the sensitivity and specificity of the Retinow AI device in screening these three important eye diseases.
Research device	Cloud-Based Retinow AI Software for Diagnosing Retinal Disorders
Number of Participants	915

Inclusion criteria	Patients with diabetic retinopathy, glaucoma or macular degeneration Volunteers with written informed consent form Volunteer must be 18 years or older Healthy individuals without retinal disorders
Exclusion criteria	Volunteers who do not want to have fundus imaging Cases that do not comply with fundus photography for any reason Patients with conjunctival and corneal infections, People with hereditary or congenital retinal diseases, People with cataracts, People with uveitis, Patients with permanent visual impairment in one or both eyes, Patients with correction of + 6D and above – 6D, Pregnant patients. [redacted]
Study objectives	To demonstrate the sensitivity and specificity of the automatic image analysis of the Retinow AI device in order to screen diabetic retinopathy, glaucoma, macular degeneration and healthy individuals with no pathological findings in their retinas who come to the retina and glaucoma unit for these diseases.
Endpoints	Analysis of sensitivity, specificity and accuracy of the Retinow AI device.
Planned duration of clinical trial	01.06.2023-01.10.2023

4. Identification of Research Device

4.1. Summary Description of The Investigational Device

Retinow AI is a software, a medical device that aims to solve a global problem that eliminates the risk of vision loss, especially in developed countries. Retinow AI provides rapid screening and triage without the need for a trained expert to evaluate digital retina (fundus) images. Digital retina images pass through the Retinow AI cloud system and are interpreted with the help of artificial intelligence, helping to detect diabetic retinopathy, glaucoma and macular degeneration diseases.

4.2. Intended Use

Retinow AI is a cloud and artificial intelligence based retinal scanning and identification system. Retinow AI is used to analyze diabetic retinopathy (DR), age-related macular degeneration (AMD) and glaucoma diseases of patients who have not previously been diagnosed with the disease, in a short time, through fundus images, thanks to artificial intelligence. Retinow AI presents a report to the user through the system without the need for any expert opinion. It works as a decision support mechanism for specialist or non-specialist physicians. It detects pathological areas in the retina and automatically detects problems.

4.3. Clinical Device Traceability

To ensure traceability during the clinical trial, only one version of the Retinow AI software (software number RAI01-V01.0.1) will be used. No changes will be made to the software version during the clinical trial.

4.4. Use of Device for Research Purposes

Retinow AI is designed for use by healthcare providers. The user must have sufficient understanding of the language in which the user manual was prepared. Researchers who will conduct the study will be sufficiently informed about the device with the help of the user manual before the study starts. The IFU document and researcher brochure will be provided to researchers to access the instructions for use of the Retinow AI software to be used for research purposes before the clinical study. (See TF.01.IFU.01, TF.01.IBF.01)

4.5. Indications

Retinow AI software is used in the diagnosis of diabetic retinopathy, glaucoma and macular degeneration diseases.

4.6. Contraindications

Contraindications for Retinow AI software are listed below;
o Patients with conjunctival and corneal infections,
o People with hereditary or congenital retinal diseases,
o People with cataracts,
o People with uveitis,
o Patients with permanent visual impairment in one or both eyes,
o Patients with correction of + 6D and above – 6D,
o Pregnant patients. [redacted]

[redacted]

4.7. Target User Groups

Retinow AI is designed for use by healthcare providers. The user must have sufficient understanding of the language in which the user manual was prepared.

4.8. Target Patient Population and Research Population

There is no restriction on the gender and physical structure of the patient where our device will be used. Our device should be used for 3 identified diseases: Macular degeneration, diabetic retinopathy and glaucoma. Retinow AI software should be used on patients who are 18 years old or older. The target patient population and study population were persons aged eighteen years and over who presented to an ophthalmologist for an eye examination to detect diabetic retinopathy, macular degeneration, and glaucoma.

4.9. Side Effects and Risks

The device does not have any undesirable side effects.

[redacted]

[redacted]

[redacted]

4.12. Working Principle of the Device

The working principle of the Retinow AI system is as follows.

- The user logs in to retinow.com.tr.
- The user login on the site enters the system with the license given by Retinow AI.
- Through the cloud system in Retinow AI, the user uploads patient information and fundus images of the patient to the system.
- Retinow AI analyzes the uploaded fundus images and presents them to the user in the form of a detailed report.
- The user can follow up the patient from the system. Can examine images in detail and keep records.

4.13. Details of the Manufacturer of the Device

Name:	Retinow Sağlık Teknolojileri ve ARGE Sanayi A.Ş.
Address:	Bahçelievler mah. 319.cad Ankara Üni Teknokent No:35-8 /B46
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4.14. Clinical Study Device Information

Device Name	Device Brand	Device Model
Cloud-based software Retinow AI for diagnosis of retinal disorders	Retinow	RAI01

Product Code - Referance No: RAI01-V01

[redacted]

[redacted]

[redacted]

7. Objectives and Hypotheses of Clinical Research

The main purpose of this clinical study is to evaluate the effectiveness and reliability of Retinow AI software in the diagnosis of common eye diseases such as diabetic retinopathy, glaucoma and macular degeneration. Retinow AI is a cloud-based artificial intelligence software that aims to detect diabetic retinopathy, glaucoma and macular degeneration diseases through fundus photographs. The software stands out with its ability to detect disease symptoms at an early stage and accelerate the diagnosis process. In addition, it is claimed that this software, which has reached a 90% accuracy rate during pre-clinical validation studies, can achieve similar results to the diagnostic accuracy of specialist physicians. This study examines the usability of Retinow AI software by both specialist and non-specialist physicians and its potential to save time in diagnostic processes. It is anticipated that the software can improve patient management, reduce costs and increase the efficiency of general healthcare services by accelerating the diagnosis of eye diseases. Certain eligibility criteria have been defined for the subjects and users to be examined within the scope of the study. [redacted] Retinow AI is designed for use by healthcare providers. The user must have sufficient understanding of the language in which the user manual was prepared.

Primary Objective:

The primary objective is to evaluate the capability of Retinow AI software to diagnose diabetic retinopathy, glaucoma, and macular degeneration diseases with high accuracy from fundus photographs. The performance of the software will be compared with the diagnoses made by expert physicians and the accuracy, sensitivity, and specificity metrics will be measured. The hypothesis that Retinow AI can reach 90% accuracy will be tested. In this context, the capability of Retinow AI to consistently identify the same disease symptoms in different fundus images will be evaluated by analyzing false positive and false negative results.

Primary Hypothesis:

It is hypothesized that Retinow AI software can diagnose eye diseases such as diabetic retinopathy, glaucoma, and macular degeneration at an early stage with 90% accuracy from fundus photographs. It is anticipated that the software will be able to achieve sensitivity and specificity rates similar to those of expert physicians in the diagnosis of these diseases.

8. Design of Clinical Trial

This clinical trial was designed based on the evaluation of preclinical studies conducted. This clinical trial is a single-center, observational, prospective and cross-sectional study planned to be conducted at Ankara Bilkent City Hospital to determine the primary endpoints of sensitivity, specificity and accuracy of the Retinow AI device for diabetic retinopathy, glaucoma and macular degeneration diseases.

The clinical trial, clinical trial plan, clinical trial results report will be conducted in accordance with the ethical principles of the Declaration of Helsinki, SS-EN ISO 14155:2020 principles and current national and international regulations governing this clinical trial. A signed Declaration of Helsinki will be obtained from all participants in the clinical trial.

Healthy participants who do not have Diabetic Retinopathy, glaucoma, macular degeneration diseases or any eye disease (no pathological findings in the retina) will be included in the study. Inclusion and exclusion criteria of the participants are specified in section 9.

Methods and tools to be used in the study:

- A non-mydriatic fundus camera will be used to diagnose diabetic retinopathy, glaucoma and macular degeneration, to analyze the retina of healthy individuals and to enable specialist physicians to diagnose diseases from fundus images. This camera allows detailed visualization of the vessels and retinal structure at the bottom of the eye by taking high-resolution retinal photographs. The cleaning of optical components will be

done regularly by hospital staff.

• Retinow AI software: Retinow software will be used by retina specialists to evaluate fundus images and compare results for clinical validation of the Retinow AI device. Retinow AI is an artificial intelligence-based software that diagnoses eye diseases by analyzing fundus images. The computer systems on which the software runs will be checked regularly, virus scans and security updates will be made. The analysis results of the software will be compared periodically with the results of specialist ophthalmologists. Since the latest version of the Retinow AI software will be used, no changes will be made to the software during the clinical study.

The clinical study protocol will be carried out in the following steps:

1. Participant Selection: Participants who apply to the retina and glaucoma clinic and meet the study inclusion and exclusion criteria will be determined by the specialist physicians in the study.

2. Information and Consent: Participants who meet the eligibility criteria will be provided with detailed information about the study and written informed consent will be obtained from them. The content of the informed consent form is arranged in accordance with the relevant integrity and data protection legislation. In the volunteer information and the informed consent form, the volunteer will be fully informed about how the clinical trial data will be collected, used and published.

3. Imaging Directions: Participants will be directed to the fundus imaging room by a specialist doctor for fundus photography. Retinal patients diagnosed with diabetic retinopathy, glaucoma, and macular degeneration will be sent for color fundus photography after the initial diagnosis examination. Similarly, healthy participants with no pathological findings in their retinas will be sent for a control fundus photography.

4. Fundus Photography: In this study, no invasive procedure will be applied to the patient, and the retinal photography will be taken by the camera operator with a special non-mydriatic digital camera called a fundus camera. In some patients diagnosed with Retinow AI, pharmacological dilatation (mydriasis) using a dilatation solution may be required to obtain a fundus image of sufficient quality. The dilatation procedure will be performed only by healthcare personnel (general practitioners, nurses, etc.) who are competent and trained in this regard.

5. Recording of Images: Right and left fundus images of each participant will be taken and these images will be recorded by the responsible researcher. The principal investigator will download the images via the hospital's PACS system.

6. Analysis of Images: Fundus photographs will be analyzed by the Retinow AI device. Then, they will be analyzed by expert ophthalmologists for gold standard evaluation.

[redacted]

[redacted]

8. Gold Standard Assessment: The gold standard assessment results performed by specialist doctors will be used to determine the sensitivity and specificity of the Retinow AI device.

[redacted]

[redacted]

AI Analysis: Retinow AI software will analyze the collected images within 24 hours of image acquisition. This rapid analysis will allow for a near real-time comparison with expert diagnoses.
Clinical data will be fed into Retinow AI software and the success metrics (Accuracy, Sensitivity, Specifity) will be evaluated. Diagnostic labels provided by Retinow AI software will be compared with labels provided by expert ophthalmologists. Performance metrics of accuracy, sensitivity and specificity will be calculated.

[redacted]

The clinical study will be completed when the predicted number of data is reached

9. Subjects

9.1. Inclusion Criteria

Patients with diabetic retinopathy, glaucoma or macular degeneration
Volunteers with written informed consent form
Volunteer must be 18 years or older
Healthy individuals without retinal disorders

9.2. Exclusion Criteria

Volunteers who do not want to have fundus imaging
Cases that do not comply with fundus photography for any reason
Patients with conjunctival and corneal infections,
People with hereditary or congenital retinal diseases,
People with cataracts,
People with uveitis,
Patients with permanent visual impairment in one or both eyes,
Patients with correction of + 6D and above – 6D,
Pregnant

9.3. Subject Withdrawal and Unfollowing Process and Cessation of Device Use

[redacted]

9.4. Relationship of Research Population with Target Population

This clinical study aims to evaluate the accuracy and reliability of Retinow AI software in diagnosing diabetic retinopathy, glaucoma and macular degeneration diseases. The study population includes individuals over the age of 18 who are suspected or diagnosed with these diseases, as well as healthy individuals with no pathological findings in their retinas.

The target population is individuals diagnosed with diabetic retinopathy, glaucoma and macular degeneration. The study population was selected to represent the target population; thus, the effectiveness of Retinow AI software in diagnosing these diseases can be evaluated under real-world conditions. The clinical characteristics of the study population and its similarity to the target population are important in revealing how effective and reliable the software will be in widespread use. In this way, the performance and general validity of the software will be evaluated through tests with the targeted patient group.

10. Procedures

10.1. Explanation of Clinical Research Procedures to Subjects

[redacted]

10.2. Disclosure of Activities of Sponsor Representatives

[redacted]

[redacted]

10.3. Factors That May Compromise the Results of a Clinical Trial

[redacted]

11. Data Management

[redacted]

[redacted]

12. Amendments to the CIP

[redacted]

13. Deviations from CIP

[redacted]

14. Informed Consent Process

[redacted]

[redacted]

15. Adverse Events, Adverse Device Effects and Device Deficiencies

20.1. Definitions of Adverse Events and Adverse Device Effects

Adverse Event
An Adverse Event (AE) is any untoward clinical manifestation, including an unintended medical event, unintended illness or injury, or abnormal laboratory findings, occurring in subjects, users, or other persons in the context of a clinical trial, whether or not related to the trial.
This definition includes expected events as well as unexpected events.
This definition includes events occurring in the context of a clinical trial related to an investigational device, comparator, or related procedure.
Adverse Device Effect
An Adverse Device Effect (ADE) is any AE related to the use of an investigational medical device. This definition includes adverse events resulting from inadequate or inadequate use, placement, implantation, setup or operating instructions, or any malfunction of the investigational medical device. This definition includes any event resulting from an error in use or intentional misuse of the investigational medical device. This includes the 'comparator' if the comparator is a medical device.

20.2. Description of Device Deficiencies

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

20.3. Definitions of Serious Adverse Events

Serious Adverse Event
A Serious Adverse Event (SAE) is any AE that results in any of the following: death, serious deterioration in the subject's health resulting in any of the following: life-threatening illness or injury, permanent impairment of a

body structure or body function, hospitalization or extension of hospital stay, medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment of body structure or body function, chronic disease, fetal distress, fetal death, or congenital physical or mental impairment or birth defect.

Serious Adverse Device Effect
A Serious Adverse Device Event (SADE) is an ADE that results in any of the characteristic consequences of a serious adverse event. SAEs related to procedures mandated by the clinical trial plan but not related to the use of the device will not be considered Serious Adverse Device Events.

Unanticipated Serious Adverse Device Effect
An unexpected SAE is an effect that is not identified in the current risk assessment by its nature, incidence, severity or consequence. Procedures related to the use of a device are addressed in the risk assessment, which makes it possible to determine whether the procedure for the SAEs is an Unexpected Serious Adverse Device Effect. SAEs related to procedures mandated by the clinical trial plan but not related to the use of the device will not be considered Serious Adverse Device Effects.

[redacted]

20.7. Emergency Contact Information

Sponsor

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Single Registration Number (SRN)	TR-MF-000035284

Sponsor Representative

Name and surname:	**Tuğba Haklı**
Phone	554-5446786
Email	tugbahakli@retinow.com.tr

[redacted]

16. Publishing Policy

The clinical trial ends when the last subject completes the final follow-up. The sponsor will notify TITCK within 15 days following the end of the clinical trial and will send the clinical trial report, which includes an easy-to-understand summary, within 1 year after the end of the clinical trial. The clinical trial will be registered in a public database before the start of the recruitment activities, and the content will be updated throughout the conduct of the clinical trial, and the results will be entered after the completion of the clinical trial. This clinical trial will be registered in a recognized public database for clinical trials (e.g. ClinicalTrials.gov, EU Clinical Trials Register) in order to ensure transparency and traceability of international clinical trials. This registration will include the main purpose of the trial, methodology, target population, outcome measures, and other relevant information. The findings and results of this trial will be published in a way that is accessible to the scientific community and the public. The trial results will be submitted for publication in peer-reviewed scientific journals and presented at national and international conferences. In addition, these results will be reported to the relevant health authorities and regulatory bodies. The results of the clinical trial will be published within the specified time frame after the completion of the study. A first draft report of the trial results will be prepared within 6-12 months after the completion of the study. The sponsor will play an active role in the analysis, reporting and publication of the trial results. The sponsor will also perform or have performed independent statistical analysis to ensure that the results are presented accurately and unbiased. Authorship criteria will be determined in accordance with the guidelines established by the International Committee of Medical Journal Editors (ICMJE). Authorship will be limited to investigators who have made a significant contribution to the study. This includes those who contributed to the study design, data collection, analysis, interpretation of the results and writing of the manuscript. Each author will confirm the accuracy of the results and approve the final version of the manuscript.

17. References

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ANNEX 1.

STATISTICAL ANALYSIS PLAN

Analysis Population and Procedures

Analyses will be performed on a Per Protocol (PP) basis only. The PP analysis will include participants who completed the study per protocol and this population will accurately reflect the effectiveness and reliability of the software in diagnosing diabetic retinopathy, glaucoma and macular degeneration.

Baseline Data and Endpoints Descriptive Statistics

Baseline Data:

Baseline data includes the age and gender information of all patients participating in the clinical study. This data does not affect the results of the Retinow AI software. It will only be collected to obtain information about the age and gender distribution.

Endpoints Descriptive Statistics:

Endpoints are the sensitivity, specificity and accuracy rates of the Retinow AI software in diagnosing diabetic retinopathy, glaucoma and macular degeneration diseases. These rates show how well the software agrees with the diagnoses made by specialist physicians. Descriptive statistics are used to measure these rates. The definitions of these rates are provided below.

Sensitivity: The ability of the software to correctly identify individuals with the disease. High sensitivity reduces the probability that the software will miss signs of the disease. (True positive rate).

Specificity: The ability of the software to correctly identify healthy individuals. High specificity minimizes false positive results. (True negative rate).

Accuracy: It is defined as the percentage of correct results in all diagnoses of the software.

These descriptive statistics will be used to further evaluate the reliability, effectiveness, and usability of the Retinow AI software in clinical applications.

Analytical Procedures

The comparisons of the diagnosis of disease results in the clinical trial by the doctor and the Retinow AI software will be examined. The results will be analyzed with Cohen's Kappa analysis. The parameters to be analyzed are sensitivity, specificity and accuracy values. Sensitivity is defined as the accuracy between positive findings according to the clinical reference standard; It will be calculated as the ratio of eyes with positive findings according to the reference standard and positive results with the Retinow AI system. Specificity is defined as the accuracy between negative findings according to the clinical reference standard; It will be calculated as the ratio of eyes with negative findings according to the reference standard and negative results with the Retinow AI system. (Positive findings indicate being sick, negative findings indicate being healthy)

Statistical analyses will be performed using the Python programming language version 3.11.4 and the TensorFlow library version 2.10.0. In addition to these calculations, the Cohen's Kappa method will also be used for the analysis of the results. These analyses involve the use of the specified software versions and tools in the data processing and model building stages. This process aims to specify the relevant software and versions to ensure the reliability and framework of the research results. Considering the referenced cases as 'positive' and the non-referenced cases as 'negative', the sensitivity, specificity and accuracy scores are clinically significant measurements and will be calculated with 95% confidence intervals. For each disease, tables will be created to compare the sensitivity and specificity of the algorithm with the reference standard. The reference standard is defined as the majority decisions of the ratings of 3 expert ophthalmologists. The definitions of the positive and negative cases to be analyzed are given below.

		Retinow AI				
		Disease	No Disease	Total	Kappa	p
Doctor	Disease	TP	FN			
	No Disease	FP	TN			
	Total					

Kappa Score: Cohen's Kappa score is a statistical method used to measure the agreement between two raters or observers. It shows how much the two parties agree, taking into account the probability of random agreement.

P: It is used in statistical tests to determine whether the results are significant. In a hypothesis test, it shows how much the data deviates from the expected distribution and expresses the probability that the results occurred randomly.

True Positive (TP): This refers to the situation where the software correctly diagnoses the disease. That is, it occurs when the software classifies an actual disease as a patient.

True Negative (TN): This refers to the situation where the software does not correctly diagnose the disease. That is, it occurs when the software classifies an actual healthy state as healthy.

False Positive (FP): This refers to the situation where the software incorrectly diagnoses the disease. That is, it occurs when the software classifies an actually healthy condition as sick.

False Negative (FN): This refers to the situation where the software does not incorrectly diagnose the disease. So it happens when the software classifies a real disease as healthy.
These terms are used to evaluate the accuracy and precision of software in classifying a disease or condition. True Positive and True Negative results represent conditions that were correctly diagnosed, while False Positive and False Negative results represent conditions that were misdiagnosed. Below is the calculation of sensitivity, specificity and accuracy values in our clinical study.

Sensitivity = TP/(TP + FN)
Specificity = TN/(TN + FP)
Accuracy = (TN + TP)/(TN + TP + FN + FP)

The passing criteria for the Retinow AI software in the clinical study will be based on its accuracy, sensitivity and specificity in diagnosing diabetic retinopathy, glaucoma and macular degeneration. The passing criteria were determined as 90% accuracy, 90% sensitivity and 90% specificity for all diseases. These threshold values are necessary for the software to be used as a reliable diagnostic tool in the clinical setting. In addition, it will be mandatory for the reliability of the study and the validity of the results to be kept below 10% of the possible technical errors and data loss rates. When these criteria are met, Retinow AI will be considered successful; otherwise, the software will not pass the study.

Sample Size

The required sample size for each study whose results will be analyzed with Cohen's Kappa analysis was calculated using Arifin's [82] calculation tool, which was developed based on the formula presented by Donner and Eliasziw [81].

However, in order to provide additional safety margin against possible data loss and participant losses at each stage of the study, it was planned to conduct the study with 305 people for each disease (diabetic retinopathy, glaucoma and macular degeneration). In this way, the reliability of the data and the statistical validity of the results will be preserved. The sample size calculations made in the calculation tool are given below.