Research Protocol Name: DETECTION AND CLASSIFICATION OF DIABETIC RETINOPATHY FROM POSTERIOR POLE IMAGES WITH A DEEP LEARNING MODEL

Protocol Number: EC-2021DR-TR

Research Type / Phase: First Application for Non-CE Marked Medical Device Research (Excluding Thesis and Academic Studies)

We have read the current version of the Declaration of Helsinki, Good Clinical Practices (ICU) Guidelines and Good Laboratory Practices (ILU) Guidelines, and that we have read the current version of our clinical study, "Detection and Classification of Diabetic Retinopathy from Back Pole Photographs with a Deep Learning Model", which we will carry out with 900 volunteer patients, by the medical consultant and responsible researchers. We declare and undertake that it will be carried out in accordance with the approved and authorized protocol, the Declaration of Helsinki, IKU/ILU. In addition, the researchers named below were informed in detail about the study by the Principal Investigator (single center) of this study.

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1. PROTOCOL REVISION HISTORY

Rev No	History	Reason
00	01.07.2021	First version (v1.0)
01	05.10.2021	Second version (v1.0) - Moved the research starting date forward

2. RESEARCH INFORMATION

2.1. Supporting Organization

Name: URAL Telecommunication Industry Trade Limited Company

Address: Pınarbaşı Mah. Hurriyet Cad. Akdeniz University Antalya Technopolis R&D 2

Uluğbey Building No:3A/Z14, 07070 Konyaaltı/ANTALYA

Name-surname of the official: Rim KHAZHIN

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2.2. Supporting Legal Representative

Only the sponsor has the authority to sign. There is no legal representative.

2.3. Medical Consultants and Associated Medical Qualified Physician

Project supervisor:

Name Surname: Ahmet Burak Bilgin
Title: Assoc. Dr.
Specialization: Eye Diseases-Retinal Diseases
Work Address: Akdeniz University Department of Eye Diseases
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Researcher:

Name Surname: Ramazan Sarı
Title: Prof. Dr.
Specialization: Endocrinology and Metabolic diseases
Work Address: Akdeniz University, Department of Internal Medicine
Phone number: 0242 249 6735

Assistant researcher:

Name Surname: Mehmet Erkan Doğan
Title: Dr. Faculty Member
Specialization: Eye Diseases-Retinal Diseases
Work Address: Akdeniz University Department of Eye Diseases
Phone number: 0242 249 6640

2.4. The centers where the research will be conducted and the areas where data collection is planned:

Akdeniz University Department of Ophthalmology - Dumlupınar Boulevard Akdeniz University Hospital 07059, Campus, ANTALYA

Akdeniz University Department of Endocrinology and Metabolism Diseases - Dumlupınar Bulvarı Akdeniz University Hospital 07059, Campus, ANTALYA

CONTENTS

1. ABBREVIATIONS

DR: Diabetic retinopathy

mtmDR: more than mild diabetic retinopathy

vtDR: vision-threatening DR - Vision threatening diabetic retinopathy

ML: Machine learning

ORF: Case Report Form

ADE: Adverse Device Event

UADE: Unanticipated Adverse Device Effects

EDC: Electronic Data Capture

2. LOGIN

2.1. Research Design

This study is a prospective safety/efficacy study.

In the European Union, approximately 32.7 million adults were found to have diabetes in 2017. It is also estimated that 12.8 million people have undiagnosed diabetes. The age-standardized prevalence of diabetes among adults was 6% on average in EU countries in 2017. This rate is 11.9% for our country, which corresponds to approximately 9.6 million diabetic patients. Diabetes has high morbidity and there are millions of people who need to be screened for diabetic retinopathy (DR). The number of ophthalmologists is insufficient corresponding to the high patient density that needs to be screened.

Diabetic retinopathy is a retinal disease that can often be stopped with an early diagnosis but can lead to severe vision loss, including permanent blindness, in case of neglect. The diagnosis and stage of the disease can often be made only through fundus examination or fundus photographs. Artificially intelligent retinal diagnostic softwares present a solution to the shortage of trained ophthalmologists, the evaluation of retinal photographs taken by an ophthalmologist in another center and making a diagnosis (telemedicine - telemedicine); Recently, by using artificial intelligence algorithms, it has become possible to obtain meaningful information from large volumes of data (more from scanned patients/fundus photos) in a shorter period of time with much less human intervention. With the artificial intelligence algorithm in which pathological lesions are taught by using posterior pole photos of the eye, DR lesions are identified with high accuracy and reliability, faster, and at a lower cost. This offers an excellent screening advantage for the early diagnosis and treatment of DR and other retinal diseases.

Methods and tools to be used in the research:

i. Fundus photography with non-mydriatic camera and classification of diabetic retinopathy with artificial intelligence algorithm
ii. Evaluation of images by retina specialists and comparison of results for clinical validation of the system.

Clinical and laboratory tests to be performed:

i. Fundus photography with a non-mydriatic camera. In this examination, a non- invasive procedure is applied to the patient. The retinal photographs will be taken with special digital cameras called 'fundus cameras'. In patients whose non-mydriatic images cannot be obtained, tropicamide drops will be instilled to dilate the pupil, and then photographs will be taken.
ii. Pupil dilation will be achieved by instilling Tropicamide drops in both eyes of the patient, and then 4 quadrant photographs of both eyes will be taken with a mydriatic fundus camera.

Among the patients admitted at the Akdeniz University Endocrinology and Metabolic Diseases Department with a diagnosis of diabetes, those who want to participate in the clinical study will be referred to the clinical study by the endocrinology polyclinic. The authorized nurse involved in the clinical study will explain the study to the volunteer and ask for the consent form to be signed, and consent will be obtained. Fundus images will be taken with a non-mydriatic fundus camera by a designated technician. Ural Telekom firm, EyeCheckup project and Assoc. Dr. It is planned to diagnose and classify the images in terms of DR with the artificial intelligence (AI) algorithm developed with the consultancy of A. Burak Bilgin. Images obtained using eye drops will be evaluated by the faculty members of the Department of Ophthalmology, Retina Unit, and compared with AI to determine sensitivity and specificity. In this way, it will be possible to screen millions of diabetic patients who need to be screened for diabetic retinopathy in much shorter intervals and with less manpower.

The research will be carried out in a single center at Akdeniz University Faculty of Medicine. The control group will not be used. The EyeCheckup software used in the clinical study does not have a CE mark. However, the Fundus cameras used to take retinal images from the patient in the clinical study are CE-marked and EyeCheckup does not have any direct interaction with the patient. Since the performance and effectiveness of our EyeCheckup software will be measured in the study, the study will be conducted as a Non-CE Marked Medical Device Research (Excluding Thesis and Academic Studies).

The duration of the study is planned to be 12 months, but the study may be terminated if the artificial intelligence algorithm is validated and the intended number of 900 volunteer patients is reached in a shorter time. Since fundus images of the patients will be used, follow-up time is not required. The planned trial time is a maximum of 30 minutes per patient.

There is no other diagnosis/treatment method to be applied together. It is only a study to diagnose DR.

2.2. References and Literature full text

2.2.1. Ting DSW, Cheung CY, Lim G, Tan GSW, Quang ND, Gan A, Hamzah H, Garcia-Franco R, San Yeo IY, Lee SY, Wong EYM, Sabanayagam C, Baskaran M, Ibrahim F, Tan NC, Finkelstein EA , Lamoureux EL, Wong IY, Bressler NM, Sivaprasad S, Varma R, Jonas JB, He MG, Cheng CY, Cheung GCM, Aung T, Hsu W, Lee ML, Wong TY. Development and Validation of a Deep Learning System for Diabetic Retinopathy and Related Eye Diseases Using Retinal Images From Multiethnic Populations With Diabetes. JAMA. 2017 Dec 12;318(22):2211-2223. doi: 10.1001/jama.2017.18152.

2.2.2. Abràmoff MD, Lavin PT, Birch M, Shah N, Folk JC. Pivotal trial of an autonomous AI-based diagnostic system for detection of diabetic retinopathy in primary care offices. NPJ Digit Med. 2018 Aug 28;1:39. doi: 10.1038/s41746-018-0040.

3. STUDY SUMMARY

3.1. Summary of Clinical Findings

All documents required by the standard for EyeCheckup software have been created, risk analysis has been made and precautions have been taken against possible risks.

EyeCheckup clinical trial will be performed in a single center at Akdeniz University Hospital. The target population is people aged 18 and over, who have been diagnosed with diabetes in the Endocrinology Clinic of Akdeniz University Hospital and have not been diagnosed with diabetic retinopathy (DR) before, and whose retinal image can be taken. To better align the analysis population with the proposed target population, those who do not meet certain additional predetermined criteria (eg: less than 18 years of age, visually impaired) will be excluded. Volunteers will be taken to the research area allocated by the hospital at Akdeniz University. Before any volunteers are recruited, candidates will need to verify that they understand the research and have given written informed consent. Study; **CE marking will** be made to measure the success of Artificial Intelligence software in terms of specificity and sensitivity, which detects the presence of mild DR (mtmDR) and vision-threatening DR (vtDR) for each eye by taking retinal images from 3 different fundus cameras and using these images.

The artificial intelligence model was trained with fundus images taken from Akdeniz University Hospital Ophthalmology Clinic with the approval of the Akdeniz University Ethics Committee.

The publicly available Kaggle Diabetic Retinopathy Detection Competition (EyePACS dataset), Kaggle APTOS 2019 Blindness Detection Competition dataset, Messidor, Messidor 2, IDRiD Dataset, and DIARETDB0 - Standard Diabetic Retinopathy Database datasets were used as test datasets. A retrospective study was performed on a total of 4000 test images (dataset). As a result of the test studies, more than 92% specificity and 92% sensitivity were obtained. The result of the most successful algorithm is listed below. The most successful algorithm was built on the Google ML Platform, and this first prototype will be used as a Non-CE Marked Medical Device Research (Excluding Thesis and Academic Studies).

Diagnosis	Truth
normal eye	97.19%
Mild/Moderate Diabetic Retinopathy	96.43%
Severe / Proliferative Diabetic Retinopathy	100.00%
Diabetic Macular Edema	100.00%

3.2. Study Schedule and Duration

Baseline (first patient enrollment): 01 November 2021

End (last patient to complete study): 01 November 2022

3.3. Flow Chart of Study

Visit	Scanning Day 1, Visit 1	Registration/Basic Day 1, Visit 1	Run Termination Day 1, Visit 1
Be Informed	x	x	x
Inclusion/Exclusion Criteria	x	x	x
Demography	x	x	x
Medical History (Additional Disease History)	x	x	x
Study Intervention	x	x	x
Dilated Ophthalmoscopy	x	x	x
Full Case Report Forms (Orfs - E-Orf)		x	x
Adverse Events			x

3.4. Rationale / Importance and Contribution of the Research

EyeCheckup is an automated software instrument designed to analyze digital color photographs of the ocular fundus to quickly screen for diabetic retinopathy (DR).

The main purpose of the study was to detect the presence of mild diabetic retinopathy or sight-threatening diabetic retinopathy from retinal fundus images in adult patients who applied to the endocrinology outpatient clinic due to diabetes, to grade and to determine the sensitivity and specificity of diabetic retinopathy, and to identify and classify the images with the developed

artificial intelligence algorithm. It is a comparison of diagnosis done by artificially intelligent algorithms and classification of DR done by doctors.

The primary efficacy endpoint in the study was that EyeCheckup's intended image capture workflow could be successfully used in conjunction with the EyeCheckup device to diagnose 80% or more of the participants for more than mild diabetic retinopathy (mtmDR) and vision-threatening diabetic retinopathy (vtDR) separately with a minimum 90% sensitivity and 90% specificity.

The secondary efficacy endpoint in the study was

Additional non-primary analyzes will also be performed to assess the following general conditions:

- Positive Predictive Value of EyeCheckup test for mtmDR and vtDR,
- Negative Predictive Value EyeCheckup test for mtmDR and vtDR.
- Positive and negative odds ratios for mtmDR and vtDR.

The study will include approximately 900 people with diabetes, excluding exclusions. They will be recruited voluntarily through 1 clinical center. Two photographs of the ocular fundus (one optic disc centered, one macula centered) will be obtained per eye using a non-mydriatic eye fundus camera from both eyes of the participants. These images will be analyzed by EyeCheckup. Then, pupil dilation will be achieved by instilling Tropicamide drops in both eyes of the patient and 4 quadrant photographs of both eyes will be taken with a fundus camera. Ophthalmologists will then evaluate and record the condition of the eyes based on images obtained with pupil dilation.

There is no similar or equivalent product in our country. It is the first locally produced and developed product. Equivalent FDA-approved and CE-marked products are available abroad. Similar clinical studies have been conducted with equivalent products abroad. Detection and classification of diabetic retinopathy is planned in the first version of our product. In the next stages, we aim to detect more than 20 diseases, including glaucoma, cataract, and age-related macular degeneration, by developing the product. Most similar products only work in the field of diabetic retinopathy.

3.5. Success Criteria of Study

Three different doctors will evaluate the volunteer's fundus images taken from fundus cameras and will make a decision about the presence of DR: Not more than Mild DR, More than mild DR (mtmDR), and Vision-threatening DR (vtDR). Decisions will be made by majority vote. The doctors' decision will be Ground Truth for us.

EyeCheckup will decide for both eyes of each volunteer. If it is the same as the doctors' decision, this decision will be considered correct.

Total correct number / Total number of eyes = Success rate

Our criteria for successful completion of the clinical trial: Success rate > 90%

At the same time, the Specificity and Sensitivity values should be calculated separately for mtmDR and vtDR and each should be above 90%.

Eye doctors (Normal, mtmDR, vtDR) make their decisions according to the ETDRS guidelines. Main signs to check for: Microaneurysms, Intreretinal hemorrhages (Intraretinal hemorrhage), Venous beading, IRMA, Neovascularization, Intravitreal hemorrhage, Preretinal hemorrhage

3.6. The benefit of the Research, Possible risks and precautions to be taken against harm:

Benefits;

According to the 2018 data from the World Health Organization, 285 million people worldwide have a visual impairment. It is known that more than 80% of all visual disorders can be prevented or treated. The retinal examination should be performed by an ophthalmologist and/or retinal specialist in order to prevent retinal-related visual disorders by making an accurate diagnosis, but people only consult an ophthalmologist when they feel any discomfort. Typically, by the time symptoms appear, the disease has reached advanced stages and requires a variety of expensive medical and surgical treatments. Unfortunately, at this stage, the disease often results in severe and permanent visual impairment and vision loss.

EyeCheckup analyzes the patient's fundus/retinal health with images taken from the fundus camera. If it sees a problem, it directs the patient to the doctor, if not, it recommends scanning again after an appropriate period of time recommended within the AAO PPP. Thanks to the early detection of eye problems, early diagnosis and treatment can prevent vision loss and visual impairment. The most important aim of EyeCheckup is the early diagnosis of diabetic retinopathy and thus the prevention of possible vision loss and blindness. Secondary objectives of EyeCheckup are using less trained manpower and screening for DR in populations without access to an ophthalmologist.

Possible Risks;

The images used in our study do not pose any risk or harm to the patients. Only fundus images of the patients will be evaluated. The images will be recorded anonymously, and doctors or the Artificial Intelligence algorithm will not be able to access the identity and health information of the patients. There will be no harmful use of personal data or health information.

The study is expected to pose minimal risk to both camera operators and participants, as the camera systems used have been previously approved by the FDA for ocular fundus photography, and tropicamide 1% eye drops for pupil dilation is an FDA-approved drug product and have been shown to have minimal side effects.

3.7. Type of Research

In this study, the reliability and effectiveness of our EyeCheckup software will be measured. Therefore, the study will be carried out as Medical Device Research (Excluding Thesis and Academic Studies) Without CE Mark, as determined by TITCK.

3.8. Research Population

All adult patients (male-female) aged 18 years and over who were diagnosed with diabetes but not diagnosed with diabetic retinopathy by the endocrinology outpatient clinic.

3.9. Inclusion Criteria for Volunteers

Fundus images of 900 volunteer patients with evaluable quality, with or without pathology, who applied to Akdeniz University Endocrinology and Metabolism Diseases Department with the diagnosis of diabetes, who were not diagnosed with Diabetic Retinopathy before and whose images can be taken from the posterior polar region of the eye with a fundus camera, will be included in the study.

- Diabetes must have been diagnosed
- Diabetic Retinopathy must not be diagnosed yet,
- The participant must understand the study and have signed informed consent,
- No history of any other retinal vascular disease, cataract, or other diseases that may affect the appearance of the retina or optic disc (refractive defect and ocular surface disease are allowed),
- No history of intraocular surgery other than cataract surgery, ocular laser therapy for any retinal disease, or ocular injection for diabetic macular edema or proliferative disease,
- No ambient blur preventing good retina photography
- Persons aged 18 and over are included in the study.

If at least one of these conditions is not met, the participant is not included in the study.

[one] Inan, UU, F. Ozturk, and SS Ermis, Pharmacologic pupil dilation in diabetic patients. Retina, 2003. 23(2): p. 254-6

3.10. Exclusion Criteria for Volunteers

Fundus images that have corneal or lens opacification that will prevent imaging, and that are not evaluable due to intravitreal hemorrhage or vitreous will not be included in the study. Patients followed or treated for DR will not be included in the study.

- If the volunteer are not diagnosed with diabetes,
- If the potential participant cannot understand the study or informed consent,
- If the volunteer has a history of retinal vascular disease other than diabetic retinopathy, glaucoma, or any other disease that may affect the appearance of the retina or optic disc.
- If the volunteer have had previous intraocular surgery including than cataract, laser intervention on the retina, or previous intraocular intervention for the treatment of diabetic retinopathy,
- If there is a permanent visual impairment in one or both eyes,
- If under the age of 18,

- If the participant is contraindicated for imaging with the fundus imaging systems used in the study,
- Exclude if there is an ambient blur in both eyes severe enough to impede good retinal photography.

If at least one of the above conditions is present, the participant is not included in the study.

3.11. Withdrawal of Volunteers from the Study - Exclusion Criteria

The volunteer may withdraw from this study at any time without giving any reason, provided that the principal investigator/doctor is informed. He assumes no liability for his refusal or subsequent withdrawal from this study, and this does not in any way affect the medical care that the patient needs now or in the future.

The researcher/doctor or the supporting organization, who is the coordinator of the study, may exclude the subject from the study without the consent of the subject, due to their negligence in fulfilling the requirements of the study program or in order to improve the quality of the medical care received by the patient. Fundus images that have corneal or lens opacification that will prevent imaging, and that are not evaluable due to intravitreal hemorrhage or vitreous will not be included in the study. Patients already diagnosed with DR will not be included in the study.

Participants withdrawing from the study for a serious or non-serious ACE should be monitored by the investigator until the clinical outcome of the ADE is determined. Any participant experiencing an ADE may withdraw from the study at any time at the discretion of the investigator. ADE(s) should be noted with appropriate ORFs and participant progress should be monitored until the ADE is resolved. The medical monitor or project manager should be informed.

4. STUDY TREATMENTS

4.1. Route of administration, dosage, dosing regimen, and Duration of Treatment of Subjects

No intervention will be made to the body. Since the medical device is software, there will be no drug use and no dosage. Pupil dilatation will be provided by instilling 1-2 drops of Tropicamide drops into both eyes to enlarge the pupil. Since tropicamide drops are eye drops that are always used during routine eye examinations, they will not be considered a drug intervention in a clinical study. The processing time is equal to the growth time of the pupil and the time to obtain 2 images from both eyes from the fundus camera. While it takes about 20-30 minutes for the pupils to grow, it takes 1-2 minutes for the photos to be taken. These procedures are not the application of the EyeCheckup product to the patient; It is the process of obtaining retinal images with the standard method using CE-marked eye drops and a CE-marked fundus camera.

There is no follow-up period, as no follow-up is required for the patient whose fundus image was taken. Since the device is not used for treatment purposes, there is no treatment period. For the patient with any finding in their eyes, a referral is made to the doctor. This process is advanced by the doctor.

4.2. Drugs Not Allowed Before And/or After Research

There are no drugs or treatments that are required or are not authorized prior to the trial. Since only fundus images of the patient will be used, there is no drug use that will affect image acquisition. Before image acquisition, only 1-2 drops of Tropicamide will be instilled into the eye.

There is no drug or treatment application after the fundus image is taken.

4.3. Volunteer Compliance Monitoring Methods

Follow-up and treatment of volunteers after fundus photography is not planned. The study will continue through the photographs obtained from the volunteer.

5. RELIABILITY STATEMENT

5.1. Device Reliability Assessment

Ongoing safety monitoring will be performed by the responsible person who will regularly review reported adverse effects (AEs) or unexpected adverse device effects (UADEs) from the clinical trial site and promptly report them to the sponsor.

5.2. Adverse device effect (ADE)

Adverse device effect (ADE) means an adverse event associated with the use of an investigational medical device.

All adverse events that are suspected, observed, or voluntarily reported causally related to the study will be recorded on the adverse event page of the electronic case report form.

5.3. Unexpected Adverse Device Effects (UADE)

Unexpected adverse device effect (UADE) is any serious adverse effect on health or safety, or any life-threatening problem or death, resulting from or associated with its use, not previously identified in nature, severity, or extent.

UADEs occurring on the visit will be monitored to adequately assess the participant's safety or until the event has stabilized. When the case is resolved, a resolution date should be written on the case report form. All UADEs will be followed up until resolution or until the participant is medically stable. All adverse events that are suspected, observed or voluntarily reported causally related to the study will be recorded on the adverse event page of the case report form, then entered into the electronic data capture (EDC) system.

5.4. Adverse device effect notification - Unexpected Adverse Device Effects notification

“Adverse Device Effect” notification will be made to the Ministry and Ethics Committees in accordance with the provisions of the relevant legislation.

All recordable ADEs will be entered into the security data system within 7 days of identification. Recordable UADEs will be entered into the data system within 24 hours of identification. If there

are any technical difficulties, UADE will be notified by telephone or fax communication. This data will be entered into the electronic data capture (EDC) system as soon as the system is available.

6. STATISTICS

6.1. Analysis

Fundus images of 900 volunteer patients with evaluable quality, with or without pathology, who applied to Akdeniz University Endocrinology and Metabolism Diseases Department with the diagnosis of diabetes, were not diagnosed with Diabetic Retinopathy before, and whose images can be obtained from the posterior polar region of the eye with a fundus camera, will be included in the study, which will be carried out as a single-center study. The sample size was determined by Akdeniz University Statistics Consultancy Application and Research Center, taking into account the incidence of diabetic retinopathy in diabetic patients. Upon confirmation that the AI algorithm is working successfully, the trial will be terminated when the intended number of 900 patients is reached. The success criterion of the study is specified in Article 3.5.

The classification performance of the AI algorithm will be evaluated with reference to the diagnosis made by the doctors. Gold standard test results will be obtained based on the diagnosis from three different doctors. At this stage, the compatibility between the diagnosis from the doctors will be evaluated according to the Kappa statistics, and the similarity of the decisions made by the doctors with each other will be examined. The diagnoses of the patients will then be evaluated together with the results of the AI algorithm, and performance measures of the AI algorithm (sensitivity, selectivity, positive predictive value, negative predictive value, overall accuracy, etc.) will be obtained. Whether the performances of the AI algorithm are clinically acceptable or not will be evaluated with ratio tests (single sample population ratio significance test, Fisher Exact test, Chi-square tests, etc.) according to the threshold values to be determined by experts. A data analysis software will be selected among various software (R, SPSS, TURCOSA, Stata, etc.) to do the statistical analysis in accordance with the purpose. For statistical analysis, the level of significance will be taken as 0.05. **(Annex-1 Analysis Plan)**

6.2. Determination of Sample Size

The sample size was calculated by evaluating whether the AI algorithm achieved a success rate of more than 90%, considering 5% Type-I error, 80% power, and different effect sizes listed below.

Power	N	Proportion Given H0 (P0)	Proportion Given H1 (P1)	Target Alpha	Actual Alpha	Beta	Reject H0 If Z>=This
0,8033	5341	0,9000	0,9100	0,0500	0,0511	0,1967	1,6449
0,8002	2286	0,9000	0,9150	0,0500	0,0520	0,1998	1,6449
0,8015	1255	0,9000	0,9200	0,0500	0,0525	0,1985	1,6449
0,8004	778	0,9000	0,9250	0,0500	0,0530	0,1996	1,6449
0,8012	523	0,9000	0,9300	0,0500	0,0541	0,1988	1,6449
0,8047	376	0,9000	0,9350	0,0500	0,0545	0,1953	1,6449
0,8092	284	0,9000	0,9400	0,0500	0,0539	0,1908	1,6449
0,8076	212	0,9000	0,9450	0,0500	0,0565	0,1924	1,6449
0,8004	164	0,9000	0,9500	0,0500	0,0553	0,1996	1,6449

Considering the situation marked in the table above as an example, if at least 778 people are included in the study, the case that the AI algorithm will achieve at least 2.5% above the 90% level can be detected at 80% power and 5% type-1 error level. If the success rate of the AI algorithm increases at a level of 2.5% or less from 90%, this difference will not be statistically significant. **(Annex-1 Analysis Plan)**

6.3. Measurement and evaluation of effectiveness parameters

The Diabetic Retinopathy diagnosis of EyeCheckup and Diabetic Retinopathy diagnosis results made by specialist doctors will be compared, and evaluation and statistical analysis will be made by the researchers.

7. STUDY MANAGEMENT

7.1. Recording Data

The site coordinator will ensure that all data obtained during patient visits is quickly entered into the electronic case report form in accordance with other specific information provided. The explanation for not entering any required data should be stated on the appropriate page.

The site coordinator and the principal investigator must sign with a digital signature to confirm the accuracy of the information entered in the electronic case report form, thus declaring that they take responsibility for the accuracy of all case record data.

7.2. Protocol Changes

If a change to the protocol is required, it will be submitted to the ethics committee for approval, and the investigator will ensure that the change is referenced and approved in a timely manner.

7.3. Storage of operating data

The investigator must retain all legal/study documents, signed informed consent forms (BGOF), electronic case report forms, and source documents for ten years after study completion.

As the owner of the data, the coordinating investigator must keep all other documentation of the study for as long as the product is available. These documents and procedures will include all written reflections on the protocol and procedures, original copies of case report forms for each study patient, any raw/source data provided by the investigator, the final report, and inspection certificates, if available.

It will be guaranteed that the highest possible accuracy is achieved during the processing of the data. The collected data is compiled and analyzed within the framework of statistical models. According to this analysis, a Clinical Research Report is prepared.

7.4. Sharing and publishing results

All information obtained as a result of the study should be treated as CONFIDENTIAL. Before the conclusion of the abstract, article, or visual presentation, it is acceptable that the results of this study will be shared in scientific meetings or publications if the researchers and the coordinator

researcher mutually agree on the contents and conclusion comments. This agreement also applies to any changes requested later by reviewers or journal editors.

7.5. Patient Confidentiality

All personal information collected and processed in accordance with the purpose of this study will be handled by the researcher and their team, with appropriate measures to ensure the confidentiality of this data, and in accordance with applicable national and/or local laws and regulations regarding personal data protection.

In our clinical research, the records that will show that the identity of the volunteers are kept confidential, and not disclosed to the public, and the identity of the volunteers remains confidential even if the research results are published.

Viewers, pollers, the Ethics Committee, the Ministry of Health, and other relevant health authorities can directly access the original medical records. By signing the informed voluntary consent form, only the persons and institutions mentioned are granted access.

8. PERSON AND/OR INSTITUTION WITH DIRECT ACCESS AUTHORITY

There is no person and/or institution with direct access authority. The only authorized institution is URAL Telekom.

9. ETHICAL ASSESSMENTS

9.1. Examining the Ethical Issues of the Study

Due to its design, this study does not interfere with the diagnosis and treatment approaches of physicians. The procedures performed within the scope of the study will be carried out in accordance with the revised Declaration of Helsinki and the ethical rules determined by all national and international regulations.

Ethics committee and TR Ministry of Health approval letters will be sent to the participating institution before the study is started.

The formation of Ethics Committees should comply with the relevant Turkish laws, regulations, and guidelines.

Fidelity: Data will be obtained from observations using scientific methods only. Interpretation and evaluation of data will be based on scientific methods. Any unobtained result will not be shown as a research result.

No Harm in Scientific Research: Volunteers will not be harmed in any way during the research process. Volunteers will be informed about the study and a minimum notification consent form will be signed.

Responsibilities and Rights: The principal investigator will inform the volunteers about **the** research findings and warn them about possible harmful practices.

Authors: The names of all researchers are published in proportion to their contributions. The names of people who did not contribute effectively to the planning, execution, and preparation of the research cannot be published in the list of authors.

Citations and Citations: The books, journals, and all kinds of citation sources used in the publication of the research results will be indicated. Any work and information cannot be used or published without permission and reference.

9.2. Be Informed

Written informed consent will be obtained from each patient prior to entry into the study, that is, prior to any screening evaluation or any study-related activity. For patients whose written informed consent cannot be obtained, the patient's legal guardian or guardian must sign the informed consent form. This form will be received from each individual in accordance with the recommendations of the revised Declaration of Helsinki. An independent staff member will explain the form, purpose, and risks of the study. The patient will then be given sufficient time to consider the study before deciding whether or not to participate. In all cases, the patient will be given a copy of the signed and voluntary informed consent form.

10. FINANCE AND INSURANCE

EyeCheckup is a software, it has no contact or interaction with the patient. Our study will be performed with fundus images taken from 900 volunteer patients diagnosed with diabetes from CE-marked fundus cameras. The EyeCheckup software will not be tested directly on the patient and has no contact with the patient. It will be installed on the computer and will evaluate the photos using artificial intelligence algorithms on the cloud.

Since our EyeCheckup software does not have an EC certificate, all volunteers who will participate in the research will be insured by Ural Telekom.

11. PUBLICATION POLICY

- All citations used in the article are referenced.
- The research result in the article is presented openly and honestly, without fabrication, false or inappropriate data manipulation.
- Scientific contribution to the article is guaranteed.
- Names of people who contributed to the article and consent to be named as co-authors are included in the article.
- If deemed necessary, access to the data sets in the article is provided.
- The author is responsible for the opinions expressed in the article.

12. SIGNATURE OF THE APPLICANT

With this application form, on behalf of the applicant myself;

- All documents submitted in the application are the same as the originals,
- The information provided in the application is correct,
- The research will be carried out in accordance with the protocol, the relevant legislation and the principles of good clinical practice;
- The research important change application is not made to more than one of the ethical committees established within the scope of the relevant Regulation,
- I certify that the proposed change is suitable for implementation.

Applicant
(The applicant must be an authorized signatory.)

Name and surname:

Date (as day/month/year): …/…/….

Signature:

Researcher Commitment

Research Protocol Name: DETECTION AND CLASSIFICATION OF DIABETIC RETINOPATHY FROM BACK POLE PHOTOS WITH A DEEP LEARNING MODEL

Protocol Number: EC-2021DR-TR

Version: v1.0

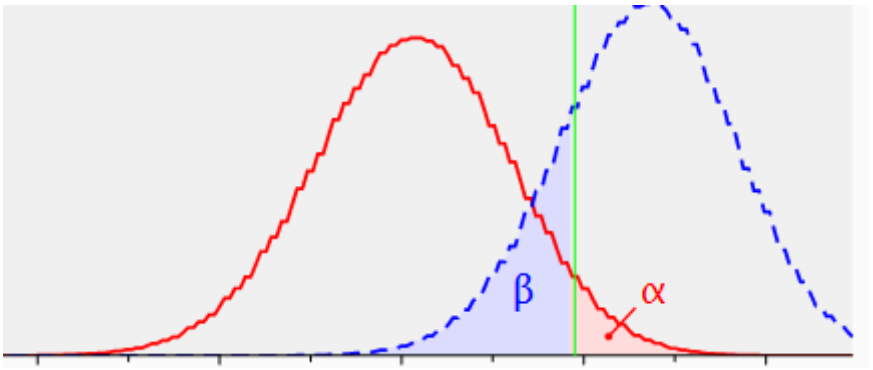
I have carefully read this study protocol and confirm that it contains all the information necessary to conduct the study. I declare and accept that I will conduct the study in accordance with the protocol ICH GCP, the Good Clinical Practices Guidelines and the regulations of the applicable competent authorities.

Name and surname:

Date (as day/month/year): …/…/….

Signature:

ANNEX-1 ANALYSIS PLAN



The diagnosis of the patients will be made by 3 doctors by evaluating the images and a joint diagnosis decision will be made by combining the diagnosis made by the doctors for each patient. This diagnosis will be considered the "Gold Standard" for the study. With the developed AI algorithm, it will be investigated to what extent the diagnosis made by the doctors can be predicted. The AI algorithm developed for the diagnosis of DR is expected to achieve a success rate of 90% or more. A success above this level will show that the developed AI algorithm will be usable. For this purpose, whether the AI algorithm achieves a success rate of 90% or more will be investigated with the one-way hypothesis pair given below.

$H_0: P = 0.90\ H_1: P > 0.90$

The sample size was calculated by evaluating whether the AI algorithm achieved a success rate of more than 90%, considering 5% Type-I error, 80% power, and different effect sizes listed below.

Power	N	Proportion Given H0 (P0)	Proportion Given H1 (P1)	Target Alpha	Actual Alpha	Beta	Reject H0 If Z>=This
0,8033	5341	0,9000	0,9100	0,0500	0,0511	0,1967	1,6449
0,8002	2286	0,9000	0,9150	0,0500	0,0520	0,1998	1,6449
0,8015	1255	0,9000	0,9200	0,0500	0,0525	0,1985	1,6449
0,8004	778	0,9000	0,9250	0,0500	0,0530	0,1996	1,6449
0,8012	523	0,9000	0,9300	0,0500	0,0541	0,1988	1,6449
0,8047	376	0,9000	0,9350	0,0500	0,0545	0,1953	1,6449
0,8092	284	0,9000	0,9400	0,0500	0,0539	0,1908	1,6449
0,8076	212	0,9000	0,9450	0,0500	0,0565	0,1924	1,6449
0,8004	164	0,9000	0,9500	0,0500	0,0553	0,1996	1,6449

Considering the situation marked in the table above as an example, if at least 778 people are included in the study, the case that the AI algorithm will achieve at least 2.5% above the 90% level can be detected at 80% power and 5% type-1 error level. If the success rate of the AI algorithm increases at a level of 2.5% or from to 90%, this difference will not be statistically significant. From this point of view, at least how high the AI algorithm will be above the threshold value should be determined and the sample size should be taken into account over this difference. For example, the 91% performance of the AI algorithm compared to the threshold value and investigating the statistical significance of the 1% difference may not be clinically appropriate, however, an increase of 2% or more may be considered clinically significant. At this point, it is important to determine the minimum effect size (distance to 90% level) that should be taken into account in order to

demonstrate clinical success (in other words, the AI algorithm performs more than 90%). (If it is necessary to evaluate the graph given above, the red distribution is the reference point for clinical success, and the blue distribution is the distribution showing how much the AI algorithm can exceed this threshold value. The effect size is the distance between the red and blue distributions.)

Statistical Analysis Plan

The diagnostic performance of the AI algorithm will be evaluated with reference to the decisions made by the doctors. Gold standard test results will be obtained based on the diagnosis provided by three different doctors. At this stage, the compatibility between the diagnosis from the doctors will be evaluated according to the Kappa statistics, and the similarity of the diagnosis made by the doctors with each other will be examined. The diagnoses of the patients will then be evaluated together with the results of the AI algorithm, and performance measures of the AI algorithm (sensitivity, selectivity, positive predictive value, negative predictive value, overall accuracy, etc.) will be obtained. Whether the performances of the AI algorithm are clinically acceptable or not will be evaluated with ratio tests (single sample population ratio significance test, Fisher Exact test, Chi-square tests, etc.) according to the threshold values to be determined by experts. A data analysis software will be selected amongst various softwares (R, SPSS, TURCOSA, Stata, etc.) to do the statistical analysis in accordance with the purpose. For statistical analysis, the level of significance will be taken as 0.05.