CHAPTER III

RESEARCH DESIGN OVERVIEW

3.1 THE RESEARCH QUESTION

Primary research question

Can single field nonmydriatic color fundus photography interpreted by family physician be able to use as an alternative method for diabetic retinopathy screening in Thailand?

3.2 THE RESEARCH OBJECTIVE

To evaluate single field nonmydriatic color fundus photography interpreted by family physician as an alternative method for diabetic retinopathy screening in Thailand.

3.3 RESEARCH HYPOTHESIS

The single-field fundus photography interpreted by family physician can serve as a screening tool for diabetic retinopathy to identify patients with retinopathy for referral for ophthalmic evaluation and management.

3.4 RESEARCH DESIGN

Cross-sectional, comparative, diagnostic test

3.5 DESIGN JUSTIFICATION AND SELECTION OF THE REFERENCE STANDARD

In this study, we want to answer the question "Can single-field fundus photography interpreted by family physician serve as a screening tool for diabetic patients to identify those with retinopathy to refer for ophthalmic evaluation and management?" to provide appropriate and effective health care for diabetic patients. It is necessary to distinguish between cases in the population who have diabetic retinopathy which needs to be referred and who do not. This is an important challenge, both in the clinical arena, where patient care is the issue and in the public health arena, where secondary prevention programs that involve early disease detection and

intervention is being considered. Thus, we also concern for the quality of screening and diagnostic test as a critical issue.

How good is the test in separating populations of people with and without diseases in question? First, how good is the test in correctly identifying those who has the disease.(sensitivity) Second, how good is the test in correctly identifying those who do not have the disease.(specificity) As in previous chapter, the single-field fundus photography interpreted by experienced graders showed the sensitivity of 80-90 percents and the specificity of 90 percents in detecting any retinopathy. It has been proven that the single-field fundus photography itself is a good tool in screening diabetic retinopathy, it show good quality image and adequate retinal field that is enough for detecting retinopathy. But if we use this tool interpreted by family physicians, we want to know its sensitivity and specificity. Is it good enough to be a screening tool for referral for ophthalmic evaluation? Diabetic retinopathy that needs to be referred for further ophthalmic evaluation is a serious condition. The screening test for diabetic retinopathy to refer for ophthalmic evaluation need high sensitivity and specificity. Because patients with serious retinopathy need timely photocoagulation to prevent visual loss, it is indeed critical to miss no single one. But this may cause more false positives and all people with false positive results should be referred to the tertiary care hospital. This is a burden to the healthcare system and may increase the anxiety of the patients. However overdiagnosis in such a serious condition is more acceptable than miss diagnosis.

To calculate the sensitivity and specificity of the test, we must know who really has the disease and who does not from another source than the test we are using. We are in fact comparing our test results with some gold standard or reference standard, an external source of truth regarding the disease status of each individual in the population. In clinical trials, seven-standard field stereoscopic fundus photography graded by more than one independent grader is the most reliable reference standard [53]. However indirect ophthalmoscopy with precorneal lens is the preferred and widely accepted method and more practical when screening for diabetic retinopathy, especially in Thailand. Thus, it is a logical reference standard for screening procedure to be evaluated. And it is superior for detecting retinal thickening and neovascularization than

seven-standard field stereoscopic fundus photography. So we decide to use indirect ophthalmoscopy with precorneal lens as a reference standard in this study.

3.6 OPERATIONAL DEFINITIONS

3.6.1 Selection of the classification system of diabetic retinopathy

A standard set of definitions that describes the severity of retinopathy and macular edema are critical in clinical decision making and for communication among colleagues and between medical specialties. The ETDRS severity scale was based on the modified Airlie House classification of diabetic retinopathy and was used to grade fundus photographs of standard stereoscopic fields [54-56]. Each lesion is evaluated in each of nine subfields, and the severity of retinopathy is summarized after complex assessment of the lesions. Although it is recognized as "the gold standard" for grading the severity of diabetic retinopathy in clinical trials, its use in everyday clinical practice has not proven to be easy or practical. The photographic grading system has more levels than might be necessary for clinical care, and specific definitions of the levels are detailed, require comparison with standard photographs, and are difficult to remember and applying in a clinical setting.

Several unpublished contemporary surveys have documented that most physicians managing diabetic patients did not use the full ETDRS severity scale, because it is too complex for application and communication in clinical practices.

In several countries, simplified severity scales have been developed in an effort to improve both the screening of patients with diabetes and communication among care givers. For example, in Japan 1983, a simplified diabetic retinopathy severity scale has been developed. And in 1993 a simplified scale was developed as part of "The initiative for the prevention of diabetic eye disease sponsored by the German society of Ophthalmology"

The severity of retinopathy might lead to different treatment recommendations in different regions, because practice patterns and healthcare delivery systems for patients with diabetes differ around the world.

Despite the development of different severity scales, there remains a genuine need for a single standardized practical classification system that can be used around

the world to facilitate communication across groups of practitioners. An optimal classification system should be useful for a broad range of care givers with varying skills and diagnostic equipment, ranging from retinal specialists with contemporary equipment to trained physician assistants using only direct ophthalmoscope.

In September 2001, American Academy of Ophthalmology launched a consensus development project regarding a new clinical severity scale for diabetic retinopathy. This system is simplified, clinically meaningful and easily adapted for clinical practices. The AAO board of trustees formally approved the final scales in February 2003.

In this study, we decide to use the Proposed International Clinical Diabetic Retinopathy and Diabetic macular edema disease severity scale by the reasons described above [57].

Table 2 The Proposed International Clinical Diabetic Retinopathy disease severity scale

Proposed Disease Severity Level	Findings Observable upon Dilated Ophthalmoscopy
No Apparent Retinopathy	No abnormalities
Mild Non-Proliferative Diabetic Retinopathy	Microaneurysms only
Moderate Non-Proliferative Diabetic Retinopathy	More than just microaneurysms but less than severe NPDR
Severe Non-Proliferative Diabetic Retinopathy	Any of the following: ■ More than 20 intraretinal hemorrhages in each of 4 quadrants ■ Definite venous beading in 2+ quadrants ■ Prominent IRMA in 1+ quadrant And no signs of proliferative retinopathy
Proliferative Diabetic Retinopathy	One or more of the following: ■ Neovascularization ■ Vitreous/preretinal hemorrhage

Referral criteria

The design of study is diagnostic test with dichotomous results, refer or not refer. The referral criteria for further ophthalmic evaluation is; any patients with retinopathy at moderate NPDR or greater and ungradable images by each family physician.

3.6.2 Referral criteria justification

According to 2 major randomized controlled trials of laser photocoagulation, the DRS and ETDRS, they suggest that type 2 diabetic patients with severe NPDR and PDR are more likely to benefit from photocoagulation surgery. Many studies use the referral cut point at severe NPDR. But in this study we decide to use moderate NPDR to be the referral cut point to preserve for more safety margin. I decided to include the ungradable images because most of them caused from cataract and need to be referred to the ophthalmologist.

3.7 BRIEF OVERVIEW OF THE STUDY

All type 2 diabetic patients who visit ophthalmologic out patient department at Khon Kaen Regional hospital and fulfill the inclusion and exclusion criteria were recruited for the study. All participants underwent the 2 diagnostic examinations, the first one is the digital fundus camera. The digital images were captured by a research associated photographer. (In cases of small pupils, the digital images may be obtained after use of mydriatics.) After performing the digital images, patients received pharmacologic dilatation and the ophthalmologist performed the second diagnostic test, the indirect ophthalmoscpy with precorneal lens. The results from indirect ophthalmoscopy with precorneal lens grading by the Proposed International Clinical Diabetic Retinopathy and Diabetic macular edema disease severity scales were recorded in case record forms.

The digital images obtained by the digital fundus camera were sent to 5 family physicians to interpret by the same grading system. The validity of the test was calculated, sensitivity and specificity for each family physician (as a dichotomous data,

refer or not refer) The results from indirect ophthalmoscopy followed by slit lamp precorneal lens by the ophthalmologists were used as reference standard.

3.8 RESEARCH METHODOLOGY

3.8.1 Population and sample

Target population: Type 2 diabetic patients with any disease duration

Study population: Type 2 diabetic patients registered at Khonkaen Regional Hospital, Khonkaen, Thailand during August to November 2006

Sample population: patients who meet the following eligibility criteria

Inclusion criteria

a. Diabetic patients(type 2) with any disease duration

b. Agree to participate the study and sign the written informed consent

Exclusion criteria

a Prior laser photocoagulation or posterior segment surgery

b Media opacity (other than cataract and vitreous hemorrhage from diabetic retinopathy)

c Incomplete examination of both tests

The target population in this study is type 2 diabetic patients because the prevalence of type 2 diabetes is considered to be more than the 95% of cases. The population sample needs to be the representatives of the Thai diabetic patients in making generalization. But we conduct this study at Khon Kaen Regional hospital which is a tertiary care setting, this may lead to higher prevalence of more severe cases than general diabetic population. Moreover majority of diabetic patients registered at Khon Kaen hospital came from local primary care units and nearby districts. The other reason for selecting to do this research in Khon Kaen hospital is that the research team works in this hospital and the cooperation will be smooth and prompt to accomplish the study.

For the exclusion criteria, we excluded patients with prior laser photocoagulation or posterior segment surgery because fundus findings in such patients may be altered and difficult to interpret. We also excluded patients with media opacity other than

cataract and vitreous hemorrhage from DR as this may result in ungradable images. It is problematic to exclude all patients with cataract. (the main cause of media opacity) Cataract is the common eye disease in elderly population who are more prevalent of diabetes too. If we excluded all of them, this will effect to generalizability of the study. The image quality in patients with some degree of cataract can be improved by using mydriatics. However patient were excluded if cataract is more opaque to obscure the view even after use of mydriatics.

3.8.2 Sample size calculation

To ensure reasonably precise estimates of sensitivity, we considered sample size during the planning stages of the study. We had to calculate how precise the estimation of test accuracy for a particular diagnostic situation and report these calculations with confidence intervals. These calculations require authors to think about the minimum precision needed for a test to be clinically meaningful. It will be easier for readers to interpret reported confidence intervals if they have access to these data. The sample size estimation is based on 95% confidence interval of sensitivity as shown in the following formula.

$$n = \frac{Z^2_{\alpha/2}\, P(1-P)}{d^2}$$

Where n = number of diabetic patients with moderate NPDR or greater

α = probability of type I error = 0.05 (2-sided)

$Z\alpha/2 = 1.96$

P = expected sensitivity = 0.9

d = allowable error = 0.05

We accepted the probability of type 1 error at 0.05. (2-sided) The $Z\ \alpha/2$ is 1.96. The expected sensitivity is 0.9 because we set the referral threshold at moderate NPDR or greater which is a serious condition. At this threshold, it is necessary to set high expected sensitivity. For the allowable error, we give 0.05 for the minimum precision

needed for a test to be clinically meaningful. We calculate the sample size needed for sufficiently narrow confidence intervals.

Thus, the number of diabetic patients with moderate NPDR or greater needed is 139. Since the prevalence of diabetic retinopathy in diabetic patients is 0.4. [58]

The number of the diabetic patients required in this study become n / 0.4 or 345.

3.8.3 Sampling technique

All patients who met the inclusion criteria and willing to participate in the study were recruited. For each diabetic patient, both eyes were examined for diabetic retinopathy. Result from only one eye was randomly chosen and used in the calculation of sensitivity. (Because if both eyes were selected, there may be asymmetry of severity of DR in both eyes. And this may cause more patients to be referred by chance of interpreted result from only more severe eye.) In case of one eligible eye, there is no need for random selection. The eligible eye was recruited automatically.

3.8.4 The outcome measurement

The outcomes were measured in number of cases as positive test, negative test, positive disease and negative disease, as described below.

- Number of cases who met the referral criteria stated by each family physician with fundus camera (positive test)

- Number of cases who did not meet the referral criteria stated by each family physician with fundus camera (negative test)

- Number of cases who met the referral criteria stated by ophthalmologist with indirect ophthalmoscopy (positive disease)

- Number of cases who did not meet the referral criteria stated by ophthalmologist with indirect ophthalmoscopy (negative disease)

3.8.5 Intervention

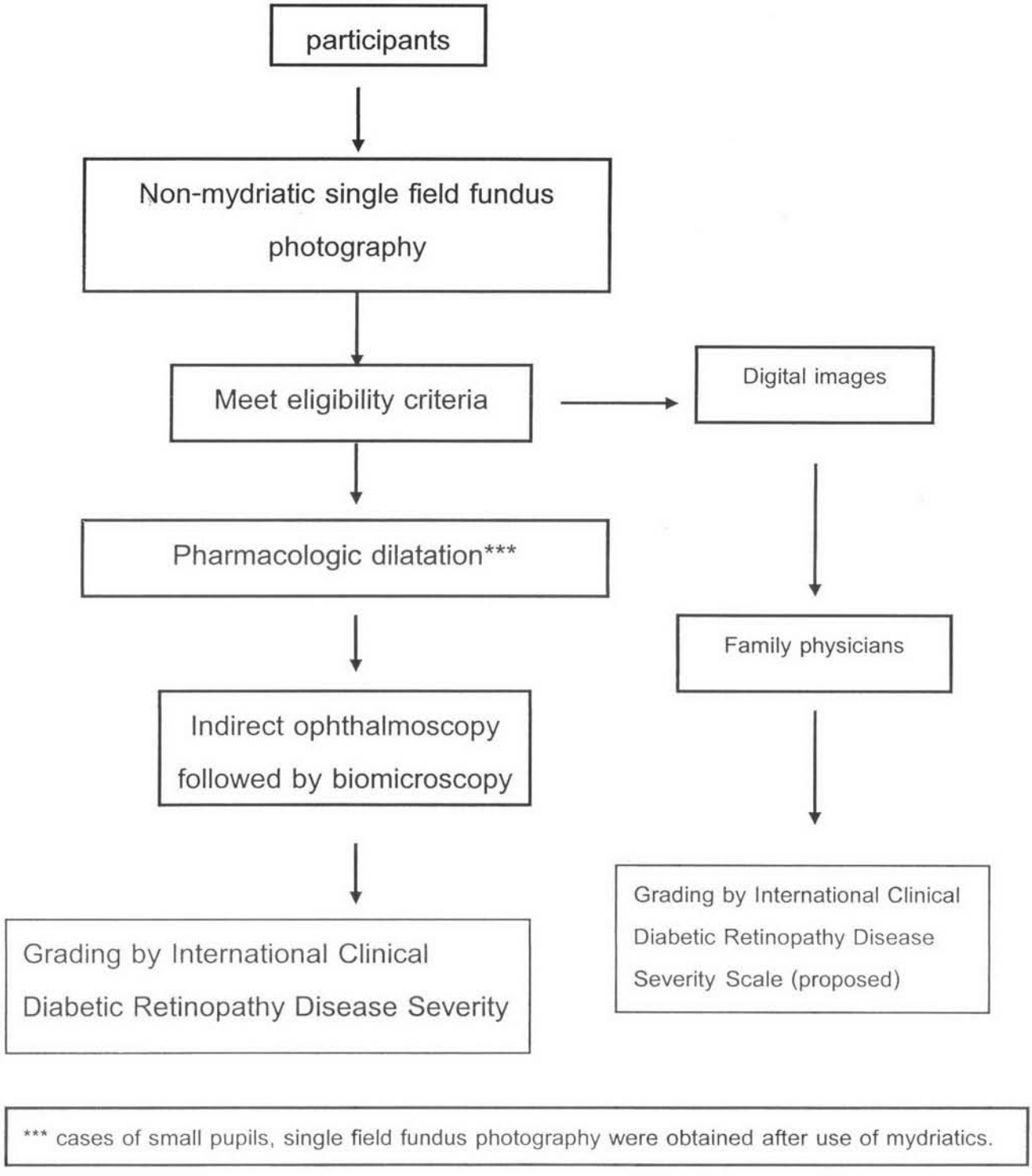

Figure 1 The Flow diagram of the intervention of the study

3.9 OBSERVATIONAL INTERVENTION

All participants undergo the following diagnostic examinations

3.9.1 Single field nonmydriatic digital color fundus photography (45 degrees)

3.9.1.1 The nonmydriatic fundus camera (TOPCON-PRC-NW 200) is the property of Munjakiree community hospital. The camera can be used in case of pupil diameter not less than 3.7 mm.

3.9.1.2 Acquisition of non-mydriatic digital images

Each participant remained in a darken room for approximately one minute before image was taken, to allow pupils dilate naturally. The nonmydriatic digital images were captured by an experienced technician in the use of the digital image system.

Each participant had two images taken. The mean file size of each 3.15 megapixels was 530 kilobytes (ranging 200 – 580). The image file saved in JPEG format.

(one image from each eye) The camera operators were instructed to recapture any images of poor quality at the same sitting.

The single field of 45 degrees photograph is centered on a point halfway between the temporal edge of the optic disk and the fovea and include areas of the retina on either side of both structures. (figure1) that include posterior area of seven-standard field stereoscopic 30 degrees fundus photography as in dash lines.

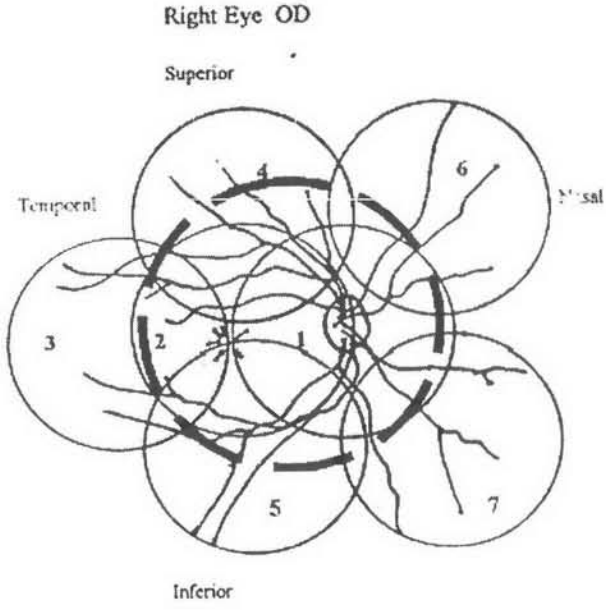

Figure 2 The area of fundus revealed by single field fundus photography

3.9.2 Performance of mydriatic ophthalmoscopy

The mydriatic ophthalmoscopy examination was performed by the experienced ophthalmologists (1 retina specialist, 1 oculoplastic specialist, 1 general ophthalmologist), through dilated pupils with indirect ophthalmoscopy.

Each eye was examined and the entire fundus was scanned for diabetic retinopathy changes. Indirect ophthalmoscopy was followed by slit-lamp biomicroscopy using a precorneal lens (Superfield ®, Volk) to examine the fundus. Ophthalmoscopy results were recorded using Proposed International Clinical Diabetic Retinopathy and Macular Edema Disease Severity Scale.

3.9.3 Image interpretation by trained family physician

All digital images were read by 5 family physicians who work in Family medicine department, Khon Kaen hospitals (who are trained, experienced for using Proposed International Clinical Diabetic Retinopathy Disease Severity Scale). There are no exact number of the image interpretators which are represented the reliable results. The reason we used 5 family physicians was there are the only 5 family physicians in Khon Kaen hospitals.

The training course was 2 hours of lecture and 2 weeks of practice. The lecture includes the natural course of DM, the classification system, the normal fundus findings, the frequent abnormal fundus findings, the standard photographs from DRS and common pitfalls in interpreting DR. We gave CD which included the standard ETDRS photographs of all DR staging, sample photographs with key answer, the lecture detail and the preferred practice pattern of DR by AAO. All family physician were informed about the thesis objective.

The family physicians have 2 weeks for interpreting the photographs. Results of the read images of each family physician were collected on paper data collection forms. The family physicians were masked to identity of the patients.

3.10 SAFETY MEASURES

3.10.1 All patients are advised for temporary punctual occlusion after administered of topical mydriatrics for decreasing systemic absorption

3.10.2 Use only topical tropicamide eyedrop in patient with uncontrolled hypertension (avoid from topical phenylephrine which are potent adrenergic drug)

3.10.3 Patient with history of allergy to topical mydriatic drug or its preservatives were performed intervention without dilatation.

3.10.4 Pupil mydriasis: The risk of precipitating angle closure glaucoma is actually very small [59]. In case of acute angle closure glaucoma precipitated by mydriatics, patients will be received prompt standard treatment.

3.10.5 Patients should be accompanied by a relative and instructed not to drive home.

3.11 DATA COLLECTION (see detail in Case Report Form)

Case report form (CRF) is generated for each individual patient to keep patients' data in sheets, which include

3.11.1 The patients' demographic data and baseline characteristics including age, sex, previous ocular disease and surgery, duration of DM, visual acuity, underlying disease.

3.11.2 The results of digital images interpreted by each family physician using Proposed International Clinical Diabetic Retinopathy Disease Severity Scale.

3.11.3 The results of indirect ophthalmoscopy performed by an ophthalmologist using Proposed International Clinical Diabetic Retinopathy Disease Severity Scale.

3.12 DATA ANALYSIS

This is an important stage of the research process. It is the process of presenting and interpreting numerical data. This section contains descriptive statistics and inferential statistics including measurement of central tendency (Mean) and measurement of variability about the average (range and standard deviation).

This research generates mass of data and to make sense of this data, it needs to be summarized in some way. We use descriptive or summary statistics to make the

readers to have an idea of the typical values in the data and construct a picture of the data they relate to.

We attempt to describe typical scores that reflect how the data is similar and how the data varies or is dispersed (spread out). Quoting both a measure of central tendency and the relevant measure of dispersion for one set of data gives a much better picture of the data than quoting one alone. The variables, type of variables and the ways of presentation are shown below. (subheadings, table 3,4)

3.12.1 The patients' demographic data and baseline characteristics were presented by descriptive statistics.

3.12.2 The inter-observer agreement between 5 family physicians was measure by intraclass correlation (two way random effect with single measurement, quadratic weight)

3.12.3 The intra-observer agreement of the first and third family physician was measured by intraclass correlation. (two way random effect with single measurement, quadratic weight) The 80 photographs were interpreted by the first and third family physician two times with 2 months interval.

3.12.3 The sensitivity and specificity of the single field nonmydriatic color fundus photography interpreted by each family physician compared to reference standard were also be presented. (95% CI)

3.12.4 The positive predictive value, negative predictive value were calculated.

Table 3 The variables, type of variables and values

Variables	Type of variables	Values
Age	continuous	Mean (SD, range)
Gender	categorical	F/M (frequency , %)
Previous ocular diseases	categorical	Specified (frequency , %)
Previous ocular surgeries	categorical	Specified (frequency , %)
Duration of DM	Continuous categorical	Mean (SD), frequency , %
Visual acuity	categorical	Visual impairment**/no visual impairment (frequency , %)
DR Grading by family physician (digital images) ***	categorical (ordinal)	Specified (frequency , %) ***
DR Grading by ophthalmologist (indirect ophthalmoscopy) ***	categorical (ordinal)	Specified (frequency , %) ***

** visual impairment : the best corrected visual acuity is 6/24 or worse

***grading by the Proposed International Clinical Diabetic Retinopathy disease severity scale

3.13 ETHICAL CONSIDERATION

This study has been conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki revised 2004. Before initiation of this study, foreseeable risks and inconveniences such as risk in mydriatics induced acute angle closure glaucoma attack [59], uncomfortable from the intense light during clinical examination, blurred vision from mydriatics, all are weighed against the anticipated

benefits for the individual study subject and society. We found that the anticipated benefits justify the risks.

This study is scientifically and described in a clear, detailed protocol. The nonclinical and clinical information on clinical examination and single field fundus photography is adequate to support the proposed clinical study. The medical care given to, and medical decisions made on behalf of, subjects are always under the responsibility of a qualified physician. Each individual involved in conducting this research is qualified by education, training, and experience to perform his or her respective tasks.

Freely given informed consent is obtained from every subject prior to clinical research participation. All eligible patients were asked by a trained research assistant to participate in the study. They were thoroughly explained the detail of the study procedure, the risk and safety of screening technique. In addition, they were explained about the usefulness of the results for themselves and for other patients in regarding to recommendation of diabetic retinopathy screening. Participants' confidentiality were exercised by recording their data in a case record form with code identifiable and kept by only researchers. Then consent form will be obtained. All participants have not to pay for single field nonmydriatic color fundus photography screening but they need to pay for routine ophthalmic examination in according to their health insurance services. They do not receive money or any gift for participation.

All the information from this study is recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.

This research is conducted in compliance with the protocol that has received prior institutional review board approval opinion from Khon Kaen Regional Hospital and faculty of Medicine Chulalongkorn University.