Bangladesh PRODUCTIVity in Eyecare (B-PRODUCTIVE) Trial

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Protocol

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Final Protocol

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Sponsor: Orbis

Collaborators: Digital Diagnostics Inc. and Deep Eye Care Foundation (DECF)

Study Aim: To assess the impact of using autonomous artificial intelligence (AI) for identification of diabetic retinopathy (DR) and diabetic macular edema on productivity of retina specialists in Bangladesh.

Hypothesis: Autonomous AI increases retina specialist productivity

Main Study Question: Will retina specialists complete a greater number of diabetic eye exams per working hour (including persons reviewed by AI whom the retina specialist does not need to see personally) when they use autonomous AI in a randomized clinical trial?

Design: Cluster-randomized (by clinic day) controlled trial.

Randomization: By clinic day. Each morning the clinic manager will be notified if it is an Intervention (AI) or Control (non-AI) day.

Interventions: All patients in both groups go through the eligibility checklist. If approved, they will be evaluated by autonomous AI. This is done to decrease potential bias (neither patients nor physicians know the group assignment of participants) and concealment (so that neither patients nor doctors can arrange visits on a known "Intervention Day").

Intervention Group: On randomly selected "Intervention" clinic days, if patients screen positive or have insufficient image quality, they continue to the retina specialist. If not eligible for autonomous AI, they proceed straight to the retina specialist without autonomous AI evaluation. If patients receive a negative result, they do not see the retina specialist, and are referred for a visit at the regular eye clinic (not the retina clinic) in 3 months.

Control Group: On randomly-selected "Control Days," all patients see the retina specialist, irrespective of the results of autonomous AI evaluation.

Masking: The retina doctors are masked both patient group assignment (that is, whether autonomous AI was used for pre-screening or not on the particular clinic day)

and also masked to the results of the AI on Intervention days. Patients are also masked to group assignment and autonomous AI results.

Study Design

Study Type: Interventional (Clinical Trial)
Estimated Enrollment: 924 participants
Allocation: Randomized
Intervention Model: Parallel Assignment
Intervention Model Description: Cluster-randomized (by clinic day) controlled trial.
Masking: Double (Participant, Patient)
Masking Description: The retina specialists are masked both to patient group assignment (that is, whether autonomous AI results were used or not on the particular clinic day) and also masked to the results of the autonomous AI on Intervention days. Patients are also masked to group assignment and autonomous AI screening results.
Primary Purpose: Diagnostic
Official Title: Assessing the Impact of Using Autonomous Artificial Intelligence (AI) for Pre-screening of Diabetic Retinopathy (DR) and Diabetic Macular Edema on Physician Productivity in Bangladesh
Actual Study Start Date: March 20, 2022
Estimated Primary Completion Date: December 2022

Arms and Interventions

Arm	Intervention
Experimental: Intervention group Autonomous AI results are used to evaluate if the participant needs to see the retina specialist (positive result0 or not (negative result).	Diagnostic test: results utilized from autonomous AI diagnostic system for diabetic retinopathy and/or diabetic macular edema. If patients receive a negative result they do not see the retina specialist
No Intervention: Control group	

All participants see the retina specialist irrespective of the results of their autonomous AI evaluation.	

Outcome Measures

Primary Outcome Measures:

1. Number of examined participants with diabetes per retina specialist working hour
    a. Number of examined participants with diabetes per retina specialist working hour. Numerator is the number of examined participants (including persons evaluated by autonomous AI on Intervention Days who are determined not to need to see the retina specialist). The denominator is retina specialist working time in hours.
2. Number of (all) patients per retina specialist working hour
    a. Number of examined patients (all types) per retina specialist working hour. Numerator is the number of examined participants (including persons evaluated by autonomous AI on Intervention Days who are determined not to need to see the retina specialist). The denominator is retina specialist working time in hours.

Secondary Outcome Measures:

1. Change in complexity score
    a. Change from baseline in mean complexity score of participants seen per hour per retina specialist. The complexity score is determined by external masked graders using a standard system adapted from Wilkinson et al. International Clinical Diabetic Retinopathy (DR) and Diabetic Macular Edema (DME) Severity Scales. The complexity score for an eye will be the sum of points with higher score as increased complexity (0=No or Mild Non-Proliferative DR (NPDR), 1 = Moderate NPDR or Severe NPDR, 3 = Proliferative DR (PDR), 2 = DME), and for a person it will be the sum of both eyes.
2. Satisfaction with autonomous AI assessed by questionnaire.

a. Retina specialist, technician and participant satisfaction with autonomous AI assessed by questionnaire using a 5 point Likert scale (1 = Very Satisfied 2 = Satisfied, 3 = Dissatisfied, 4 = Very Dissatisfied and 5 = N/A).

Outline of main analysis: Raw and adjusted (for above physician and patient predictors of productivity) intra-group difference in change in the number of patients with diabetic retinopathy passing through the clinic per hour per physician, cases of DR treated per week, and complexity score for each ophthalmologist.

Inclusion Criteria:

Retina specialists regularly seeing patients with DR

- Routinely examines >= 20 patients with diabetes without known diabetic retinopathy or diabetic macular edema per week
- Routinely provides laser treatment or intravitreal injections to >= 3 DR patients/month

AI Participants

- Diagnosed with type 1 or 2 diabetes
- >=22 years
- Presenting visual acuity >= 6/18 best corrected visual acuity in the better-seeing eye

Exclusion Criteria:

Retina specialists:

- Currently using an AI system integrated into their clinical care and/or inability to provide informed consent.

AI Participants:

- Inability to provide informed consent or understand the study; persistent vision loss, blurred vision or floaters; previously diagnosed with diabetic retinopathy or diabetic macular edema; history of laser treatment of the retina or injections into either eye, or any history of retinal surgery; contraindicated for imaging by fundus imaging systems

B-PRODUCTIVE Statistical Analysis Plan

1. Background and Design

The purpose of the study is to assess the impact of using autonomous artificial intelligence (AI) (IDx-DR, Digital Diagnostics, USA) for identification of diabetic retinopathy (DR) and diabetic macular edema on productivity of retina specialists in Bangladesh. The **B**angladesh **PRODUCTIV**ity in **E**yecare (B-PRODUCTIVE) Trial is a cluster-randomized (by clinic day) controlled trial. The trial will take place at a single clinic, Deep Eye Care Foundation (DECF), in Bangladesh collaborating with the on-going Orbis World Diabetes Federation DR project.

2. Outcome Measures

2.1. Main Study Outcome:

The number of examined patients with diabetes per retina specialist working hour between AI and non-AI days.

- Numerator: number of examined patients
    - Sum of the number of patients diagnosed with diabetes mellitus (type 1 or type 2) examined for DR per day
    - Patients included have not been previously diagnosed with DR
    - Includes all patients evaluated by autonomous AI on AI days, even if they are not seen by the retina specialist
- Denominator: retina specialist working time (hours)
    - Sum of retina specialist time spent on all diabetes patients examined per day
    - Does not include patient time spent during autonomous AI evaluation
    - Excluding treatment or surgical time
    - Including retina specialist time spent on ordering & reviewing diagnostic studies and scheduling treatment/surgery

2.2 Secondary outcomes:

2.2.1 Number of examined patients (all clinic patients, not only patients with diabetes) per retina specialist working hour between AI and non-AI days

2.2.2 Number of patients with diabetic retinopathy per day scheduled for any treatment including injections, implants, laser or surgery.

2.2.3 Retina specialist and AI-eligible patient satisfaction with autonomous AI.

2.2.4 Mean complexity score of patients seen per hour per retina specialist.

3. Data

3.1. Data collection methods

3.1.1. Ophthalmologist clinic records as audited by study personnel.

3.1.2. Masked documentation of physician time spent with patients.

3.1.3. Complexity score for each patient will be calculated by a masked UK NHS grader using the International Grading system, which is adapted from Wilkinson et al. International Clinical Diabetic Retinopathy and Diabetic Macular Edema Severity Scales.

3.1.4. AI-eligible patient and Specialist questionnaires.

3.2. Data Completion

- Questionnaires will be completed by specialist participants at the end of the trial.
- AI-eligible patient demographic data will be completed prior to the AI exam, and applicable satisfaction surveys will be completed following the AI exam.
- Specialist hours will be tracked daily for clinic time and number of clinic exams completed by each specialist will be tracked daily (all patients examined and patients with diabetes examined)

4. Sample Size Calculations

The null hypothesis is that diabetic patients without known DR seen by retina specialist per doctor hour for regular clinic days and AI days are the same. We are estimating the sample size needed to reject this null hypothesis. In calculating the sample size we used 80% power (the probability of rejecting a false null hypothesis). The sample size estimate is 924 patient participants.

Inputs for the sample size estimate calculations are:

- 80% power; power is the probability of rejecting a false null hypothesis.
- Alpha of 5%; probability of rejecting a true null hypothesis.
- Average cluster size of 8 and cluster size coefficient of variation of 0.45 (based on March data).
- Mean number of diabetic patients without known DR seen per doctor hour is 1.34 (based on Quarter 1 data). Hospital records that were used to calculate the sample size show that there are approximately 366 diabetic patients seen at the hospital per month. The retina clinic examines approximately 237 patients with diabetes per month.
- We changed some factors, but decided on one estimate.

Mean of Group 1	Mean of Group 2	Mean Difference	Intra-cluster correlation coefficient	Sample Size estimate

1.34	1.68	0.34	0.15	924

5. Randomization and Masking

The **B**angladesh **PRODUCTIV**ity in **E**yecare (B-PRODUCTIVE) Trial is a cluster-randomized (by clinic day) controlled trial. The study will assess the change in number of examined patients with diabetes per retina specialist working hour for three fully-qualified ophthalmologists regularly seeing patients with DR. All eligible patients (aged >= 22, known diabetes, no previous DR diagnosis, consented) receive autonomous AI for DR detection. This is done for purposes of masking (neither patients nor physicians know the group assignment of eligible patients) and concealment. On randomly selected “Intervention” clinic days, if eligible patients receive a positive DR diagnosis or have insufficient image quality, they continue to the ophthalmologist. If eligible patients receive a negative DR diagnosis, they do not see the retina specialist, and are referred for a visit at the regular eye clinic (not the retina clinic) in 3 months. On randomly selected “Control Days,” all patients see the ophthalmologist, irrespective of the results of the autonomous AI report. The retina doctors are masked both to patient group assignment (that is, whether autonomous AI was used or not on the particular clinic day) and also masked to the results of the autonomous AI on Intervention days. Patients are also masked to group assignment and autonomous AI results.

6. Analysis

Raw and adjusted (for above physician and patient predictors of productivity) group differences in the number of patients with diabetic retinopathy passing through the clinic per hour per physician will be calculated for AI and non-AI days. The two clinic day patient groups will compared with Chi-square testing for categorical variables. Age as a continuous variable was summarized with mean and standard deviation and the two groups will be compared with the student t-test.

Study outcomes of encounters per retina specialist hour and confidence intervals will be calculated for each clinic day for all patients, as well as specifically for diabetic patients and retina specialty patients. Rates will be compared across AI and non-AI clinic days with student t-testing. Associations between the main outcome, diabetic patients examined per hour, and potential predictors will be assessed utilizing linear regression modeling with generalized estimating equations that include clustering effect of day. Residuals will be assessed to confirm that a linear model fits the rate outcome. A multivariable model will include sex, gender and variables that have p-value<0.10 in the univariate analysis.

6.1 Recruitment and follow-up

The flow of participants through each stage of screening, enrolment into the study, randomization and follow-up to study exit will be illustrated using a CONSORT flow diagram (Cluster extension).

6.2 Baseline characteristics

Clinic characteristics include number of clinic hours per day, total clinic hours during the trial, total completed specialist visits for diabetes patients and total completed specialist visits for all patients.

AI-eligible patient characteristics include age, sex, and estimated monthly income.

Specialist participant characteristics include age, sex, and years as a retina specialist.