B3.1. Approach: Specific Aim #1: Determine the long-term comparative effectiveness of a telemedicine system to traditional methods of surveillance for detection and progression of diabetic retinopathy.

Our comparative effectiveness project has been recruiting participants for approximately two years and currently includes 588 participants -- 296 in the telemedicine group and 292 in the traditional surveillance group. At the end of the proposed project, we will have followed these participants for 3 to 6 years after enrollment. This will allow us to determine the long-term comparative effectiveness of telemedicine as compared to traditional surveillance techniques of attaining an annual eye exam. This long-term assessment (from 3 to 6 years) is critical to comparative effectiveness research to determine the generalizability and long-term viability.[60] (See discussion of Power, below.)

Hunter Health Clinic and Yellowhawk Tribal Health Center used their clinical databases to identify diabetic patients. The research assistants at each site contacted potential participants by letter and phone prior to their medical visit to explain the project. They recruited in high-traffic areas of the medical clinic or diabetic education area. We used a random number generator to randomly assign study participants to one of two groups: an intervention group, also referred to as the Telemedicine group; and a non-intervention group, also referred to as the Traditional Surveillance group.

The Telemedicine group receives retinal imaging using the nonmydriatic camera, while the Traditional Surveillance group continues to receive their eye care with local eye care providers. For the intervention group, the research assistants use the nonmydriatic camera to capture and send images to DEI for diagnosis and report generation. The nonmydriatic camera does not require dilation. Therefore, research assistants are able to collect medical information, photograph the patient, and send the information to DEI in less than fifteen minutes. This can occur when it is convenient for the patient, such as when they are waiting to make appointments, having lab tests performed or when picking up medications.

The research assistants will perform photography using the modified Diabetic Retinopathy Study protocol.[62, 63] This protocol includes six fundus photographs of each eye: two stereoscopic photographs centered on the optic disc; two centered on the macula; one centered on the superior temporal retina; and one centered on the inferior temporal retina. This series of photographs has been demonstrated to allow excellent diagnostic precision compared to dilated fundus exams with a kappa level greater than 0.9.[62, 63] The multiple locations for photographs moves any shadows that may appear, a phenomenon that is commonly found with nonmydriatic imaging, to different areas of the retina- allowing the entire retina to be evaluated. In addition, the optic disc and macula photographs allow us to screen for glaucoma and macular degeneration. While macular degeneration and glaucoma are not primary endpoints of this study, we collect this information and report abnormal results to the patient and their providers. The research assistant also has the option of photographing suspicious areas on the retina such as choroidal tumors.

After taking these photos, the research assistants assign them to their respective locations using the Devers web-based transfer program (see Innovation-Telemedicine) and note any difficulties that may have occurred while imaging (such as cataracts or small pupils). In addition, the research assistants enter demographic information (age, sex, ethnicity), medical history (systemic medications, oral medications, ocular surgical history), socioeconomic data (insurance status), and biometric data (systemic blood pressure and hemoglobin A1c) onto the website. Finally, they send the images and clinical data to the Devers Eye Institute's Reading Center. Dr. Demirel and Dr. Mansberger review the images within one business day and grade them according to standard, scalable criteria (Table 2) based on an international classification scale[64] and the Proliferative Diabetic Retinopathy study.[65]

Table 2: Description of stages of retinopathy* and macular edema

Retinopathy/Macular edema	Description
Stage 0	No abnormalities
Stage 1-Mild NPDR	Small microaneurysms only
Stage 2-Moderate NPDR	More than microaneurysms (such as venous beading) but less than severe NPDR
Stage 3-Severe NPDR	Contains one of the three characteristics termed the 4:2:1 rule: 1) approximately 20 dot blot hemorrhages in all 4 midperipheral quadrants; 2) venous beading in 2 quadrants; 3) or severe intraretinal microvascular abnormalities in 1 quadrant without PDR

Stage 4-Very Severe NPDR	Two of the three characteristics of Stage 3 without PDR
Stage 5-PDR	Neovascularization of the optic disc or elsewhere; or vitreous hemorrhage associated with neovascularization of any part of the eye of 1/2 disc diameter in area or evidence of previous panretinal photocoagulation
Clinically significant macular edema	Retinal edema within 500 microns of the fovea; exudates associated with retina edema within 500 microns of the fovea; or retinal edema 1500 microns in size within 1500 microns of the fovea

*NPDR=nonproliferative diabetic retinopathy; PDR=proliferative diabetic retinopathy.

We have devised a comprehensive, illustrated training manual that describes each step in the imaging and data uploading process. This manual assists when new training is required (in the event of personnel loss or required re-training). Additionally, the Reading Center provides monthly feedback regarding the number and quality of the photographs, and if needed, methods to improve the fundus imaging. The software generates quality reports when the photographs are too dark or of un-readable quality; emails these reports directly to the sites; and includes a series of troubleshooting steps to prevent future poor image quality issues.

Participants assigned to the non-intervention group (Traditional Surveillance) undergo fundus grading using indirect ophthalmoscopy by their eye care provider. All participating clinics make referrals to a small number of local eye care providers. Dr. Mansberger has contacted each of these providers to explain the purpose of the project and provide project information. Each of the providers voiced willingness to participate. For each eye care provider visit, the patient brings a postage-paid postcard with a detailed explanation and representative photos for the eye care providers to fill out and we also mail a copy of this postcard to the eye care provider's office. This postcard includes the person's subject number without any identifying information. The providers also have the option of entering data via a secure, web-based application. They report the level of diabetic retinopathy using the same standard scale reported above (Table 2).

Data/Power analysis for Prediction 1.1: A telemedicine system will increase the proportion of diabetic patients who receive annual eye exams when compared to traditional surveillance methods.
Since we are recruiting and testing the intervention group on the same day, we would expect a higher proportion of eye exams when compared to those in the non-intervention group at year 1, simply due to study design. However, the primary comparison between the groups will occur when participants reach Year 2 and beyond after enrollment. This success (and attrition) when controlled for leaving the facility for other reasons (death, moving out of the area, etc.) represents feasibility of nonmydriatic testing from the patient and separately, from the clinic perspective.

Studies estimate that approximately 50% of all diabetics receive annual eye exams, though these numbers may vary widely. We used this 50% proportion as the baseline for diabetics enrolled in the non-intervention group, and hypothesize that there would be at least a 10% increase the proportion of annual eye exams for those in the intervention group. To detect a difference of 10% at an alpha level of 0.05 and with a power of .80, our sample would need to include 194 participants (approximately 100 participants per group). We have enrolled 588 participants because of our sample size estimate for the detection of diabetic progression (Hypothesis 1.2-see Power analysis below). Overall, this sample size is more than enough to test the hypothesis that telemedicine increases the probability of attaining eye exams over the long-term.

Data/Power analysis for Prediction 1.2: A telemedicine system will have increased sensitivity to detect progression of diabetic eye disease in individual patients when compared to traditional surveillance methods.
Progression will occur when a diabetic participant progresses to a subsequent stage (see above-Table 4). We will compare the number of patients with progression in the intervention group to the number with progression in the non-intervention group at the 2-year time point and beyond. We hypothesize that the intervention group will contain a larger number of patients with progression because the participants will be examined at regular intervals and imaging will be more sensitive to the detection of progression, especially at early levels of diabetic retinopathy.

We do not know the number of diabetic retinopathy eyes progressing within a 2-year period in AI/AN patients. Previous studies suggest a wide range, from 26% to 45% over a two-year period, or odds ratios ranging from 1.4 to 3.3 with a power of approximately 0.80. We based these progression rates on data from the Wisconsin Eye Study (Caucasians) showing that the probability of disease progression is approximately 20% over 2

years[66], and data from a study in Pima Indians (AI/AN) showing a higher progression rate than in other groups, estimated at 40%.[67]

Beginning during Year 1 of the proposed grant, and after each quarterly data cleaning, we will model progression of diabetic retinopathy (1=progressed, 2=did not progress) as the dependent variable in a Generalized Estimating Equations (GEE) logistic regression model with Telemedicine or Traditional Surveillance group as the independent predictor. Analyses of disease progression will be conducted for individual subjects. Therefore, we must account for a clustering effect (correlation) between eyes and among subjects within a location by using methods appropriate for correlated binary data, such as the GEE.[68]

The analysis will include clinic as a clustering factor. We assume a low, constant correlation between pairs of eyes (i.e. compound symmetric correlation structure) of ρ=0.01. Based on these figures we calculated *c*, the variance inflation factor due to clustering, which then yielded an estimate of the robust variance/covariance estimator, v_r, for GEE. Tests of significance in a GEE logistic regression model rely on a robust estimator of the variance/covariance matrix. Pan[69] outlined sample size and power formulae based on values of this robust estimator. Table 3 shows the sample sizes needed with estimating a lower progression rate for the control subjects, but a higher progression rate for the intervention subjects.

Based on the power analysis in Table 3, we will have enough participants (currently n= 588) to detect differences between telemedicine and non-intervention groups at the 2-year point considering a 15% or more difference in progression (first and second row) between the groups. However, we will be just under our sample size estimate for the 14% to 15% difference (last row), which requires 300 participants in each group (600 overall). We will do a preliminary data analysis as soon as funding starts and increase sample size if needed. In addition, we will model a longer duration of follow-up (3 to 6 years) and its effect on sensitivity.

Table 3 - Power to Detect Specified Differences in Disease Progression over 2 years between the Intervention and Control Group Assuming GEE Logistic Regression Analysis

# Subjects per treatment group	*Pr(progression) control tribes*	*Pr(progression) intervention tribes*	*Odds Ratio (Effect Size)*	*Power*
150	0.20	0.38 0.39	2.45 2.55	.7932 .8299
225	0.20	0.35 0.36	2.15 2.25	.7624 .8089
300	0.20	0.34 0.35	2.06 2.15	.7743 .8231

Both analyses (Prediction 1.1 and 1.2) may suffer from incomplete data for several reasons: 1) diabetic patients may not obtain eye exams at regular intervals; 2) providers may not complete or mail the postcards; and 3) patients may move or become deceased. We will deliver postcards to each eye care provider prior to the patient's visit. Finally, to encourage data delivery from the providers, we have developed a web-based application for data entry to limit delays in obtaining data. Despite these measures to increase the completeness of data, we have included a chart review as a measure of internal validity. In the 2nd quarter of Year 2 of the proposed project, we will randomly select 100 participants, 50 each from the telemedicine and traditional surveillance groups and request their medical records from their eye care providers. Dr. Mansberger, Dr. Demirel, and Joanne Fraser, COT will abstract their ophthalmic results into a database and compare this database to the results of the web-based relational database. If the databases show similar results, we will be confident in the validity. If the databases show more than 10% missing data in the abstracted database as compared to the telemedicine database, we will attain the eye charts from the remaining patients and abstract the results.

Preliminary Data for: Specific Aim #1: Determine the long-term comparative effectiveness of a telemedicine system to traditional methods of surveillance for detection and progression diabetic retinopathy. Qualitative Data: In both telemedicine locations, we were able to train staff quickly even though they had minimal knowledge of ocular anatomy, ophthalmic equipment, ophthalmic photography, or data systems. As a result, local administrators and staff have embraced the protocol and praised its ease of use. Likewise, study

participants state that they have enjoyed having the opportunity to see what is “inside” of their eyes. This latter characteristic will help foster interest in their own ocular health promotion and promote healthy behaviors

Quantitative Data: We require at least 4 years of follow-up to compare the long-term effectiveness of telemedicine to traditional surveillance methods. This proposal will achieve this duration of testing. We have currently enrolled 588 randomly assigned participants, with 532 participants enrolled for at least 1 year; 268 (50%) assigned to the intervention group (telemedicine) and 264 (50%) to the non-intervention group (traditional surveillance methods with their eye care provider). Over the last 2 years of testing, ninety percent (90%) of images were graded as acceptable or better, with only 10% of images being marked as unsuitable for grading. The majority of these were too dark to evaluate, typically the result of cataracts or small pupils. Once reviewed, an electronic notification system alerts the sites in the event that images are poor or unable to be reviewed. These processes have resulted in significant improvements in image quality since the project was initiated.

Within the 532 participants, we found 84.7% with no diabetic retinopathy, 11.6% with mild non-proliferative diabetic retinopathy (NPDR); 2.6% with moderate NPDR; and 1.1% with proliferative diabetic retinopathy. To examine diabetic progression, we included data from 226 eyes of 115 patients with at least 1 follow-up imaging visit. We determined the severity of diabetic retinopathy using a modified International Classification Scale for Diabetic retinopathy[64] which ranges from Stage 0 (no diabetic retinopathy) to Stage 5 (Proliferative Diabetic Retinopathy, or PDR). We defined progression of diabetic retinopathy as at least one stage increase from the enrollment date to last imaging date. Over an average follow-up time of 537 days, a total of 28 eyes (12.4%) had progression of diabetic retinopathy. The average time to progression was 500 days. In comparison to those who did not have diabetic retinopathy progression, those with progression were older (58.0 (8.4) vs. 53.3 (11.6), p=0.01) and tended to be female (68% vs. 54%, p>0.05), but gender was not significantly associated with progression. Although these data are preliminary and assume a linear rate of diabetic retinopathy progression, these 1-year rates of progression (12.4%) would result in a similar rate to our power analysis estimates of progression (between 10-18% per year-Table 3). To accommodate a non-linear rate of progression, Dr. Gardiner will consider a proportional odds logistic regression model[70] with severity stage as an ordered factor variable (instead of continuous variable) since this may achieve greater power to determine differences.