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Wills Eye Community Intervention to Improve Glaucoma Detection and Follow-up Care

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Study Protocol

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Component A: Improving Glaucoma Detection and Management
Wills Eye Community Intervention to Improve Glaucoma Detection and Follow-up Care

A. BACKGROUND AND SIGNIFICANCE

A.1. Prevalence and Economic Burden of Glaucoma: Glaucoma is a chronic optic neuropathy resulting in visual field defects and progressive vision loss[1-3]. It is the second leading cause of irreversible blindness in the United States.[4,5] Primary open-angle glaucoma (POAG), the most common form of glaucoma, affects approximately 2.2 to 2.7 million Americans, and given the rapidly aging population, rates of glaucoma are projected to increase by 50% to 3.36 million people by 2020[6-8].

The increasing prevalence of glaucoma is expected to cause a significant economic and quality-of-life burden, as annual U.S. healthcare costs associated with glaucoma are estimated at $2.9 billion[4,9]. Consequently, *Healthy People 2020* includes objectives specifically aimed at reducing vision impairment due to glaucoma by 10% in adults 45 years and older by 2020[10,11]. The American Academy of Ophthalmology (AAO) and the American Glaucoma Society recommend that all adults should obtain eye exams to detect glaucoma beginning at age 40[12].

A.2. Risk Factors: Risk factors for glaucoma include advanced age (65+ years), family history of glaucoma, race (African American, Asian), and ethnicity (Hispanic/Latino)[13-19]. Diabetes is also an independent risk factor for glaucoma and patients with diabetes are twice as twice as likely to develop glaucoma as those without[16,20-24]. Glaucoma is 3 times more prevalent in African Americans than in non-Hispanic whites[25,26]. African Americans also develop glaucoma at a younger age, progress more rapidly, and are almost 7 times more likely to go blind than non-Hispanic whites[27].

Asians have an increased risk for narrow-angle glaucoma because their ocular anatomy predisposes them to glaucomatous changes[4]. Approximately 4.7% of Hispanics have POAG, compared to 1.7% of non-Hispanic whites. Asians have the highest rate of undetected POAG (75% in Hispanics/Latinos, 50% in non-Hispanic whites, and 58% in African Americans)[7,26,28]. Without appropriate treatment and frequent long-term follow-up with an eye care provider, glaucoma can progress and cause irreversible vision loss and blindness, worsening an already major public health issue[28,29].

A.3. Barriers to Follow-up Adherence: Poor outcomes in patients with glaucoma are often attributed to barriers to care such as limited knowledge about glaucoma, access to and utilization of eye care, cost of treatment, and medication adherence[30-35]. The cost of co-payments for eye exams, eye surgery, and prescription medication are barriers, especially for African-Americans and Hispanics[36]. Denying the risk of blindness, lower education level, poor individual-provider communication, and low-health literacy levels, may result in disparities related to glaucoma detection, treatment, management, and follow-up eye care[33,37-40].

Patients with glaucoma report difficulty finding transportation to eye care appointments, lack access to a car, have no one to accompany them during eye exams, and are more likely to live alone[41-45]. Overall, non-adherent patients with POAG lack the social support needed to comply with proper follow-up and thus are more likely to develop visual impairment[46]. Furthermore, according to the Baltimore Eye Survey, blindness from glaucoma was inversely related to socioeconomic status and educational level[26]. This trend is consistent in patients of Hispanic ethnicity who show poor follow-up with primary care physicians (PCPs) and ophthalmologists, and have little or no recollection of receiving glaucoma-related education from clinic staff[29].

Poor understanding of the insidious and often asymptomatic nature of glaucoma and the necessity for life-long treatment, contribute to non-adherence to follow-up eye care[29,47]. In addition, despite the advanced technology

and available diagnostic testing, 50% of people with glaucoma remain undiagnosed because vision loss progresses slowly and initially affects one eye[4,48]. When glaucoma is diagnosed early, appropriate treatment and management can be initiated to prevent blindness[49-51]. Therefore, it is a research priority to design community-based interventions to improve access and utilization of eye care, particularly in high-risk patient populations, to detect previously undiagnosed glaucoma and other eye diseases.

A.4. Health Disparities: Glaucoma patients who have low attendance rates at follow-up appointments are significantly more likely to be African American or Hispanic than Caucasian[29]. Regardless of insurance status, African Americans are less likely than other ethnic groups to attend ocular exams[44,52,53]. Only 36% of the participants in the Latino Eye Study over age 40 underwent an eye exam in the previous 12 months and only 57% admitted to ever receiving a dilated fundus exam (DFE)[54]. The National Eye Institute (NEI) has reported that African Americans are skeptical of and lack knowledge about eye care[55]. Additionally, denying the personal risk of blindness, varying health belief systems, poor patient-provider communication, and low literacy levels result in disparities related to glaucoma screening, treatment, management, and follow-up[37-39].

Asian Americans may face barriers to receiving ophthalmic care because of language and traditional beliefs about health and self-care. For example, to combat disease or illness, they might use exercise, diet, or home remedies instead of prescribed medications. A total of 43% of Asian American respondents to a survey believed herbal home remedies to be as effective as Western medicine. As a result of this perspective, many Asian Americans turn to friends and family for health advice. Based on the idea of fatalism, many Asian Americans seek help from a physician only as a last resort and are less satisfied with physicians who do not speak their native language[18].

A.5. History of Glaucoma Screenings: Community eye care services can improve glaucoma detection by identifying and targeting those at risk, while offering practical treatment and management options[56]. However, previous efforts to improve access and utilization of eye care with community- or hospital-based glaucoma screenings in high-risk populations have yielded only marginal results[39,41,57-59]. Compounding these challenges, patients positively screened for glaucoma have not consistently adhered to follow-up recommendations in office-based settings. Many patients reported difficulty scheduling and traveling to their appointments[41-45].

The Hoffberger Program in Baltimore attempted to reduce these barriers by providing community eye screenings over 4-years[60]. This program required no out-of-pocket costs and offered incentives, such as transportation, discounted eyeglasses, and Saturday appointments in an office-based setting. However, these incentives were inadequate in persuading patients to schedule follow-up visits, and 50% of those who scheduled appointments did not attend. Even when these missed visits were rescheduled, many patients still failed to attend. Given that African Americans with adequate health insurance coverage are less likely than other groups to obtain ocular exams, innovation is necessary to address the problem of access to care and non-adherence [52,53].

Therefore, a new model of follow-up care is needed to ensure improved access to and utilization of eye-care services. The AAO's *Primary Open Angle Glaucoma Preferred Practice Pattern* recommendations guide our focus on high-yield and cost effective glaucoma screenings targeting populations at high-risk for glaucoma, such as African-American, Asian, and Hispanics[12,61].

A.6. Development of Deep Learning Algorithms: Deep learning algorithms for analyzing fundus photos have been established for the screening and diagnosis of diabetic retinopathy.[62,63] For the diagnosis of glaucoma, it has been used in the analysis of visual fields, RNFL thickness, but there is only very limited data on algorithms to detect glaucoma based on fundus or disk images.[64,65] With the correct application, this automated diagnostic tool could contribute to glaucoma screening programs throughout the world.

Research Question/Specific Aims

Aim 1) Determine the effectiveness of an innovative, telemedicine, community-based intervention using fundus photography of the optic nerve and macula to increase the detection of previously undiagnosed glaucoma, glaucoma suspect, other eye diseases, and vision loss in high-risk populations.

Hypothesis 1: Diagnosis of glaucoma and glaucoma suspect using undilated optic disc images, tonometry pressure results, and medical history will predict a comprehensive eye exam diagnosis.

Aim 2) Evaluate the effectiveness of an evidence-based, enhanced intervention using patient navigators and a social worker to improve eye-care access, utilization, and follow-up care in community settings among those with newly diagnosed glaucoma, glaucoma suspect, other eye diseases, and vision impairment.

Hypothesis 2: Patients randomized to the enhanced intervention group will have higher rates of adherence to follow-up eye care with general ophthalmologists over a 3-year period than the usual care group.

Aim 3) Conduct a comprehensive cost study to estimate the intervention costs and cost-effectiveness of detecting eye diseases and vision impairment in a high-risk population.

Hypothesis 3: The enhanced intervention group will be cost-effective compared to usual care and consistent with commonly cited cost-effectiveness thresholds.

Aim 4) Replicate and disseminate protocols, materials, tools, and results with other communities in order to develop a public health repository of interventions to detect, manage, and follow-up patients with glaucoma, other eye diseases, and vision impairment.

Hypothesis 4: The replication and dissemination of study materials will allow further refinement and sustainability of these interventions for national implementation in additional community settings.

B: INNOVATION

B.1. Teleophthalmology: Digital imaging systems, image-reading software, and advanced telecommunications technology now allow ophthalmologists to evaluate information transmitted from remote locations. The Medical Imaging and Technology Alliance has established Digital Imaging and Communications in Medicine (DICOM) standards to regulate the transmission of data and patient information from imaging gateways to Health Insurance Portability and Accountability Act (HIPAA)-protected servers[62]. The Wills Eye Telemedicine Department (WETD) follows these standards and can manage high volumes of information safely. Our proposed teleglaucoma initiative will work efficiently within the infrastructure already in place for teleophthalmic data collection.

Retinal specialists worldwide use teleophthalmology to read remote fundus photographs to diagnose diabetic retinopathy (DR) and other eye conditions. This process has improved adherence to the American Diabetes Association's and AAO's annual eye care recommendations for people with diabetes[63-66].

The technology to implement remote screening for glaucoma is currently available because photographs of the posterior fundus provide monoscopic and stereoscopic images for assessing the optic disc[67]. Research from the Ocular TeleHealth Center at the Boston Veterans Administration (VA) Hospital indicates that images previously screened for DR can also identify optic discs that were indicative of glaucoma. Investigators found that readers who retrospectively analyzed images obtained through the Boston VA teleretinal program rarely missed discs that showed glaucomatous changes[68,69]. These data suggest that, with some modifications, a telemedicine program that effectively detects glaucomatous changes to the optic nerve can be used in community settings[67].

Combining fundus photography with medical history and intraocular pressure (IOP) measurements may further improve the sensitivity of glaucoma detection. The advent of new tonometers (such as ICare Rebound

Tonometry) has led to decreased risk of corneal injury and does not require anesthesia[70,71]. Through the implementation of this initiative, we propose that teleophthalmology will allow earlier diagnosis of glaucoma, improve access to care for potential glaucoma suspects, and provide better disease surveillance for glaucoma patients[72]. Utilizing this technology, we will be able to offer detection, referral, and ultimately, continuous follow-up care for high-risk patients diagnosed with glaucoma and other eye diseases. These technologies for glaucoma detection are still in pilot stages, and Wills Eye would be an ideal institution to develop and standardize the application of teleophthalmology practices.

B.2. Cultural Competency Training: The NIH *Strategic Plan to Reduce Health Disparities* states that cultural competence is the "understanding of diverse attitudes, beliefs, behaviors, practices, and communication patterns attributable to a variety of factors (such as race, ethnicity, religion, socio-economic status, historical and social context, physical or mental ability, age, gender, sexual orientation, or generational and acculturation status)[73]". Betancourt et al. name three types of barriers to care that may account for racial/ethnic health disparities: 1) Organizational barriers (e.g., lack of ethnic diversity in leadership and workforce). 2) Structural barriers (e.g., lack of interpreter services, lack of continuity of care). 3) Clinical barriers (e.g., poor provider-patient communication; dissonant beliefs about health; trust issue, provider stereotyping, and bias)[74]. Therefore, our intervention aims to reduce some of these barriers to care by providing culturally competent intervention using patient navigators and a social worker, as described below.

B.3. Patient Navigation: Patient navigators guide medically underserved patients through the healthcare system and directly address any barriers that inhibit prevention, screening, early detection, and/or treatment of disease[75-80]. These barriers could include insurance and financial issues, lack of transportation, limited family support, and health literacy[76]. Ineffective navigation of the healthcare system by patients may lead to poor outcomes because of delayed care, failure to receive proper care or treatments, or care being received in more expensive locations (i.e., emergency rooms)[81]. Patient navigators direct patients to appropriate healthcare resources, coordinating and scheduling appointments, verifying insurance status, and arranging transportation. By using patient navigators for this innovative, evidence-based intervention study, we aim to improve access and continuation of vision care for individuals with previously undiagnosed glaucoma and other eye diseases.

B.4. Social Worker: Social workers assess, track, and lessen psychosocial barriers to care in order to improve quality-of-life and subjective well-being of underserved individuals, groups, and communities [82,83]. By understanding systemic iniquities and using a culturally competent approach towards the communities they work within, social workers can help decrease barriers to quality healthcare[74,84] "Medical social work" is a sub-discipline of social work, requiring state licensure and a master's degree (MSW) for work in a hospital or other healthcare setting. Medical social workers have the clinical training to develop psychosocial treatment plans and provide emotional support so that patients can better understand and manage their disease process. The use of a medical social worker as part of an interdisciplinary team can help bridge the gap between the complexities of the medical system and a patient's continuity of care.

Research is limited on whether social workers can improve access to and utilization of eye care services. Social workers have the ability to confront barriers that tend to disproportionately burden racial and ethnic minorities. These barriers include financial and insurance issues, cultural beliefs, and language barriers; as well as issues related to transportation, childcare, and neighborhood resources[84]. By understanding systemic inequities and being culturally competent toward the community they work in, social workers can work to decrease barriers to quality healthcare[74]. The preliminary data of our pediatric-social worker intervention described in Section C.4 describes an evidence-based approach that has significantly improved the ability of children to return for needed eye care after being referred to an ophthalmologist at school vision-screening programs.

B.5. Integration of Primary Care and Public Health: A 2012 Institute of Medicine (IOM) Report *Primary Care and Public Health: Exploring Integration to Improve Population Health* suggests a framework for action between Centers for Disease Control and Prevention (CDC) and Health Resources and Services Administration (HRSA), with the continued support and management of FQHC[85]. Our partners, Health Federation of Philadelphia and Public Health Management Corporation, will facilitate the implementation of this research study in 10 FQHC in Philadelphia. With the addition of Temple Physicians, Inc. , we have commitment and adoption at an additional 7 primary care offices (Appendix B). This innovative project is a potential community-based model of integration between primary care and public health that could be replicated in other communities. Preliminary data described in Section C.2 shows that patients with diabetes who had a self-reported reported A1C value in their ocular chart were more likely to adhere to follow-up DFE recommendations.

Patients who smoked were less likely to obtain a DFE. It is important for glaucoma specialists to know the patient's blood pressure because diastolic readings below 60 mmHg are linked to increases in IOP measurements[86]. In addition, a recent study suggests that high blood pressure and elevated body mass index (BMI) are positively associated with IOP in middle-aged and older Japanese people[87]. Therefore, Visits 1 and 2 will take place in primary care settings, and we will document the patients' blood pressure, hemoglobin A1C, smoking status, BMI. Our approach will also include providing 360-degree communication between ophthalmologists and primary care physicians (PCPs) in order to improve detection, management, and follow-up.

B.6. Expected Contributions to Public Health: In addition to a reduction of vision impairment due to glaucoma, *Healthy People 2020* addresses impairments due to DR, age-related macular degeneration, cataract, and refractive error, noting that "visual impairment is associated with loss of personal independence, decreased quality-of-life, and difficulty maintaining employment[10,11]". We suggest a new paradigm to detect patients at-risk for glaucoma and other eye diseases who also have limited access to eye-care by evaluating a telemedicine intervention at the health centers and PCP offices. Those with ocular disease will be referred within 1-month for a comprehensive dilated eye exam in the same location to confirm their diagnosis. We expect that this 5-year sustainable research project will further our understanding of glaucoma detection and management, with the potential for generalizability. Using short-term and long-term outcomes, as well as the cost analysis findings, we believe that this study will produce very meaningful results and contribute substantially to the field of public health. Also, the high-quality data of fundus photographs, their interpretation by glaucoma specialists, and confirmation examination, could be used to develop a software that would allow automated detection of glaucoma-suspicious discs. Such a tool could decrease the dependence on highly trained glaucoma specialists and have a far reaching effect on screening.

C. APPROACH

C.1.a. Research Environment: The Wills Eye Hospital, part of the Wills Eye Health System, is a nonprofit specialty institution that was established in 1832 and is governed by the Board of Directors of City Trusts (See Facilities and Appendix A). *U.S. News & World Report* ranks Wills Eye as the #2 eye hospital in the U.S. The 5-year research intervention will be conducted by Wills' Department of Research, Glaucoma Service, Glaucoma Research Center, and Telemedicine Department, under the leadership of Julia A. Haller, MD; L. Jay Katz, MD; and Lisa Hark, PhD, RD. The Wills Eye Glaucoma Service is one of the largest in the nation, with over a century of experience effectively identifying, examining, managing, treating, and following patients diagnosed with glaucoma or glaucoma suspect. Both the Wills Eye Department of Research (PI: Haller) and the Glaucoma Research Center (PI: Katz) have received Cooperative Agreements from the CDC, as described in the preliminary data section C.2. The Facilities Section describes these department and centers and our partner

organizations (Appendix B). Wills Eye Hospital is located adjacent to Thomas Jefferson University, with whom it has a long-standing academic, research, and clinical relationship.

C.1.b. Investigators: Drs. Haller, (PI), Katz (PI), and Hark, (Project Director), have assembled a highly-experienced, multidisciplinary, collaborative, and ethnically diverse team of researchers and community partners. Wills Eye is uniquely qualified to effectively plan, develop, implement, evaluate, and disseminate community-based interventions to improve access and utilization of eye care services to promote the detection and follow-up of glaucoma, other eye diseases, and vision loss to reduce the disease burden and related-vision loss in high-risk populations. As described in detail in their biosketches and organizational chart (Appendix C):

- Dr. Haller is a world-renowned retina specialist, Ophthalmologist-in-Chief at Wills Eye Hospital, Professor of Ophthalmology, and Chair of the Department of Ophthalmology at Jefferson Medical College (JMC).
- Dr. Katz is an internationally recognized glaucoma specialist, Chief of the Wills Glaucoma Service, and Professor of Ophthalmology at JMC.
- Dr. Hark is Director of the Wills Eye Department of Research, Director of the Glaucoma Research Center, Professor of Ophthalmology and Professor of Medicine at JMC. She is also a registered dietitian.

The team has worked together for 5 years, and key personnel have more than 20 years' experience conducting research studies and directing projects. The departments complement each other: Dr. Hark directs both the Department of Research and the Glaucoma Research Center and reports to both Dr. Haller and Dr. Katz. We continue to subcontract with Jefferson to conduct economic studies (Pizzi) and statistical analysis (Leiby, Dai), and with Temple University (Henderer) to recruit patients and conduct confirmation diagnosis exams. Letters of support from Advisory Board are shown in Appendix D.

C.1.c. Evidence for Selecting Outreach Intervention: Drs. Katz, Haller, and Hark, and the research team at Wills Eye have the knowledge, experience, and track record to implement this multi-site, multi-component community-based 5-year intervention. Our partners have the ability to address the vision needs of high-risk, underserved populations. The Philadelphia Department of Public Health, Public Health Management Corporation, Health Federation of Philadelphia, and Temple Physicians Inc have provided direct community-based health services for decades to Philadelphia's underserved populations. The AAO recommends that eye screenings may be more useful and cost-effective when targeting populations at high risk for glaucoma[12,61]. We know that individuals with advancing age (65+ years), diabetes, a family history of glaucoma, and/or are African-American, Hispanic, or Asian are at greatest risk for glaucoma[1,17,18,20,22,88,89]. Therefore, our target populations are African American, Hispanic/Latino, and Asian individuals over age 40, other adults age 65+, and individuals over age 40 with a family history of glaucoma or who have diabetes.

C.1.d. Capacity to Work within a Public Health Model: Wills Eye Hospital has successfully worked within a public health model for decades. Annually, *Wills on Wheels'* community outreach programs, in cooperation with local organizations, provide essential eye care, including exam, management, treatment, and follow-up services, to 1,900 Philadelphians. We have also been implementing the CDC demonstration project described in the preliminary data section C.2. *Healthy People 2010 Determinants of Health Model* recommends that when organizations and communities design, implement, and evaluate interventions, they should consider physical and social environments in order to change patient behavior and improve access to quality eye care[10]. We have applied the recommendations made by *Healthy People 2010 and 2020* for this proposal and developed a Logic Model for the project as shown in Appendix E.

C.1.e. Diversity and Importance of the Intervention: We will recruit patients from our community partners' primary care offices and health centers. The demographic compositions of these sites vary, as described in the Facilities Section. According to the 2010 Census, the Philadelphia population includes 42.2% African

Americans, 36.9% Caucasians, 12.3% Hispanics, and 6.3% Asians[90]. Nearly 25% of Philadelphia families live in poverty, representing the highest poverty rate among the top 10 largest cities in the nation[90,91]. In addition, 19% of older Philadelphians live in poverty[90,91]. Philadelphia African Americans are exposed to poverty at a rate of 24.8%, nearly 3 times higher than whites. Hispanics are more than 3 times more likely than whites to live in impoverished communities with an average poverty rate of 25.4%[90]. Philadelphia also has the second-highest ratio of Asian-to-white exposure to poverty, as Asians live in neighborhoods with a 13.4% poverty rate.

C.2. Indication from Preliminary Studies

C.2.a. Wills Eye CDC Glaucoma Demonstration Project (PI: Katz)**:** In 2012, the Wills Eye Hospital Glaucoma Research Center, under the leadership of L. Jay Katz, MD and Lisa Hark, PhD, RD, received a $1.8 million Cooperative Agreement from the CDC to conduct a demonstration project titled *Improving Access to Eye Care Among Persons at High-Risk for Glaucoma in Philadelphia.* This unique 2-year project mobilized 40 sites to plan, develop, implement, and evaluate an integrated community-based, targeted intervention for African Americans over age 50 and other adults over age 60. This project aims to improve detection, management, treatment, and follow-up eye care of persons at high-risk for glaucoma in Philadelphia in order to enhance access and utilization of eye care and to reduce the disease burden and related vision loss.

During the initial and follow-up visits, ocular technicians document ocular and systemic history using an electronic medical record (EMR). The focused ophthalmic exam, conducted by a glaucoma specialist, includes: 1) best correct visual acuity measurement using Snellen eye charts, 2) slit-lamp biomicroscopy, 3) IOP, 4) undilated optic nerve evaluation, 5) optic disc color photography, 6) central corneal thickness measurement, 7) visual field analysis using the Octopus visual field analyzer, and 8) gonioscopy. On each exam day, the Wills team transports, sets up, and dismantles equipment.

Based on the exam and test results, the ophthalmologist makes a diagnosis and recommends treatment (Table 1). People diagnosed with glaucoma, glaucoma suspect, narrow-angle, or receiving laser therapy are scheduled for follow-up visits at the same site, unless they request to go to Wills Eye Hospital or follow up with their own ophthalmologist. For those prescribed ophthalmic medications, frequency, use, and side effects are documented at each visit. Those diagnosed with other eye conditions are advised to see a local, general ophthalmologist, whose name and phone number they receive.

Table 1: Recommended Treatment and Follow-up Based on Diagnosis and Test Results

Visual Field	Optic Nerve	IOP	Gonioscopy	Diagnosis	Recommended Treatment	Initial Follow-up	Second Follow-up
Abn	Abn	NL or high	Open-angle	Open-angle glaucoma	Eye drops or selective laser trabeculoplasty	4-6 weeks	4-6 months
NL	NL	NL or high	Occludable	Anatomically narrow-angle	Laser peripheral iridotomy	4-6 weeks	4-6 months
NL	Abn	NL	Open-angle	Glaucoma suspect	Observe	4-6 months	Refer to ophtho.
NL=normal, Abn=abnormal. *Source: American Academy of Ophthalmology, American Glaucoma Society*[12]							

C.2.b. Preliminary Glaucoma CDC Results: We have successfully partnered with Westat, an independent evaluation firm appointment by the CDC, to collect and analyze data for this project. Patients represent a diverse population with respect to gender, race, and ethnicity. Of the 1,290 people who had a community eye exam between 1/1/13 and 2/1/14, 66% are female. Mean age is 69, with 15% aged 50 to 59 years and 85% age 60+ (Table 2).

Table 2: Demographics of Patients Examined

Total Exams (n=1290)	African American	Caucasian	Asian	Hispanic
Number of people examined	825	194	194	77
Percentile	64%	15%	15%	6%

Of these people, 483 (37.4%) have been identified with previously undiagnosed glaucoma, glaucoma suspect, or anatomically narrow-angles. All required ongoing follow-up eye exams, a number that is higher than nationally reported statistics (Table 3). A total of 144 patients (11%) were diagnosed with age-related macular degeneration (AMD), DR, and visually significant cataracts that required follow-up evaluation.

Table 3: Diagnoses of Patients Examined

Total exams n=1290	Glaucoma	Glaucoma-Suspect	Narrow-Angle	Existing Glaucoma	Visually Significant Cataract	Macular Degeneration Diabetic Retinopathy	No Glaucoma
# Diagnosed	52	276	155	85	92	52	684
Percentile	4%	21.4%	12%	6.6%	7%	4%	52%

Thus far, cancellations and no-show rates have been minimal (20%) for initial and follow-up exams. This project has successfully detected glaucoma in this population and illustrates the need for a new healthcare delivery model for ongoing follow-up care. Considering the lack of success with glaucoma patient follow-up adherence in office settings, the proposed telemedicine detection program, combined with an enhanced intervention, may contribute valuable new scientific information.

Initial patient-satisfaction data obtained from post-exam surveys are described in Table 4. Generally, patients reported either "very satisfied" or "satisfied" in the overall eye exam experience, duration of exam, and quality of staff. In the preliminary study, 91% of patients said that they would be very likely to obtain a follow-up eye exam, which indicates potential for a sizeable benefit of the intervention relative to current practice. These data have been presented at the 2013 American Public Health Association Conference, 2013 CDC Vision Health Initiative Symposium and 2014 American Glaucoma Society Conference. They will be presented at the Association for Research in Vision and Ophthalmology annual meeting in Orlando, Florida in May2014.

Table 4: Satisfaction Survey Results

Question	Very Satisfied	Satisfied	Dissatisfied	Very Dissatisfied
Satisfaction with the exam	82%	16%	0%	0.4%
Satisfaction with the duration of exam	57%	36%	5%	0.6%
Satisfaction with the staff	86%	12%	0.4%	0.6%
Convenience of location of exam	84%	13%	0%	1%

C.2.c. Preliminary Cost Analysis Results: Under the leadership of Laura Pizzi, PharmD, MPH, we evaluated costs in order to identify potential efficiencies for refinements and translation of the project by other institutions or to other settings. The preliminary costs of this study are reported at $143,830 ($131 per examined patient). It took between 5 and 14 minutes for staff members to complete each step. The visual field test and the physician exam required the most time; human costs were reported at $42.44/participant. Medical equipment contributed the most to the non-human costs, which were reported at $87.34/participant. The cost/glaucoma detected was

used to measure the effectiveness of this program, and costs were reported at $1,189/case of glaucoma detected. Costs for glaucoma suspects were higher: $578/case. Any other eye detected disease was reported at $116/case.

C.3. Wills Eye CDC Diabetes Demonstration Project (PI: Haller): In 2010, the Wills Eye Hospital Department of Research, under the leadership of Julia A. Haller, MD; Lisa Hark, PhD, RD; and Ann P. Murchison, MD, MPH received a $1.45 million Cooperative Agreement from the CDC to conduct a demonstration project titled *Improving Access to Eye Care Among Persons with Diabetes in Philadelphia.* The 5-year project aims to develop a database of patients with diabetes who received care at Wills Eye within the previous 10 years.

C.3.a. Aim 1 Results: The research staff conducted a retrospective chart review of 1,968 patients over age 40 with diabetes seen in 2011-2012 in the Wills Eye Primary Eye Care Clinic. These patients first visited the clinic between 1/2007 and 12/2010. The review evaluated individual factors that impact utilization of vision care, including demographic information, insurance, smoking status, medications, glasses prescription, dates of DFE, and first reported hemoglobin A1C and blood glucose levels. The primary outcome was timely DFE follow-up adherence following the initial visit. Overall, 41.6% of patients adhered to follow-up recommendations.

In a multivariate analysis conducted in the fall of 2012, patients with severe DR were more adherent than patients with mild DR (Odds ratio [OR]: 3.65; 95% Confidence Interval (CI): 2.84-4.69). Other variables associated with increased adherence were advanced age (OR: 1.46; 95% CI: 1.18-1.80), insulin use (OR: 1.33; 95% CI: 1.08-1.65), having reported A1C (OR 1.58; 95% CI: 1.26-1.98) or blood glucose levels (OR: 1.78; 95% CI: 1.43-2.22). Current smoking status was associated with decreased adherence (OR: 0.55; 95% CI: 0.43-0.71). Our team recommended that, to reduce vision loss from DR, interventions should target younger patients, smokers, and those with mild and moderate DR, all of whom are at-risk for poor follow up eye care. This study provides additional evidence that targeting at-risk populations beginning at age 40 is critical.

C.3.b. Aim 2 Results: To evaluate the effectiveness of a multi-pronged intervention on DFE adherence, we also conducted a prospective, single-blind, randomized, controlled trial of 521 patients with diabetes who were due for follow-up DFEs. Patients were randomly assigned to usual care or the intervention group. Patients in usual care (n=259) received a form letter reminding them to make an appointment and an automated reminder phone call the day prior to their scheduled visit. Intervention patients (n=262) received an educational brochure about diabetic eye disease, with a personalized letter encouraging them to schedule an eye exam. Two weeks after mailing the letter and brochure, a patient navigator called intervention patients to help schedule their eye exam. Intervention patients also received a reminder letter 3 weeks before their appointment, plus an automated phone call the day prior to the scheduled visit.

Patients were mostly female (66%) and African-American (70%), with a mean age of 61. Patients in the intervention group were significantly more likely to schedule (63% vs. 40%; $P < 0.0001$) and attend their appointment (48% vs. 30%; $P < 0.0001$) than those in usual care. The intervention significantly improved diabetic DFE adherence. This study provides additional evidence that using navigators to call patients, schedule appointments, address barriers, and provide educational information improves follow-up adherence to eye care appointments.

C.3.c. Network Study Results: Through our CDC Innovative Network for Sight Research Group (INSIGHT), Wills Eye collaborates with investigators at the Wilmer Eye Institute at Johns Hopkins, Bascom Palmer at the University of Miami, and the University of Alabama at Birmingham. This collaborative, pilot project tested the use teleophthalmology in people with diabetes at community locations. The Wills Eye Telemedicine Department Reading Center evaluated and interpreted all fundus photographs. The study evaluated patients' adherence to recommended follow-up eye-care after receiving this free eye screening in 4 different community

settings. All subjects were notified of their eye exam results within 3 weeks of screening and completed a telephone questionnaire 3 months after that. Each site recruited between 500 and 600 patients with diabetes, most of whom were female and between 45 and 65 years old. Racial/ethnic distribution varied by site by community location: Philadelphia had 68.7% African American, Alabama had 84.4% African American, and Miami had 41% Hispanic and 33.8% African American.

Of the 1,949 patients photographed, 24% showed signs of DR and 50% showed signs of ocular pathology (cataract, ocular hypertension, or glaucoma). Approximately 6% of patients showed signs of glaucoma suspect. Approximately 11% of the images were unreadable. Over 97% of patients at all sites were satisfied with their screening experience, and over 70% would be willing to pay for a similar service in the future. Three months following the screening, approximately equal proportions of patients with abnormal and normal results reported seeing an eye-care provider (35% vs. 32%, respectively).

Of those who had not followed up, the percentage of patients with abnormal versus normal results who planned on attending an eye appointment was similar (71% vs. 70%, respectively). This study demonstrates that non-mydriatic retinal photography in community settings is a viable screening method for DR and other ocular diseases. However, methods to increase follow-up adherence after outpatient screenings must be explored. Therefore, our proposed intervention aims to improve follow-up adherence in high-risk, newly diagnosed patients with glaucoma, glaucoma suspect, and other eye diseases detected in a community setting. We are ideally prepared to implement this study because of our established research infrastructure, commitment from community partners, and collaborations.

C.4. Pediatric Adherence Program Results: Wills Eye Hospital's collaborative efforts with community and public school-based outreach programs in underserved areas of Philadelphia identified children who need to be examined by an ophthalmologist. Past experiences have indicated that less than 5% of parents or guardians returned with their children to Wills Eye Hospital for a subsequent eye exam. In a unique 2013 initiative, Wills hired a pediatric medical social worker to track, assess, and reduce some of the psychosocial barriers that previously led to poor attendance rates. By implementing the Children's Eye Care Adherence Program (CECAP), the social worker's primary goal was to increase follow-up rates in underserved, often uninsured, children. A total of 1,200 children were included in the CECAP study. Children involved in the sample were screened at an annual free, day-long community event (Give Kids Sight Day) and through an Eagles Eye Clinic held at Wills Eye Hospital throughout 1year. A total of 120 (10%) of children under age19 failed the exam and required a subsequent ophthalmology follow-up visit. With continued support and intervention by a pediatric social worker , CECAP results for follow-up return rates with a pediatric ophthalmologist have dramatically increased – from less than 5% to 59.2% (n=120) ($P<.001$).

C.4. Research Design and Methods

C.4.a: Project Overview: The Wills Eye Glaucoma Research Center will conduct a 5-year prospective, randomized controlled trial to evaluate an innovative, community intervention using posterior fundus photographs of the optic nerve and macula to improve access and utilization of eye care to detect, treat, and manage high-risk patients with previously undiagnosed glaucoma, glaucoma suspect, and other eye diseases. L. Jay Katz, MD; Julia A. Haller, MD; and Lisa Hark, PhD, RD, will lead the research study.

Our diverse targeted, at-risk population includes African Americans, Hispanics, and Asians over age 40; other older adults (aged 65+); individuals over age 40 with a family history of glaucoma and/or with diabetes. Approximately 1250 patients will be recruited from geographically diverse locations across Philadelphia and Chester counties, with the help of our community partners. **Phase 1** will consist of detecting eye disease in 7

primary care offices and 10 FQHC using telemedicine (Visit 1), followed by a comprehensive eye exam by a Wills glaucoma specialist in the same setting to confirm the diagnosis (Visit 2). Based on preliminary data, 30% of patients (approximately 750) will have abnormal optic nerve and/or macula images. The predictive accuracy of the optic nerve images to detect glaucoma and glaucoma suspect as confirmed by the comprehensive eye exam will be evaluated.

Phase 2 will involve consenting, enrolling, and randomizing 374 patients to either the usual care group (n=187) or the enhanced intervention group (n=187). The enhanced intervention will consist of using patient navigators and a social worker to reduce barriers to follow-up eye care. **Phase 3** will consist of following patients proximally (6 months) and distally (3 years) while they attend appointments with a local, eye care provider (Visits 3-7). Adherence to follow-up recommendations for eye care will be the primary outcome measure. A comprehensive cost study to estimate the intervention costs and cost-effectiveness of detecting eye diseases and vision impairment in a high-risk population will also be conducted. Protocols, materials, outcomes, and results will be disseminated to other communities in order to expand detection of glaucoma, other eye diseases, and visual impairment, and to further refine these approaches to successfully scale the program up to a national level.

During the final closeout visit at the primary care office, patients will be contacted by letter (and follow-up phone call if needed) by a member of the study team and will be scheduled to return to their primary care provider for the following:

Review of current eye medications
Review of current systemic medications
Review of demographics (address & phone number(s)
Results of A1C reading (from PCP office)
Blood pressure reading
Intraocular Pressure reading
Smoking status
Completion of Satisfaction Closeout Survey
Completion of NEIVFQ questionnaire

C.4.b. Specific Roles of Collaboration/Partnerships: The successful implementation of this research project builds upon Wills' current community partnerships from our CDC demonstration project and new collaborations and infrastructure established by the WETD. Our partnerships maximize the capacity of the intervention to reach and identify people with undiagnosed glaucoma, glaucoma suspect, other eye diseases; and visual impairment among high-risk, vulnerable patients they serve. Patients within each organization are racially and ethnically diverse, as described in Facilities. To ensure the broadest reach and ownership of the proposed intervention, our community partners have been invited to collaborate by joining the Advisory Board and engaging in planning, developing, implementing and evaluating the interventions. These partners include the Public Health Management Corporation, Philadelphia Department of Public Health, Health Federation of Philadelphia, and Temple Physicians, Inc. Since each organization has its own detection and referral system for vision and eye care services, we have developed our specific aims and study design with input from our partners and Advisory Board members (Appendix D).

Partners will also assist in remediating organizational, community, and cultural barriers and will provide facilitators and resources to ensure replication of our protocols, results, and outcomes. We believe that the breadth of the governmental, community, non-profit, and university-based partner organizations and the

diversity of the targeted at-risk patient populations will allow the results of our research to be sustainable and generalizable to other geographic areas within the United States. We will continue to work closely with each partner to refine the project goals and best methods to improve access, utilization, treatment, and follow-up eye care. The integration of these partners is essential to the proposed research structure, which will allow us to achieve a high-functioning system to overcome barriers and improve facilitators for eye disease and vision loss detection in newly diagnosed high-risk individuals (Appendix A and C).

C.4.c. Sequence of Activities: The *RE-AIM Framework* (Section D) described the aims of the proposed study and the ways our intervention is integrated into a vision and eye-care system[92]. At the present time, under the leadership of Jay Federman, MD and Shae Reber, COA, the WETD has contracted with our partner organizations to provide fundus photography for any patient with diabetes referred by the PCP in their health system or FQHC. By partnering with our own telemedicine department, our detection and management study will be able to reach populations and individuals at high risk for vision loss and eye disease.

Beginning in January 2015, after IRB approval at all collaborating institutions, additional patients that meet our inclusion criteria will be referred and recruited as described below in Section C. Partners and Advisory Board members will contribute to the successful implementation of eye disease and functional vision loss detection interventions by providing oversight within their own organizations and health centers. They will assist with submitting IRB applications and amendments, develop satisfaction surveys for their patients, establish tracking methods to assess follow-up eye-care utilization, help determine the best methods to contact patients, and attend quarterly research meetings with Wills research staff members.

C.5.a. Case Findings/Outreach/ Recruitment: The proposed intervention has been planned and developed to detect glaucoma, other eye diseases, and functional vision loss. A significant initiative has already taken place within our partner organizations by our WETD to inform all referring PCPs about the locations where fundus photographs are taken for their patients with diabetes. Ongoing referrals have been successfully generated but only 50% of those patients scheduled show up for the detection exam. Therefore, all participants will receive reminder phone calls and letters as part of our recruitment and retention strategies.

Community partners' quality control and information technology staff have agreed to provide patient reports at each practice using the inclusion criteria. Using these lists, we will adopt "opt-out" recruitment methods so we can call all patients to describe the study, confirm eligibility, and schedule them for the detection exam (Visit 1). We will also develop customized, linguistically appropriate flyers for waiting rooms. We will submit all of these documents with our initial IRB applications at each partner institution so there are no delays in initiating recruitment. We will work with each partner's medical director to develop these materials. All eligible patients who are scheduled for Visit 1 will receive a personal phone call to remind them of the appointment, discuss the importance of attending this visit, and answer any questions. Many patients lack knowledge regarding the permanency of vision loss due to glaucoma and diabetes and even perceive that it is not important to attend all follow-up visits[29]. Therefore, our study staff will continue to educate patients through phone calls and personal contact. A total of up to 3 attempts will be made in total to schedule or reschedule cancelled/no-show appointments.

C.5.b. Inclusion/Exclusion Criteria: The targeted, diverse, at-risk populations for the implementation research are people with previously undiagnosed glaucoma or glaucoma suspect, other eye diseases, and vision loss.
Inclusion Criteria:

- African-American, Hispanic, or Asian individuals over age 40
- Caucasian individuals over age 65
- Individuals of any ethnicity, over age 40 with a family history of glaucoma

- Individuals of any ethnicity, over age 40 with diabetes
- Individuals who meet one of the above criteria who have not seen an ophthalmologist in the past year

Exclusion Criteria: Any patient with previously diagnosed glaucoma, glaucoma suspect, or eye diseases who is currently being followed by an ophthalmologist.

C.5.c. Visit 1: Identification and Detection (PCP Office): Currently, the WETD owns and operates 2 Volk Pictor Plus auto-focus fundus cameras. Our ocular photographers, technicians and glaucoma staff have extensive experience and training using these cameras. A 3-person team comprised of 1 ocular technician and 2 study coordinators, will travel to the community sites and take posterior fundus photographs (3 per eye) using the Volk Pictor Plus camera. Monoscopic and stereoscopic optic nerve images and the macula of each eye will be visible.

The footprint for data acquisition consists of the patient, an imaging device/acquisition system, and a laptop computer. Approximately 25 patients are able to receive undilated fundus photographs of the optic nerve and macula in a 4-hour period. We will also assess the patient's medical and ocular history, family history of glaucoma, and eye pressure using rebound tonometry[12].

NOTE: A single IOP measurement will be obtained using the iCare tonometer for each eye. If IOP measurement is >22mmHg, a second IOP measurement will be obtained. If the difference between the 2 measurements is <=2mmHg, the average between the 2 measurements will be calculated and recorded. If the difference between the IOP is >2mmHg, a third measurement will be obtained and the median value of the 3 measurements will be recorded.

Standard measures of vision impairment, including visual acuity using the Snellen chart will also be conducted. Together, these results and the patient's images will be forwarded immediately to the Wills Eye Telemedicine Reading Center. Also during Visit 1, the research staff will document blood pressure, A1C, and BMI from the patient's PCP medical record. Our telemedicine infrastructure has laid the groundwork for this 5-year research project.

NOTE: During Visit 1 if the IOP is elevated based on the criteria outlined below by glaucoma specialists, the subject will be asked to skip Visit 2 and will be eligible to continue to Visit 3 with the local ophthalmologist. The subject will sign the Part II consent and get randomized during Visit 1. They will also complete the NEI-VFQ-25. If the subject chooses not to continue with the study, the team along with the PCP will make sure to stress the importance of seeing an ophthalmologist of their choosing in the time frame outlined.

IOP in either eye > 30 mm Hg subject to visit ophthalmologist within 2 weeks
IOP in either eye > 35 mm Hg subject to visit ophthalmologist within 1 week
IOP in either eye > 40 mm Hg subject to visit ophthalmologist within 1 day

A Wills Eye Hospital ophthalmologist will call a local eye care provider to advise them of the elevated eye pressure and the need for a timely appointment.

When images are received at WETD, a trained reader reviews the data and confers with the glaucoma and/or retina specialist, who determines if clinical pathology merits further evaluation and treatment and establishes relevant diagnoses. In addition to glaucomatous changes and DR, ocular hypertension, cataract, branch retinal vein and arterial occlusion, central retinal vein and arterial occlusion, epi-retinal membrane, macular degeneration, drusen and pigmentary disturbance will be documented on the report. Reports (Appendix F) are

uploaded to a secure password-protected, HIPAA-compliant web site, where the PCPs can access these records and link the report to their own patient's medical record. Patients with ocular pathology or patients who have photographs that are unreadable will be contacted and scheduled within 1-2 months for Visit 2 to confirm the diagnosis. Any patient with emergency eye issues, such as a detached retina, will be called immediately and scheduled for Visit 2. The patient's PCP will also be notified by phone immediately and a follow-up letter will be sent to the patient's home.

C.5.d. Ongoing Education/Training/Fidelity: Extensive training will take place during Phase 1 to ensure that all research staff adhere to policies and procedures. The Director of the Department of research and Glaucoma research center will be responsible for training Wills Eye Department of Research staff in cultural competency. The Director of Operations for Wills Eye Hospital's Telemedicine Department will be responsible for ongoing training on the Volk Pictor Plus camera for all ocular technicians and study staff. Glaucoma specialists will be trained to read the optic nerve images. Study Investigators will develop letters to send to local ophthalmologists to inform them about the study and invite them to participate. In addition, but before we begin the study, in conjunction with our general ophthalmology advisor, we will plan and develop definitions of adherence for all patients during Visits 3-8[12].

C.6. Visit 2: Baseline Assessment Measures and Confirming Diagnosis (PCP Office): Patients who have been diagnosed with glaucoma, glaucoma suspect, other eye diseases, vision impairment or have photographs that are unreadable who require non-emergent follow-up, will be notified by mail and telephoned by the study staff to schedule Visit 2 within 4 weeks of the detection visit. We will call all patients to remind them of the exam, discuss steps to prepare for an eye exam, and answer any questions. There will be no cost for this comprehensive eye exam. Any patient with an emergency eye issue at Visit 2 will be contacted immediately by phone and scheduled for an appointment at Wills Eye Hospital.

To conduct Visit 2, a leased van will transport the research team and all necessary equipment to the site each day. During the visit, an ocular technician and a glaucoma specialist will assess the patient's ocular, systemic, and family history and conduct a undilated eye exam including: 1) visual acuity measurement using Snellen eye charts, 2) slit-lamp biomicroscopy of the anterior segment, 3) IOP, 4) undilated optic nerve head evaluation (although if patient has diabetes they may be dilated),5) central corneal thickness measurement, 6) visual field analysis using the Octopus visual field analyzer and 7) gonioscopy.

The glaucoma specialist will review the results and final diagnosis with each patient. Criteria for glaucoma or glaucoma suspect will be defined as IOP (>21mm Hg), suspicious disks including a cup-to-disk (C:D) ratio greater than 0.5, C:D asymmetry (> 0.2), disk hemorrhage, or a combination of IOP and C:D appearance[72]. Other eye disease diagnoses, such as DR, will be made using standard *AAO Practice Pattern Guidelines*. Assessment measures and study schedule for Visits 1 through 8 are shown in Table 5.

Table 5: Assessment Measures and Study Schedule (PCP=Primary care physician, OPHTHO=general ophthalmologist)

Assessment Measures	Eye Detection Exam Visit 1 PCP	Confirm Diagnosis Baseline Visit 2 PCP	Initial Follow-Up Eye Exam Visit 3 OPHTHO	Ongoing Follow-Up Eye Exam Visit 4 OPHTHO	Ongoing Follow-Up Eye Exam Visit 5 OPHTHO	Ongoing Follow-Up Eye Exam Visit 6 OPHTHO	Ongoing Follow-Up Eye Exam Visit 7 OPHTHO	Final Follow-Up Visit 8 or Final Visit PCP & OPHTHO
Medical, family history	✓	✓	✓	✓	✓	✓	✓	✓
Eye fundus photographs	✓							
Complete eye exam		✓	✓	✓	✓	✓	✓	✓

Intraocular pressure**	✓	✓	✓	✓	✓	✓	✓	✓
Central Corneal Thickness*		✓	✓	✓	✓	✓	✓	✓
Visual field test*		✓	✓	✓	✓	✓	✓	✓
Visual acuity (Snellen)*****	✓	✓	✓	✓	✓	✓	✓	✓
Blood pressure (PCP) ***	✓							✓
Hemoglobin A1C (PCP) ***	✓							✓
Body mass index (PCP) ***	✓							✓
Smoking status	✓	✓	✓	✓	✓	✓	✓	✓
NEI-VFQ-25		✓			✓			✓
Satisfaction survey****	✓	✓	✓	✓	✓	✓	✓	✓
Current eye medications								✓
Current systemic meds.								✓
Confirm type of health insurance								✓
Current demographics (address & phone number(s)								✓

* Testing will be performed at the discretion and according to the follow-up recommendation of the local ophthalmologist
** IOP at Visit 1 & final visitwill be measured by iCARE rebound tonometer by study team.
*** AIC will be captured from the medical record. Blood pressure will be taken at the final visit by a member of the study team.
**** Satisfaction surveys will be administered for Visit 1 and Visit 2 and then 2-4 times a year based on randomization; a study closeout satisfaction survey will be administered at the final visit.

***** Visual Acuity (Snellen) will be taken by study team at the final visit.

C.6.a. National Eye Institute-Visual Function Questionnaire (NEI-VFQ): A member of the research team will consent all patients and administer the validated NEI-VFQ-25 questionnaire at Visit 2, Visit 5 and Visit 8 to assess barriers and the influence of their vision impairment on their health-related quality-of-life[93-95]. The 12 subscales are calculated by adding the relevant items and transforming the scores into a scale from 0 to 100. Higher scores indicate better quality-of-life. The composite score will be calculated as the average of 12 subscale scores. Patient navigators will use these results to assess barriers and refer patients to appropriate professionals, such as a social worker, low vision specialist, psychiatrist, occupational therapist, Medicare/Medicaid insurance advisor, and/or cataract surgeon. All materials will be culturally and linguistically appropriate and translated into other languages as necessary using trained medical interpreters and we will track all process measures.

*NEIVFQ surveys will be administered in person to all patients at Visit 2. For Visits 5 and 8 questionnaires will be administered over the phone by a patient navigator or social worker.

C.6.b. Patient Satisfaction Survey: With assistance from Westat, our partners, and Advisory Board members, we will create a new survey instrument and administer it at the end of each of the study visits. We will ask patients to rate their satisfaction with the exam, its duration, its convenience, the staff, and the likelihood of attending a follow-up eye exam. These surveys will optimize patient engagement and report outcomes that are important to patients and stakeholders.

*Satisfaction surveys will be administered in person to all patients for Visits 1 and 2. For Visit 5 surveys will be administered over the phone by a patient navigator or social worker for all enrolled patients. For Visits 3, 4, 6, and 7 satisfaction surveys will be administered according to randomization.
For Visit 8 (or final visit), a Study Closeout Satisfaction Survey will be administered at the primary care office by a member of the study team.

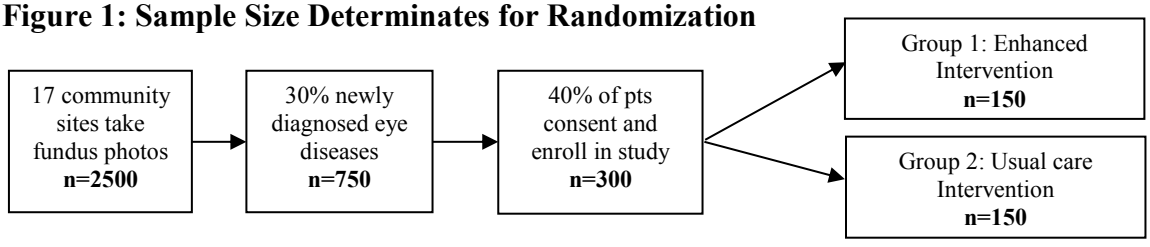
Usual care patients will be mailed the survey with a self-addressed stamped envelope to return the instrument to Wills Eye Hospital upon completion. Intervention group patients will be called and the survey will be conducted over the phone by a patient navigator or social worker. Satisfaction surveys will be administered 2 to 4 times a year within a 4 week window of their follow-up visit.

C.7. Enhanced Intervention Versus Usual Care Group:
Group 1: Enhanced Intervention Group with Patient Navigation and Social Worker: Patients randomized to Group 1 will be provided a list of eye care providers to choose from for follow-up. Patients can also choose to follow-up with an eye care provider not on our list. In that instance we would require a record release to be signed by the patient for the purpose of having access to their follow-up records throughout the study. Prior to all follow-up visits, patients in the enhanced group who have scheduled an appointment will receive a personal phone call reminding them to attend. These patients will receive any necessary interpretation services and educational materials.

Group 2: Usual Care: Patients randomized to Group 2 will be recommended to follow-up for eye care with a local eye care provider. These patients will be provided a list of eye care providers to choose from for follow-up. Patients can also choose to follow-up with an eye care provider not on our list. In that instance we would require a record release to be signed by the patient for the purpose of having access to their follow-up records throughout the study. Group 2 represents a realistic choice currently available for patients. Practice patterns will vary depending on the resources, staff time, and services available within each local eye care providers practice.

C.7.a. Sample Size Determination: As shown in Figure 1, we have based our sample-size calculations on the current preliminary CDC-project results as well as telemedicine statistics. We project that 30% of those fundus photographs will be abnormal and that, of those, 40% of patients will likely agree to consent and enroll in the study. These patients will be randomized to either the Enhanced Intervention Group 1 or Usual Care Group 2.

Figure 1: Sample Size Determinates for Randomization



C.7.b. Randomization Groups: The biostatistician, will randomize patients who meet the inclusion criteria with a fixed scheme 1:1 allocation ratio to the 2 study groups. Eligible patients will be consented and randomized to either the usual care group or the enhanced intervention group using the method of random permuted blocks.

C.7.c. The following two sites have eye care providers and all patients of these sites will receive initial and follow-up care throughout this study within these specific sites. As a result of this situation the following two sites will differ slightly from the other sites in terms of randomization and intervention:

Philadelphia Department of Public Health - Health District #5 (All Patients Usual Care): Patients will not be randomized at this site, they will all be assigned to usual care. Patients will be seen only by the eye care provider at Health District #5 for their follow-up eye care. They will be scheduled for their first appointment within 4 to 6 weeks from the date of Visit 2 and will then be responsible for scheduling the remainder of their follow-up appointments.

PHMC - Mary Howard Health Center (All Patients Intervention): Patients will not be randomized at this site, they will all be assigned to intervention. Patients will be seen by the eye care provider at Mary Howard Health Center. They will be scheduled for their first appointment within 4 to 6 weeks from the date of Visit 2. Prior to all follow-up appointments a patient navigator ill call and remind them about the date and time of their next appointment. The navigator will also be available to answer any insurance questions they may have or help to arrange transportation to their appointments.

C.8. Patient Navigation Protocol (Appendix I): The use of patient navigators and social workers has proven successful in cancer care programs, showing higher rates of follow-up care, while increasing patient satisfaction and decreasing anxiety[81]. Patient navigation shows promise as the missing link between available services and healthcare delivery to vulnerable populations[80]. By educating and guiding patients, navigators can lessen the disparities among racial/ethnic groups at risk for eye disease. Our study staff, project managers, ocular technicians, and research assistants have been trained to serve as patient navigators. Their responsibilities will include: phoning patients to schedule appointments; confirming appointments by mailings, emails and/or text messaging; arranging transportation through Customized Community Transportation (CCT) and Philadelphia Paratransit Service; and scheduling trained medical interpreters.

Wills Eye ocular technicians will also assist patients in the enhanced intervention group across 17 sites with medication refills and obtaining free medications from pharmaceutical companies. Our patient navigators can identify cultural and language differences and are aware of health literacy issues. We will also provide multiple outreach strategies as additional barriers are identified. Results will be discussed at our weekly research team meetings, quarterly meetings with each partner, and annual meetings with our Advisory Board.

C.8.a. Identifying Barriers to Follow-up Using Social Workers: Research shows that individuals at high risk for glaucoma are not likely to participate in screening programs or ongoing follow-up with an ophthalmologist in an office-based setting[32,33,37-39]. Appendix J describes how innovative approaches to identifying and remediating barriers have been accomplished in our current CDC glaucoma detection program and can be tested, refined, and implemented in this proposed study (Section C.2.a). Educational materials may help non-adherent patients to understand the benefits of taking glaucoma medications regularly[29,42,47].

In the same way that social-work interventions have proven beneficial for patients with cancer, such interventions can enhance outcomes in those affected by glaucoma and other eye diseases. Medical social workers understand and value a patient's right to self-determination. They can work with patients directly to empower them to seek appropriate methods of treatment and follow-up vision care. Therefore, we have budgeted for one part-time, medical social worker who will assist the research team with identifying cultural, racial/ethnic, costs, trust, and language barriers as described by Bentacourt[74]. She will work interact with any social workers employed at the FQHCs; supervise, train, and mentor the patient navigators; and contact patients enrolled in the enhanced intervention group. By testing and refining our approaches to removing these barriers, we hypothesize that patient navigators and a social worker will significantly improve patients' follow-up vision care, patient satisfaction, and quality-of-life.

C.9. Management and Follow-up Visits 3-8: To ensure that all patients receive appropriate treatment and that outcomes are tracked yearly, adherence to follow-up eye care access and utilization will be our primary outcome measure. All patients who fulfill the inclusion criteria, have consented, and completed Visit 2 will be randomized and either referred or scheduled (depending on assigned randomization) for Visit 3 within 4 weeks with a local, general eye care provider or earlier at the glaucoma specialist's discretion. All medical records from our confirming diagnostic exam will be faxed to the local eye care provider who will examine the patient. A form acknowledging receipt of records by the local eye care provider will be requested (requiring signature). Participating eye care providers will be informed about the study during Phase 1 and blinded to the patient's intervention group. We will refer patients diagnosed with glaucoma or glaucoma suspect to an office that is able to conduct visual field testing.

During Visit 3 the eye care provider will assess the patient's ocular, systemic, and family history and conduct a eye exam that includes: 1) best correct visual acuity measurement using Snellen eye charts, 2) slit-lamp biomicroscopy of the anterior segment, 3) intraocular pressure (IOP), 4) optic nerve head evaluation, 5) central corneal thickness measurement, 6) visual field analysis using a visual field analyzer (such as Octopus or Humphrey), and 7) gonioscopy (Table 5). Based on these results, the ophthalmologist will reconfirm their ocular diagnosis and adjust therapy as needed. Most individuals will be recommended at the appropriate follow-up intervals shown in Table 6. In conjunction with our general ophthalmology advisor and the CDC, we will plan and develop definitions of adherence for all patients during Visits 3-8[12]. Follow-up recommendations for other eye disease diagnoses will also be made using standard *AAO Practice Pattern Guidelines*.

Table 6: Summary Benchmarks Preferred Practice Pattern Guidelines for POAG

Target IOP Achieved	Progression of Damage	Duration of Control (months)	Appropriate Follow-up Interval (months)
Yes	No	<6	6
Yes	No	>6	12
Yes	Yes	NA	1-2
No	Yes	NA	1-2
No	No	NA	3-6

Source: American Academy of Ophthalmology[12]

D. EVALUATION/PERFORMANCE MEASUREMENTS

We have created distal and proximal follow-up protocols to measure public health outcomes during Phases 1, 2, and 3, with the capacity to improve quality of vision and eye health and quality-of-life in real-life settings. Outcomes may vary among our study populations depending on the diagnosis and follow-up recommendations. We have developed the research project within the *RE-AIM Framework,* as described below and focus on integrating into the vision and eye care systems of each of our partners.[92] Westat will assist with to the evaluation process.

D.1.a. Reach: The number of patients from our partners' primary care offices and health centers who have not seen an ophthalmologist in the past year is estimated to be more than 10,000. We conservatively estimate that 2,500 of these patients will schedule, attend, and participate in Visit 1 in the primary care setting, where we will detect glaucoma and other eye diseases using telemedicine. Based on previous demonstration projects, 2,500 patients is a reasonable and realistic number to recruit. The proportion of patients who are African American,

Caucasian, Hispanic, and Asian at each partner organization is described in the Facilities section. We will report on the demographics of the study sample, defined as the similarity to or differences between participants and eligible people who do not enroll. If differences exist in the demographic variables between our intervention and control group, our intervention may be less generalizable in other patient populations. If differences do not exist, then a stronger case can be made for generalizing the intervention into additional settings.

D.1.b. Effectiveness/Efficacy**:** We will evaluate the impact of our enhanced intervention on our proposed outcomes, including quality-of-life, and economic efficiency. Determining the effectiveness of our intervention is critically important because patients with undetected glaucoma and other eye diseases can suffer lasting visual impairment that can affect their quality-of-life, economic status, morbidity, and ultimately mortality. New strategies are necessary to improve patient access and utilization of eye care. Our study aims to determine if adherence to follow-up recommendations changes as a result of the enhanced intervention. We will determine the effectiveness of the intervention by examining the effect size associated with our intervention and specified outcomes (adherence to follow-up recommendations and vision-related quality-of-life).

D.1.c. Adoption**:** Our letters of support from Advisory Board members and partner institutions demonstrate a strong commitment and willingness to participate in this research study. We are working closely with primary care offices, health centers, universities, governmental agencies, and community organizations. We expect to notice variations in patient behavior based on the number of resources available to them. These varying settings and intervention modalities are critical to the current and potential impact of our intervention. If differences exist among sites, this is evidence of differential adoption.

D.1.d. Implementation: At each setting, implementation refers to the intervention agents' fidelity to all elements of the protocol. This includes consistency of delivery as intended and the time and cost of the intervention. Investigators in coordination with Westat and the project manager will determine the extent to which the intervention was delivered. We will assess implementation by reporting on the percentage of process objectives that were achieved, such as: What proportion of patients received the confirming diagnosis enrolled in the study? How many patients followed up with the general ophthalmologists at the initial 6-month, 1-year, 2-year, and 3-year visits. We will also conduct a cost analysis and report costs of all levels of the intervention, including recruiting patients, reading images, confirming diagnoses, randomization, and 3-year follow-up (Table 7).

D.1.e. Maintenance: Our research has the advantage of building on existing infrastructure of both the WETD, and currently established community referrals to general ophthalmologists, which will remain in place after the research is completed. The extent to which a program or policy becomes institutionalized at each community partner will be evaluated. This project will allow evaluation data to be captured at all detection and implementation levels. Following the completion of the 5-year study, we will communicate our results to our partners', present data, and discuss strategies that worked to improve patient care. The outcomes of our study will be highly applicable for improving the cost of eye care for newly diagnosed patients with glaucoma and other eye diseases. In anticipating the success of our proposed study, we plan to institutionalize the program in Philadelphia, and monitor long-term outcomes after 6 or more months. Using the *RE-AIM Framework*, we will track intervention data shown in Table 7.

Table 7: Tracking Measures Using *RE-AIM Framework* Approach

RE-AIM	Evaluation Question	Tracking Measures	Data Source
Adoption	How were community partners and primary care settings engaged in the study?	# of participating community partners and primary care settings (offices, health centers). Primary care offices' satisfaction with participation.	Contact log On-site observations On-site interviews

Reach	To what extent are high risk target populations being reached?	Patient characteristics (demographics, insurance status, ocular history, ocular risk factors).	Intake form/EMR
Implementation	How was the program implemented?	Patient navigator, cultural competency training conducted. # of staff at each onsite activity. # of patients who follow up with general ophthalmologists. Time taken per patient and for each eye exam. # of confirmatory diagnosis from fundus photos. # of referrals made based on NEI-VFQ.	Planning log On-site observations EMR
Efficacy/ effectiveness	Did the intervention work? (Comparison between intervention and control groups)	# of patients from each group adhering per year. Average percentage of visits attended per year. Clinical measures (visual acuity, IOP, VF). Health related quality-of-life (Visits 2 and 8). Satisfaction with eye services at each visit.	EMR EMR NEI-VFQ Patient satisfaction survey
Maintenance	To what extent has the program been institutionalized?	Willingness of partners and PCPs to continue with telemedicine and community model.	On-site interviews

E. Outcome Assessments and Comparators for Analysis

E.1.a. Tracking Outcome Performance: We are committed to implementing a comprehensive process and outcome evaluation to monitor and track all outcome performances and identify best practices to replicate and disseminate efforts (Table 8). Investigators in collaboration with CDC and Westat, have created an evaluation plan containing specific, measurable, achievable, realistic, and time-limited (SMART) goals. The biostatistician will clean and manage the data. Our evaluation will be consistent with the CDC's *Framework for Program Evaluation*. We anticipate that the results will be generalizable and that our study can serve as a framework for similar interventions elsewhere.

E.1.b. Summative and Formative Evaluation Plan: We will assess measurable, immediate and long-term outcomes and develop a comprehensive plan for dissemination. With the assistance of Westat, all evaluation tools and reports produced will harmonize with other CDC Cooperative Agreements. Wills Eye will track data on individuals and on the intervention to understand the success, limitations, timeliness, and effectiveness of the project. We have created data collection tools to track data at all levels of the study. On-site tracking will be conducted by trained ocular technicians, study staff, and primary care and ophthalmology office staff. Using a customized, HIPAA compliant, NextGen EMR template, all participants will be assigned a unique medical record number (MRN). This number will be linked to each exam and include all clinical variables. Final diagnosis, proposed treatment, and follow-up recommendations will be documented.

E.1.c. Data Management/Quality Assurance: Exam results and treatment dates will be linked with MRNs and stored in a password-protected, encrypted, hard drive. The biostatistician and data manager, using SAS software, will create a separate list linking patient names and exam and treatment dates. To track follow-up adherence and scheduling, we will document on EPM the exam/treatment dates. We will also note the number of follow-up visits that each patient schedules, keeps, reschedules, cancels, and misses. The project manager will also monitor and store results, such as the NEI VFQ-25 and the satisfaction survey. De-identified, aggregated data will be sent to Westat in an Excel spreadsheet. Upon completion of the project, all data and databases will be securely housed for 3 years. Wills Eye Hospital will maintain the confidentiality of records according to the provisions of Title 42 of the Code of Federal Regulations, Part II. (See Table 8)

Table 8: Process Measures to Be Tracked

Process Measures	Phase 1 Plan, Develop Detection	Phase 2 Confirm Diagnosis Follow-up	Phase 3 Follow-Up Disseminate Replicate
# of partners and primary care offices for recruitment sites	✔		
# of patients received by each primary care offices and health centers	✔		
# of letters mailed/calls made to patients from recruitment and Visit 1	✔		
# of patients scheduled, confirmed, attended detection eye exam Visit 1-2	✔	✔	
# of patients who cancelled and assessment of barriers to attending exam	✔	✔	✔
# of patients/doctors sent letters with normal/abnormal eye exam results	✔	✔	✔
# of patients diagnosed with glaucoma, suspect, and other eye diseases	✔	✔	✔
# of patients who attended exams with an ophthalmologist (Visits 3-8)		✔	✔
# of patients recommended to follow-up in 1-2 weeks, 1-2 months, 3-6 months, 6 months, and 12 months from baseline Visits 2-8		✔	✔
# of people prescribed ocular medication, laser therapy, or eye surgery		✔	✔
# of patients who requested medication assistance for eye drops	✔	✔	✔
# of patients who requested and used translation/interpreter services	✔	✔	✔
# of patients who requested and used transportation services	✔	✔	✔
# of referrals for a low-vision specialist, cataract surgeon, etc.		✔	✔
# of referrals for a Medicare/Medicaid advisor or to complete application		✔	✔

E.1.d. Patient Satisfaction Surveys: With Westat, the CDC and Advisory Board members, we will develop brief questions regarding the patient's satisfaction. We will survey patients at the conclusion of all visits. Wills Eye research staff will administer surveys during the detection and baseline visits. We hypothesize that satisfaction will be greater for those in the intervention group than in the usual care group.

E.2. Data Analysis for Aims 1 and 2

E.2.a. Primary Analysis for Aim 1: The primary analysis for Aim 1 will be to estimate the positive predictive value (PPV) of the teleophthalmology intervention for diagnosing of glaucoma. We hypothesize that the diagnosis of glaucoma and glaucoma suspect using undilated optic disc images, tonometry pressure results, and medical history will predict the comprehensive eye exam diagnosis. That is, we will calculate the proportion of patients diagnosed with glaucoma or glaucoma suspect whose diagnosis was confirmed at Visit 2 with an exact two-sided binomial confidence interval. We will conclude that the telemedicine intervention has good performance if the lower bound of the confidence interval is above 80%.

The expected sample size for this aim is 250 patients as we anticipate approximately 50% of those diagnosed with eye pathology and who return for the confirmation Visit 2 will have been diagnosed with glaucoma or glaucoma suspect at Visit 1. Data from Maa (2014) can be used to estimate the PPV for glaucoma at 85%[72]. With 250 patients, we have 50% power to conclude the PPV is greater than 80% if the true PPV is 85% and over 99% power to conclude the PPV is greater than 80% if the true PPV is 90% using a 2-sided test with alpha=0.05. We will repeat this analysis looking at the proportion of patients diagnosed with eye pathology who in fact have an ocular diagnosis (whether or not the exact abnormality was correct).

E.2.b. Primary Outcome Measure for Aim 2: Patient baseline demographic and clinical characteristics will be summarized overall and by randomization assignment (in Aim 2) using means, medians, standard deviations, and ranges or frequencies and percentages, as appropriate. Our general approach from the randomized trial is to analyze patients as randomized regardless of the amount of intervention received. The primary outcome measure for Aim 2 is attendance at recommended follow-up visits (Visit 4 and later). Since the expected

number of appointments will differ based on diagnosis and disease severity, which may change over time, attendance will be summarized annually.

For each year under observation, an expected number of visits will be determined based on the recommended follow-up at the first visit for that year (Table 9). For purposes of this calculation, attendance at appointments within 13 months of the first visit will be assessed. We recognized that follow-up recommendations will vary for each patient depending on eye pressure control, medication adherence, disease severity, and surgery/laser appointments. Therefore, the research team, in conjunction with Dr. Blecher and the CDC, will plan and develop definitions of adherence for patients during Visits 3-8.

Table 9: Assessment of Adherence to Follow-Up Recommendations

Recommended Follow-up	Number of visits per year considered adherent to recommendations
1-2 months	At least 6 visits per year with an eye care provider
3-6 months	At least 3 visits per year with an eye care provider
6 months	At least 2 visits per year with an eye care provider
12 months	At least 1 visit per year with an eye care provider

E.2.c. Primary Analysis for Aim 2: The primary outcome of the study is adherence to recommended follow-up in each year as described in section E.1.c. For each of the 3 years of follow-up, we have a dichotomous measure of adherence. We will model this longitudinal dichotomous outcome using Poisson regression within a generalized estimating equation (GEE) framework[96,97]. Our model will include time (Year 1, 2, and 3), randomization assignment, randomization by treatment interaction, and baseline individual characteristics believed to be associated with adherence to follow-up, including age, diagnosis, vision impairment, and overall vision-related quality-of-life. Within this model, we will test 2 hypotheses.

First, we will compare randomization groups at Year 1 to test whether there are differences in early adherence. Second, we will calculate the average effect of randomization across Years 2 and 3 and test the long-term efficacy of the intervention. In both cases, we will estimate the overall relative risk of adherence along with its associated confidence interval. Each test will be performed with alpha=0.025. The primary analysis will include all patients who were randomized and have some adherence data (see section on missing data below).

E.2.d. Power for the Primary Analysis for Aim 2: Our estimated available sample size is given in Figure 2. We will randomize 300 patients (150 per group). Assuming up to 10% dropout where adherence cannot be calculated due to death or study withdrawal (i.e., final analysis dataset of n=135 per group), we calculate power to detect a 20% improvement in adherence under various assumptions of adherence under Usual Care. We have greater than 80% power to detect these differences using a two-sided chi-square test with alpha=0.025 (Table 10).

Table 10: Determination of Power Calculation

Percent Adherence Under Usual Care	Percent Adherent Under Enhanced Intervention	Relative Risk	Power
35%	55%	1.57	86%
40%	60%	1.5	86%
45%	65%	1.44	86%
50%	70%	1.4	87%
55%	75%	1.36	89%
60%	80%	1.33	92%

E.2.e. Secondary Analyses for Aim 2: We will perform a secondary analysis to test for differences in the average number of appointments kept per person-year of follow-up. We will use Poisson regression to model

the total number of appointments after Visit 3 by randomization assignment. The offset term will be time under observation measured from Visit 3 to end of follow-up. We will adjust baseline for age, diagnosis, vision impairment, and vision-related quality-of-life. Change in continuous clinical and quality-of-life measures (IOP, visual acuity, NEI-VFQ, etc) will be modeled using mixed effects linear regression. Fixed effects will be time (treated continuously), randomization assignment, treatment by time interaction, age, and diagnosis. A first-order autogressive correlation structure will be assumed to model correlation among repeated measurements. When possible, random slope and intercept terms may also be included. Effects of intervention on these measures will be tested by the significance of the interaction term.

E.2.f. Exploratory Analyses for Aim 2: We will consider whether the effect of the intervention differs by baseline patient characteristics of glaucoma severity (using VF mean deviation), and vision-related quality-of-life (NEI VFQ score). The primary model will be extended to include the interaction between these variables and randomization assignment to allow for estimation of intervention effects by baseline categories.

E.2.g. Missing Data/Lost to Follow-up: Since primary outcome data will be obtained from EMRs, we do not anticipate much missing outcome data unless patients formally withdraw from the study or die during the follow-up period. For these patients, data will be missing for a year (and all years following) if they withdraw during that year of follow-up. We will fit our longitudinal models with all available data from all randomized patients. Patients who are simply lost to follow-up due to lack of contact will be considered non-adherent. Our approach to analysis provides valid estimates under the assumption that data are missing completely at random (MCAR). We will compare those who withdraw to those who do not withdraw, with respect to baseline characteristics. We will consider imputing outcomes using multiple imputations as a sensitivity analysis if it appears that the MCAR assumption is not valid. Analysis for continuous outcomes yields unbiased estimates under the missing at random assumption, and we will not impute data for these analyses.

E.3. Aim 3: Conduct a Comprehensive Cost Study

Building upon previous research, which reported that a glaucoma follow-up unit was cost effective compared to usual care, we will conduct a comprehensive cost study to estimate the intervention costs and cost-effectiveness of detecting eye diseases and vision impairment in a high-risk population. We have proposed an economic framework to minimize program costs, maximize program impact, and measure return on investment.

Building upon research by Holtzer-Goor KM, which reported that a glaucoma follow-up unit was cost effective compared to usual care, we will analyze the cost effectiveness of our enhanced intervention[98]. The cost analysis will assess the feasibility of the study and identify areas where program costs can be minimized to estimate the net cost of replicating the intervention in additional communities to achieve similar outcomes once development and evaluation costs are removed.

E.3.a. Cost Measures for Aim 3: Cost measures will include intervention costs, glaucoma-related healthcare service use, glaucoma-related medications, and patient travel costs. The glaucoma exams of this project consist of five steps conducted by ophthalmic technicians, ophthalmologists, and study staff. The main tests performed on the patient include fundus photography, visual acuity, and a visual field analysis. Intervention costs will be measured for each step in the examination process and will include human costs as well as non-human costs. Trained research assistants and fellows will conduct site visits to observe and record the time each staff member takes to complete each step.

Direct personnel costs are calculated based on the mean duration for each step. Wage rates for personnel will be obtained based on job classifications, available from the 2013 US Bureau of Labor Statistics for Philadelphia. It

is assumed that most of the steps could be performed by ophthalmic technicians or medical assistants, whose wage rate is approximately $16 per hour. Physicians participating in this project are estimated to have a wage rate of approximately $87 per hour. Fringe benefits will be added to the wage costs at an estimated 35%. Time costs for each step are calculated with the following equation:

Staff member= mean # of minutes x (wage rate + benefits)

If additional staff members assisted with a step, then it will be assumed that they were there for half the time and additional time costs will be calculated as:

Additional staff members= (mean # of minutes/2) x (wage rate for medical assistant + benefits)

Non-human costs to be collected include telemedicine platform, medical equipment and supplies, office supplies, community partners' recruitment, communication (internet hotspots), van rental and maintenance, and travel inclusive of fuel, and mileage. Medical equipment is expensive; however, it has been shown that once the investment is made, the operational costs are fairly low[99]. Since the telemedicine platform and the medical equipment have been donated from WETD and the previous CDC-funded project, the cost of this study will be dramatically reduced.

The intervention will be examined to determine which services are billable to healthcare insurers, and the extent to which such reimbursement covers the costs. Even though it may not have a direct impact on exams, data on patient travel will also be collected. During check-out, project staff will ask patients about their satisfaction and type of transportation used. The costs of the transportation methods will be estimated based on the reported fares from Southeastern Pennsylvania Transportation Authority (SEPTA). Buses and subways cost $2.25 per ride. Customized Community Transportation (CCT), for elderly and handicapped individuals, costs $4 each way. When patients drive or take taxis, costs are estimated at $1.65 and $15 each way, respectively. Individuals who walk have no transportation costs. Previous studies have shown that "convenience of travel" contributed to patient satisfaction[99,100]. Previous research has also reported that decreased patient traveling saved $55 per visit[99]. Additionally, work-productivity costs may be considered, since we are recruiting people who may be employed.

E.3.b. Effectiveness Measure for Aim 3: In addition to conducting a comprehensive examination of costs, we will systematically examine these costs in the context of the intervention's societal benefits by conducting a formal cost-effectiveness analysis. The cost-effectiveness analysis will employ quality-adjusted life years (QALYs) as the primary measure of societal benefits. We will capture QALY over the course of 2 years using the Health Utilities Index, v.2/3 (HUI-2/3). HUI-2/3 is a utility measurement instrument that consists of 15 items that capture 8 attributes of health-related QoL: vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain.

The scoring algorithm will be obtained from Health Utilities, Inc. and is based on Canadian health preference weights. Utility scores from this instrument range from 0-1, with a higher score indicating better quality-adjusted life. Previous research has shown that the HUI-3 has consistent validity in people with glaucoma, diabetic retinopathy, and cataracts[101]. QALY will be measured as the amount of utility gained or lost over each year of the program.

E.3.c. Incremental Cost-Effectiveness Ratio: The primary cost-effectiveness measure will be defined as the incremental difference between cost of the enhanced intervention and usual care, divided by the difference in health utility-Incremental Cost Effective Ratio (ICER). The ICER thus will indicate the additional costs to bring about one additional unit of benefit (QALY) from the enhanced intervention compared to usual care. The

reference case, which will be defined as usual care. The ICER obtained will be compared to acceptable thresholds of $50,000 to $100,000-QALY. A secondary measure will be cost per diagnosis made.

E.3.d. Sensitivity Analysis for Aim 3: To account for uncertainty in our primary ICER, cost and effectiveness data will be entered into a decision analytic model. This is particularly important since the study will be powered based on the primary outcome, not the cost-effectiveness measure. Sensitivity analyses will ensure robustness of the ICER. Both univariate sensitivity analysis (whereby 1 variable is changed at a time and impact on the ICER will be examined), and probabilistic sensitivity analysis (PSA), whereby all relevant variables are simultaneously modified within reasonable ranges will be conducted. Sensitivity analyses will include those variables where we anticipate "real world" uncertainty.

The PSA will consist of a Monte Carlo simulation model based on estimated distributions for each variable in the model, with each distribution based on the mean and standard deviation of all probabilities, costs, and effectiveness measures. If the standard deviation of a variable is not available, it will be assumed to be 10% of the mean. The simulation will consist of 10,000 random iterations, with the goal of determining the likelihood that the enhanced intervention is cost-effective compared to usual care. The PSA will be performed using the TreeAge Pro software program (Williamstown, MA). Since the trial employs a time horizon of >1 year, discounting future costs and benefits will be performed at a rate of 3% each year beyond the first.

F: Aim 4: Replication, Dissemination and Transition Plan

Wills Eye and its partners are very eager to share insights, successes, progress, and barriers with key stakeholders, including public health practitioners, academic researchers, primary care providers, governmental agencies, private organizations, and patients. Under the leadership of Wills Eye Hospital Investigators, and working with Westat and the CDC, Wills Eye will disseminate and translate our interventions via the internet, free of charge, for implementation in communities across the nation.

We aim to build a capacity to develop a sustainable intervention that can be freely shared and implemented in additional communities in the following ways:

- Provide training to public health and academic researchers, study staff, FQHC directors, PCPs, ocular technicians, and eye care specialists to enable them to apply best practices to their own settings to address vision-health disparities.
- Publish methodology and final research results about all aspects of the project and its impact in peer-reviewed literature for audiences in primary care, diabetes, telemedicine, and eye care.
- Create presentations and exhibit posters at conferences including the American Glaucoma Society, American Academy of Ophthalmology, American Public Health Association, American Academy of Family Physicians, American Diabetes Association, and National Association of Community Health Centers.
- Disseminate information about this project and its impact through the Wills Eye website (www.willseye.org) and other Wills Eye electronic and print materials, such as webinars, chat rooms, pod casts, and list serves.
- Present information about our project and its impact on vision and eye care to the broader Philadelphia community at meetings and conferences and through local publications.
- Provide information about this project to Philadelphia's public health officials.
- Share project outcomes regarding the FQHC with HRSA and other policy makers.
- Develop and design an inventory of assessment and outcome measures to guide replication and expansion of the teleophthalmology methods and the Patient-Navigation Training Manual (Appendix I).
- Create electronic handbooks for professional that define setting, partners, scope, intensity, reporting, and outcome measures for detecting and managing eye disease and functional vision loss.

Dissemination plan will begin in Year 2. Methodology papers will be written on the baseline population. We will share research findings through websites, webinars, conference presentations, reports/fact sheets, peer-reviewed journal articles, and electronic manuals. All products and tools will define the setting, partners, scope, intensity, reporting, and outcome measures. Using the *RE-AIM Framework* described in Section D, we will focus on implementation and maintenance. Our dissemination plan aims to ensure that our educations materials, data capturing tools, electronic handbook, and patient navigator/social worker protocols will be publicly available. The intervention has sufficient rigor and fidelity to be replicated and implemented in communities across the nation.

In collaboration with the Tel-Aviv Medical Center and the Bar-Ilan University (Israel), we plan to develop a deep learning algorithm to detect glaucoma using the optic disk and fundus photography obtained at Visit 1, as well as demographic and clinical data from visits 1 and 2. A password protected hard drive with the de-identified data (fundus photos and clinical information) will be shared with Drs. Michael Waisbourd at the Tel-Aviv Medical Center and Yosi Keller at Bar-Ilan University. The deidentified data will remain stored on secure servers protected by two passwords at the Tel-Aviv Medical Center and at the Bar-Ilan University. HIPAA compliance will be achieved through the Safe Harbor method.

Our aim is to develop a software for detection of glaucoma suspicious discs, based on deep-learning algorithm. The software will be available for research purposes for investigators from other institutions worldwide by using cloud-based open-access platform. Researchers will be able to upload images and evaluate the ability of the suggested software to detect suspicious discs, free of charge. The end-user will be able to upload color fundus images to the website. The images will be sent to our cloud servers, where each image will be processed and a glaucoma detection report will be sent back to the user. In case the user does not approve sharing the images they will not be saved in our database. Otherwise, these images will help us improve the proposed algorithm and expand our database.

G: Study Timeline, Monitoring, and Community Advisory Board

G.1.a. Study Timeline and Milestones: We will implement and evaluate the project tasks and measureable, milestones according to the timeline in Appendix K. We have identified realistic milestones including baseline and follow-up assessments, data collection, data management, and data analysis for the 5-year period. Beginning September 30, 2014, we will initiate IRB protocol submissions at Wills Eye and the partner institutions including Public Health Management Corporation, Philadelphia Department of Public Health, Health Federation of Philadelphia, and Temple Physicians, Inc. This will allow adequate time from the funding notification to obtain IRB approval. After IRB approval, patient enrollment will begin 1/1/15and last 15 months. Table 8 describes the process measures.

G.1.b. Independent Study Oversight: Data Safety and Monitoring Board (DSMB): This study will utilize a DSMB that has been established specifically for this CDC project. This group will assure that protocols are followed properly, case reports match the source documents, inclusion and exclusion criteria are followed, and all subjects are consented properly. In addition, the DSMB will review safety data after we have enrolled subjects at all sites.

The DSMB will meet annually and develop a monitoring plan for transmitting reports to the IRB. The report will provide individual findings, overall safety assessment, and recommendations. The summary report will include the study's protocol, participant enrollment, procedures, and data quality. The report will also inform study investigators of the DSMB members' conclusions with respect to the study's progress or need for modification of the protocol. Meetings will also allow investigators and the DSMB to review data including

VFQ results, rates of follow-up eye care, sensitivity analysis of glaucoma detection using telemedicine images vs. comprehensive glaucoma exam, recruitment, and enrollment reports, and satisfaction questionnaire results.

G.1.c. Community Advisory Board: To assist the research team with planning, developing, implementing, evaluating, and disseminating results and materials, we have established an ethnically diverse, community Advisory Board, made up of stakeholders from each of our partners, patients, and various content experts (Appendix D). For example, Natalie Levkovich, CEO of the Health Federation of Philadelphia, will help to identify the 5 FQHCs that will participate. Key organizations, such as the Philadelphia Corporation for Aging (PCA), Greater Philadelphia Chinese Association, and the Council of Spanish Speaking Organizations (CONCILIO) have also expressed interest to assist with community outreach and recruitment.

We have invited an expert in teleglaucoma (Louis Pasquale, MD, Director of the Massachusetts Eye and Ear Glaucoma Service as well as the Ophthalmology Telemedicine program) and a cost-effectiveness expert (Anja Tuulonen, MD, PhD, Head of the Department of Ophthalmology at the Tays Eye Centre at Tampere University Hospital in Tampere, Finland). Two Wills Eye faculty members- Marlene Moster, MD, a glaucoma specialist and Mark Blecher, MD, a general ophthalmologist, will also participate. Our Advisory Board also includes patients from our existing community interventions who have been diagnosed with glaucoma and other eye diseases. Annual Advisory Board meetings will help to improve communication and establish a feedback loop across all sites. Formal and informal meetings with members will also take place during the study.

G.1.d. Communication and Coordination with CDC: Based on Wills Eye Hospital's current CDC Cooperative Agreements, Wills Eye Investigators understand that CDC staff will be substantially involved in this 5-year research project, providing approval of the study design, definition of primary outcomes, cost analysis, data analysis, report writing, and dissemination of findings. The research team will submit proposed plans to the CDC prior to IRB submission, allowing sufficient time for review and comments by CDC staff. The CDC will be especially interested in reviewing: 1) logic models, 2) cost analysis strategies, 3) performance indicators used to monitor and evaluate projects, and 4) publications, technical reports, and manuscripts to disseminate evaluation findings. The intervention team will be available for monthly conference calls with CDC staff. Investigators are budgeted to attend two meetings each year at the CDC during the 5-year funding cycle to present progress reports and outcomes data for Specific Aims 1, 2, 3, and 4.

In Summary: We believe this proposed, evidence-based intervention addresses a critical gap in current patient care. It has the potential to improve detection, management, treatment, and follow-up adherence in persons at high-risk for glaucoma and other eye diseases causing vision impairment. We will design our materials so they can be replicated for communities across the nation. Our concurrent cost study is designed to estimate the feasibility of implementing the intervention in primary care offices and FQHCs, followed by referrals to local general ophthalmologists. We hypothesize that implementing telemedicine technologies for glaucoma- and ocular-disease detection will allow patients to receive care in a comfortable, convenient, and familiar setting. Our patient-centered intervention involving patient navigators and a social worker will address transportation, language, and insurance barriers and aims to improve follow-up adherence.

Any educational information and clinical interactions will be culturally sensitive and linguistically appropriate for the patients' needs. This is the first study to compare usual care to an enhanced intervention using patient navigators and a social worker to improve follow-up adherence for patients with newly diagnosed glaucoma, glaucoma suspect, and other eye diseases. As we assess the benefits of a community intervention to improve eye care accessibility for patients, we will, in contrast to previous studies, focus on patient-centered outcomes that are important to the community stakeholders and collaborators. Considering the low follow-up rates in office-based settings, our enhanced intervention strives to prevent visual impairment by addressing an important

gap between detection and follow-up eye care, particularly in high-risk patients diagnosed with glaucoma, glaucoma suspect, other eye diseases leading to vision impairment and blindness.

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