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Comparison of Neovascular Age-Related Macular Degeneration Populations in the United States

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Abstract

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Susan Lynette Coultas

MS, University of North Texas, 1985

BS, Texas Wesleyan University, 1983

Dissertation Submitted in Partial Fulfillment

of the Requirements for the Degree of

Doctor of Philosophy

Public Health

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Abstract

Age-related macular degeneration (AMD) is one of the leading causes of blindness in the United States in people who are 50 and older. The safety and efficacy of aflibercept for the treatment of late stage neovascular AMD (NAMD) has been demonstrated by clinical trials among several populations; however, it is unclear whether all NAMD patients respond in the same manner as was studied in the clinical trials. The purpose of this study was to examine if populations of patients treated with aflibercept for the treatment of NAMD were significantly different from one another in terms of health characteristics, treatment regimens, and treatment outcomes. The burden of treatment theory was used to guide this study. Data collected from electronic medical records were used to investigate NAMD characteristics 199 patients from 3 private, retinal practices in the United States. Data were analyzed using one-way ANOVA, χ^2, Spearman's correlation, and point-biserial correlation tests. The results of this study showed the specific retinal practice populations of NAMD patients treated with aflibercept were generally similar with respect to selected health characteristics, treatment regimens, and treatment outcomes. By using the information reported from this research, public health initiatives can be developed that focus on the need for early detection of AMD to capture changes that represent NAMD and move to early treatment for better outcomes. The positive social change that could result from this research is that retinal specialists may gain insight into the use and outcomes of aflibercept treatment.

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Dedication

This dissertation and the work that has gone into earning my Ph.D. in Public Health, Epidemiology is dedicated in loving memory to my father, John Coultas, who showed me his love for learning throughout his life and instilled that love in me. He weathered the loss of his hearing and then his sight to NAMD with courage and strength and a touch of humor. My father was the kindest man I have ever known, and I know his spirit has been and will continue to guide me through the remainder of my life.

As well, this work is dedicated to my mother, Odessa Coultas, who loves language and grammar and syntax and words and all things written. She taught me so many things about speaking and writing well…not the least of which was that if a phrase is awkward to read or speak…say it in a different way. That's a lesson I have applied to many aspects of my life…do not let your life be awkward (AWK).

Finally, I dedicate this work to my wife, Jill Coultas. Jill has been my greatest advocate for completing this process. When I was ready to quit, she stood beside me and helped me see that I could finish. When I felt hopeless, she gave me hope. She listened to my ramblings about what I was doing in my research project and always acted interested. Jill, I know the time I have spent on this degree has not been easy for you, and I am truly grateful to have had your loving support. Now, we get to play!!!

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Chapter 1: Introduction to the Study

Introduction

Age-related macular degeneration (AMD) is the leading causes of blindness in the United States in people 50 years of age and older (National Eye Institute [NEI], 2014). Further, the NEI (2014) reported the U.S. 2010 prevalence of AMD for all ages and all races/ethnicities to be 2.09% translating to 2,069,403 cases. Projections for increase in AMD are estimated to be 3,664,044 by 2030 and 5,442,265 by 2050 (NEI, 2014). The majority of patients with AMD of all types are Caucasian (prevalence 2.46%) and 86% of patients with AMD are female (NEI, 2014). The risk of developing AMD increases significantly with aging from 0.36% in the 50s to 11.73% in the 80s (NEI, 2014).

The burden of AMD encompasses not only vision loss, but also issues of depression, falls, and cost in time and finances for treatment (Dawson, Mallen, Gouldstone, Yarham, & Mansell, 2014; Silver, 2014; Wood et al., 2011). Treatment for neovascular AMD (NAMD) with current vascular endothelial growth factor inhibitors (anti-VEGF) was estimated to be approximately 1 to 2 billion dollars per year, which is approximately 10% of the total Medicare Part B drug apportionment budget per year (Silver, 2014). One objective of the U.S. health improvement and disease prevention program, Healthy People 2020, is to reduce the incidence of AMD by 10% from 15.5 per 1,000 individuals to 14.0 per 1,000 (Department of Health and Human Services [DHHS], 2015). More specifically, the goal is to reduce the impact of visual impairment and disability caused by AMD in the population in which AMD is most prevalent (i.e., individuals 45 years of age and older; DHHS, 2015). In support of this objective,

researchers in ophthalmology investigate disease mechanisms and risk factors in order to design and develop novel therapeutic interventions in this disease population (Avery et al., 2014; Hagstrom et al., 2013; Kovach, Schwartz, Flynn, & Scott, 2012).

Before being marketed, therapeutic interventions must undergo strict clinical research testing according to the U.S. Food, Drug, and Cosmetic Act (Federal Food, Drug, and Cosmetic Act, 1938). While clinical trials are performed to establish the safety and efficacy of new therapies, research at this level can only begin to describe how a therapeutic agent may perform in all populations in which the disease manifests (Drolet & Lorenzi, 2011). Consequently, researchers must continue to evaluate interventions in targeted populations to provide ongoing information pertinent to the use of new therapies. Elucidating information, such as ongoing evaluation of therapeutic agents, could lead to positive social change by ensuring developers of new drug products take into consideration how differences in population characteristics could impact clinical outcomes.

In Chapter 1, I will examine the background of AMD and provide information pertaining to how this study extended the knowledge base regarding use of aflibercept in NAMD by evaluating selected health characteristics, treatment regimens, and treatment outcomes of a novel therapeutic intervention in populations of NAMD patients. In Chapter 1, I will also elaborate the nature of the study performed, including the research questions and hypotheses addressed in the study. In the remainder of Chapter 1, I will address the assumptions, limitations, and significance of this research, and I will preview the remaining chapters.

Background of the Study

AMD is a progressive and chronic ophthalmic condition wherein changes to the macula of the eye manifest and have an impact on visual function (Lim, Mitchell, Seddon, Holz, & Wong, 2012). The various phases of AMD are characterized by increasingly severe anatomical manifestations ranging from (a) early AMD wherein fatty deposits (i.e., drusen) form that create little visual disturbance (NEI, 2015b); (b) intermediate AMD, in which drusen become larger and changes in the color and appearance of the retinal pigment epithelium (RPE) become evident (NEI, 2015b); and (c) the late phase, in which either increased atrophy in the RPE, choriocapillaris, and photoreceptors, known as geographic atrophy (GA), or the development of new blood vessels into the choroidal space of the macula, known as choroidal neovascularization (CNV), manifests (Lim et al., 2012). Risk factors noted to be associated with AMD, include increased age, cigarette smoking, cataract extraction, and family history of AMD (Chakravarthy et al., 2010). Lim et al. (2012) further noted hyperopic refraction and sunlight exposure as significant risk factors.

The early and intermediate forms of AMD have little impact on visual function; therefore, prophylaxis rather than treatment is the focus of these phases (Singer, Amir, Herro, Porbandarwalla, & Pollard, 2012). Once a patient's disease has progressed to NAMD, the standard of care treatment is injections with anti-VEGF drugs (e.g., ranibizumab, bevacizumab, or aflibercept) that are designed to inhibit proliferation of new blood vessels (Gower, 2012; Rakic et al., 2013). In general, anti-VEGF injections are intended to be given on a monthly basis for at least 3 months after which the schedule

of additional injections is based on visual function results achieved (Kovach et al., 2012; Rakic et al., 2013). Obviously, treatment outcomes vary; however, investigators have reported that patients may regain as much as 50% of the vision lost in the initial onslaught of NAMD, if the condition is caught early (Lim et al., 2012). The three anti-VEGF drugs currently approved for treatment of NAMD (i.e., Avastin, Macugen, and Eylea) are quite costly and make up a substantial portion of Medicare Part B payouts (Levinson, 2011). A fourth drug, bevacizumab, is often used "off label" to treat NAMD as it is significantly cheaper than the alternatives; however, the practice of "off label" treatment with bevacizumab has not been supported by the Office of Inspector General as its safety and efficacy have not been evaluated in the NAMD population (Levinson, 2011).

Through the process of deduction, I determined an appropriate approach for this study to be to evaluate the gap in the discipline that existed regarding specifically identified populations to determine whether selected health characteristics, treatment regimens, and treatment outcomes were significantly different between population centers. Furthermore, I determined the need to evaluate what associations existed between selected health characteristics, treatment regimens, and treatment outcomes in the selected population centers. The results of a study exploring the identified gap should lead to a better understanding of not only which patients should be treated and what the best treatment regimen was for the optimal outcome but also what impact treatment had on personal and public heath burden.

Problem Statement

While the safety and efficacy of aflibercept for the treatment of NAMD was demonstrated in clinical trial populations to the satisfaction of the Food and Drug Administration (FDA; Heier et al., 2012), the issue of ongoing evaluation of this treatment continues. As with prior anti-VEGF treatments, the matter was unclear whether all populations of NAMD respond in the same manner as was studied in the clinical trials used to support the marketing of aflibercept (Al-Qureshi & Shaikh, 2012; Chakravarthy et al., 2012; Rakic et al., 2013). NAMD treatment costs make up a substantial portion of the payouts made by Medicare; therefore, appropriate treatment of patients who will gain the most benefit is of utmost importance to both the personal and public financial burden created by NAMD (Schmier, Covert, & Lau, 2012; Silver, 2014; Stein, Hanrahan, Comer, & Sloan, 2013).

By evaluating selected health characteristics, aflibercept treatment regimens, and aflibercept treatment outcomes of NAMD patients in geographically disperse population centers, I aimed to add to the body of knowledge pertaining to how aflibercept was being used, should be used, and in what patient populations aflibercept was the most appropriate treatment. My goal was to address whether significant differences existed regarding selected health characteristics, treatment regimens, and treatment outcomes for patients with NAMD treated with aflibercept from three private, retinal practices in geographically disperse population centers in the United States. Potential associations between selected health characteristics, treatment regimens, and treatment outcomes were evaluated to address the gap in the literature related to aflibercept and how aflibercept

treatment for NAMD performs in populations with characteristics different from or treated in a manner that differed from the clinical trial populations.

Purpose of the Study

The primary purpose of this quantitative, secondary data analysis was to determine if differences exist between geographically disperse NAMD patient populations treated with aflibercept (grouping variable) with regard to selected health characteristics (independent variables). The secondary purpose was to evaluate associations that may be present between populations. This evaluation would aid in determining if and how selected health characteristics (independent variables) and aflibercept treatment regimens (independent variables) impacted treatment outcomes (dependent variables).

Research Questions and Hypotheses

I conducted evaluations using patients from three private, retinal practices in geographically disperse populations centers in the United States who had been diagnosed with NAMD and had been treated with aflibercept. The following research questions were addressed:

Research Question 1: Were there significant differences between selected health characteristics of populations of NAMD patients treated with aflibercept in three private, retinal practices in geographically disperse population centers in the United States? Health characteristic variables included: age, gender, number of ocular comorbidities, number of systemic comorbidities, number of days between NAMD diagnosis and first treatment with aflibercept in the study eye, baseline

best corrected visual acuity (BCVA), and baseline optical coherence tomography (OCT).

$H_0 1$: $\mu_1 = \mu_2$

There were no differences in proportions between selected health characteristics of populations of NAMD patients treated with aflibercept in three private, retinal practices in geographically disperse population centers in the United States.

$H_a 1$: $\mu_1 \neq \mu_2$

There were differences in proportions between selected health characteristics of populations of NAMD patients treated with aflibercept in three private, retinal practices in geographically disperse population centers in the United States.

Research Question 2: Were there significant differences between aflibercept treatment regimens used to treat NAMD patient in three private, retinal practices in geographically disperse population centers in the United States? Treatment regimen variables included: average number of aflibercept treatments injections received during 1 year from initial aflibercept treatment and average number of days between aflibercept treatments.

$H_0 2$: $\mu_1 = \mu_2$

There were no differences in the aflibercept treatment regimens used to treat populations of NAMD among patients at three private, retinal

practices in geographically disperse population centers in the United States.

H_a2: $\mu_1 \neq \mu_2$

There were differences in aflibercept treatment regimens used to treat populations of NAMD among patients at three private, retinal practices in geographically disperse population centers in the United States.

Research Question 3: Were there significant differences between aflibercept treatment outcomes reported for NAMD patients in the three private, retinal practices in geographically disperse population centers in the United States? Treatment outcome variables included: average change from baseline in BCVA and average change from baseline in OCT.

$H_0 3$: $\mu_1 = \mu_2$

There were no differences between aflibercept treatment outcomes reported for NAMD patients in three private, retinal practices in geographically disperse population centers in the United States.

H_a3: $\mu_1 \neq \mu_2$

There were differences between aflibercept treatment outcomes reported for NAMD patients in three private, retinal practices in geographically disperse population centers in the United States.

Research Question 4: What associations existed between selected health characteristics and aflibercept treatment regimens used to treat NAMD patients in three private, retinal practices in geographically disperse population centers in the United States?

$H_0$4: $ß_K$=0

There were no associations between selected health characteristics and aflibercept treatment regimens used to treat NAMD patients in three private, retinal practices in geographically disperse population centers in the United States.

H_a4: $ß_K \neq 0$

There were associations between selected health characteristics and aflibercept treatment regimens used to treat NAMD patients in three private, retinal practices in geographically disperse population centers in the United States.

Research Question 5: What associations existed between selected health characteristics and aflibercept treatment outcomes reported for NAMD patients in three private, retinal practices in geographically disperse population centers in the United States?

$H_0$5: $ß_K$=0

There were no associations between selected health characteristics and aflibercept treatment outcomes reported for NAMD patients in three

private, retinal practices in geographically disperse population centers in the United States.

H_a5: $ß_K \neq 0$

There were associations between selected health characteristics and aflibercept treatment outcomes reported for NAMD patients in three private, retinal practices in geographically disperse population centers in the United States.

Research Question 6: What association existed between aflibercept treatment regimens used and aflibercept treatment outcomes reported for NAMD patients in three private, retinal practices in geographically disperse population centers in the United States?

$H_0 6$: $ß_K = 0$

There were no associations between aflibercept treatment regimens used and aflibercept treatment outcomes reported for NAMD patients in three private, retinal practices in geographically disperse population centers in the United States.

$H_a 6$: $ß_K \neq 0$

There were associations between aflibercept treatment regimens used and aflibercept treatment outcomes reported for NAMD patients in three private, retinal practices in geographically disperse population centers in the United States.

Theoretical Framework

May, Montori, and Mair (2009) described the theoretical framework of burden of treatment as based on recognition that chronic disease was increasingly burdensome for patients, not just because of the health issues related to the disease, but also due to the treatments prescribed for chronic diseases. May et al. discussed the impact complicated treatments may have on patients due to nonadherence as causing additional health complications along with financial and health burdens associated with changes in health status. These researchers called for minimally disruptive treatments and treatment regimens that could be managed by patients with chronic conditions. May et al. (2014) further elaborated on the burden of treatment theory as being the predominant manner by which to describe a patient's "struggles to endure the symptoms of illness and to look after themselves and others" (p. 1).

As the life span of humans has increased, the face of illness has changed from acute, infectious disease to chronic, long-term, debilitating conditions that pose not only a burden based on the need to endure the symptoms but also based on the ongoing need to address treatment of the condition (May et al., 2014). The treatment paradigm expands further when one chronic, long-term disease leads to additional comorbidities that each have specialized healthcare providers, treatments, and treatment schedules and results in conditions that are no longer cured, as in the case of infections, but rather must be managed for the remainder of the patient's life span (May et al., 2014). Previously, illness and its cure were predominantly a burden under the purview of the healthcare provider (May et al., 2014). With the change to long-term management, the burden of

illness and treatment have been shifted by healthcare providers to the patient, who is accountable for managing time, treatments, compliance, and self-care along with the other activities of normal life (May et al., 2014). In order to be managed, the burden must be distributed within a patient's network of friends, family, and caregivers. These issues, then, become the burden not just of the illness but also of the treatment for the illness (May et al., 2014).

NAMD meets the criteria of being a long-term, debilitating disease that requires management by a specialized healthcare provider; specialized treatments that forestall or prevent progression; and the use of a patient's network of friends, family, and caregivers in order to manage not just the burden of illness (e.g., assistance with activities of daily living for prevention of comorbidities that impact quality of life [QOL]) but also the burden of treatment (e.g., multiple visits to physicians to receive complicated treatments) (May et al., 2014). By evaluating specific populations of NAMD patients treated with aflibercept, my purpose for this study was to assess whether selected health characteristics, treatment regimens used, and treatment outcomes differed from what had been noted in prior literature. Further, I evaluated the presence or absence of associations between health outcomes, treatment regimens, and treatment outcomes as a secondary analysis to determine if the burden of treatment was being assigned to appropriate populations.

Nature of the Study

This study was a retrospective, contrasted group, cross-sectional, secondary analysis of data obtained from three geographically disperse NAMD patient populations

wherein the patients had been treated with aflibercept. I evaluated specific selected health characteristics, treatment regimens, and treatment outcomes across the three populations to determine whether differences and associations existed. Advantages of using secondary data analysis were that the study was relatively economical and made use of data that was available but had not been previously analyzed in the manner proposed (Green & Salkind, 2010). Disadvantages of the secondary analysis design included that the fit of the data available for the questions explored were not always appropriate, and the quality of the data was not as accurate as data collected as primary data (Green & Salkind, 2010). These data were analyzed by ANOVA, Welch ANOVA, χ^2 analysis, point-biserial analysis, or Spearman's rank-order correlation of the various selected health characteristics, treatment regimens, and treatment outcomes.

Definitions

Age-related macular degeneration (AMD): Progressive and chronic ophthalmic condition wherein changes to the macula of the eye manifest and have an impact on visual function (NEI, 2015b)

Early Treatment Diabetic Retinopathy Study (ETDRS) charts: Visual acuity testing charts utilized in clinical trial applications (Kaiser, 2009)

Neovascular AMD (NAMD): The later stage of AMD in which new, leaky blood vessels grow into the macular region of the eye and cause catastrophic changes in the macular tissues resulting in central visual changes that may become permanent blindness if not treated (NEI, 2015b)

Logarithm of the mean angle of resolution (logMAR): the notation that is used to

indicate the visual acuity achieved when using ETDRS charts (Kaiser, 2009)

Macula: A small area near the center of the retina, the health of which is necessary for maintaining sharp, central vision that allows individuals to see directly ahead (NEI, 2015b)

Oculus Dexter (OD): Right eye ("Oculus dexter," 2009)

Oculus Sinister (OS): Left eye ("Oculus sinister," 2009)

Oculus Uterque (OU): Both eyes ("Oculus uterque," 2009)

Optical Coherence Tomography (OCT): An imaging technique that uses light to provide cross-sectional images of tissues (Fujimoto, Pitris, Boppart, & Brezinski, 2000). It is used in ophthalmic indications to visualize the retinal tissue.

Visual Acuity (VA): The measure of the clarity of an individual's vision. This measurement specifically deals with the ability of the visual system to resolve spatial details (Committee on Disability Determination for Individuals with Visual Impairments, National Research Council, Division of Behavioral and Social Sciences and Education, & Board on Behavioral, Cognitive, and Sensory Sciences, 2002)

Assumptions

My primary assumption for this study was that the data to be gathered at the various geographic locations were assumed to be characteristic of the general population of patients being treated with aflibercept; therefore, these data could be used to describe what the general population characteristics were, what treatment regimens were being used, and what treatment outcomes were experienced in these populations. I also assumed that all patients who had NAMD in these retinal practices had been

appropriately coded per International Classification of Disease, Version 9 (ICD-9) of 362.52 (exudative senile macular degeneration of retina). Finally, I assumed that those patients with the ICD-9 code of 362.52, after the approval of aflibercept in 2011, were given the opportunity to be treated with aflibercept.

Scope and Delimitations

I carried out this study in a specific subpopulation of the AMD general population, NAMD. The rationale for culling the NAMD subgroup from within the larger AMD general population was that more treatment options were available in the selected population than in the non-NAMD populations (National Institutes of Health [NIH], 2014). Also, the NAMD population was more easily identified as patients were actively seeking treatment from medical professionals due to noticeable loss of vision (Singer et al., 2012). While it was important to understand the characteristics of NAMD populations and the reality of how patients were identified and treated for NAMD, evaluating NAMD populations may advance the larger question of generalizability and applicability of clinical research versus general patient populations in other therapeutic areas.

Limitations

General NAMD population characteristics may be able to be identified easily through public databases; however, treatments and treatment outcomes are not typically provided in public databases. As such, it was necessary to identify and gain the consent of retina specialists in various parts of the country to capture information to evaluate demographic and selected health characteristics as well as treatment regimens and

treatment outcomes for NAMD patients treated with aflibercept. Gaining access to electronic medical records (EMR) data that were consistent across the three retinal centers limited what could be analyzed in this study. Consistency in data capture between retinal centers was a key element to the design of the study as this was the method of establishing the populations as single entities and as a collective. Without consistency, my ability to determine the impact of the independent variables on the dependent variable was limited. To avoid issues of consistency, I evaluated EMR systems at retinal practices to determine whether all the proposed variables were present and what format was used to capture findings. A final limitation was that the potential associations between selected health characteristics, treatment regimens, and treatment outcomes may have been subtle enough so as not to be detected in this study.

Significance of the Study

By using secondary analysis of EMR data in a variety of NAMD populations treated with aflibercept, I was able to perform evaluations to assist in understanding population differences. Researchers have speculated about different populations of NAMD and what the outcome of treatment with anti-VEGF medications might be (Heier, 2013). The results of this study could add to the body of knowledge pertaining to how aflibercept was being used in retinal practices treating NAMD patients and elucidate the impact differences in population outcomes have on personal and public health. Since NAMD treatment makes up a significant portion of the public financial burden in the form of Medicare payouts, determining if patients being treated were those that received

the greatest benefit from treatment was an important question to answer (Schmier et al., 2012; Silver, 2014; Stein et al., 2013).

Significance to Practice

Significant differences in health characteristics, treatment regimens, and treatment outcomes that could be observed between the NAMD populations would aid in defining the importance this has on public health and clinical research. If this findings of this study were to show that there were differences existed between the populations identified, research into the development of different types of sampling methods, research study designs, or methods of translation from clinical research to clinical practice would be beneficial (Kessler & Glasgow, 2011; Lenfant, 2003; Sung et al., 2003). The social benefit of creating better testing methods could result in moving clinical research in a direction that is more beneficial to a greater portion of the disease population, thereby creating better outcomes and stronger evidence-based information on which the public can rely (Kessler & Glasgow, 2011; Lenfant, 2003). Creating more interest in clinical research could also increase confidence that the process of clinical research, as a valuable part of product development and translation of study findings from clinical research to clinical practice, would be more valuable (Drolet & Lorenzi, 2011; Kessler & Glasgow, 2011; Lenfant, 2003).

Significance to Social Change

The positive social change implication of this study was to gain a better understanding of how treatment outcomes were affected by selected health characteristics and treatment regimens in NAMD. Having a better understanding could lead to more

appropriate information about treatment options for AMD and NAMD patients and could inform the design of AMD and NAMD clinical studies to represent more accurately the target population in which the therapeutic intervention was to be used. Further, public health initiatives could be designed to identify at-risk AMD and NAMD populations to provide education germane to the need for early diagnosis and treatment. The impact on the personal, familial, and societal burdens related to blindness could be ameliorated by use of summary information provided to public health organizations, medical professionals, and patients.

Summary

NAMD is a significant a public health issue since it has a substantial economic and health impact both at the individual and population levels. The aim of this study was to assess selected health characteristics, treatment regimens, and treatment outcomes in NAMD patients treated with aflibercept in geographically disperse retinal practices in the United States to determine whether there were differences in the populations, and secondarily, to evaluate what associations existed between the selected variables. Ascertaining whether differences existed between populations of NAMD patients was clearly of importance in making the appropriate translation of findings from the clinical trial phase into the clinical treatment phase. Treating appropriate patients with appropriate interventions could lessen the burden of illness on both patient and the public. In Chapter 1, I provided a general overview of the study, including the background of the study, the problem statement, the purpose of the study and the associated research questions and hypotheses. The theoretical framework of burden of treatment theory was

introduced along with how this theory related to the research problem. Furthermore, I reviewed the nature of the study, definitions, assumptions, scope and delimitations, limitations, and significance of the study. In Chapter 2, I will review research relevant to NAMD; general population characteristics, including risk factors, comorbidities, and genetic profiles; and current therapeutic intervention with anti-VEGF treatments.

Chapter 2: Literature Review

Introduction

Aflibercept treatment for NAMD has been clinically tested and approved by the FDA (2011); however, the selected health characteristics, treatment regimens, and treatment outcomes experienced by general patient populations may or may not differ from each other and the way the clinical research studies were conducted. In this study, I evaluated three geographically disperse population centers to determine whether there were differences between NAMD patients treated with aflibercept, and secondarily, whether associations existed between selected health characteristics, treatment regimens, and treatment outcomes. In this chapter, a description of the methods I used to identify appropriate literature for this chapter will follow the introduction. Moreover, I will provide a review of literature identified to support the theoretical framework of burden of treatment. The following section will be a description of the risk factors associated with NAMD, the prevalent types of treatment for NAMD, and associated treatment outcomes. Additionally, I will present the evaluation of interventions used to treat NAMD including treatment regimens, especially as compared to those used in clinical trials. I will also discuss treatment outcomes to elucidate the need to determine how selected health characteristics and treatment regimens may impact outcomes. Finally, a summary of the literature review will conclude the chapter.

Literature Search Strategy

This literature review was based on my search for relevant literature using Google and Google Scholar search engines as well as direct literature searches using Walden

University Library's Thoreau search of all applicable databases. The search was focused on peer-reviewed, full text articles that were published between the years 2011 through 2015. In some cases, it was necessary for me to purchase a full text article when I determined that the information the article contained would significantly contribute to the literature review. Websites for the following associations or agencies were also used in the literature search: Age-Related Eye Disease Study (AREDS), American Academy of Ophthalmology, Association for Research in Vision and Ophthalmology, American Foundation for the Blind, U.S. Census Bureau, U.S. Centers for Disease Control and Prevention, FDA, National Center for Advancing Translational Science, NEI, and NIH. Keywords used alone or in combination included: *age-related eye disease study, age-related macular degeneration, AMD, anti-VEGF, AREDS, behavior, burden, comorbidities, diet, environment, ethics, ethnicity, genetics, neovascular, race, risk factor, side effect, translation, treatment,* and *vascular endothelial growth factor*. These searches yielded a wide range of articles that proved to be applicable to this study for burden of treatment, AMD, NAMD, treatments, and treatment outcomes. Since the burden of treatment theory was a relatively new concept, fewer articles that pertained to this subject were available. I used a total of nine articles that either discussed the burden of treatment or evaluated burden of treatment in a chronic condition or began the discussion of developing an instrument to measure the burden of treatment in patient populations. I located approximately 43 appropriate aflibercept treatment covering issues including initial results of clinical trials in treatment-naïve subjects, use of aflibercept after treatment with other anti-VEGF treatments, use of aflibercept in polyploidal

choroidal neovascular AMD, and use of aflibercept in treatment resistant patients. Approximately 480 articles were identified that pertained to some aspect of AMD, including phases, risks, burden of disease, epidemiology, treatments, and outcomes. I used this information to build a literature-based framework for the study investigating different population centers to determine whether there were differences in the selected health characteristics, aflibercept treatment regimens, and aflibercept treatment outcomes.

Theoretical Framework

The burden of treatment theory aims to facilitate a new understanding of the interaction between capacity for action and the work that healthcare systems pass on to a patient and his or her relational networks" (May et al., 2014, p. 2). May, Montori et al. (2009) began the discussion of burden of treatment due to the increasing disease burden experienced by patients with chronic diseases, which have displaced acute, infectious diseases as the main cause of ill health. Tran et al. (2012) noted that around 45% of the general population currently live with at least one chronic disease. This increases to approximately 88% as individuals reach 65 or older (Tran et al., 2012). May, Montori et al. also explained that the burden of disease theory was not only about the disease. Bearing the burden of a disease also means bearing the burden of its treatments (May, Montori et al., 2009). A patient is no longer a bundle of symptoms to be cured by acute treatment, but rather patients must engage in a multitude of treatment and service interactions that require management (May, Montori et al., 2009). This situation is aggravated as patients acquire multiple comorbidities having competing treatments, services, outcomes, and impact on each other (May, Montori, et al., 2009). The

imperative of the theory was to identify and address issues "to help alleviate treatment burden and tailor treatment regimens to the realities of people's daily lives" (Sav et al., 2013, p. 312).

May et al. (2014) described the process by which burden of treatment theory was derived. The initial focus of the researchers was on normalization process theory in which the ways an individual incorporates new ideas, methods, or ways of thinking or working into the fabric of his or her life (May, Mair et al., 2009). Normalization process theory was also the foundation of minimally disruptive medicine as described in May, Montori et al. (2009). As normalization theory applies to chronic disease, May et al. (2014) explained that chronic disease treatment management must become embedded into a patient's normal daily activities for the patient to manage the lifetime trajectory of his or her illness. Previously, the management of treatment and services related to illness were the purview of the physician and his or her staff (May et al., 2014). The work of managing chronic disease has now been transferred to the patient, who may have little understanding of the complexities of managing single chronic illness issues let alone those associated with multiple multimorbid conditions (May et al., 2014).

The cumulative complexity model, as elaborated by Shippee, Shah, May, Mair, and Montori (2012), supported the issue of the complexity faced by patients with chronic multiple multimorbid conditions and was the second conceptual model that was formative in the development of burden of treatment theory. The cumulative complexity model deals specifically with how the work of managing healthcare has been transferred to patients and how this management was best structured to facilitate his or her meeting

the demands of additional healthcare work (Shippee et al., 2012). Indeed, as the need for treatment in multiple multimorbid conditions accumulates, the work that must be managed to accomplish all that is necessary with regard to treatment, self-monitoring, attention, and coordination can become overwhelming to a patient resulting in confusion, nonadherence, poor health outcomes, and inappropriate resource utilization (May et al., 2014). Finally, May et al. (2014) described concepts pertaining to "demand, self-care, and social networks" (p. 282) as espoused by Blickem et al. (2013), Pickard and Rogers (2012), and Vassilev et al. (2013), using the concepts to elaborate how the burden of treatment was not a function of just the patient but of the patient's familial and social network and his or her community. In most cases, patients must find a support network to help with the demand of the work of their disease and self-care.

Some patients endeavor to manage all of the treatments related to chronic disease conditions, while other patients may not choose to maintain treatment regimens (May et al., 2014). Although the best course for any patient would seem to be to follow treatment regimens prescribed, patients have a variety of meaningful reasons for not doing so (May et al., 2014). Financial issues play a major role in decisions about chronic care; a patient may simply not be able to afford the cost of the treatments necessary to support his or her illness (May et al., 2014). Other reasons noted by May et al. (2009) included an inability to manage complicated and disruptive dosing schedules. In some cases, patients may have such a wide variety of treatments and dosing schedules that he or she simply cannot understand what medications are taken at any given time (May et al., 2014). Alternatively, time may be a driving factor in determining whether to adhere to service

and treatment schedules (May et al., 2014). Patients may not be able to take the time from other life activities (e.g., work, family) in order to attend doctor or treatment visits (May et al., 2014). Whatever the reason, choosing this path may lead to further decline of health and increased need for even more costly treatments, creating a substantial personal and public health burden by "wast[ing] of increasingly scarce healthcare resources" (Mair & May, 2014, p. 1).

Eton et al. (2012) performed a qualitative study to begin the process of building a patient-reported outcomes instrument to measure burden of treatment. Patients identified for participation in the study were those who were medical outpatients at Mayo Clinic in Rochester, MN and had agreed to participate in a medication management program (Eton et al., 2012). All subjects had comorbidities that required significant management of treatment, including ophthalmic conditions such as glaucoma and cataracts (Eton et al., 2012). From this study, the researchers identified major themes and subthemes that were used to inform the elaboration of burden of treatment theory and to develop a conceptual framework for a pilot questionnaire pertinent to burden of treatment theory patient-reported outcomes (Eton et al., 2012).

Tran et al. (2012) developed the first validated questionnaire that addressed the burden of treatment for chronic illness across a multitude of chronic conditions and treatment modalities. In this study, 502 subjects were included in validation of the questionnaire that had been derived from literature review as well as from interviews (Tran et al., 2012). The instrument took into account not only treatments for chronic diseases but also the ancillary issues of disease surveillance, self-care, and lifestyle

changes associated with increases in the burdens of disease and treatment (Tran et al., 2012). The findings of the study provided further credence to burden of treatment theory as a reliable conceptual framework for addressing chronic and debilitating diseases experienced in aging populations (Tran et al., 2012).

Eton et al. (2013) looked at patient-reported measures of burden of treatment in the three chronic diseases of diabetes, chronic kidney disease, and heart failure as a part of their systematic review. Through the review of the available literature, Eton et al. identified 57 patient-reported measures in 98 articles relevant to the evaluation of treatment burden. The majority of the articles were identified from the diabetes population, but measures were also identified in kidney disease and heart failure articles that supported the need to evaluate other chronic diseases (Eton et al., 2013). This effort was undertaken to determine how patient reported measures of treatment burden were derived in disease categories and how best to incorporate prior work in the area into a more reliable and comprehensive methodology for assessing the burden of treatment across diseases (Eton et al., 2013). The work by Eton et al. expanded on the prior qualitative analysis of treatment burden and was to be used in the further refinement of the theoretical framework of burden of treatment theory.

Ridgeway et al. (2014) performed a qualitative study to evaluate factors that may impact the burden of treatment for chronic conditions of diabetes, heart failure, and renal failure. The aim of this qualitative study was to identify ways in which the burden of treatment can be decreased for patients with multiple multimorbid conditions. Interviews and focus groups were conducted that led to identifying major areas of burden and ways

in which the study subjects were able to lessen their impact (Ridgeway et al., 2014). Five major areas were identified as being associated with perception not only of treatment burden but also successful management of that burden (Ridgeway et al., 2014). This research clearly identified management strategies that increase the perception of control over the disease and the corresponding treatment burden allowed patients to cope more effectively and adhere to complicated and time-consuming treatment and service regimens (Ridgeway et al., 2014).

May, Montori et al. (2009) and May et al. (2014) clearly described the criteria that set apart diseases as burdensome. NAMD meets the criteria because it is a long-term, debilitating disease and requires therapeutic management by a specialized healthcare provider. Additionally, NAMD requires specialized treatments to forestall or prevent progression. The burden of NAMD not only falls on the patient but also on the patient's network of friends, family, and caregivers in order to manage not just the burden of illness (e.g., assistance with activities of daily living for prevention of comorbidities that impact quality of life [QOL]) but also the burden of treatment (e.g., multiple visits to physicians to receive complicated treatments; May et al., 2014). With this study, my goal was to evaluate specific populations of NAMD patients treated with aflibercept to assess whether health characteristic, treatment regimens used, and treatment outcomes differ from what has been noted in prior literature. Additionally, I wanted to evaluate the presence or absence of associations between health outcomes, treatment regimens, and treatment outcomes to determine if the burden of treatment was being assigned to appropriate populations.

Age-Related Macular Degeneration

AMD is a progressive and chronic ophthalmic condition wherein changes to the macula of the eye manifest and have an impact on visual function (Lim et al., 2012). The macula is a small area near the center of the retina, and its health is necessary for maintaining sharp, central vision that allows individuals to see directly ahead (NEI, 2015b). The early phase of AMD occurs when fatty deposits, drusen, collect in the macula and present with a characteristically dry appearance (NEI, 2015b). Individuals with this form of AMD do not typically report any significant vision loss, and the condition is referred to as dry or atrophic AMD (NEI, 2015b). Intermediate AMD occurs when the RPE displays changes that appear to be a disruption in the color or general appearance of the RPE and/or drusen become larger creating more prominent changes in visual function (NEI, 2015b). The late phase of AMD is characterized by either increased atrophy in the RPE, choriocapillaris, and photoreceptors, known as GA, or the development of new blood vessels into the choroidal space of the macula, known as CNV (Lim et al., 2012). The physical changes in ocular vasculature seen in this phase are not healthy structures and tend to leak blood, lipids, and other fluids into the surrounding macular tissue causing a fibrous scar buildup (Lim et al., 2012). The late phase is referred to as wet, exudative, or NAMD and is often related to increased levels of VEGF-A secretion (NEI, 2015b). VEGF-A is "a diffusible cytokine that plays a key role in the formation of CNV lesions through promotion of angiogenesis and vascular permeability" (Rakic et al., 2013, p. 1850). NAMD and GA represent the foremost causes of blindness in the world with an estimated global prevalence of 6.8% for early phase AMD and 1.5%

for late phase AMD (Dawson et al., 2014; Lim et al., 2012; Rakic et al., 2013; Yuzawa, Fujita, Tanaka, & Wang, 2013).

Based on a recent meta-analysis, Chakravarthy et al. (2010) identified risk factors with a consistent and strongly positive association with AMD that included increased age, cigarette smoking, cataract extraction, and family history of AMD. Other risk factors with a consistent and moderately positive association included increased body mass index, cardiovascular disease history, increased levels of plasma fibrinogen, and hypertension (Chakravarthy et al., 2010). Lim et al. (2012) further noted hyperopic refraction and sunlight exposure as significant risk factors.

An individual with NAMD or GA may not have been diagnosed with the early forms of the disease previously, but may present to his or her physician with complaints of straight lines becoming wavy or blank/hazy spots in the center of the visual field (i.e., metamorphosia) or the inability to see faces of people (Yuzawa et al., 2013). Once identified by these complaints, an ophthalmologist will perform several ophthalmic examinations to confirm the presence and extent of NAMD. These evaluations include performing (a) BCVA testing, (b) dilated ophthalmoscopy, (c) Amsler grid testing, (d) fluorescein angiography (FA), and (e) OCT (NEI, 2015b).

The manifestation of NAMD is not only loss of VA in the central field of vision; there are concurrent impairments of color vision and contrast sensitivity (Yuzawa et al., 2013). Patients with NAMD can often not distinguish colors clearly making it difficult to read colored text, and the ability see the contrasts between light and dark may be significantly impaired (Yuzawa et al., 2013). While peripheral vision is not impacted by

NAMD, the loss of central vision is significantly disruptive to a patient's activities of daily living including recognizing faces, driving, and reading (Yuzawa et al., 2013).

Currently no treatments for the early or intermediate, dry forms of AMD exist, rather intervention is focused on preventing progression to NAMD (Singer et al., 2012). Watchful waiting, an understanding of the changes that might occur, and a plan of action for changing vision along with nutritional support are the prophylactic means by which individuals manage the earlier phases of AMD. As reported by the NEI (2015b), nutritional support includes Vitamin C, Vitamin E, zinc (as zinc oxide), copper (as cupric oxide), and beta-carotene or lutein and zeaxanthin. The standard of care treatment used for advanced NAMD are injections with anti-VEGF drugs (e.g., ranibizumab, bevacizumab, aflibercept) that are recombinant, humanized monoclonal antibody fragments. These fragments neutralize active forms of VEGF-A, thereby inhibiting proliferation of new blood vessels (Gower, 2012; Rakic et al., 2013). Anti-VEGF injections are approved to be given intravitreally on a monthly basis for at least three months (Kovach et al., 2012; Rakic et al., 2013). After that time, patients may receive additional injections as determined by the ophthalmologist (Kovach et al., 2012). Outcomes vary with anti-VEGF treatment; however, regaining up to 50% of the vision lost in the initial onslaught of neovascularization and leakage has been reported when damage is caught early (Lim et al., 2012).

Risk Factors Associated with NAMD

The risk factors most commonly associated with NAMD as have been elaborated by The Foundation of the American Academy of Ophthalmology are age, genetic

predisposition, environment, and behavior (The Foundation of the American Academy of Ophthalmology, 2015). As this is the case, it is important to explore the known risk factors to determine whether they are present in the identified patient populations to be evaluated in this study. The risk factors section includes a description of racial/ethnic factors, and comorbidities, genetic factors, and behavioral factors.

Racial/Ethnic Factors

NAMD has been characterized as a chronic condition largely affecting Caucasian females (Coleman, Chan, Ferris III, & Chew, 2008). With the advent of better and more abundant use of technology, such as FA, fundus photography, indocyanine green angiography (ICGA), and OCT, an increase interest in determining whether this profile still holds true has been generated (Coscas et al., 2014). Of special interest is whether other types of populations, especially Asian populations, are similar to or different from Caucasian populations with regard to risk and prevalence of AMD (Coscas et al., 2014; Nakata et al., 2013; Wong et al., 2014). In a study performed by Nakata et al. (2013), the Nagahama study, which was a community based, cross-sectional, prospective cohort study, the investigators evaluated the prevalence and characteristics Japanese patients with early and late AMD. The study included 5,595 Japanese individuals aged greater than or equal to 50 year of age with gradable AMD recruited from 2008 to 2010 (Nakata et al., 2013). Similar rates of early AMD were observed in this Japanese population as compared to Caucasian populations (Nakata et al., 2013). As well, similar rates of late AMD were observed in this Japanese population as compared Caucasian populations in individuals less than 70 years of age (Nakata et al., 2013). At age 70 and higher, the rate

of AMD decreased in this Japanese population and was considered to be significantly lower than in Caucasian populations (Nakata et al., 2013). Findings of differences in early or late AMD between males and females were not apparent (Nakata et al., 2013).

In a later retrospective review performed by Coscas et al. (2014), the authors evaluated both technology used to assess patients for NAMD and prevalence of subtypes of NAMD (i.e., AMD with Type 1 CNV, AMD with Type 1 and 2 CNV, AMD with Type 2 CNV, chorioretinal anastomosis, polyploidal choroidal vasculopathy [PCV] without CNV, and PCV with Type 1 or 2 CNV) in 94 French and 99 Japanese patients with presumed exudative AMD. PCV was found to be at a higher rate in Japanese patients, and Type 1 CNV was found to be at a higher rate in French patients (Coscas et al., 2014). Similarities were noted in Type 2 CNV and chorioretinal anastomosis rates between the two populations (Coscas et al., 2014).

Wong et al. (2014) integrated a large number of population-based AMD studies that previously suggested different disease prevalence based on racial or ethnic parameters. By identifying qualified population-based studies using a systematic literature review, these investigators analyzed "129,664 individuals (aged 30-97), with 12,727 cases from 39 studies" (Wong et al., 2014, p. e106). This large review indicated that the global burden of all types of AMD is 8.7% (Wong et al., 2014). The projection for the number of cases in 2020 was estimated at approximately 196 million and by 2040, the estimate was approximately 288 million (Wong et al., 2014). The prevalence of early onset AMD was shown to be higher in studies based on European populations than in Asian populations; however, late stage AMD prevalence comparison between these two

groups was similar (Wong et al., 2014). The findings from the studies analyzed, however, did not consistently show whether the diagnoses included PCV, which is more prevalent in Asian populations and may respond differently to treatment (Wong et al., 2014). Females of any race were not found to have a strong association with prevalence of AMD, and strong evidence refuted previously reported findings that male, Asians who smoked were at higher risk than other populations (Wong et al., 2014). Finally, Wong et al. suggested that Asian countries will see the highest increase in all forms of AMD in the future despite having a low reported prevalence for the period investigated.

The findings from these studies are significant for several reasons. Future research should include a significant contribution of patients from Asian populations to represent all aspects of the NAMD disease process (Coscas et al., 2014; Nakata et al., 2013; Wong et al., 2014). Physicians should be aware that the prevalence of AMD in Asian populations approaches that of Caucasian populations in order to provide proper diagnosis and treatment (Coscas et al., 2014; Nakata et al., 2013; Wong et al., 2014). Differentiating subtypes through the use of available technology could lead to a difference in treatment (Coscas et al., 2014; Nakata et al., 2013; Wong et al., 2014).

Comorbidities

Due to the specialty area that ophthalmology has become, Cheung and Wong (2014) noted that AMD has been thought of as a localized disease with an association with certain risk factors (e.g., smoking, prior cataract surgery, family history). AMD has not been assessed in relation to comorbidities of the whole individual (e.g., hypertension, dyslipidemia, cardiovascular disease; Cheung & Wong, 2014). Based on information

from Chou et al. (2013) and Cheung and Wong, assessing the whole patient in relation to comorbidities and association with the risk of AMD is a reasonable approach.

Chou et al. (2013) performed an analysis on 2012 National Health and Nutrition Examination Survey (NHANES) data to determine the source of age-related conditions associated with visual impairment among U.S. adults. The analysis included 5,222 individual included in the 2012 NHANES who were 40 years of age or older (Chou et al., 2013). From this analysis, the investigators were able to determine the prevalence of visual impairment was 7.5% and prevalence of visual impairment not due to refractive error was 2.5% (Chou et al., 2013). These findings suggest an estimated population of 9 million adults in the United States over the age of 40 have some visual impairment (Chou et al., 2013). While a significant portion of the study population whose visual impairment could be corrected simply by providing proper refractive correction, of greatest concern was the 25% of visual impairment attributed to factors other than refractive error (Chou et al., 2013). Chou et al. reported AMD to be the most commonly associated with visual impairment not related to refractive error.

Cheung and Wong (2014) performed an extensive literature review of articles published from January 1, 2012 through December 31, 2013, examining various systemic risk factors to determine which were most highly associated with increased risk of AMD. An interesting aspect of the evaluation was that the assessment was originally concerned with determining what systemic conditions increased the risk of AMD; however, a corollary that AMD may be an indicator of potential manifestation of systemic disease was revealed during this investigation (Cheung & Wong, 2014). The systemic diseases

or conditions found to be most highly associated with increased risk of AMD were cerebrovascular disease and coronary heart disease (Cheung & Wong, 2014). Hypertension and dyslipidemia were shown to have a moderate association with increased risk of AMD but the strength and consistency of the association was not as apparent from the review of literature (Cheung & Wong, 2014). Evaluation of the potentially correlated systemic risk factors was suggested to be of importance in identifying patients at risk for developing NAMD (Cheung & Wong, 2014).

Systemic therapies were also evaluated by Cheung and Wong (2014). Antioxidant supplements such as those found in the AREDS formulations were found to result in a reduction in intermediate AMD to advanced AMD by approximately 25% over approximately 6 years (Cheung & Wong, 2014). Aspirin used prophylactically for cardiovascular disease may actually increase the risk of AMD although the mechanism of the potential increase was not clearly understood (Cheung & Wong, 2014). Use of statins has not been shown to reduce the risk of or progression of AMD consistently in the literature (Cheung & Wong, 2014).

These investigations lend further credence for the need to ascertain whether NAMD population treated with anti-VEGF differ with regard to comorbidities and whether an association exists with a difference in treatment outcome. While aging has been clearly associated with AMD, subjects with prevalent comorbidities associated with immune response would typically be excluded from clinical trials to minimize the issue of confounding factors. While it may not be acceptable to include subjects with

significant systemic comorbidities in early clinical trials, later phase clinical trials should examine the impact of intervention when significant systemic comorbidities are present.

Genetics

Inroads into the understanding of genetic factors associated with NAMD were slow moving until 2005 with the identification of *complement factor H* (CFH) that was determined to increase the risk of NAMD significantly (Fritsche et al., 2014). From this beginning, an explosion of research led to the identification of at least 19 alleles associated with genetic predisposition for NAMD (Fritsche et al., 2014). With these findings come the prospect of advances not only in understanding of AMD but also of more and better treatments for all phases of the disease (Fritsche et al., 2014).

Hagstrom et al. (2013) evaluated 834 (73%) of the subjects who participated in the Comparison of AMD Treatment Trial (CATT) at 43 of the CATT clinical sites. These investigators enrolled the identified subjects in a clinical trial to determine whether subjects of differing genotypes had different responses to the anti-VEGF therapies, ranibizumab and bevacizumab. Each of the subjects "was genotyped for [single nucleotide polymorphisms] rs1061170 (CFH), rs10490924 (ARMS2), rs11200638 (HTRA1), and rs2230199 (C3)" (Hagstrom et al., 2013, p. e43). These alleles have been noted to have potential impact on the development of AMD; however, no statistically significant differences were noted in any of the clinical assessments measured based on the genotypes studied, including in the instance of multiple alleles that were present in any individual subject (Hagstrom et al., 2013).

Nussenblatt et al. (2014) provided investigation into the genetic components of AMD and reported, "recent genetic meta-analysis has confirmed 19 loci…that account for up to 50% of the heritability of AMD susceptibility" (p. 6). This finding along with environmental factors (e.g., smoking, diet, and weight) "play a crucial role in AMD etiology" (Nussenblatt et al., 2014, p. 6). Further, Nussenblatt et al. noted that both genetic and environmental issues need to be considered in the context of aging, as aging remains the primary risk factor for AMD. An aging immune system, or immunosenescence, accounts for an increased production of inflammatory cells and a decreased ability to clear these types of cells (Nussenblatt et al., 2014). As such, the immune system becomes overloaded and cannot maintain a homeostatic state within the body, or specifically the eye (Nussenblatt et al., 2014). The research by Nussenblatt et al. further supports the assertion that AMD is not an isolated disease process but rather is a localized manifestation of the immunosenescence of the aging body.

Cheung and Wong (2014) also noted that genetic markers and pathogenesis support the hypothesis that AMD is more than a localized condition. Inflammation may play an important role in the pathogenesis of AMD (Cheung & Wong, 2014). CFH and age-related maculopathy susceptibility 2/HtrA serine peptidase 1 genes have been noted to be associated with AMD. Cheung and Wong concluded, "there is accumulating evidence to support the concept that AMD is a localized ocular manifestation of broader systemic processes and is closely associated with a range of systemic diseases" (p. 148).

As a result of the aforementioned studies, the importance of gathering and analyzing genotype information in clinical practice and clinical research was established.

Collecting genotype information for NAMD patients adds complexity to patient or subject visits. As well, the cost of the testing may prohibitive. However, the benefit of clearly understanding the genetic basis of the disease to develop more appropriate and targeted treatments is critical to eradicating this debilitating disease.

Behavioral Risks

Behavioral factors that may increase risk of AMD have been enumerated by The Foundation of the American Academy of Ophthalmology (2015) and include smoking, overexposure to sunlight, and diet. While smoking and overexposure to sunlight have been included in clinical trial investigations for quite some time, the issue of diet is more difficult to evaluate. That stated, a number of investigators have endeavored to evaluate the link between AMD and dietary intake (Amirul Islam et al., 2014; Arnold, Jentsch, Dawczynski, & Böhm, 2013; Chiu et al., 2014; Christen et al., 2012).

Christen et al. (2012) performed a long-term, prospective study in physicians to determine if Vitamin E and Vitamin C had an impact on the development of AMD. Subjects in this study were randomized to either intervention with a regimen of Vitamin E and Vitamin C or to a regimen of placebo. Subjects were asked to report on an annual basis regarding the development of AMD (Christen et al., 2012). If an AMD diagnosis was reported, medical records were reviewed to confirm the self-report (Christen et al., 2012). After 8 years of evaluation, no differences were found between the incidence of AMD in the two groups suggesting that Vitamins E and C were neither harmful nor beneficial to the development of AMD (Christen et al., 2012).

Arnold et al. (2013) performed a pilot study to determine if a diet high in oleaginous extract of *Brassica oleracea* var. *sabellica* L. (kale) could impact concentration of xanthophyll in both plasma and the macula. An inverse risk has been suggested to exist between xanthophyll concentration and AMD (Arnold et al., 2013). Twenty subjects were enrolled in this well-designed and controlled study (Arnold et al., 2013). Subject participation included both an intervention period and a washout period after intervention (Arnold et al., 2013). While both plasma and macula levels of xanthophyll were elevated during the intervention portion of the study, the effect was not present after the 4-week washout (Arnold et al., 2013). This led Arnold et al. to surmise that the "distribution of the xanthophylls in the macula seems to be more dynamic than originally assumed" (p. 1412). In order to maintain a high level of xanthophylls, consumption of kale and other xanthophyll-containing foods would need to be kept at a continuously high level (Arnold et al., 2013).

Amirul Islam et al. (2014) attempted to discover specific dietary intake patterns associated with the risk of developing AMD based on primary food intake scale (F1 = fruits, F2 = vegetables, F3 = grains, fish, boiled or steamed chicken, and nuts, F4 = red meat, F5 = processed foods, and F6 = salad). No clear delineation of specific food types was found to be associated with a higher risk of AMD. An association with decreased risk of AMD seemed to be indicated in subjects with diets higher in fruits, vegetables, chicken and nuts than in those with diets higher in red meat consumption (Amirul Islam et al., 2014).

Chiu et al. (2014) hypothesized that the American dietary pattern put individuals a higher risk for the development of AMD. In a cross-sectional study of subjects participating in the AREDS study, Chiu et al., classified 8,103 eyes per the AMD classifications developed by AREDS. These included 2,739 subjects without AMD who served as the control group, 4,599 subjects with early AMD, and 765 with late AMD. By evaluating the diets of these subjects, Chiu et al. identified two main dietary types (i.e., Oriental and Western) based on the principal components consumed. Subjects who consumed more fresh fruits, vegetables, and fish were considered to follow an Oriental dietary pattern (Chiu et al., 2014). Those subjects who consumed more processed, refined, high fat foods and red meat were considered to follow a Western dietary pattern (Chiu et al., 2014). The findings indicated that both dietary patterns are associated with early or late AMD (Chiu et al., 2014). The subjects who consumed food according to an Oriental pattern showed reduced odds of developing AMD, with the more adherent subjects gaining additional protection (Chiu et al., 2014). The subjects who consumed food according to a Western pattern showed increased odds of developing AMD, with additional risk associated with greater consumption of a Western diet (Chiu et al., 2014).

The findings from these studies are widely varied from direct support for dietary impact on both increasing and lowering risk of AMD to no clear support for either a beneficial or harmful impact on the development of AMD. The absence of clearly understood mechanisms suggests an importance exists in understanding what type of diet patients typically consume to find additional means for lowering the burden of this disease. Collecting information pertaining to weight or dietary intake in ophthalmic

clinical practice or clinical research is atypical. Consequently, coordination between several medical disciplines would be necessary to integrate dietary patterns with ophthalmic findings.

Treatments for NAMD

Treatment of NAMD was exceedingly limited until the relatively recent therapeutic approvals of anti-VEGF treatments (Wang & Ohji, 2013). In the 1980s, the treatment option was argon laser photocoagulation (Stein et al., 2013). For this procedure, argon laser was applied to the lesion in the macula, which destroyed the tissue but stopped the leakage and destruction of macular cells by essentially cauterizing the lesion (Stein et al., 2013). Continued visual loss was typically ameliorated, but no VA gains were evident, and a risk of iatrogenic vision loss was apparent (Stein et al., 2013).

In 2000, the FDA approved photodynamic therapy (PDT) with verteporfin (Visudyne) indicated for subfoveal choroidal neovascularization treatment (Stein et al., 2013). Treatment consisted of the injection of verteporfin intravitreally activated by exposure to a laser light source in order to cause occlusion of the neovascularization in the macula (Curtis et al., 2012). As with argon laser photocoagulation, PDT can stop the progression of neovascularization but does not restore vision lost by the initial growth of vessels into the macula (Curtis et al., 2012).

Treatment for NAMD has changed dramatically over the past 12 years with the approval in 2004 of the first of the anti-VEGF treatments, pegatinib (Macugen), and approval of ranibizumab (Lucentis) followed in 2006 and aflibercept (Eylea) in 2011 (Stein et al., 2013). Although not approved for NAMD, bevacizumab (Avastin) has also

been used in for NAMD treatment due to its identification as a much less costly alternative the anti-VEGF treatments approved for treatment of NAMD (Stein et al., 2013). With the advent of anti-VEGF therapy, no longer was the treatment modality one of stopping progression as with PDT; anti-VEGF treatment offered patients the hope of regaining some of the vision that had been previously lost (Curtis et al., 2012). Anti-VEGF therapy utilizes recombinant, humanized monoclonal antibody fragments to neutralize active forms of VEGF-A present in the affected, thereby inhibiting proliferation of new blood vessels (Curtis et al., 2012). Patients experience an amelioration of progressive vision loss as well as a recovery of vision over the course of continued injections (Curtis et al., 2012).

Yannuzzi, Patel, Bhavsar, Sugiguchi, and Freund (2014) performed a cross-sectional, physician survey to determine if anti-VEGF treatments had a negative impact on intraocular pressure (IOP). The study conducted was limited in that it was a cross-sectional study, and the prevalence of sustained IOP increases were reported by the physicians and were not objectively reported by means of IOP data submission and analysis (Yannuzzi et al., 2014). Nonetheless, the findings were interesting in that the investigators were able to determine that "higher injection volumes [of anti-VEGF] with a rapid injection technique may potentially lead to sustained IOP elevation" (Yannuzzi et al., 2014, p. 319). Utilizing treatment regimen or treatment techniques that are not supported by clinical research may lead to negative outcomes in visual function and other aspects of ophthalmic disability.

Concern has also been expressed regarding the potential for anti-VEGF therapies used to treat NAMD to increase risk of negative cerebrovascular and cardiovascular effects (Cruess & Giacomantonio, 2014). This concern came about with the off-label use of bevacizumab for NAMD and was based at least in part on the systemic findings of the anti-VEGF class of drugs (Cruess & Giacomantonio, 2014). The systemic findings centered around the impact that anti-VEGF therapy had on VEGF in systemic circulation that decrease the patency of vessel walls and may cause vessel leakage and destruction of tissues (Semeraro et al., 2014). Thus, investigations were initiated into the issue with interesting findings that do not necessarily support the concern for ophthalmic use of anti-VEGF treatment. Semeraro et al. (2014) expressed the concern that intravitreal injection with anti-VEGF could have an impact on circulating VEGF systemically; however, the evaluation of clinical studies performed by these investigators did not support an association between the use of anti-VEGF therapies intravitreally and an increased incidence of thromboembolitic events (Semeraro et al., 2014). The incidence of cerebrovascular accident, myocardial infarction, and death was similar in both treated and untreated subjects observed (Semeraro et al., 2014).

Similarly, Ng et al. (2015) expressed concern regarding the use of anti-VEGF treatments. These investigators, too, communicated that although no signals had been found to support concern in the products approved for intravitreal injection for NAMD, the same could not be said for bevacizumab as it had not been evaluated in the same manner as the anti-VEGF treatments approved for NAMD treatment. As has been mentioned, bevacizumab is not approved for intravitreal injection to treat NAMD but is

often used off-label due to the lower cost of the product. Ng et al. evaluated a large cohort of subjects who had been treated predominantly with bevacizumab. The results from the analysis of these subjects supported the same conclusions as those of Semeraro et al. (2014); no association between the use if intravitreal bevacizumab and increased risk of cerebrovascular or cardiovascular events or death was found (Ng et al., 2015).

Aflibercept Dosing Regimen and Outcomes

Specifically in NAMD populations, studies of all phases are often performed in treatment naïve subjects in order not to have prior treatments obfuscate the findings in the trial under investigations (Christen et al., 2012; Gambon et al., 2014; Mazaraki, Fassnacht-Riederle, Blum, Becker, & Michels, 2015; Rush, Rush, Aragon II, & Ysasaga, 2014; Tan et al., 2013). While approaching clinical studies in this manner may lead to a clearer understanding of the mechanisms underlying certain treatments, unless these same types of studies are performed in subjects who have been exposed to NAMD treatments, there is a knowledge burden that will be faced by the NAMD population that is not naïve to anti-VEGF treatments. External validity of the clinical research study has been sacrificed for internal validity. The ability of an NAMD patient treated with multiple therapies and his or her physician to make appropriate treatment decisions is hampered by the lack of knowledge about how this additional therapy might impact the patient's health and wellbeing.

FDA approval for the aflibercept was predicated on two Phase 3, multicenter, randomized, active-controlled, clinical trials in which a total of 2,419 subjects were randomized to one of the following study arms:

- 0.5 mg intravitreal aflibercept dosed monthly
- 2 mg intravitreal aflibercept dosed monthly
- 2 mg intravitreal aflibercept dosed every 2 months after 3 initial monthly doses
- 0.5 mg intravitreal ranibizumab dosed monthly (Heier et al., 2012)

The primary visual outcome used to evaluate the efficacy of aflibercept in NAMD was proportion of subjects who maintained gains in BCVA by ETDRS logMAR scoring assessed 52 weeks after treatment (Heier et al., 2012). Anatomical features such as CNV lesion size and central retinal thickness were also considered significant outcome measures (Heier et al., 2012). Aflibercept was required to meet a noninferiority standard of no less than 10% difference from ranibizumab outcomes (Heier et al., 2012). All aflibercept study arms were considered to be as effective in improving BCVA and preventing BCVA loss as ranibizumab (Heier et al., 2012). Additionally, similar results were detected with regard to anatomic measures (Heier et al., 2012). As a result, the dose of aflibercept recommended and approved was "2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (monthly) for the first 12 weeks (3 months), followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months)" (FDA, 2011, sec. 2.2). This protocol, then, is the standard by which populations should be judged when evaluating the safety and efficacy of aflibercept in a realistic analysis of clinical practice.

Both the issue of knowledge burden and confounding may apply to the issue of racial diversity in clinical trials. As has been noted previously by Coscas et al. (2014),

Nakata et al. (2013), and Wong et al. (2014), a genetic difference between Caucasian and Asian patients with NAMD seemed to exist. Although race is collected in clinical trials, the use of this information is not supportive of the translation of prior epidemiological studies of these populations into clinical trials (Thornicroft, Lempp, & Tansella, 2011). Statisticians may analyze race between randomized groups in a study to show whether or not differences occurred between the numbers and types of individuals randomized to each group (Kessler & Glasgow, 2011). Whether race is then analyzed as a subgroup that might have an impact the outcomes seen based on the use of the investigational product is unclear. Because analyses of race/ethnicity and outcome are not conducted, a knowledge burden for patients and physicians is produced for determining the best treatment options as the potential confounding effect of race has not been adequately investigated. The possibility exists that a patient may be treated with a product that is not particularly effective based on the patient's race (Coscas et al., 2014; Nakata et al., 2013; Wong et al., 2014). This increases the burden on the patient both financially and functionally, since the visual outcome might not be optimal (Muether, Hermann, Koch, & Fauser, 2011). Further, it places an increased burden on healthcare and public health systems, since optimal visual function outcomes have not been met and additional outlay of public funds may be necessary to support the increased disability of the patient due to blindness (Muether et al., 2011; Schmier et al., 2012).

Rakic et al. (2013) noted that realistic clinical practice outcomes for patients who were treated with ranibizumab showed both initial and continuing improvement in a prospective, multicenter, observational study of open-label treatment with 0.5 mg of

ranibizumab according to realistic clinical practice conditions. The realistic clinical practice paradigm effectively means that the treatment regimen was according to the FDA labeling for ranibizumab and not proscribed by a protocol different from the labeling (Rakic et al., 2013). A total of 267 subjects were initially treated in the study and were followed for up to 24 months (Rakic et al., 2013). Investigators were asked to follow the normal procedures of treatment, document procedures in medical records, request completion of QOL questionnaires by enrolled subjects, and schedule standard follow-up visits at 6, 12, and 24 months, which is usual in this indication (Rakic et al., 2013). The investigators were asked to follow the treatment regimen recommended by the labeling of ranibizumab, which includes monthly injections of 0.5 mg ranibizumab for the first 3 months followed by monthly BCVA checks and additional injections based on the visual outcome findings (Rakic et al., 2013). As noted by Rakic et al., (2013), the mean number of injections delivered during the loading phase did approximate that noted in the labeling (2.5 ± 0.7 injections over 2.5 ± 2 weeks). This mean, however, does not completely depict what transpired with subjects. Specifically, about half of subjects (52.6%) received all three injections, 39.2% received two injections, and 8.2% received one injection in the first 3 months (Rakic et al., 2013). During the follow-up phase of the study over the remaining 21 months, re-injection was based on findings of the visual outcomes assessments (Rakic et al., 2013). If the physician diagnosed progression of NAMD, additional injections were given (Rakic et al., 2013). If no progression was present, the subject did not receive additional injections (Rakic et al., 2013). This treatment paradigm does differ from that of several of the large, pivotal trials that

substantiated the approval of ranibizumab wherein subjects were treated monthly for approximately 12 months. By using the labeled treatment regimen, Rakic et al. (2013) noted that the number of injections was significantly lower than that of the clinical trial treatment regimen (5.9 ± 3.6 injections over 11.5 ± 9.5 weeks). These more variable treatment conditions based on observation and clinician judgment did lead to positive visual outcomes, but the outcomes were not as strongly positive as had been demonstrated in the approval-based clinical trials that used a protocol of monthly injections (Rakic et al., 2013).

In an evaluation of the outcomes from a retrospective review of data presented by Holekamp et al. (2014), the authors evaluated a large claims database to determine if the methods elaborated for treatment regimen in randomized, controlled trials (RCTs) were used in clinical practice. For the anti-VEGF treatments available at the period of time investigated, the treatment regimen advocated based on RCTs was monthly monitoring and frequent intravitreal injection to maintain the best visual outcomes, which translated to approximately monthly injections with anti-VEGF treatment in the RCTs (Holekamp et al., 2014). This study evaluated over 19,000 patients with claims based on new diagnoses. The findings for the period investigated (i.e., 2006–2007) for ranibizumab and bevacizumab use were quite different from what had been shown to be safe and effective in RCTs. Rather than the twelve injections supported by the approval-based clinical studies, patients received a mean annual number of 4.6 injections in the bevacizumab-treated group and 6.9 injections in the ranibizumab-treated group. (Holekamp et al., 2014). Further, these patients received substantially fewer follow up

clinic visits to assess visual outcomes and adjust treatment as needed. Although these investigators were not able to determine the direct effect on visual outcomes based on their use of the claims data, almost certainly an addition burden was placed on patients who were not treated according to the established treatment regimen (Holekamp et al., 2014).

Translating procedures and findings from both clinical trials and epidemiological studies to clinical practice is a change that needs to occur in our healthcare paradigm for the best outcomes for patients and physicians. The level of clinical care provided by the investigators evaluated in Rakic et al. (2013) seems to have surpassed that of those evaluated in Holekamp et al. (2014). This difference would suggest a decline in outcomes would be more profound as noted by the information provided by Rakic et al. (2013).

Summary

Aflibercept treatment has been approved for marketing in NAMD patients by the FDA; however, the use of this intervention and outcomes associated with its use in populations that differ from the clinical research population have not been well-characterized. In this study, my goal was to evaluate whether differences existed between three retinal practice populations of NAMD patients treated with aflibercept with regard to selected health characteristics, treatment regimens, and treatment outcomes. A secondary analysis evaluated associations between the selected variables. The literature reviewed supported that several different variables (i.e., race/ethnicity, comorbidities, genetic factors, and behavioral factors) were associated with an increased

risk of NAMD but may not be evaluated in NAMD clinical trials. As well, the literature review supported the need for examination of different population centers to determine if differences or associations existed between the populations with regard to selected health characteristics, treatment regimens, and treatment outcomes. The research methodology employed could help to fill a gap in the literature related to the aflibercept treatment regimens and outcomes and could extend the body of knowledge pertaining to aflibercept treatment and NAMD outcomes in a variety of populations. I will discuss the methodology for this study in Chapter 3.

Chapter 3: Research Method

Introduction

In this study, I evaluated three geographically disperse private retinal practices to determine if differences between NAMD patients treated with aflibercept existed, and secondarily, whether associations regarding selected health characteristics, treatment regimens, and treatment outcomes existed. In this chapter, I will provide details of the specifics for the research methodology used, including the research design and rationale, target population, sample and sampling procedures, and data collection procedures. I will also elaborate the operationalization of all variables in the study, the data analysis plan, and any threats to the validity of the study. Finally, I will review ethical considerations and the implications of these on the data collection method.

Research Design and Rationale

In this study, I used a retrospective, cross-sectional study design wherein the categorical groups of NAMD patients treated with aflibercept from three geographically disperse private retinal practices (grouping variable) were contrasted with respect to demographic and selected health characteristics (independent variables), treatment regimens (independent variables), and treatment outcomes (dependent variables). As noted by Frankfort-Nachmias and Nachmias (2007), using contrasting groups creates a situation wherein "straightforward comparative statistical analyses" (p.119) can be performed on the various dependent variables under observation. Campbell and Stanley (1963) clarified that contrasting group research is not the same as the pretest-posttest control group design in that subjects in a contrasting group project could not be randomly

assigned to the categorical groups described. For this study, I used categorical groups rather than the randomization of subjects since both the primary objectives involved categories by which the groups are naturally divided and into which individuals could not be randomized (Campbell & Stanley, 1963; Frankfort-Nachmias & Nachmias, 2007). I collected the data for this study by traveling to one of the retinal practices to work directly with the personnel who manage the EMR system. For the other two practices, the data were available by direct access to the EMR system. By using direct interaction with the selected retinal practices, I gathered the most appropriate information in the most efficient manner. Time constraints were a limiting issue for the personnel at the retinal practices with a direct impact on the timeliness of gathering data. Travel costs were also prohibitive in gaining access to data at the physician's practice that was in California. The result was that data for fewer subjects were made available at this practice.

Population

The population for this study included patients identified at participating retinal centers who had a diagnosis code in ICD-9 of 362.52 (exudative senile macular degeneration of retina). Specifically, I included patients in the study from three retina centers located in three population centers in the United States, based on review of EMR, if they meet the following criteria:

- Diagnosis of NAMD in at least one eye during the period of 2011 to 2014.
- Treatment with aflibercept intravitreal injections after approval in 2011.
- At least one BCVA and OCT assessment within the approximately 1-month period prior to treatment with aflibercept.

- At least three BCVA and OCT assessments during the approximately 1-year period following treatment with aflibercept.

Sampling and Sampling Procedures

I used a one-way ANOVA to evaluate continuous variables (i.e., age, number of ocular and systemic comorbidities, number of days between initial NAMD diagnosis to the first aflibercept treatment, baseline VA, baseline OCT, the average number of days between treatments, the average number of treatments giving during the approximately 1-year period following the first aflibercept treatment in the study eye, change from baseline VA, and change from baseline OCT) to determine whether differences were present between the three geographically disperse retinal practices. χ^2 analysis was used to evaluate the categorical variable of gender to determine if differences existed in this variable between the three retinal practices. Associations were evaluated using Spearman's rank-order correlation for the comparison of two continuous variables and point-biserial analysis for comparison of the combination of categorical and continuous variables. When assumptions were violated, I performed the appropriate nonparametric testing as deemed appropriate. This included using a Welch one-way ANOVA with post hoc testing for variables in which the homogeneity of variance assumption was violated.

As noted by Sheperis (2013), most researchers accept a power of 0.80 (80%) when determining sample size estimates; however, clinical research studies typically depend on a power of .90 to .95 (90% to 95%) for studies for which FDA approval for marketing is sought. The proposed analysis for this study was based on 95% power calculation. With this information and estimating a modest effect size of 0.25, a sample

size of 252 participants and two degrees of freedom in the numerator and 249 degrees of freedom in the denominator resulted in 95.1% chance of detecting a statistically significant difference between the three groups (i.e., retinal practices) at $\alpha = 0.05$ using a fixed effects, omnibus, one-way ANOVA. The sample size estimate was calculated using G*Power, version 3.1.9.2 (Faul, Erdfelder, Buchner, & Buchner, 2007).

I chose a purposive sampling method for the general NAMD patient population in order to capture data for all patients identified within the period specified previously at each of the retina specialists' offices. Each site provided a de-identified data set with the appropriate patients included. Since three retinal practices were identified, the sample was proposed to be divided by the number of practices and data from approximately 84 patients was to be collected at each site ($N = 252$). Patients were: (a) identified working from the most recently diagnosed patients, (b) with at least one year of follow-up, (c) starting at 2015 and working backward in time until the appropriate number of patients had been identified. The proposed accrual was a total of 84 patients identified at each site.

Procedures for Recruitment, Participation, and Data Collection

For the general NAMD population, three retinal specialist sites located in various geographic locations within the United States gave me permission to review patient EMR under strict adherence to Health Insurance Portability and Accountability Act (HIPAA) of 1996 rules pertaining to the privacy of patient medical information. I conducted my review to identify those patients at the retinal practices who met the first of the criteria (i.e., having NAMD diagnosis in at least one eye during the period of 2011 to 2014).

Once appropriate patients were identified within the EMR database, I separated those patients who met the remaining criteria from the whole of the EMR records for de-identification. Only those fields necessary for analysis were collected. Fields that were not captured in the final database included: name, work place name, personal and work addresses, personal and work telephone numbers, personal and work e-mail addresses, insurance, and any other information that might lead back to the individual's identification. Due to the retrospective nature of this study and the fact that patient information was de-identified, there was no need for me to collect informed consent for use of the data.

Operationalizing Variables

To operationalize the data, a definition of each of the variables was necessary. The variables that I proposed to collect in the general population dataset are described in greater detail in Table 1.

Table 1

Planned Variables and Coding for General NAMD Population

Variable	Definition	Nature of Variable	Coding of Variable
Patient ID	De-identified Patient Identification Number	Text	Site 1 = 1001 – 1999 Site 2 = 2001 – 2999 Site 3 = 3001 – 3999

(table continues)

Variable	Definition	Nature of Variable	Coding of Variable
Gender	Patient's Gender	Dichotomous	1 = Male 2 = Female
Race/Ethnicity	Patient's reported race or ethnicity	Categorical	1 = White 2 = Black or African American 3 = Hispanic or Latin 4 = American Indian and Alaska Native 5 = Asian 6 = Native Hawaiian and Other Pacific Islander 7 = Multiple Race/Ethnicity (check all that apply) 1 = White 2 = Black or African American 3 = Hispanic or Latin 4 = American Indian and Alaska Native

(table continues)

Variable	Definition	Nature of Variable	Coding of Variable
			5 = Asian 6 = Native Hawaiian and Other Pacific Islander
Age	Age in years calculated from the date of birth compared to the date of the dataset	Numeric	__.__ years
Iris Color	The predominant color of the iris in each eye	Categorical	1 = Gray 2 = Blue 3 = Green 4 = Hazel 5 = Brown 6 = Black 7 = Other

(table continues)

Variable	Definition	Nature of Variable	Coding of Variable
Ocular Comorbidities	Does the patient have any of the following ocular comorbidities? (check all that apply)	Categorical	1 = Cataract 2 = Cytomegalovirus Retinitis 3 = Diabetic Macular Edema 4 = Glaucoma or Ocular Hypertension 5 = Keratoconus 6 = Posterior Vitreous Detachment 7 = Retinal Detachment 8 = Retinal Vein Occlusion 9 = Uveitis 10 = N/A
Systemic Comorbidities	Does the patient have comorbidities associated with any of the following body	Categorical	1 = Circulatory 2 = Digestive 3 = Endocrine 4 = Immune 5 = Integumentary 6 = Muscular

(table continues)

Variable	Definition	Nature of Variable	Coding of Variable
	systems? (check all that apply)		7 = Nervous 8 = Reproductive 9 = Respiratory 10 = Skeletal 11 = Urinary 12 = N/A
Comorbidities	If yes, diagnosis associated with body system	Text	Text entered in this field will be coded based on the Medical Dictionary for Regulatory Activities (MedDRA).
Smoking	Does the patient report a history of smoking?	Dichotomous	1 = No 2 = Yes
Alcohol Abuse	Does the patient report a history of alcohol abuse	Dichotomous	1 = No 2 = Yes

(table continues)

Variable	Definition	Nature of Variable	Coding of Variable
Genotype	Does the physician report either of the genotypes for the patient?	Categorical	1 = rs11200638 of the *HTRA1* gene 2 = rs10611710 of the *CFH* gene 3 = Other 4 = N/A
Eye Involved	Which eye(s) have a diagnosis of NAMD	Categorical	1 = OD 2 = OS 3 = OU
Diagnosis Date	Date the patient's ophthalmologist diagnosed NAMD for each eye	Date	ODDiag = DD MON YYYY OR OSDiag = DD MON YYYY OUDiag = DD MON YYYY
Length of Diagnosis	Calculated from the date of diagnosis to the date of the dataset	Numeric	ODLength = __.__ years OSLength = __.__ years OULength = __.__ years

(table continues)

Variable	Definition	Nature of Variable	Coding of Variable
Dates of Treatment	Aflibercept treatment dates for the study eye	Date	ODTrt1 = DD MON YYYY OR OSTrt1 = DD MON YYYY OUTrt1 = DD MON YYYY
Study Eye	The eye which received the first injection of aflibercept	Categorical	1 = OD 2 = OS
Baseline BCVA	BCVA prior to receiving initial aflibercept treatment for the study eye	Number	ODVABL = _.__ OSVABL = _.__ Snellen BCVA will be converted to ETDRS logMAR equivalent

(table continues)

Variable	Definition	Nature of Variable	Coding of Variable
Follow-Up BCVA	BCVA associated with each injection of aflibercept	Number	ODVA1 = _.__ OR OSVA1 = _.__ Snellen BCVA will be converted to ETDRS logMAR equivalent
Baseline OCT	Central retinal thickness prior to receiving initial aflibercept treatment	Number	ODOCTBL = ___._ μm OSOCTBL = ___._ μm
Follow-Up OCT	Central retinal thickness associated with each injection of aflibercept	Number	ODOCT1 = ___._ μm OSOCT1 = ___._ μm

Table 2 is a representation of the proposed general NAMD population data set.

Table 2

Example of Data Set for General NAMD Population

Variable	Definition	Coding of Variable
Patient ID	De-identified Patient Identification Number	1001
Gender	Patient's Gender	2
Race/Ethnicity	Patient's reported race or ethnicity	1
Age	Age in years calculated from the date of birth compared to the date of the dataset	65
Iris Color	The predominant color of the iris in each eye	ODIris = 2 OSIris = 2
Ocular Comorbidities	Does the patient have any of the following ocular comorbidities? (check all that apply)	1 4

(table continues)

Variable	Definition	Coding of Variable
Systemic Comorbidities	Does the patient have comorbidities associated with any of the following body systems? (check all that apply)	1 8 9 10
Comorbidities	If yes, diagnosis associated with body system	1 = Systemic Hypertension 8 = Hysterectomy 9 = Chronic Obstructive Pulmonary Disease 10 = Osteoarthritis
Smoking	Does the patient report a history of smoking?	2
Alcohol Abuse	Does the patient report a history of alcohol abuse	1
Genotype	Does the patient either of the genotypes?	3
Eye Involved	Which eye(s) have a diagnosis of NAMD	1
Diagnosis Date	Date the patient's ophthalmologist diagnosed NAMD for each eye	ODDiag = 16 Nov 2012

(table continues)

Variable	Definition	Coding of Variable
Length of Diagnosis	Calculated from the date of diagnosis to the date of the dataset	ODLength = 2.72 years
Study Eye	The eye which received the first injection of aflibercept	1 = OD
Dates of Treatment	Aflibercept treatment dates for each eye treated	ODTrt1 = 19 Nov 2012 ODTrt2 = 24 Dec 2012 ODTrt3 = 21 Jan 2013 ODTrt4 = 18 Feb 2013 ODTrt5 = 22 Apr 2013 ODTrt6 = 22 Jul 2013 ODTrt7 = 21 Oct 2013
Baseline BCVA	BCVA prior to receiving initial aflibercept treatment for each eye treated	ODVABL = 1.00

(table continues)

Variable	Definition	Coding of Variable
Follow-Up BCVA	BCVA associated with each injection of aflibercept	ODVA1 = 0.98 ODVA2 = 0.72 ODVA3 = 0.60 ODVA4 = 0.56 ODVA5 = 0.50 ODVA6 = 0.50 ODVA7 = 0.54
Baseline OCT	Central retinal thickness prior to receiving initial aflibercept treatment	ODOCTBL = 608
Follow-Up OCT	Central retinal thickness associated with each injection of aflibercept	ODOCT1 = 606 ODOCT2 = 580 ODOCT3 = 560 ODOCT4 = 500 ODOCT5 = 460 ODOCT6 = 445 ODOCT7 = 450

The patient data noted in Table 2 represents a 65-year-old, Caucasian, female, with blue irides diagnosed with NAMD in the right eye (OD) on November. 16, 2008 (2.72 years prior to data collection). The patient was also diagnosed with ocular conditions of

cataract and glaucoma and systemic conditions of hypertension, hysterectomy, chronic obstructive pulmonary disease, and osteoarthritis. The patient received seven treatments OD (i.e., the study eye) with aflibercept between the dates of November. 19, 2012 and October 21, 2013, with baseline BCVA of 1.00 logMAR, which improved to 0.54 logMAR by the final treatment and baseline central retinal thickness of 608 μm, which improved to 450 μm by the final treatment.

Data Analysis Plan

The research questions for this study were:

Research Question 1: Were there significant differences between selected health characteristics of populations of NAMD patients treated with aflibercept in three private, retinal practices in geographically disperse population centers in the United States? Health characteristic variables included: age, gender, number of ocular comorbidities, number of systemic comorbidities, number of days between NAMD diagnosis and first treatment with aflibercept in the study eye, baseline BCVA, baseline OCT.

$H_0 1$: $\mu_1 = \mu_2$

There were no differences in proportions between selected health characteristics of populations of NAMD patients treated with aflibercept in three private, retinal practices in geographically disperse population centers in the United States.

H_a1: $\mu_1 \neq \mu_2$

There were differences in proportions between selected health characteristics of populations of NAMD patients treated with aflibercept in three private, retinal practices in geographically disperse population centers in the United States.

My analysis for this research question included several different comparisons. The categorical variable of gender was compared using the incidence of males and females at each retinal practice using a two-tailed analysis with $\alpha = 0.05$. I used a χ^2 test of homogeneity to compare the variable incidence in each of the three retinal practices to determine if differences in gender existed between the practices. The continuous variables of age, number of ocular comorbidities, number of systemic comorbidities, number of days between NAMD diagnosis and first treatment with aflibercept in the study eye, baseline BCVA, and baseline OCT were compared using mean values for each variable for each eye treated using a two-tailed analysis with $\alpha = 0.05$. I used a one-way ANOVA to compare the mean values of each variable in each of the three retinal practices to determine differences exist between the practices.

Research Question 2: Were there significant differences between aflibercept treatment regimens used to treat NAMD patient in three private, retinal practices in geographically disperse population centers in the United States? Treatment regimen variables included: average number of aflibercept treatments injections received during one year from initial aflibercept treatment and average number of days between aflibercept treatments.

$H_0 2$: $\mu_1 = \mu_2$

There were no differences in the aflibercept treatment regimens used to treat populations of NAMD among patients at three private, retinal practices in geographically disperse population centers in the United States.

$H_a 2$: $\mu_1 \neq \mu_2$

There were differences in aflibercept treatment regimens used to treat populations of NAMD among patients at three private, retinal practices in geographically disperse population centers in the United States.

My analysis for this research question was a comparison of the two continuous variables. This was accomplished using mean values for each variable for the study eye treated using a two-tailed analysis with $\alpha = 0.05$. I used a one-way ANOVA to compare the mean values of each variable in each of the three retinal practices to determine differences exist between the practices.

Research Question 3: Were there significant differences between aflibercept treatment outcomes reported for NAMD patients in the three private, retinal practices in geographically disperse population centers in the United States? Treatment outcome variables included: average change from baseline in BCVA and average change from baseline in OCT.

$H_0$3: $\mu_1=\mu_2$

There were no differences between aflibercept treatment outcomes reported for NAMD patients in three private, retinal practices in geographically disperse population centers in the United States.

H_a3: $\mu_1\neq\mu_2$

There were differences between aflibercept treatment outcomes reported for NAMD patients in three private, retinal practices in geographically disperse population centers in the United States.

My analysis for this research question was a comparison of the two continuous variables. This was accomplished using mean values for each variable for the study eye treated using a two-tailed analysis with $\alpha = 0.05$. I used a one-way ANOVA to compare the mean values of each variable in each of the three retinal practices to determine differences exist between the practices.

Research Question 4: What associations existed between selected health characteristics and aflibercept treatment regimens used to treat NAMD patients in three private, retinal practices in geographically disperse population centers in the United States?

$H_0$4: $ß_к=0$

There were no associations between selected health characteristics and aflibercept treatment regimens used to treat NAMD patients in three private, retinal practices in geographically disperse population centers in the United States.

H_a4: $\beta_K \neq 0$

There were associations between selected health characteristics and aflibercept treatment regimens used to treat NAMD patients in three private, retinal practices in geographically disperse population centers in the United States.

My analysis for this research question included the use of comparisons and correlations. I compared the categorical variable of gender using the incidence of males and females compared to each of the treatment regimen variables at each retinal practice using a two-tailed analysis with $\alpha = 0.05$. Point-biserial correlation was used to determine if associations existed between gender and treatment regimens. The continuous variables of age, number of ocular comorbidities, number of systemic comorbidities, number of days between NAMD diagnosis and first treatment with aflibercept in the study eye, baseline BCVA, and baseline OCT were compared using mean values for each variable for each eye treated using a two-tailed analysis with $\alpha = 0.05$. I also used Spearman's correlation to determine if associations existed between the selected health characteristics and treatment regimens.

Research Question 5: What associations existed between selected health characteristics and aflibercept treatment outcomes reported for NAMD patients in three private, retinal practices in geographically disperse population centers in the United States?

$H_0$5: β_K=0

There were no associations between selected health characteristics and aflibercept treatment outcomes reported for NAMD patients in three private, retinal practices in geographically disperse population centers in the United States.

H_a5: $\beta_K \neq 0$

There were associations between selected health characteristics and aflibercept treatment outcomes reported for NAMD patients in three private, retinal practices in geographically disperse population centers in the United States.

I analyzed data for this research question in the following ways. The categorical variable of gender was compared using the incidence of males and females compared to each of the treatment regimen variables at each retinal practice using a two-tailed analysis with $\alpha = 0.05$. I used a point-biserial correlation to determine if associations existed between gender and treatment outcomes. The continuous variables of age, number of ocular comorbidities, number of systemic comorbidities, number of months since NAMD diagnosis, baseline BCVA, and baseline OCT were compared using mean values for each variable for each eye treated using a two-tailed analysis with $\alpha = 0.05$. I used Spearman's correlation to determine if associations existed between the selected health characteristics and treatment outcomes.

Research Question 6: What association existed between aflibercept treatment regimens used and aflibercept treatment outcomes reported for NAMD patients in

three private, retinal practices in geographically disperse population centers in the United States?

$H_0$6: $ß_K$=0

There were no associations between aflibercept treatment regimens used and aflibercept treatment outcomes reported for NAMD patients in three private, retinal practices in geographically disperse population centers in the United States.

H_a6: $ß_K \neq 0$

There were associations between aflibercept treatment regimens used and aflibercept treatment outcomes reported for NAMD patients in three private, retinal practices in geographically disperse population centers in the United States.

My analysis for this research question was a comparison of the two continuous treatment regimen variables and the two continuous treatment outcomes variables. This was accomplished using mean values for each variable for the study eye treated using a two-tailed analysis with $\alpha = 0.05$. I used Spearman's correlation to determine if associations existed between the selected health characteristics and the treatment outcomes.

Analyses were conducted using IBM SPSS Statistics 23. Data were imported from site EMR files and entered directly into the final SPSS database. The various independent variables were classified into three groups based on the ophthalmic practice from which the data were obtained (i.e., CA, KY, and OH). Data were assessed for

outliers, normality, missing data, multicollinearity, and homogeneity of variance. Means and standard deviations were reported for each variable from the secondary analysis of the NAMD populations. Results of the ANOVA analyses were reported as *F*-statistic with the associated between groups degrees of freedom followed by the within groups degrees of freedom and the *p*-value. Results of the Spearman's correlation were reported as the correlation coefficient, r_s, with the number of degrees of freedom followed by the *p*-value.

Threats to Validity

Threats to validity include issues that jeopardize the ability of a researcher to draw thorough and appropriate conclusions based on the data collected (Frankfort-Nachmias & Nachmias, 2007). Internal validity refers to the way in which studies are designed and the manner in which data are collected (Frankfort-Nachmias & Nachmias, 2007). For this study, threats to internal validity occurred with respect to the general NAMD population selection. This study was not randomized; therefore, it was necessary identify patients based on diagnosis, treatment, and outcome measure availability in the EMR systems of the participating sites. External validity deals with how well the results of the study can be translated to a larger population (Frankfort-Nachmias & Nachmias, 2007). Generalizability from this study to other therapeutic interventions in NAMD and in ophthalmology should be robust but may be questionable for other medical conditions. Statistical conclusion validity was based on several issues pertaining to detecting errors due to the analysis and/or data being analyzed. This study was initially designed to have 95% power to detect a Type 1 error. As well, the assumptions associated with analysis

by ANOVA were tested to make certain that the inferences made, based on the analysis of these data, were appropriate. As data were collected it became apparent that the required number of patients (i.e., 252) to support the 95% power computation were not available at the retinal practices identified. A total of 199 patients were identified, which lowered the power of the study to detect a Type 1 error to 90%.

Ethical Procedures

All data collected in this study were de-identified prior to analysis as suggested by the HIPAA. Data use agreements and letters of cooperation were completed with each of the three retinal practice physicians in order to gain access to the EMR data for patients at each office (Appendices A–C). As well, all applicable laws regarding privacy and confidentiality were followed. This study was submitted to the Walden University Institutional Review Board (IRB) for approval (IRB Approval Number 01-20-16-0246251) to ascertain whether the study complied with the ethical standards of the university and U.S. federal regulations. Data were housed on a password-protected computer with limited access by me only. Data will be destroyed 5 years after completing the study.

Summary

This study was a retrospective, contrasted-groups, cross-sectional study design wherein the categorical groups of three NAMD patient populations were contrasted with respect to selected health characteristics, treatment regimens, and treatment outcomes. The study was focused on the research question of whether disparities existed between the three geographically disperse NAMD patient populations. NAMD patient population

data were collected from three retina specialists located around the United States. Secondary data analyses were performed on variables from this data collection to determine the means and standard deviations in the general NAMD patient population. One-way ANOVA and χ^2 analyses were performed to determine whether there were differences between each of the retina practices with respect to selected health characteristics, aflibercept treatment regimens, and aflibercept treatment outcomes. Spearman's correlation and point-biserial correlation were performed to determine whether associations existed between selected health characteristics, aflibercept treatment regimens, and aflibercept treatment outcomes. I will document the results of these analyses in Chapter 4, and Chapter 5 will be used to elaborate how the results from this study relate to other previously published literature.

Chapter 4: Research Method

Introduction

The purpose of this study was to evaluate whether significant differences existed regarding selected health characteristics, treatment regimens, and treatment outcomes for patients with NAMD treated with aflibercept from three private, retinal practices in geographically disperse population centers in the United States. The research questions and hypotheses that guided this study were:

Research Question 1: Were there significant differences between selected health characteristics of populations of NAMD patients treated with aflibercept in three private, retinal practices in geographically disperse population centers in the United States? Health characteristic variables included: age, gender, number of ocular comorbidities, number of systemic comorbidities, number of days between NAMD diagnosis and first treatment with aflibercept in the study eye, baseline BCVA, and baseline OCT.

$H_0 1$: $\mu_1 = \mu_2$

There were no differences in proportions between selected health characteristics of populations of NAMD patients treated with aflibercept in three private, retinal practices in geographically disperse population centers in the United States.

$H_a 1$: $\mu_1 \neq \mu_2$

There were differences in proportions between selected health characteristics of populations of NAMD patients treated with aflibercept

in three private, retinal practices in geographically disperse population centers in the United States.

Research Question 2: Were there significant differences between aflibercept treatment regimens used to treat NAMD patient in three private, retinal practices in geographically disperse population centers in the United States? Treatment regimen variables included: average number of aflibercept treatments injections received during one year from initial aflibercept treatment and average number of days between aflibercept treatments.

$H_0 2$: $\mu_1 = \mu_2$

There were no differences in the aflibercept treatment regimens used to treat populations of NAMD among patients at three private, retinal practices in geographically disperse population centers in the United States.

$H_a 2$: $\mu_1 \neq \mu_2$

There were differences in aflibercept treatment regimens used to treat populations of NAMD among patients at three private, retinal practices in geographically disperse population centers in the United States.

Research Question 3: Were there significant differences between aflibercept treatment outcomes reported for NAMD patients in the three private, retinal practices in geographically disperse population centers in the United States? Treatment outcome variables included: average change from baseline in BCVA and average change from baseline in OCT.

$H_0 3$: $\mu_1 = \mu_2$

There were no differences between aflibercept treatment outcomes reported for NAMD patients in three private, retinal practices in geographically disperse population centers in the United States.

$H_a 3$: $\mu_1 \neq \mu_2$

There were differences between aflibercept treatment outcomes reported for NAMD patients in three private, retinal practices in geographically disperse population centers in the United States.

Research Question 4: What associations existed between selected health characteristics and aflibercept treatment regimens used to treat NAMD patients in three private, retinal practices in geographically disperse population centers in the United States?

$H_0 4$: $ß_\kappa = 0$

There were no associations between selected health characteristics and aflibercept treatment regimens used to treat NAMD patients in three private, retinal practices in geographically disperse population centers in the United States.

$H_a 4$: $ß_\kappa \neq 0$

There were associations between selected health characteristics and aflibercept treatment regimens used to treat NAMD patients in three private, retinal practices in geographically disperse population centers in the United States.

Research Question 5: What associations existed between selected health characteristics and aflibercept treatment outcomes reported for NAMD patients in three private, retinal practices in geographically disperse population centers in the United States?

$H_0 5$: $ß_K = 0$

There were no associations between selected health characteristics and aflibercept treatment outcomes reported for NAMD patients in three private, retinal practices in geographically disperse population centers in the United States.

$H_a 5$: $ß_K \neq 0$

There were associations between selected health characteristics and aflibercept treatment outcomes reported for NAMD patients in three private, retinal practices in geographically disperse population centers in the United States.

Research Question 6: What association existed between aflibercept treatment regimens used and aflibercept treatment outcomes reported for NAMD patients in three private, retinal practices in geographically disperse population centers in the United States?

$H_0 6$: $ß_K = 0$

There were no associations between aflibercept treatment regimens used and aflibercept treatment outcomes reported for NAMD patients in three

private, retinal practices in geographically disperse population centers in the United States.

H_a6: $ß_K \neq 0$

There were associations between aflibercept treatment regimens used and aflibercept treatment outcomes reported for NAMD patients in three private, retinal practices in geographically disperse population centers in the United States.

The research questions for this study were designed to evaluate potential differences and associations between selected health characteristics, treatment regimens, and treatment outcomes. This design was necessary to address the gap in the literature related to aflibercept. Specifically, this study was designed to determine how aflibercept treatment for NAMD compared in populations with characteristics different from or treated in a manner that differed from the clinical trial populations.

In Chapter 4, I will present data collection methods along with any discrepancies from the plan presented in Chapter 3. I will also provide descriptive statistics pertaining to the three retinal practice populations. Statistical analyses as proposed in Chapter 3 will be presented and explained relative to the research question posed.

Data Collection

I obtained the data for this study from EMR data from three retinal practices located in Hollywood, CA, Paducah, KY, and Cuyahoga Falls, OH from March 22, 2016 through October 26, 2016. Permission to use these data was granted by both the Walden University IRB and by each of the physicians in the retinal practices chosen. As this was

a retrospective study wherein subject information was de-identified, it was not necessary to obtain informed consent to review the patients' EMR information. The original plan was to collect information on race/ethnicity, iris color, and NAMD genotype as a part of the selected health characteristics; however, these characteristics were not reported in the medical records of the selected retina specialists. As well, the age variable was originally going to be calculated as the date of the database compared to the birthdate. This calculation was determined to be faulty in that it could result in ages beyond which the subject had lived. Instead, the age was calculated comparing the birthdate to the first day of aflibercept treatment. Other changes in data collection or data naming conventions are defined in Table 3 and included: (a) the eye involved field was deleted as it was deemed to be unnecessary in that only study eye (SE) data were analyzed; (b) only data for the selected SEs were collected resulting in the renaming of several fields that had originally been specific to either OD or OS; (c) field renaming resulted in the following: DiagDate_SE, DiagTrtTime, Aflib1_SE with all subsequent treatment dates coded sequentially from Aflib1_SE, LogMAR1_SE with all subsequent VAs coded sequentially from LogMAR1_SE, OCT1_SE with all subsequent OCTs coded sequentially from OCT1_SE ; (d) a field of OCTDate1_SE and subsequent additional OCT dates were added to the data capture since the OCT date was not always the same as the treatment date; (e) additional ocular comorbidities and all systemic comorbidities were collected as verbatim terms and were not coded into body system categories as it was not deemed necessary; and (f) the data captured with regard to timing of diagnosis were compared to the date of first aflibercept treatment rather than the date of the database, as researchers

have stated that the improvement seen is more significant if the neovascularization is caught in its early phase (Lim et al., 2012). The final database structure was as follows in Table 3.

Table 3

Actual Variables and Coding for General NAMD Population

Variable	Definition	Nature of Variable	Coding of Variable
Patient_No	De-identified Patient Identification Number	Text	Site 1 (CA) = 1001 – 1999 Site 2 (KY) = 2001 – 2999 Site 3 (OH) = 3001 – 4999
DB_Date	Date of the final database	Date	DD MMM YYYY
Gender	Patient's Gender	Dichotomous	1 = Male 2 = Female
Birthdate	Patient's Date of Birth	Date	DD MMM YYYY
Age	Age in years at the time the first Aflibercept treatment was given	Numeric	__.__ years

(table continues)

Variable	Definition	Nature of Variable	Coding of Variable
SmkHx	Does the patient report a history of smoking?	Dichotomous	1 = No 2 = Yes
AlcAbuse	Does the patient report a history of alcohol abuse?	Dichotomous	1 = No 2 = Yes
Total_OMH	The total number of ocular comorbidities	Numeric	Number derived from summation of Ocular Comorbidities and OcuSpec1 through OcuSpec5
Ocular Comorbidities	Does the patient have any of the following ocular comorbidities? CAT = Cataract CMV = Cytomegalovirus Retinitis DME = Diabetic Macular Edema GLAUC = Glaucoma KCON = Keratoconus	Numeric	1 = No 2 = Yes 3 = Unknown

(table continues)

Variable	Definition	Nature of Variable	Coding of Variable
	PVD = Posterior Vitreous Detachment RVO = Retinal Vein Occlusion UV = Uveitis OTHER = Other (Specify)		
OcuSpec1 through OcuSpec5	Specification of other Ocular Comorbidities	Text	Free text description of other ocular comorbidities not specified in the supplied list.
Total_SMH	The total number of systemic comorbidities	Numeric	Number derived from summation of SysComor1 through SysComor20

(table continues)

Variable	Definition	Nature of Variable	Coding of Variable
SysComor1 through SysComor20	Specification of Systemic Comorbidities	Text	Free text description of other systemic comorbidities.
Study Eye	The study eye is identified as that eye which received treatment with Aflibercept first	Categorical	1 = OD 2 = OS
DiagDate_SE	Date the patient's ophthalmologist diagnosed NAMD for the study eye	Date	DD MON YYYY
DiagTrtTime	Number of days from diagnosis of NAMD to treatment with aflibercept as calculated from the date of diagnosis to the date of the first treatment with Aflibercept	Numeric	__.__ days
AflibTrt1_SE through AflibTrt13_SE	Aflibercept treatment dates for the study eye	Date	DD MON YYYY

(table continues)

Variable	Definition	Nature of Variable	Coding of Variable
LogMAR1_SE through LogMAR13_SE	BCVA reported as ETDRS logMAR values for each treatment date	Numeric	_.__
OCTDate1_SE through OCTDate13_SE	OCT evaluation dates for the study eye	Date	DD MON YYYY
OCT1_SE through OCT13_SE	OCT central retinal thickness associated with each injection of aflibercept	Number	___._ μm

For this study, I collected data from physicians' EMR databases from March 22, 2016 through October 26, 2016. It was necessary to travel to the physician's office in Hollywood, CA, to collect the required data for the project. Data from the Paducah, KY and the Cuyahoga Falls, OH sites were made available online by the system administrator for the practice. The patients identified as being appropriate for inclusion in this study comprised 199 total patients from the three retinal practices. These 199 patients were culled from a total of 1,501 potential patients which was a 13.3% catchment. My selection of the patients was based on the following criteria:

- Diagnosis of NAMD in at least one eye.
- Treatment with aflibercept intravitreal injections after approval in 2011.

- At least one BCVA and OCT assessment within approximately 1-month period prior to treatment with aflibercept.
- At least three BCVA and OCT assessments during the approximately 1-year period following treatment with aflibercept.

The first of these criteria was changed from the original plan to increase the potential subject pool. The original criterion included a date restriction of between 2011 and 2014. The date restriction was determined unnecessary since the criterion associated with use of aflibercept resulted in a more effective culling of patients. Originally, it was proposed to have collected 252 cases from the three retinal practices to achieve a 95% power to detect a Type 1 error at $\alpha = 0.05$. Based on the data available in the EMRs for these practices, 199 Patients were identified from the three retinal practices. Nonetheless, power to detect a Type 1 error at an $\alpha = 0.05$ was maintained at 90% with the 199 patients included in the project.

There were 179 patients identified from the initial sampling of EMR data at the retinal practice in Hollywood, CA. From the initial sampling at this practice, the final number of patients included in the project database was 44. This represents 24.6% of the total patients from the CA site and 22.1% of the total population. There were 178 patients from the initial sampling of EMR data at the retinal practice in Paducah, KY. From the initial sampling at this practice, the final number of patients included was 101. This represents 56.7% of the total patients from the KY site and 50.8% of the total population. There were 1,144 patients from the initial sampling of EMR data at the retinal practice in Cuyahoga Falls, OH. From the initial sampling at this practice, the

final number of patients included in the project database was 54. This represents 4.7% of the total patients from the OH site and 27.1% of the total population.

Results

General Population Demographics

Overall demographic descriptive statistics were performed on the final data sample collected. The data from all three retinal practices combined included 78 males (39.2%) and 121 females (60.8%). This represents a population that is slightly skewed (-0.446) toward women. This type of skewness is appropriate based on findings that NAMD is more prevalent in women (NEI, 2014). The mean age of the population at the time of the subject's first treatment with aflibercept was 78.8 ± 8.542 years. This is skewed towards older age (-0.410), which is to be expected due to the age-related nature of NAMD (NEI, 2014). The minimum age reported was 45 years and the maximum age was 95 years. As has been mentioned previously, AMD is the most common cause of visual impairment after the age of 55 with the risk reaching 11.73% by the time individuals approach their eighth decade (Coleman et al., 2008; NEI, 2014).

The smoking history and alcohol abuse findings were somewhat unexpected as having a history of smoking or alcohol abuse have been reported as being associated with incidence of NAMD (The Foundation of the American Academy of Ophthalmology, 2015). In the population studied, 137 (68.8%) patients reported no smoking history, 47 (23.6%) patients reported having a history of smoking, and 15 (7.5%) patients did not report their smoking history; therefore, they were classified as unknown. The findings for alcohol abuse were much less robust than had been anticipated with 174 (87%)

patients reporting no history of alcohol abuse, two (1%) patients reporting a history of alcohol abuse, and 24 (12%) patients not reporting their alcohol abuse history. The patients with no report of alcohol abuse were also coded as unknown. Since the patient reports of smoking and alcohol abuse history did not seem reliable, no further evaluations were performed on these variables.

Patients in the population under study had an average of 3.00 ± 1.12 ocular comorbidities. The minimum number of ocular comorbidities was one, and the maximum number was seven. All patients were reported to have a diagnosis of AMD (ICD-9 code of 362.52). The most common comorbidity reported other than AMD was cataract with 174 (87.4%) patients being diagnosed with cataract in at least one eye. Other ocular comorbidities reported were glaucoma (n = 29, 14.6%), posterior vitreous detachment (n = 20, 10.1%), retinal vein occlusion (n = 8, 4.0%), and uveitis (n = 1, 0.5%). Other ocular comorbidities that were not specified in the original listing were reported by 111 patients (55.8%). The patients in this population reported having 5.65 ± 3.15 systemic comorbidities. The minimum number of systemic comorbidities reported was zero and the maximum number was 20. The most common systemic comorbidities (incidence > 15%) are listed in Table 4.

Table 4

Systemic Comorbidities Reported at >15% Incidence

Comorbidity	Frequency and Percentage of Systemic Comorbidities (N = 199)	
Hypertension	132	66%
Arthritis	87	44%
Cancer	58	29%
Hyperlipidemia	50	25%
Hypothyroidism	38	19%
Depression	35	18%
Diabetes	34	17%
Cardiovascular Disease	32	16%

Note. N = Total number of patients.

Regarding variables specific to NAMD for the overall study population, time from diagnosis to first aflibercept treatment, baseline BCVA, and baseline OCT were evaluated. The mean between diagnosis with NAMD and the first treatment with aflibercept was 323.6 ± 410.6 days. The large degree of variation in this variable was notable and was most likely due to NAMD diagnoses that were well before aflibercept was approved and marketed in 2011. Mean baseline VA for the general population reported in ETDRS logMAR was 0.53 ± 0.39 and mean baseline OCT was 333.26 ± 110.79 µm. The mean number of aflibercept treatments given during the approximately

1-year period following the first aflibercept treatment was 7.24 ± 1.861 and the mean number of days between treatments was 63.4858 ± 33.02454. Mean change from baseline BCVA was -0.0073 ± 0.30373 and mean change from baseline OCT was -43.8750 ± 96.27885.

Statistical Analyses

Research Question 1.

A one-way ANOVA was conducted to determine if age at the time of first treatment with aflibercept (AGE) was different between the three physician groups. AGE had no significant outliers and was normally distributed across the population and between the physician groups, as assessed by visual inspection of a normal Q-Q Plot. There was homogeneity of variances as assessed by Levene's test of homogeneity of variance ($p = 0.468$). AGE data are presented as mean ± standard deviation in Table 5.

Table 5

AGE (years) Mean and Standard Deviation by Physician Group and Total

Physician Group	Number of Patients	Mean	Standard Deviation
CA	44	79.98	9.444
KY	101	77.88	8.222
OH	54	79.50	8.332
Total	199	78.78	8.542

AGE was not statistically significantly different between the three physician practices, $F(2,196) = 1.185$, $p = 0.308$. The null hypothesis was not rejected.

A χ^2 test of homogeneity was conducted to determine if GENDER was different between the three physician groups. Gender data are presented as frequencies in Table 6.

Table 6

GENDER Frequencies by Physician Group and Total

Physician Group	Number of Patients	Male	Female
CA	44	19 (43.2%)	25 (56.8%)
KY	101	42 (41.6%)	59 (58.4%)
OH	54	17 (31.5%)	37 (68.5%)
Total	199	78 (39.2%)	121 (60.8%)

GENDER was not statistically significantly different between the three physician groups, $\chi^2 = 1.1883$, $p = 0.390$. The null hypothesis was not rejected.

A one-way ANOVA was conducted to determine if the average number of ocular comorbidities (OCULAR) per patient was different between the three physician groups. OCULAR had no significant outliers and was normally distributed across the population and between the physician groups, as assessed by visual inspection of a normal Q-Q Plot. There was homogeneity of variances as assessed by Levene's test of homogeneity of variance ($p = 0.470$). OCULAR data are presented as mean ± standard deviation in Table 7.

Table 7

OCULAR Mean and Standard Deviation by Physician Group and Total

Physician Group	Number of Patients	Mean	Standard Deviation
CA	44	3.23	1.236
KY	101	2.83	1.059
OH	54	3.13	1.082
Total	199	3.00	1.115

OCULAR was not statistically significantly different between the three physician practices, $F(2,196) = 2.467$, $p = 0.087$. The null hypothesis was not rejected.

A one-way Welch ANOVA was conducted to determine if the average number of systemic comorbidities (SYSTEMIC) per patient was different between the three physician groups. SYSTEMIC had no significant outliers and was normally distributed across the population and between the physician groups, as assessed by visual inspection of a normal Q-Q Plot. There was heterogeneity of variances as assessed by Levene's test of homogeneity of variance ($p = 0.042$). SYSTEMIC data are presented as mean ± standard deviation in Table 8.

Table 8

SYSTEMIC Mean and Standard Deviation by Physician Group and Total

Physician Group	Number of Patients	Mean	Standard Deviation
CA	44	3.23	1.236
KY	101	2.83	1.059
OH	54	3.13	1.082
Total	199	5.65	3.160

SYSTEMIC was statistically significantly different between different physician groups, Welch's $F(2,196) = 4.106$, $p = 0.018$. Games-Howell testing in the variable, SYSTEMIC, revealed a statistically significant difference between KY and OH with a mean difference in the number of systemic medical history items reported of 1.479 (95% CI [0.40,2.56, $p = 0.004$]). The null hypothesis was rejected for SYSTEMIC between KY and OH. For all other relationships, the null hypothesis was not rejected.

A one-way Welch ANOVA was conducted to determine if the numbers of days between the diagnosis of NAMD and the first treatment with aflibercept (DIAGTRT) was different between the three physician groups. DIAGTRT had no significant outliers and was normally distributed across the population and between the physician groups, as assessed by visual inspection of a normal Q-Q Plot. There was heterogeneity of variances as assessed by Levene's test of homogeneity of variance ($p < 0.001$). DIAGTRT data are presented as mean ± standard deviation in Table 9.

Table 9

DIAGTRT (days) Mean and Standard Deviation by Physician Group and Total

Physician Group	Number of Patients	Mean	Standard Deviation
CA	44	484.25	594.997
KY	101	338.01	337.864
OH	54	164.96	282.467
Total	199	323.39	410.607

DIAGTRT was statistically significantly different between different physician groups, Welch's $F(2,196) = 7.986$, $p < 0.001$. Games-Howell testing in the variable, DIAGTRT, revealed a statistically significant difference in DIAGTRT between CA and OH with mean difference reported as 319.287 (95% CI [84.62,553.95, $p = 0.005$]), and the mean difference between KY and OH reported as 173.047 (95% CI [51.93,294.16, $p = 0.003$]). The null hypothesis was rejected for DIAGTRT between CA and OH as well as between KY and OH. For all other relationships, the null hypothesis was not rejected.

A one-way ANOVA was conducted to determine if the Baseline VA (BLVA) was different between the different physician groups. BLVA had no significant outliers and was normally distributed across the population and between the physician groups, as assessed by visual inspection of a normal Q-Q Plot. There was homogeneity of variances as assessed by Levene's test of homogeneity of variance ($p = 0.106$). BLVA data are presented as mean ± standard deviation in Table 10.

Table 10

BLVA (logMAR) Mean and Standard Deviation by Physician Group and Total

Physician Group	Number of Patients	Mean	Standard Deviation
CA	44	0.4377	0.32155
KY	101	0.6051	0.43855
OH	54	0.4807	0.33678
Total	199	0.5344	0.39416

BLVA was statistically significantly different between the three physician practices, $F(2,196) = 3.539$, $p = 0.031$. Tukey Post Hoc analysis revealed the mean increase in BLVA from KY to CA (0.16742, 95% CI [0.0014, 0.3335, $p = 0.048$]) was statistically significant. The null hypothesis was rejected for BLVA between KY and CA. For all other relationships, the null hypothesis was not rejected.

A one-way ANOVA was conducted to determine if the Baseline OCT (BLOCT) was different between the different physician groups. BLOCT had no significant outliers and was normally distributed across the population and between the physician groups, as assessed by visual inspection of a normal Q-Q Plot. There was homogeneity of variances as assessed by Levene's test of homogeneity of variance ($p = 0.224$). BLOCT data are presented as mean ± standard deviation in Table 11.

Table 11

BLOCT (μM) Mean and Standard Deviation by Physician Group and Total

Physician Group	Number of Patients	Mean	Standard Deviation
CA	44	294.23	104.688
KY	101	364.90	114.007
OH	54	305.89	92.238
Total	199	333.26	110.795

BLOCT was statistically significantly different between the three physician practices, $F(2,196) = 9.201$, $p < 0.001$. Tukey Post Hoc analysis revealed the mean increase in BLOCT from KY to CA (70.674, 95% CI [25.25, 116.09, $p = 0.001$]) was statistically significant. The null hypothesis was rejected for BLOCT between KY and CA. For all other relationships, the null hypothesis was not rejected.

Research Question 2.

A one-way ANOVA was conducted to determine if the average total number of aflibercept treatments given in the approximately 1-year period after the first aflibercept (NUMTRT) was different between the different physician groups. NUMTRT had no significant outliers and was normally distributed across the population and between the physician groups, as assessed by visual inspection of a normal Q-Q Plot. There was homogeneity of variances as assessed by Levene's test of homogeneity of variance ($p = 0.355$). NUMTRT data are presented as mean ± standard deviation in Table 12.

Table 12

NUMTRT Mean and Standard Deviation by Physician Group and Total

Physician Group	Number of Patients	Mean	Standard Deviation
CA	44	8.55	1.956
KY	101	7.08	1.647
OH	54	6.46	1.634
Total	199	7.24	1.861

NUMTRT was statistically significantly different between the three physician practices, $F(2,196) = 18.759$, $p < 0.001$. Tukey Post Hoc analysis revealed the mean increase in NUMTRT from CA to KY (1.466, 95% CI [0.74, 2.20]) was statistically significant ($p < 0.001$), and the mean increase in NUMTRT from CA to OH (2.082, 95% CI [1.26, 2.90]) was statistically significant ($p < 0.001$). The null hypothesis was rejected for NUMTRT between CA and KY as well as for CA and OH. For all other relationships, the null hypothesis was not rejected.

A one-way ANOVA was conducted to determine if the average number of days between aflibercept treatments (NUMDAY) was different between the different physician groups. NUMDAY had no significant outliers and was normally distributed across the population and between the physician groups, as assessed by visual inspection of a normal Q-Q Plot. There was homogeneity of variances as assessed by Levene's test of homogeneity of variance ($p = 0.196$). NUMTRT data are presented as mean ± standard deviation in Table 13.

Table 13

NUMDAY (days) Mean and Standard Deviation by Physician Group and Total

Physician Group	Number of Patients	Mean	Standard Deviation
CA	44	45.9056	16.79308
KY	101	55.8789	20.76874
OH	54	58.1092	21.49334
Total	199	54.2790	20.58245

NUMDAY was statistically significantly different between the three physician practices, $F(2,196) = 5.081$, $p = 0.007$. Tukey Post Hoc analysis revealed the mean increase in NUMDAY from KY to CA (0.97327, 95% CI [1.3686,18.5780,] $p = 0.018$) and the mean increase in NUMDAY from OH to CA (12.20354, 95% CI [2.5290, 21.8780], $p = 0.009$). The null hypothesis was rejected for NUMDAY between KY to CA as well as between OH and CA. For all other relationships, the null hypothesis was not rejected.

Research Question 3.

A one-way ANOVA was conducted to determine if change from baseline VA reported in the approximately one-year period following the first aflibercept treatment (BCVA) was different between the different physician groups. BCVA had no significant outliers and was normally distributed across the population and between the physician groups, as assessed by visual inspection of a normal Q-Q Plot. There was homogeneity of variances as assessed by Levene's test of homogeneity of variance ($p = 0.731$). BCVA data are presented as mean ± standard deviation in Table 14.

Table 14

BCVA (logMAR) Mean and Standard Deviation by Physician Group and Total

Physician Group	Number of Patients	Mean	Standard Deviation
CA	44	-0.0804	0.32370
KY	101	0.0113	0.30985
OH	54	0.0174	0.26973
Total	199	-0.0073	0.30373

BCVA was not statistically significantly different between the three physician practices, $F(2,196) = 1.654$, $p < 0.194$. The null hypothesis was not rejected.

A one-way Welch ANOVA was conducted to determine change from baseline OCT reported in the approximately one-year period following the first aflibercept treatment (OCT) was different between the three physician groups. OCT had no significant outliers and was normally distributed across the population and between the physician groups, as assessed by visual inspection of a normal Q-Q Plot. There was heterogeneity of variances as assessed by Levene's test of homogeneity of variance ($p = 0.042$). OCT data are presented as mean ± standard deviation in Table 15.

Table 15

OCT (μM) Mean and Standard Deviation by Physician Group and Total

Physician Group	Number of Patients	Mean	Standard Deviation
CA	44	-36.5779	93.35451
KY	101	-57.4915	110.93797
OH	54	-24.3527	59.59982
Total	199	-43.8750	96.27885

OCT was not statistically significantly different between different physician groups, Welch's $F(2,196) = 2.276$, $p = 0.105$. The null hypothesis was not rejected.

Research Question 4.

A Spearman's rank-order correlation was conducted to assess the relationship between AGE and NUMDAY. There was a monotonic relationship between AGE and NUMDAY, as assessed by visual inspection of a scatterplot. There was no statistically significant correlation between AGE and NUMDAY, $r_s(199) = -0.066$, $p = 0.356$. The null hypothesis for association between AGE and NUMDAY was not rejected. Further, a Spearman's rank-order correlation was conducted to assess the relationship between AGE and NUMTRT. There was a monotonic relationship between AGE and NUMTRT, as assessed by visual inspection of a scatterplot. There was a statistically significant positive correlation between AGE and NUMTRT, $r_s(199) = 0.151$, $p = 0.033$; therefore, the null hypothesis for association between AGE and NUMTRT was rejected.

A point-biserial correlation was conducted between GENDER and NUMDAY. Assumption analyses of GENDER and NUMDAY showed (a) there were outliers, as

assessed by boxplot; (b) score was not normally distributed, as assessed by Shapiro-Wilk's test ($p < 0.05$); but (c) there was homogeneity of variances, as assessed by Levene's test for equality of variances. Although the assumptions were not all met, it was determined that the point-biserial correlation would be performed to gain some insight into whether an association might exist between GENDER and NUMDAY. There was no statistically significant correlation between GENDER and NUMDAY, $r_{pb}(199) = -0.021$, $p = 0.773$ The null hypothesis for association between GENDER and NUMDAY was not rejected. As well, a point-biserial correlation was conducted between GENDER and NUMTRT. Assumption analyses of GENDER and NUMTRT showed (a) there were outliers, as assessed by boxplot; (b) score was not normally distributed, as assessed by Shapiro-Wilk's test ($p < 0.05$); but (c) there was homogeneity of variances, as assessed by Levene's test for equality of variances. Although the assumptions were not all met, it was determined that the point-biserial correlation would be performed to gain some insight into whether an association might exist between GENDER and NUMTRT. There was no statistically significant correlation between GENDER and NUMTRT, $r_{pb}(199) = 0.036$, $p = 0.618$. The null hypothesis for association between GENDER and NUMTRT was not rejected.

A Spearman's rank-order correlation was conducted to assess the relationship between OCULAR and NUMDAY. There was a monotonic relationship between the OCULAR and NUMDAY, as assessed by visual inspection of a scatterplot. There was no statistically significant correlation between OCULAR and NUMDAY, $r_s(199) = 0.027$, $p = 0.705$; therefore, the null hypothesis for association between OCULAR and

NUMDAY was not rejected. Further, a Spearman's rank-order correlation was conducted to assess the relationship between OCULAR and NUMTRT. There was a monotonic relationship between OCULAR and NUMTRT, as assessed by visual inspection of a scatterplot. There was no statistically significant correlation between OCULAR and NUMTRT, $r_s(199) = -0.007$, $p = 0.922$; therefore, the null hypothesis for association between OCULAR and NUMTRT was not rejected.

A Spearman's rank-order correlation was conducted to assess the relationship between SYSTEMIC and NUMDAY. There was a monotonic relationship between SYSTEMIC and NUMDAY, as assessed by visual inspection of a scatterplot. There was a no statistically significant correlation between SYSTEMIC and NUMDAY, $r_s(199) = -0.046$, $p = 0.520$; therefore, the null hypothesis for SYSTEMIC and NUMDAY was not rejected. Further, a Spearman's rank-order correlation was conducted to assess the relationship between SYSTEMIC and NUMTRT. There was a monotonic relationship between SYSTEMIC and NUMTRT, as assessed by visual inspection of a scatterplot. There was no statistically significant correlation between SYSTEMIC and NUMTRT, $r_s(199) = -0.107$, $p = 0.134$; therefore, the null hypothesis for association between SYSTEMIC and NUMTRT was not rejected.

A Spearman's rank-order correlation was conducted to assess the relationship between DIAGTRT and NUMDAY. There was a monotonic relationship between DIAGTRT and NUMDAY, as assessed by visual inspection of a scatterplot. There was a statistically significant negative correlation between DIAGTRT and NUMDAY, $r_s(199) = -0.220$, $p = 0.002$; therefore, the null hypothesis for DIAGTRT and NUMDAY was

rejected. Further, a Spearman's rank-order correlation was conducted to assess the relationship between DIAGTRT and NUMTRT. There was a monotonic relationship between DIAGTRT and NUMTRT, as assessed by visual inspection of a scatterplot. There was statistically significant positive correlation between DIAGTRT and NUMTRT, $r_s(199) = 0.200$, $p = 0.005$; therefore, the null hypothesis for association between DIAGTRT and NUMTRT was rejected.

A Spearman's rank-order correlation was conducted to assess the relationship between BLVA and NUMDAY. There was a monotonic relationship between BLVA and NUMDAY, as assessed by visual inspection of a scatterplot. There was no statistically significant correlation between BLVA and NUMDAY, $r_s(199) = 0.008$, $p = 0.911$; therefore, the null hypothesis for BLVA and NUMDAY was not rejected. Further, a Spearman's rank-order correlation was conducted to assess the relationship between BLVA and NUMTRT. There was a monotonic relationship between BLVA and NUMTRT, as assessed by visual inspection of a scatterplot. There was no statistically significant correlation between BLVA and NUMTRT, $r_s(199) = -0.098$, $p = 0.169$; therefore, the null hypothesis for association between BLVA and NUMTRT was not rejected.

A Spearman's rank-order correlation was conducted to assess the relationship between BLOCT and NUMDAY. There was a monotonic relationship between BLOCT and NUMDAY, as assessed by visual inspection of a scatterplot. There was a statistically significant negative correlation between BLOCT and NUMDAY, $r_s(199) = -0.141$, $p = 0.047$; therefore, the null hypothesis for BLOCT and NUMDAY was rejected. Further, a

Spearman's rank-order correlation was conducted to assess the relationship between BLOCT and NUMTRT. There was a monotonic relationship between BLOCT and NUMTRT, as assessed by visual inspection of a scatterplot. There was no statistically significant correlation between BLOCT and NUMTRT, $r_s(199) = 0.089$, $p = 0.210$; therefore, the null hypothesis for association between BLOCT and NUMTRT was not rejected.

Research Question 5.

A Spearman's rank-order correlation was conducted to assess the relationship between AGE and BCVA. There was a monotonic between AGE and BCVA, as assessed by visual inspection of a scatterplot. There was no statistically significant correlation between AGE and BCVA, $r_s(199) = -0.055$, $p = 0.438$. The null hypothesis for association between AGE and BCVA was not rejected. Further, a Spearman's rank-order correlation was conducted to assess the relationship between AGE and OCT. There was a monotonic relationship between AGE and OCT, as assessed by visual inspection of a scatterplot. There was no statistically significant correlation between AGE and OCT, $r_s(199) = 0.000$, $p = 0.997$; therefore, the null hypothesis for association between AGE and OCT was not rejected.

A point-biserial correlation was conducted between GENDER and BCVA. Assumption analyses of GENDER and BCVA showed (a) there were outliers, as assessed by boxplot; (b) score was not normally distributed, as assessed by Shapiro-Wilk's test ($p < 0.05$); but (c) there was homogeneity of variances, as assessed by Levene's test for equality of variances. Although the assumptions were not all met, it was determined that

the point-biserial correlation would be performed to gain some insight into whether an association might exist between GENDER and BCVA. There was no statistically significant correlation between GENDER and BCVA, $r_{pb}(199) = -0.008$, $p = 0.912$. The null hypothesis for association between GENDER and BCVA was not rejected. As well, a point-biserial correlation was conducted between GENDER and OCT. Assumption analyses of GENDER and OCT showed (a) there were outliers, as assessed by boxplot; (b) score was not normally distributed, as assessed by Shapiro-Wilk's test ($p < 0.05$); but (c) there was homogeneity of variances, as assessed by Levene's test for equality of variances. Although the assumptions were not all met, it was determined that the point-biserial correlation would be performed to gain some insight into whether an association might exist between GENDER and OCT. There was no statistically significant correlation between GENDER and OCT, $r_{pb}(199) = 0.059$, $p = 0.409$. The null hypothesis for association between GENDER and OCT was not rejected.

A Spearman's rank-order correlation was conducted to assess the relationship between OCULAR and BCVA. There was a monotonic relationship between OCULAR and BCVA, as assessed by visual inspection of a scatterplot. There was no statistically significant correlation between OCULAR and BCVA, $r_s(199) = 0.011$, $p = 0.881$; therefore, the null hypothesis for association between OCULAR and BCVA was not rejected. Further, a Spearman's rank-order correlation was conducted to assess the relationship between OCULAR and OCT. There was a monotonic relationship between OCULAR and OCT, as assessed by visual inspection of a scatterplot. There was no statistically significant correlation between OCULAR and OCT, $r_s(199) = 0.042$, $p =$

0.557; therefore, the null hypothesis for association between OCULAR and OCT was not rejected.

A Spearman's rank-order correlation was conducted to assess the relationship between SYSTEMIC and BCVA. There was a monotonic relationship between SYSTEMIC and BCVA, as assessed by visual inspection of a scatterplot. There was no statistically significant correlation between SYSTEMIC and BCVA, $r_s(199) = -0.102$, $p = 0.152$; therefore, the null hypothesis for SYSTEMIC and BCVA was not rejected. Further, a Spearman's rank-order correlation was conducted to assess the relationship between SYSTEMIC and OCT. There was a monotonic relationship between SYSTEMIC and OCT, as assessed by visual inspection of a scatterplot. There was no statistically significant correlation between SYSTEMIC and OCT, $r_s(199) = -0.051$, $p = 0.477$; therefore, the null hypothesis for association between SYSTEMIC and OCT was not rejected.

A Spearman's rank-order correlation was conducted to assess the relationship between DIAGTRT and BCVA. There was a monotonic relationship between DIAGTRT and BCVA, as assessed by visual inspection of a scatterplot. There was no statistically significant correlation between DIAGTRT and BCVA, $r_s(199) = 0.128$, $p = 0.071$; therefore, the null hypothesis for DIAGTRT and BCVA was not rejected. Further, a Spearman's rank-order correlation was conducted to assess the relationship between DIAGTRT and OCT. There was a monotonic relationship between DIAGTRT and OCT, as assessed by visual inspection of a scatterplot. There was statistically significant

positive correlation between DIAGTRT and OCT, $r_s(199) = -0.044$, $p = 0.533$; therefore, the null hypothesis for association between DIAGTRT and OCT was not rejected.

A Spearman's rank-order correlation was conducted to assess the relationship between BLVA and BCVA. There was a monotonic relationship between BLVA and BCVA, as assessed by visual inspection of a scatterplot. There was a highly statistically significant negative correlation between BLVA and BCVA, $r_s(199) = -0.308$, $p < 0.001$; therefore, the null hypothesis for BLVA and BCVA was rejected. Further, a Spearman's rank-order correlation was conducted to assess the relationship between BLVA and OCT. There was a monotonic relationship between BLVA and OCT, as assessed by visual inspection of a scatterplot. There was highly statistically significant negative correlation between BLVA and OCT, $r_s(199) = -0.193$, $p = 0.006$; therefore, the null hypothesis for association between BLVA and OCT was rejected.

A Spearman's rank-order correlation was conducted to assess the relationship between BLOCT and BCVA. There was a monotonic relationship between BLOCT and BCVA, as assessed by visual inspection of a scatterplot. There was no statistically significant correlation between BLOCT and BCVA, $r_s(199) = -0.025$, $p = 0.726$; therefore, the null hypothesis for BLOCT and BCVA was not rejected. Further, a Spearman's rank-order correlation was conducted to assess the relationship between BLOCT and OCT. There was a monotonic relationship between BLOCT and OCT, as assessed by visual inspection of a scatterplot. There was a highly statistically significant negative correlation between BLOCT and OCT, $r_s(199) = -0.721$, $p < 0.001$; therefore, the null hypothesis for association between BLOCT and OCT was rejected.

Research Question 6.

A Spearman's rank-order correlation was conducted to assess the relationship between NUMDAY and BCVA. There was a monotonic relationship between NUMDAY and BCVA, as assessed by visual inspection of a scatterplot. There was no statistically significant correlation between NUMDAY and BCVA, $r_s(199) = 0.103$, $p = 0.148$; therefore, the null hypothesis for NUMDAY and BCVA was not rejected. Further, a Spearman's rank-order correlation was conducted to assess the relationship between NUMDAY and OCT. There was a monotonic relationship between NUMDAY and OCT, as assessed by visual inspection of a scatterplot. There was a highly statistically significant negative correlation between NUMDAY and OCT, $r_s(199) = 0.197$, $p = 0.005$; therefore, the null hypothesis for association between NUMDAY and OCT was rejected.

A Spearman's rank-order correlation was conducted to assess the relationship between NUMTRT and BCVA. There was a monotonic relationship between NUMTRT and BCVA, as assessed by visual inspection of a scatterplot. There was no statistically significant correlation between NUMTRT and BCVA, $r_s(199) = -0.032$, $p = 0.656$; therefore, the null hypothesis for NUMTRT and BCVA was not rejected. Further, a Spearman's rank-order correlation was conducted to assess the relationship between NUMTRT and OCT. There was a monotonic relationship between NUMTRT and OCT, as assessed by visual inspection of a scatterplot. There was a highly statistically significant negative correlation between NUMTRT and OCT, $r_s(199) = -0.191$, $p = 0.007$; therefore, the null hypothesis for association between NUMTRT and OCT was rejected.

Summary

In this study, I examined whether significant differences existed with regard to selected health characteristics, treatment regimens, and treatment outcomes for patients with NAMD treated with aflibercept from three private, retinal practices in geographically disperse population centers in the United States. Potential associations between selected health characteristics, treatment regimens, and treatment outcomes were evaluated to address the gap in the literature related to aflibercept. Finally, I evaluated how aflibercept treatment for NAMD performed in populations with characteristics different from or treated in a manner that differed from the clinical trial populations.

There were differences between the three different retinal practices regarding the number of systemic medical history items reported for KY/OH. Additionally, the time from the initial diagnosis with NAMD and the first treatment with aflibercept differed between CA/OH and KY/OH. BLVA and BLOCT differences were noted between KY/CA. The number of days between aflibercept treatments differed between OH/CA, and the total number of aflibercept treatments differed between CA/KY and CA/OH. Associations were noted in age and number of aflibercept treatments, time from diagnosis to first aflibercept treatment and number of days between aflibercept treatments, time from diagnosis to first aflibercept treatment and total number of aflibercept treatments, BLVA and BCVA, BLVA and OCT, and BLOCT and OCT.

In Chapter 5, I will review the results provided in Chapter 4 and how they related to current literature and the appropriateness of extrapolating the results to the larger population of patients being treated with aflibercept. In Chapter 5, I will also provide

insight into the limitations of the study and any recommendations for future research in this field. Finally, conclusions pertaining to this study will be detailed.

Chapter 5: Discussions, Conclusions, and Recommendations

Introduction

This study was a retrospective, contrasted group, cross-sectional, secondary analysis of data. The purpose of this study was to evaluate selected health characteristics, treatment regimens, and treatment outcomes for patients with NAMD treated with aflibercept from three private, retinal practices in geographically disperse population centers in the United States. The aim of the study was to determine whether differences or associations existed in these populations.

The key findings from this study were that NAMD patients included from the three geographically disperse retinal practices were similar with respect to the some of the more general selected health characteristics (i.e., age, gender, and ocular comorbidities). There were significant differences between NAMD patients in these physician practices with regard to some of the more specific selected health characteristics (i.e., systemic comorbidities, time from initial diagnosis to first treatment with aflibercept), treatment regimens, and treatment outcomes. The correlation analyses that I performed were run with the NAMD patient data from all three geographically disperse retinal practices. In the NAMD populations evaluated from the three retinal practices, there was little correlation between the selected health characteristics as compared to treatment regimens or to treatment outcomes; however, there were significant associations noted between treatment regimens and treatment outcomes. I will use the remainder of Chapter 5 to elaborate the specifics of these findings and provide

insight into how this research applies not only to prior reviewed literature but also to what impact this study research could have on future research.

This study was limited by the inaccessibility to the variables of race/ethnicity, iris color, and genotype in the EMR of the three retinal practices. As such, these three variables were not a part of the final comparisons. If these variables had been available, there would have been the opportunity for additional understanding of the health characteristics of the NAMD population used in this study. Additionally, this study was somewhat limited by the number of patients originally planned to be captured versus the amount of data available in the EMR. Although it was the case that data from 199 instead of 252 patients were included, the statistical findings were still robust as I will further discuss in this chapter.

As for this study's implications for positive social change, this type of study that can be performed on existing electronic data could lead to a better understanding of when and how medications are used. Studies could be performed on a single practice basis or on larger populations (e.g., city, state, country). Fostering use of EMR data for gaining an understanding of patient demographics and health characteristics could impact the use of treatment regimens and lead to better treatment outcomes.

Interpretation of Findings

Results Pertaining to Prior Literature

Comparing the findings of this study to the prior literature reviewed for this study led to a better understanding of how these three geographically disperse retinal practice populations fit into the overall population of NAMD patients treated with aflibercept. It

was unfortunate that the race/ethnicity and iris color data were not available in the EMRs for the retinal practices used, as this might have increased understanding of the associations between the variables evaluated. Both the overall (60.8%) and the three specific NAMD populations (CA = 56.8%, KY = 58.4%, and OH = 68.5%) were made up of greater numbers of females. This skewing towards a greater risk of developing NAMD for females is supported by the literature (Coleman et al., 2008; NEI, 2014). Additionally, the mean age in the general population (78.78 ± 8.542) and the three specific populations (CA = 79.98 ± 9.449, KY = 77.88 ± 8.222, OH = 79.50 ± 8.332) was similar to that reported in in prior literature (Lim et al., 2012; NEI, 2015b). With regard to ocular comorbidities, this study supported the findings of prior literature (The Foundation of the American Academy of Ophthalmology, 2015) with the finding that the presence of cataract was noted in 174 (87.4%) of the NAMD patients in the study.

The package insert for aflibercept that provides the instructions for administration of the product states that aflibercept should be given once per month for the first 3 months and then every other month for the remaining 9 months of the year (FDA, 2011). This translates to a total of approximately 7.5 doses per year. The findings of this study were quite close to that recommendation with 7.24 ± 1.861 doses given in the overall population of 199 patients. Change from baseline BCVA and change from baseline OCT showed promising increase in visual function (-0.0073 ± 0.30373 logMAR) and decrease in central macular thickness (-43.8750 ± 96.27885), which are how efficacy of aflibercept treatment is evaluated in the NAMD patient populations (FDA, 2011).

Generally, the findings of this study show that the population characteristics of NAMD patients in the three retinal practices were similar to an epidemiologically appropriate patient population, at least with respect to the variables that could be collected from the EMR at the practices used. The number of injections patients receive in these practices is aligned with the aflibercept package insert. The timing of the injections was also aligned with the information provided in the aflibercept package insert.

Results Pertaining to Retinal Practices

Research Questions 1–3 pertained to determining whether the three geographically disperse retinal practices used in this study were comparable to each other. I evaluated a total of 1,501 NAMD EMRs for patients at the three retinal practices to capture information on selected health characteristics, treatment regimens, and treatment outcomes based on treatment with aflibercept. Of this total, 199 patients were considered qualified for further review based on the criteria noted Chapter 3. For Tables 16 and 17, a plus sign (+) denotes that the mean differences between the retinal practice combinations noted in the table for a health characteristic showed not statistically significant differences. A minus sign (-) denotes that statistically significant mean differences were noted in the health characteristic noted in the table between the retinal practice combination noted. The testing performed for the selected health characteristic comparisons between retinal practices was either a one-way ANOVA or a one-way Welch ANOVA. My determination of the use of the Welch one-way ANOVA was based on whether the variances were different between the retinal practices being compared on

the health characteristics. Table 16 reports comparisons for the selected health characteristics between the three retinal practices.

Table 16

Comparison of Selected Health Characteristics by Physician Group

Physician Group Combinations	Age	Gender	Ocular Comorbidities	Systemic Comorbidities	Days from NAMD Diagnosis to First Aflibercept Treatment	BL VA	BL OCT
CA/KY	+	+	+	+	+	-	-
KY/OH	+	+	+	-	-	+	+
CA/OH	+	+	+	+	-	+	+

Note. "+" denotes no statistically significant difference in the mean differences for site pairing.

"-" denotes statistically significant difference in the mean differences for site pairing.

The practices were alike in the main demographic and health characteristics of AGE, GENDER, and OCULAR. No statistically significant differences were noted in these three general health characteristics, and AGE, GENDER, and OCULAR were aligned with what has been noted epidemiologically for the NAMD patient population (NEI, 2014, 2015b). Consequently, I determined that the retinal practices were representative of the general NAMD population in the health characteristics that were significant to have been reported by an ophthalmologist (e.g., age, gender, and ocular and systemic comorbidities).

There were more inconsistencies between KY and the other two retinal practices (i.e., CA and OH) regarding selected health characteristics. In this evaluation, baseline BCVA and baseline OCT findings were especially notable in the mean difference between CA and KY. Considering that the mean baseline BCVA for the general population was 0.53 ± 0.39 logMAR, a mean difference between CA and KY of 0.17 logMAR indicates that KY's patients were significantly more visually impaired at the beginning of their aflibercept treatment cycles. The same issue holds true for baseline OCT. Mean baseline OCT for the general population was 333.26 ± 110.795 μm. The mean difference reported between CA and KY (70.674 μm), again, means that KY's patients started at a much more advanced level or central retinal thickness at the initiation of their aflibercept treatment cycles. The comparison between KY and OH further supports the notion that KY's retinal practice may have been somewhat different with regard to the health characteristics than either CA or OH.

While not as significant, KY did show a disparity on the number of systemic medical history items and the days from diagnosis to first treatment with aflibercept. The differences between the three retinal practices that pertain to NAMD specifically may be due to the difference in sample size between the three practices. KY accounted for slightly over 50% of the total patients in this research project. A difference in methodology for capturing BCVA or OCT assessments or in recording information such as diagnosis date into the EMR may have caused this practice to exhibit notable differences. Table 17 reports comparisons for treatment regimens and treatment outcomes.

Table 17

Comparison of Treatment Regimens and Treatment Outcomes by Physician Group

Physician Group Combinations	Number of Days between Treatments	Number of Treatments	Best Corrected Visual Acuity	Optical Coherence Tomography
CA/KY	-	-	+	+
KY/OH	+	+	+	+
CA/OH	-	-	+	+

Note. "+" denotes no statistically significant difference in the mean differences for site pairing. "-" denotes statistically significant difference in the mean differences for site pairing.

Pertaining to treatment regimens, there were significantly notable differences within the CA practice as compared to the other two retinal practices. CA provided more aflibercept treatments (8.55 ± 1.956) to each patient than either KY (7.08 ± 1.647) or OH (6.46 ± 1.634) with CA having significantly fewer days between aflibercept treatments (45.9056 ± 16.79308) than OH (58.1092 ± 21.49335) or KY (55.8789 ± 20.76874). These treatment regimen differences between the three retinal practices did not translate to significant differences in the treatment outcomes. In general, it appears that the three retinal practices were quite similar to each other and to the general population of patients treated for NAMD with aflibercept. Although I noted differences in some of the health characteristics and aflibercept treatment regimens, this did not translate to significant differences in the treatment outcomes.

Results Pertaining to Associations

Research Questions 4–6 pertained to whether there were associations between the selected health characteristics, treatment regimens, or treatment outcomes in the NAMD populations I analyzed from the three geographically disperse retinal practices in the United States. In Table 18, findings for associations between health characteristics and treatment regimens are reported.

Table 18

Significant Spearman's Correlations for Selected Health Characteristics, Treatment Regimens, and Treatment Outcomes

Comparison	Spearman Correlation Coefficient	*p*-value
AGE + NUMTRT	r_s (199) = 0.151	0.033
DIAGTRT + NUMTRT	r_s (199) = - 0.200	0.005
DIAGTRT + NUMDAY	r_s (199) = - 0.220	0.002
BLVA + BCVA	r_s (199) = - 0.308	< 0.001
BLVA + OCT	r_s (199) = - 0.193	0.006
BLOCT + OCT	r_s (199) = - 0.721	< 0.001
BLOCT + NUMDAY	r_s (199) = -0.141	0.047
NUMDAY + OCT	r_s (199) = 0.197	0.005
NUMTRT + OCT	r_s (199) = - 0.191	0.007

The first of the comparisons in Table 18 indicated that a positive correlation existed between age at the time of first aflibercept treatment and number of aflibercept treatments given meaning that as the age at first treatment with aflibercept increased as

did the number of treatments given. Although this is a statistically significant correlation, it is not intuitively reasonable. This would seem to mean that the older the patient was when they were first started aflibercept treatment, the more likely they were to receive more treatments. This is an interesting correlation, if it were to hold true in future research, as it may indicate that physicians treat more aggressively with older patients.

There was a negative correlation between both the time from NAMD diagnosis to first aflibercept treatment as compared to the number of aflibercept treatments given and the number of days between aflibercept treatments. This indicated that the longer the time period was between when the subject was diagnosed with NAMD and when they first received aflibercept treatment, the more likely they were to receive fewer treatments with aflibercept in a shorter period of time. While neither of these correlations was strongly negative (-0.200 and -0.220, respectively), the correlation is highly statistically significant ($p = 0.005$ and $p = 0.002$, respectively). This finding indicated that the three retinal specialists used for this study were seemingly not as aggressive in their treatment of NAMD patients with more advanced disease.

There was also a negative correlation between baseline BCVA and change from baseline BCVA, baseline BCVA and change from baseline in OCT, and baseline OCT and change from baseline OCT. As baseline BCVA increased, change from baseline BCVA and change from baseline OCT both decreased. As baseline OCT increased, change from baseline OCT decreased. Decreases in both change from BCVA and in change from baseline OCT were considered an improvement. The meaning of this was that with worse initial VA, there was a greater possibility for improvement in both BCVA

and in OCT findings. As well, increased initial central retinal thickness as seen on OCT was more likely to improve. The correlations between baseline BCVA and change from baseline BCVA and change from baseline OCT were not strongly negative (-0.308 and -0.193, respectively) but were highly statistically significant ($p < 0.001$ and $p = 0.006$, respectively). The correlation between baseline OCT and change from baseline OCT was strongly negative (-0.721) and highly statistically significant ($p < 0.001$). This indicated that although a patient may start from a significantly negative assessment in terms of BLVA and BLOCT findings, there was a correlation with this negative initial assessment and a greater improvement with aflibercept treatment in these three retinal practices.

Finally, there was a positive correlation between the number of days between treatments and both baseline OCT and change from baseline in OCT. As the number of days between treatments increased the baseline OCT was seen to be increased (worse) and the change from baseline OCT increased (worse). There was a negative correlation between and the number of treatments given and change from baseline in OCT. As the number of treatments increased, the change from baseline OCT decreased (better).

When evaluating these results in terms of the burden of treatment theoretical framework, it is clear that the burden of aflibercept treatment is onerous both on a financial and a personal basis. Having to receive over seven intravitreal injections over the course of a year takes not only a great deal of time but also financial and personal resources as well. However, it can be posited that by receiving these injections, the appropriate patient population can benefit from the treatment. More treatments may mean greater time and money, but it may also mean a greater chance to regain some

visual function. Gaining visual function could lessen the burden of blindness due NAMD to the benefit of the patient, the healthcare system, and the community.

Limitations of the Study

One of the main limitations of the study with respect to what was originally planned was that race/ethnicity, iris color, and NAMD genotype were not available in the EMRs of the retinal practices. This limited the study to examination of age and gender as the main demographic characteristics that were evaluated. Although this was a significant limitation, the remainder of the data collected was quite robust and provided an ample view of how aflibercept treatments are performed and what the outcomes of the treatments were. A secondary limitation was that the number of cases that could be culled from the EMR data at the three retinal practices was somewhat lower than anticipated and was not evenly dispersed between the three practices. Nonetheless, the power to detect a Type 1 error at an $\alpha = 0.05$ was maintained at 90% with the 199 patients included in the project.

Recommendations

Since this study supported prior literature and clinical research findings pertaining to the population, health characteristics, treatment regimens, and treatment outcomes, it is imperative for this information to be shared and expanded upon in different therapeutic areas. Use of EMR has been shown to be an effective means of gathering and analyzing available data to evaluate important medical conditions and treatments. Expanding the use of EMR in the manner employed in this study is not difficult and not particularly time consuming. EMR is an untapped resource that could and should be used in

postmarketing efforts, in clinical research, and public health programs. Additional studies of interest would be to evaluate other retinal conditions (e.g., diabetic macular edema, retinal vein occlusion, retinitis pigmentosa) and other treatments to determine whether the outcomes from different diseases can be followed by using EMR. Further, looking at the same type of NAMD population as pertains to other treatments would be elucidating and would not cost a great deal in terms of financial or personal investment. Finally, the information gleaned from this study could be used to develop public health initiatives that would target specific populations for early testing, watchful waiting, prophylactic care with vitamin supplements, and early treatment leading to better treatment outcomes.

Implications

The major implication of this study is that the clinical research performed in support of marketing aflibercept as an effective treatment for NAMD has been reinforced by general use of the product in NAMD patients in the three retinal geographically disperse practices used. Results of this study will be provided to the three retinal practices, allowing the retinal specialist at the identified practices to gain more insight into their NAMD patient population. It is apparent from analysis of the data, NAMD patients from these three retinal practices did benefit from aflibercept treatment when the approved dosing regimen was used. As well, the correlation that was seen that increasing the number of aflibercept treatments and decreasing the number of days between aflibercept treatments could provide the clinical justification needed to provide additional treatments when clinically indicated. With NAMD treatment being a significant portion

of the public financial burden in the form of Medicare payouts (Silver, 2014), this study may help alleviate some of the uncertainty associated with trying to determine the most appropriate regimen (i.e., number and timing of aflibercept treatments) for a patient. Although the financial burden is still onerous, it is justified when treatments are used on appropriate patient populations

Regarding social change, research that can be performed on existing electronic data could lead to a better understanding of when and how treatments are used. Fostering use of EMR data for gaining an understanding of patient demographics and health characteristics could impact treatment regimens and lead to better treatment outcomes. Evidence-based and data driven treatment of patients would seem to be an optimal method of practicing medicine, which drives improvements in the health of the population. Having access to data collected in EMR, it would behoove a physician to use the information to the best of his or her ability and to the benefit of his or her patients. Changing to an electronic format of capturing health information should be a boon to the medical industry (i.e., both medical practice and public health) for the potential to be used effectively and efficiently to find, educate, and treat patients. One final implication for the use of EMR to understand populations and treatments is to share appropriate information on a patient or summary basis with public health authorities. Again, basing public health initiatives, programs, budgets, and outcomes on evidence found in EMR data could lead to better public understanding of disease and treatment.

This study will be shared with each of the practices involved for the retina specialists to gain a better understanding of their own practice and what can be

accomplished by mining the data they already have. It is intended that the methods used to capture and analyze the data for this project will be shared and appropriate personnel taught how best to find, organize, and analyze the available data. The aim for such sharing of information is to teach others in medicine and public health how to use data already available.

Conclusion

Generally, the findings of this study showed that the population characteristics of NAMD patients evaluated from three retinal practices were similar to an epidemiologically appropriate patient population (NEI, 2014, 2015a), at least with respect to the selected health characteristic variables that could be collected from the EMR (e.g., age, gender, and ocular and systemic comorbidities). Additionally, treatment regimens used by these three retinal practices were aligned with the information provided in the aflibercept package insert. Based on the treatment outcomes of increase in visual function (BCVA) and decrease in central macular thickness (OCT), the indication is that aflibercept treatment was effective in the population culled from the three retinal practices. Finally, the findings are supported by prior literature and indicate that the foundation laid by aflibercept clinical research performed in support of the approval to market aflibercept as an effective product for the NAMD patient population was used for the benefit of the NAMD patients in the three geographically disperse retinal practices.

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Appendix A: Data Use Agreement for Hollywood, CA Retinal Practice

DATA USE AGREEMENT

This Data Use Agreement ("Agreement"), effective as of 20 Jan 2016 ("Effective Date"), is entered into by and between Susan L. Coultas ("Data Recipient") and Retina-Vitreous Associates Medical Group ("Data Provider"). The purpose of this Agreement is to provide Data Recipient with access to a Limited Data Set ("LDS") for use in research **in accord with laws and regulations of the governing bodies associated with the Data Provider, Data Recipient, and Data Recipient's educational program.** In the case of a discrepancy among laws, the agreement shall follow whichever law is more strict.

1. Definitions. Due to the study's affiliation with Laureate, a USA-based company, unless otherwise specified in this Agreement, all capitalized terms used in this Agreement not otherwise defined have the meaning established for purposes of the USA "HIPAA Regulations" and/or "FERPA Regulations" codified in the United States Code of Federal Regulations, as amended from time to time.

2. Preparation of the LDS. Data Provider shall prepare and furnish to Data Recipient a LDS in accord with any applicable laws and regulations of the governing bodies associated with the Data Provider, Data Recipient, and Data Recipient's educational program.

Data Fields in the LDS. **No direct identifiers such as names may be included in the Limited Data Set (LDS).** In preparing the LDS, Data Provider shall include the **data fields specified as follows**, which are the minimum necessary to accomplish the research:

Table 1

Variables and Coding for General nAMD Population

Variable	Description	Nature of Variable	Coding of Variable
Patient ID	De-identified Patient Identification Number	Text	Site 1 = 1001 – 1999 Site 2 = 2001 – 2999 Site 3 = 3001 – 3999
Gender	Patient's Gender	Dichotomous	1 = Male 2 = Female
Race/Ethnicity	Patient's reported	Categorical	1 = White

Variable	Description	Nature of Variable	Coding of Variable
	race or ethnicity		2 = Black or African American 3 = Hispanic or Latin 4 = American Indian and Alaska Native 5 = Asian 6 = Native Hawaiian and Other Pacific Islander 7 = Multiple Race/Ethnicity (check all that apply) 1 = White 2 = Black or African American 3 = Hispanic or Latin 4 = American Indian and Alaska Native 5 = Asian 6 = Native Hawaiian and Other Pacific Islander
Age	Age in years calculated from the date of birth	Numeric	__.__ years

Variable	Description	Nature of Variable	Coding of Variable
	compared to the date of the dataset		
Iris Color	The predominant color of the iris in the each eye	Categorical	1 = Gray 2 = Blue 3 = Green 4 = Hazel 5 = Brown 6 = Black 7 = Other
Ocular Comorbidities	Does the patient have any of the following ocular comorbidities? (check all that apply)	Categorical	1 = Cataract 2 = Cytomegalovirus (CMV) Retinitis 3 = Diabetic Macular Edema 4 = Glaucoma or Ocular Hypertension 5 = Keratoconus 6 = Retinal Detachment 7 = Retinal Vein Occlusion 8 = Uveitis 9 = N/A
Systemic	Does the patient	Categorical	1 = Circulatory

Variable	Description	Nature of Variable	Coding of Variable
Comorbidities	have comorbidities associated with any of the following body systems? (check all that apply)		2 = Digestive 3 = Endocrine 4 = Immune 5 = Integumentary 6 = Muscular 7 = Nervous 8 = Reproductive 9 = Respiratory 10 = Skeletal 11 = Urinary 12 = N/A
Comorbidities	If yes, diagnosis associated with body system	Text	Text entered in this field will be coded based on the Medical Dictionary for Regulatory Activities (MedDRA).
Smoking	Does the patient report a history of smoking?	Dichotomous	1 = No 2 = Yes
Alcohol Abuse	Does the patient report a history of alcohol abuse	Dichotomous	1 = No 2 = Yes

Variable	Description	Nature of Variable	Coding of Variable
Genotype	Does the physician report either of the genotypes for the patient?	Categorical	1 = rs11200638 of the *HTRA1* gene 2 = rs10611710 of the *CFH* gene 3 = Other 4 = N/A
Eye Involved	Which eye(s) have a diagnosis of nAMD	Categorical	1 = OD 2 = OS
Diagnosis Date	Date the patient's ophthalmologist diagnosed nAMD for each eye	Date	ODDiag = DD MON YYYY OSDiag = DD MON YYYY
Length of Diagnosis	Calculated from the date of diagnosis to the date of the dataset	Numeric	ODLength = __.__ years OSLength = __.__ years
Dates of Treatment	Aflibercept treatment dates for each eye treated	Date	ODTrt1 = DD MON YYYY OSTrt1 = DD MON YYYY

Variable	Description	Nature of Variable	Coding of Variable
Baseline BCDVA	BCDVA prior to receiving initial aflibercept treatment for each eye treated	Number	ODVABL = _.__ OSVABL = _.__ Snellen BCDVA will be converted to Early Treatment Diabetic Retinopathy Study (ETDRS) LogMAR equivalent
Follow-Up BCDVA	BCDVA associated with each injection of aflibercept	Number	ODVA1 = _.__ OSVA1 = _.__ Snellen BCDVA will be converted to Early Treatment Diabetic Retinopathy Study (ETDRS) LogMAR equivalent
Baseline OCT	Central retinal thickness prior to receiving initial aflibercept treatment	Number	ODOCTBL = ___._ µm OSOCTBL = ___._ µm
Follow-Up OCT	Central retinal thickness	Number	ODOCT1 = ___._ µm OSOCT1 = ___._ µm

Variable	Description	Nature of Variable	Coding of Variable
	associated with each injection of aflibercept		

3. Responsibilities of Data Recipient. Data Recipient agrees to:

   a. Use or disclose the LDS only as permitted by this Agreement or as required by law;

   b. Use appropriate safeguards to prevent use or disclosure of the LDS other than as permitted by this Agreement or required by law;

   c. Report to Data Provider any use or disclosure of the LDS of which it becomes aware that is not permitted by this Agreement or required by law;

   d. Require any of its subcontractors or agents that receive or have access to the LDS to agree to the same restrictions and conditions on the use and/or disclosure of the LDS that apply to Data Recipient under this Agreement; and

   e. Not use the information in the LDS to identify or contact the individuals who are data subjects.

4. Permitted Uses and Disclosures of the LDS. Data Recipient may use and/or disclose the LDS **for its Research activities only.**

5. Term and Termination.

   a. Term. The term of this Agreement shall commence as of the Effective Date and shall continue for so long as Data Recipient retains the LDS, unless sooner terminated as set forth in this Agreement.

   b. Termination by Data Recipient. Data Recipient may terminate this agreement at any time by notifying the Data Provider and returning or destroying the LDS.

   c. Termination by Data Provider. Data Provider may terminate this agreement at any time by providing thirty (30) days prior written notice to Data Recipient.

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d. For Breach. Data Provider shall provide written notice to Data Recipient within ten (10) days of any determination that Data Recipient has breached a material term of this Agreement. Data Provider shall afford Data Recipient an opportunity to cure said alleged material breach upon mutually agreeable terms. Failure to agree on mutually agreeable terms for cure within thirty (30) days shall be grounds for the immediate termination of this Agreement by Data Provider.

e. Effect of Termination. Sections 1, 4, 5, 6(e) and 7 of this Agreement shall survive any termination of this Agreement under subsections c or d.

6. Miscellaneous.

a. Change in Law. The parties agree to negotiate in good faith to amend this Agreement to comport with changes in federal law that materially alter either or both parties' obligations under this Agreement. Provided however, that if the parties are unable to agree to mutually acceptable amendment(s) by the compliance date of the change in applicable law or regulations, either Party may terminate this Agreement as provided in section 6.

b. Construction of Terms. The terms of this Agreement shall be construed to give effect to applicable federal interpretative guidance regarding the HIPAA Regulations.

c. No Third Party Beneficiaries. Nothing in this Agreement shall confer upon any person other than the parties and their respective successors or assigns, any rights, remedies, obligations, or liabilities whatsoever.

d. Counterparts. This Agreement may be executed in one or more counterparts, each of which shall be deemed an original, but all of which together shall constitute one and the same instrument.

e. Headings. The headings and other captions in this Agreement are for convenience and reference only and shall not be used in interpreting, construing or enforcing any of the provisions of this Agreement.

IN WITNESS WHEREOF, each of the undersigned has caused this Agreement to be duly executed in its name and on its behalf.

David Boyer, MD
Retina-Vitreous Associates Medical Group

Signed: David Boyer

Print Name: DAVID BOYER

Print Title: senior partner

Susan L. Coultas, PhD Candidate

Signed: Susan L. Coultas

Print Name: Susan L. Coultas

Print Title: PhD Candidate

Appendix B: Data Use Agreement for Paducah, KY Retinal Practice

DATA USE AGREEMENT

This Data Use Agreement ("Agreement"), effective as of 01 Mar 2016 ("Effective Date"), is entered into by and between Susan L. Coultas ("Data Recipient") and Carl Baker, MD, of The Ophthalmology Group, LLP ("Data Provider"). The purpose of this Agreement is to provide Data Recipient with access to a Limited Data Set ("LDS") for use in research **in accord with laws and regulations of the governing bodies associated with the Data Provider, Data Recipient, and Data Recipient's educational program.** In the case of a discrepancy among laws, the agreement shall follow whichever law is more strict.

1. Definitions. Due to the study's affiliation with Laureate, a USA-based company, unless otherwise specified in this Agreement, all capitalized terms used in this Agreement not otherwise defined have the meaning established for purposes of the USA "HIPAA Regulations" and/or "FERPA Regulations" codified in the United States Code of Federal Regulations, as amended from time to time.

2. Preparation of the LDS. Data Provider shall prepare and furnish to Data Recipient a LDS in accord with any applicable laws and regulations of the governing bodies associated with the Data Provider, Data Recipient, and Data Recipient's educational program.

Data Fields in the LDS. **No direct identifiers such as names may be included in the Limited Data Set (LDS).** In preparing the LDS, Data Provider shall include the **data fields specified as follows**, which are the minimum necessary to accomplish the research:

Table 1

Variables and Coding for General nAMD Population

Variable	Description	Nature of Variable	Coding of Variable
Patient ID	De-identified Patient Identification Number	Text	Site 1 = 1001 – 1999 Site 2 = 2001 – 2999 Site 3 = 3001 – 3999
Gender	Patient's Gender	Dichotomous	1 = Male 2 = Female

Variable	Description	Nature of Variable	Coding of Variable
Race/Ethnicity	Patient's reported race or ethnicity	Categorical	1 = White 2 = Black or African American 3 = Hispanic or Latin 4 = American Indian and Alaska Native 5 = Asian 6 = Native Hawaiian and Other Pacific Islander 7 = Multiple Race/Ethnicity (check all that apply) 1 = White 2 = Black or African American 3 = Hispanic or Latin 4 = American Indian and Alaska Native 5 = Asian 6 = Native Hawaiian and Other Pacific Islander
Age	Age in years calculated from	Numeric	__.__ years

Variable	Description	Nature of Variable	Coding of Variable
	the date of birth compared to the date of the dataset		
Iris Color	The predominant color of the iris in the each eye	Categorical	1 = Gray 2 = Blue 3 = Green 4 = Hazel 5 = Brown 6 = Black 7 = Other
Ocular Comorbidities	Does the patient have any of the following ocular comorbidities? (check all that apply)	Categorical	1 = Cataract 2 = Cytomegalovirus (CMV) Retinitis 3 = Diabetic Macular Edema 4 = Glaucoma or Ocular Hypertension 5 = Keratoconus 6 = Retinal Detachment 7 = Retinal Vein Occlusion 8 = Uveitis 9 = N/A

Variable	Description	Nature of Variable	Coding of Variable
Systemic Comorbidities	Does the patient have comorbidities associated with any of the following body systems? (check all that apply)	Categorical	1 = Circulatory 2 = Digestive 3 = Endocrine 4 = Immune 5 = Integumentary 6 = Muscular 7 = Nervous 8 = Reproductive 9 = Respiratory 10 = Skeletal 11 = Urinary 12 = N/A
Comorbidities	If yes, diagnosis associated with body system	Text	Text entered in this field will be coded based on the Medical Dictionary for Regulatory Activities (MedDRA).
Smoking	Does the patient report a history of smoking?	Dichotomous	1 = No 2 = Yes
Alcohol Abuse	Does the patient report a history of	Dichotomous	1 = No 2 = Yes

Variable	Description	Nature of Variable	Coding of Variable
	alcohol abuse		
Genotype	Does the physician report either of the genotypes for the patient?	Categorical	1 = rs11200638 of the *HTRA1* gene 2 = rs10611710 of the *CFH* gene 3 = Other 4 = N/A
Eye Involved	Which eye(s) have a diagnosis of nAMD	Categorical	1 = OD 2 = OS
Diagnosis Date	Date the patient's ophthalmologist diagnosed nAMD for each eye	Date	ODDiag = DD MON YYYY OSDiag = DD MON YYYY
Length of Diagnosis	Calculated from the date of diagnosis to the date of the dataset	Numeric	ODLength = __.__ years OSLength = __.__ years
Dates of Treatment	Aflibercept treatment dates for each eye	Date	ODTrt1 = DD MON YYYY OSTrt1 = DD MON YYYY

Variable	Description	Nature of Variable	Coding of Variable
	treated		
Baseline BCDVA	BCDVA prior to receiving initial aflibercept treatment for each eye treated	Number	ODVABL = _.__ OSVABL = _.__ Snellen BCDVA will be converted to Early Treatment Diabetic Retinopathy Study (ETDRS) LogMAR equivalent
Follow-Up BCDVA	BCDVA associated with each injection of aflibercept	Number	ODVA1 = _.__ OSVA1 = _.__ Snellen BCDVA will be converted to Early Treatment Diabetic Retinopathy Study (ETDRS) LogMAR equivalent
Baseline OCT	Central retinal thickness prior to receiving initial aflibercept treatment	Number	ODOCTBL = ___._ µm OSOCTBL = ___._ µm
Follow-Up OCT	Central retinal	Number	ODOCT1 = ___._ µm

Variable	Description	Nature of Variable	Coding of Variable
	thickness associated with each injection of aflibercept		OSOCT1 = ___._ µm

3. Responsibilities of Data Recipient. Data Recipient agrees to:

    a. Use or disclose the LDS only as permitted by this Agreement or as required by law;

    b. Use appropriate safeguards to prevent use or disclosure of the LDS other than as permitted by this Agreement or required by law;

    c. Report to Data Provider any use or disclosure of the LDS of which it becomes aware that is not permitted by this Agreement or required by law;

    d. Require any of its subcontractors or agents that receive or have access to the LDS to agree to the same restrictions and conditions on the use and/or disclosure of the LDS that apply to Data Recipient under this Agreement; and

    e. Not use the information in the LDS to identify or contact the individuals who are data subjects.

4. Permitted Uses and Disclosures of the LDS. Data Recipient may use and/or disclose the LDS **for its Research activities only.**

5. Term and Termination.

    a. Term. The term of this Agreement shall commence as of the Effective Date and shall continue for so long as Data Recipient retains the LDS, unless sooner terminated as set forth in this Agreement.

    b. Termination by Data Recipient. Data Recipient may terminate this agreement at any time by notifying the Data Provider and returning or destroying the LDS.

    c. Termination by Data Provider. Data Provider may terminate this agreement at any time by providing thirty (30) days prior written notice to Data Recipient.

d. For Breach. Data Provider shall provide written notice to Data Recipient within ten (10) days of any determination that Data Recipient has breached a material term of this Agreement. Data Provider shall afford Data Recipient an opportunity to cure said alleged material breach upon mutually agreeable terms. Failure to agree on mutually agreeable terms for cure within thirty (30) days shall be grounds for the immediate termination of this Agreement by Data Provider.

e. Effect of Termination. Sections 1, 4, 5, 6(e) and 7 of this Agreement shall survive any termination of this Agreement under subsections c or d.

6. Miscellaneous.

a. Change in Law. The parties agree to negotiate in good faith to amend this Agreement to comport with changes in federal law that materially alter either or both parties' obligations under this Agreement. Provided however, that if the parties are unable to agree to mutually acceptable amendment(s) by the compliance date of the change in applicable law or regulations, either Party may terminate this Agreement as provided in section 6.

b. Construction of Terms. The terms of this Agreement shall be construed to give effect to applicable federal interpretative guidance regarding the HIPAA Regulations.

c. No Third Party Beneficiaries. Nothing in this Agreement shall confer upon any person other than the parties and their respective successors or assigns, any rights, remedies, obligations, or liabilities whatsoever.

d. Counterparts. This Agreement may be executed in one or more counterparts, each of which shall be deemed an original, but all of which together shall constitute one and the same instrument.

e. Headings. The headings and other captions in this Agreement are for convenience and reference only and shall not be used in interpreting, construing or enforcing any of the provisions of this Agreement.

IN WITNESS WHEREOF, each of the undersigned has caused this Agreement to be duly executed in its name and on its behalf.

Carl Baker, MD, Partner
The Ophthalmology Group, LLP

Signed: _____

Print Name: Carl W. Baker

Print Title: Partner

Susan L. Coultas, PhD Candidate

Signed: Susan L. Coultas

Print Name: Susan L. Coultas

Print Title: PhD Candidate

Appendix C: Data Use Agreement for Cuyahoga Falls, OH Retinal Practice

DATA USE AGREEMENT

This Data Use Agreement ("Agreement"), effective as of 01 Mar 2016 ("Effective Date"), is entered into by and between Susan L. Coultas ("Data Recipient") and Thomas Hull, MD, of The Retina Group of Northeast Ohio, Inc. ("Data Provider"). The purpose of this Agreement is to provide Data Recipient with access to a Limited Data Set ("LDS") for use in research in accord with laws and regulations of the governing bodies associated with the Data Provider, Data Recipient, and Data Recipient's educational program. In the case of a discrepancy among laws, the agreement shall follow whichever law is more strict.

1. Definitions. Due to the study's affiliation with Laureate, a USA-based company, unless otherwise specified in this Agreement, all capitalized terms used in this Agreement not otherwise defined have the meaning established for purposes of the USA "HIPAA Regulations" and/or "FERPA Regulations" codified in the United States Code of Federal Regulations, as amended from time to time.

2. Scope and Purpose. This Agreement sets forth the terms and conditions pursuant to which Data Provider will Disclose certain information to Data Recipient. Except as otherwise specified herein, Data Recipient may make all Uses and Disclosures of the Limited Data Set necessary to conduct the research described herein: a comparison of neovascular age-related macular degeneration populations in the United States, with the goal of identifying variations in response to treatment with aflibercept.

3. Preparation of the LDS. Data Provider shall prepare and furnish to Data Recipient a LDS in accord with any applicable laws and regulations of the governing bodies associated with the Data Provider, Data Recipient, and Data Recipient's educational program.

Data Fields in the LDS. No direct identifiers such as names may be included in the Limited Data Set (LDS). In preparing the LDS, Data Provider shall include the data fields specified as follows, which are the minimum necessary to accomplish the research:

Table 1

Variables and Coding for General nAMD Population

Variable	Description	Nature of	Coding of Variable
Patient ID	De-identified	Text	Site 1 = 1001-1999

Variable	Description	Nature of Variable	Coding of Variable
	Patient Identification Number*		Site 2 = 2001-2999 Site 3 = 3001-3999 * (not based on a direct identifier)
Gender	Patient's Gender	Dichotomous	1 =Male 2 =Female
Race/Ethnicity	Patient's reported race or ethnicity	Categorical	1 =White 2 = Black or African American 3 = Hispanic or Latin 4 = American Indian and Alaska Native 5 =Asian 6 =Native Hawaiian and Other Pacific Islander 7 = Multiple Race/Ethnicity (check all that apply) 1 =White 2 = Black or African American 3 = Hispanic or Latin 4 = American Indian and

Variable	Description	Nature of Variable	Coding of Variable
			Alaska Native 5 =Asian 6 =Native Hawaiian and Other Pacific Islander
Age	Age in years calculated from the date of birth compared to the date of the dataset	Numeric	__._years
Iris Color	The predominant color of the iris in the each eye	Categorical	1 =Gray 2 =Blue 3 =Green 4 =Hazel 5 =Brown 6 =Black 7 =Other

Variable	Description	Nature of Variable	Coding of Variable
Ocular Comorbidities	Does the patient have any of the following ocular comorbidities? (check all that apply)	Categorical	1= Cataract 2 = Cytomegalovirus (CMV) Retinitis 3 = Diabetic Macular Edema 4 = Glaucoma or Ocular Hypertension 5 = Keratoconus 6 = Retinal Detachment 7 = Retinal Vein Occlusion 8 = Uveitis 9 = N/A
Systemic Comorbidities	Does the patient have comorbidities associated with any of the	Categorical	1 = Circulatory 2 = Digestive 3 = Endocrine 4 =Immune 5 = Integumentary

Variable	Description	Nature of Variable	Coding of Variable
	following body systems? (check all that apply)		6 =Muscular 7 =Nervous 8 =Reproductive 9 = Respiratory 10 = Skeletal 11 =Urinary 12 =N/A
Comorbidities	If yes, diagnosis associated with body system	Text	Text entered in this field will be coded based on the Medical Dictionary for Regulatory Activities (MedDRA).
Smoking	Does the patient report a history of smoking?	Dichotomous	1 =No 2=Yes
Alcohol Abuse	Does the patient report a history of alcohol abuse	Dichotomous	1 =No 2=Yes

Variable	Description	Nature of Variable	Coding of Variable
Genotype	Does the physician report either of the genotypes for the patient?	Categorical	1 = rs11200638 of the *HTRA1* gene 2 = rs10611710 of the *CFH* gene 3 =Other 4=N/A
Eye Involved	Which eye(s) have a diagnosis ofnAMD	Categorical	1 =OD 2=0S
Diagnosis Date	Date the patient's ophthalmologist diagnosed nAMD for each eye	Date	ODDiag = DD MON YYYY OSDiag = DD MON YYYY
Length of Diagnosis	Calculated from the date of diagnosis to the date of the dataset	Numeric	ODLength = __.___ years OSLength = __.___ years
Dates of Treatment	Aflibercept treatment dates for each eye treated	Date	ODTrtl = DD MON YYYY OSTrtl = DD MON YYYY
Baseline BCDVA	BCDVA prior to receiving initial	Number	ODVABL = __.___ OSVABL = __.___

Variable	Description	Nature of Variable	Coding of Variable
	aflibercept		
	treatment for each eye treated		Snellen BCDVA will be converted to Early Treatment Diabetic Retinopathy Study (ETDRS) LogMAR equivalent
Follow-Up BCDVA	BCDVA associated with each injection of aflibercept	Number	ODVA1 = __.___ OSVA1 =__.___ Snellen BCDVA will be converted to Early Treatment Diabetic Retinopathy Study (ETDRS) LogMAR equivalent
Baseline OCT	Central retinal thickness prior to receiving initial aflibercept treatment	Number	ODOCTBL = __.___mm OSOCTBL = __.___mm
Follow-Up OCT	Central retinal Thickness associated with each injection of aflibercept	Number	ODOCT1 = __.___mm OSOCTI = __.__ mm

4. Responsibilities of Data Recipient. Data Recipient agrees:

   a. Not to Use or Disclosure the LDS for any purpose other than the Research Project or as Required by Law;

   b. Not to Use or further Disclose any information in a way that, if done by the Data Provider, would violate the HIPAA Privacy Rule;

   c. To Use or Disclose the LDS only as permitted by this Agreement or as Required by Law;

   d. To use appropriate safeguards to prevent Use or Disclosure of the LDS other than as permitted by this Agreement or Required by Law;

   e. To report to Data Provider any use or disclosure of the LDS of which it becomes aware that is not permitted by this Agreement or Required by Law, including without limitation any Disclosure of PHI to an unauthorized contractors, within ten (10) days of its discovery;

   f. To require that any of its subcontractors or agents that receive or have access to the LDS agree to the same restrictions and conditions on the Use and/or Disclosure of the LDS that apply to Data Recipient under this Agreement; and

   g. Not to Use the information in the LDS to identify or contact the individuals who are data subjects.

5. Permitted Uses and Disclosures of the LDS. Data Recipient may use and/or disclose the LDS **for its Research Project activities only.**

6. Term and Termination.

   a. Term. The term of this Agreement shall commence as of the Effective Date and shall continue for so long as Data Recipient retains the LDS, unless sooner terminated as set forth in this Agreement.

   b. Termination by Data Recipient. Data Recipient may terminate this Agreement at any time by notifying the Data Provider and returning or destroying the LDS.

   c. Termination by Data Provider. Data Provider may terminate this Agreement at any time by providing thirty (30) days prior written notice to Data Recipient.

   d. For Breach. Data Provider shall provide written notice to Data Recipient within ten (10) days of any determination that Data Recipient has breached a material term of this Agreement. Data Provider shall afford

Data Recipient an opportunity to cure said alleged material breach upon mutually agreeable terms. Failure to agree on mutually agreeable terms for cure within thirty (30) days shall be grounds for the immediate termination of this Agreement by Data Provider.

e. Mitigation. Data Recipient agrees to mitigate, to the full extent practicable, any harmful effect that is known to Data Recipient of a Use or Disclosure of the LDS (by Data Recipient, its agents or subcontractors, or otherwise) in violation of the requirements of this Agreement.

f. Effect of Termination. Sections 1, 2, 4, 5, 6, 7, and 8 of this Agreement shall survive any termination of this Agreement under this section.

7. Indemnification. Data Recipient will indemnify, defend, and hold harmless Data Provider and any of Data Provider's affiliates and their respective trustees, officers, directors, owner, emloyees, and agents ("Indemnitees") from and against any claim, cause of action, liablity, damage, cost or expense (including, without limitation, reasonable attorney's fees and court costs) arising out of or in connection with any unauthorized or prohibited Use or Disclosure of the Limited Data Set or any other breach of this Agreement by Data Recipient or any subcontractor, agent, or person under Data Recipient's control.

8. Miscellaneous.

a. Change in Law. The parties agree to negotiate in good faith to amend this Agreement to comport with changes in federal law that materially alter either or both parties' obligations under this Agreement. Provided however, that if the parties are unable to agree to mutually acceptable amendment(s) by the compliance date of the change in applicable law or regulations, either Party may terminate this Agreement as provided in Section 6.

b. Construction of Terms. The terms of this Agreement shall be construed to give effect to applicable federal interpretative guidance regarding the HIPAA Regulations.

c. No Third Party Beneficiaries. Nothing in this Agreement shall confer upon any person other than the parties and their respective successors or assigns, any rights, remedies, obligations, or liabilities whatsoever.

d. Counterparts. This Agreement may be executed in one or more counterparts, each of which shall be deemed an original, but all of which together shall constitute one and the same instrument.

e. Headings. The headings and other captions in this Agreement are for convenience and reference only and shall not be used in interpreting, construing or enforcing any of the provisions of this Agreement.

IN WITNESS WHEREOF, each of the undersigned has caused this Agreement to be duly executed in its name and on its behalf.

Thomas Hull, MD
The Retina Group of Northeast Ohio, Inc.

Signed: _____

Print Name: Thomas Hull, MD

Print Title: President

Susan L. Coultas, PhD Candidate

Signed: _____

Print Name: SUSAN L COULTAS

Print Title: PhD CANDIDATE

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