Riitta Kauranen

“How happy are patients and caregivers?”

Humanistic burden of neovascular age-related macular degeneration

Metropolia University of Applied Sciences
Master´s Degree Programme
Health Business Management
Thesis
May 3, 2019

Author(s) Title Number of Pages Date	Riitta Kauranen “How happy are the patients and caregivers?” Humanistic Burden of age related macular de-generation 58 pages + 1 appendices May 3, 2019
Degree	Master´s Degree Programme
Degree Programme	Health Business Management
Instructor(s)	Juha Havukumpu, Senior Lecturer

Age-related macular degeneration (AMD) causes 8,7% of all blindness worldwide and is the most common cause of blindness in developed countries, particularly in people older than 60 years. The prevalence of AMD is increasing due to the fast growing aging population of the world. It is estimated that there will be nearly 30 million AMD patients by 2040. The treatment for the nonvascular type of AMD (nAMD) has significantly changed and advanced during the last decade. New anti-vascular growth factor, (anti-VEGF) ocular injections have replaced old therapies. Patients have now an effective treatment, which can prevent AMD related blindness and even restore vision.

The aim of this study is to explore how patients, their caregivers and health care professionals do experience the treatments and the connected humanistic burden. More particularly, this study is looking into the research and studies done on the humanistic burden caused connected to current AMD treatment. Therefore, this study is a literature review exploring this topic.

This literature review was conducted by carefully selecting the search words, searching relevant databases and selecting the studies fulfilling the inclusion criteria. The search yielded very few results thus each selected study is reported separately in this review.

AMD is a chronic and progressive disease; the treatments are expensive and regular injections in the eye. Treatments can continue many years even as often as monthly. nAMD is associated with major economic burden. Moreover, the research results show that the frequent treatments, older patient population, declining vision combined with other diseases and travel to treatment center are a major burden for patients and those assisting and caring for patients. The review shows that nAMD deteriorates patients and caregivers quality of life; it causes anxiety and depression to both parties even if treatment is successful and appreciated by patients and their caregivers. In the light of the reviewed studies, nAMD treatments limit patients social and physical functioning and contacts. Furthermore, this review highlighted the need to explore and understand the treatment from patients and caregivers perspective and take into consideration national differences. In addition, there is almost no recent research on the huge burden to health care professionals caused by nAMD treatments.

Keywords	Age-related macular degeneration, AMD, nAMD, burden, humanistic burden, disease burden, quality of life, health care

Contents

1 Introduction

The demographic change sets increasing demands to reorganize and personalize patient care. Additionally the health care reform in Finland encouraging public as well as private health care sector to investigate options for cost-effective ways to diagnose and treat patients. In many diseases, the patients are aged and may have several comorbidities. On the current economic landscape and demographic situation, the decision makers mainly look at cost effectiveness. However the has been demonstrated that the humanistic burden caused by treatments have a pivotal role in the health status of the patient. In decision-making and it is important to consider not only the safety and efficacy of the treatment but the humanistic burden to the patient, caregivers and health care providers by the treatment.

Age related macular degeneration (AMD) can be divided into two main categories dry AMD and neovascular AMD this research looks into to patients with neovascular age related macular degeneration (nAMD). The disease effects patients macular which is the central area in the retina responsible for sharp and clear vision. nAMD deteriorates this specific area rapidly. Even though current treatments options are effective, nAMD is the leading cause of blindness in developed countries including Finland. 10–20 % of all AMD-patients suffer from nAMD. (Käypä hoito 2016) Of all the visual impairments registered in the Finnish Federation of the Visually Impaired registry 41 % are caused by AMD and the number is over 59 % for visually impaired over the age of 65. Half of these visual impairments are caused by nAMD. (Ojamo 2018)

Intravitreal anti–vascular endothelial growth factor (anti-VEGF) therapy has become the established treatment of nAMD over the last decade. Various regimens have been developed to address the vast burden of treatment for nAMD. They are mainly aimed to. Minimizing the visit frequency by lengthening the visit and injection interval. (Rodrigues 2016) Currently many wAMD patient have monthly monitoring visits with a health care professional regardless of the status of their disease. At the monitoring visit, the health care professional makes the decision if there is a need for a treatment or not. (Käypä hoito 2016)

Patient’s quality of life and treatment burden experienced by the patients is measured seldom. Vision related quality of life is measured only in about 10 % of nAMD studies.

(Rodrigues 2016) Furthermore, quality of life measures have a larger scope than vision related quality of life.

The purpose of this literature review is to describe humanistic burden associated with nAMD. nAMD is a disabling disease which affect mostly elderly people, the youngest patients being 50 years old and prevalence increases at age 60 and especially among over 70 year olds. nAMD leads to impaired vision and possible to blindness. (Ojamo 2018) Therefor it is important to understand the burden of the treatment for the patient's side to optimize the treatment and health care recourses.

2 Theoretical background

Chapter 2 presents the theoretical background of this Master's thesis. It outlines AMD patient population and stakeholder groups, the importance of vision and introduces AMD as a disease, and the current treatment. Furthermore, it presents the importance of the treatment, unmet need related to the disease, and current burden of disease.

2.1 Aging population

The statistics show that the population of Finland does have a growing trend and therefor the share of over 65 years old will steadily grow in the population. According to Statistics Finland, population forecast from 2018 predicts that this specific age group will grow from 23 % to 33 % in ten years from 2020 to 2030. (Statistics Finland 2018). (Figure 1 and 2.) Elderly part of the population may have many health related challenges including impaired or decreased vision. Compromised vision reduces functional and mental capability in many ways. (Koskinen 2016)

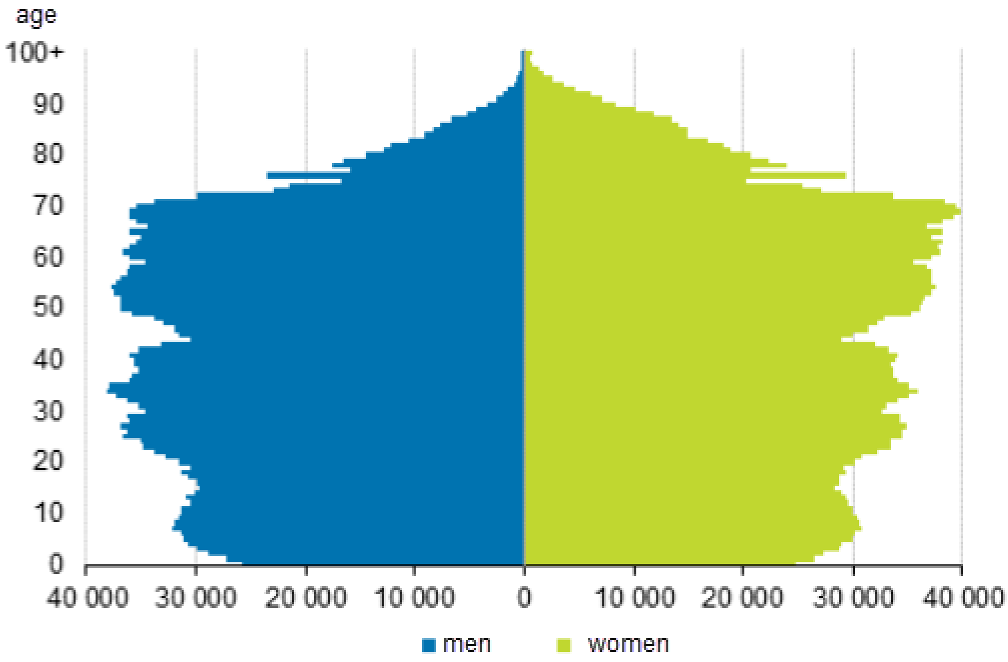


Figure 1. Finnish population by age and gender in 2017. (Statistics Finland 2018)

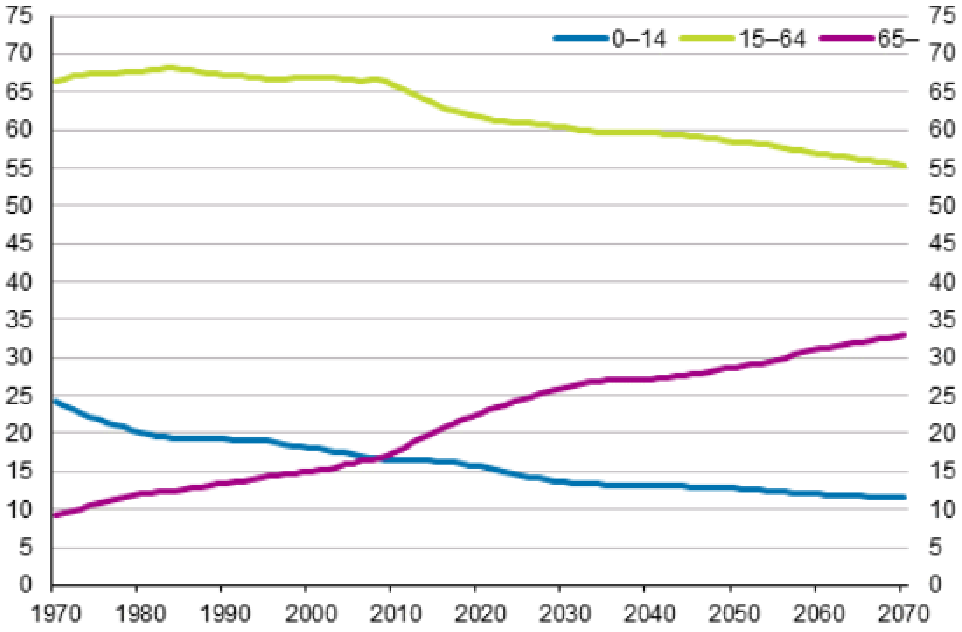


Figure 2. The share of each age group of the Finnish population 1970–2017 and forecast for s 2018–2070, in percentage. (Statistics Finland 2018)

Elderly population is the age group, which is using the primary health care services and about 20 % of over 75 year olds need external help at least once a day (Koskinen 2012).

To be able to see well people need increasingly more light. At the age of 40, the need for light has already doubled. Additionally color vision and contrast sensitivity decreases and visual field get narrower by age. 22 % of 75 year olds suffer from decreased vision. (Lupsakko 2008) With decreased vision, elderly experience often problems with moving and keeping their balance. Moreover, they may have trouble with household chores such as cooking, cleaning, finding things, reading daily paper and even getting their mail from the mailbox, navigating outside their homes or shopping. (Nordqvist 2003)

2.2 Age related macular degeneration

AMD is a common eye condition and a leading cause of vision loss among people age 50 and older. It causes damage to the macula, a small spot near the center of the retina and the part of the eye needed for sharp, central vision, which lets us see objects that are straight ahead. (National Eye Institute 2015) According to World Health Organization, the cause of the disease is not fully discovered and current medical and scientific understanding support at multi factorial ethology. The main risk factor is ageing. Other risk factors may include smoking, heritage, Caucasian race, arterial hypertension, exposure to ultraviolet rays, and a non-balanced diet. (WHO 2019) People with a family history of AMD are at higher risk. Researchers had identified nearly 20 genes that can affect the risk of developing AMD. Many more genetic risk factors are suspected. (American Academy of Ophthalmology 2015)

In some people, AMD advances so slowly that vision loss does not occur for a long time. In others, the disease progresses faster and may lead to a loss of vision in one or both eyes. As AMD progresses, a blurred area near the center of vision is a common symptom. Over time, the blurred area may grow larger or you may develop blank spots in your central vision. Objects also may not appear to be as bright as they used to be. (National Eye Institute 2015)

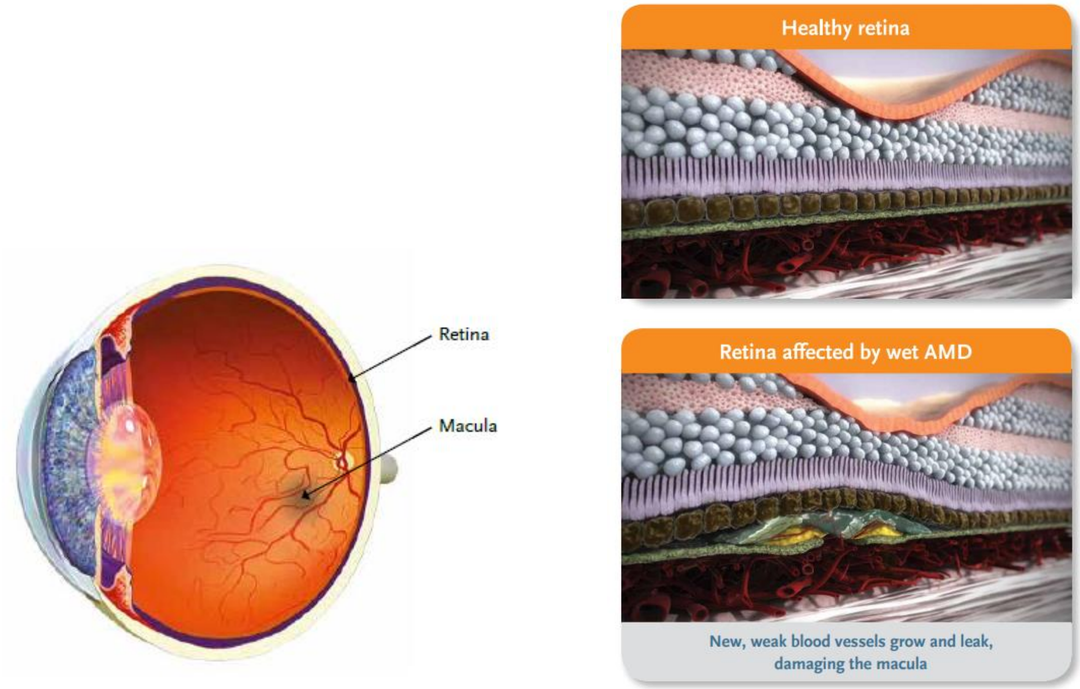
AMD by itself does not lead to complete blindness, with no ability to see. However, the loss of central vision in AMD can interfere with simple everyday activities, such as the ability to see faces, drive, read, write, or do close work, such as cooking or fixing things around the house. (American Academy of Ophthalmology 2015) AMD is the most common cause of permanent low and impaired vision in Finland. (Ojamo 2018) AMD affects the central part of retina and the sensory receptors in that area are damaged and gradually stop functioning. (Seppänen 2018)

AMD is the most common cause of irreversible visual loss in industrialized countries. In the USA, it is responsible for around 54% of severe sight loss in Caucasians. The prevalence increases with age and symptoms are rare in patients under 50 years of age. (Kanski 2016) AMD is a major medical and socioeconomic challenge worldwide and, based on increased life expectancy and a growing negative impact of environmental risk factors, particularly arteriosclerosis, obesity and smoking, its incidence is expected to at least double by 2020. (Schmidt-Erfurth 2014)

There are two main types of AMD dry and so called wet or neovascular AMD. Dry AMD is the most common form, covering around 90% of diagnosed disease. Neovascular AMD is much less common than dry, but is associated with more rapid progression to advanced sight loss. Furthermore, patients with AMD in one eye, have about a 50% chance of developing advanced AMD in the fellow eye within 5 years. (Kanski 2016) This highlights the need to rapid and effective treatment when nAMD is diagnosed.

2.3 Neovascular age related macular degeneration

Neovascular AMD is an acute onset and rapidly progressing disease, which impacts central vision. (Schmidt-Erfurth 2014). In nAMD, abnormal blood vessels grow in the eye, which can leak and cause vision loss. nAMD is a condition that affects the macula, a part of the retina at the back of the eye (Picture 1 left). The macula is the area that lets you see sharply in the center of your vision. With age, and with the build-up of waste products, changes can occur in the retina. This can result in new, weak blood vessels growing and leaking under the macula, damaging your central vision (Picture 1 right). (Genentech 2018).



Picture 1: Left: Anatomy of the eye. Right top: Healthy retina. Right bottom: Retina affected by wet AMD. (Medical gallery of Blausen Medical 2014)

2.4 Diagnosis and treatment of neovascular age related macular degeneration

Early AMD is not always easy to detect because early and intermediate stages of AMD usually start without symptoms. The disease can only be detected in a comprehensive eye examination by an ophthalmologist. The ophthalmologist may include the following test in the examination:

- visual acuity test for distance vision ability.
- retina and optic nerve examination with a magnifying lens for signs of AMD
- looking at Amsler grid. Changes in the central vision may cause the lines in the grid to disappear or appear curvy.
- Fluorescein angiogram. The test is done by injecting fluorescent dye into the patients arm and pictures are taken as the dye passes through the blood vessels in the eye. This enables the ophthalmologist to see leaking blood vessels typical to AMD.
- Optical coherence tomography (OCT). OCT capture images all retinal layers with light waves. With OCT the ophthalmologist can detect sign of AMD inside the retina. (National Eye Institute 2018)

At this moment, there is no treatment, that will completely restore vision loss, but the treatment options are able to slow or prevent addition vision loss or even improve remaining vision in some extent. Nutrition seems to play a role in the initiation and development of AMD. Lutein or zeaxanthin may have beneficial effect in reducing progression of AMD but further research and studies are needed in this area. (American Academy of Ophthalmology 2015)

The introduction of anti-vascular growth factor (anti-VEGF) injections around fifteen years ago represented a major advance for patients with wAMD. VEGF is a protein that promotes the growth of new abnormal blood vessels. Before each injection, your eye will be numbed and cleaned with antiseptics. To further reduce the risk of infection, you may be prescribed antibiotic drops. Photodynamic therapy is another less frequntly used treatment option and it involves laser treatment of select areas of the retina. Laser surgery is less common than other treatments but used in certain cases of nAMD. (National Eye Institute 2018)

Anti-VEGF injection therapy blocks this growth. The anti-VEGFs are the current mainstay of treatment for nAMD. These injections are made regarding to the vision loss in every 4-6 weeks by health care professionals. This intravitreal therapeutics have demonstrated efficacy in improving visual acuity in patients with nAMD. (Prenner 2015) nAMD treatment includes a monthly monitoring and/or injections for nAMD patients. Recent studies have shown that different treatment regimens can be adapted and longer injection interval implemented. Never the less many patients have monthly injection for the first 3 to 6 months and often even longer. Additionally patients may need to visit the clinic for control without injection. This requires some scheduling from patients and caregivers, and results in a significant burden on patients and their family. (Giocanti-Aurégan 2018) Thus, the management of patients with neovascular AMD is costly and time consuming from caregivers and patients perspective. Furthermore, providing high-quality care requires commitments of significant time and services from physicians, staff, patients, and caregivers. (Prenner 2015)

However, the burden of treatment and frequent monitoring visits is increasing with the aging population. wAMD patients are usually older and need to visit clinic up to twelve times a year. They often drop out of the treatment or visit the clinic less frequently this will lead to worse outcomes. Real-world data suggest that patients in clinical practice have less-frequent monitoring, receive fewer injections and experience less optimal outcomes than those seen in clinical trials (Schmidt-Erfurth 2014).

Laser surgery. Eye care professionals treat certain cases of neovascular AMD with laser surgery, though this is less common than other treatments. It involves aiming an intense “hot” laser at the abnormal blood vessels in your eyes to destroy them. This laser is not the same one used in photodynamic therapy which may be referred to as a “cold” laser. This treatment is more likely to be used when blood vessel growth is limited to a compact area in your eye, away from the center of the macula, that can be easily targeted with the laser. Even so, laser treatment also may destroy some surrounding healthy tissue. This often results in a small blind spot where the laser has scarred the retina. In some cases, vision immediately after the surgery may be worse than it was before. But the surgery may also help prevent more severe vision loss from occurring years later. (National Eye Institute 2018)

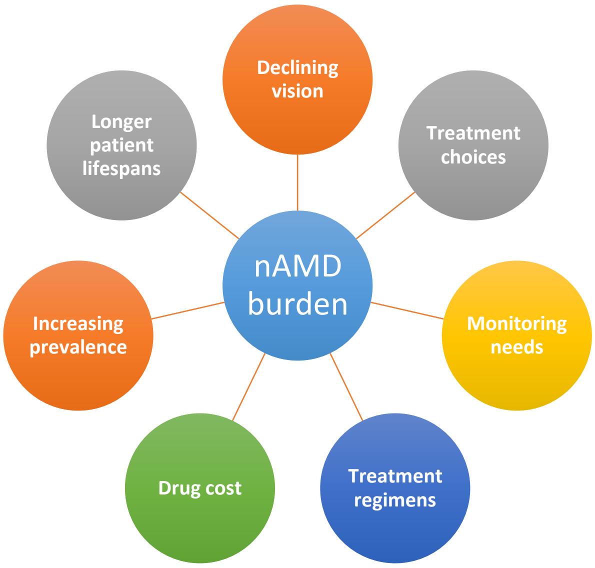
2.5 Stakeholders

In nAMD there are various stakeholders related to the patient and health care services. Furthermore, due to the relatively high age of the nAMD patients there are more stakeholders involved. There is no identified common endpoint for the treatment and thus the patient population is aging rapidly. This demographic development is demanding more recourses from home care, health care staff as well as other groups such as relatives. (Stakeholder map, picture 2).

Picture 2. Stakeholder map created by the author.

Increasing prevalence coupled with high resource utilization is extremely difficult for healthcare systems to manage. (Schmidt-Erfurth, et al., 2014) In real-world clinical situations, vision continues to decline in nAMD patients, and this is linked to the underutilization of treatment and monitoring. (Holz, et al., 2015) The major challenges are connected to patient visits (picture 3):

- More patients: aging population
- Capacity: Increasing demand creates a capacity shortage
- Frequent patient visits
- High injection frequency
- Scheduling difficulties
- Need to streamline office procedures
- Increasing demand for devices: OCT, fundus camera etc.
- Financial burden



Picture 3. The challenges with wAMD treatment. (Schmidt-Erfurth 2014)

2.6 Unmet medical need and burden of disease in nAMD

As visual impairment progresses, independence and overall quality of life decline in similarly. As visual function declines, the negative impact on activities of daily living substantially increases. This has been shown to have a detrimental impact on mental health, with 1 in 7 patients with AMD showing deterioration in mental capabilities. Patients with AMD have also shown an increased risk of depression compared with patients without AMD. (Prenner 2015)

As many as one-third of patients with AMD require caregiving services owing to their AMD. As AMD progresses, these indirect costs for caregiver services form a greater proportion of total costs, and caregiver burden can be substantial. (Schmier 2006)

Patients in real-world studies have fewer clinic visits than those in clinical trials and receive fewer injections than those in clinical trials. The anti-VEGF treatment schedule requires monthly monitoring visit and treatment if needed according to EMA medical product Summary of product characteristics guideline. This meant minimum of 12 visits per year. According to one-year, follow-up data from an observational nAMD treatment study with over two thousand patients the average number of injections were 5.2 per year and number of visits 7.4 per year. This is confirmed by other studies where the injection frequency is as low as 3.2 per year. (Michell 2014) Both diagnostics and experience with the treatment of nAMD have been extensively studied since and study finding have made it possible to extend the treatment interval. Despite this, some patients need monthly monitoring and/or monthly injections. The rapid progression of the disease still requires regular monitoring of disease activity and thus regular visits to the ophthalmology clinic.

The frequent treatment and monitoring requirements place a heavy burden on patients. Frequent visits to the clinic preoccupy patients' lives. (Boulanger-Chemama 2015) The most common reasons for the too high burden given by patients were transportation issues and the high time demands. Treating physicians report as the most common reasons the too high burden of visit the following, cost, logistics and patient number, patient age and compliance problems. (Wolf & Kampik, 2014) . Patients, caregivers commonly experienced sadness, fear, frustration, and depression due to the disease and connected treatment. Due to frequent injections, patients undergo treatment fatigue with anti-VEGF therapies, and some opt to discontinue treatment. (Varano 2016)

There is a need to build on successes in nAMD care and continually innovate to prevent blindness caused by the disease. Increasing prevalence coupled with high resource utilization is extremely difficult for healthcare systems to manage. (Schmidt-Erfurth, et al., 2014) In real-world clinical situations, vision continues to decline in nAMD patients, and this is linked to the underutilization of treatment and monitoring. (Holz 2015)

Fimea has published a report on biological medication in nAMD management in Finland in 2015 (Fimea 2015). Using the statistics from 2013 Fimea estimated the number of nAMD treated patients in Finland to be close to 11 500 approximately (table 1). The number is rising with about 400 patients every year. The total number of regional and university hospitals is 23 in Finland (Koponen 2015) while when information of patient numbers from nine regional hospitals is missing from Fimea statistics.

The number of injections within one year per eye is between two and nine according to the health care professionals. The number of injections is depending on the patient's disease status and hospital treatment algorithm.

year	Number of patients	Average number of injections per year	total
2017	11 500	5,2	59 800
2025	14 700	5,2	76 440

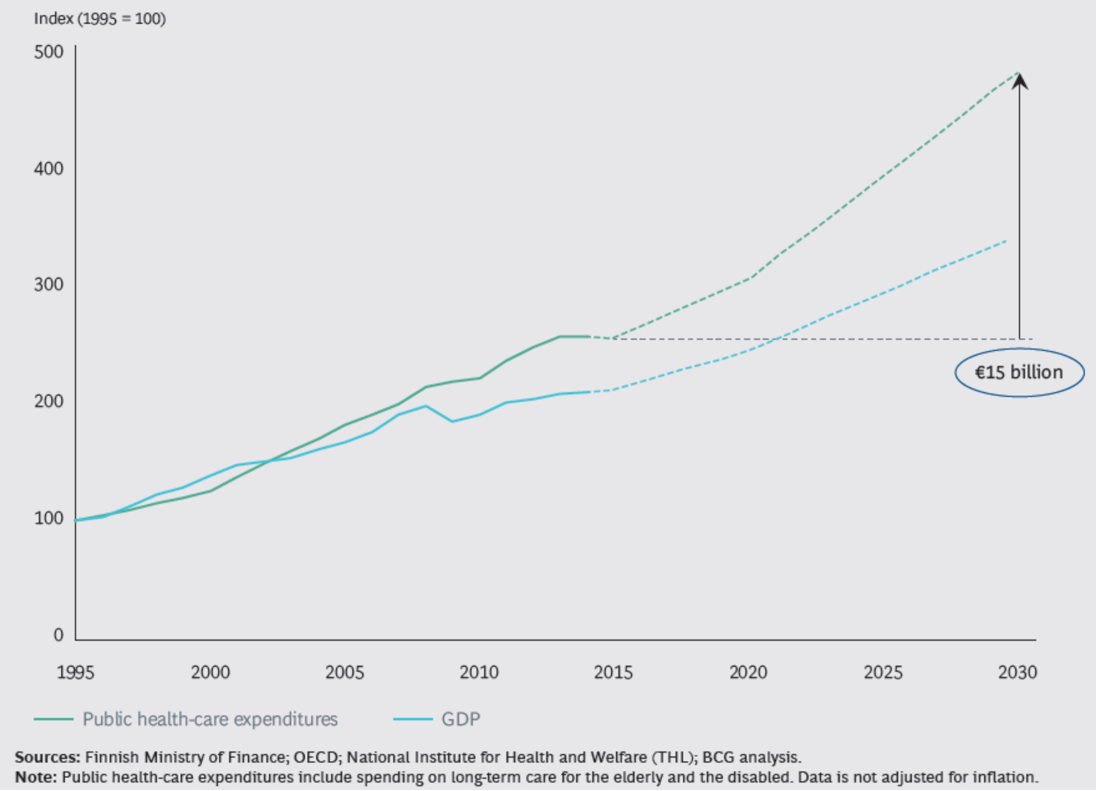
Table 1. Number of patients and injections in 2017 and estimate for 2025 if the number of injections is stable and patient population increases by 400 patients per year. (Based on HCP discussions and Fimea estimates).

2.7 Cost effectiveness and recourses

AMD results in substantial economic impact in terms of direct health care costs. Costs also increase in direct proportion to disease progression. (Schmier 2012)

The Finnish health care offers universal coverage; costs are relatively low and quality above average (OECD 2017). However lately the Finnish health care system is facing some severe challenges; not only the current social and health care reform (SOTE) but also the aging population and higher cost associated with new medicines and health technologies. The current rate and growth of expenditure is unsustainable (Ministry of Finance 2018) (Figure 3). Additionally Finland is facing a shortage of human recourses to meet the increasing demand of health services. This will lead to constrains in access to health care services and shortage of key medical personnel. Even though due to the delay of the health care reform (SOTE) decisions and implementation, municipals are not recruiting as many health care professionals as in previous years. The uncertain situation is lowering the human recourses demand and making it less predictable. (Koponen 2015)

There is no current statistics available in Finland but according to Swedish Macula Register 46 % of AMD-patients' visits to clinics do not lead to treatment. (Makularegistrets Årsrapport 2016) A patient in a standard of care control frequency visits a clinic on average 8.6 times a year. (Writing Committee for the UK Age-Related Macular Degeneration EMR Users Group 2014) According to this statistics, the patient visits the clinic four times per year unnecessarily. The average cost for a visit is 66 euros without any testing or examination done (Vottonen and Kankaanpää, 2016). Given this, the potential saving can be calculated to be 261 euros per year per patient. In Finland there are approximately 11 500 patients treated for nAMD yearly (Fimea 2015) thus the potential saving could reach up to 3 million euros.



Sources: Finnish Ministry of Finance; OECD; National Institute for Health and Welfare (THL); BCG analysis.
Note: Public health-care expenditures include spending on long-term care for the elderly and the disabled. Data is not adjusted for inflation.

Figure 3. Spending on health care in Finland is increasingly outpacing growth in GDP. (The Boston Consulting Group 2016)

It is important to discuss the value of care or how to deliver better high quality care and improved health care outcomes with the same cost. One and perhaps only way to control the costs while improving the quality is by concentrating in value. Value is defined as a particular health outcome for a certain level of total cost. It has also been shown that investments in quality of care may not increase but reduce the total costs. (The Boston Consulting Group 2016)

Currently health care provider i.e. public hospitals, measure productivity. Productivity is the relationship between the outcome and the investments (total costs) used to reach the outcome. Both costs and produced services influence the productivity. Thus if the costs and services produced increase in the same ratio, the productivity stays the same or if cost go up but services stay in the previous level, the productivity goes down. (THL 2017).

Drugs such as anti-VEGF injections used to treat nAMD are administered in hospitals and thus paid by the municipality. Contrary to outpatient drugs which are mainly reimbursed by the National Social Security System (KELA). The drugs administered at the hospital are paid from the hospital budget. The number of patients with nAMD is increasing due to the demographic change and the key stakeholders in the medical community understand the challenge. The university hospital ophthalmology departments estimate in 2018 that the situation will become unsustainable within the next one to two years.

2.8 Summary

There is a need a successful nAMD care pattern and continuously innovate to prevent blindness and impaired vision caused by the disease. Increasing prevalence coupled with high recourse utilization may lead to further difficulties for health care systems to manage. In clinical practice, fewer injections are administered than what is recommended and needed. This may result in declining vision. Patients undergo treatment fatigue with anti-VEGF therapies, and some decide to discontinue treatment.

3 Purpose, aim and research objectives

There is a limited amount of research done on humanistic burden of disease in nAMD. These patients are often elderly and have other health related limitation. Furthermore, depression and other mental challenges are mentioned in connection to ocular diseases affecting visual acuity. nAMD patients need anti-vascular growth factor treatment immediately after diagnosis and regularly after the first treatment. (Käypä hoito 2016)

Existing anti-VEGF treatments are injections given at hospital premises in a regular schedule. The total number of injections given to a patient per year is approximately seven to eight and can be as often as once a month as long as the disease is considered active and treatment relevant by the treating physician. (Kataja 2017) Due to the demographic change, the economic burden of nAMD to society is increasing. Additionally there frequent treatments cause burden to patients, caregivers and health care system. (Schmidt-Erfurth 2014)

The aim of this systematic literature review is to collate and describe the evidence pertaining to the humanistic burden associated with nAMD. In addition, the aim of this review is to give a better understanding of the concept of nAMD treatment from patients and caregivers perspective.

More specifically, this study is exploring the burden of frequent anti-VEGF injections to patients and caregivers in their daily life. Additionally this study was set out to examine how the patient experience could be improved. What kind of suggestions and wishes patients and caregivers have expressed in currently published studies.

Majority of current research is addressing, investigating and comparing treatment efficacy and safety, but there seem to be very little research on patients’ and caregivers’ experiences, preferences, expectations, and disease related burden. It can be discussed why the treatment compliance is not always optimal.

4 Materials and methods of systematic literature review

This chapter describes the research methodology and research method used in this study. Additionally the chosen research approach is discussed, and furthermore the data collection and analysis methods are presented.

4.1 Motivation for the chosen review type

In this study, the researcher aims to explore humanistic burden of treatment. Burden is very subjective and individual experience and to understand the phenomena or draw conclusions large number of subjects have to be researched or interviewed. The researcher has explored different research options and arrived into conclusion that systematic literature review generates the most information in a limited time. To answer the research questions the researcher used comprehensive pre-planned search strategy and clear inclusion and exclusion criteria. (Saunders 2007) The search strategy is presented in detail in this chapter.

Furthermore, systematic literature review discusses the research question from different perspectives and gives a broader understanding of the topic than other research types. (Tranfield 2003) The objective is to increase the understanding of treatment burden based on current literature. Therefore, systematic review including a comprehensive synthesis of the individual studies gives the most extensive presentation of the current knowledge of the subject is thus chosen as the method of this work.

4.2 Systematic literature review

A systematic review summarizes the results of available studies on a defined topic and provides a higher level of evidence as well as builds a consolidated picture of current research results or identifies existing problems areas. Judgments may be made about the evidence and informed recommendations for healthcare. (Salminen 2011)

A systematic review attempts to organize all empirical evidence that fits pre-specified eligibility, inclusion and exclusion criteria in order to answer a specific research question or hypothesis. It uses transparent and systematic methods to collect data, attempts to minimize bias, and thus provide more reliable findings from which conclusions can be drawn and decisions made. (Higgs and Green 2011)

Systematic literature review requires careful planning and description of the process to enable to copy and implement the same process identically (Metsämuuronen 2011). A literature review can highlight important articles and findings, bring them into discussion and common knowledge. In this study, the systematic review aims to explore the extend of studies regarding patient and caregiver experiences about and during nAMD treatment. The studies are not chosen randomly rather all included studies are systematically chosen with fair rationale and justification. Systematic data selection enables reliable research results. (Aveyard 2011)

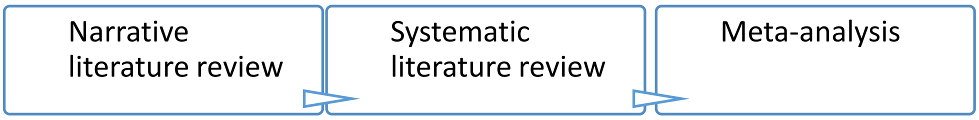
The key characteristics of a systematic review are:

- a clearly stated set of objectives with pre-defined eligibility criteria for studies
- an explicit, reproducible methodology

(Higgs and Green 2011)

4.3 Narrative literature review and meta-analysis

There are three main types of literature reviews, narrative review, systematic review and meta-analysis. Narrative literature review is one of the most frequently used literature review types. It could be characterized as an overview of a specific topic without rigorous and mandatory rules. Despite this, the phenomenon in question can be described and represented widely and the characteristics of the phenomenon classified. Additionally the study question is broader than in a systematic review or a meta-analysis. In some cases narrative review is written to create discussion and the viewpoint of the review may not always be objective. Even if narrative literature review is an independent method, it frequently offers substance for a systematic review. (Salminen 2011) (Picture 2)



Picture 2. Different literature review types. Adapted from Salminen (2011)

Meta-analysis is most demanding type of literature review. In meta-analysis the researcher combines quantitative studies and generalizes the results with statistical methods. This enables the researcher to make conclusions from the content of different studies and create congruence. Meta-analysis creates more holistic view of the study topic compared to individual studies. The most important strength of meta-analysis is its ability to form numeric results from a large data set. (Green 2006)

4.4 Systematic literature review design

Systematic literature review process can be divided roughly in three separate stages, planning phase, constructing and executing the search including data analysis, and reporting the results. In the planning phase, the researcher creates a comprehensive study plan and scrutinizes earlier research on the topic. When the research question is defined, the researcher selects the most appropriate research method. Moreover, the most suitable databases and the most appropriate search terms are determined in this stage. (Salminen 2011) The researcher defines one to three research questions (Metsämuuronen 2011).

One of the features that distinguish a systematic review from a narrative review is the pre-specification of criteria for including and excluding studies in the review. This reflects to relevance of the material. Eligibility criteria are a combination of aspects of the research question and specification of the types of studies that have addressed these questions. The criteria should be easy to implement in the data selection phase. Outcomes usually are not part of the criteria for including studies. (Higgs and Green 2011)

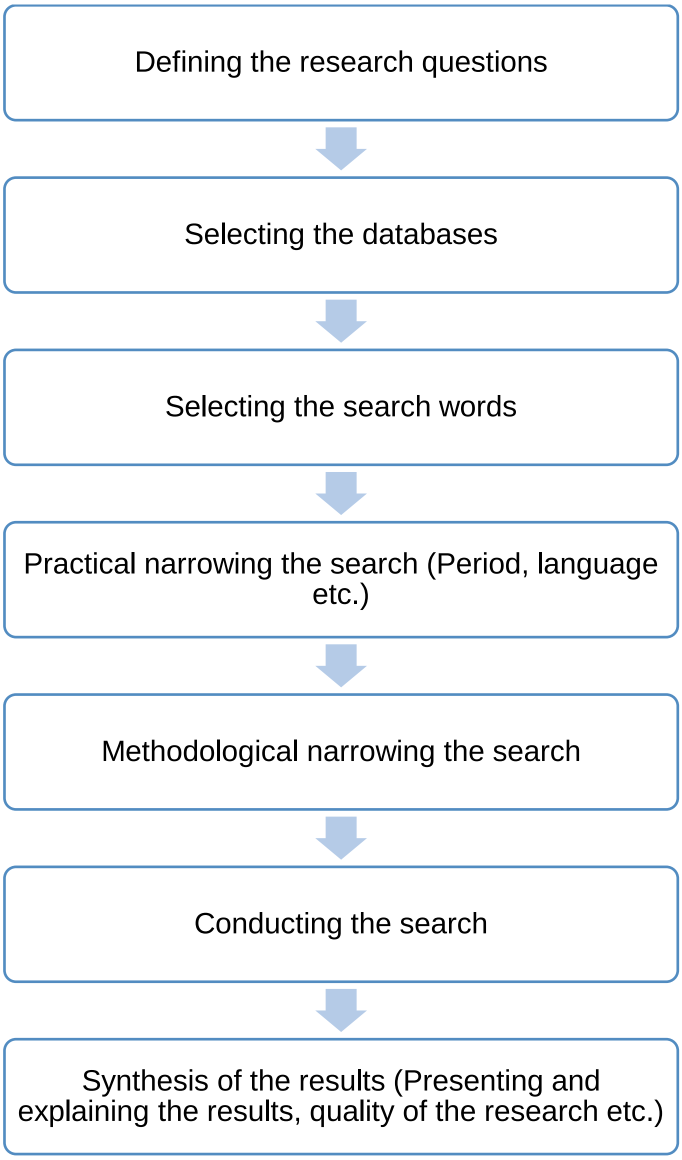
In the second phase, the researcher selects the studies using the eligibility criteria for studies to be included in the review .The eligibility criteria will specify the types of designs, types of participants, types of intervention and, in some cases, the types of outcomes to be addressed. The selected studies are then analysed in this phase. To ensure reliability, relevance and reproducibility it is advisable to record all literature review steps in detail. Finally, in the last phase results are reported with conclusion drawn from all the obtained results. (Higgs and Green 2011; Metsämuuronen 2011)

This systematic literature review follows a standardized methodology which Fink's (2010) systematic review model as the starting point. Which the writer this study has made minor adjustments (picture 3).

Fink has divided the process of conducting a literature review in seven steps. The review starts with finding and formulating the research question. The research question is the engine moving the literature review forward to the correct direction during the whole process. This step is followed by selection of the appropriate sources, literature and databases to conduct the searches. The courses may include literature and article databases (usually internet-based databases), other websites and other courses such as article reference lists and clinical study sites. The third step is to select the search words. The search word may consist of word, several words, or a phrase. Using the search word the researcher can gather articles, books or report to answer the research question. The first searches usually yields a high number of articles, but most of them are not relevant to the research question. Therefor the fourth and fifth phase of the process relate to screening of the material. In the fourth phase, the already above-mentioned precise inclusion and exclusion criteria are decided and implemented. Such criteria may consist of limited period i.e. ten years or six months, language, accessibility without cost or the status of the publication. (Salminen 2011)

In the fifth phase the researcher evaluates the search results in the light of the methodology i.e. making a critically appraising the scientific level of the selected research and studies. The sixth phase in the process is the writing of the review itself. The reliable of the review requires a standard data collection process, which is meticulously followed. In the last phase, the collected data is synthesized and results described. In this phase there is a risk of superficially describing the results thus it is important to thoroughly explain the results and the quality of the study.   (Salminen 2011)

The phases used in this literature review are shown in picture 3.



Picture 3. The steps of a systematic literature review (Salminen 2011)*

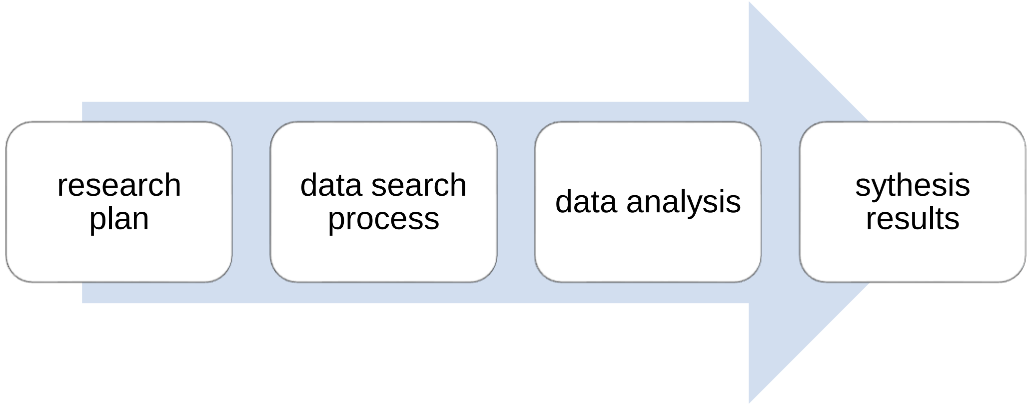
---

*picture 3 is an adaptation from Salminen' (2011) picture. The picture by Salminen is an adaptation from Fink's (2005) original model.

4.5 Research methodology - the research process

The aim of this study is answer the defined research question regarding the burden of frequent anti-VEGF injections to patients and caregivers in their daily life "how do patient experience the nAMD treatments?" In addition, the aim of this review is to give a better understanding of the concept of nAMD treatment from patients' and caregivers' perspective and how the patient experience could be improved.

The Fink's literature review step model presented above was further refined and steps combines for this study. The final research process is shown in the picture 4.



Picture 4. Final research process used in this research.

In this study, the first phase was formulating the research plan and the second phase the concrete data search. The data search was conducted using electronic databases through specific database web sites. The collected and identifies material was analyzed in the thirds phase. In addition, in the last, fourth phase the researcher finalized the synthesis of the study. In the synthesis, the researcher discussed and documented the results, summary of the results and conclusions based on the study. Different phases of the study were conducted partly simultaneously and the process was not progressing systematically as in the illustrations and models show. The researcher started the data search process first before the final research plan and research question were finalized to follow through the process and to understand the landscape of inclusion and exclusion criteria better and to recognize the best search terms. Furthermore, the researcher wanted to identify how much relevant information was available about the entire topic of the study.

4.5.1 Research protocol, question, inclusion and exclusion criteria

In the systematic literature review, the research plan is called research protocol. It functions as a guideline during the full study project and it guarantees the systematic execution of the research. Secondly, the protocol secures that the research approach answers the research question as closely as possible. Like any other, literature review including this study needs a detailed and pre-planned protocol with a full description of the research process and methods to be used. Thus the protocol ought to include the research question, inclusion and exclusion criteria and the method use. Additionally the protocol ought to include the information how the researcher is planning to evaluate the included studies and articles as well as how she is planning to formulate the synthesis from the obtained information. (Coren 2006)

In the protocol of this study, the researcher attempts to find factors influencing the humanistic burden associated to nAMD treatment and care from the giver's perspective patients and caregivers have.

The formulation of inclusion and exclusion criteria have a significant role in the protocol process as well as in the execution and results of the research. (Table 2) Hence, the selection of the final studies is guided by these preselected criteria. (Metsämuuronen 2011) In a systematic literature review, material is chosen by selecting it with the defined criteria. Inclusion and exclusion criteria set the limits for as large as possible selection of materials, which at the same time attempt to answer the research question. (Aveyard 2010)

Inclusion criteria

- articles and studies (material) published in English
- material published between 2010 and February 2019
- electronic material available free of charge
- material published in a peer reviewed journal
- full text available
- locan and/or international reference groups
- different reseach methods
- material content include and address nAMD and patient or/and care giver experience related to nAMD treatment

exclusion criteria

- original reseach and/or publication language different from english
- materials not filling the common scientific reseach criteria
- articles and publications that do not inlcude and patient or/and care giver experience related to nAMD treatment
- articles and publications that only have a treatment or pharmaceutical related comparisons or data
- data used in the publication or article is before 2010 when anti-VEGF treatments were not globally accepted first line treatments.

Table 2. Study inclusion and exclusion criteria

In this study the aim of the study and research question formed the main limitations to the inclusion and exclusion criteria. In language selection, only materials in English language were accepted and all other languages were excluded. The current publications in ophthalmology field are almost all in English. All relevant articles written by Finnish or Nordic scientists, which would be of great interest due to locality, are as a rule published in English. Materials directed to patients or larger public are usually published in local language however, these materials would not fulfil the scientific inclusion criteria for this study.

This study only accepts material from 2010 to 2019. Anti-VEGF treatments started as a mainstream and first line treatment only 2007 or later in most countries. For a study to be published in a peer review paper takes often more than a year after the paper is written. Thus, the author of this study tries to avoid searching among publications, which do not have anti-VEFG as the treatment option for nAMD.

Today almost all publications and papers are available on websites therefor only electronic publications are included. This choice is furthermore supported by the time period selection. If the period were longer, it would have been more difficult to find all available material from web pages. It was also considered mandatory that the articles were published as full text and free of charge. Getting a comprehensive idea of the article only based on abstract would have been questionable and comparing full articles to abstract information would not have been scientifically sound. Additionally the articles were to be free of charge and not to create extra cost to the researcher. Moreover currently most publications are available free of charge even papers with highest scientific journal ranking.

The materials from publications were to be full articles but different research methods in studies the article presented were accepted. Already in the preliminary data search, process became apparent that there is only limited number of studies and publications on humanistic burden of nAMD treatments. At the same time, there is a waste amount of studies comparing treatments, pharmaceuticals, costs as well as how different treatments and treatment regimens affect costs. Because of this, the researcher accepted studies, which are done with different methods and included a clinical study search in European and US study sites with both published and ongoing studies.

The most important inclusion criteria was the selection of search words. The researcher decided to use several search words and phrases. Most articles and publications in the first searches had numerous hits, several tens of thousands. The clear majority of the articles described studies regarding treatments, treatment regimens and/or pharmaceutical related comparisons or data. Since the humanistic burden of disease is the central theme of this study, it was important to include expression of burden in the search words or phrases. During the trial searches, it became apparent that only very few search words could be used with expression *burden of disease* or *disease burden* to obtain any results from databases. Without some expression of burden or quality of live, the search yielded more than 500 000 hits which number of articles is beyond the capacity of the researcher to scan through even superficially. The selection of search words is explained in the next chapter.

4.5.2 Databases and search words

The searches and material collection was done in several steps including selecting the search terms and databases, collecting and selecting the materials. The first step was to select the databases. The researcher selected well-known, medical and scientific databases, which are commonly used in studies. The researcher also included both US and EU clinical trials sites. The selected databases:

- Embase
- Medline
- Pubmed
- Cochrane Library
- US National Library of Medicine, ClinicalTrials.gov
- EU Clinical Trials Register

Search words and terms were selected according to the disease area, nAMD. The final search terms for disease were *macular degeneration* or *age-related macular degeneration* which are official terms for nAMD and therefor more likely to be found in the scientific publications.

The second chosen search term was *burden*. The word burden can stand for many different themes and was not limiting enough in the search. Thus, the search term *disease burden* was selected. The term disease burden is used in several contexts including comparative medication and treatment burden to economic burden to the health care system and society caused by the treatment as well as burden to patients and caregivers. The terms were connected as follows, macular degeneration or age-related macular degeneration and disease burden.

In an optimal search, more search words could have been added. Yet in the preliminary trial searches adding terms with word *or*, such as quality of life or patient yielded more than 500 000 results therefor it was only possible to connect the search terms with *and*.

Term quality of live yields thousands of hits for the reason that it has been a popular research topic in health care, social sciences and even in economic studies for few decades. World Health Organization defines Quality of Life as an individual's perception of their life in the context of the culture and value systems in which they live. It is a broad concept affected by the person's physical health, psychological state, personal beliefs, social relationships and their relationship to their environment. (WHO 2019)

The term quality of life is inherently ambiguous, as it can refer both to the experience an individual has of his or her own life and to the living conditions in which individuals find themselves. Hence, quality of life is highly subjective. Whereas one person may define quality of life according to wealth or satisfaction with life, another person may define it in terms of capabilities. A disabled person may report a high quality of life. Thus, quality of life refers to the degree to which an individual subjectively feels healthy, comfortable, and able to participate in or enjoy life events. (Jenkinson 2019)

Equally using the search terms macular degeneration or age-related macular degeneration and burden or disease burden yielded more than 27 000 hits with or without term quality of life. The selected terms and connecting words are show in table 3.

	•Macular degeneration
OR	•Age related macular degeneration
AND	•Disease burden/burden of disease
OR	•Quality of life

Table 3. Selected search terms and connecting words.

4.5.3 Database search structure and strategy

The searches were conducted using the selected search words and term in combination. Initially the researcher aimed to use the selected search words in a similar format in all database searches. The results of these original searches with the initial terms in the original format are explained in the below text. For some of the databases the search terms needed to be modified due to excessive amount of hits. All the searches were conducted between February 27th and March 1st 2019. The modifications of the terms are shown in the following text.

- The Embase search database is a highly flexible, multipurpose and up-to-date biomedical database. It covers the most important international biomedical literature, all articles are indexed by Embase thesaurus, and advanced searches can be done with Emtree, which uses extensively this indexing. In the Embase search the researcher included Pubmed and Medline as this was possible to be done in in the Embase search. In this study Embase database basic search function was used with the initial search term combination from Embase thesaurus;

  macular degeneration or age related macular degeneration and disease burden or quality of life.

  All the search terms were searches *all fields*, thus all fields in the articles were searched for the search terms. This search yielded over 500 000 hits. If term quality of life was removed the number of hits reduced to 52. These results included many in the disease area of geographic atrophy, which is a different type of macular degeneration than nAMD, and not in the scope of this study. The search was modified changing the word *or* to word *and* between disease burden and quality of life and time was limited to years from 2010 to 2019. The final search terms were

  ('macular degeneration'/exp OR 'macular degeneration' OR 'age related macular degeneration') AND 'disease burden' AND 'quality of life' AND [2010-2019]/py

  This search yielded 15 results, which were included in the final study. (Embase 2019)

- Cochrane Library is aimed for all individuals, societies, researchers, decision makers and everyone interested in using high-quality information to make health decisions. Cochrane's global independent network gathers and summarizes the best evidence from research to help others to make informed choices about treatment. The goal and vision of Cochrane is to enable decisions about health and health care to be

made based on informed by high quality, relevant and up-to-date synthesized research evidence. There are now over 7,500 Cochrane systematic reviews, which are published in the Cochrane Library. (Cochrane 2019)
In the Cochrane Library search, the advanced search function was used. In the first search *all text was* used as search filter and the search was limited to the period of January 1st 2010 to March 1st 2019*.* The initially selected search words were used

"macular degeneration" OR "age related macular degeneration" AND "burden of disease" OR "quality of life"

The search yielded 1808 results. Therefor the researcher modified the search term by connecting terms *burden of disease* and *quality of life* with word *and*.

"macular degeneration" OR "age related macular degeneration" AND "burden of disease" AND "quality of life"

66 Cochrane Reviews matching on *"macular degeneration" OR "age related macular degeneration" AND "burden of disease" AND "quality of life"* in *all text* - with Cochrane Library publication date between January 2010 and March 2019 including automatic word variations search.

Additionally Cochrane Library searches other documents than articles. The search identified eleven Cochrane protocols, 1639 trials, one editorial and six clinical answers matching the search terms and period. This study includes the Cochrane protocols, editorial and clinical answers in the search results. However, the 1639 trial documents are excluded as searches in both US Clinical Trials and EU Clinical trials sites are included in this study.

- US National Library of Medicine, ClinicalTrials.gov is a database of privately and publicly funded clinical studies conducted around the world. There are 298,505 research studies from US and 208 other countries. The site is listing the studies but the listing does not mean that the study has been evaluated by the U.S. Federal Government.ClinicalTrials.gov is provided by the U.S. National Library of Medicine. (ClinicalTrials.gov 2019)

  The ClinicalTrials.gov search function has three fields, condition or disease, other term and country. In this search, the researcher used terms *macular degeneration or*

Age Related Macular Degeneration as condition or disease and *burden of disease or quality of life* as other terms.

burden OR 'burden of disease' OR 'quality of life' | *'macular degeneration' OR 'Age Related Macular Degeneration'*

There was not need to limit the studies to specific countries. Neither was period limited. These search terms yielded 94 hits. From the 94 studies, only four filled the inclusion criteria. Most of the studies in the database are comparative between pharmaceutical products or treatment regimes. Additionally the search included many dry AMD studies, which were out of the scope of this study. Changing the search terms to

burden OR 'burden of disease' AND 'quality of life' | *'macular degeneration' OR 'Age Related Macular Degeneration'*

yielded 23 results but only one study was eligible. Therefor the researcher decided to use the first search terms with the word *or* between burden of disease and quality of life. Consequently, the search on ClinicalTrials.gov follow the initially planned search terms but the search was different from Embase search, which did not follow the initially planned search term formulation and used the word *and* between burden of disease and quality of life.

This search yielded 94 results, which were included in the final study.

- The EU Clinical Trials Register contains information on interventional clinical trials on medicines conducted in the European Union, or the European Economic Area. In this Register, it is possible to view the description of phase II to phase IV adult clinical trials and diverse paediatric clinical trials where the investigator sites are in the EU/EEA. (EU Clinical Trials Register 2019)

  The search with search term *macular degeneration* with period limited from 2010 to 2019 yielded 40 results. All of the result trials were phase IV studies, despite that they were all either comparative trials or safety and efficacy trials. These types of trials only include information about the medicine and not from the patient or caregivers. The search was repeated with additional one-word search terms *burden* or *quality.* The searches with these term combinations did not yield any results. Therefor The EU Clinical Trials Register database was excluded from the study.

4.5.4 Final data collection

After the first search and material selection process, the researcher had identified 166 eligible articles or studied. These studies included the search inclusion terms. By reading the tittles and abstracts, 14 of the studies fulfilled the inclusion criteria. In the next step, the researcher read the full articles and based on careful reading and following the inclusion criteria, six studies were included in this study.

Critical appraisal and critical appraisal tools enable researchers to systematically assess the trustworthiness, relevance and results of published papers. In this study, the researcher has used publically available Critical Appraisals Skills Programme (CASP) tools to evaluate the selected studies. (CASP 2019) The CASP Checklist consists of ten questions to understand qualitative research and the usefulness a study. In this case, the tool is used to all selected studies, which will be read fully. In general terms three broad issues need to be considered when appraising a qualitative study: Are the results of the study valid? What are the results? Will the results help locally? (Table 4). The first two questions are screening questions and can be answered quickly. If the answer to both is "yes", it is worth proceeding with the remaining questions. The questions are all answered "yes", "no" or "cannot tell". The more yes answers the reader can give the better the quality of the study is. (Critical Appraisal Skills Programme (CASP) checklist 2018)

Section A: Are the results valid?

- Was there a clear statement of the aims of the research?
- Is a qualitative methodology appropriate?
- Was the research design appropriate to address the aims of the research?
- Was the recruitment strategy appropriate to the aims of the research?
- Was the data collected in a way that addressed the research issue?
- Has the relationship between researcher and participants been adequately considered?

Section B: What are the results?

- Have ethical issues been taken into consideration?
- Was the data analysis sufficiently rigorous?
- Is there a clear statement of findings?

Section C: Will the results help locally?

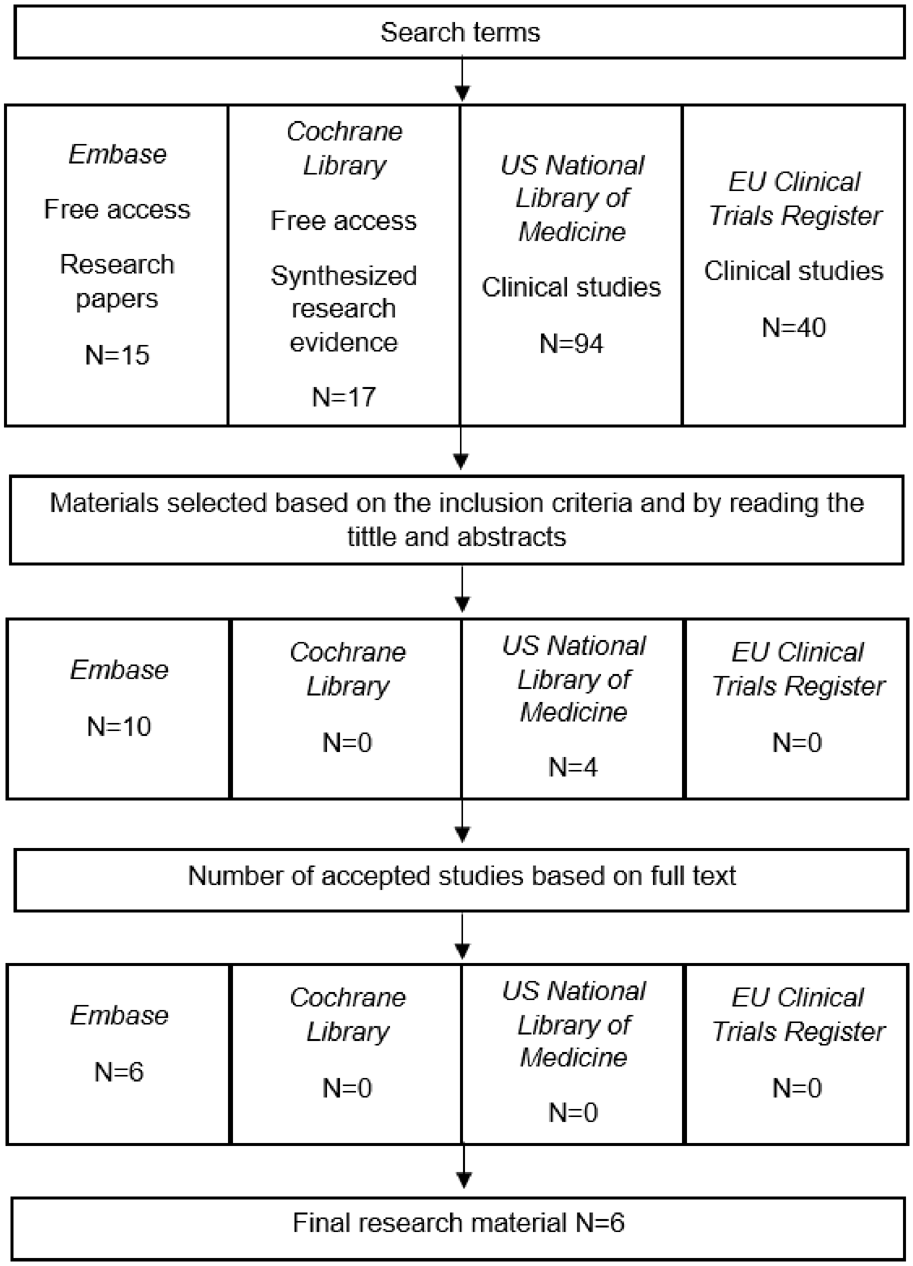
- How valuable is the research?

Table 4. Ten questions to help evaluate a qualitative research. All questions to be answered *yes, no* or *cannot tell*. The more yes answers the reader can give the better the quality of the study is. (Critical Appraisal Skills Programme (CASP) checklist 2018)

Furthermore, the author of this study used critical appraisal questions from the Qualitative Study checklist published by Center for Evidence Based Management. (Center for Evidence Based Management 2014) Appendix 1.

In the critical qualitative and critical evaluation of the selected 14 studies is challenging but important to avoid the already existing biases and misleading in the included studies. (Aveyard 2014) The aim is to evade repeating the same biases in this study.

During the critical reading of the articles and studies, the researcher evaluated how well each article or study corresponded to the inclusion criteria but also how well they answer the research question. Most of the selected studies did not include in sufficiently patient and/or caregiver experiences when the research question was taken into consideration. It was important to differentiate the efficacy studies having burden of treatment to patient, or health care provider merely as a minor additional outcome, not as purpose or aim of the study. Therefor four of the studies selected from Embase database had to be excluded. Furthermore, two of the Clinical Trials database studies did not have published results in the database or in the form of a published article. One of the Clinical Trials database studies was publishes only as a research protocol article without results. Additionally one of the Clinical Trials database studies published 2011 had a study period between January 1, 2006 and December 31, 2009 and therefor the results did not reflect the current anti-VEGF treatment results. The treatment results before the current mainstream anti-VEGF treatments were considerably worse for the patient leading to fast progressing visual decline and visual impairment despite treatment. The treatment change to anti-VEGF has a vast impact on patient’s quality of life in many ways both positive and negative, which other previous treatments did not have. Because of the careful consideration and reading the Clinical Trials database studies again, the researcher concluded that none of the studies could be included in this study. The full search and evaluation process is shown below in picture 5.



Picture 5. The selection process of the research material

4.6 Description and Analysis of the research material

The analysis of the material aims to clarify the research materials and thus create new data regarding the research topic. In this analysis, the researcher is striving to summarize and collect different available material and information without losing the primary content of the material and answering the research question.

In this study, the researcher is also using content analysis due to the low number of the included materials. Content analysis is a research technique used to make conclusions by interpreting textual material, the similarities and differences of the contents of the materials. (Duriau 2007)

The studies were read again and the rudiments were collected and summarized. The researcher collected all the information into a table to enable easier examining of the material details and contents. In the table, the researcher collected the following information

- name of the article and writers
- publication
- publication year
- aim of the research
- research method
- population
- main findings and results
- critical evaluation of the article.

In the searches, the publication period was limited from 2010 to 2019. The publication years of the articles were spread towards the resent year. This is explained by the treatment change to anti-VEGF treatments only during the last ten to thirteen years. Additionally this confirms the assumption that burden of treatment and quality of life studies are conducted in a later stage than efficacy and safety studies. Furthermore, this highlights the importance of the topic. (Table 5)

Publication year	**Number of publications**
2015	**2**
2016	**1**
2018	**3**
Total	**6**

Table 5. Number of publications by publication year.

The selected articles are published in seven different scientific publications with impact factors range from 1,5 in Clinical Ophthalmology to 4,8 in The American Journal of Ophthalmology. (Table 6)

Publication	Number or articles
Eye	**1**
BMC Ophthalmology	**1**
Health and Quality of Life Outcomes	**1**
Clinical Ophthalmology	**1**
The American Journal of Ophthalmology	**1**
Journal of Comparative Effectiveness Research	**1**

Table 6. Publications of the articles

The studies in the selected articles were conducted in wide variety of countries. Two studies had patients from Australia, two from US, and four form European countries. However none from Nordic countries.

4.7 Summary

in this research systematic literature review is used as the research method. The research is conducted in four steps, research plan, data search process, data analysis and synthesis of the results. Inclusion and exclusion as well as the search terms are based on research questions. The search terms *macular degeneration or age related macular degeneration and disease burden or quality of life* are systematically searched in six different databases. The final data section and inclusion is done with the help of critical appraisal questions. Six study articles is accepted in this study. The accepted studies are presented in chapter five.

5 Results

In this chapter, the researcher introduces the major themes, which came up during the analysis process of the articles. Based on the themes that come up the researcher attempts to provide data and information to answer the research question. The research question has a large scope, which is reflected as well in the selected articles. The aim of this systematic literature review is to collate and describe the evidence pertaining to the humanistic burden associated with nAMD. In addition, the aim of this review is to give a better understanding of the concept of nAMD treatment from patients and caregivers perspective. Furthermore, this study is exploring the burden of frequent anti-VEGF injections to patients and caregivers in their daily life and possible improvements of the current situation.

5.1 Themes of the research articles

Six study articles were selected through a rigorous process. The studies are briefly presented in the below table (table 7). Since the number of the studies is low and they are quite different from each other, the researcher chose summarize each study from the research question point of view in addition to arranging the data by relevant themes.

The study researcher(s) and Year **Name of the article** **Publication**	**Purpose, goal and aim of the study**	**Research method** **Population**	**Most important results and/or conclusions**	**Evaluation by the writer**
Spooner, Mhlanga, Hong, Broadhead, Chang (2018) The burden of nAMD: a patient's perspective Clinical Ophthalmology	To quantify the burden and quality of life of patients and their caregivers in a cohort of patients with nAMD in an Australian clinical setting.	103 patients undergoing anti-VEGF therapy for nAMD were asked to complete questionnaires relating to the financial and time burdens of nAMD.	Loss in productivity due to attendance of appointments was 4.4±1.7 hours per month, with additional time lost by caregivers. Qualitative indirect costs due to loss of productivity for the patient, unpaid caregivers, and loss of productivity due to premature mortality were also a considerable burden.	Together with the quality-of-life burden on the patients, the management of nAMD has a significant societal impact.
Jaffe, Chan, Bezlyak, Skelly (2018) The economic and humanistic burden of patients in receipt of current available therapies for nAMD	To determine the economic and humanistic burden of nAMD in a cohort of patients treated with anti-VEGF in Europe and the US.	79 respondents from the EU and 63 from the US with a self-reported diagnosis of nAMD and in current receipt of treatment were compared with non-nAMD controls.	The burden of care associated with nAMD on EU and US healthcare systems, and on patients who are in receipt of nAMD therapy, is significant and likely to be unsustainable.	

Journal of Comparative Effectiveness Research				
Giocanti-Aurégan, Chbat, Darugar, Morel, Morin, Conrath, Devin (2018) Influence of new societal factors on nAMD outcomes BMC Ophthalmology	Primary outcome was the impact of family support and disease burden on functional improvement in nAMD.	Charts of 94 nAMD patients treated in one center in France were reviewed. Phone interviews were conducted to assess societal factors, including transportation, living status, daily reading and social security scheme	Societal factors could influence functional outcomes in nAMD patients treated with anti-VEGFs. They could contribute to the healing process or sustain disease progression.	
Bertelmann, Feltgen, Scheffler, Hufenbach, Wiedon, Wilhelm, Ziemssen (2016) Vision-related quality of life in patients receiving intravitreal ranibizumab injections in routine clinical practice: baseline data from the German OCEAN study Health and Quality of Life Outcomes	to describe baseline VFQ-25 visual function scores to determine which contributing factors (e.g. indication, age, gender) affect VFQ-25 scores and to identify its impact on driving.	Non-interventional study to evaluate the real world situation of patients treated with ranibizumab anti-VEGF. The NEI-VFQ-25 questionnaire was conducted at baseline, months 4, 12 and 24. 4844 patients completed the VFQ-25 questionnaire at baseline. Thereof, 3414 treatment-naïve patients were further analyzed.	the VFQ sub score general health was most affected by the ocular disease. A tendency towards a more decreased VFQ-25 composite score was observed for nAMD, for elderly patients, for female patients, for patients with low baseline visual acuity. The knowledge of a patient's subjective disease burden is crucial to understanding anxieties and mental anguish.	
Prenner, Halperin, Rycroft, Hogue, Liu, Seibert (2015) Disease Burden in the Treatment of AMD: Findings From a Time-and-Motion Study	To examine the time burden of managing nAMD imposed on physicians, staff, patients, and caregivers.	Mixed-methods, prospective, observational time-and-motion study. The study was conducted from March 2011 through August 2012. A survey was administered to 75 nAMD patients aged ≥50	Fifty-six physicians provided data for 221 patients with nAMD. An average patient visit for nAMD was 90 minutes. Patients reported an average time per visit of almost 12 hours.	

The American Journal of Ophthalmology		years who received ≥1 anti-VEGF injection in the past 6 months. Telephone interviews were conducted with 13 nAMD patient caregivers.	Patients stated that caregivers took time away from work and personal activities to provide transportation to appointments. nAMD management imposes a substantial time burden on physicians, staff, patients, and caregivers.	
McCloud, Lake (2015) Understanding the patient’s lived experience of nAMD: a qualitative study Eye	The study aims to understand the patient’s experience of nAMD, including ongoing treatment with anti-VEGF.	Twenty-five participants from one clinical site were qualitatively interviewed to elicit their experiences of treatment for nAMD.	Two major themes were identified. A life negotiated by nAMD captures the participants’ experience of living with the condition and uncertainty displayed their appraisal of life, treatment and their perceived future. Anxieties and thankfulness emerged from the data analysis. Knowledge of the experiences, anxieties and concerns of this patient population can be used to inform clinical practice and lead to patient-centred care.	

Table 7. The main points and results of the studies.

5.1.1 The burden of nAMD - patient’s perspective

In the Spooner et al. (2018) study the aim was to quantify the burden and quality of life of patients and their caregivers in a cohort of patients with nAMD in an Australian clinical setting. The study was carried out by using patient questionnaire and caregiver interviews. Patients reported details of potential burdens suffered over a 3-month period. Additionally they completed a self-reporting questionnaire to provide additional information on their health-related quality of life and National Eye Institute Visual Function Questionnaire 25 interviewer-administered questionnaire. This included the number of visits at the health care provider, financial expenses related to their eye care and vision, as well as time. In addition, the time spent on activities of daily living by caregivers was also gathered, such as household chores, administrative tasks, and leisure activities. Spooner et al. study calculated the caregiver burden in time spent taking care of the patient or patient's needs, time lost from leisure activities, or time taken off from work to assist the patient with the treatment of nAMD.

From patient's perspective the most significant barriers to treatment adherence identified were the frequency and travel times associated with treatment i.e. intravitreal injections. Many patients reported also the high number of other medical appointments they had to manage due to other comorbidities related to aging. The patients had a total number of about ten appointments or/and injections within a 12-month period, and the mean travel time for ophthalmic appointments was about 1.2 hours in each direction. The total time spend on one visit amounted to about 4.4 hours per visit. Furthermore, patients may need up to a day of recovery after an intravitreal injection.

The caregivers reported the time they spent accompanying the patient to their nAMD treatment took an average of 6.2 hours per month. Additionally, caregivers reported the time given to various activities in the daily life of the patient amounting to 4.3 hours per week.

The quality of life assessment showed a result score of 64.8 on average while the score among normal healthy controls have been shown to be around 80–90. Similarly, the relatively low vision function questionnaire scores may represent the impact of AMD on these patients' subjective appraisal of their condition.

5.1.2 The economic and humanistic burden of patients in current therapies for nAMD

In the Jaffe et al. study published 2018 the authors explored the economic and humanistic burden of nAMD in a cohort of patients treated with anti-VEGF in Europe and the US. The primary objective of this retrospective, cross-sectional analysis was to estimate the burden of illness associated with nAMD in patients were compared with adults without nAMD in terms of health-resource. Secondary objectives included an estimation of illness burden associated with nAMD compared to adults without nAMD in terms of health related quality of life, activity impairment and health status. According to Jaffe et al. patients with nAMD had lower physical function and mental status scores compared with controls as well as lower health utility scores. Patients with nAMD had greater overall activity impairment compared with their matched controls but health status parameters were comparable between groups in EU.

Additionally health care recourses utilization and self-reported anxiety were assessed. In the article Jaffe et al. state that in EU the average number of ophthalmologist visits in the previous 6 months were greater for nAMD patients than their non-nAMD matched controls for HCP visits (14.80 versus 6.28).

In US the results were different than in EU. Although the average number of ophthalmologist visits in the previous 6 months were greater for nAMD patients than their non-nAMD matched controls (1.67 versus 0.33) in the same way as in EU even if the visit numbers differ considerably. Jaffe et al. report that no group differences were observed in physical function scores between nAMD subjects and controls or health utility scores additionally health status parameters were comparable between the groups.

In the conclusions Jaffe t al. discuss the future therapies need to focus on reducing the treatment burden or repeated regular injections. Thus lessen the treatment burden of nAMD on health care system.

5.1.3 Influence of new societal factors on nAMD outcomes

The article by Giocanti-Aurégan et al. (2018) assesses the impact of societal factors for nAMD on functional outcomes after anti-VEGF treatments. The study was conducted using phone interviews and the study assessed societal factors, such as transportation, living status, daily reading and social security scheme. Primary outcome was the impact of family support and disease burden on functional improvement in nAMD.

Thus this study is starting from the fact that at the time of our study nAMD treatment included a monthly monitoring and/or injections requiring a scheduling for patients and caregivers, and resulting in a significant burden on patients and their family. This therapeutic scheme involves new societal factors that may influence the course and functional outcomes of nAMD patients treated with anti-VEGFs. The study was a retrospective analysis of patient charts treated for nAMD in one French clinic from October 2010 to October 2012.

The societal parameters of interest were assessed by conducting phone interviews. The interview questions ranged from outpatient follow-up, living status, transportation, commuting time, low vision rehabilitation, daily reading type, and the burdensome of the consultation for the patient. In this study, patients were monitored monthly and thus there were monthly visits to the health care center. The primary endpoint was to assess the impact of the above-mentioned societal factors on patient's vision. In this respect, this Giocanti-Aurégan et al. study differs from other included studies.

This study did not find any statistically significant association between the severity of the disease and outpatient follow-up, family, daily reading or travel time to the clinic. However, low vision rehabilitation and burdensome of the consultation for the patient significantly correlated with vision outcomes. In their study Giocanti-Aurégan et al. found that the patients who reported pain related to the treatment seemed to have better outcomes. On the other hand, nAMD and other chronic diseases are usually associated with anxiety and depression. According to Giocanti-Aurégan et al. societal factors, seem to play an important yet unclear role in the functional outcomes in nAMD patients treated with anti-VEGFs. They may either contribute to the healing process or sustain the disease process together with stress or depression.

5.1.4 Vision-related quality of life in patients treatment

Bertelmann et al. (2016) conducted this large study in Germany. This non-interventional study evaluated the real world situation of patients treated with anti-VEGF injections (ranibizumab) by using a standardised quality of life questionnaire. 5760 patients completed the questionnaire at baseline. Thereof, 3414 patients were further analysed. About 66% of these patients had nAMD and the rest had other retinal diseases, which are regularly treated with anti-VEGF injections. The questionnaire used covers general health, quality of vision and vision-related quality of life such as driving, role limitations, dependency, social function and mental health. Overall, general health, general vision and driving seem to be most affected in the study patients. The most decreased visual function is detected for nAMD patients, with significantly worse results compared to the other indications.

According to Bertelmann at al. using a visual function questionnaire is crucial to understand a patient's anxieties, to encourage compliance with initiated intravitreal anti-VEGF therapy and regular monitoring, as well as to support the physician's and staff 's empathy. Visual function scores can help medical staff to provide patients with optimized medical treatment and emotional attention.

Bertelmann et al. also discuss patient's emotional wellbeing and increased expectations with current anti-VEGF treatments. According to the writers intravitreally injected anti-VEGF substances have, besides anatomic and functional considerations, a major impact on social and mental aspect by increasing patient's quality of life. Additionally Bertelmann et al. argue that visual function score is dependent from patient's age. Depression might occur more frequently in older patients and it was formerly demonstrated that depression interferes with visual quality scores. This is of importance because the proportion of older patients will increase in the future maintains Bertelmann et al.

Bertelmann et al. make the conclusion that a strict anti-VEGF treatment has the potential to significantly increase the medical and mental condition of patients, to reduce anxiety, prevent depression development and to support therapeutic compliance.

5.1.5 Disease Burden in the Treatment of AMD

In their study, Prenner et al. (2015) examine the time burden of managing nAMD imposed on physicians, staff, patients, and caregivers. Prenner et al. conducted an observational study to understand the total physician and patient burden of current standard of care for management of nAMD in the US. The study included three parts: an ethnographic study, qualitative interviews of patients with a diagnosis of nAMD and their caregivers, and quantitative surveys of retina specialists and patients with a diagnosis of nAMD. The ethnographic study included patient shadowing and post observation debriefs with different health care provider's representatives. The qualitative research was a one-hour in-depth telephone interview with 17 patients and 13 caregivers. Prenner et al. aimed to understand the burden of care for nAMD, identify drivers and barriers to treatment, and understand the patient experience beyond the injection process in terms of the impact on patient/caregiver quality of life and the burden of time and effort involved.

The last part of the research was a quantitative survey. A telephone survey for patients, a paper-based survey and a form for retina specialists was carried out. This retina specialist survey showed that on average 22 staff members were involved in a nAMD patient management. The duration of one patient was on average 90 minutes.

Prenner et al. derive into conclusion that nAMD management imposes a substantial time burden on physicians, staff, patients, and caregivers additionally some preparatory steps were taken at the clinic ahead of patient visit. Retina specialists also considered that patient monitoring and frequency of injections caused a major burden to the clinics. Two-thirds of physicians stated they would find it very desirable to reduce patient visits.
Furthermore Prenner et al. did a survey amongst 75 patients. Patients reported that the average time commitment per visit for their nAMD management was 11.7 hours, including pre-appointment preparation, travel, waiting time, treatment time, and an average of 9 hours of post appointment recovery. Moreover, the majority of patients were driven to their appointment by a caregiver. The caregiver had to take time off from work or personal activities to accompany the patient to the appointment.

Prenner et al. debated that their study show that most physicians desired to reduce injection frequency. In their opinion a treatment that requires fewer injections would be desirable, would be more likely to be prescribed, and would ultimately reduce the burden on health care staff time and the use of resources such as materials and office space. This could ultimately lead to a reduction in the overall burden of nAMD.

5.1.6 Understanding the patient’s lived experience of nAMD

The McCloud and Lake (2015) study intended to understand the participant’s experience of nAMD. The study aimed to expand on what is known to be meaningful and important to people as they progressed through a rigorous treatment process where visual disability can be stabilised. The study was conducted in one clinic and it included 25 patients. This study recruited 25 people for in depth unstructured interviews with questions such as ‘tell me of your experiences of ARMD and the treatment you are receiving?’ additionally nursing staff focus group was organised. The focus group provided information from the perspective of clinical staff.

McCloud and Lake used thematic analysis in the study. The two major themes identified from the narratives of the participants. The coded segments were merged into larger sub-themes and then into two major themes: ‘A Life negotiated by nAMD’; and ‘Uncertainty’.

The theme ‘A Life negotiated by nAMD’ addresses the need for regular ongoing anti-VEGF injections. This was for most participants a life changing event that evoked a range of feelings and fears, from high anxiety to pragmatic acceptance. Many participants expressed relief after understanding that the condition could be treated. Many participants found that positive experiences of the process helped them to cope well with the injections. Patient developed familiarity with the processes and interventions although the injection continued to be a source of anxiety, particularly when an unknown clinician was to give the injection. Never the less participants expressed a belief that they were receiving an excellent service that was maintaining their sight for as long as possible.

McCloud and Lake report that all participants described recovery behaviours that limited daily activities, such as driving, watching TV or reading, from a few hours to a few days. According to the participants, the treatments were pragmatically accepted due to the ongoing threat of blindness. Additionally a number of participants reported that the frequent treatments had influence on their lifestyle. Many participants felt inconvenienced by the need to structure their lives around appointments, and subsequently adopted lifestyle modifications and limitations. Participants who were active and wanted to engage in many leisure activities described sadness at the loss of enjoyment of life that occurred as a result of the treatment regime and vision limitations.

The second theme that emerged was ‘uncertainty’. Even though patients were optimistic they knew that, the treatment could fail at any time. McCloud and Lake discuss that the relationship between the healthcare facility staff and participants was crucial in helping overcome anxieties regarding treatment, recovery, and disease progression. Reassurance, caring communication and feeling supported by known staff members all contributed to participants enduring the rigours of the treatment. Participants accepted that they would need to have treatment for very long periods to help maintain their vision. Although they endured the treatments, there was often an underlying knowledge and fear that treatment could fail and they would slide into visual disability.

5.1.7 Keywords and themes of the studies

In addition to the summaries of the main topics of the studies the researches has collected the themes that come up repeatedly in the studies event if the studies have different endpoint and aims. The researcher identified key words and themes by reading the studies carefully and searching through the materials. The identified keywords and themes are related to the research questions and related to the humanistic burden of the current nAMD treatment. Focusing on the topic and question of this research limited the amount of the themes and keywords to keep them all relevant. Some other topics such as burden to society, payers and health care financing along with treatment regimens including regimen comparisons and visual acuity results which were as well covered in some of the selected studies. By selecting some prominent key topics from the selected studies, the researcher attempts to find out, report what these studies bring up, and add to the current knowledge of the area.

There were 36 key words were identified for the topic of humanistic burden of nAMD treatment. The keywords were divided in in to themes. The major themes are used time management, anxiety, quality of life and care. Some of the keywords in each theme are presented in the table 8.

time management	anxiety	QoL	care and recourses
•treatment frequency •travel •treatment •recovery time for patient •caregiver time used •travel time for patient and caregiver •caregiver burden •cost	•treatment procedure •treatment results •burden of treatment •health status stability •QoL changes •blindness •depression •quality of vision •mental health status •patients do not dare to tell their perspective to health care provider	•activity impairment •dependacy from others (caregivers) •quality of ivision: daily reading and driving ability •depsression •low vision rehabilitation •mental health •recpvery time from treatment •lost productivity for patient	•patient compliance and persistance with appointments •burden of consultation to patient •cost to health care provider (staff, patient care, treatment) •recourses constrains with staff , frequent visits and treatments

Table 8. Presents the most important themes on top and the identified keywords are listed below. (QoL: quality of life)

A classification by patient, caregiver and health care professional/provider could have been beneficial but in the studies did give only sporadic and limited information of the humanistic burden of caregiver and health care professional/provider. Most of the results and gathered information in the studies concerned patient experiences. Therefor these stakeholders are not used as classification criteria but rather are discussed all in each theme.

Time management

The time spent and costs associated with vision problems for patients and their carers is one of major themes. Especially the cost of the caregivers' time is highlighted in the studies. (Spooner 2018; Prenner 2015). Often financial and time burden of nAMD is connected particularly if patients and caregivers are still in work life and have to take time off from work. Caregivers, who the patients rely heavily on, were children, spouses, and friends. (Spooner 2018; Giocanti-Aurégan 2018) Loss in productivity and time due to attendance of appointments by caregivers was on average 4.4 hours per month, travel time spent per visit 2.4 hours per month, 6.2 hours spent accompanying patient to appointment and 4.3 hours other assistance. (Spooner 2018; Prenner 2015) Commuting time to the clinic was calculated to be several hours in all studies even for majority of the patients. However, that study also found that a commuting time exceeding 2 h led to better effect than a shorter commuting time. The writers argue that this is probably because of patient's higher motivation and involvement in their treatment. (Giocanti-Aurégan 2018) Many patients felt inconvenienced by the need to structure their lives around appointments and the necessity to adopt lifestyle modifications to meet the time needed for treatment visits (McCloud 2015)

One of the studies found that an average patient visit for nAMD was 90 minutes and ranged from 13 minutes to over 4 hours. Patients reported an average time per visit of almost 12 hours. . Patient also frequently felt need to rest for an extra day after the treatment. (Spooner 2018; McCloud 2015) Above the commuting time there were other time consuming moments during the clinic visits and the main complaints of patients were the long waiting time before consultation (40% of patients) (Giocanti-Aurégan 2018).

nAMD management imposes a substantial time burden not only on patients and caregivers but also on physicians, and health care staff. The management of patients with nAMD is costly and time-consuming therefor health care decision makers (ie, physicians and payers) struggle to balance quality of care with costs of care and reimbursement for time and services provided. Apart from the time, spend on consultation the average total staff time spent on all preparations was 43 minutes in one study. The majority of the retina specialists surveyed in that study felt that frequency of patient monitoring placed a significant burden on staff time. Study results include a physician argues that a treatment that requires fewer injections would be desirable, would be more likely to be prescribed, and would ultimately reduce the burden on health care staff time and the use of resources such as materials and office space. (Prenner 2015)

Furthermore, caregivers reported that time taken off work is costly and meant that they were unable to meet their personal and employment obligations when they had to bring the patient in for monthly appointments and injections. (Spooner 2018) Besides, time-consuming treatment was experienced as an impairment of quality of life when the time usually used to other activities had to be used to nAMD treatmentThe patients needed assistance also with various activities in the daily life such as household assistance and tasks like grocery shopping which increased the time burden for caregivers. (Spooner 2018)

Closely related to the time consumed to attend the frequent appointments was the travel time getting to the health care provider. It is mentioned that the most significant barriers to treatment adherence identified were the frequency and travel times associated with the treatment. (Spooner 2018). Caregivers indicated in a questionnaire that the time spent at each of the many needed monthly appointments was a significant burden (Spooner 2018).

Anxiety, depression

A commonly used visual function and quality of life test VFQ-25 measures the influence of visual disability on general health areas such as emotional well-being, social functioning and daily visual function. It indicates the extend eye diseases impact anxiety, routine activities and the interaction with family and friends. A correlation between declined visual acuity and depression has been shown previously. This in turn has negative effect on patient's daily activities and social connections. (Bertelmann 2016) Especially vision loss in nAMD has relation to lower health-related quality of life and greater likelihood of depression, which in turn affect work productivity and overall health status. Never the less in a study including 142 nAMD patients compared to non-nAMD controls the health status parameters including depression were comparable between groups. The results are based on patients' self-reporting via an online survey. (Jaffe 2018) Additionally a French study shows that patients with a considerable burden due to the treatment seem to have better outcomes, probably because of a higher motivation and involvement in their treatment. The same study explores the association and generally negative effects of nAMD to depression and treatment compliance. (Giocanti-Aurégan 2018)

Certain patient groups seemed to be in a higher risk of lower visual function and quality of life test VFQ-25 scores. Among patients with eye diseases, elderly patients over 75 years and those with nAMD had higher tendency to have lower scores in VFQ-25 test. Additionally patients might be afraid of reporting their significantly reduced quality of life and major disease burden to the examining and treating medical staff, especially older patients. It is suggested that identifying the risk and sign of depression on patients can help medical staff to provide patients with optimized medical treatment and emotional attention. This would also support increased compliance, which would result in better visual outcomes and, consequently, in an improved quality of life during and after nAMD related anti-VEGF treatments. (Bertelmann 2016) The relationship between the healthcare facility staff and patients was crucial in helping overcome anxieties regarding treatment, recovery, and disease progression. Reassurance, caring communication and feeling supported by known staff members all contributed to participants enduring the rigours of the treatment. (McCloud 2015)

It is highlighted that the knowledge of each patient’s subjective disease burden is crucial to understand the anxieties and mental anguish it can cause. This enables the medical staff to encourage patients’ compliance with a comprehensive anti-VEGF therapy. (Bertelmann 2016)

Declining vision has a profound influence on patient’s health and ability to drive. Overall, general health, general vision and driving seem to be most affected in patients with eye diseases leading to role-limitations, poorer mental health and depression. (Bertelmann 2016)

An Australian study aimed to understand patient’s experience with nAMD described different courses of anxiety for the patient. A diagnosis of nAMD that required regular ongoing anti-VEGF injection was for most participants a life-changing event that evoked a range of feelings and high anxieties. Part of the anxiety was relieved relief when patients learned that the condition could be treated. On the other hand the anxiety experienced by the treatment procedure, having a ’needle’ into the eye, was only reduced if the first injection experience was less painful and better than expected. Never the less the injection continued to be a source of anxiety, particularly when an unknown clinician was to give the injection. Furthermore, an ongoing and real threat of blindness based on the knowledge that treatment was not a cure caused anxiety and added a further level of uncertainty. The optimism felt by patients was moderated by the knowledge that treatment could fail at any time. (McCloud 2015)

Quality of life

From the patient's perspective, the physical and physiological impact of vision loss represents a significant burden. Vision loss in nAMD has been shown to affect health-related quality of life including depression, and reduced work productivity and overall health status. Furthermore, the effect of nAMD results in poor mobility and limitations in daily activities because of loss of vision thus the quality of life of nAMD patients is affected by their disease. They tend to be less physically able than non-nAMD patients are. (Jaffe 2018; Spooner 2018) Number of patients reported about the influence of the frequent treatments and need to structure their lives around appointments on their quality of life. The recovery from the treatment limited daily activities, such as driving, watching TV or reading, from a few hours to a few days. Therefore, patients adopted lifestyle modifications that ranged from limitations to a planned day event to constraints to a way of life that they had previously pursued and valued such as extended travel during the wintertime. Patients who were active and wanted to engage in many leisure activities described sadness at the loss of enjoyment of life that occurred because of the treatment regime and vision limitations. (McCloud 2015)

Patients with nAMD had lower scores in physical and mental functioning compared with controls. Additionally, patients with nAMD had greater overall activity impairment compared with their matched controls. Because of not being able to engage in everyday activities their quality of life is reduce. (Jaffe 2018; Spooner 2018) Mean visual quality of life rates 64.8 in a questionnaire where scores among normal healthy controls have been shown to be around 80–90. Furthermore, nAMD patient had lower scores in general health and general vision, being able to do distance activities and driving. The scores for driving and social functioning were considerably lower making the nAMD patients very much dependant on others. (Spooner 2018; Bertelmann 2016)

Medical staff involved is patient care is interested in patient's current quality of life and individual burden of disease. The health care personnel try to optimize not only medical treatment but also emotional attention, both of which directly affect quality of life. Identifying and addressing the right factors, if possible, will help to increase patient's overall quality of life. One of the modifiable factors is visual acuity. To improve such factors as driving, ocular pain, role limitations, dependency, social function and mental health, which were considered factors that could have a good chance to improve quality of life with appropriate medical treatment and emotional attention. Furthermore, being aware of a patient's subjective quality of life is important to understand patient's anxieties and to encourage compliance with treatment and monitoring visits. Thus, anti-VEGF treatments have, besides anatomic and functional considerations, a major impact on social and mental aspect and can distinctly increase patient's quality of life. (Bertelmann 2016)

nAMD has also been shown to have emotional and physical effects on caregivers, with many reporting feelings of sadness and uselessness. There was also the concern of the patient's health, well-being and treatment continuity present continuously. (Spooner 2018)

Care and recourses

The burden of care associated with nAMD on healthcare systems is significant and likely to be unsustainable. A greater number of nAMD patients reported visiting any health care professional and ophthalmologist in the previous 6 months compared with controls likewise the average number of visits were greater for nAMD patients than their non-nAMD matched controls. Consequently nAMD patients in the EU utilize healthcare resources to a greater extent than non-nAMD patients, which is reflected in a greater number of health care professional visits, emergency room visits, hospitalizations and ophthalmologist visits. (Jaffe 2018)

The typical nAMD patient is on average over 70 years older and have additional comorbidities. (Jaffe 2018; McCloud 2015) Very few patients reported seeking advice from the clinic when difficulties arose, usually choosing to wait for symptoms to subside. Patients endured the ongoing treatment and follow up of the disease. Very few participants expressed a desire to stop treatment, despite the frequent visits and other rigors. Patients' endurance of invasive treatments was reinforced by the fear of blindness and treatment experiences were considered by many in light of an ongoing threat of blindness and thus pragmatically accepted. (McCloud 2015) Sometimes patients might be afraid of reporting their major disease burden to the examining and treating medical staff, especially at a higher age. Even though this would be beneficial information for the treatment of the patient and restoring vision. (Bertelmann 2016)

Nevertheless, a strict anti-VEGF treatment is important. It could possibly including a treatment interval extension strategy, which has the potential to significantly improve the medical and mental condition of the patient, relieve the health care provider burden and increase compliance. (Bertelmann 2016)

The results of a US retina specialist survey showed that on average, 23 staff members were involved in the management of nAMD patients. The management of nAMD patients accounted for an average of 20% of the staff's time. Almost half of retina specialists reported that the frequency of injections was an impactful burden on office space and it accounted for a disproportionate use of resources. Besides 35% considered frequency of patient monitoring to be an important motivator in choosing a treatment with less frequent administration. Two-thirds of physicians stated they would find it very desirable to reduce office visits. A treatment that requires fewer injections would be required. It would ultimately reduce the burden on health care staff time and the use of resources such as materials and office space and may ultimately lead to a reduction in the overall burden of nAMD. (Prenner 2015)

5.2 Summary of results

In this chapter, the selected articles are explored carefully to identify and collect the relevant data concerning the topic of humanistic burden of nAMD. The results of each study article separate due to the low number of studies. Key topics are collected from each study. Subsequently the results are also presented by key topics, which have emerged from the studies. The key topics are time management, anxiety, quality of life and care & recourses.

Patients, caregivers and health care providers consider that nAMD treatment demands considerable lengths of time because the treatment are given at a clinic and the treatment frequency is high. Anti-VEGF treatment is effective but may cause concerns in patients and caregivers because it is given as an injection. Patient's quality of life is declining due to frequent treatments, excessive travel and treatment times, and declining vision. Patients are more dependent on other, their relatives, caregivers, and friends. Furthermore, recourses are needed in health care sector to cope with the increasing patient population and compliance.

6 Discussion

Chapter 6 attempts to present the results of this literature review in relation to the theoretical background and current understanding of the humanistic burden of nAMD. This chapter discusses the results presented in the previous chapter and deliberates different themes of the research topic in the light of the findings. Additionally reliability and validity as well as ethical aspects are addressed in this chapter.

6.1 The research process and key findings

The aim of this master's thesis was to create study by using a systematic literature review as a research method. The goal was to investigate and systematically analyse the humanistic burden nAMD treatment is causing to different stakeholders when anti-VEGF treatment is used. In this study the researcher set out to explore the extend of the available research and studies on the treatment burden to patients and caregivers and additionally to health care system. It was known that the nAMD treatment has fundamentally changed during the last 13 years when anti-VEGF treatment was introduced. Collecting information from time before the broad use of anti-VEGFs would have steered the results in a wrong direction. The efficacy of the treatments before the introduction of anti-VEGF were marginal and treatment intervals much longer. Consequently, the humanistic burden was greater due to rapidly declining vision. (Dawson 2014) Furthermore, it is vital to separate dry and neovascular AMD due to their different treatment options. Currently there is not treatment for dry AMD and thus combining the experiences of patients with dry and neovascular AMD would not serve the study objective. Many of the studies combine these diseases or they are conducted before the widespread use of anti-VEGFs when the patient experiences were more similar in both diseases. Thus the anticipation of vision deteriorating, how rapidly it has already deteriorated, the length of time since diagnosis and the possibility of available treatments are all important factors which could affect patients' psychologically. (Dawson 2014)

This thesis is a systematic literature review. A review summarizes the results of available studies to study a defined topic and gain more information on the chosen topic. In this study, the researcher attempted to answer the question about humanistic burden of nAMD when anti-VEGF treatment is used. Additionally, this systematic review explores the extend of studies regarding patient and caregiver experiences about and during nAMD treatment.

Systematic literature review requires careful planning and description of the process to enable to copy and implement the same process identically. Systematic literature reviews considered reliable and valid research method to combine previous research results. (Metsämuuronen 2011). In this review, the researcher has systematically search all relevant databases for suitable studies. The study search included searching through the preliminary accepted studies' reference lists. It was a very time consuming, but rewarding and interesting process to search and read all the articles and studies. The literature search process is carefully documented and can be duplicated by anyone if so preferred.

The researcher was aware of the possibility that the number of studies on humanistic burden may be low. Previously, before anti-VEGF, there was more attention to the disease burden to patients because of the lack of proper treatments and patients need to adapt to the situation and rehabilitation including low vision care devices. Furthermore, previously patients needed caregiver help in a larger scale faster for their everyday shores such as cooking and reading. Current anti-VEGF treatments keep patients more functional for a longer time on the other hand patients need more help to get their treatment appointments. The number of appointments is higher the current treatment. This is not a surprise to anyone never the less since anti-VEGF treatments have been in wide use only about ten years it seems that scientific community is still mostly focused on efficacy and safety of the treatment. For the aim of this study, the introduction of anti-VEGF is a key point. Brown at al. (2009) describe the difference between anti-VEGF and previous verteporfin photodynamic treatments in a large phase III study. The results are so much better with anti-VEGF treatment that all the patients in the verteporfin photodynamic treatment group are switched to anti-VEGF for ethical reasons. (Brown 2009)

When this research was started, the researcher knew about the burden of nAMD treatments to the health care provider and the budget constrains in Finnish health care system. (Vottonen 2016) The researches visited several university and regional hospitals to get experience and understand the treatment process and patient flow at the clinics. Anti-VEGF treatments are administered at a clinic and covered by hospital budget, thus the financial constrain if on the hospital or hospital district and not on the patient. Therefor, and based on visiting the clinics including the injection procedures the assumption of the researcher was that the major burden lies on the healthcare providers side. During the visits, the researcher learned that most of the elderly nAMD patients have a caregiver with them for travel and during the procedure. A group of patients is regularly asked to come at the same time to prepare all at the same time for the injection. Due to this practice, many patients end up waiting for their treatment over an hour. From the clinics point of view this is a practical arrangement but may cause major burden in loss of time and income for the patient and patient's caregiver.

Currently the all nAMD patients need to be treated as soon as possible once the diagnosis is confirmed preferably the same day. On top of the treatment, there are many other costs involved such as medical visit, fluorescein angiography, OCT, treating adverse events related to the treatment, rehabilitation visits, and low vision aids.(Vottonen 2016). The frequency and cost of the injections cause major burden to the health care system. Therefor a strong focus is on cutting the costs of nAMD treatments. Cutting the costs will reflect on the patient care if no new medical innovation is replacing the frequent injections in the near future. The systematic reading of nAMD burden related articles reveal very few studies on health care personnel's experiences of the treatment. A large reduction of clinic visits that require detailed examinations, should allow clinical teams to manage the treatment burden of nAMD more efficiently, consider how to reduce visits that are the time-consuming part of patient care. Clinical burden is an important, but often ignored, factor in determining the optimal treatment regimen to use, and unnecessary examinations waste clinical resources that could be better applied elsewhere. (Mantel 2014) Moreover, a respectful interaction between patients and health care professionals is necessary for patients to obtain beneficial health care. Good care is achieved when health care professional acknowledge patients and provided information continuously. Patients feel that they are compelled to accept this treatment because they might otherwise become blind. (Emsfors 2017)

The systematic literature search demonstrated that there is plentiful of efficacy and comparative studies on Anti-VEGF treatments in nAMD disease area. Then again very limited number of qualitative studies humanistic burden. From the 166 eligible articles, which studies included the search inclusion terms only six studies were eligible to be included in this study. That demonstrates the lack of patient and caregiver related studies. On the other hand, the search terms limited the search and different search terms or words could have yielded different result. Never the less it is few studies exploring the effects of nAMD on patients and especially on caregivers. (Varano 2016)

Qualitative research allows the researcher to describe and express the research results. The researcher has tried carefully avoiding bias even though bias may occur unnoticed.

Bias is systematic error introduced into sampling or testing, which tends to produce results or conclusions that differ from the truth. (Merriam-Webster) Qualitative research is primarily exploratory research and the main purpose is to gain an understanding of underlying reasons, opinions, and motivations as well as dive deeper into problems. Why do people behave and why do things happen as they do. It provides insights into the problem or helps to develop ideas or hypotheses for potential quantitative research. (DeFranzo 2011) The purpose of this study was to gain more understanding on how do the patient and patient's caregivers experience the nAMD injection treatment. There may have been preconception that even if injections are an effective treatment they are very burdensome to patients. Current publications emphasize that nAMD has a significant negative impact on the lives of patients, including vision-related depression, poor mobility, and limitations in day-to-day activities. (Varano 2016) Regardless of this, it was obvious from the studies included in this research that patients are equally relieved by the knowledge that there is a treatment for the disease. Even if patients feel that, the treatment injections are painful or otherwise uncomfortable, they strive to stay compliant with the treatments. Surprisingly the patients feeling the most constrains and burden connected to the treatment have the best visual acuity gains. This may reflect the psychological and placebo effects of the treatment as well as this may tell about the patients' desire and eagerness to gain results when the treatment is uncomfortable. Additionally investigating these parameters is essential because nAMD seems to be associated with depression or induce mood disorders like numerous chronic diseases. (Giocanti-Aurégan 2018). Obviously, it is in the interest of all stakeholders to comprehend the extend of different mechanisms which influence the visual gains.

Despite the positive finding, this study indicate that there is a range of emotional and physical problems associated with nAMD patients, including vision-related depression, mobility, and limitations in day-to-day activities. The impact on nonprofessional caregivers may also be underestimated in terms of emotional impact such as depression and loss of productivity. However, patients do not feel supported even if they are taken care by their caregivers and health care personnel. Previous reports suggest that health care professionals may underestimate the impact of nAMD. (Varano 2016) This raises the question why do the understanding of the impact of nAMD and impressions of patients, caregivers and health care professional not meet. One has to consider that almost all nAMD patients are old and may have several other age related diseases and ailments, which decreases their physical functioning and possibly their mental capability. In real world studies, the average age of the patients is around 75 to 80 years and often the treatments only start at that age. (Prenner 2015; Spooner 2018).

Health related quality of life usually refers to aspects of patients' lives that are dominated or significantly influenced by mental or physical well-being. Quality of life is often measured via a questionnaire. This allows a better understanding of the relationship between the eye disease and patient-reported functioning. As AMD incidence increases, it is important to understand how it affects visual function and quality of life for both the patients the caregivers. (Taylor 2016) In a systematic review, Taylor et al. (2016) claimed that no quality of life studies have been done in AMD population for the previous ten years. Taylor et al. found that AMD affects negatively patients' mobility, travel patterns, driving skills, falls, recognizing faces, places, and computer use. Findings also showed increased depression. Activities of daily life was affected in different degree in different studies. Results suggest that psychological well-being may be affected in particular by those with AMD are at risk for reduced psychological well-being. (Taylor 2016). This literature review confirms this finding in patients who had been treated with current anti-VEGF injections and thus are much more likely to maintain their vision or have an increase in their visual acuity. Taylor et al. literature review included studies from time before and after current anti-VEGF treatments.

It was found in many studies that declining vision has a high impact in quality of life in many ways. Furthermore, declining quality of life causes depression. Dawson et al. (2014) observed that depression is more prevalent among those with AMD than those without. Furthermore, worse disease severity was associated with increased depressive symptoms. (Dawson 2014) This study found similar results from the included studies. Quality of life is based on questionnaires on personal feelings and opinions how patients experience their lives. It is a very subjective way of measuring results. On the other hand, if all results are showing similar trends the results are more likely to reflect real life experiences.

These findings also highlight the need for a more holistic approach to the problems encountered by nAMD patients. The disease has a major impact on all stakeholders, the patients, and caregivers, health care professional and health care providers including the society. Patients and caregivers are often close relatives or friends and therefor they suffer from patients' declining vision and quality of life. They have a high burden on patients' medical appointments as well as on patients' deteriorating ability to take care of everyday tasks. On the other hand, the health care professionals feel increased stress due to treat steadily growing number of nAMD patients. Health care professionals are concerned about their ability to give proper and timely care; in addition, they should consider the communication with patients and their caregivers. Finally, the growing number of nAMD patients is a huge financial burden to society and payers. It is not only the financial constrains caused by regular appointments with the health care professionals and frequent treatments but also the financial burden caused by other connected conditions and services the patients need.

6.2 Reliability and validity

Reliability refers to how well the used data collection techniques and analysis procedures will yield consistent findings if reproduced. (Easterby-Smith 2008) The researcher has attempted to secure the reliability of this research by carefully documenting the research process. Each step of the process and the rationale of each research documents, material and implementation related choices have been recorded and explained. The research material was chosen with a systematic procedure and evaluation of the original study articles. (Saunders 2007) One of the restrictions of this research was the size of the research material. In the end, only six studies were qualified to be included in this research. Therefore, the researcher acknowledge that this research may not cover all aspects of humanistic burden related to current nAMD treatments furthermore this study could have missed some aspects of the humanistic burden which have not been included in the latest research. Additionally modern technology have potentially already solved some of the issues brought up in this research.

Validity of a research concerns with whether the conclusions are correct and if they can be accepted as valid results to add on the scientific knowledge. (Saunders 2007) One cannot generalize the results of this study. The included studies were geographically limited and there was no studies from Finland or any other Nordic country. Thus, this research does not give any specific local results but rather a general overview of the humanistic burden of nAMD. and it is mainly explaining the current situation. (Saunders 2007). It is highly likely that the burden and stakeholders are very similar in all countries, but there were obvious cultural, geographical and health care financing differences when in the included studies. The research results could have been different if some Nordic or Finnish studies would have been included. If the researcher would have included studies from a longer period the results would most likely been different in many ways. Changing inclusion and exclusion and even the key search terms have a considerable impact on the results. Current key terms were selected by the researcher’s best knowledge but other key terms could have perhaps brought up different studies and articles. Current key terms were selected by the researcher’s best knowledge but other key terms could have perhaps brought up different studies and articles. The robustness of this study and its conclusions could be tested by exposing them to other research settings in a follow-up study. (Saunders 2007)

6.3 The ethics of the research design

There are several reasons why it is important to follow the ethical norms in research. First, norms support the research objective, such as increased knowledge, truth, and avoidance of error. According to this, there should be no fabricated or falsified information, or misinterpretations of the used research data. The conducted research should promote the truth and minimize error. Many of the ethical norms control and coordinate the different people and interests involved. They help to ensure that researchers can be held accountable to each other and the public. It is essential that people can trust the quality and integrity of research. (Resnik 2015)

This research attempts to follow the ethical research principles including integrity, meticulousness, accuracy of conducting the research, and evaluating the research results. Furthermore, the researcher explains carefully the methods used for data gathering as well as for research and evaluation. The research process and scientific criteria of the research are thus ethically sustainable. (TENK 2012)

In a systematic review the researcher is not involved with the subjects of the studies the researcher in including in the review. Therefore, one is required to study the ethical conduct of the studies in the review studies and approve them before inclusion. At the process of reviewing and writing a her/his own review the researcher is obligated to address all valid themes and topics as they appear in the material whether they support the research's hypothesis or not. In this study the researches has collected and presented the information in a systematic and transparent manner as it presented in the original materials. (Saunders 2007)

The research results will be publishing and communicated in an open manner and according to ethical rules to increase scientific knowledge in this research area. (TENK 2012)

7 Conclusions

In summary, the finding of this literature review give useful overview of the research, which has been done on humanistic burden of nAMD during the current anti-VEGF era. This review gives information from the patient's, caregivers and health care professional's point of view. The results also clearly show that there is very few studies on the subject. Of the studies identifies in this review concentrate on the patient's quality of life and the burden visual decline alone or in connection with the burden caused by the frequent visits to the medical center. This study found that caregivers' suffer from similar anxiety, sadness, loss of time from own activities and work as the patients. This review clearly indicate that especially the burden of frequent visits to the health care centers creates a major recurrent burden to caregivers. Additionally caregivers fell similar anxiety and depression as the patients due to the disease diagnosis and progression but also due to the declining mental and physical condition of the patient.

Most of the current studies concentrate on treatment efficacy and some on the treatment burden to the patients. These finding indicate that more focus should be directed to the burden to the caregivers. It is important to understand what the root cause of this burden is. Identifying the root cause will enable the health care system and society to focus on correct improvements in the treatments and services for nAMD patients. In turn, this would ease the burden on caregivers. One of the current trends to alleviate the treatment burden is to increase the treatment intervals. Health care professionals and researchers are investigating different treatment algorithms and new longer lasting treatment options are underway. Both of these solution options are important from the patients and caregivers viewpoint but more innovative solution are needed to secure sufficient, acceptable and cost effective treatment for all future nAMD patients. The future solution should alleviate the burden and be acceptable by all stakeholders.

Only two of the included studies discuss the humanistic burden from the health personnel's perspective. The current treatments are creating enormous constrains to health care personnel and treatment centers are constantly forced to create more effective schemas to treat nAMD patients. In many cases, this leads to less personalized care, shorter appointment and longer waiting times at the health care centers. This trend is not in the interest of the health care personnel or the patients. However, this topic was not thoroughly investigated in this review and needs more research to get a full picture of the health care provider's humanistic burden and how to address that.

This review reveals that all stakeholders are different and have different position, possibilities, expectations and access to influence nAMD treatment and the humanistic burden caused by that. Therefor it is essential to conduct local national surveys and research to map the current situation and explore the best future alternative in Finland.

References

American Academy of Ophthalmology 2015. About Preferred Practice Patterns. Age-Related Macular Degeneration PPP - Updated 2015. Internet document. <https://www.aao.org/preferred-practice-pattern/age-related-macular-degeneration-ppp-2015 >. Read 10.3.2019.

Aveyard, H. 2011. Doing a Literature Review in Health and Social Care A Practical Guide Second edition. Internet document. < https://www.ncbi.nlm.nih.gov/pubmed/27712339 >. Read 22.2.2019.

Boulanger-Chemama, E., Sayag, D., Ha Chau Tran, T. Quaranta-El Maftouhi, M. Chemama, S.,Raynard, B.,Antoun, S. 2015. Ranibizumab for age-related macula degeneration: A five-year study of adherence to follow-up in a real life setting. Journal francois d'ophtalmologie, Volym 38, pp. 620-627. Internet document. <https://www.ncbi.nlm.nih.gov/pubmed/25913443 >. Read 25.2.2018.

Brown, D., Michels, M., Kaiser, P., Heier, J., Sy, J. , Ianchulev, T. 2009. Ranibizumab versus Verteporfin Photodynamic Therapy for Neovascular Age-Related Macular Degeneration: Two-Year Results of the ANCHOR Study. Ophthalmology. Internet document. <https://www.ncbi.nlm.nih.gov/pubmed/19118696>. Read 11.3.2019.

Center for Evidence Based Management, 2014. Critical Appraisal Checklist for a Qualitative Study. Internet document.< https://www.cebma.org >. Read 1.3.2019.

ClinicalTrials.gov, US National Library of Medicine, 2019. Internet document. < https://clinicaltrials.gov/>. Read 27.2.2019.

Cochrane. Cochrane Library, 2019. Internet document. <https://www.cochranelibrary.com/>. Read 27.2.2019.

Coren, E. & Fisher, M. 2006. The conduct of systematic research reviews for SCIE knowledge reviews. Lontoo: SCIE. Internet document. <https://lx.iriss.org.uk/sites/default/files/resources/The%20conduct.pdf>. read 24.2.2019

Critical Appraisals Skills Programme (CASP) 2019. Internet document. <https://casp-uk.net/ >. Read 1.3.2019.

Critical Appraisal Skills Programme 2018. CASP (Systematic Review Checklist 2018) Checklist. Internet document. < https://casp-uk.net/casp-tools-checklists/ >. Read 1.3.2019.

Dawson, S., Mallen, C., Gouldstone, M., Yarham, R., Mansell, G. 2014. The prevalence of anxiety and depression in people with age-related macular degeneration: a systematic review of observational study data. BMC Ophthalmology. Interent document. < https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4094542/ >. Read 11.3.2019.

DeFranzo, S. 2011. What's the difference between qualitative and quantitative research? Snapsurveys. Internet document. <https://www.snapsurveys.com/blog/qualitative-vs-quantitative-research/ >. Read 12.3.2019.

Duriau,v., Reger, R., Pfarrer, M. 2007. A Content Analysis of the Content Analysis Literature in Organization Studies: Research Themes, Data Sources, and Methodological Refinements.Sage Journals. Internet document. < https://journals.sagepub.com/doi/abs/10.1177/1094428106289252 >. Read 2.3.2019.

Easterby-Smith, M., Thorpe, R. Jackson, P. and Lowe, A. 2008. Management Research. 3rd edition. Sage: London.

Embase Search 2019. Internet document.< https://www.embase.com/#search >. Read 26.2.2019.

Emsfors, Å., Christensson, L., Elgán, C. 2017. Nursing actions that create a sense of good nursing care in patients with wet age-related macular degeneration. Internet document. Journal of Clinical Nursing. <https://www.ncbi.nlm.nih.gov/pubmed/28152206>. Read 11.3.2019.

EU Clinical Trials Register, 2019. Internet document. <https://www.clinicaltrialsregister.eu/ >. Read 28.2.2019.

Fimea, Lääkealan turvallisuus- ja kehittämiskeskus 2015. Biologiset Lääkkeet Silmänpohjan Kostean Ikärappeuman Hoidossa. Lääkealan Internet document.

<http://palveluvalikoima.fi/documents/1237350/1950230/FIMEAn+selvitys+Biologiset+l%C3%A4%C3%A4kkeet+silm%C3%A4npohjan+kostean+ik%C3%A4rappeuman+hoidossa%E2%80%9D+%282015%29/ce0039a3-e5ce-4184-8743-d002b5a9c06d >. Read 25.3.2018.

Genentech. 2018. Internet document <http://www.lucentis.com/wet-age-related-macular-degeneration-information>. Read 25.3.2018

Giocanti-Aurégan, A., Chbat, E., Darugar, A., Morel, C., Morin, B., Conrath, J., Devin, F. 2018. Influence of new societal factors on neovascular age-related macular degeneration outcomes.BMC Ophthalmology.internet document. < https://www.ncbi.nlm.nih.gov/pubmed/29385989 >. Read 26.2.2019.

Green, B, 2006. Writing Narrative Literature Reviews for Peer Reviewed Journals: Secrets of the Trade. Journal of Chiropractic Medicine 5: 3, 101–117. Internet document. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2647067/>. Read 22.2.2019.

Higgs, J. and Green, S. 2011. Cochrane Handbook for Systematic Reviews of Interventions. Internet document < http://handbook-5-1.cochrane.org/>. Read 21.2.2019.

Holz, F. et al. 2015. British Journal of Ophthalmology. Interenet document. <http://bjo.bmj.com/content/bjophthalmol/99/2/220.full.pdf >. Read 25.2.3018.

Jenkinson, C. 2019. Quality of life. Encyclopaedia Britannica. Internet document. <https://www.britannica.com/topic/quality-of-life >. Read 25.2.2019.

Kanski, J. 2016. Kanski's Clinical Ophthalmology. Retina. Internet docement. <https://www4.expertconsult.com/home/Novartis/index.html#978-0-7020-5572-0>. Read 9.3.2019.

Kataja, M., Hujanen,P., Huhtala, H., Kaarniranta, K., Tuulonen, A., Uusitalo-Jarvinen, H. 2017. Outcome of anti-vascular endothelial growth factor therapy for neovascular age-related macular degeneration in real-life setting. British Journal of Ophthalmology. Internet document. <https://bjo.bmj.com/content/102/7/959 >. Read 11.3.2019.

Koskinen, J., Tast, T., Vähätiitto, R. 2016. Näköaistin Huomioonottaminen Ikääntyneiden Hoitotyössä.

Käypä hoito –suositus. Kostea silmänpohjan ikärappeuma (AMD). 2016. internet document. < http://www.kaypahoito.fi/web/kh/suositukset/suositus?id=hoi50107 >. Read 21.2.2019.

Koponen M-L. 2015. Sosiaali- ja terveysalan työvoiman riittävyys nyt ja tulevaisuudessa. Työ- ja elinkeinoministeriön julkaisuja 2015:11. Internet document. < http://julkaisut.valtioneuvosto.fi/bitstream/handle/10024/161102/47-2018-ROBOFINN_raportti_.pdf>. Read 10.6.2018.

Koskinen, S., Lundqvist, A. & Ristiluoma, N. 2012. Terveys, toimintakyky ja hyvinvointi Suomessa 2011. THL-raportti. Interenet ducument. <http://www.julkari.fi/bitstream/handle/10024/90832/Rap068_2012_netti.pdf?sequence=1>. Read 9.3.2019.

Lupsakko, T. & Ikäheimo. K. 2008. Iäkkäiden aistiongelmat: kun ei kuule ja näkökin reistaa. In the book: Hartikainen S, Lönnroos E, toim. Geriatria. Arvioinnista kuntoutukseen, Helsinki: Edita , 2008.

Makularegistrets Årsrapport 2016. Internet document. <http://rcsyd.se/makulareg/wp-content/uploads/sites/2/2018/02/%C3%85rsrapportSMRallm%C3%A4nheten.pdf>. Read 1.4.2018.

Mantel, I., Niderprim, S-A, Gianniou, C., Deli, A., Ambresin, A. 2014. Reducing the clinical burden of ranibizumab treatment for neovascular age-related macular degeneration using an individually planned regimen. British Journal of Ophthalmology. Internet document. < https://www.ncbi.nlm.nih.gov/pubmed/24729031 >. Read 11.3.2019.

Merrian-Webster Dictionary. Internet document. <https://www.merriam-webster.com/dictionary/bias>. Read 11.3.2019.

Metsämuuronen, J. 2011. Tutkimuksen tekemisen perusteet ihmistieteissä. Internet document. < https://www.booky.fi/lainaa/1011>. Read 22.2.2019.

National Eye Institute 2015. facts about Age-Related Macular Degeneration <https://nei.nih.gov/health/maculardegen/armd_facts >. Read 23.2.2018

Michell, P., 2014. LUMINOUS: Ranibizumab treatment in routine clinical practice: One-year follow-up data from the first cohort of 2000 patients with wet age-related macular degeneration. Presented at Tokyo, World Ophthalmology Congress WOC 2014.

Ministry of Finance 2018. Economic Survey Spring 2018. Ministry of Finance publications – 9b/2018:20-21. Internet document. <http://vm.fi/documents/10623/7694810/Economic+Survey%2C+Spring+2018%2C+corrected+version/79bbe299-a3ea-4154-b98b-f34bc3b75d8e?version=1.0> . Read 10.6.2018.

National Eye Institute 2018. Facts about Age-Related Macular Degeneration. Internet document. < https://nei.nih.gov/health/maculardegen/armd_facts >. Read 11.3.2019.

Nordqvist, B. 2003. Nähdä. Teoksessa Salminen, A-L. (toim.) Apuvälinekirja. Tampere: Tammer-Paino Oy.

OECD (2017), Health at a Glance 2017: OECD Indicators, OECD Publications, Paris. Internet document. http://dx.doi.org/10.1787/health_glance-2017-en . Read 8.6.2018.

Ojamo, M. 2018. Näkövammareksiterin vuosikirja 2017.

Resnik, D. 2015. What is ethics in research and why is it important? National Institute of Environmental Health Sciences. Internet document. <https://www.niehs.nih.gov/research/resources/bioethics/whatis/index.cfm >. Read 14.3.2019.

Rodrigues et al. 2016 Defining a Minimum Set of Standardized Patient-centered Outcome Measures for Macular Degeneration. *Americal Journal of Ophthalmology.*Internet document. < http://ichom.org/files/articles/MDG_Final_Publication.pdf>. Read 9.3.2019

Salminen, A, 2011. Mikä kirjallisuuskatsaus? Johdatus kirjallisuuskatsauksen tyyppeihin ja hallintotieteellisiin sovelluksiin. Vaasan Yliopiston Julkaisuja.

Saunders, M., Louis, P., Tornhill, A. Research Methods for Business Students. Fifth edition. Prentice Hall 2007.

Schmidt-Erfurth, U. et al. 2014. *British Journal of Ophthalmology.* Internet document. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4145443/>. Read 25.2.3018.

Schmier, J., Halpern, M., Covert, D., Delgado, J., Sharma, S. 2006. Impact of visual impairment on use of caregiving by individuals with age-related macular degeneration. Retina. Internet document.< https://www.ncbi.nlm.nih.gov/pubmed/17151494 >. Read 11.3.2019.

Schmier, J., Covert, D., Lau E. 2012. Patterns and costs associated with progression of age-related macular degeneration. American Journal of Ophthalmology. Internet document. <https://www.scopus.com/record/display.uri?eid=2-s2.0-84866358655&origin=inward >. Read 11.3.2019.

Seppänen, M., Holopainen, J., Kaarniranta, K., Setälä, N, Uusitalo, H. 2018. Silmätautien Käsikirja. Duodecim.

Souied, E.H., Aslam, T., Garcia-Layana, A., Holz, F.G., Leys, A., Silva, R., Delcourt, C. 2016. Omega-3 Fatty Acids and Age-Related Macular Degeneration Ophthalmic Research 2016. Interent document. < https://www.ncbi.nlm.nih.gov/pubmed/26610051>. Read 10.3.2019

Statistics Finland. Tilastot 2018. Väestö ikäryhmittäin koko maa 1900 – 2070. internet document. <https://www.stat.fi/til/vaenn/2018/vaenn_2018_2018-11-16_tau_001_fi.html>. Read 9.3.2019.

Taylor, D., Hobby, A., Binns, A.,Crabb, D. 2016. How does age-related macular degeneration affect real-world visual ability and quality of life? A systematic review. BMJ. Internet document. <https://www.ncbi.nlm.nih.gov/pubmed/27913556 >. Read 13.3.2019.

TENK, Tutkimuseettinen Neuvottelukunta. 2012. Responsible conduct of research and procedures for handling allegations of misconduct in Finland. Internet document. < https://www.tenk.fi/sites/tenk.fi/files/HTK_ohje_2012.pdf >. Read 27.4.2019.

THL, Terveyden ja Hyvinvoinnin Laitos. Sairaaloiden tuottavuus 2015. Tilastoraportti 6/2017. Internet document. <https://www.julkari.fi/bitstream/handle/10024/132118/Tr6_2017.pdf?sequence=5&isAllowed=y >. Read 10.6.2018.

The Boston Consulting Group 2016. The Missing Piece in Finnish Health Care Reform. 2016:4. Internet document. <https://media-publications.bcg.com/BCG-The-Missing-Piece-in-Finnish-Health-Care-Reform-July-2016.pdf >. Read 10.6.2018.

Tranfield, D., Denyer, D. and Smart, P. 2003 Towards a methodology for developing evidence informed management knowledge by means of systematic review. British Journal of Management. Internet document. < https://www.cebma.org/wp-content/uploads/Tranfield-et-al-Towards-a-Methodology-for-Developing-Evidence-Informed-Management.pdf >. Read 27.4.2019.

Varano, M., Eter, N., Winyard, S., Wittrup-Jensen, K., Navarro, R., Heraghty, J. 2016. The emotional and physical impact of wet age-related macular degeneration: findings from the wAMD Patient and Caregiver Survey. Clinical Ophthalmology. Internet document.< https://www.ncbi.nlm.nih.gov/pubmed/26893539 >. Read 11.3.2019.

Vottonen et Kankaanpää, Cost-effectiveness of treating wet age-related macular degeneration at the Kuopio University Hospital in Finland based on a two-eye Markov transition model. Acta Ophthalmologica 2016. Internet document. <https://onlinelibrary.wiley.com/doi/abs/10.1111/aos.13185>. Read 1.3.2019.

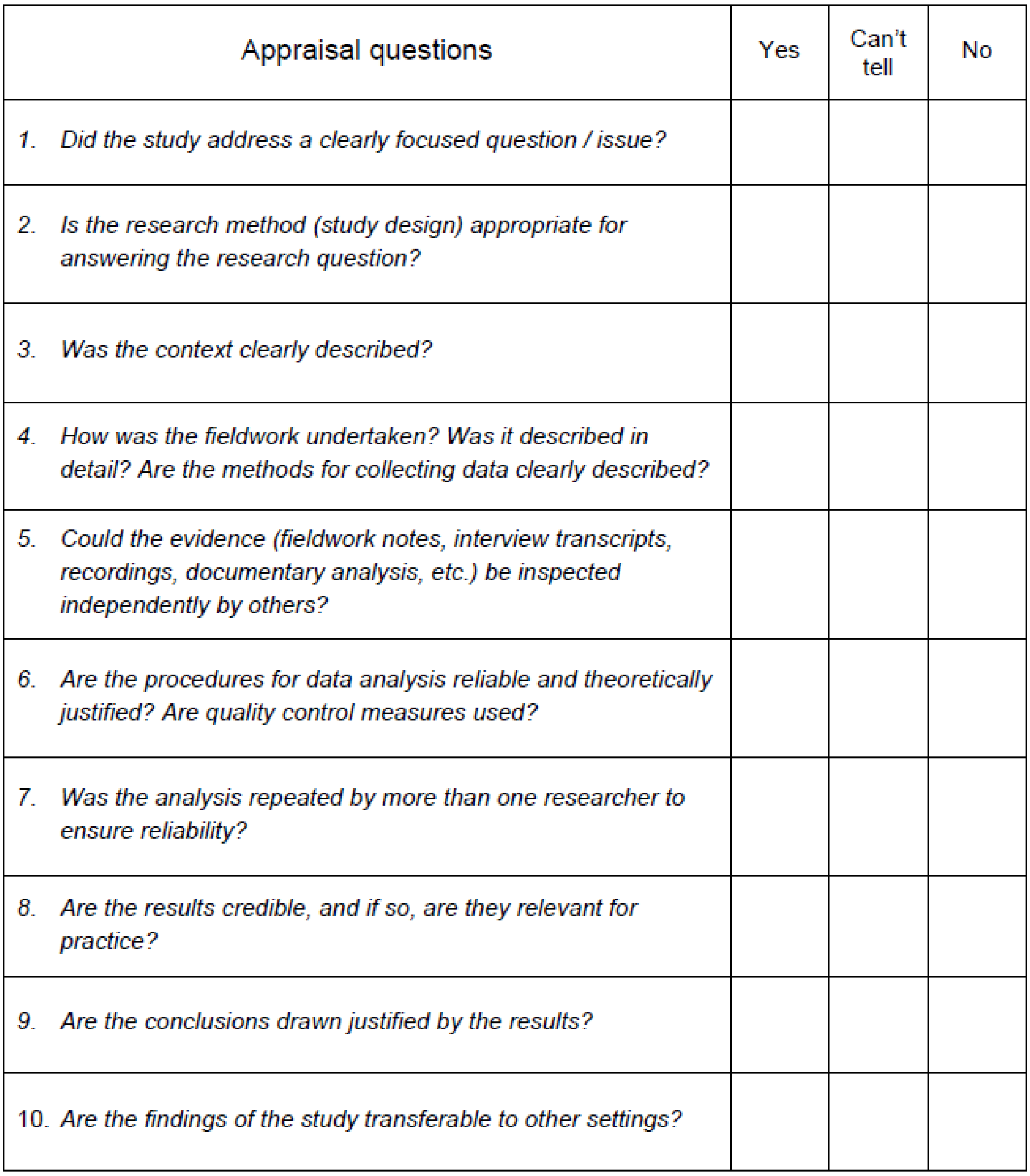
World Health Organization (WHO) 2019. Blindness and vision impairment prevention. Priority eye diseases. Internet document. < https://www.who.int/blindness/causes/priority/en/index7.html >. Read 9.3.2019.

WHO 2019. WHOQOL: Measuring Quality of Life. Internet document. < https://www.who.int/healthinfo/survey/whoqol-qualityoflife/en/>. Read 25.2.2019

Wolf, A. & Kampik, A., 2014. Graefes Arch Clin Exp Ophthalmol. Internet document. <https://www.ncbi.nlm.nih.gov/pubmed/24424409 >. Read 25.2.2018.

Writing Committee for the UK Age-Related Macular Degeneration EMR Users Group. Ophthalmology. 2014 May;121(5):1092-101. Internet document. <http://www.aaojournal.org/article/S0161-6420(13)01153-6/pdf>. Read 1.4.2018.

Critical Appraisal of a Qualitative Study



Appraisal questions	Yes	Can't tell	No
1. *Did the study address a clearly focused question / issue?*			
2. *Is the research method (study design) appropriate for answering the research question?*			
3. *Was the context clearly described?*			
4. *How was the fieldwork undertaken? Was it described in detail? Are the methods for collecting data clearly described?*			
5. *Could the evidence (fieldwork notes, interview transcripts, recordings, documentary analysis, etc.) be inspected independently by others?*			
6. *Are the procedures for data analysis reliable and theoretically justified? Are quality control measures used?*			
7. *Was the analysis repeated by more than one researcher to ensure reliability?*			
8. *Are the results credible, and if so, are they relevant for practice?*			
9. *Are the conclusions drawn justified by the results?*			
10. *Are the findings of the study transferable to other settings?*			

Adapted from Crombie, The Pocket Guide to Critical Appraisal; the critical appraisal approach used by the Oxford Centre for Evidence Medicine, checklists of the Dutch Cochrane Centre, BMJ editor's checklists and the checklists of the EPPI Centre. (Center for Evidence Based Management 2014)

Center for Evidence Based Management (July, 2014), Critical Appraisal Checklist for a Qualitative Study. Retrieved (month, day, year) from https://www.cebma.org