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Investigating the visual outcome and safety in a randomised controlled trial, exploring nurse satisfaction and calculating costs

Doctoral thesis

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Norwegian University of Science and Technology
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Trondheim, November 2022

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Norsk sammendrag

Et oppgaveglidningsprosjekt hvor sykepleiere blir opplært i øye injeksjoner.

Pasienter med flere ulike netthinnesykdommer får sprøytet medisin inn i øyet for å beholde skarpsynet. Behovet for denne behandlingen har vokst svært mye de siste to tiårene og mange steder har øyeavdelingene måttet tenke nytt for å kunne håndtere pasientmengden. Tradisjonelt er det leger som har behandlet pasientene, men på øyeavdeling ved St. Olavs Hospital i Trondheim bestemte vi oss for å lære opp sykepleiere til å sette øye injeksjonene.

I 2014 begynte opplæringen av sykepleiere. Da sykepleierne var ferdig sertifiserte inkluderte vi 342 pasienter i en klinisk studie hvor halvparten av pasienten ble randomisert til å få injeksjoner av en lege og halvparten av en sykepleier. Resultatene viste at sykepleierne kunne gjøre jobben like trygt som legene, med et like godt synsresultat hos pasientene. Pasientene var også svært godt fornøyd med sykepleiere som behandlere. Vi ønsket samtidig å evaluere om de opplærte sykepleierne følte seg tilfredse med den nye oppgaven og om de var fornøyde med opplæringen de hadde fått. Dette munnet ut i en kvalitativ studie hvor 12 opplærte sykepleiere ble intervjuet, enten på tomannshånd, eller i et gruppeintervju. Det kom frem at sykepleierne likte at arbeidsdagen ble mere variert, de fikk større respekt fra omgivelsene og økt selvtillit. Samtidig hadde de flere gode forlag til forbedring av opplæringsprogrammet som deretter ble utbedret.

Etter et vellykket oppgaveglidningsprosjekt som førte til fornøyde pasienter og sykepleiere, gjenstod det å se på kostnadene. Vi trodde øyeavdelingen kom til å spare mye penger på denne oppgaveglidningen, men da de økonomiske analysene forelå, viste det seg at besparelsen var liten for sykehuset og lik null for samfunnet. Dette kan nok skyldes store utgifter til medisiner og transport som utlignet besparelsen i lønnsforskjellene mellom leger og sykepleiere. Uansett er fordelene ved

oppgaveglidning mange. Legene fikk frigjort tid og kunne utføre andre presserende oppgaver på avdelingen. Behandlingskapasiteten opprettholdes, og pasientene slipper å vente lenge på behandling. Sykepleierne følte seg verdsatt som en viktig bidragsyter i behandlingen av pasientene. Avdelingsledelsen fikk større handlingsrom for å kunne håndtere den store pasientmengden. Slike oppgaveglidningsprosjekter kan også overføres til andre spesialiteter på sykehuset og til andre øyeavdelinger i Norge og internasjonalt.

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Veiledere: *Dordi Austeng (hovedveileder), Turid Follestad, Vidar Halsteinli og Kari Hanne Gjeilo (biveiledere)*

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Abbreviations

AMD = age-related macular degeneration

anti-VEGF = anti-vascular endothelial growth factor

BCVA = best-corrected visual acuity

CATT = comparison of Age-Related Macular Degeneration Treatment Trials

CBA = cost-benefit analysis

CEA = cost-effectiveness analysis

CI = confidence interval

CG = comparable group

CMA = cost-minimization analysis

CUA = cost-utility analysis

DM = diabetes mellitus

DMO = diabetic macular oedema

DR = diabetic retinopathy

ETDRS = early treatment diabetic retinopathy study chart

EPR = electronic patient record

FDA = US Food and Drug Administration

GEFAL = French Evaluation Group Avastin Versus Lucentis

IOP = intraocular pressure

IVAN = inhibition of VEGF in age-related choroidal neovascularization

IVI = intravitreal injection

ITT = intention-to-treat

MeSH = medical subject heading

NTNU = Norwegian University of Science and Technology

nAMD = neovascular age-related macular degeneration

OCT = optical coherence tomography

OD = oculus dexter

OS = oculus sinister

QoL = quality of life

RCT = randomised controlled trial

RVO = retinal vein occlusion

SD = standard deviation

SAE = serious adverse event

StO study = St. Olavs study (the randomised controlled trial, Paper II)

UK = United Kingdom

QALY = quality-adjusted life years

QoL = quality of life

List of papers

Paper I

Austeng, D., Morken, T.S., Bolme, S., Follestad, T., & Halsteinli, V. (2016): Nurse-administered intravitreal injections of anti-VEGF: study protocol for non-inferiority randomised controlled trial of safety, cost and patient satisfaction. BMC Ophthalmology 16: 169.

Paper II

Bolme, S., Morken, T. S., Follestad, T., Sørensen, T. L., & Austeng, D. (2020). Task-shifting of intraocular injections from physicians to nurses: a randomised single-masked non-inferiority study. *Acta Ophthalmologica*, *98*(2), 139-144. https://doi.org/10.1111/aos.14184

Findings presented at the Association for Research in Vision and Ophthalmology, ARVO 2018, Honolulu, Hawaii, at Nordic Congress of Ophthalmology, NOK 2018, Oslo, Norway, and at Euretina, Congress of the European Society of Retina Specialists, EURETINA 2018, Vienna, Austria.

Paper III

Bolme, S., Austeng, D., & Gjeilo, K. H. (2021). Task-shifting of intravitreal injections from physicians to nurses: a qualitative study. *BMC Health Services Research*, *21*(1), 1185.

Findings presented at the Association for Research in Vision and Ophthalmology, ARVO virtual meeting 2021 and at the autumn meeting for ophthalmologists in Norway, NOF 2021, Oslo, Norway.

Paper IV

Bolme, S., Austeng, D., Morken, T. S., Follestad, T., Halsteinli, V. Cost analysis of nurse versus physician-administered intravitreal injections in a tertiary hospital in Norway. Submitted 28.06.2022

Findings presented at the Nordic Congress of Ophthalmology, NOK 2022, Reykjavik, Island.

Summary

With the ageing population, the patient pool eligible for anti-VEGF treatment has rapidly expanded over the last two decades. The physicians in ophthalmology departments have tried to meet the growing demand for intravitreal injections (IVIs). In 2013, the Royal College of Ophthalmologists acknowledged task-shifting from physicians to nurses to utilize healthcare resources in the best possible way. Several observational studies have shown that task-shifting IVI administration to nurses is safe and produces satisfied patients. However, no one had tested it until our randomised controlled trial (RCT) was published in 2020 (Paper II), showing nurses non-inferior to physicians in administrating anti-VEGF injections. The study protocol was published as a part of this thesis (Paper I).

After the RCT, our ophthalmology department established a nurse-driven injection clinic where nurses administered all anti-VEGF injections to cooperative and not-so-cooperative patients. Satisfied nurses are important to a successful nurse-driven IVI clinic since satisfied health personnel are transmittable and lead to happy patients. No studies have earlier explored nurse satisfaction with task-shifting.

Therefore, we conducted a qualitative study interviewing the trained nurses to explore their thoughts and opinions on the training program and the new task (Paper III). Twelve nurses were interviewed and felt proud of being trusted with this new task, earning more respect from their surroundings and higher self-esteem. They suggested alterations to improve the training program.

The reason for the task shift was to test whether nurses could do the job as safely as physicians to better utilize the resources in the department. We hypothesised that a nurse-led IVI clinic would lower costs compared to a physician-led clinic. Therefore, we conducted a health economic analysis to provide a thorough ground for decision-makers. The costs of the task shift in a hospital and the societal context were calculated, and we found modest hospital cost savings but no societal savings. We also projected the costs of future injections for 2022–2027 and found possible annual savings for the hospital equivalent to two-thirds of

an injection nurse's wages (Paper IV). The result would be more prominent in other countries with a larger gap between physicians' and nurses' wages. The task-shifting concept is nevertheless here to stay and a way to better utilize available personnel resources.

1 Introduction

"Specific tasks are moved, where appropriate, from highly qualified health workers to health workers with shorter training and fewer qualifications in order to make more efficient use of the available human resources for health" (World Health Organization, 2008, page 2).

1.1 History of task-shifting

The task-shifting concept has historically been useful as the demand for healthcare has outgrown available resources. An example from recent years was the discovery and prevalence of the HIV epidemic in the early 1980s. The workload within healthcare increased while many health workers were infected and died in an eternally vicious circle (Samb et al., 2007). This outcome forced governments to rethink their healthcare system and utilize the available resources in the best possible way (Zachariah et al., 2009).

Although the HIV epidemic accelerated the task-shifting concept, the idea was not new. Throughout the second millennium, physician substitutes emerged to provide care where available physicians were scarce. There were many examples, including the *practicante* in Puerto Rico between the 19th and 20th centuries (Strand, 2006), "the assistant medical officer" in Sri Lanka during the late 20th century (De Silva et al., 2013) and the Russian *feldsher* who developed during the 19th century. The *feldsher* offered something to those living in rural areas who otherwise lacked everything with basic medical training and the skills to provide first aid and simple care (Ramer, 2018).

Another example from Europe emerged in France. After the French Revolution in the 18h century, medical education was in crisis. Because of physician shortages, charlatans established unofficial examination boards while, at the same time, the French Army and Navy desperately needed medical personnel. Newly established medical schools began educating health officers, *officier de santé,* and the qualifications included three years in medical schools instead of the physician's six years. Many were deployed in medically underserved areas (Heller, 1978; Perdicoyianni-Paleologou, 2017).

Task-shifting continued worldwide, with another early example in China in the mid-20th century. China already had 500 million inhabitants, with over 90% living in rural areas involving agriculture. At that time, medical schools were situated in cities, educating approximately 200,000 physicians, not nearly enough.

Consequently, a substitute emerged, the "barefoot doctors", who were not authentic physicians. They were trained for a short time, from three months to two years and managed public healthcare centres in rural areas. They were oriented to health prevention because, at that time, Mao Zedong and the Communist party were influenced by the Soviet Union.

The short-term training required for barefoot doctors radically multiplied medical personnel in agricultural areas. They received a monthly salary, generally half the amount of a regular physician (Lee & Kim, 2018). By 1970, approximately 1 million barefoot doctors were employed in rural China (Sidel, 1972).

In more recent times, task-shifting has also been embraced in high-income countries, not motivated by war or serious crisis but by the utilization of available human resources. Thus, nurses have been trained to follow up on patients with multiple sclerosis (Thotam & Buhse, 2020) and breast cancer (Stahlke et al., 2017), and to perform echocardiography in rheumatic heart patients (Engelman et al., 2015).

1.1.1 Task-shifting in surgery

In 2012, 300 million surgical procedures were completed worldwide, yet only a small portion (6%) occurred in countries comprising the poorest one-third of the world's population. In a report from 2015, the Lancet Commission estimated that 75% of the world's population had inadequate access to safe surgical care (Meara et al., 2015; Weiser et al., 2008). Thus, a team-based approach has become a possible solution to meet the demand. Task sharing is defined as the sharing of common surgical responsibility between specialists and non-specialists, under the supervision of specialists (Mearea 2015). Surgical task-shifting has also grown in high-income countries, perhaps in a more supervised, less independent form. A systematic

literature review found that physicians supervised most surgical task shifts in high-income countries, making task sharing a more suitable name, whereas in low-income countries, nurses commonly worked independently (Federspiel et al., 2015).

1.2 Advantages and limitations of task-shifting

Many health professionals spend considerable time undertaking activities for which they are overqualified, resulting in poor resource utilization while affecting employee satisfaction with tasks and opportunities for further development at work. A vertically staged task shift, with tasks transferred from a higher to a lower level of competence, can have many advantages. Indeed, it can optimize utilization of the available workforce, reduce costs, give health workers more varied tasks, increase motivation, make health services more accessible and increase the quality of care. Thus, task-shifting can enhance the health system's resilience, allowing professional groups to substitute for one another (Delamaire & Lafortune, 2010; EU, 2019; World Health Organization, 2008).

However, task-shifting has limitations and concerns. Shifting responsibility from a higher to a lower level requires changes to legislation and regulation. The rules and borders for legal liability can be blurry and vague, creating an unresolved situation if something goes wrong or someone makes a mistake. For example, the WHO found insufficient evidence of a regulatory framework supporting the task-shift concept (World Health Organization, 2008). Changing someone's responsibilities is likely to lead to a change in their status and expectations, challenging traditional hierarchies, making some feel less important and creating conflicts between professionals involved.

The situation is further complicated when changing responsibilities has financial implications. Patients might doubt the treatment quality and be dissatisfied, or the cost of training new health workers could be a large investment. Moreover, after a task shift, healthcare personnel may have less competency, posing a risk to good treatment quality. Supervision from health personnel with a higher level of competency is necessary to ensure treatment quality, which could be costly and resource demanding (Delamaire & Lafortune, 2010; Malterud et al., 2020; World Health Organization, 2008).

1.2.1 Legal indemnity when task-shifting

Since the rise of modern healthcare in the late 19th century, laws and legislation have developed to license physicians and nurses, establishing a scope of practice. The aim is to protect patients by forming standardized certifications as markers of competence. However, these laws do not always specify what a specific health personnel group is allowed to do, which has been a barrier to task-shifting (EU, 2019).

An observational study examined state regulations for physician substitutes in all states in the US between 2001–2010, discovering a trend toward less restrictive regulations. Thus, physician substitutes were granted more independence with less physician involvement while the educational requirements before certification increased (Gadbois et al., 2015). A growing trend toward nurse role advancement is also happening in Europe, and legislation is slowly changing to extend nursing roles. However, large variations among countries exist. Indeed, if countries developed a standardized educational requirement, the comparability and acknowledgement of new nursing roles would be easier across countries (Maier & Aiken, 2016).

Norway has no significant task-shifting activity, so task-shifting legislation lags (World Health Organization, 2008). When task-shifting is practised in Norway, "The Health Personnel Act" regulates the professional practice of health personnel. Paragraph 4, chapter 2 defines the health personnel's obligation to act with prudence and caution. For every health personnel, the prudential requirement entails a duty to act per current professional norms and statutory requirements for practice, including the expectation that national guidelines are followed (Helsedirektoratet, 2011). The management at every health institution is responsible for giving the healthcare personnel adequate training and certification to perform their jobs. Always having updated quality-assured procedures ensures that the practice stays consistent. When following procedures, employees are not held personally responsible for an unfortunate incident. Thus, only in rare cases when health personnel act grossly negligently, can they be held personally responsible. This approach yields physicians and nurses working in Norwegian hospitals.

1.3 The history of intravitreal injections (IVI) with vascular endothelial growth inhibitors

During the 1950s, an American ophthalmologist, Georg N. Wise, discovered “factor x”, later known as vascular endothelial growth factor (VEGF), associated with the hypoxic retina as part of the system that restores the oxygen supply to tissues when blood circulation is inadequate, such as in ischaemic retinopathies (Wise, 1956). In the early 1970s, it was suggested that control of tumour blood vessel growth potentially could be an important target for cancer therapy (Folkman, 1971). During the next decade, the VEGF molecule was isolated, and scientists discovered that it increased vascular permeability and inflammation, promoting the growth of vascular endothelial cells (Ferrara & Henzel, 1989).

Later, in the 1990s, Kim et al. (1993) discovered that a monoclonal antibody targeting VEGF could suppress tumour growth, leading to the development of a humanised anti-VEGF monoclonal antibody (Ferrara et al., 2004; Hurwitz et al., 2004). In 2004, the US Food and Drug Administration (FDA) approved the first anti-VEGF therapy, bevacizumab, developed by Genentech (Avastin, Genetech, Inc., South San Francisco, CA, USA) for the treatment of metastatic colorectal cancer combined with chemotherapy.

Parallel with developing anti-VEGF therapies for cancer, VEGF was found to play an important role in age-related macular degeneration (AMD; (Gragoudas et al., 2004). The growth of choroidal neovascular vessels depends on VEGF, similar to tumour vessels. The FDA approved pegaptanib (Macugen, Eyetech Pharmaceuticals) in 2004 as the first antiangiogenic therapy for ocular neovascularisation. In 2005, the first reports suggested that intravitreal bevacizumab (Avastin) injections were superior to pegaptanib in treating neovascular AMD (nAMD; (Rosenfeld et al., 2005). Later, more drugs were approved, first ranibizumab (Lucentis, Genetech, FDA-approved in 2006) developed by using a fragment of bevacizumab (Ferrara et al., 2006), followed by aflibercept (Eylea, Bayer HealthCare and Regeneron Pharmazceuticals, Inc., Tarrytown, NY, USA), approved by the FDA in 2011 when it tested non-inferior to ranibizumab (Heier, Brown, et al., 2012). Furthermore, three multicenter randomised controlled trials (RCTs) revealed the non-inferiority of bevacizumab to the ranibizumab testing visual outcome, so because of lower costs, bevacizumab became widely

used as intravitreal therapy off-label (Chakravarthy et al., 2013; Kodjikian et al., 2013; Martin et al., 2011).

1.4 The increase in anti-VEGF therapy

Anti-VEGF treatment has significantly impacted retina healthcare. Before the anti-VEGF era, the best treatment for ischaemic retinopathies was laser treatment to preserve vision but not restore it (Brown et al., 2006; Group, 1987; Nguyen et al., 2012). The first reports of the effect of anti-VEGF showed 90% preservation of vision and 30% improvement in vision versus 60% and 5% with traditional laser treatment (Brown et al., 2006; Rosenfeld et al., 2006). The anti-VEGF therapy was quickly approved for numerous ischaemic retinopathies, the three most common being nAMD, diabetic macular oedema (DMO) and retinal vein occlusion (RVO; (Heier, Campochiaro, et al., 2012; Mitchell et al., 2011; Rosenfeld et al., 2006).

Most treated diseases, especially nAMD, are age dependent. Since anti-VEGF was introduced, the number of patients and injections has increased annually because of the ageing population. Patients needing repetitive treatments, some as often as every fourth week, have also increased the number of anti-VEGF injections. Between 2009 and 2019, Moorfield Eye Hospital in London reported a nearly 11-fold increase in injection numbers (Chopra et al., 2021), and St. Olavs Hospital experienced a five-fold increase during the same period. Moreover, Oslo University hospital reported a 100-fold increase in yearly IVIs from 2006–2018. Other high-income countries have also reported massive increases (Patel, 2018). Thus, anti-VEGF has become a cornerstone of retinal care, and IVIs are now the most common intraocular procedure worldwide (Grzybowski et al., 2018).

1.5 Retinal diseases treated with anti-VEGF

1.5.1 Age-related macular degeneration

AMD is the leading cause of visual disability in the industrialized world (Pennington & DeAngelis, 2016). The estimated number of people with the disease worldwide in 2020 was 196 million (Wong et al., 2014). AMD affects the central area of the retina (the macula) and is classified as early- or late-stage AMD. Late-stage is further stratified into a nonexudative

(dry) and an exudative (wet) form (nAMD). The dry form usually has a slow course with gradual vision loss over several years. So far, there is no treatment for the dry form of the disease. In contrast, the wet form can occur overnight and cause severe vision loss if left untreated.

A systematic review looking at the European population 50+ found an incidence of 1.4 per 1,000 individuals (Li, Welchowski, Schmid, Mauschitz, et al., 2020), while another study of a population with European ancestors found 3.5/1,000/year, 50+ (Rudnicka et al., 2015). Because increased age is a strong risk factor for AMD, the prevalence of AMD will increase as the population ages. Indeed, one study projected 288 million worldwide in 2040 (Wong et al., 2014), while another, looking only at Europe, projected 77 million by 2050 (Li, Welchowski, Schmid, Mauschitz, et al., 2020).

1.5.2 Diabetic macular oedema

DMO is a leading cause of vision loss among people with diabetes. The pathogenesis is still not fully understood but is a condition characterized by fluid accumulation in the macular extracellular space (Otani et al., 1999). People with DMO can experience sudden vision loss due to blood leakage into the eyeball or more slowly developed blindness due to oedema in the macula (sharp vision area). While DMO can occur independently of diabetic retinopathy (DR), it appears to be strongly associated with the severity of DR (Graue-Hernandez et al., 2020). Non-invasive imaging using optical coherence tomography (OCT) has detected mild levels of DMO to monitor progress and guide treatment.

Although laser photocoagulation was the traditional mode of treatment, intravitreal administration of anti-VEGF agents is now the standard of care (Mitchell et al., 2011; Schmidt-Erfurth et al., 2017; Virgili et al., 2018). It remains uncertain if treatment with anti-VEGF for DMO is lifelong, but patients in the Protocol T extension study received 15 IVIs during the first two years and seven IVIs during the next three years. Aflibercept was the drug of choice in DMO eyes with baseline BCVA below 69 letters, showing superiority to bevacizumab over two years and ranibizumab in the first year of treatment (Glassman et al., 2020).

A recent meta-analysis found a global DMO prevalence of 5.5% in people with diabetes (Im et al., 2022). A previous study a few years earlier examined the European population and found a prevalence of 3.7% (Li, Welchowski, Schmid, Letow, et al., 2020). The estimated global DM population was 463 million in 2019, projected to be 700 million by 2045 (Saeedi et al., 2019) and indeed, 28.61 million of these will have DMO (Teo et al., 2021).

1.5.3 Retinal vein occlusion

RVO is a vascular occlusion of either a branch (BRVO) or the central retinal vein (CRVO). In patients with BRVO, retinal ischaemia results in the elevated secretion of VEGF, resulting in increased vascular permeability and vasodilatation, which could cause macular oedema (MO; Gale et al., 2021). Currently, the first-line treatment for MO due to RVO is anti-VEGF therapy (Nicholson et al., 2022). Long-term outcome studies have suggested the need for anti-VEGF to drop after the first year from five IVIs to one IVI in the fifth year, with half of the patients not requiring IVIs after the first year of treatment (Corazza et al., 2022). Another study reported that patients needed four IVIs eight years after initiating treatment (Spooner et al., 2022). The global prevalence of RVO is suggested to be 0.8% (30–89 years; Song et al., 2019). RVO is highly age-driven; therefore, the numbers will increase in the years to come due to the global demographic ageing process. The number of patients in Europe with RVO is projected to increase by almost 20%, from 900,000 today to 1.1 million in 2050 (Li et al., 2019).

1.6 IVIs and task-shifting

Before 2013, there were no publications on IVIs by nurses. Researchers from the United Kingdom (UK) were the first to report nurse-led anti-VEGF injections. The UK experienced the same exponential rise in IVIs as other Western countries, with fewer specialists in ophthalmology per capita than any other country in the EU (Statista, 2020). They already embraced the modernization of staff roles in other parts of ophthalmology, for instance, nurses performing laser capsulotomy treatment (Forbes, 2013) and chalazion surgery (Jackson & Beun, 2000).

Until 2013, both the Royal College of Ophthalmologists and the American Academy of Ophthalmology recommended that IVIs with anti-VEGF should only be administered by ophthalmologists (Michelotti et al., 2014). Furthermore, Novartis Pharmaceuticals stated that ranibizumab "must be administered by a qualified ophthalmologist experienced in IVIs". (Novartis 2022, section 4.2). Descriptions of nurse-led IVI services were presented in May 2013 at the Royal College of Ophthalmologists Annual Congress by Exeter Hospital and Moorfield Hospital in the UK. One month before the congress, the Royal College of Ophthalmologists made a statement opening the possibility that healthcare personnel other than ophthalmic doctors could administer IVIs with anti-VEGF (Royal College of Ophthalmologists, 2013). In the first half of 2013, the National Institute for Health and Care Excellence (NICE) approved ranibizumab for DMOs and RVOs, increasing the demand for intravitreal therapy further (NICE, 2013b, 2013c).

1.6.1 Training nurses

In April 2013, Sunderland Eye Infirmary, in the northeast UK, published an article describing how they had expanded the nurse role to deliver IVIs. They submitted a business case for nurse-led IVI service development. Only the Exeter hospital had done the same. Four specialist nurses were trained.

The training program consisted of classroom lectures on the anatomy and physiology of the eye and surgical techniques, including complications. The program also included a series of wet lab sessions that provided nurses with adequate training on patient preparation, equipment handling, surgical techniques and post-treatment management of patients undergoing IVIs. A stepwise training approach was followed on aseptic cleaning and draping, the insertion of the lid speculum, topical anaesthesia and the correct technique for IVI. Competency for each step was approved before the nurse could proceed to the next step. A total of 25 IVIs were to be competently completed before the nurses could work independently (Varma D, 2013).

1.6.2 Safety

Serious adverse events (SAE) after IVIs are rare. The most feared complication is endophthalmitis, purulent inflammation of the eye's interior cavity that could make the eye blind (Pancholy et al., 2021). The rate of post-injection endophthalmitis has ranged from 0.03% to 0.06% in various studies (Patel et al., 2020).

The first studies to evaluate safety after nurse-led IVIs were observational with historical comparisons. Two hospitals in the northwest UK started training nonmedical staff to administer IVIs after approval from the surgical directorate and governance committee in February 2012. Three experienced nurse practitioners who had observed > 1,500 IVIs were trained and administered the first 200 IVIs under the supervision of an ophthalmic specialist before being allowed to inject independently. Over 18 months, 3,355 IVIs were administered by nurses with no SAEs (Michelotti et al., 2014).

Varma et al. (2013) collected data postoperatively on 1,400 IVIs, and the result was no visually threatening events. Moorfield also registered SAEs postoperatively after 4,000 nurse-administered IVIs. The results were no SAEs (DaCosta et al., 2014). In comparison, Exeter Hospital reported four cases of endophthalmitis after two trained nurses administered 10,000 IVIs from 2008–2013, with an incidence rate comparable to two large studies where physicians administered the IVIs. Therefore, Simcock et al. (2014) concluded that nurse-administered IVIs were safe (Brown et al., 2006; Rosenfeld et al., 2006). At that time, there was no literature from outside the UK, but one talked about nurse-administered IVIs clinics in Spain and Denmark (Michelotti et al., 2014). A safety report from New Zealand was published in 2016 where three experienced nurses, for 18 months starting in July 2013, administered 2,900 IVIs with a post-injection endophthalmitis rate of 0.07% (Samalia et al., 2016).

1.6.3 Patient satisfaction

In the first half of 2014, three studies which reported high levels of patient satisfaction after nurse-led IVIs were published. All three observational studies had no control group. The first study was conducted in 2013 at Sunderland Eye Infirmary (Varma D, 2013). Later the same

year, East Lancashire Hospitals Trust (ELHT), a general hospital in the northwest UK, presented a patient satisfaction study about IVIs by nonmedical staff at the Oxford Ophthalmological Congress in July 2013 (Michelotti et al., 2014). The following year Moorfield's Eye Hospital in London published a prospective observational study reporting patient satisfaction after 4,000 nurse-administered IVIs (DaCosta et al., 2014).

1.6.4 Comparing physician- and nurse-administered IVIs

To that point, no UK Hospitals had published data comparing physician- and nurse-administered IVIs. Then, in 2015, the first retrospective observational case series from Glostrup Hospital in Denmark was published (Hasler et al., 2015). Glostrup Hospital trained 58 physicians and four nurses who administered 38,503 IVIs between 2007 and 2011. Of the 14 endophthalmitis cases, four were injected by nurses. The study concluded that using physicians in training and nurses to administer IVIs was safe (Hasler et al., 2015). Later, the Central Middlesex Hospital in London published a patient satisfaction survey comparing physician- and nurse-administered IVIs, with similar results (Mohamed et al., 2018).

1.7 Task-shifting IVIs to nurses at St. Olavs Hospital: The beginning

In St. Olavs Hospital's ophthalmology department, the number of IVI treatments increased from 200 in 2006 to 2,622 in 2012. The department reached a threshold for what it could deliver with the available resources. In April 2013, IVIs were outsourced to a private hospital, which gave the ophthalmology department at St. Olavs Hospital an opportunity to discover possible solutions for resource deficiencies. Thus, a task-shifting idea emerged.

A study investigating whether nurse-administered IVIs were non-inferior to physician-administered IVIs began. With funding from the RHA, St. Olavs Hospital provided enough healthcare personnel to establish an injection clinic. When the planning started in early 2014, the project was called *Prosjekt Øyenstikker*, named after the dragonfly, which means "eye-stinger" in Norwegian (Figure 1). Since the name does not have the same symbolic meaning in English, this trial is referred to as the StO study in this paper.

Figure 1*: A dragon fly*

Small children in Norway believe that dragonflies can stab people in the eye since the Norwegian name for dragonfly means "eye-stinger".

1.8 Study designs

Previous studies performed in task-shifting IVIs were observational or surveys without control groups. These studies did not possess the highest quality of evidence and were more likely biased than RCTs (Hariton & Locascio, 2018). Since these observational studies were not randomised, the exposure (i.e. nurse-administered IVIs) might have been linked to a hidden confounder (e.g. nurses only injecting "easy" patients). Therefore, this thesis addresses various study designs and research methods, starting with a non-inferiority, single-blinded RCT, then a semi-structured interview, followed by a health economic analysis.

1.8.1 Randomised controlled trials

In 1948, the first RCT was published in the British Medical Journal: "Streptomycin treatment of pulmonary tuberculosis". One of the authors was Sir Austin Bradford Hill, credited with conceiving the modern RCT (Brown, 1998; Stolberg et al., 2004). In RCTs, patients randomly receive one of several allocated clinical interventions to reduce bias. Thus, RCTs are the reference standard for studying causal relationships between interventions and outcomes

(Hariton & Locascio, 2018). In a review of task-shifting in primary care, Norway was the country in northern part of Europe where nurses had the least tradition of assuming extended roles (World Health Organization, 2008). Hence, an RCT, the gold standard, was deemed necessary when introducing nurse-administered IVIs in central Norway.

1.8.2 Non-inferiority trials

One way of classifying RCTs is by the hypotheses: superiority, non-inferiority or equivalence trials (Wang et al., 2017). A superiority trial aims to show that one treatment is clinically better than another by demonstrating superiority. In an equivalence trial, the statistical test aims to show that two treatments are equivalent within some predefined limits of equivalence.

However, we chose a non-inferiority design, inspired by the multicenter RCTs (Berg et al., 2015; Chakravarthy et al., 2012; Kodjikian et al., 2013; Martin et al., 2011) comparing different anti-VEGF agents with a non-inferior design. A non-inferior study aims to demonstrate that the intervention is not worse than the established standard treatment comparator by more than a pre-specified amount (the non-inferiority). Notably, if nurses were non-inferior to physicians administrating IVIs, advantages would include lower costs (our hypothesis) and more flexibility. A non-inferiority trial usually has the smallest sample size of the three hypotheses and our sample size was limited by the number of patients treated.

1.8.3 Qualitative research

Qualitative researchers study events and phenomena in their natural settings, trying to interpret and understand the meaning to provide in-depth insights. In contrast, quantitative methods have traditionally been considered the best way to perform medical research focused on cause and effect, where treatment *X* is the cause of improvement *Y*. By the 1960s, battle lines were drawn between quantitative and qualitative supporters as quantitative allies demoted qualitative research to a subordinate status. In 1962, Thomas Kuhn wrote “The Structure of Scientific Revolutions”, claiming that we can never rely wholly upon objectivity alone (Kuhn, 1962). Science must also account for subjective perspectives since all objective

conclusions are established on subjective conditioning. Therefore, we must be aware of our preconceptions.

This awareness helped silence some criticism towards qualitative methods, opening the idea that every research method is biased because researchers will always bring their previous experiences and preconceptions. In 2003, PubMed assigned “qualitative research” as a MeSH (search word) in their database. A study examining the top-rated medical journals during 1999–2008 found that the portion of qualitative articles published was less than 1% (Gagliardi & Dobrow, 2011). Although there is still an ongoing debate about which methodological approach is best, the research question should determine the method used (i.e. RCTs can demonstrate that an intervention is successful but rarely explain why). Thus, a qualitative study could enrich the understanding (Curry et al., 2009). Illustrated also in the growing popularity of mixed methods research which combines the strengths of both qualitative and quantitative methods (Shorten & Smith, 2017).

1.8.3.1 The qualitative interview

Paul Felix Lazarsfeld, the possible father of qualitative research, showed how psychology could provide a framework to interpret human behaviour. He introduced the scientific world to interviews and group discussions and highlighted answering the important “why” (Bailey, 2014).

Using an interview to collect data in qualitative research is not uncommon. In the interview, one can investigate the unknown and discover new connections, capturing verbal and non-verbal cues, emotions and behaviour. The interview is a situational execution, so the answer depends on the responder (Donalek, 2005). In contrast, a questionnaire, more commonly used in quantitative research, investigates areas of previous knowledge, connecting isolated variables. The questionnaire is mechanically executed, and the answer depends on the pre-specified options (Harris & Brown, 2010).

Interviews can be open, where informants speak freely, or structured, answering specific questions. A mix of both is a semi-structured interview controlled by topics. In semi-structured interviews, the interviewer follows up on informants' answers, allowing them to speak freely. The individual interview can go in-depth on a topic with a face-to-face conversation exploring issues in detail. In contrast, a focus group interview uses group interactions to generate data (Kallio et al., 2016).

While individual interviews feel safe and bring out the entire breadth of a topic, group interviews give a condensed common opinion highlighting a common agreement. (Polit & Beck, 2020). It is easier to build trust in an individual interview, but it also demands a certain ability to communicate, while in a group setting, the moderator (interviewer) must have the ability to manage meetings. When seeking data completeness, it is assumed that each interview method reveals complementary views, expanding the depth that may enrich the data (Lambert & Loiselle, 2008).

1.8.4 Economic evaluations

Economic evaluations provide useful insights into how healthcare can be organized cost-effectively, providing a framework for policymakers (WHO, 2022). Rising healthcare costs force more cost-effective ways to deliver healthcare, such as task-shifting (EU, 2019). The health expenditure per capita in Norway increased by 67% from 2010–2020 (OECD.Stat, 2022), while the consumer price index increased only by 22% (Statistics Norway, 2022a). In 2012, the Norwegian Directorate for Health published guidelines for economic evaluation in the health sector for the first time. The report highlighted the increased demand for the efficient use of resources, describing how to facilitate more economic evaluation of new procedures in the health sector (Helsedirektoratet, 2012).

Economic evaluations are important because all resources (i.e. people, time, knowledge and equipment) are scarce. The basic tasks of any economic evaluation are to identify, and measure, the costs of the available alternatives (Drummond, 2015). The WHO's guidelines

identified cost analyses as an evidence gap when implementing a task shift (World Health Organization, 2008).

There are four different economic evaluation methods and they all involve systematic identification and measurement of the costs and outcomes. Cost-effectiveness analysis (CEA) is characterized by disease-specific outcomes and cannot compare cost-effectiveness between different patient groups or diseases. A cost-utility analysis (CUA) can compare the costs and outcomes because the outcome measure is health-related quality of life. Using a preference-based instrument such as EQ-5D (Rabin & de Charro, 2001) you can calculate quality adjusted life years (QALYs) which embraces both longevity and quality of life (NICE, 2013a). Cost-benefit analysis (CBA) is a type of economic evaluation that translate effects (i.e. QYALYs gained) into a monetary value. Costs of two or more interventions with identical outcomes can be evaluated with a cost-minimization analysis (CMA), then choosing the intervention representing the lowest costs. Interventions are rarely identical, which is a limitation of CMA. It could only be used where the effects have been tested and found to be equal (i.e. previous research or professional opinion; Drummond, 2015).

1.8.5 The accuracy of costing

Analysts must decide how accurate cost estimates must be within a given study. There are two main approaches when collecting cost information, top-down and bottom-up. The top-down approach picks relevant intervention costs from hospital's annual budget. Using such easily accessible data has low costs but could limit transparency and consistency. In contrast, the more extensive and time-consuming bottom-up approach identifies each component of resource (i.e. laboratory tests, surgery equipment) and matches this with the unit costs for each item. The bottom-up approach, also called micro-costing, is the most precise (Wordsworth et al., 2005). It Is easier to undertake micro-costing if the economic evaluation is based upon a prospective clinical study, because then the analysts have access to individual patient data (Drummond, 2015).

2 Aims

This thesis aims to study several aspects of task-shifting the administration of intravitreal injections from physicians to nurses to accomplish the following:

- Investigate whether patients treated by nurses have a non-inferior visual acuity after one year compared to patients treated by physicians (Paper II),
- Evaluate the incidence of SAEs in the two groups during the StO study (Paper II),
- Compare the number of IVIs, the length of intervals between injections and the success of nurse- versus physician-administered IVIs (Paper II),
- Evaluate patient satisfaction with nurse-administered IVIs compared to physician-administered IVIs (unpublished material),
- Evaluate whether the nurses were confident and in control after participating in the training program (Paper III),
- Evaluate whether nurses were satisfied with the training and the new task (Paper III),
- Investigate the hospital costs per IVI nurse versus physician-administered IVIs (Paper IV),
- Investigate the societal costs per patient per year nurse versus physician-administered IVIs (Paper IV) and
- Forecast a six-year cost projection of nurse- versus physician-administered IVIs for a Norwegian tertiary hospital (Paper IV).

3 Material and methods

3.1 Study designs

A study protocol was prepared prior to the study and published (Paper I). The protocol was written in line with the principles of the SPIRIT guidelines (Standard Protocol Items: Recommendations for Interventional Trials; Chan et al., 2013)).

3.1.1 Randomised controlled non-inferiority, single-masked trial (Paper II)

We designed a prospective RCT where the standard of care, physician-administered IVIs, were compared to an intervention, nurse-administered IVIs with a non-inferiority margin.

3.1.2 Qualitative study (Paper III)

This qualitative study had an inductive descriptive design using semi-structured interviews to interview the nurses trained in administrating IVIs. We used both individual (n = 5) and focus group interviews (n = 7).

3.1.3 Cost calculations (Paper IV)

The data gathered in the randomised controlled prospective trial, mentioned in 3.1.1, was analysed to compare the societal cost of physician-administered IVIs to nurse-administered IVIs. A CMA with a bottom-up approach was used.

3.2 Intervention

3.2.1 Nurse-administered IVIs as the intervention group (Paper II)

Nurses were trained to administer IVIs with anti-VEGF as safe and efficient as physicians; the intended number of IVIs was 22 per day. In the nurse-administered IVI group, a nurse checked the patient for contraindications, such as blepharitis or ongoing antibiotic treatment. Contraindications for IVI treatment were part of the theoretical training. If approved (no contraindications), the nurse prepared the patient following procedure with local anaesthetic

eye drops and antiseptic povidone-iodine. The patient was then taken into the injection room, where another nurse administered the IVI following a sterile procedure, gave information about possible complications, scheduled the next appointment and documented treatment in the electronic patient record (EPR; Figure 2 and 3).

In the physician-administered group, the preparation for IVI was the same as for the nurse-administered IVIs, and the physician was responsible for the remaining procedure. Both physicians and nurses had the opportunity to ask a consultant for advice.

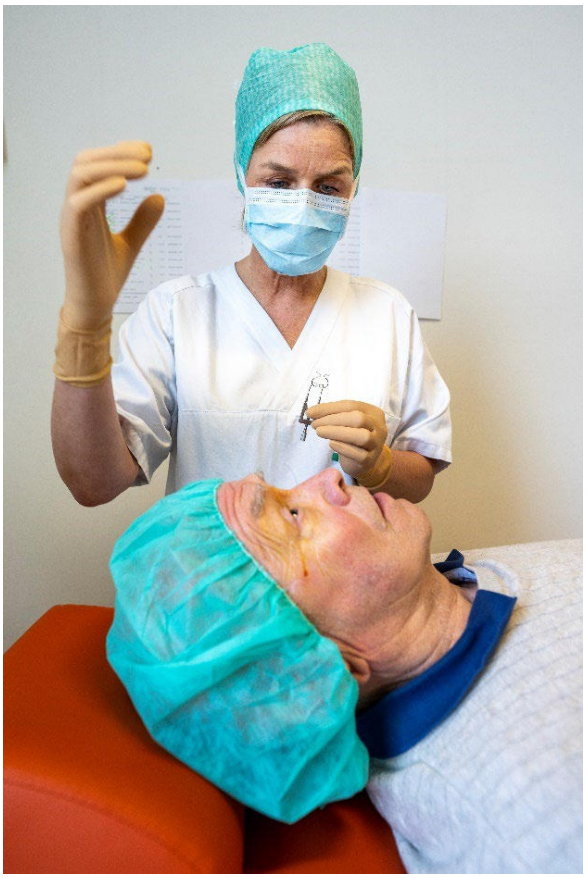

Figure 2*: A nurse preparing to place the lid speculum before injection*

The patient and the nurse gave their consent to publish this picture (taken via infinitiv.no).

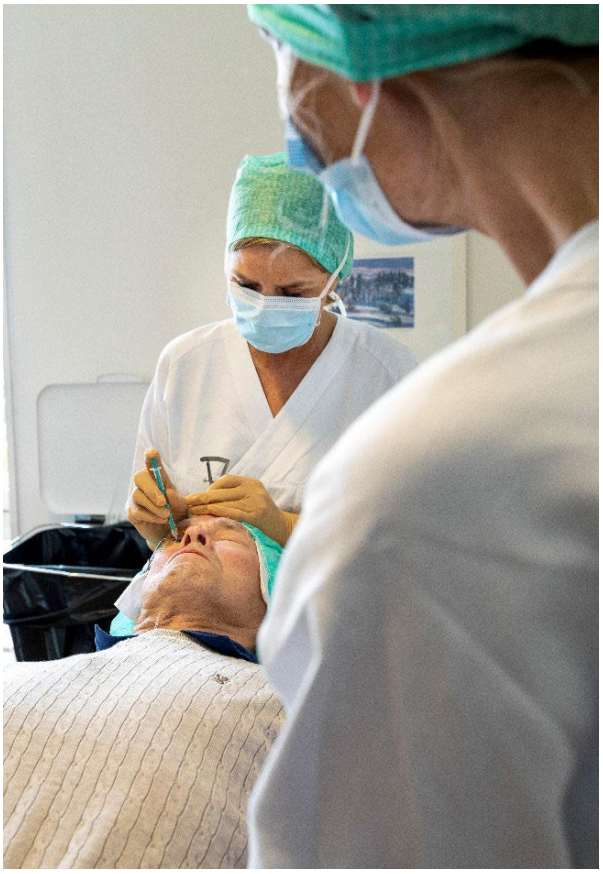

Figure 3*: A patient injected with aflibercept (Eylea)*

The patient and the nurses gave their consent to publish this picture (taken via infinitiv.no).

3.2.2 Training nurses (Paper I)

Six nurses were trained during 2014, prior to the StO study starting in March 2015. The experience level of the nurses varied from very experienced to new graduates. Two more nurses entered the training program but changed their minds along the way and dropped out.

The first part of the training program was three theoretical lectures (Figure 4). The first lecture introduced IVIs, eye anatomy, technical information on injections and contraindications. The second lecture entailed diseases treated, different anti-VEGF medicines and possible complications after IVI. The third lecture discussed blepharitis and learning when to inject or postpone an injection.

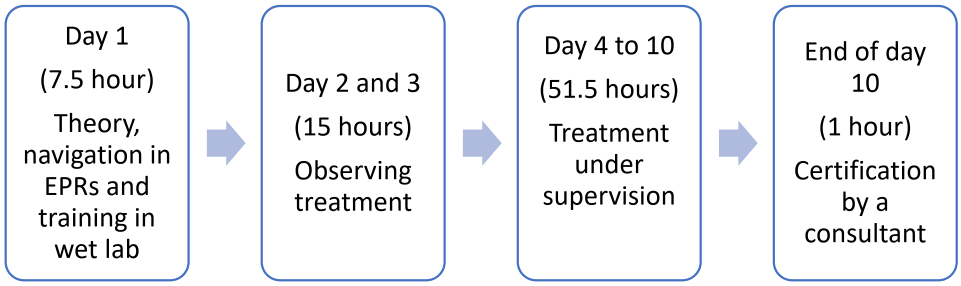

Figure 4 *The training program for nurses and physicians*

Then, the nurses were introduced to the practical part in a wet lab, rehearsing injection techniques on pig eyes (Figure 5). The teacher was a retina surgeon.

Although all nurses were familiar with EPRs, they had never documented a treatment. Therefore, a physician showed them how to navigate and document in the EPR. Next, the nurses were ready to join the physicians in the injection room, only observing patient treatment initially. When they felt ready, the nurses performed procedures like putting on sterile glows, aseptic cleaning, insertion of the lid speculum, topical anaesthesia, measuring the correct distance from the limbus and the correct IVI technique.

Every nurse controlled the pace of their graded exposure to new procedures in the injection room. Nurses were required to administer 100 IVIs before a consultant not involved in the training would approve three IVIs to grant the nurse certification to administer IVIs independently. At first, nurses only injected the “easy” patients able to cooperate fully, and the next step was to inject every other patient before they felt confident enough to inject all patients.

Figure 5*: Nurses rehearsing injection techniques in our wet lab.*

The nurses gave their consent to publish this picture.

3.3 Setting (Paper I, II and III)

The St.O study was performed in the injection clinic on the fifth floor of the ophthalmology department at St. Olavs Hospital (Figure 6 and 7). The outpatient clinic is located on the ground floor. The ophthalmology department treats more than 23,000 patients annually and serves a population of ~ 300,000 individuals living in 19 municipalities in central Norway. Patients are remitted to the injection clinic by ten ophthalmologist clinics situated outside the hospital, most of them in Trondheim city centre.

Figure 6: *The waiting area and secretary space at the ophthalmology department at St. Olavs Hospital*

Figure 7*: The injection room*

The individual interviews and the focus group interview happened in a conference room at St. Olavs Hospital.

3.4 Study population (Paper I, II and IV)

At the time of the RCT, the ophthalmology department had approximately 900 patients needing anti-VEGF (i.e. over one-third of the patient pool was included in the study). Inclusion criteria were having either AMD, RVO or DMO eligible for anti-VEGF treatment. We included both treatment-naïve and earlier-treated patients with anti-VEGF.

3.5 Randomization (Paper I, II and IV)

Patients were randomised to be treated by either a physician or a nurse for one year. The web-based algorithm was provided by the Norwegian University of Science and Technology. The randomization was stratified by diagnosis and whether the patient was treatment-naïve.

3.6 Masking (Paper I, II and IV)

Participants were masked to the experimental group by dressing physicians and nurses in similar hospital clothing, surgical caps and masks, introducing themselves by first name only, not their profession. All patients were asked at the study's end if they believed a physician, or a nurse had treated them over the past year to check if the masking worked.

3.7 Sampling and data collection (Paper III)

The idea for the qualitative study was to use a total sampling strategy. After the RCT ended, an additional nurse was trained, totaling seven nurses administering injections. These nurses were interviewed individually from April through August 2016. The interviews lasted between 14 and 30 minutes. Later, five more nurses were trained and interviewed in a focus group in March 2019. The group interview lasted 50 minutes. All twelve nurses agreed to be interviewed.

There was a great range among the 12 nurses. Both sexes were represented; some had years of experience, while others were almost new to the ophthalmology discipline. The

educational background was fifty-fifty at the master's and bachelor's levels, and the age of the participating nurses ranged from 26–60 years. There was a time gap between the individual and the focus group interviews due to the maternity leave of the PhD candidate of one year.

The nurses were interviewed by a female PhD candidate, the first author (SB). At the time of the interviews, SB worked fifty-fifty as a PhD candidate and resident at the ophthalmology department at St. Olavs Hospital. SB had worked with the interviewed nurses for a few years at the department but did not have an outside-the-office relationship with them. SB had not previously conducted a qualitative study but attended a PhD course in qualitative research where she practised interview techniques.

The last author/co-supervisor (KHG) had experience with qualitative research methods and supervised the process. The interviews were carried out in the ophthalmology department in a room where we were not disturbed. The opening question of the interview guide used in the five individual interviews was, "Why did you want to become one of the injection nurses?"

SB increased her knowledge of qualitative research between the individual interviews and the focus group, so the guide was altered with fewer and more open questions. The opening question in the focus group interview was, "What experiences have you gained as an injection nurse?" In the focus group, the PhD candidate was the moderator and KHG, who had never met the nurses before, was an observer. All interviews were taped using a voice recorder and transcribed shortly after by the PhD candidate.

3.8 Outcomes

3.8.1 Primary outcome (Paper I and II)

The primary outcome was a mean change in the BCVA during the 12 ± 2-month inclusion time. The BCVA was measured using the early treatment diabetic retinopathy study (ETDRS) chart (Brown et al., 2006). The ETDRS test was carried out at two metres.

3.8.2 Secondary outcomes (Paper I and II)

Secondary outcomes were ocular SAEs needing treatment, the number of IVIs, the length of intervals between injections and the success of the masking. The number of IVIs and interval lengths were registered during the study by the person administering the IVIs.

3.8.3 Secondary outcomes (Paper IV)

We calculated the annual societal costs per patient and future cost projections in the health economic analysis. Societal costs included hospital costs, other healthcare costs and transport costs. To estimate the societal costs per patient, we used hospital costs per IVI multiplied by the number of IVIs and added other healthcare costs, including ophthalmology consultations, community-based homecare and transport costs (patient transport and caregiver time; see Table 1).

Table 1. *Cost categories within societal costs*

Societal cost categories	From per IVI to per patient					Outcome
Hospital costs						
Certification costs						
Injection personnel wage costs						
Clinical support costs	costs per IVI	x	number of IVIs	=	Cost per patient per year	
Support personnel wage costs						
Eqiupment including medicine						
Running expenses of the premises						
Other halthcare costs						= Societal costs per patient per year
Ophthalmology consultations						
Homecare costs					Cost per patient per year	
Transport costs						
Patient transport costs						
Cost of caregivers time						

Hospital costs are calculated as costs per IVI and can be changed into cost per patient per year if multiplied with the number of IVIs

To estimate a certification cost per IVI we needed to know how many IVIs a physician and a nurse would administer after being certified. We estimated the career years for a nurse at the IVI clinic to be ten years. To uphold a stable service in these ten years, trough sick leaves and vacations, six nurses were trained. Prior to the study the physicians in training (residents) administrated all IVIs. Ten physicians were trained in ophthalmology every five years, i.e. they spend six months administering IVIs as part of their education to become a consultant. For every tenth year twenty physicians are trained.

Total training costs for six nurses and twenty physicians was divided by the number of IVIs each personnel group performed during the period from the study's end in 2017 through 2027, to calculate the certification costs per IVI.

3.8.3.1 Cost projections

To estimate a cost projection ten years after the RCT study, we used the number of IVIs at St. Olavs Hospital from 2014–2021, combined with population projections from Statistics Norway (Statistics Norway, 2022b) and the number of IVIs in the various age categories during the RCT.

The number of IVIs at St. Olavs Hospital from 2014–2021 was obtained from the hospital's computer system (Nirvaco, LOGEX Healthcare Analytics). All IVIs administered during the study were categorized after the participant's age. The youngest participant was 31 years. Therefore, we made five-year age groups from 30 to 89 and a ten-year age group from 90 to 99.

Next, we divided the number of IVIs at St. Olavs Hospital from 2014–2021 by the total number of IVIs during the study and multiplied by 100% to calculate the percentage of IVIs per age category. Next, we multiplied this result by the number of IVIs at St. Olav in 2016 to calculate the number of IVIs per age category in the St. Olav area. We chose the mid-year of the study (2016) as the reference year.

The number of IVIs in the different age categories in the St. Olav area was then divided by the number of inhabitants in the St. Olavs Hospital area in 2016, obtained from Statistics Norway. The result was again multiplied by the number of inhabitants in different years to determine the number of IVIs. We then projected the number of IVIs from 2022–2027 based on a growth factor found by taking the one-year IVI rate divided by the previous year's IVI rate. We also needed an accumulated growth factor found by multiplying the one-year growth factor by the next year's growth factor. When calculating the number of IVIs for 2021, our projection was 359 higher than the actual number. Therefore, we adjusted our projection down by 359 IVIs.

To find the potential hospital cost savings, we multiplied the number of IVIs in one year by the difference in the hospital cost per IVI between the physician and nurse group.

3.8.4 Patient satisfaction (Paper I)

All randomised patients answered a questionnaire at the study's start and end about the satisfaction and safety when injected (Austeng et al., 2016). When planning the study, we could not find an existing satisfaction questionnaire adapted to a relatively simple surgical procedure performed under local anaesthesia. Therefore, we contacted the Norwegian Knowledge Centre for Health Services, which advised us about making a questionnaire. We wanted it short; therefore, two questions were created and then piloted on ten patients before alterations, with a new pilot on another ten patients. The secretary working at the reception asked the satisfaction questions. Five alternatives were available from 1 = not satisfied/safe at all to 5= very satisfied/safe.

3.8.5 Additional perspectives on the outcomes (Paper III)

The complexity of the intervention and outcomes was explored in the qualitative study. Through the interview process the nurses expressed important perspectives which elaborated our understanding of the StO study.

3.9 Analyses

3.9.1 Qualitative content analyses (Paper III)

Conducting a qualitative study was not part of the original plan. Hence, it was not described in Paper I. After having trained six nurses in IVI techniques, we searched for a way to evaluate the training. At the same time, we were curious to know if the nurses trained were content with the new task. The idea of a qualitative study with interviews came to life and we searched for a person connected to NTNU with knowledge in this area. Kari Hanne Gjeilo (KHG) was connected to the Department of Public Health and Nursing and immediately responded with a positive attitude. Together we discussed different methods for analysis and concluded that Graneheim and Lundman's (Graneheim & Lundman, 2004) qualitative content analysis with an inductive approach was suitable for our data. The inductive approach was also used in the PhD course on qualitative research methods attended by the candidate.

The inductive approach is a "bottom-up" method for analyzing the text, starting with finding the smallest units of meaning (i.e. sentences, words or phrases that evolve around the study's aim). The units of meaning are close to the text, so there are no interpretations. Then, these units are gathered into clusters with the same meaning, and again, the labels are collected based on an interpretation of the preliminary categories (subthemes). Two or more subthemes form one theme at the end. Most often, there are 3–5 themes.

The first author (the PhD candidate) read all the raw data several times to form the bigger picture and then executed the analysis as explained above. Both the subthemes and the themes were discussed with KHG. The second author (DA), the PhD candidate's main supervisor, was also part of the analysis process at the end, discussing if the subthemes and themes were representative of the text.

The analysis was first done by hand with the text on paper, marking units of meaning with a marker pen and cutting the units with scissors, clustering similar topics. After one year's maternity leave of the PhD candidate, the analyses were repeated, this time with the help of the data program NVivo 12, a computer-assisted qualitative data analysis software (QSR

International). The results of the two analyzing methods were then compared and found to be similar.

3.9.2 Statistical analysis (Papers II and IV)

All statistical analyses were performed using the SPSS software version 23 (SPSS Inc., Chicago, IL) and Excel (Microsoft®, Redmond, Washington, USA, 2016) was used for the cost projections.

A one-sided *t*-test for non-inferiority was used to test for non-inferiority in the BCVA between the two groups. A non-inferiority margin of three letters was used. The uncertainty in the estimate was assessed by a 95% confidence interval, that corresponds to a 2.5% significance level for the one-sided *t*-test. Data were controlled for normal distribution using the Kolmogorov-Smirnov test in SPSS and visually inspection of the QQ-plot. For the normally distributed BCVA data, the independent samples *t*-test (mentioned above) was applied. Data not considered normally distributed, i.e. cost calculations, the Mann Whitney U test was applied. *P*-values < 0.05 were considered statistically significant, except for the one-sided t-test where the significance level was < 0.025.

3.9.2.1 Sample size (Papers I and II)

When reading earlier non-inferiority RCT papers, the researchers had compared different anti-VEGF medicines and used a more homogenous participant group than ours (Martin et al., 2012). For example, Martin et al. (2012) had only treatment-naïve patients with AMD, while we had most patients earlier treated and with DMO and RVO, along with AMD. Therefore, when Martin et al. chose a five-letter margin (one line on the ETDRS chart), we chose a three-letter margin.

We assumed our standard deviation (*SD*) of BCVA would be ten letters, somewhat less than in the second year of the Comparison of Age-Related Macular Degeneration Treatment Trials (CATT). In addition, most of our patients were not treatment naïve as in the CATT. Therefore,

we expected smaller changes during the study year (Martin et al., 2011). The sample size was calculated by taking our three-letter non-inferiority margin ($\delta_L = 3$), standard deviation (*SD* = 10) and the significance level and feeding them into SPSS's formula for comparing two means in a non-inferiority trial (SPSS Sample Power 3). We then needed 140 patients in each group. We anticipated a participant dropout rate of 8%, so at least 152 patients needed to be included in each group.

3.10 Patient involvement (Paper II)

The patients were involved in the design of the patient satisfaction questionnaire. Twice the questionnaire was piloted on ten patients and altered according to advice from the patients. Once the RCT study was published, patients were informed of the results through a poster in the waiting room and the departments' website.

3.11 Ethics

3.11.1 Papers I, II and IV

Written informed consent was obtained from all patients. The StO study was approved by the Regional Committee of Ethics in Medical Research (2014/1719) and adhered to the Declaration of Helsinki. The study protocol was registered at ClinicalTrials.gov (NCT02359149). The data was analyzed and presented according to the CONSORT guidelines for reporting non-inferiority trials (Piaggio et al., 2012).

When deciding the non-inferior delta margin, we considered the ethical aspect of the hypothesised cost savings against the possibility of patients losing visual acuity when treated by nurses. If nurses were found inferior to physicians administering IVIs, we had to consider how many letters were ethical to lose.

When masking the patients in the intervention group, nurses and physicians wore white hospital clothes and did not tell their profession during the procedure. This may be considered an ethical challenge in our study, and we discussed this thoroughly before study start. In a

retrospective view this seemed to be a minor ethical issue due to the results and the patient feedback.

3.11.2 Paper III

The nurses were asked face-to-face to participate by the PhD candidate (first author, SB). The interviews were taped but immediately deleted after transcription. The nurses could withdraw their consent anytime. No specific characteristics were given to keep their identities hidden. The consolidated criteria for reporting qualitative research (COREQ), a 32-item checklist for interviews and focus groups, was adhered to in the reporting of Paper III (Tong et al., 2007).

The PhD candidate had worked with the nurses for several years before the interview process. Interviewing co-workers may be troublesome when getting confidential information. Being too superficial might reduce the quality of the research in terms of credibility and validity but may reduce the discomfort of the nurses. Being too invasive might stir up painful emotions but could produce valuable answers (Aase, 2006). More likely in the individual interviews where the setting is more intense than a focus group. This ethical aspect was considered, but the interview theme was limited and did not involve too many emotional topics.

4 Results

4.1 Paper II

4.1.1 Participants

Of the 342 randomised participants, 318 met the inclusion criteria of the safety population (i.e. receiving at least one injection). Notably, 2,077 IVIs were administered to the safety population during the study. In the safety population, 155 were randomised for treatment by physicians and 163 for treatment by nurses. After the study started, two participants became life-threateningly ill for other reasons, so both withdrew consent, and the remaining 316 participants were eligible for the intention-to-treat analysis (Figure 8).

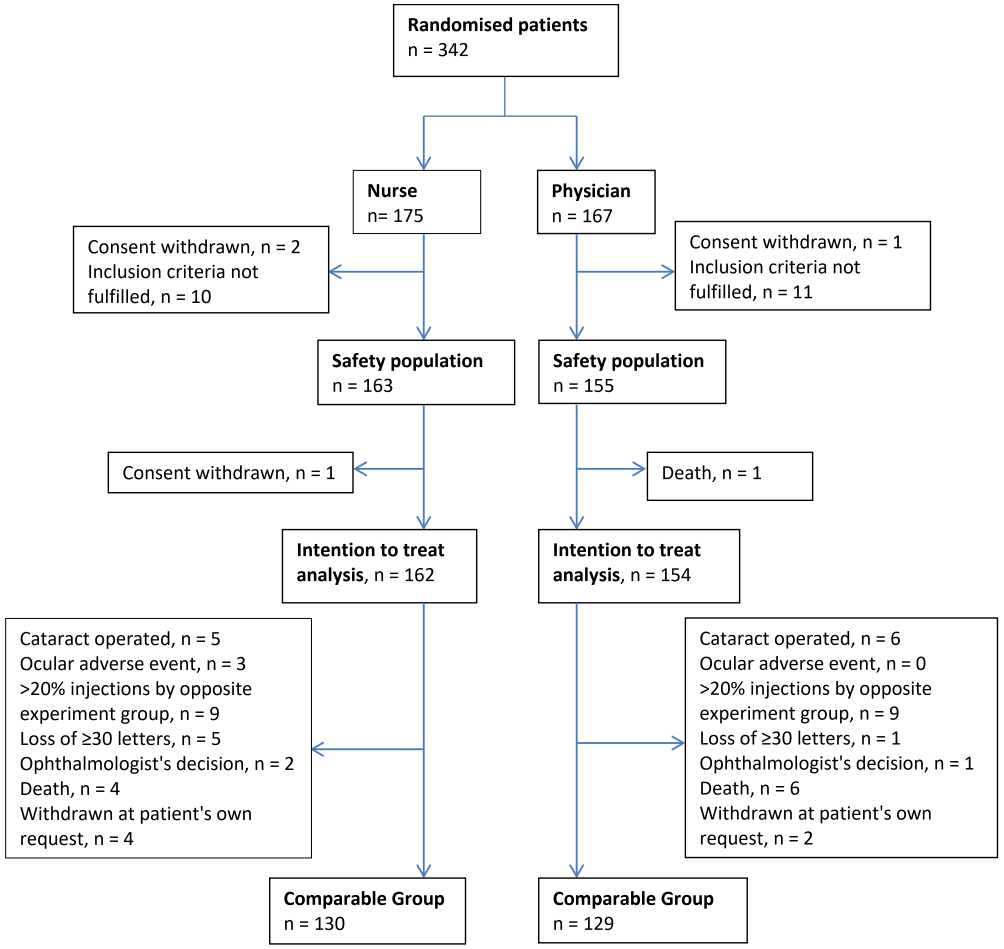

Figure 8: *Flow diagram of the randomised patients.*

Baseline characteristics for the intention-to-treat population appear in Table 2.

Table 2: *Baseline Patient Characteristics for the Intention-to-Treat Population*

	Nurse-administered IVIs (*n* = 162)		Physician-administered IVIs (*n* = 154)	
Diagnosis				
AMD, earlier treated	104	(64.2)	103	(66.9)
AMD, treatment-naïve	3	(1.9)	1	(0.6)
RVO, earlier treated	39	(24.1)	36	(23.4)
RVO, treatment-naïve	1	(0.6)	0	(0.0)
DMO	15	(9.3)	14	(9.1)
Medicine				
Bevacizumab	93	(57.4)	85	(55.2)
Ranibizumab	55	(34.0)	53	(34.4)
Aflibercept	14	(8.6)	16	(10.4)
Eye				
O.D.	93	(57.4)	83	(53.9)
O.S.	69	(42.6)	71	(46.1)
Sex				
Female	87	(53.7)	75	(48.7)
Male	75	(46.3)	79	(51.3)
Age (yrs)				
Median (range)	76.0	(37-93)	76.5	(31–93)
Mean (*SD*)	75.4	(10.0)	75.4	(10.7)
Age category				
< 50 yrs	2	(1.2)	4	(2.6)
50–59 yrs	11	(6.8)	8	(5.2)
60–69 yrs	29	(17.9)	27	(17.5)
70–79 yrs	56	(34.6)	50	(32.5)
80–89 yrs	57	(35.2)	57	(37.0)
≥ 90 yrs	7	(4.3)	8	(5.2)
BCVA				
Median (range)	72.0	(5–85)	71.0	(8–85)
Mean (*SD*)	66.7	(16.4)	66.4	(16.6)
BCVA category and Snellen equivalent				
≤ 37 letters, ≤ 20/200	12	(7.4)	13	(8.4)
38–52 letters, 20/160–100	20	(12.3)	9	(5.8)
53–67 letters, 20/80–50	30	(18.5)	38	(24.7)
68–77 letters, 20/40–32	55	(34.0)	59	(38.3)
≥ 78 letters, ≥ 20/25	45	(27.8)	35	(22.7)

Values are numbers (%) unless otherwise specified. AMD = age-related macular degeneration, RVO = retinal vein occlusion, DMO = diabetic macular oedema, BCVA = best correct visual acuity, SD = standard deviation, OD= oculus dexter and OS= oculus sinister.

Two-thirds of the patients had their AMD treated earlier. Most of the remaining patients had RVO treated earlier. Only five patients were treatment-naïve, one in the physician and four in the nurse group. Eighteen patients in the intention-to-treat analysis received more than 20% of the injections from the wrong randomization group (i.e. a randomised patient for treatments by physicians received > 20% of the injections from nurses). These 18 patients (nine in each group) were excluded for analysis in the comparable group, along with 39 other patients who either were cataract operated on, had an ocular adverse event, lost ≥ 30 letters due to macular atrophy, were excluded due to protocol violation, died or withdrew their consent. These exclusions left 129 patients in the physician and 130 in the nurse group eligible for the comparable group analyses. In SPSS, a two-way ANOVA was used for analysing differences between participants with 0%, 1%–20% and > 20% of IVIs administered by the wrong personnel group to see if it influenced the results. No significant change in the mean difference in the BCVA between the three groups mentioned above was found.

4.1.2 Primary outcome

The lower limit of the 95% confidence interval (CI) in the comparable group did not violate the predetermined three-letter limit meaning that nurse-administered IVIs were non-inferior to physician-administered IVIs (95% CI of the difference in mean change: –2.9 to +1.0; p = 0.019, one-sample t-test). On average, patients in the nurse group gained 0.7 letters while included in the study compared to 1.6 letters gained in the physician group.

In the ITT analysis, patients in the nurse group lost on average 1.2 letters compared with 1.0 letter gain in the physician group (95% CI of the difference in mean change, –4.4 to 0.0; p = 0.242, one-sided t-test). The lower limit of the 95% CI exceeded the three-letter limit. Therefore, we could not find evidence that nurse-administered IVIs were non-inferior to physician-administered IVIs.

4.1.3 Secondary outcomes

No significant difference between the two treatment groups was found regarding the mean number of IVIs: 6.6 IVIs in the nurse and 6.8 IVIs in the physician group (95% CI of the difference: –0.8 to 0.6, p = 0.702). No difference between the two treatment groups was found regarding the mean number of weeks between IVIs: 10.8 weeks in both groups (95% CI of the difference: –2.4 to 2.4, p = 0.572). Of the 259 patients included in the comparable group analysis, 37 received one or two injections from the wrong profession, while 15 were treated with anti-VEGF in both eyes and received the injections in the non-study eye from the opposite profession.

After one year, seven of the patients in the physician group and four in the nurse group had died (p = 0.370; Table 3). Three patients experienced ocular SAEs: one endophthalmitis (0.05% per IVI), one PED rupture and one central RVO. A total of six patients lost 30 letters or more (five in the nurse group), all due to atrophy (p = 0.685).

Table 3*: Serious adverse events in the safety population*

Serious adverse event	Nurse (n = 163)	Physician (n = 155)
Death	4 (2.5)	7 (4.5)
Cardiovascular disease	2 (1.1)	3 (1.9)
Cancer	1 (0.6)	2 (1.3)
Haematological disease	1 (0.6)	0
Reason unknown	0	2 (1.3)
Ocular SAEs	3 (1.8)	0
Endophthalmitis	1 (0.6)	0
Uveitis	1 (0.6)	0
Lens damage	0	0
Retinal tears	0	0
Intraocular haemorrhages	0	0
Pigment epithelial rupture	1 (0.6)	0
CRVO	1 (0.6)	0
Loss of ≥ 30 letters	5 (3.1)	1 (0.6)

Data are the number of patients (%), SAE = serious adverse event, CRVO = central retinal vein occlusion.

4.1.3.1 The success of masking patients in the randomization group

At the study's end, patients were asked if they believed nurses or physicians had treated them during the study year. Answers from 22 patients were missing, leaving 185 answers available for analysis, with 112 patients (60.5%) not knowing or incorrectly answering when asked if a nurse or a physician had injected them during the RCT (Table 4).

Table 4*: The success of masking patients in the randomization group*

Patient answer	Number of patients (%)	
Correct guess	73	(39.5)
Wrong guess	22	(11.9)
Did not know	90	(48.6)

4.2 Themes and subthemes emerging post-analysis (Paper III)

After analyzing the transcript, four themes and eight subthemes emerged (Table 5). The ambience in the individual interviews was good, with some laughter between the questions. In the focus group interview, the five nurses kept the conversation going themselves after the moderator asked a question. The answers seemed remarkably honest, and the nurses seemed safe, truthfully speaking as if no one else were in the room on several occasions. For instance, some nurses shared an opinion that physicians were inferior to nurses in administering IVIs, considering that the moderator was a physician. Overall, the mood was light, with a good vibe in the room.

Table 5: *Themes and subthemes emerging after analyzing the interview transcripts.*

Main themes	Procedure and challenges	Motivation	Cooperation and confidence	Evaluation
Subthemes	Routine versus variation	Responsibility and respect	Working as a team	Continual learning
	Challenges	Making a difference	Confidence	Adjustments

4.3 Health economic analyses (Paper IV)

4.3.1 Hospital costs per IVI

Certification costs per person were higher for a nurse than a physician, but the certification costs per IVI were lower for a nurse over ten years. A physician was projected to administer 2,875 IVIs over ten years compared to 9,583 IVIs administered by a nurse. Because the uneven number of physicians and nurses trained to administer all IVIs over a ten-year period.

The hospital cost per IVI was 281.6 € for a physician and 276.1 € for a nurse. The difference of 5.5 € was due to nurses' lower training costs and wages. Nurses' wages were 47 € per hour versus 61 € per hour for physicians (2017). The estimated training cost per IVI was 0.6 € for a nurse and 1.4 € for a physician.

4.3.2 Societal costs

There was no significant difference in the societal costs per participant per year between the two groups: 4,963 € (*SD* 4,413) in the physician group and 5,389 € (*SD* 6,825) in the nurse group ($p = 0.403$). Per participant annually, physician and nurse groups together, the hospital costs were 1,920 € (*SD* 748), costs for ophthalmology consultations were 776 € (*SD* 398), homecare costs were 1,393 € (*SD* 5,529), transport costs were 723 € (*SD* 971) and costs of caregiver time were 370 € (*SD* 495).

4.3.3 Cost projections

The estimated number of IVIs with a 4% growth factor at St. Olavs Hospital for the six years to come (2022–2027) were 7,339, 7,893, 8,515, 9,161, 9,859 and 10,602, with corresponding savings for the same years (in euros): 40,367, 43,413, 46,828, 50,387, 54,222 and 58,310, totalling 293,528 €. The mean savings per year was 60% of one injection nurse's annual wage.

4.4 Patient satisfaction (unpublished material)

Of the 318 participants in the safety population, 263 (83%) patient answers were available for analysis at the study's start and 276 (86%) at the study's end. Regardless of the randomization group, most patients answered very satisfied/safe at the start and end. There was no significant difference between patients treated by nurses or physicians (Table 6 and 7).

Table 6*: Patient satisfaction scores at the study's start*

	Nurse *n* = 145		Physician *n* = 118		*P*-value
Satisfied					
Mean (*SD*)	4.86	(0.43)	4.95	(0.30)	0.514
Very satisfied	127	(87.6)	106	(89.8)	
Satisfied	16	(11.0)	12	(10.1)	
Satisfied to some extent	1	(0.7)	0	(0.0)	
Not very satisfied	1	(0.7)	0	(0.0)	
Not satisfied at all	0	(0.0)	0	(0.0)	
Safe					
Mean (*SD*)	4.69	(0.51)	4.65	(0.58)	1.000
Very safe	134	(92.4)	109	(92.4)	
Safe	10	(6.9)	9	(7.6)	
Safe to some extent	0	(0.0)	0	(0.0)	
Not very safe	1	(0.7)	0	(0.0)	
Not safe at all	0	(0.0)	0	(0.0)	

Values are numbers (%) unless otherwise specified. *P*-values were calculated using the Mann-Whitney U test.

Table 7*: Patient satisfaction scores at the study's end*

	Nurse *n* = 142		Physician *n* = 130		*P*-value
Satisfied					
Mean (*SD*)	4.60	(0.67)	4.63	(0.60)	0.842
Very satisfied	96	(67.6)	89	(68.5)	
Satisfied	38	(26.8)	35	(26.9)	
Satisfied to some extent	6	(4.2)	5	(3.8)	
Not very satisfied	1	(0.7)	1	(0.8)	
Not satisfied at all	1	(0.7)	0	(0.0)	
Safe					
Mean (*SD*)	4.68	(0.51)	4.64	(0.58)	0.665
Very safe	100	(70.4)	89	(68.5)	
Safe	39	(27.5)	36	(27.7)	
Safe to some extent	3	(2.1)	4	(3.1)	
Not very safe	0	(0.0)	1	(0.8)	
Not safe at all	0	(0.0)	0	(0.0)	

Values are numbers (%) unless otherwise specified. *P*-values were calculated using the Mann-Whitney U test.

5 Discussion

5.1 Major findings

This thesis explored task-shifting IVIs with anti-VEGF from physicians to nurses. The main findings indicated that this task shift was safe with a non-inferior visual acuity. Both patients and nurses were satisfied and felt safe during the treatment. Although task-shifting IVIs to nurses resulted in minor savings for the hospital and no societal savings, the task shift had other advantages:

- identifying the costly categories and where to potentially achieve cost savings,
- physician resources could be reallocated to other urgent tasks in the department and
- satisfied nurses reported more variation throughout the work week and enjoyed more respect from their surroundings.

The findings in this thesis showed that nurses with fewer qualifications and less education than physicians could be trained to perform this surgical procedure. To the best of our knowledge, this is the first time an RCT involving task-shifting was executed on a surgical procedure in a developed Western country with modern healthcare. The RCT is timely as the distribution of the population shifts towards older ages. Two years ago, the world's population > 60 years outnumbered children younger than five years (WHO, 2021).

Due to the ageing population, a considerable increase in patients needing anti-VEGF is expected (Li et al., 2019; Li, Welchowski, Schmid, Mauschitz, et al., 2020; Saeedi et al., 2019). Thus, all available health resources must be utilized in the best possible way to meet future demands (EU, 2019). More efficient ways of working are prioritized in the Faculty of Medicine and Health Science strategy plan for 2018–2025, and research can make important contributions (NTNU, 2022).

This thesis has contributed to more efficient ways of treating patients needing anti-VEGF IVIs by shifting the task to less competent health personnel. The nurses experienced professional

challenges and received new work assignments that renewed their professional pride. The cost savings will probably be greater in countries with a larger wage gap between physicians and nurses.

5.2 Methodological considerations

Our ophthalmology department at St. Olavs Hospital was not the first department to implement nurse-led IVIs. Previous studies were either retrospective or prospective observational task shift studies (DaCosta et al., 2014; Hasler et al., 2015; Michelotti et al., 2014; Samalia et al., 2016; Simcock et al., 2014; Varma D, 2013). Indeed, randomization in a clinical trial avoids selection bias, so it might be that nurses were assigned patients more prone to cooperation with fewer concomitant diseases than patients injected by physicians. By randomizing patients, this bias could be avoided.

However, a study was published in 2018 where 61 patients in a hospital in London were randomised for IVI treatment from physicians or nurses. The study focused on patient satisfaction as the primary outcome (Mohamed et al., 2018). Before we designed the RCT, earlier studies implementing nurse-administered IVIs had focused on patient satisfaction, patient pain, adverse events and increased capacity as their main outcomes (DaCosta et al., 2014; Hasler et al., 2015; Michelotti et al., 2014; Simcock et al., 2014; Varma D, 2013). Indeed, Varma et al. (2013) were the only ones to include visual acuity as an outcome. We chose visual acuity as our main outcome because good vision is important to patients (Assi et al., 2021), and it was the main outcome in large studies of anti-VEGF (Berg et al., 2015; Maguire et al., 2016; Rosenfeld et al., 2006). Our RCT was not designed to have a sample size large enough to statistically compare adverse events as the primary outcome.

Our country does not have a widespread tradition of task-shifting in healthcare, which was an important aspect when planning the RCT (World Health Organization, 2008). As far as we know, only Tønsberg Hospital in southeast Norway implemented a nurse-led injection clinic before us. There was no written material on nurse-administered IVIs in Norway at the time. We chose to plan and conduct this RCT to convince healthcare personnel, patients and hospital management that nurses were non-inferior to physicians administrating IVIs.

Our RCT was single-masked, and patients were not told their randomisation group. Most patients knew the department well, having received several treatments before volunteering for the study. Only five patients included in the study had not earlier been treated with IVI. Nevertheless, less than half of the patients correctly guessed which health personnel had treated them during the study year. These results indicate that we managed to keep the randomisation secret from the participating patients.

It would have been interesting to ask the patients the reason behind the correct/wrong guess. Maybe it was unimportant to patients what type of health personnel injected medicine into their eyes. In DaCosta et al.'s (2014) study, 13 patients of the first 100 declined nurses as injection administrators and preferred physicians (DaCosta et al., 2014). Hence, the rest of the patients had no problem with nurses taking over the injections.

5.3 Reflections of the nurse's role and the training program

We designed a purposeful training program to enhance nurses' confidence while administering injections. A few studies had already created a program, so we took inspiration from them (DaCosta et al., 2014; Varma D, 2013). All training programs had a theoretical part, a wet lab rehearsing IVI techniques on pig eyes and a period observing injections on patients before gradual exposure to independent administration. However, there were some differences compared to previous training programs. We recruited six nurses with various experiences, while Varma et al. (2013) recruited *senior nurses with a surgical background* (Varma D, 2013) and DaCosta et al. (2014) recruited *band-7 nurses,* denoting the salary level (DaCosta et al., 2014) as very experienced (same salary level as the nurses in Varma et al.'s study).

Moreover, Michelotti et al. (2014) trained two experienced nurses who had observed over 1,000 IVIs before the independent injection carrier. Simcock et al. (2014) trained a nurse who had previously conducted minor lid surgery and sub-Tenon's anaesthesia. After certification, our six nurses were trained to inject every patient; in contrast, the nurses in Hasler et al.'s (2015) study did not inject patients who cooperated poorly, had experienced complications,

had significant concomitant eye disease (e.g. infection, nystagmus, malformations) or significant generalized disease or disabilities like tremors or kyphosis (Hasler et al., 2015).

After Sunderland Eye Infirmary introduced independent nurse-led IVIs, it enabled physicians to focus increasingly on complex pathology, poor responders and other high-risk patients, implicitly stating that nurses did not inject these kinds of patients (Varma D, 2013). While both Varma et al. (2013) and Hasler et al. (2015) executed task-sharing, our department did task-shifting because our trained nurses injected every patient in the injection clinic, including the more complicated ones.

Although all six nurses volunteered, there was some resistance among the nurses when we introduced the idea that administering IVIs would mean more responsibility and accepting more room for errors. At first, it surprised us because the experience we had was that physicians in their first year of training needed minimal instructions before they started administering injections. However, their six-year medical education was somewhat different from the three-year bachelor's to become a nurse. Traditionally, as physicians' education is more focused on independence, and taking responsibility, nursing education is more focused on care and communication (Davies, 2000). Hence, nurses and physicians handle new challenges differently.

We had to change the mindset of everyone involved, especially the nurses who had to accept more responsibility. The first six nurses took much longer to train, illustrating how much time was needed to adjust to the task-shifting idea. After the first six nurses were trained, recruiting and training more nurses was much smoother. We experienced that all the hesitations and scepticism were gone as if the first nurses helped change the mindset and prepare the following nurses to accept more responsibility.

With this thesis, we have shown that every nurse, regardless of the experience level, can be trained to administer anti-VEGF IVIs. Nurses gained self-confidence and pride after learning the new task and experienced good feedback from patients and more respect from

colleagues, management and patients. The satisfaction level among the trained nurses increased.

Indeed, we could not find studies exploring health workers' experiences with a task shift and training to learn a new task, but asking the trained personnel is a way to examine a program's effectiveness from the participants' views. This approach could evaluate the quality from the insider's perspective (Shek & Wong, 2010). Therefore, we decided to interview the nurses.

A qualitative study exploring the nurse's experience with the training program and the new task was not part of the original plan. The need for an evaluation emerged when more nurses were trained after the end of the RCT. We knew that satisfied health workers led to satisfied patients (Mohr et al., 2011), so we wished to improve the training program and started planning the qualitative study.

We evaluated our training program by interviewing the nurses (Paper III). One of the anonymous reviewers for Paper III wrote, "*Using a qualitative study to explore the training program is appropriate and timely*". The nurses had several suggestions for improving the program (i.e. requesting a chance to refresh knowledge, so we organized a re-certification every other year). After the nurses' requests, more theoretical lessons about retina diseases treated with anti-VEGF were also added. Hence, the nurses influenced the design of the training program.

After the training program and the RCT results were published, we received several inquiries from other ophthalmology departments in Norwegian hospitals asking for help training their nurses. We observe that in a few other hospitals, physicians continued with IVIs as before. Perhaps they did not experience a shortage of physicians as we did and did not feel the pressure to utilize healthcare resources, or they experienced some of the limitations of task-shifting like economic loss for physicians (World Health Organization, 2008).

5.4 Cost implications

It is well-known that IVIs seize large resources and represent a huge economic burden (Almony et al., 2021; Ruiz-Moreno et al., 2021). However, there is a data gap in the health economic literature in ophthalmology (Burton et al., 2021). We found no prior studies looking at the societal costs of IVIs. Therefore, we wanted to investigate if the hospital and society could save money after a task shift.

We found minor cost savings for the hospital and no cost savings for society, but we identified various cost categories, making it clear where the potential cost savings were. Transport costs were high, but they could potentially be lowered with mobile IVI clinics, minimizing the use of taxis, or organizing the treatment so that the consultations and the injections could happen at the same clinic on the same day. Another costly category was the medical costs, which are huge in Norway and beyond (Patel, 2018). These medical costs could be minimised by using the anti-VEGF medicine with the lowest cost, bevacizumab (Avastin), developing longer-acting anti-VEGF medicines and finding new ways of administrating the drugs, like implants (Singer & Rahman, 2020).

5.5 Strengths and limitations

Rigour is always a challenge in qualitative research, so we tried to achieve rigour and strengthen the study by adhering to the COREQ guidelines and being transparent in information about the research team and their reflexivity, the study design, the analysis, and the findings. Some consider trustworthiness a more appropriate criterion for evaluating qualitative studies (Morse, 2015). By interviewing nurses with good knowledge about IVIs, the interview theme, we tried to obtain credibility. The PhD candidate knew the interviewed nurses in advance, and the interview theme was limited with limited emotional topics, ensuring a quick interview start and quick response from the nurses when the questions were asked. We described the context thoroughly to obtain transferability and dependability. Confirmability was attempted by having an experienced qualitative researcher (second author) analyse the interviews together with the PhD candidate.

> Information power indicates that the more information the sample holds, relevant for the actual study, the lower number of participants is needed. We suggest that the size of a sample with sufficient information power depends on (a) the aim of the study, (b) sample specificity, (c) use of established theory, (d) quality of dialogue, and (e) analysis strategy. (Malterud et al., 2016)

The aim of the qualitative study was narrow and specific, not demanding much disclosure from the participants' point of view. A large sample was unnecessary to obtain sufficient information power because all our participants had a specific characteristic in common: experience from the injection clinic. We applied an established theory per Graneheim and Lundman's (2004) qualitative content analysis. There was strong and clear communication between the researchers and participants. The PhD candidate had administered IVIs at the same clinic for some years and therefore had good knowledge about the interview topic.

Several research methods were applied strengthening the results and conclusions of this thesis. An RCT was conducted which is widely considered the gold standard within the hierarchy of evidence and the research protocol was published, also considered a strength (Ohtake & Childs, 2014). However, some limitations should be acknowledged. We did not calculate the cost of lowered quality of life (QoL) even though impaired vision lowers the QoL (Assi et al., 2021). Furthermore, we did not cost-calculate hospital admissions for ophthalmological or concomitant diseases, examining the cause of death of the deceased randomised patients (Paper II).

When cost-calculating the transport costs, there were limitations. When calculating transport costs, we therefore used the mean cost of taxis and buses for every patient's distance between home and hospital. Hence, the transport costs were only an estimate. However, we based all the cost calculations on prospectively registered information in an RCT with wide inclusion criteria, making it close to reality while providing a solid foundation for hospital management when evaluating this new intervention.

When we designed the study, we chose three letters as a non-inferiority limit, which was strict. Prior studies had chosen a five-letter limit when comparing two different medications (bevacizumab vs ranibizumab; Berg et al., 2015; Kodjikian et al., 2013) and two treatment strategies (pro-re-nata vs monthly injections; Martin et al., 2011). The IVAN study also chose a strict non-inferiority limit of a 3.5-letter limit but could not prove non-inferiority (Chakravarthy et al., 2012). It might have been considered unethical if shifting the task to nurses resulted in patients losing a whole line (five letters) on the ETRDS vision board.

When planning the RCT, we decided that physicians and nurses would inject randomised patients two weekdays each, which gave us challenges when the original plan was changed, for instance, if a patient had to postpone an injection for various reasons. It would have been advantageous to foresee this issue when planning the study, including other unexpected issues like patient cataract surgeries during the study or developing the end stage of the disease and naturally discontinuing the injection treatment. The researchers at the CATT had considered these events and included them in their protocol (Martin et al., 2011). Nevertheless, these challenges gave us valuable experience that we will bring forward in planning the next clinical study.

6 Conclusion

In this thesis, nurses were non-inferior to physicians administrating IVIs of anti-VEGF. Patients injected by nurses had the same visual outcome and felt as safe and satisfied as patients injected by physicians. The certified nurses said they gained self-esteem and felt proud after learning a new task. We found minor savings for the hospital but no societal savings.

7 Final significance and future direction

This research was conducted in a high-income country with a small gap between the wages of physicians and nurses. Thus, countries with larger wage gaps could adopt the task shift and train their nurses to inject intravitreally and experience larger cost savings. Transferring tasks from personnel with a higher level of competence to personnel with a lower level can be further explored in new areas in ophthalmology and other specialities. Task-shifting from physicians to nurses will be one of many measures for health services to meet the future demand.

8 References

Almony, A., Keyloun, K. R., Shah-Manek, B., Multani, J. K., McGuiness, C. B., Chen, C. C., & Campbell, J. H. (2021). Clinical and economic burden of neovascular age-related macular degeneration by disease status: a US claims-based analysis. *J Manag Care Spec Pharm*, *27*(9), 1260-1272. https://doi.org/10.18553/jmcp.2021.27.9.1260

Assi, L., Chamseddine, F., Ibrahim, P., Sabbagh, H., Rosman, L., Congdon, N., Evans, J., Ramke, J., Kuper, H., Burton, M. J., Ehrlich, J. R., & Swenor, B. K. (2021). A Global Assessment of Eye Health and Quality of Life: A Systematic Review of Systematic Reviews. *JAMA Ophthalmol*, *139*(5), 526-541. https://doi.org/10.1001/jamaophthalmol.2021.0146

Austeng, D., Morken, T. S., Bolme, S., Follestad, T., & Halsteinli, V. (2016). Nurse-administered intravitreal injections of anti-VEGF: study protocol for noninferiority randomized controlled trial of safety, cost and patient satisfaction. *BMC Ophthalmology*, *16*(1), 169. https://doi.org/10.1186/s12886-016-0348-4

Bailey, L. F. (2014). The origin and success of qualitative research. *International Journal of Market Research*, *56*(2), 167-184. https://doi.org/10.2501/ijmr-2014-013

Berg, K., Pedersen, T. R., Sandvik, L., & Bragadottir, R. (2015). Comparison of ranibizumab and bevacizumab for neovascular age-related macular degeneration according to LUCAS treat-and-extend protocol. *Ophthalmology*, *122*(1), 146-152. https://doi.org/10.1016/j.ophtha.2014.07.041

Brown, D. (1998). *Landmark study made research resistant to bias*. The Washington Post,. Retrieved May 14th from https://www.washingtonpost.com/archive/politics/1998/11/02/landmark-study-made-research-resistant-to-bias/2f9685fd-5369-44d1-9aa7-b13fb7018833/

Brown, D. M., Kaiser, P. K., Michels, M., Soubrane, G., Heier, J. S., Kim, R. Y., Sy, J. P., & Schneider, S. (2006). Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *New England Journal of Medicine*, *355*(14), 1432-1444. https://doi.org/10.1056/NEJMoa062655

Burton, M. J., Ramke, J., Marques, A. P., Bourne, R. R. A., Congdon, N., Jones, I., Ah Tong, B. A. M., Arunga, S., Bachani, D., Bascaran, C., Bastawrous, A., Blanchet, K., Braithwaite, T., Buchan, J. C., Cairns, J., Cama, A., Chagunda, M., Chuluunkhuu, C., Cooper, A., … Faal, H. B. (2021). The Lancet Global Health Commission on Global Eye Health: vision beyond 2020. *Lancet Glob Health*, *9*(4), e489-e551. https://doi.org/10.1016/s2214-109x(20)30488-5

Chakravarthy, U., Harding, S. P., Rogers, C. A., Downes, S. M., Lotery, A. J., Culliford, L. A., & Reeves, B. C. (2013). Alternative treatments to inhibit VEGF in age-related choroidal neovascularisation: 2-year findings of the IVAN randomised controlled trial. *Lancet*, *382*(9900), 1258-1267. https://doi.org/10.1016/s0140-6736(13)61501-9

Chakravarthy, U., Harding, S. P., Rogers, C. A., Downes, S. M., Lotery, A. J., Wordsworth, S., & Reeves, B. C. (2012). Ranibizumab versus bevacizumab to treat neovascular age-related macular degeneration: one-year findings from the IVAN randomized trial. *Ophthalmology*, *119*(7), 1399-1411. https://doi.org/10.1016/j.ophtha.2012.04.015

Chan, A. W., Tetzlaff, J. M., Altman, D. G., Laupacis, A., Gøtzsche, P. C., Krleža-Jerić, K., Hróbjartsson, A., Mann, H., Dickersin, K., Berlin, J. A., Doré, C. J., Parulekar, W. R., Summerskill, W. S., Groves, T., Schulz, K. F., Sox, H. C., Rockhold, F. W., Rennie, D., & Moher, D. (2013). SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Annals of Internal Medicine*, *158*(3), 200-207. https://doi.org/10.7326/0003-4819-158-3-201302050-00583

Chopra, R., Preston, G. C., Keenan, T. D. L., Mulholland, P., Patel, P. J., Balaskas, K., Hamilton, R. D., & Keane, P. A. (2021). Intravitreal injections: past trends and future projections within a UK tertiary hospital. *Eye (London, England)*, 1-6. https://doi.org/10.1038/s41433-021-01646-3

Corazza, P., D'Alterio, F. M., Savastano, M. C., Kabbani, J., Duguid, G., Savastano, A., & Younis, S. (2022). Long-term outcomes of anti-VEGF treatment of macular oedema due to retinal vein occlusions. *European Journal of Ophthalmology*, 11206721221085870. https://doi.org/10.1177/11206721221085870

Curry, L. A., Nembhard, I. M., & Bradley, E. H. (2009). Qualitative and mixed methods provide unique contributions to outcomes research. *Circulation*, *119*(10), 1442-1452. https://doi.org/10.1161/circulationaha.107.742775

DaCosta, J., Hamilton, R., Nago, J., Mapani, A., Kennedy, E., Luckett, T., Pavesio, C., & Flanagan, D. (2014). Implementation of a nurse-delivered intravitreal injection service. *Eye (London, England)*, *28*(6), 734-740. https://doi.org/10.1038/eye.2014.69

Davies, C. (2000). Getting health professionals to work together. *BMJ*, *320*(7241), 1021-1022. https://doi.org/10.1136/bmj.320.7241.1021

De Silva, V., Strand de Oliveira, J., Liyanage, M., & Østbye, T. (2013). The assistant medical officer in Sri Lanka: mid-level health worker in decline. *Journal of Interprofessional Care*, *27*(5), 432-433.

Delamaire, M.-L., & Lafortune, G. (2010). Nurses in Advanced Roles. https://doi.org/doi:https://doi.org/10.1787/5kmbrcfms5g7-en

Donalek, J. G. (2005). The interview in qualitative research. *Urologic Nursing*, *25*(2), 124-125.

Drummond, M. F., Sculpher. M. J., Claxton. K., Stoddart. G. L., Torrance. G. W. (2015). *Methods for the economic evaluation of health care programmes* (fourth ed.). Oxford University Press.

Engelman, D., Kado, J. H., Reményi, B., Colquhoun, S. M., Watson, C., Rayasidamu, S. C., & Steer, A. C. (2015). Teaching focused echocardiography for rheumatic heart

disease screening. *Annals of Pediatric Cardiology*, *8*(2), 118-121. https://doi.org/10.4103/0974-2069.157024

EU. (2019). *Task shifting and health system design* (978-92-76-08892-9). (Report of the Expert Panel on effective ways of investing in Health (EXPH), Issue. European Union. https://ec.europa.eu/health/system/files/2019-11/023_taskshifting_en_0.pdf

Federspiel, F., Mukhopadhyay, S., Milsom, P., Scott, J. W., Riesel, J. N., & Meara, J. G. (2015). Global surgical and anaesthetic task shifting: a systematic literature review and survey. *Lancet*, *385 Suppl 2*, S46. https://doi.org/10.1016/s0140-6736(15)60841-8

Ferrara, N., Damico, L., Shams, N., Lowman, H., & Kim, R. (2006). Development of ranibizumab, an anti-vascular endothelial growth factor antigen binding fragment, as therapy for neovascular age-related macular degeneration. *Retina*, *26*(8), 859-870. https://doi.org/10.1097/01.iae.0000242842.14624.e7

Ferrara, N., & Henzel, W. J. (1989). Pituitary follicular cells secrete a novel heparin-binding growth factor specific for vascular endothelial cells. *Biochemical and Biophysical Research Communications*, *161*(2), 851-858. https://doi.org/10.1016/0006-291x(89)92678-8

Ferrara, N., Hillan, K. J., Gerber, H. P., & Novotny, W. (2004). Discovery and development of bevacizumab, an anti-VEGF antibody for treating cancer. *Nat Rev Drug Discov*, *3*(5), 391-400. https://doi.org/10.1038/nrd1381

Folkman, J. (1971). Tumor angiogenesis: therapeutic implications. *New England Journal of Medicine*, *285*(21), 1182-1186. https://doi.org/10.1056/nejm197111182852108

Forbes, M. (2013). Bursting the bubblewrap: evolution and monitoring of nurse-performed Nd: YAG laser capsulotomy service. *International Journal of Ophthalmic Practice*, *4*(4), 157-162.

Gadbois, E. A., Miller, E. A., Tyler, D., & Intrator, O. (2015). Trends in state regulation of nurse practitioners and physician assistants, 2001 to 2010. *Medical Care Research and Review*, *72*(2), 200-219. https://doi.org/10.1177/1077558714563763

Gagliardi, A. R., & Dobrow, M. J. (2011). Paucity of qualitative research in general medical and health services and policy research journals: analysis of publication rates. *BMC Health Services Research*, *11*, 268. https://doi.org/10.1186/1472-6963-11-268

Gale, R., Gill, C., Pikoula, M., Lee, A. Y., Hanson, R. L. W., Denaxas, S., Egan, C., Tufail, A., & Taylor, P. (2021). Multicentre study of 4626 patients assesses the effectiveness, safety and burden of two categories of treatments for central retinal vein occlusion: intravitreal anti-vascular endothelial growth factor injections and intravitreal Ozurdex injections. *British Journal of Ophthalmology*, *105*(11), 1571-1576. https://doi.org/10.1136/bjophthalmol-2020-317306

Glassman, A. R., Wells, J. A., 3rd, Josic, K., Maguire, M. G., Antoszyk, A. N., Baker, C., Beaulieu, W. T., Elman, M. J., Jampol, L. M., & Sun, J. K. (2020). Five-Year Outcomes after Initial Aflibercept, Bevacizumab, or Ranibizumab Treatment for Diabetic Macular Edema (Protocol T Extension Study). *Ophthalmology*, *127*(9), 1201-1210. https://doi.org/10.1016/j.ophtha.2020.03.021

Gragoudas, E. S., Adamis, A. P., Cunningham, E. T., Jr., Feinsod, M., & Guyer, D. R. (2004). Pegaptanib for neovascular age-related macular degeneration. *New England Journal of Medicine*, *351*(27), 2805-2816. https://doi.org/10.1056/NEJMoa042760

Graneheim, U. H., & Lundman, B. (2004). Qualitative content analysis in nursing research: concepts, procedures and measures to achieve trustworthiness. *Nurse Education Today*, *24*(2), 105-112. https://doi.org/10.1016/j.nedt.2003.10.001

Graue-Hernandez, E. O., Rivera-De-La-Parra, D., Hernandez-Jimenez, S., Aguilar-Salinas, C. A., Kershenobich-Stalnikowitz, D., & Jimenez-Corona, A. (2020). Prevalence and associated risk factors of diabetic retinopathy and macular oedema in patients recently diagnosed with type 2 diabetes. *BMJ Open Ophthalmol*, *5*(1), Article e000304. https://doi.org/10.1136/bmjophth-2019-000304

Group, E. T. D. R. S. R. (1987). Treatment techniques and clinical guidelines for photocoagulation of diabetic macular edema: Early Treatment Diabetic Retinopathy Study Report Number 2. *Ophthalmology*, *94*(7), 761-774.

Grzybowski, A., Told, R., Sacu, S., Bandello, F., Moisseiev, E., Loewenstein, A., & Schmidt-Erfurth, U. (2018). 2018 Update on Intravitreal Injections: Euretina Expert Consensus Recommendations. *Ophthalmologica*, *239*(4), 181-193. https://doi.org/10.1159/000486145

Hariton, E., & Locascio, J. J. (2018). Randomised controlled trials - the gold standard for effectiveness research: Study design: randomised controlled trials. *BJOG: An International Journal of Obstetrics and Gynaecology*, *125*(13), 1716. https://doi.org/10.1111/1471-0528.15199

Harris, L. R., & Brown, G. T. (2010). Mixing interview and questionnaire methods: Practical problems in aligning data. *Practical Assessment, Research, and Evaluation*, *15*(1), 1.

Hasler, P. W., Bloch, S. B., Villumsen, J., Fuchs, J., Lund-Andersen, H., & Larsen, M. (2015). Safety study of 38,503 intravitreal ranibizumab injections performed mainly by physicians in training and nurses in a hospital setting. *Acta Ophthalmol*, *93*(2), 122-125. https://doi.org/10.1111/aos.12589

Heier, J. S., Brown, D. M., Chong, V., Korobelnik, J. F., Kaiser, P. K., Nguyen, Q. D., Kirchhof, B., Ho, A., Ogura, Y., Yancopoulos, G. D., Stahl, N., Vitti, R., Berliner, A. J., Soo, Y., Anderesi, M., Groetzbach, G., Sommerauer, B., Sandbrink, R., Simader, C., & Schmidt-Erfurth, U. (2012). Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. *Ophthalmology*, *119*(12), 2537-2548. https://doi.org/10.1016/j.ophtha.2012.09.006

Heier, J. S., Campochiaro, P. A., Yau, L., Li, Z., Saroj, N., Rubio, R. G., & Lai, P. (2012). Ranibizumab for macular edema due to retinal vein occlusions: long-term follow-up in the HORIZON trial. *Ophthalmology*, *119*(4), 802-809. https://doi.org/10.1016/j.ophtha.2011.12.005

Heller, R. (1978). Officiers de santé: the second-class doctors of nineteenth-century France. *Medical History*, *22*(1), 25-43. https://doi.org/10.1017/s0025727300031732

Helsedirektoratet [The Norwegian Directorate for health] (2012). *Guidelines for economic evaluation in the health sector*. T. N. D. f. health. https://www.helsedirektoratet.no/veiledere/okonomisk-evaluering-av-helsetiltak/%C3%98konomisk%20evaluering%20av%20helsetiltak%20%E2%80%93%20Veileder.pdf/_/attachment/inline/a4c0d8f4-6420-47a5-a052-344a5f2d0e76:637c45a5f29eda29afb9625968759e6fa4c4af61/%C3%98konomisk%20evaluering%20av%20helsetiltak%20%E2%80%93%20Veileder.pdf

Helsedirektoratet [The Norwegian Directorate for health] (2011) Helsepersonelloven [The Health personnel act]. https://lovdata.no/dokument/NL/lov/1999-07-02-64/KAPITTEL_2#%C2%A74

Hurwitz, H., Fehrenbacher, L., Novotny, W., Cartwright, T., Hainsworth, J., Heim, W., Berlin, J., Baron, A., Griffing, S., Holmgren, E., Ferrara, N., Fyfe, G., Rogers, B., Ross, R., & Kabbinavar, F. (2004). Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *New England Journal of Medicine*, *350*(23), 2335-2342. https://doi.org/10.1056/NEJMoa032691

Im, J. H. B., Jin, Y. P., Chow, R., & Yan, P. (2022). Prevalence of diabetic macular edema based on optical coherence tomography in people with diabetes: A systematic review and meta-analysis. *Survey of Ophthalmology*. https://doi.org/10.1016/j.survophthal.2022.01.009

Jackson, T. L., & Beun, L. (2000). A prospective study of cost, patient satisfaction, and outcome of treatment of chalazion by medical and nursing staff. *British Journal of Ophthalmology*, *84*(7), 782-785. https://doi.org/10.1136/bjo.84.7.782

Kallio, H., Pietilä, A. M., Johnson, M., & Kangasniemi, M. (2016). Systematic methodological review: developing a framework for a qualitative semi-structured interview guide. *Journal of Advanced Nursing*, *72*(12), 2954-2965.

Kodjikian, L., Souied, E. H., Mimoun, G., Mauget-Faysse, M., Behar-Cohen, F., Decullier, E., Huot, L., & Aulagner, G. (2013). Ranibizumab versus Bevacizumab for Neovascular Age-related Macular Degeneration: Results from the GEFAL Noninferiority Randomized Trial. *Ophthalmology*, *120*(11), 2300-2309. https://doi.org/10.1016/j.ophtha.2013.06.020

Kuhn, T. (1962). 1970. The structure of scientific revolutions. In (Vol. 2, pp. 210): Chicago: University of Chicago Press.

Lambert, S. D., & Loiselle, C. G. (2008). Combining individual interviews and focus groups to enhance data richness. *Journal of Advanced Nursing*, *62*(2), 228-237. https://doi.org/10.1111/j.1365-2648.2007.04559.x

Lee, Y., & Kim, H. (2018). The Turning Point of China's Rural Public Health during the Cultural Revolution Period: Barefoot Doctors: A Narrative. *Iranian Journal of Public Health*, *47*(Suppl 1), 1-8. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6124148/

Li, J. Q., Terheyden, J. H., Welchowski, T., Schmid, M., Letow, J., Wolpers, C., Holz, F. G., & Finger, R. P. (2019). Prevalence of Retinal Vein Occlusion in Europe: A Systematic Review and Meta-Analysis. *Ophthalmologica*, *241*(4), 183-189. https://doi.org/10.1159/000494224

Li, J. Q., Welchowski, T., Schmid, M., Letow, J., Wolpers, C., Pascual-Camps, I., Holz, F. G., & Finger, R. P. (2020). Prevalence, incidence and future projection of diabetic eye disease in Europe: a systematic review and meta-analysis. *European Journal of Epidemiology*, *35*(1), 11-23. https://doi.org/10.1007/s10654-019-00560-z

Li, J. Q., Welchowski, T., Schmid, M., Mauschitz, M. M., Holz, F. G., & Finger, R. P. (2020). Prevalence and incidence of age-related macular degeneration in Europe: a systematic review and meta-analysis. *British Journal of Ophthalmology*, *104*(8), 1077-1084. https://doi.org/10.1136/bjophthalmol-2019-314422

Maguire, M. G., Martin, D. F., Ying, G. S., Jaffe, G. J., Daniel, E., Grunwald, J. E., Toth, C. A., Ferris, F. L., 3rd, & Fine, S. L. (2016). Five-Year Outcomes with Anti-Vascular Endothelial Growth Factor Treatment of Neovascular Age-Related Macular Degeneration: The Comparison of Age-Related Macular Degeneration Treatments Trials. *Ophthalmology*, *123*(8), 1751-1761. https://doi.org/10.1016/j.ophtha.2016.03.045

Maier, C. B., & Aiken, L. H. (2016). Task shifting from physicians to nurses in primary care in 39 countries: a cross-country comparative study. *European Journal of Public Health*, *26*(6), 927-934. https://doi.org/10.1093/eurpub/ckw098

Malterud, K., Siersma, V. D., & Guassora, A. D. (2016). Sample Size in Qualitative Interview Studies: Guided by Information Power. *Qualitative Health Research*, *26*(13), 1753-1760. https://doi.org/10.1177/1049732315617444

Malterud, K., Aamland, A., & Fosse, A. (2020). How can task shifting put patient safety at risk? A qualitative study of experiences among general practitioners in Norway. *Scandinavian Journal of Primary Health Care*, *38*(1), 24-32. https://doi.org/10.1080/02813432.2020.1714143

Martin, D. F., Maguire, M. G., Fine, S. L., Ying, G. S., Jaffe, G. J., Grunwald, J. E., Toth, C., Redford, M., & Ferris, F. L., 3rd. (2012). Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. *Ophthalmology*, *119*(7), 1388-1398. https://doi.org/10.1016/j.ophtha.2012.03.053

Martin, D. F., Maguire, M. G., Ying, G. S., Grunwald, J. E., Fine, S. L., & Jaffe, G. J. (2011). Ranibizumab and bevacizumab for neovascular age-related macular degeneration. *New England Journal of Medicine*, *364*(20), 1897-1908. https://doi.org/10.1056/NEJMoa1102673

Meara, J. G., Leather, A. J., Hagander, L., Alkire, B. C., Alonso, N., Ameh, E. A., Bickler, S. W., Conteh, L., Dare, A. J., Davies, J., Mérisier, E. D., El-Halabi, S., Farmer, P. E., Gawande, A., Gillies, R., Greenberg, S. L., Grimes, C. E., Gruen, R. L., Ismail, E. A., Kamara, T. B., Lavy, C., Lundeg, G., Mkandawire, N. C., Raykar, N. P., Riesel, J. N., Rodas, E., Rose, J., Roy, N., Shrime, M. G., Sullivan, R., Verguet, S., Watters, D., Weiser, T. G., Wilson, I. H., Yamey, G., & Yip, W. (2015). Global Surgery 2030: evidence and solutions for achieving health, welfare, and economic development. *Lancet*, *386*(9993), 569-624. https://doi.org/10.1016/s0140-6736(15)60160-x

Michelotti, M. M., Abugreen, S., Kelly, S. P., Morarji, J., Myerscough, D., Boddie, T., Haughton, A., Nixon, N., Mason, B., & Sioras, E. (2014). Transformational change: nurses substituting for ophthalmologists for intravitreal injections - a quality-improvement report. *Clinical Ophthalmology (Auckland, N.Z.)*, *8*, 755-761. https://doi.org/10.2147/opth.s59982

Mitchell, P., Bandello, F., Schmidt-Erfurth, U., Lang, G. E., Massin, P., Schlingemann, R. O., Sutter, F., Simader, C., Burian, G., Gerstner, O., & Weichselberger, A. (2011). The RESTORE study: ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema. *Ophthalmology*, *118*(4), 615-625. https://doi.org/10.1016/j.ophtha.2011.01.031

Mohamed, R., Ramcharan, D., Srikaran, S., & Mensch, E. (2018). A model of clinical practice: a randomised clinical study evaluating patient satisfaction of nurse-led vs consultant-led intravitreal injection. *Eye (London, England)*, *32*(6), 1148-1149. https://doi.org/10.1038/s41433-017-0008-9

Mohr, D. C., Young, G. J., Meterko, M., Stolzmann, K. L., & White, B. (2011). Job satisfaction of primary care team members and quality of care. *American Journal of Medical Quality*, *26*(1), 18-25. https://doi.org/10.1177/1062860610373378

Morse, J. M. (2015). Critical Analysis of Strategies for Determining Rigor in Qualitative Inquiry. *Qualitative Health Research*, *25*(9), 1212-1222. https://doi.org/10.1177/1049732315588501

National Institute for Health and Care Excellence (NICE). (2013a). *NICE Process and Methods Guides* (Guide to the Methods of Technology Appraisal 2013, Issue. H. National Institute for & E. Care. https://www.nice.org.uk/process/pmg9/resources/guide-to-the-methods-of-technology-appraisal-2013-pdf-2007975843781

National Institute for Health and Care Excellence (NICE). (2013b). *Ranibizumab for treating diabetic macular oedema*. National Institute for Health and Clinical Excellence. Retrieved May 11th from https://www.nice.org.uk/guidance/ta274

National Institute for Health and Care Excellence (NICE). (2013c). *Ranibizumab for treating visual impairment caused by macular oedema secondary to retinal vein occlusion*. National Institute for Health and Clinical Excellence. Retrieved May 11th from https://www.nice.org.uk/guidance/ta283

Nguyen, Q. D., Brown, D. M., Marcus, D. M., Boyer, D. S., Patel, S., Feiner, L., Gibson, A., Sy, J., Rundle, A. C., Hopkins, J. J., Rubio, R. G., & Ehrlich, J. S. (2012). Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. *Ophthalmology*, *119*(4), 789-801. https://doi.org/10.1016/j.ophtha.2011.12.039

Nicholson, L., Talks, S. J., Amoaku, W., Talks, K., & Sivaprasad, S. (2022). Retinal vein occlusion (RVO) guideline: executive summary. *Eye (London, England)*, *36*(5), 909-912. https://doi.org/10.1038/s41433-022-02007-4

Norwegian University of Science and Technology (NTNU; 2022). *Faculty of Medicine and Health Sciences. Health for a better world. Strategy 2018-2025*. The Norwegian University of Science and Technology. Retrieved June 21st from https://www.ntnu.edu/mh/strategy

Novartis (2022). *Summary of product characteristics: Lucentis 10 mg/mL solution for injection. Lucentis prescribing information.* Novartis Pharmaceuticals UK Ltd. Retrieved Mai 10th from https://www.medicines.org.uk/emc/medicine/19409/SPC

OECD.Stat. (2022). *Health expenditure and financing* The Organisation for Economic Co-operation and Development. Retrieved May 20th from https://stats.oecd.org/Index.aspx?DataSetCode=SHA

Ohtake, P. J., & Childs, J. D. (2014). Why publish study protocols? In (Vol. 94, pp. 1208-1209): Oxford University Press.

Otani, T., Kishi, S., & Maruyama, Y. (1999). Patterns of diabetic macular edema with optical coherence tomography. *American Journal of Ophthalmology*, *127*(6), 688-693. https://doi.org/10.1016/s0002-9394(99)00033-1

Pancholy, M., Storey, P. P., Levin, H. J., Obeid, A., Patel, S. N., Kuley, B., Hsu, J., Spirn, M. J., Fineman, M., Klufas, M. A., Gupta, O., Ho, A. C., & Garg, S. J. (2021). Endophthalmitis following Intravitreal Anti-Vascular Endothelial Growth Factor Therapy: Changes in Incidence and Outcomes over a 9-Year Period. *Current Eye Research*, *46*(9), 1370-1377. https://doi.org/10.1080/02713683.2021.1874023

Patel, S. (2018). Medicare Spending on Anti-Vascular Endothelial Growth Factor Medications. *Ophthalmol Retina*, *2*(8), 785-791. https://doi.org/10.1016/j.oret.2017.12.006

Patel, S. N., Gangaputra, S., Sternberg, P., Jr., & Kim, S. J. (2020). Prophylaxis measures for postinjection endophthalmitis. *Survey of Ophthalmology*, *65*(4), 408-420. https://doi.org/10.1016/j.survophthal.2019.12.005

Pennington, K. L., & DeAngelis, M. M. (2016). Epidemiology of age-related macular degeneration (AMD): associations with cardiovascular disease phenotypes and lipid factors. *Eye Vis (Lond)*, *3*, 34. https://doi.org/10.1186/s40662-016-0063-5

Perdicoyianni-Paleologou, H. (2017). The officier de santé in 19th-century France: A PA prototype. *Jaapa*, *30*(9), 1-3. https://doi.org/10.1097/01.JAA.0000522140.98940.ad

Piaggio, G., Elbourne, D. R., Pocock, S. J., Evans, S. J., & Altman, D. G. (2012). Reporting of noninferiority and equivalence randomized trials: extension of the CONSORT 2010 statement. *JAMA*, *308*(24), 2594-2604. https://doi.org/10.1001/jama.2012.87802

Polit, D. F., & Beck, C. T. (2020). *Nursing research : generating and assessing evidence for nursing practice* (Eleventh edition.; International edition. ed.). Lippincott Williams & Wilkins.

Rabin, R., & de Charro, F. (2001). EQ-5D: a measure of health status from the EuroQol Group. *Annals of Medicine*, *33*(5), 337-343. https://doi.org/10.3109/07853890109002087

Ramer, S. C. (2018). The Russian feldsher: A PA prototype in transition. *Jaapa*, *31*(11), 1-6. https://doi.org/10.1097/01.Jaa.0000546484.94936.30

Rosenfeld, P. J., Brown, D. M., Heier, J. S., Boyer, D. S., Kaiser, P. K., Chung, C. Y., & Kim, R. Y. (2006). Ranibizumab for neovascular age-related macular degeneration. *New England Journal of Medicine*, *355*(14), 1419-1431. https://doi.org/10.1056/NEJMoa054481

Rosenfeld, P. J., Moshfeghi, A. A., & Puliafito, C. A. (2005). Optical coherence tomography findings after an intravitreal injection of bevacizumab (avastin) for neovascular age-related macular degeneration. *Ophthalmic Surgery, Lasers & Imaging*, *36*(4), 331-335.

Royal College of Ophthalmologists. (2013). *College Statement on intra-ocular injections by non-medical health care professionals (HCPs)*. Retrieved May 10th from http://bmec.swbh.nhs.uk/wp-content/uploads/2013/03/RCOphth-Intra-ocular-injections-by-non-medical-staff.pdf

Rudnicka, A. R., Kapetanakis, V. V., Jarrar, Z., Wathern, A. K., Wormald, R., Fletcher, A. E., Cook, D. G., & Owen, C. G. (2015). Incidence of Late-Stage Age-Related Macular Degeneration in American Whites: Systematic Review and Meta-analysis. *American Journal of Ophthalmology*, *160*(1), 85-93.e83. https://doi.org/10.1016/j.ajo.2015.04.003

Ruiz-Moreno, J. M., Arias, L., Abraldes, M. J., Montero, J., & Udaondo, P. (2021). Economic burden of age-related macular degeneration in routine clinical practice: the RAMDEBURS study. *International Ophthalmology*, *41*(10), 3427-3436. https://doi.org/10.1007/s10792-021-01906-x

Saeedi, P., Petersohn, I., Salpea, P., Malanda, B., Karuranga, S., Unwin, N., Colagiuri, S., Guariguata, L., Motala, A. A., Ogurtsova, K., Shaw, J. E., Bright, D., & Williams, R.

(2019). Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9(th) edition. *Diabetes Research and Clinical Practice*, *157*, 107843. https://doi.org/10.1016/j.diabres.2019.107843

Samalia, P., Garland, D., & Squirrell, D. (2016). Nurse specialists for the administration of anti-vascular endothelial growth factor intravitreal injections. *New Zealand Medical Journal*, *129*(1438), 32-38. https://assets-global.website-files.com/5e332a62c703f653182faf47/5e332a62c703f6838d2fd442_Samalia-2005-NZMJ-1438-FINAL.pdf

Samb, B., Celletti, F., Holloway, J., Van Damme, W., De Cock, K. M., & Dybul, M. (2007). Rapid expansion of the health workforce in response to the HIV epidemic. *New England Journal of Medicine*, *357*(24), 2510-2514. https://doi.org/10.1056/NEJMsb071889

Schmidt-Erfurth, U., Garcia-Arumi, J., Bandello, F., Berg, K., Chakravarthy, U., Gerendas, B. S., Jonas, J., Larsen, M., Tadayoni, R., & Loewenstein, A. (2017). Guidelines for the Management of Diabetic Macular Edema by the European Society of Retina Specialists (EURETINA). *Ophthalmologica*, *237*(4), 185-222. https://doi.org/10.1159/000458539

Shek, D. T., & Wong, K. K. (2010). Qualitative evaluation of the training program of the Project P.A.T.H.S. in Hong Kong. *International Journal of Adolescent Medicine and Health*, *22*(3), 413-423. https://doi.org/10.1515/ijamh.2010.22.3.413

Shorten, A., & Smith, J. (2017). Mixed methods research: expanding the evidence base. *Evidence-Based Nursing*, *20*(3), 74-75. https://doi.org/10.1136/eb-2017-102699

Sidel, V. W. (1972). The barefoot doctors of the People's Republic of China. *New England Journal of Medicine*, *286*(24), 1292-1300. https://doi.org/10.1056/nejm197206152862404

Simcock, P., Kingett, B., Mann, N., Reddy, V., & Park, J. (2014). A safety audit of the first 10 000 intravitreal ranibizumab injections performed by nurse practitioners. *Eye (London, England)*, *28*(10), 1161-1164. https://doi.org/10.1038/eye.2014.153

Singer, M., & Rahman, E. Z. (2020). Update on Longer-Acting Anti-VEGF Therapies

An expansive horizon is coming into focus. *Retinal Physician*, *17*(April 2020), 38-41. https://www.retinalphysician.com/issues/2020/april-2020/update-on-longer-acting-anti-vegf-therapies

Song, P., Xu, Y., Zha, M., Zhang, Y., & Rudan, I. (2019). Global epidemiology of retinal vein occlusion: a systematic review and meta-analysis of prevalence, incidence, and risk factors. *J Glob Health*, *9*(1), 010427. https://doi.org/10.7189/jogh.09.010427

Spooner, K. L., Fraser-Bell, S., Hong, T., Wong, J. G., & Chang, A. A. (2022). Long-term outcomes of anti-VEGF treatment of retinal vein occlusion. *Eye (London, England)*, *36*(6), 1194-1201. https://doi.org/10.1038/s41433-021-01620-z

Stahlke, S., Rawson, K., & Pituskin, E. (2017). Patient Perspectives on Nurse Practitioner Care in Oncology in Canada. *Journal of Nursing Scholarship*, *49*(5), 487-494. https://doi.org/10.1111/jnu.12313

Statista. (2020). *Number of ophthalmologists per 10,000 population in Europe in 2020*. Health, Pharma & Medtech›Health Professionals & Hospitals. https://www.statista.com/statistics/711061/number-of-ophthalmologists-in-european-union-eu/

Statistics Norway. (2022a). *Consumer price index*. Statistics Norway. Retrieved May 20th from https://www.ssb.no/priser-og-prisindekser/konsumpriser/statistikk/

Konsumprisindeksen. To calculate consumer price.

Statistics Norway. (2022b). *Official statistics since 1876*. Statistics Norway. Retrieved 22.01.24 from https://www.ssb.no/en. To retrieve population numbers.

Stolberg, H. O., Norman, G., & Trop, I. (2004). Randomized controlled trials. *AJR: American Journal of Roentgenology*, *183*(6), 1539-1544. https://doi.org/10.2214/ajr.183.6.01831539

Strand, J. (2006). ThePracticante: Puerto Rico Physician Assistant Prototype. *The Journal of Physician Assistant Education*, *17*(2), 60-62. https://www.researchgate.net/publication/242741008_The_Practicante_Puerto_Rico_Physician_Assistant_Prototype

Teo, Z. L., Tham, Y. C., Yu, M., Chee, M. L., Rim, T. H., Cheung, N., Bikbov, M. M., Wang, Y. X., Tang, Y., Lu, Y., Wong, I. Y., Ting, D. S. W., Tan, G. S. W., Jonas, J. B., Sabanayagam, C., Wong, T. Y., & Cheng, C. Y. (2021). Global Prevalence of Diabetic Retinopathy and Projection of Burden through 2045: Systematic Review and Meta-analysis. *Ophthalmology*, *128*(11), 1580-1591. https://doi.org/10.1016/j.ophtha.2021.04.027

Thotam, S. M., & Buhse, M. (2020). Patient Satisfaction with Physicians and Nurse Practitioners in Multiple Sclerosis Centers. *Int J MS Care*, *22*(3), 129-135. https://doi.org/10.7224/1537-2073.2018-042

Tong, A., Sainsbury, P., & Craig, J. (2007). Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *International Journal for Quality in Health Care*, *19*(6), 349-357. https://doi.org/10.1093/intqhc/mzm042

Varma D, L. D., Johnson P, Stanley S. (2013). A novel approach to expanding the role of nurses to deliver intravitreal injections for patients with age-related macular degeneration *International Journal of Ophthalmic Practice*, *4* (2), 68-74.

Virgili, G., Parravano, M., Evans, J. R., Gordon, I., & Lucenteforte, E. (2018). Anti-vascular endothelial growth factor for diabetic macular oedema: a network meta-analysis. *Cochrane Database Syst Rev*, *10*(10), Cd007419. https://doi.org/10.1002/14651858.CD007419.pub6

Wang, B., Wang, H., Tu, X. M., & Feng, C. (2017). Comparisons of Superiority, Non-inferiority, and Equivalence Trials. *Shanghai Arch Psychiatry*, *29*(6), 385-388. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5925592/

Weiser, T. G., Regenbogen, S. E., Thompson, K. D., Haynes, A. B., Lipsitz, S. R., Berry, W. R., & Gawande, A. A. (2008). An estimation of the global volume of surgery: a modelling strategy based on available data. *Lancet*, *372*(9633), 139-144. https://doi.org/10.1016/s0140-6736(08)60878-8

WHO. (2021). *Ageing and health*. World Helath Organization. Retrieved June 21st from https://www.who.int/news-room/fact-sheets/detail/ageing-and-health

WHO. (2022). *Economic Evaluation & Analysis*. World Helath Organization,. Retrieved May 20th from https://www.who.int/teams/health-systems-governance-and-financing/economic-analysis

Wise, G. N. (1956). Retinal neovascularization. *Transactions of the American Ophthalmological Society*, *54*, 729-826. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1312655/

Wong, W. L., Su, X., Li, X., Cheung, C. M., Klein, R., Cheng, C. Y., & Wong, T. Y. (2014). Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. *Lancet Glob Health*, *2*(2), e106-116. https://doi.org/10.1016/s2214-109x(13)70145-1

Wordsworth, S., Ludbrook, A., Caskey, F., & Macleod, A. (2005). Collecting unit cost data in multicentre studies. Creating comparable methods. *Eur J Health Econ*, *6*(1), 38-44. https://doi.org/10.1007/s10198-004-0259-9

World Health Organization. (2008). *Task shifting: global recommendations and guidelines*. World Health Organization. Retrieved Nov 17th from http://apps.who.int/iris/bitstream/handle/10665/43821/9789?sequence=1#:~:text=The%20recommendation%20endorses%20task%20shifting,in%20human%20resources%20for%20health.

Zachariah, R., Ford, N., Philips, M., Lynch, S., Massaquoi, M., Janssens, V., & Harries, A. D. (2009). Task shifting in HIV/AIDS: opportunities, challenges and proposed actions for sub-Saharan Africa. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, *103*(6), 549-558. https://doi.org/10.1016/j.trstmh.2008.09.019

Aase, M. (2006). Interviewing colleagues—Ethical and methodological challenges. *Center for kvalitativ metodeudvikling*, *41*, 48-54.

9 Paper I - IV

Paper I

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STUDY PROTOCOL Open Access

Nurse-administered intravitreal injections of anti-VEGF: study protocol for noninferiority randomized controlled trial of safety, cost and patient satisfaction

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Abstract

Background: Intravitreal injections (IVI) of anti-vascular endothelial growth factor (anti-VEGF) now improve or stabilize visual acuity in a number of previously untreatable eye diseases, of which the main are age-related macular degeneration, retinal vein occlusion and diabetic macular edema. Most patients require multiple injections over lengthy periods of time and the prevalence of treatable conditions is increasing. Anti-VEGF IVI normally administered by physicians, therefore represent a considerable workload on ophthalmologic clinics and will continue to do so in the near future. Nurse-administered IVI may relieve this workload, but the safety, cost and patient satisfaction of such an extended role for nurses in ophthalmologic clinics has not earlier been investigated. To investigate these outcomes following independent anti-VEGF IVI by trained nurses, a noninferiority randomized controlled trial is being conducted.

Methods/Design: Patients eligible for anti-VEGF treatment, minimum 304, are recruited and randomized to IVI administration by either trained nurses or physicians. The primary outcome is safety, measured by difference in mean change in visual acuity between the two groups during an observation period of 12 months. Secondary outcomes are incidence of ocular adverse events, cost per patient and patient satisfaction.

Discussion: This study protocol describes the design of the first randomized controlled trial of nurse-administered IVI of anti-VEGF. The study is designed to examine safety, cost and patient satisfaction during 12 months follow-up.

Trial registration: ClinicalTrials.gov NCT02359149. Registered February 4, 2015.

Keywords: Anti-VEGF, Intravitreal injection, Nurse, Randomized controlled trial, Age-related macular degeneration, Retinal vein occlusion, Diabetic macular edema

Background

Intravitreal injections (IVI) of anti-vascular endothelial growth factor (anti-VEGF) improve or stabilize visual acuity in a number of previously untreatable eye diseases, of which the main are age-related macular degeneration (AMD), retinal vein occlusion (RVO) and diabetic macular edema (DME) [1–3]. Due to its potent antiangiogenic effects, the number of IVI of anti-VEGF has risen considerably since the treatment was first introduced a decade ago [4, 5]. Elderly people with AMD make up the largest group of patients receiving IVI and the prevalence of the disease increases with age. In the UK 3.5 % of the population of 75 years or older were visually impaired due to AMD [6]. In 2010, more than two million people were blind and six million people were visually impaired due to macular diseases globally [7]. Improved diagnostics as well as increased prevalence of treatable conditions will probably cause a continued rise of IVI in the future. IVI are normally administered by physicians in ophthalmologic out-patient clinics and are given with intervals of 4–16 weeks either as monthly

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injections, injections when needed (pro re nata) or injections with gradually extended intervals (treat and extend) [8, 9]. Irrespective of the treatment strategy chosen, most patients require sequential injections during several years for their condition to stabilize. Hence, IVI of anti-VEGF represent a considerable workload on physicians in ophthalmologic clinics and is expected to continue to do so. This is a real challenge today and in the future, since the population over age 60 are growing more than twice as fast as the number of ophthalmologists [10].

Extended roles for nurses are increasingly implemented in several medical fields, and in ophthalmology nurse-administered IVI of anti-VEGF may replace physician-administered IVI. Data on nurse-administered IVI is limited so far, but there are indications that it may be safe and acceptable to patients. An observational study from the UK reported a complication rate comparable to studies in which IVI were administered by physicians [11] and other studies have reported acceptable patient satisfaction following nurse-administered IVI [12–14]. However, these outcomes have to the best of our knowledge not earlier been investigated in randomized controlled trials (RCT) and an economic evaluation of a nurse-administered IVI clinic has not earlier been reported. To this end, the present protocol describes a noninferiority RCT with the objective to investigate safety, cost and patient satisfaction following nurse-administered IVI during 12-months follow-up.

Methods

Study design

The study is a prospective, randomized noninferiority trial with two treatment arms; IVI performed by nurses and IVI performed by physicians. Treatment by physicians is considered the reference group and standard care to which treatment performed by nurses will be compared. The flow chart of the study is presented in Fig. 1.

Objectives

The primary objective is to evaluate the safety of nurse-administered IVI of anti-VEGF compared with physician-administered IVI.

The secondary objectives are:

- to evaluate cost of nurse-administered IVI of anti-VEGF compared with standard care
- to evaluate patient satisfaction of nurse-administered IVI of anti-VEGF compared with standard care

For the primary objective the evaluation will be performed using a noninferiority test, to test whether the nurses are treating the patients equally safe or better than the reference group, i.e physicians. More specifically, the null (H_0) and alternative (H_A) hypotheses are:

$$H_0 : \mu_{NURSES} - \mu_{PHYSICIANS} \leq -\delta_L \text{ and } H_A : \mu_{NURSES} - \mu_{PHYSICIANS} > -\delta_L,$$

where μ_i is the mean change in visual acuity from first visit (baseline) to last visit 12 months later in group i, and δ_L is "the noninferiority margin", which is the maximum clinically acceptable difference in change, for treatment by nurses to be considered noninferior to the reference treatment, $\delta_L > 0$

Setting

The trial is performed in the IVI clinic of the Department of Ophthalmology, St. Olavs Hospital, Trondheim University Hospital in Norway during 01.03.15-31.12.16. The IVI clinic, organized as an independent out-patient clinic, performs ~ 3000 IVI annually and serves a population of ~ 300.000 individuals in the Central Norway Health Region.

Patients are remitted to the IVI clinic by ophthalmologists working at 10 different eye centers in the region and from ophthalmologists at the Department of Ophthalmology, responsible for the diagnostic and therapeutic decisions. At the IVI clinic a secretary administers patient appointments, receive user charges and answer phone calls. Preparing the patients for IVI is performed by a nurse (Additional file 1). In standard care, a physician is responsible for performing the IVI according to the list of patients, approximately 22 IVI daily (Additional file 2). A senior consultant is available at the clinic in case medical questions need to be discussed.

Intervention

The intervention in the present study consists of replacing the physician administering the IVI, by a nurse (Additional file 2). Administration of IVI includes several skills and responsibility: assessment of whether there are any contraindications for treatment, performing the sterile IVI procedure, informing the patient, planning the next session and documentation in patient records. The preparation for IVI by a nurse (Additional file 1) and the possibility to seek medical advice from a senior consultant remains equal to standard care.

Training program

A training program for administration of IVI for nurses was developed and implemented at the Department of Ophthalmology during the year prior to the start of the RCT. Six nurses took part in the training program which aimed at enabling nurses to perform IVI independently, as safe and within equal time frame as the physicians.

The program included two interactive courses regarding eye infections and documentation in patient records. Furthermore, it included a wetlab with individual training of a safe injection technique on porcine eyes; placing

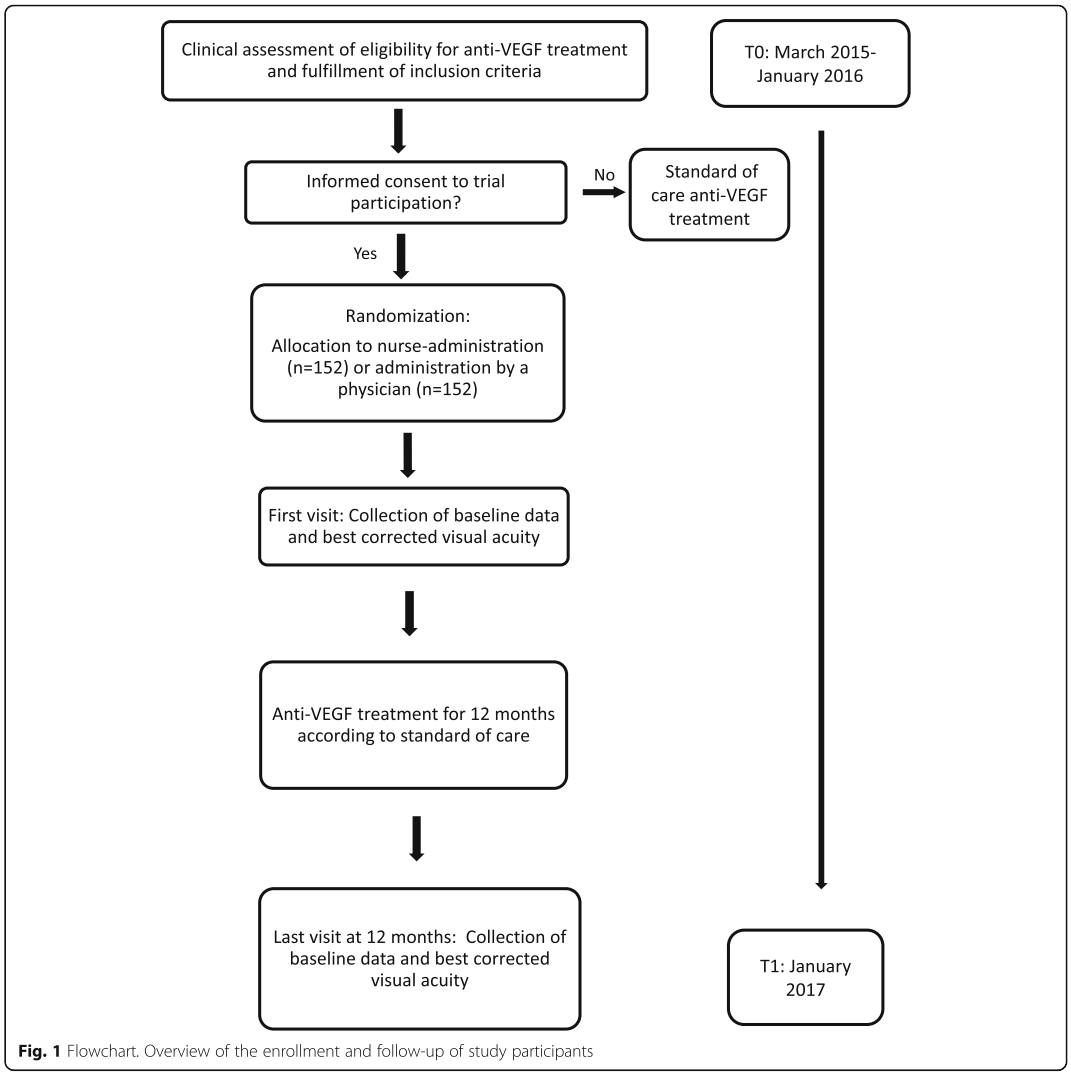

Fig. 1 Flowchart. Overview of the enrollment and follow-up of study participants

the injection 3.5 mm posterior to the limbus in any quadrant between the horizontal and vertical muscles. This was followed by graded exposure of the procedure in the injection room and finally performing IVI individually on patients under the supervision of a physician. The training program was divided into steps with increasing difficulty and the participating nurses decided themselves when they were ready to move to the next step. The nurses had to perform 100 independent IVI before final certification. The final achieved competence was evaluated by an unbiased senior consultant via observation of the nurse performing three independent IVI. If these were performed in a satisfactory manner, the nurse was certified to administer IVI individually.

Trial recruitment

All patients with AMD, RVO or DME that are eligible for anti-VEGF IVI and able to give an informed consent are invited to participate. Both newly referred patients during 01.03.15–01.01.16 as well as patients that are already receiving anti-VEGF IVI fulfil the inclusion criteria.

Patients with ocular pathology eligible for anti-VEGF IVI other than the abovementioned conditions and inability to

provide an informed consent do not fulfil the inclusion criteria and are excluded.

Information about the study will be given either face-to-face in the department or via a phone call and will also be handed out in writing. The patients will receive trial information at least 24 h before being asked to give an informed consent. If the patient agrees to enter the trial, written informed consent will be obtained. Consent forms will be stored in a locked safe to which only study management has access. Patients who do not consent to the trial will be treated according to standard care.

Randomization and blinding

Patients are randomly assigned to receive treatment by nurse or physician in a 1:1 ratio, using a web-based algorithm. The randomization is stratified by diagnosis (AMD, RVO and DME) and by number of treatments (first treatment vs treated before). The reason for choice of stratification is that there is an expected difference in change in mean visual acuity during the observation period in these groups. Only one eye per patient is included in the study. If both eyes are eligible, the eye with the better visual acuity is included.

The study is single-blinded, i.e. patients are blinded to intervention group. Patients are not told to which group they have been randomized, and both nurses and physicians will wear white hospital clothes but no nametags telling their profession during the procedure. Furthermore, when the patient enters the injection room the personnel will present themselves by first name only.

Outcomes

Primary outcome is the difference in mean change in visual acuity between the two groups during the study period of 12 months (measure 1).

Secondary outcomes are:

- incidence of ocular adverse events needing treatment (measure 2)
- cost per patient (measure 3)
- mean patient satisfaction score (measure 4)

Measures

1. *Visual acuity* is measured with the Early Treatment Diabetic Retinopathy Study (ETDRS) chart using a standardized testing protocol at a starting test distance of 2 m [4, 5]. The visual acuity is measured as number of letters read at the ETDRS chart. Each line of the chart has five letters of same size in each row. The letters of the following rows gradually become smaller, with a distance of 0,1 logMAR. This interval scale is considered a continuous variable, and the number of letters read is counted [15]. The mean number of letters scored is considered a precise measure for evaluating whether the intervention shifts the visual acuity compared to standard care.

The test is carried out under uniform conditions by a physician, orthoptist or an optician. Before testing, the refraction is corrected following a standard protocol [15], i.e. the vision tested being the best corrected visual acuity.

2. *Ocular adverse events*. Number of ocular adverse events in the population receiving IVI at the Department of Ophthalmology is recorded during the whole study period, from the first study visit to the last follow-up visit of the study. The ocular adverse events will be noted in patient record and on a dedicated study form. Only ocular adverse events needing treatment are being recorded; retinal detachment, retinal tears, endophthalmitis, uveitis, lens damage and intraocular hemorrhages.
3. *Cost per patient*. Cost data will be collected in order to take a hospital perspective, a health care perspective and a societal perspective.

Intervention costs

The calculation of out-patient clinic costs will be based on time spent by different personnel categories. Time spent will be recorded according to the three main phases of the treatment procedure: Pre-examination, the IVI-procedure and the post IVI-procedure:

a) Pre-examination services performed by secretaries and nurses
b) IVI-procedure performed by nurse (intervention) or physician (standard care) and time spent by senior consultant on on-call assistance to the nurse or physician respectively.
c) Post-IVI services performed by secretaries.

Number of hours spent will be multiplied by personnel group specific salary levels and adjusted with over-head costs. Data will be recorded on a daily basis using predefined registration forms (Additional file 3). Aggregate costs per patient will be calculated.

Extra educational costs on training nurses will be calculated based on the training program.

Other hospital costs

Utilization of hospital services outside the out-patient clinic will be assessed by examining data from the hospital administrative patient register. Costs will be calculated by combining volume of in-patient and out-patient services and their corresponding unit costs.

Health care costs outside hospital

Utilization of ophthalmologist services and general practitioner services will be collected using a patient questionnaire (Additional file 4). Costs will be calculated by combining volume of services and corresponding unit costs.

Patient costs

Travel costs will be calculated based on information on travel time and bringing a companion.

4. *Patient satisfaction*. Previously validated patient satisfaction instruments were found too comprehensive and not suitable to assess the IVI treatment in the injection room setting. A short and simple study-specific patient satisfaction questionnaire was therefore developed in accordance with guidelines for measuring the quality of health services [16]. The questionnaire was validated for reliability and feasibility in a pilot study of 10 patients. After this first pilot test, some modifications were made to the questionnaire before a second pilot test was carried out and validated. We found the best alternative for the patients with blurred vision following treatment to be a five-point grading scale and only a few questions read out load. Only two aspects of the treatment is tested; the general impression of the treatment and the confidence during the treatment in the injection room (Additional file 5). If the patient is not giving the maximum score of satisfaction, an open-ended question will be asked for recommendations of how to improve the comfort and well-being during the visit. At the last visit, the patients additionally will be asked if they think they are treated by a nurse or by a physician.

Data collection

At the first visit, background information for the economic evaluations is collected (Additional file 4). A physician, orthoptist or optician is asking these questions before refractioning the study eye and measuring the best corrected visual acuity. The study participant then goes to the injection room. After the IVI, the participant is asked to answer the patient satisfaction questionnaire by a secretary (Additional file 5). Each study participant has an individual study booklet marked with study number and patient initials. The booklet follows the patient during the visit in the department and is otherwise kept in a locked room.

In the following visits the study participant will be asked follow-up questions regarding use of health care service (Additional file 4). The questions are asked by the nurse or physician performing the IVI.

The last visit of the 12 month period is performed similar to the baseline registration (Additional file 4). The time window for the final test is 12 ± 2 months.

The nurse or physician performing the IVI, will fill in a daily report including the number of patients and eyes treated and number of questions asked a senior consultant (Additional file 3).

Researchers will continually examine the study forms in the booklets for missing data. Missing data will be sought collected via phone calls.

Statistical methods

The primary objective will be analyzed using a t-test for non-inferiority, comparing mean change in visual acuity from baseline to 12 months between nurses and physicians. A linear regression model for the change in visual acuity will be used to compare the treatments after adjusting for diagnosis, used as a stratification variable. Adjusting for the other stratification variable, first or follow up treatment, can be done similarly, but will depend on a sufficient number of included patients in each of the two groups. The data will be analyzed and presented according to the CONSORT guidelines for reporting noninferiority trials [17].

Costs will be examined by analyzing differences between nurses and physicians in total cost per patient, health service cost per patient and hospital cost per patient. Imputation will be used on missing data. Sensitivity analyses will be performed to assess parameter uncertainty.

Sample size

The sample size is calculated for the noninferiority study comparing change in visual acuity for patients treated by nurses to those treated by physicians.

Sample size considerations

In contrast to earlier studies comparing the effect of two different anti-VEGF drugs or the effect of different anti-VEGF treatment strategies, we want to test the effect of two different professions performing the treatment. Historical data from large randomized clinical AMD trials found the mean change in visual acuity during the first year of treatment to be 6–7 letters (1,2–1,4 lines) [18]. The CATT study was as the present study designed as a noninferiority study. As the noninferiority margin (δ_L) should be less than the observed change in visual acuity, five letters (one line on the visual acuity chart) was chosen as the acceptable difference for the tested treatment to be considered noninferior to the reference treatment. However, in a study of the safety of nurse-administered IVI, a noninferiority margin of five letters may be considered too wide.

First the study population in the present study is not as homogenous as the before mentioned study since it includes both patients with AMD, RVO and DME. There is an anticipated difference in treatment response in these three conditions. Second, the majority of study participants will already have received several IVI before inclusion in the study and in these patients we do not expect major changes in visual acuity during the study period. Third, we should consider the ethical aspect of having a wide noninferiority margin; if it is right to sacrifice visual acuity to gain the possible benefit of cost savings by nurses treating the patients. Taking these aspects into consideration, we find that the noninferiority margin should not exceed three letters. In other words, the present study will test whether IVI administered by nurses is not less effective than treatment by physicians, by more than three letters.

We assume that the standard deviation (SD) of the distribution of changes, σ, will be 10 letters. This is again less than in the studies forming the basis for IVI of anti-VEGF, finding a SD of 15 letters reasonable the first year. The second year, however, the standard deviation, dropped to 11 letters and in our study we do assume 10 letters would be reasonable [8].

The anticipated true difference between the treatment groups is 0. That is, the effect of the treatment is expected to be equal in the two groups.

Sample size and power calculation

The sample size is calculated by using the abovementioned assumptions and the sample size formula for comparing two means in a noninferiority trial (SPSS Sample Power 3).

Choosing a noninferiority margin δ_L =3, standard deviation SD = 10 and a significance level of 0.05, 140 participants is required in each group to have a power of 80 % to reject the null hypothesis, $H_0 \leq -\delta_L$ and conclude that nurses are treating the patients equally safe as or better than physicians, if the null hypothesis is true.

We anticipate the percentage of patients completing the final visit at 12 months to be 92 % as a dropout of 8 %, including patient death and illness, is not uncommon in similar trials. This means that to make sure that 140 participants complete a 12-month observation period; at least 152 patients should be included in each of the study arms.

Discussion

The primary objective of the study is to evaluate safety of nurse-administered IVI of anti-VEGF compared with physician-administered IVI. Anti-VEGF IVI represents a considerable workload on ophthalmologic clinics and will probably continue to do so in the near future. Extending the roles of other health workers may relieve this workload from ophthalmologists and several clinics have had good experience training nurses to perform IVIs independently [11–14]. However, none have as far as we know, investigated the safety, cost and patient acceptance of independent IVI administration by trained nurses in a RCT.

We have chosen visual acuity as the primary outcome of the present study. The major goal is to investigate safety of nurse-administered IVI and visual acuity is recommended by health authorities in clinical trials when investigating this outcome [19]. Furthermore, most patients probably want to be sure that nurse-administered IVI does not pose any increased risk of deteriorating their sight.

It is conceivable that several aspects of the IVI procedure may affect visual acuity: the injection technique may be unsatisfactory performed so that the drug may not be administered correctly into the tissue where it acts, contraindications may be misinterpreted putting the patient at risk of complications or the treatment plan may be misinterpreted so that patients receive IVI with too lengthy intervals. The training and certification of the nurses is a key in this context, and the present study is in many ways a test of whether the training of nurses was adequate or not.

We believe that the design of the study, the randomization procedure and outcome measurements will be of sufficient strength and quality to evaluate if nurses are performing IVIs as safe as the standard care. Both newly remitted patients and patients treated before are invited to participate in the study and our experience so far is that it is easier including patients familiar with the treatment than the newly remitted patients. If few newly diagnosed patients are included, the interpretation of results will be for the follow-up patients only.

The present study is not dimensioned to evaluate whether there is an increased risk of complications that need treatment, since the rates of these complications are very low. Given that nurse-administered IVI is safe, we find the secondary outcomes equally relevant and of great importance to examine adverse events, patient satisfaction and economic aspects.

Trial status

The first patient was recruited to the trial March 1. 2015 and recruitment ended December 2015. Data collection will continue until January 2017.

Additional files

Additional file 1: EQS assistant. Instructions for the assisting nurse, preparing the patients for intravitreal injections. (PDF 202 kb)

Additional file 2: EQS operator. Instructions for the operator performing the intravitreal injections. (PDF 188 kb)

Additional file 3: Daily report. Recording the number of patients and eyes treated and the number of questions asked a senior consultant. (PDF 172 kb)

Additional file 4: Patient report. Recording the use of health care service. (PDF 97 kb)

Additional file 5: Patient satisfaction questionnaire. A short questionnaire about satisfaction with the treatment asked after the first and last visit. (PDF 98 kb)

Abbreviations
AMD: Age-related macular degeneration; anti-VEGF: anti-vascular endothelium growth factor; DME: Diabetes macular edema; IVI: Intravitreal injection; RCT: Randomized controlled trial; RVO: Retinal vein occlusion; SD: Standard deviation

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Availability of data and material
Non applicable.

Authors' contributions
DA initiated the study, has led the work on research design, intervention and implementation of the study protocol. SB, VH and TF made important contributions to the research design and the study protocol. TSM has made substantial contribution to the implementation of the study protocol, testing, ongoing data collection and writing of the manuscript. All authors contributed to the writing and review of the manuscript and approved the final version.

Competing interests
The authors declare that they have no competing interests.

Consent for publication
Non applicable.

Ethics approval and consent to participate
The study adheres to the Tenets of the Declaration of Helsinki and the study is approved by the Regional Committee of Ethics in Medical Research (2014/1719). Written informed consent to participate was obtained for each subject prior to the study.

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References
1. Solomon SD, Lindsley K, Vedula SS, Krzystolik MG, Hawkins BS. Anti-vascular endothelial growth factor for neovascular age-related macular degeneration. Cochrane Database Syst Rev. 2014;8, CD005139.
2. Braithwaite T, Nanji AA, Lindsley K, Greenberg PB. Anti-vascular endothelial growth factor for macular oedema secondary to central retinal vein occlusion. Cochrane Database Syst Rev. 2014;5, CD007325.
3. Virgili G, Parravano M, Menchini F, Evans JR. Anti-vascular endothelial growth factor for diabetic macular oedema. Cochrane Database Syst Rev. 2014;10, CD007419.
4. Brown DM, Kaiser PK, Michels M, Soubrane G, Heier JS, Kim RY, et al. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. N Engl J Med. 2006;355:1432–44.
5. Rosenfeld PJ, Brown DM, Heier JS, Boyer DS, Kaiser PK, Chung CY, et al. Ranibizumab for neovascular age-related macular degeneration. N Engl J Med. 2006;355:1419–31.
6. Owen CG, Fletcher AE, Donoghue M, Rudnicka AR. How big is the burden of visual loss caused by age related macular degeneration in the United Kingdom? Br J Ophthalmol. 2003;87:312–7.
7. Jonas JB, Bourne RRA, White RA, Flaxman SR, Keeffe J, Leasher J, et al. Visual impairment and blindness due to macular diseases globally: a systematic review and meta-analysis. Am J Ophthalmol. 2014;158:808–15.
8. The CATT Research Group, Martin DF, Maguire MG, Fine SL, Ying GS, Jaffe GJ, et al. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. Ophthalmology. 2012;119:1388–98.
9. Berg K, Hadzalic E, Gjertsen I, Forsaa V, Berger LH, Kinge B, et al. Ranibizumab or bevacizumab for neovascular age-related macular degeneration according to the lucentis compared to avastin study treat-and-extend protocol: two-year results. Ophthalmology. 2015 Oct 15. doi: 10.1016/j.ophtha.2015.09.018. [Epub ahead of print]
10. Resnikoff S, Felch W, Gauthier TM, Spivey B. The number of ophthalmologist in practice and training worldwide: a growing gap despite more than 200 000 practitioners. Br J Ophthalmol. 2012;96:783–7.
11. Simcock P, Kingett B, Mann N, Reddy V, Park J. A safety audit of the first 10 000 intravitreal ranibizumab injections performed by nurse practitioners. Eye. 2014;28:1161–4.
12. DaCosta J, Hamilton R, Nago J, Mapani A, Kennedy E, Luckett T, et al. Implementation of a nurse-delivered intravitreal injection service. Eye. 2014;28:734–40.
13. Michelotti MM, Abugreen S, Kelly SP, Morarji J, Myerscough D, Boddie T, et al. Transformational change: nurses substituting for ophthalmologists for intravitreal injections—a quality-improvement report. Clin Ophthalmol. 2014;8:755–61.
14. Varma D, Lunt D, Johnson P, Stanley S. A novel approach to expanding the role of nurses to deliver intravitreal injections for patients with age-related macular degeneration. Int J Ophthalmic Pract. 2013;4:68–74.
15. Treatment of age-related macular degeneration with photodynamic therapy (TAP) Study Group. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: one-year results of 2 randomized clinical trials–TAP report. Arch Ophthalmol. 1999;117:1329–45.
16. The Norwegian Knowledge Centre for the Health Services. www.kunnskapssenteret.no. Accessed 20 Aug 2014.
17. Piaggio G, Elbourne DR, Pocock SJ, Evans SJW, Altman DG. Reporting of noninferiority and equivalence randomized trials. Extension of the CONSORT 2010 Statement. JAMA. 2012;308:2594–604.
18. The CATT Research Group, Martin DF, Maguire MG, Ying GS, Grunwald JE, Fine SL, et al. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. N Engl J Med. 2011;364:1897–908.
19. Csaky KG, Richman EA, Ferris FL. Report from the NEI/FDA ophthalmic clinical trial design and endpoints symposium. IOVS. 2008;49:479–89.

Daily report **Week no:**	Monday	Tuesday	Wednesday	Thursday
Today's date, DD.MM.YY				
Doctor or nurse administers IVI? 1=doctor, 2=nurse				
Scheduled no. of IVI / eyes				
No. of extra unscheduled IVI / eyes during the day				
Total no. of IVI / eyes injected today				
No. of patients given an IVI today				
No. of patients that did not show up to their scheduled appointment				
No. of patients not given an IVI because of blepharitis				
Total no. of questions asked to an ophthalmologist today				
No. of questions asked regarding infection				
No. of questions asked regarding future follow-up				
No of questions regarding other topics (not specified above)				
Specify questions asked regarding other topics				

Patient report Fill in the white fields only	Baseline/ IVI no. 1	IVI no. 2	IVI no. 3	IVI no. 4	IVI no. 5	IVI no. 6	IVI no. 7	IVI no. 8
Date of injection, DD.MM.YY								
Does the patient come alone or with a companion? 0 = alone, 1 = with a companion								
Has the patient seen his general practitioner since the last IVI? Mark no. of visits.								
Has the patient seen his ophthalmologist since the last IVI? Mark no. of visits.								
Patient is living: 1 = in his own home 2 = with relatives 3 = in a nursing home 4 = in a municipal shelter 5 = other								
Is the patient receiving any nursing home care from the municipality? Note no. of hours per week (rounded up to the nearest hour).								
Is the patient receiving any home services from the municipality? Note no. of hours per week (rounded up to the nearest hour)								
What is the patients source of subsistence? 1 = Retirement pension 2 = Gainful employment 3 = Employment scheme 4 = Unemployed 5 = Permanent disability benefit 6 = Other								

The Intravitreal Injection Clinic at Department of Ophthalmology,

St. Olav's Hospital, Trondheim University Hospital, Norway.

Instructions for the assistant.

Introduction:

* Intravitreal injections (IVI) of medication is a treatment method used in an ever increasing number of eye conditions.

* The largest group of patients receiving treatment with IVI containing growth factor inhibitors (anti VEGF) is patients with Age related macular degeneration (AMD), followed by patients with retinal vein occlusions, diabetes macular edema and other retinal diseases. The anti-VEGFs injected are Avastine (bevacizumab), Eylea (aflibercept) and Lucentis (ranibizumab).

* In addition to anti-VEGF, corticosteroids are injected in fluid form (Triesence) and as a depot tablet (Ozurdex).

* The treatment is implemented by authorized personnel in a facilitated treatment room at the out-patient clinic.

Objective and Scope:

* This procedure aims to ensure equality of information, observation and preparation for treatment of the patient given intraocular injections, and to minimize discomfort.

Responsibility:

*Physician/nurse at the out-patient clinic.

Working description:

Performed by:	Working task
Physician/nurse	**Preparing the room for injection**: * Take a copy of the patient list from the drawer in room 1019. * From the refrigerator in the eye policlinic storage room, collect Avastine 25 mg/ml and Lucentis 10mg/ml and Eylea 40 mg/ml and Triesence 40mg/ml. Take Orurdex in the cupboard of the injection room. * Avastine, Lucentis and Eylea are later stored in the fridge on the 6th floor after use. **Clothing:** * Cover all hair with a cap. Remove watch and jewelry. * While filling syringes and working in the operation room, the physician/nurse should use a cap and surgical mask. * The wash basin, working trolley, assistance table and the upper parts of the treatment chair is disinfected with alcohol disinfectant (70% Antibac). * Cover the assistance table with an adhesive edged sterile drape. * Place sterile syringes and syringe needles on to the sterile drape. * Wipe the vial with alcohol disinfectant (Alkotip) before extracting the medicine. * Prepare the syringes in accordance to the sterile procedure. **The extraction /portioning of the medication:** * A codan spike is inserted in to a bottle of Avastine 25mg/ml. * Extract up to 0.15ml of Avastine in a syringe Omnifix-F. * Cannula BD Mikrolance 3.30G, 0.3x13mm for injection. * For the Extraction and portioning of Lucentis 10mg/ml (Individual set in each package). * 1 syringe 10mg/ml is divided into 2 insulin syringes (micro-Fine, 0.3mm x 8mm. * Cannula BD Microlance 3.30G, 0.3 x 13mm for injection.

	*For the extraction/ portioning of Eylea 40mg/ml (Individual set in each package). * 1 syringe Eylea 40mg/ml is divided into 3 insulin syringes MikroFine 0.3mm x 8 mm. * Cannula BD Microlance 3.30 G, 0.3 x 13mm for injection. * Other medication is prepared immediately before injection.
Physician/nurse	**Storage:** * The prepared syringes with the medication are aligned on the sterile drape with some distance between them. * A Sterile drape is place over them for protection. * Medication used after lunch is put into a sterile bag and placed in a refrigerator on the 6th floor.
Nurse/Doctor	**Patient treatment:** * The patient is called in from the waiting room on the 6th floor. * Check the patient`s personalia and identify the eye to be injected. Ask if he has received injections before.  * Check the patient`s eye for infection (conjunctivitis/blepharitis). If you are in doubt; inform the operator. Patients with infections are informed of the treatment, given relevant medication and the brochure: Treatment of eye lock infection. ; The IVI is postponed until the treatment is finished. * Remove any make-up with make-up remover. * Put the cap on head and place the gauze by the correct eye. *Drip the relevant eye with Oxibuprokain eye drops, then 1 drop of Betadine 5%. (NB! Iodine allergy) * Before the patient is escorted into the injection room, ask the patient discreetly about his/her recent health status: *With recent gastric flu/ diarrhea; the patient must be symptom free the last 2 days. * With upper respiratory infection, coughing and runny nose; postpone the injection until the patient is symptom free. * With infections that require antibiotics; the IVI is postponed until the a.b. treatment is finished. * With recent heart attack or stroke; the IVI is postponed for a month.

	* Safe surgery check list. * Position the patient on the operating chair. *Give the patient the 2nd & 3rd drops of Oxibuprokain. * The eye and eyelashes are then soaked with Betadine 5%, followed by wiping the upper and lower eyelids well, using Betadine soaked gauze balls. * After the injection, apply Betadine 5% before removing the eye speculum. * Viscotears can be given to ease discomfort after the injection. NB: Iodine allergy * Chloramphenicol eye drops are administered instead of Betadine. The eye is cleansed with sterile gauze balls/or Sugi soaked with chlorhexidinalcohol 5mg/ml. * Drip with chloramphenicol eye drops after the injection before removing the eye speculum.

At the end of the day

* Medicine bottles are marked with the days date and stored for 4 weeks in the disinfection room.

* Remember to re- charge the battery of the operation chair.

* The treatment room is made tidy and equipment replaced.

* Used equipment is transported to a collection point to be collected by porters, at lunch and by the end of the day.

Related documents

Info to those who have received eye medication.

Info about treatment with anti-VEGF.

Treatment of eyelid infection. Good eyelid hygiene.

When thinking about the time you have spent with us today, the preparation for the operation, the injection and the information given; what is your general impression? How satisfied are you with today's visit (mark your choice):

1. Not satisfied at all
2. Not very satisfied
3. Satisfied to some extent
4. Satisfied
5. Very satisfied

What can we do to make you more satisfied?

How confident did you feel during the treatment today? (mark your choice)

1. Not safe at all
2. Not very safe
3. Safe to some extent
4. Safe
5. Very safe

What can we do to make you feel more safe?

QUESTION ASKED AFTER THE LAST STUDY VISIT:

Who do you think have given you injections during the past year?

1. physicians
2. nurses
3. I am not sure

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Instructions for the operator.

Introduction:

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* The largest group of patients receiving treatment with IVI containing growth factor inhibitors (anti VEGF) is patients with Age related macular degeneration (AMD), followed by patients with retinal vein occlusions, diabetes macular edema and other retinal diseases. The anti-VEGFs injected are Avastine (bevacizumab), Eylea (aflibercept) and Lucentis (ranibizumab).

* In addition to anti-VEGF, corticosteroids are injected in fluid form (Triesence) and as a depot tablet (Ozurdex).

* The treatment is implemented by authorized personnel in a facilitated treatment room at the out-patient clinic.

Intention and scope:

* The procedure aims to ensure equal treatment of patients receiving IVI in relation to information, the sterile procedure and for correct injection technique.

Responsibility:

* Physician /nurse authorized to execute IVI implementation.

Working description:

Performed by	Working task
Physician/nurse who is authorized to give injections	**Before starting the treatment** * Rings, watches and jewelry are removed. * Put on a cap and a surgical mask. * Start with a surgical hand wash (in the morning- thereafter antimicrobial disinfectant) and sterile gloves. * Collect data about the patient from the electronic patient records (EPR). Ensure that the right patient receives the right treatment in the correct eye. **Implementation** * The operator confirms the information given by the assistant in accordance with the safe surgery check list. * The sterile intravitreal instrument basket containing the eye speculum and caliper is prepared. * Check that the syringe is filled with the right amount of medicine and that air bubbles are removed. * Insert the eye speculum. * Make a mark with the caliper 3.5mm from the limbus. * Place the needle point in the cavity perpendicular to the bulbous. * Insert the needle into the eye and inject the medicine. * Remove the eye speculum after the assistant has applied Betadine 5% eye drops. **Further course of treatment** * Ensure the patient is informed of the continuing treatment. * Fill in the form, planning for the next visit. * Report in the EPR.

Patient information

* Ask the patient if he has questions concerning the treatment.

* Ensure that the patient has understood the implications of good hygiene principles for the first 3 days.

* The patient is informed to make contact if symptoms of redness or pain occur.

* Ensure the patient has been given the brochure: Information for those who have received eye medication.

Related documents

Info for those who have received eye medication.

Info about treatment with anti-VEGF

Treatment of eyelid infection. Good eyelid hygiene.

Paper II

Acta Ophthalmologica

Task shifting of intraocular injections from physicians to nurses: a randomized single-masked noninferiority study

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ABSTRACT.

Purpose: **To test if task shifting of intraocular injections to nurses in a real-world setting can result in similar visual function outcome with equal safety profile.**

Method: **All patients with either age-related macular degeneration, retinal vein occlusion or diabetic macular oedema remitted to intraocular injections at a tertiary ophthalmology department in Norway between March 2015 and May 2017, were asked to participate. The participants were randomized to either nurse- or physician-administered intraocular injections of anti-vascular endothelial growth factor. The primary outcome measure was change in best-corrected visual acuity from baseline to 1-year follow-up. The mean difference in the primary outcome between the groups was analysed by a noninferiority test with a margin of three letters in disfavour of the nurse group. Adverse events were recorded.**

Results: **Three hundred and forty-two patients entered the study. Two hundred and fifty-nine completed the 1-year follow-up and were included in the study sample for the analysis of the primary outcome. Nurse-administered intraocular injections were noninferior to physician-administered injections with 0.7 and 1.6 letters gained, respectively (95% CI of the mean difference, −2.9 to 1.0; p = 0.019, one-sided *t*-test). Two thousand and seventy-seven injections and three ocular adverse events were recorded.**

Conclusion: **Task shifting of intraocular injections to nurses can be performed without increased risk to visual function. Such a task shift can alleviate the burden of performing intraocular injections in ophthalmology departments. To our knowledge, this is the first RCT on task shifting of a surgical procedure from physicians to nurses in a high-income country.**

Key words: age-related macular degeneration – intraocular injections – noninferior – nurse training – randomized controlled trial – task shifting

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Introduction

Intraocular injections of anti-vascular endothelial growth factor (anti-VEGF) improve or stabilize visual acuity in a number of prevalent previously untreatable eye diseases, of which the main are age-related macular degeneration (AMD), retinal vein occlusion (RVO) and diabetic macular oedema (DMO). The rising number of intraocular injections, expected to continue according to projections of the increase in the elderly population, (United Nations 2017) has become a challenge for ophthalmology departments worldwide. Task shifting to nurse-administered injections may alleviate this burden (Browning 2018), and observational studies indicate this might be safe and acceptable to patients (Varma et al. 2013; DaCosta et al. 2014; Michelotti et al. 2014; Simcock et al. 2014; Hasler et al. 2015). However, no randomized controlled trial (RCT) has earlier investigated whether such a task shift can be performed without increased risk to visual function. There are few RCTs on task shifting of surgical procedures and to our knowledge none from high-income settings (Fulton et al. 2011; Gile et al. 2018). To this end, a randomized controlled single-masked noninferiority study comparing the change of best-corrected visual acuity (BCVA) between the participants in the nurse and physician group was designed (Austeng et al. 2016).

Materials and Methods

Study design

Three hundred and forty-two patients were included in a prospective, randomized controlled, noninferiority study

between March 2015 and May 2016. The study had two experiment groups; physician- and nurse-administered intraocular injections. The study period for each patient was 12 ± 2 months. Participants were masked to experiment group. The study took place at the Department of Ophthalmology, St. Olavs Hospital, Trondheim University Hospital, Norway. The Norwegian national health insurance scheme has near-universal coverage of the population, and this tertiary clinic covers the population in Sør-Trøndelag County in Central Norway; about 300.000 inhabitants. Patients were remitted for treatment from the in-Hospital outpatient clinic and from 15 ophthalmologists working in other outpatient clinics, one of them situated in the neighbouring County of Møre and Romsdal in Central Norway.

Intervention

In the nurse-administered intraocular injection group, a nurse checked the patient for contraindications and prepared the patient, another nurse-administered intraocular injections, gave information about possible complications, scheduled the next appointment and documented treatment in patient records. In the physician-administered intraocular injection group, a nurse checked for contraindications and prepared the patient, and the physician was responsible for the remaining procedure. During the study period, nurses and physicians administered injections on alternate days.

Study population

Participants were recruited from the patient population of about 900 receiving anti-VEGF at the Department of Ophthalmology. Inclusion criteria were having either AMD, RVO or DMO eligible for anti-VEGF treatment. Both treatment-naïve patients and patients earlier treated with anti-VEGF fulfilled the inclusion criteria. Exclusion criteria were not being able to give an informed consent. Participants were randomly assigned to one of two experiment groups in a 1:1 ratio using a web-based algorithm provided by the Norwegian University of Science and Technology (Fig. 1). The randomization was stratified by diagnosis and by whether the patient was treatment-naïve or not.

Nurse education programme

A training programme for nurses was developed and implemented at the Department of Ophthalmology during the year prior to the start of the study (Austeng et al. 2016). Participating nurses were trained to perform intraocular injections independently managing 30 intraocular injections per day. Four out of six participating nurses were ophthalmic nurses (2 years part-time education in addition to 3 years bachelor degree in nursing), and the other two were general nurses. Prior to independent administration of injections, the achieved competence of the participating nurses was evaluated by an unbiased retinal surgeon. During the study period, the expertise of an ophthalmologist was available to participating nurses at all times.

Outcomes

The primary outcome was change in best-corrected visual acuity (BCVA) during 1 year. Best-corrected visual acuity (BCVA) was measured using the Early Treatment Diabetic Retinopathy Study (ETDRS) chart (Brown et al. 2006). Secondary outcomes were adverse events, the number of intraocular injections, the length of intervals between injections and the success of masking. The study investigators registered ocular adverse events in need of treatment. The number of intraocular injections and the length of intervals were registered during the study by the person administering the intraocular injections, and success of masking was assessed by a survey obtained by a health worker that did not participate in the study.

Sample size

The clinical noninferiority margin was set to three letters on the ETDRS visual acuity chart (Austeng et al. 2016). The sample size was calculated for a one-sided *t*-test for comparing the mean change in BCVA between nurses and physicians in a noninferiority study (SPSS Sample Power 3). Assuming the standard deviation (SD) of the mean changes would be 10 letters (Martin et al. 2012), a sample size of 140 participants in each group was needed to obtain a power of 80% with a significance level of 5%. With an estimated dropout rate of 8%, at least 152 participants had to be included in each experiment group.

Statistical analyses

Continuous variables are presented as mean (SD) or median (range) and categorical variables as frequency (%). The primary outcome variable, the mean change in BCVA during 12 ± 2 months, was compared by a one-sided *t*-test for noninferiority with a noninferiority margin of three letters in disfavour of the nurse group. The same statistical procedure was used in the analyses of the data in accordance with the intention-to-treat principle. The uncertainty in the estimated difference in mean change in BCVA was assessed by a two-sided 95% confidence interval (CI) for the difference, corresponding to a 2.5% significance level for a one-sided *t*-test. Secondary outcomes were analysed using the independent samples *t*-test, Mann–Whitney *U*-test or Fischer's exact test as appropriate. A two-way ANOVA was used for analysing differences in BCVA between participants with 0% and 1–20% of injections administered in the opposite experiment group and any interaction between this percentage and the profession. A significance level of 5% was used. All analyses were performed using the SPSS software version 23 (SPSS Inc., Chicago, IL).

Patient Involvement

The patients were involved in the design of the patients' satisfaction questionnaire. Once the study has been published, participants will be informed of the results through the departments' website and by a poster stand in the waiting room.

Ethic

All patients remitted for intravitreal injections were informed about the study. A letter was handed out, and a poster stand was set-up in the department. The patients were made aware of the purpose of the study and that they would receive injections from either a physician or nurse the year they participated in the study. Written informed consent was obtained from all participants. The study was approved by the Regional Committee of Ethics in Medical Research (2014/

1719) and adhered to the Declaration of Helsinki. The study protocol was registered at ClinicalTrials.gov (NCT02359149).

Results

Participants

Of the 342 participants included in the study, 175 were randomized to the nurse group and 167 to the physician group. Twenty four of 342 participants were excluded as they did not meet the inclusion criteria or withdrew their consent for participation (Fig. 1). The remaining 318 participants were included in the Safety Population of which one participant died and one withdrew consent to participate during the study period. This left 316 participants eligible for intention-to-treat analyses. Baseline characteristics for the intention-to-treat population are summarized in Table 1. Fifty seven participants either died, withdrew their consent, had an ocular adverse event, were excluded due to changes in treatment at the discretion of the treating ophthalmologist or due to protocol violation. The study sample for the analysis of the primary outcome included the 259 participants who completed the 1-year visit (Fig. 1). Due to the real-world setting of the present study, where a total of 2077 intraocular injections were administered and where each participant received up to 12 intraocular injections each, a proportion of injections were unfortunately administered in the opposite experiment group, that is from the other profession. This could happen if a participant randomized to the physician group turned up for treatment on a day when injections were administered by nurses, injections being administered to each experiment group on alternate days. For ethical reasons participants were treated when they came, even though this resulted in a protocol violation. Protocol violation was defined as having more than 20% of injections administered in the opposite experiment group. Fifty eight participants received injections in the opposite experiment group, 18 of these >20% of injections. These were excluded in the primary outcome analyses of the study sample. To investigate whether injections administered in the opposite experiment group influenced the results, participants in the study sample were categorized into two groups; participants with 0% (n = 222) or 1–20% (n = 37) of the injections administered in the opposite experiment group. Only a small and non-significant differences between these two groups were found with respect to the mean change in BCVA (mean difference, 1–20% vs 0%: 1.7 letters, 95% CI: −1.1 to 4.5, p = 0.238), when adjusting for profession.

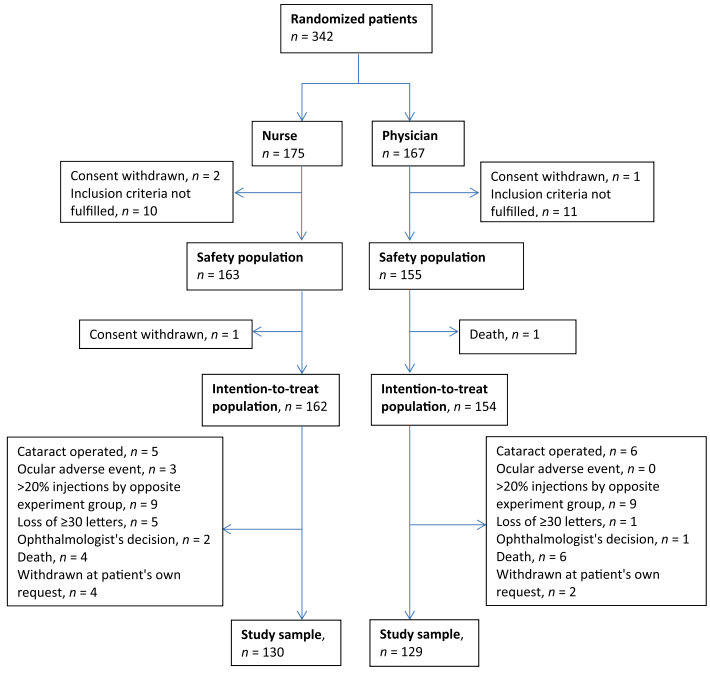

Fig. 1. Flow chart.

Primary outcome

Nurse-administered intraocular injections were noninferior to physician-administered injections in the primary outcome analyses with regards to difference in change in BCVA at 1 year (Fig. 2). The mean change from baseline BCVA was 0.7 and 1.6 letters in the nurse and physician group, respectively (95% CI of the difference in mean change: −2.9 to + 1.0; p = 0.019, one-sided t-test for noninferiority), such that the lower limit of the 95% confidence interval exceeded the noninferiority limit of −3 (Table 2). In the intention-to-treat analyses, the mean change from baseline BCVA was, respectively, −0.1 and 1.7 letters in the nurse and physician group (95% CI of the difference in mean change: −5.0 to −0.4; p = 0.403, one-sided t-test for noninferiority). Eleven patients had cataract surgery during the study period, five in the nurse and six in the physician group, with a visual gain of 37 and 105 letters in the two groups.

Secondary outcomes

During the study period (March 2015 - May 2017), 2077 intraocular injections in 2077 eyes were administered; 1076 by nurses and 1001 by physicians. The incidence of endophthalmitis was 0.5‰ per injection. Eleven participants died during the study period; 4 in the nurse and 7 in the physician-administered injection group. Ocular adverse events in three eyes of three different participants were registered (Table 3). Six participants lost ≥30 letters during the study and five of these belonged to the nurse-administered injection group.

There was little evidence of a difference between the nurse and physician group regarding the mean number of

Table 1. Baseline patient characteristics for the intention-to-treat population

	Nurse-administered intraocular injections (n = 162)	Physician-administered intraocular injections (n = 154)
Diagnosis		
AMD, earlier treated	104 (64.2)	103 (66.9)
AMD, treatment-naïve	3 (1.9)	1 (0.6)
RVO, earlier treated	39 (24.1)	36 (23.4)
RVO, treatment-naïve	1 (0.6)	0 (0.0)
DME	15 (9.3)	14 (9.1)
Medicine		
Bevacizumab	93 (57.4)	85 (55.2)
Ranibizumab	55 (34.0)	53 (34.4)
Aflibercept	14 (8.6)	16 (10.4)
Eye		
OD	93 (57.4)	83 (53.9)
OS	69 (42.6)	71 (46.1)
Sex		
Female	87 (53.7)	75 (48.7)
Male	75 (46.3)	79 (51.3)
Age (years)		
Median (range)	76.0 (37–93)	76.5 (31–93)
Mean (SD)	75.4 (10.0)	75.4 (10.7)
Age category		
<50 years	2 (1.2)	4 (2.6)
50–59 years	11 (6.8)	8 (5.2)
60–69 years	29 (17.9)	27 (17.5)
70–79 years	56 (34.6)	50 (32.5)
80–89 years	57 (35.2)	57 (37.0)
≥90 years	7 (4.3)	8 (5.2)
BCVA		
Median (range)	72.0 (5–85)	71.0 (8–85)
Mean (SD)	66.6 (16.4)	66.1 (16.7)
BCVA category and Snellen equivalent		
≤37 letters, ≤20/200	12 (7.4)	13 (8.4)
38–52 letters, 20/160–100	20 (12.3)	10 (6.5)
53–67 letters, 20/80–50	31 (19.1)	38 (24.7)
68–77 letters, 20/40–32	54 (33.3)	59 (38.3)
≥78 letters, ≥20/25	45 (27.8)	34 (22.1)

Values are n (%) unless otherwise specified.
Abbreviations: AMD = age-related macular degeneration, BCVA = best correct visual acuity, DME = diabetic macular oedema, OD = oculus dexter, OS = oculus sinister, RVO = retinal vein occlusion, SD = standard deviation.

injections (mean 6.6 and 6.8, respectively; 95% CI of the difference: −0.8 to 0.6, p = 0.702) or the mean number of weeks between injections; (10.8 and 10.8, respectively; 95% CI of the difference: −2.4 to 2.4, p = 0.572) during the study period.

Masking

Participants were masked to experiment group and in order to achieve this physicians and nurses dressed in similar hospital clothing, used surgical hood and masks and were instructed to introduce themselves by name only and not profession. We used survey data from 185 participants (185 of 259, 71%) to study the success of masking. Thirty seven participants who had received injections from the opposite experiment group were excluded. Fifteen participants treated with anti-VEGF in both eyes were also excluded since they received injections from the other profession in the non-study eye. Survey data on another 22 participants were missing. When asked if they assumed to belong to the nurse or physician group, 60.5% answered the opposite experiment group or that they did not know to which group they belonged.

Discussion

This is the first RCT to demonstrate that a task shift, with the potential to ease the burden of intraocular injections on health care systems worldwide, may be performed without increased risk to visual function. The strengths of the study are that it was performed in a real-world setting and included a heterogeneous population of participants recruited from a population with near-universal health insurance coverage. The result is therefore highly generalizable and may be applied to alleviate the burden of intraocular injections on ophthalmology departments. To the best of our knowledge, this is the first RCT that investigates the feasibility of task shifting of a surgical procedure in a high-income country.

In the present study, a noninferiority limit of three letters was chosen. This was considered to be the lowest margin of clinical interest since most of the included participants were in stable phase of their disease. Three letters are a stricter margin than in studies comparing effects of different anti-VEGF drugs and treatment strategies (Martin et al. 2011; Chakravarthy et al. 2012; Kodjikian et al. 2013; Berg et al. 2015). In the primary outcome analyses of the study sample, patients with cataract surgery and patients who developed geographic atrophy and lost more than 30 letters were excluded. This is consistent with the previously mentioned studies. The visual gain after cataract surgery was not as great in the nurse as in the physician group. More patients who belonged to the nurse than the physician group lost more than 30 letters due to geographic atrophy, part of AMD's natural history. As the intention-to-treat analyses included both patients with cataract surgery and patients who developed geographic atrophy, the confidence interval was naturally wider, but remained above the commonly used threshold of five letters, corresponding to a line on the eye chart (Martin et al. 2011; Kodjikian et al. 2013; Berg et al. 2015).

The nurses in the present study were trained to perform the intraocular injection procedure according to best practice. We observe that this practice differs from other task shifting studies, in which nurses work in parallel with physicians rather than independently and exclude patients not able to cooperate, having concomitant eye disease, general disabilities or previous complications (Hasler et al. 2015). Training according to best practice is a strength of the study since nurses that

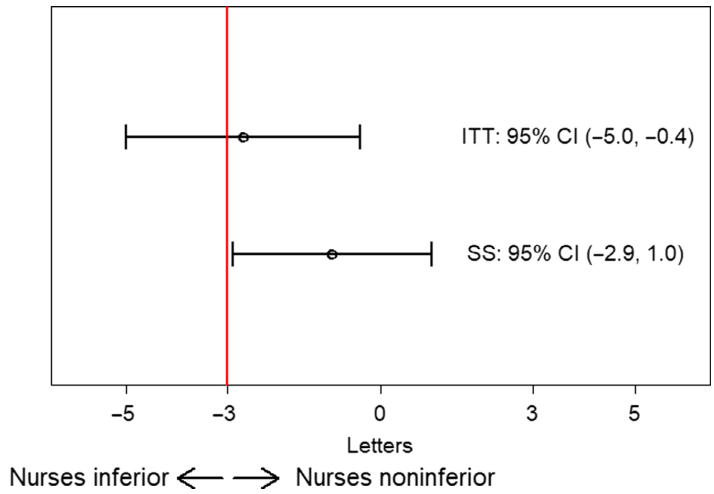

Fig. 2. Mean difference in best-corrected visual acuity (BCVA) between nurses and physicians. The circle indicates the mean difference in BCVA, and the bars indicate the 95% confidence interval in the intention-to-treat (ITT) population and in the study sample (SS).

are trained to work truly independently will be a greater resource for ophthalmology departments.

Since complications would have to be very severe if they were to be reflected on a mean best-corrected visual acuity change, we studied the relative distribution of ocular adverse events such as lens damage, retinal detachment and endophthalmitis. The incidence of endophthalmitis (0.5‰ per injection) was similar to the incidence in the Comparison of Age-related Macular Degeneration Treatments Trial (Martin et al. 2011) where all injections were physician-administered and also to observational studies from Denmark and the UK with 12 000 nurse-administered intraocular injections each (Simcock et al. 2014; Hasler et al. 2015). No lens damage or retinal detachments were observed during the study.

For the first time, we report that task shifting of intraocular injections may be performed without increased risk to visual function. In Norway, there are no national guidelines for who should perform intraocular injections and what training is required before one can perform operations independently. St. Olavs Hospital has created a comprehensive training programme for nurses that we have currently tested. An annual continuing education and re-certification of nurses who perform intraocular injections have also been introduced, to ensure good and consistent treatment. Every day, a responsible physician is available for help when needed, and with these measures, we believe it is ethically justifiable to transfer the task to nurses. Future studies should investigate the applicability of such a training programme in a setting without universal health care

Table 2. Observed values for the primary and secondary outcomes and results from the statistical analyses

	Nurse-administered intraocular injections (n = 130)	Physician-administered intraocular injections (n = 129)	Mean difference	95% CI of mean difference	p-value
Change from baseline BCVA			−0.9	−2.9 to 1.0	0.019*
Median (range)	0.5 (21 to 47)	1.0 (−22 to 20)			
Mean (SD)	0.7 (8.3)	1.6 (7.6)			
Change from baseline BCVA					
Increase of ≥15 letters	4 (3.1)	7 (5.4)			
Increase of ≥5 letters	35 (26.9)	37 (28.7)			
Change of ≤4 letters	62 (47.7)	62 (48.1)			
Decrease of ≥5 letters	25 (19.2)	19 (14.7)			
Decrease of ≥15 letters	4 (3.1)	4 (3.1)			
BCVA at 1 year					
Median (range)	73.0 (7–85)	73.0 (5–85)			
Mean (SD)	68.0 (17.2)	68.8 (16.9)			
Mean no. of treatments (SD)	6.64 (2.8)	6.78 (2.9)	−0.1	−0.8 to 0.6	0.702
Mean no. of weeks included (SD)	51.7 (4.8)	51.6 (4.3)	0.1	−1.0 to 1.2	0.909
Treatment interval (weeks)			0.0	−2.4 to 2.4	0.572**
Median (range)	8.4 (4–55)	7.8 (4– 59)			
Mean (SD)	10.8 (9.7)	10.8 (9.8)			
Treatment Interval (weeks)					
≤5	24 (18.5)	28 (21.7)			
6–10	73 (56.2)	73 (56.6)			
11–15	20 (15.4)	11 (8.5)			
≥16	13 (10.0)	17 (13.2)			

Values are number (%) unless otherwise specified. p values are calculated from independent samples t-test, unless *is specified (p-value from one-sided t-test for noninferiority) or **is specified (Mann–Whitney U-test).
Abbreviations: BCVA = best correct visual acuity, SD = standard deviation.

Table 3. Adverse events in the safety population

Adverse event	Nurse (n = 163)	Physician (n = 155)
Death	4 (2.5)	7 (4.5)
Cardiovascular disease	2 (1.1)	3 (1.9)
Cancer	1 (0.6)	2 (1.3)
Haematological disease	1 (0.6)	0
Reason unknown	0	2 (1.3)
Ocular adverse events[†]	3 (1.8)	0
Endophthalmitis	1 (0.6)	0
Uveitis	1 (0.6)	0
Pigment epithelial rupture	1 (0.6)	0
Loss of ≥30 letters	5 (3.1)	1 (0.6)

Data are number of patients (%).
[†]No patient with lens damage, retinal detachment or intraocular haemorrhage was observed.

coverage and in low-income countries. Furthermore, the possible risks of task shifting other surgical procedures should be investigated in the same rigorous manner prior to implementation in clinical practice.

References

Austeng D, Morken TS, Bolme S, Follestad T & Halsteinli V (2016): Nurse-administered intravitreal injections of anti-VEGF: study protocol for noninferiority randomized controlled trial of safety, cost and patient satisfaction. BMC Ophthalmol **16**: 169.

Berg K, Pedersen TR, Sandvik L & Bragadottir R (2015): Comparison of ranibizumab and bevacizumab for neovascular age-related macular degeneration according to LUCAS treat-and-extend protocol. Ophthalmology **122**: 146–152.

Brown DM, Kaiser PK, Michels M, Soubrane G, Heier JS, Kim RY, Sy JP & Schneider S (2006): Ranibizumab versus verteporfin for neovascular age-related macular degeneration. N Engl J Med **355**: 1432–1444.

Browning DJ (2018): Physician assistants and nurse practitioners in ophthalmology-has the time come? Am J Ophthalmol **186**: ix–xi.

Chakravarthy U, Harding SP, Rogers CA, Downes SM, Lotery AJ, Wordsworth S & Reeves BC (2012): Ranibizumab versus bevacizumab to treat neovascular age-related macular degeneration: one-year findings from the IVAN randomized trial. Ophthalmology **119**: 1399–1411.

DaCosta J, Hamilton R, Nago J, Mapani A, Kennedy E, Luckett T, Pavesio C & Flanagan D (2014): Implementation of a nurse-delivered intravitreal injection service. Eye (Lond) **28**: 734–740.

Fulton BD, Scheffler RM, Sparkes SP, Auh EY, Vujicic M & Soucat A (2011): Health workforce skill mix and task shifting in low income countries: a review of recent evidence. Hum Resour Health **9**: 1.

Gile PP, Buljac-Samardzic M & Klundert JV (2018): The effect of human resource management on performance in hospitals in Sub-Saharan Africa: a systematic literature review. Hum Resour Health **16**: 34.

Hasler PW, Bloch SB, Villumsen J, Fuchs J, Lund-Andersen H & Larsen M (2015): Safety study of 38,503 intravitreal ranibizumab injections performed mainly by physicians in training and nurses in a hospital setting. Acta Ophthalmol **93**: 122–125.

Kodjikian L, Souied EH, Mimoun G, Mauget-Faysse M, Behar-Cohen F, Decullier E, Huot L & Aulagner G (2013): Ranibizumab versus bevacizumab for neovascular age-related macular degeneration: results from the GEFAL noninferiority randomized trial. Ophthalmology **120**: 2300–2309.

Martin DF, Maguire MG, Ying GS, Grunwald JE, Fine SL & Jaffe GJ (2011): Ranibizumab and bevacizumab for neovascular age-related macular degeneration. N Engl J Med **364**: 1897–1908.

Martin DF, Maguire MG, Fine SL et al. (2012): Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. Ophthalmology **119**: 1388–1398.

Michelotti MM, Abugreen S, Kelly SP et al. (2014): Transformational change: nurses substituting for ophthalmologists for intravitreal injections - a quality-improvement report. Clin Ophthalmol **8**: 755–761.

Simcock P, Kingett B, Mann N, Reddy V & Park J (2014): A safety audit of the first 10 000 intravitreal ranibizumab injections performed by nurse practitioners. Eye (Lond) **28**: 1161–1164.

United Nations, Department of Economic and Social Affairs, Population Division (2017): World Population Prospects: The 2017 Revision, Key Findings and Advance Tables (ESA/P/WP/248). New York, NY: United Nations. https://esa.un.org/unpd/wpp/Publications/Files/WPP2017_KeyFindings.pdf. (Accessed on 2018.10.19 2018).

Varma D, Lunt D, Johnson P & Stanley S (2013): A novel approach to expanding the role of nurses to deliver intravitreal injections for patients with age-related macular degeneration. Int J Ophthalmic Pract **4**: 68–74.

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Bolme, Morken, Follestad and Austeng involved in conception and design. Bolme, Morken, Follestad, Sørensen and Austeng analysed and interpreted the data:. Bolme, Morken and Austeng collected the data. Bolme, Morken, Follestad, Sørensen and Austeng have overall responsibility.

Paper III

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RESEARCH Open Access

Task shifting of intravitreal injections from physicians to nurses: a qualitative study

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Abstract

Background: Intravitreal injections of anti-vascular endothelial growth factor are high-volume procedures and represent a considerable workload on ophthalmology departments. Several departments have tried to meet this increase by shifting the task to nurses. To maintain high-quality patient care, we developed a training program for nurses that certifies them to administer injections. This qualitative study aimed to evaluate whether the nurses were confident and in control after participating in the training program and whether they were satisfied with the training and the new task.

Methods: Between 2014 and 2018, 12 registered nurses were trained in a tertiary hospital in central Norway. All the nurses were interviewed, either individually ($n = 7$) or in a group ($n = 5$). We analysed the interviews using Graneheim and Lundman's qualitative content analysis.

Results: Eight subthemes were clustered within four main themes: 1) procedure and challenges, 2) motivation, 3) cooperation and confidence, and 4) evaluation. The nurses felt confident and in control when administering injections but experienced moments of insecurity. The new task gave the nurses a sense of achievement, and they highlighted improvement of patients' lives as positive. A greater level of responsibility gave the nurses pride in their profession. They had suggestions that could improve training efficiency but were overall satisfied with the training program.

Conclusions: Our study showed that the nurses were satisfied with the training and that learning a new task led to higher self-esteem and increased respect from patients and colleagues. Suggestions to improve the training were identified; these should be considered before implementation by other departments.

Keywords: Task shift, Intravitreal injections, Interview, Nurse, Qualitative

Introduction

Intravitreal injections (IVI) with anti-vascular endothelial growth factor (anti-VEGF) are an efficient treatment for several retinal diseases [1], and the use of anti-VEGF has had an exponential growth over the last two decades [2]. The treatment has not only had a major impact on eye health, it has also changed the division of labour in ophthalmology departments, as many have shifted the task over to nurses [3]. The basis for this is that a vertically staged task shift, with tasks transferred from a higher level of competence to a lower one, is a way to better utilize resources [4, 5]. The role of nurses is evolving [6, 7], and advanced nursing practice has enabled task shifting from physicians to nurses [8, 9]. However, it is still not common for nurses to perform surgical procedures independently. Therefore, nurses who administer intravitreal injections expand the role of nursing into a new area.

In 2019, with the first randomized controlled study, we were able to show that nurse-administered injections are just as safe and have the same positive effect as injections given by physicians [10]. Based on these results, we

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established a nurse-driven injection clinic at the University Hospital in Trondheim, Norway.

A successful nurse-driven injection clinic relies on satisfied nurses, as increased well-being raises the quality of the work [11] and leads to satisfied patients [12–14].

Job satisfaction among nurses is a recurring theme in the literature [15–17], but studies of nurses' satisfaction concerning task shifting and training are scarce. To identify the thoughts and experiences of nurses certified to administer IVIs, we conducted a qualitative study. The aim was to explore their level of confidence and control after completing the training program and their satisfaction with the new task.

Material and methods

Design and sample

This qualitative study had an inductive descriptive design, with semi-structured interviews conducted individually and in a focus group. The study took place at a tertiary hospital covering about 750,000 inhabitants in Central Norway. We developed a training program in our ophthalmology department to certify nurses to administer IVIs independently. The final version of the training program lasts 10 days and comprises workshops, wet lab, and observation before nurses perform injections (Fig. 1).

From April through August 2016, seven out of a total of 12 nurses were interviewed individually. The idea was to use a total sampling strategy, and initially, only seven nurses were trained to administer injections. Later, five more nurses were trained, and these nurses were interviewed in a focus group in March 2019. Different interview approaches were chosen to enrich the data [18, 19]. The interviews lasted between 14 and 50 min. The characteristics of the participants and type of interview are given in Table 1.

The nurses were approached and asked face-to-face to participate by the first author, and no one declined.

Data collection and analysis

The interviewer was the first author (SB), a female PhD student and part-time resident at the Department of Ophthalmology with no former interview experience. She attended a PhD course in qualitative research while performing the interviews and was trained and supervised by the last author, an experienced researcher in qualitative method. The interviews were carried out in the ophthalmology department. A semi-structured interview guide was developed prior to the individual interviews based on the research questions, previous knowledge, and literature on the task-shift concept. The interview guide was piloted in the interview with the first nurse and later used without revision. Before the focus group interview was conducted, the interview guide was further developed, based on the experience from the individual interviews and to adjust to the anticipated group dynamic. This resulted in fewer and more open questions. In the focus group, the first author was the moderator and the last author (KHG), who had never met the participants before, was an observer. The interviews were taped using a voice recorder and transcribed verbatim by the first author. Field notes on contextual information, thoughts, mood, and facial expressions during the interview were taken by the first author. Participants were not given the opportunity to give feedback on the transcripts or findings.

Both the individual interviews and the focus group interview were analysed using qualitative content analysis with an inductive approach, according to Graneheim and Lundman [20].

The first author read all the raw data several times to gain an overview. Then, the process was as follows: (1) the first step of coding was finding **units of meaning**; (2) the units of meaning were then **condensed** into fewer words; (3) the condensed units of meaning were clustered into preliminary **code groups**; (4) related codes were ordered into broader, higher-ordered **subthemes**; and (5) subthemes with similar meanings were grouped together at the highest level, called '**themes**,' which the first and last author discussed and agreed on. The consistency of major themes was ensured by comparing data from the individual interviews and focus group interview. The analysing process resulted in a coding three, illustrated in Table 2 which gives an example of the units of analyses based on one of the branches. The second author (DA), a consultant ophthalmologist, contributed by confirming the final analysis and discussing which parts of the interviews would be highlighted. The analysing process was performed with two different tools. First, in 2019, the analysis was done with paper and marker pen. It was repeated a year later, after a course in qualitative research about the analysing process, using the data program NVivo 12, a computer-assisted qualitative data analysis software (QRS International). This approach was chosen to check whether the second analysing method gave the same results and to achieve rigor [21]. During the process, there was continual discussion between the first and last author, which brought valuable perspectives as the last author is an experienced qualitative researcher. The amount of data was considered saturated as the interviews had sufficient information power [22]. The consolidated criteria for reporting qualitative research (COREQ), a 32-item checklist for interviews and focus groups, was adhered to in the reporting of this study [23].

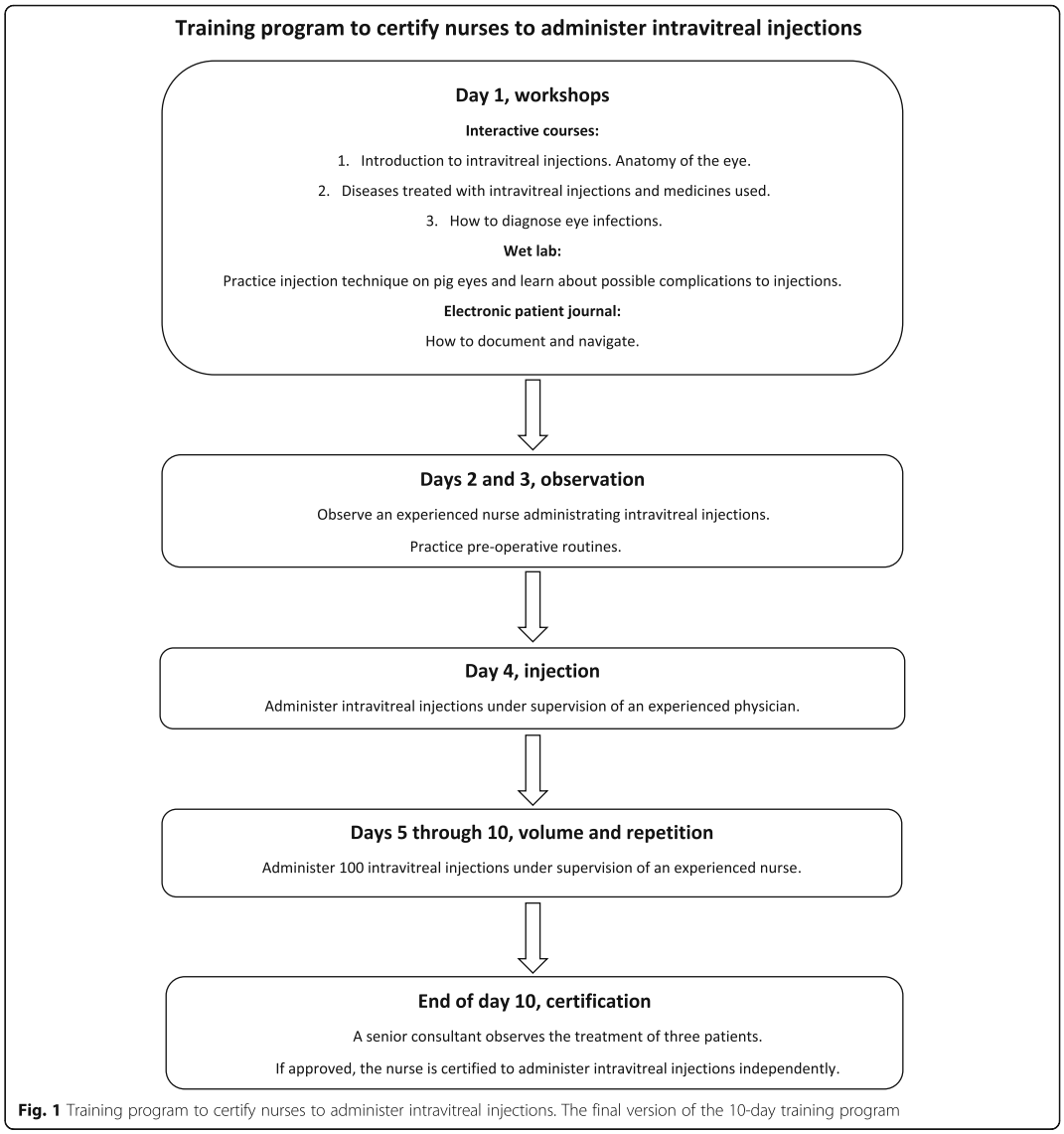

Fig. 1 Training program to certify nurses to administer intravitreal injections. The final version of the 10-day training program

Results

The 12 participants, one male, had a wide age span ranging from 26 to 60 years. Their educational background was evenly distributed at bachelor's and master's levels. The nurses' experience from clinical practice in ophthalmology ranged from two to 28 years, with a mean of eight years.

Eight subthemes emerged from the data, clustered in four main themes: 1) procedure and challenges, 2) motivation, 3) cooperation and confidence, and 4) evaluation. The themes and the eight subthemes are illustrated with quotations in the text and shown in Table 3.

Theme 1: procedure and challenges

The nurses stated they felt confident at different stages in their training, and the ones with the most experience soon saw the injections as a routine instead of a challenge. Regardless of previous experience, the nurses had moments of insecurity.

Table 1 Characteristics of the participants

ID	Age at time of interview	Educational information	Years of ophthalmological practice at time of interview	Type of Interview
N1	31–40	Master	> 6	Individual
N2	21–30	Master	1–3	Individual
N3	31–40	Master	4–6	Individual
N4	> 40	Master	> 6	Individual
N5	21–30	Bachelor	1–3	Individual
N6	21–30	Master	4–6	Individual
N7	> 40	Master	> 6	Individual
N8	> 40	Bachelor	4–6	Focus group
N9	> 40	Bachelor	1–3	Focus group
N10	31–40	Bachelor	1–3	Focus group
N11	21–30	Bachelor	4–6	Focus group
N12	31–40	Bachelor	4–6	Focus group

Routine versus variation

The nurses expressed that learning a new task gave them increased variety.

> "You get a larger repertoire and the work gets more varied." (N7).

The group of nurses disagreed on this question, and the ones with the most experience said that the new task quickly became a routine. One nurse had hoped for a greater challenge and was disappointed.

> "Every patient can be a challenge in themselves, but I will not claim to have large challenges in the injection room. It's more of a routine." (N1).

Challenges

Assessing whether patients had an eyelid infection was mentioned as a common source of insecurity. It was especially challenging if the patient came directly from a physician examination reporting that eyelid infection was not present while the nurse was convinced of the opposite.

> "A patient came from examination and the journal note written by the physician said that there were traces of blepharitis, but that it was okay to inject. This leaves us nurses a bit insecure. If it is blepharitis we should not inject, and this is what we have been trained to think. And at the end, it is us who injects the needle into the eye. Of course, it is the physician's responsibility because he says in the note that the injection was approved, but we end up having a bad feeling when we believe it is blepharitis. …" (N10).

Administering injections also brings greater responsibility, and the risk of doing something wrong can lead to insecurity. Patients not cooperating for various reasons was mentioned as challenging. One nurse expressed feeling insecure when having to take responsibility for a patient who could not fully cooperate:

> "Yesterday we had a patient who claimed she never had received an injection in her left eye and today would be her first time … and this was kind of

Table 2 Examples of the analysis

Meaning units	Condensed meaning units	Code groups	Subthemes	Theme
I feel like I do a better job when I'm working at the injection clinic than when I work in the outpatient clinic. I feel I make a difference when I administrate injections.	Really achieving something good when working at the injection clinic	Achieve something good	To make a difference	Motivation
When I'm in the injection room, I'm more aware of my blood sugar. In the outpatient clinic, we measure visual acuity and eye pressure and I can feel my belly rumbling, but it's okay, we keep going. But if I'm in the injection room, I'm more aware of that it affects me negatively and that I have to eat something before I continue.	Have to be at the top of your game	Capability	Responsibility and respect	Motivation
I find that we are given a greater confidence in relation to a so-called physician assignment being given to us nurses, which I like very much, because it shows that people also have faith in nurses.	Given greater confidence from the department	Increased respect	Responsibility and respect	Motivation

Table 3 Description of themes and subthemes identified through the interviews

Main themes	Procedure and challenges	Motivation	Cooperation and confidence	Evaluation
Subthemes	Routine versus variation	Responsibility and respect	Working as a team	Continual learning
	Challenges	To make a difference	Confidence	Adjustments

injection number 24 in that eye.... They (the patients) are growing old, some are a bit forgetful." (N9).

Another nurse explained the danger of doing a patient harm:

"Of course I am happy when the patients get to keep their vision, but … it is no fun if you end up puncturing the whole eye, causing a retinal detachment, all because the patient could not lie still." (N3).

Theme 2: motivation

Traditionally, administering IVIs is a physician's task. Mastering this task gave the nurses a sense of pride and a feeling of contributing to solving some of the department s resource challenges. The nurses also valued being more involved in the treatment of patients.

Responsibility and respect

All of the 12 nurses agreed that the new task gave them increased respect from both patients and colleagues. The expanded repertoire of tasks also increased their responsibility, which the nurses felt sharpened them and made them better nurses. One nurse explained that she had to take better care of herself to be at her best:

"When I'm in the injection room, I'm more aware of my blood sugar. In the outpatient clinic, we measure visual acuity and eye pressure and I can feel my belly rumbling, but it's okay, we keep going. But if I'm in the injection room, I'm more aware of that it affects me negatively and that I have to eat something before I continue." (N8).

Another nurse said that nurses taking over new tasks and increased responsibility is the future:

"You feel the responsibility, but it's a good kind of responsibility. This is the direction the world goes; we (the nurses) must do more and more 'physician tasks'. It's like this everywhere, with everything. It is a good development because we become more skilled professionally." (N12).

The nurses appreciated learning a new task. One nurse emphasized that it was a privilege being certified to give injections:

"I get to be a part of something unique and special." (N5).

Another nurse accentuated that learning a new procedure gave higher self-esteem:

"I feel that my skills have expanded. I learned a new procedure and mastered a new situation." (N7).

To make a difference

The nurses expressed they accomplished something good by contributing to raising patients' quality of life, and saving the department resources came as a bonus. One nurse explained why she felt more important when she was certified to give injections:

"I feel I do a better job when I am in the injection clinic than when I am doing other tasks. I feel like I make a difference when I administer injections." (N5).

Another nurse highlighted the importance of helping patients have a better quality of life:

"I think it is exciting when I hear good news about the patient's vision, because some patients actually get better visual acuity, and I think this is great … or at least they keep their visual acuity. It is fantastic to hear that they have better vision or that they stopped seeing skewed lines. I think this is very rewarding." (N4).

Theme 3: cooperation and confidence

The nurses agreed that collaborating with fellow nurses as a team could be both rewarding and demanding. A stable nursing team would provide safety for patients as they would not have to meet a new physician at every appointment. The nurses also agreed that a well-designed team of nurses could do a better job than the physicians. The nurses expressed that they felt confident administering injections after they had gained some experience.

Working as a team

Some days were busier than others, with over 30 patients receiving treatment on the same day. On days like these, the nurses highlighted the importance of working with people that they had good chemistry with. One nurse explained:

> "It's mostly positive working as part of a team, but sometimes it is not. … It depends on your energy level that day and what colleagues you cooperate with."(N10).

An advantage of teamwork was the opportunity to seek support if something went wrong. One nurse explained what she would do if she ran into problems:

> "We are very good talking things through, we nurses. If some things are difficult, I discuss it with my colleagues." (N7).

Confidence

Several of the nurses mentioned that a nurse team worked more efficiently than the physicians because they were more focused on the task. In the focus group interview, the group dynamic made this especially clear, as the nurses agreed that their skills were as good as the physicians' when it came to injecting anti-VEGF intravitreally. One nurse put it concisely:

> "The point is that we (the nurses) do it better than the physicians." (N12).

Another nurse added with a smile:

> "The physicians feel their role is more serious; they don't go along with the joke and the good vibe in the room. We nurses can have fun with the patient, but for the physicians it's just a serious procedure." (N11).

Theme 4: evaluation

All the nurses expressed they felt safe administering injections after they had gained some experience. They also appreciated that the training was voluntary and that they could spend the time they needed. They all reflected on how the training program and the injection clinic could be improved. The nurses feedback resulted in a shorter and more intensive training program.

Continual learning

The nurses were overall satisfied with the training program. Some wished for continual learning with frequent lectures on relevant topics, more training in filling out the outpatient clinic form, and regular controls of the injection technique. One nurse stated:

> "I would love to get a refresher along the way; I think that would be useful. Some theoretical repetition of blepharitis, for instance, and the rules when the patients need to postpone their injections. But the injection itself I think I have had plenty of training in." (N6).

The nurses also mentioned that it would have been satisfying to learn more about both the theory of ophthalmic diseases and the diagnostics, for reasons including two that came up repeatedly—to satisfy own curiosity and to be able to answer questions from patients:

> "It's really as easy as learning to handle the slit lamp properly. Understand what it is you see. It's easier to explain it to the patient when you have seen it yourself. They ask a lot. How does it look? Why is it like that?" (N3).

The nurses reported that patients often asked about their diagnosis and prognosis. Not being able to provide the answer, but having to refer them to a physician who could, took away some of that pride the nurses felt running the clinic.

> "It's a bit discouraging when the patients ask a lot of questions that I cannot answer; all I can say is that they should ask again in three months at your next appointment with the physician." (N5).

Adjustments

The nurses preferred another nurse as a supervisor rather than a physician.

> "I believe it's much better when a nurse is the one giving instructions. I feel they think more about everything. What does the nurse in training need to know, observe, and try, and what progression should the nurse have?" (N11).

The nurses had opinions on what would make the day run smoothly. Electronic patient journals with missing information and too many patients on the injection list could cause stress. When they had to clarify information with a physician, this was time-consuming, as explained by one nurse:

> "The physician will talk to the patient and time flies, and I have already prepared the patient and I am standing there waiting with the syringe in my hand.

Several times I think that I must give the patient anesthetic eyedrops all over again." (N10).

Giving one dedicated physician responsibility for answering questions was something all the nurses wanted. One nurse preferred shorter time between patients leading to more efficiency, but all the others favored the opposite. One of the nurses who wished for more time said:

"I want to talk more with the patients." (N5).

Discussion

Our study showed that the nurses trained to administer IVIs overall were satisfied with the training and reported that learning a new task led to higher self-esteem and increased respect. The nurses felt confident and in control when administering injections, although they experienced moments of insecurity. They had several suggestions on how to improve the training.

The training program was still under development while the first nurses were trained, and they could decide the progression of the training themselves. It became clear that a vertical task shift required changes in role identity and mindset [24]. As the first group of nurses embraced the new task, the nurses to follow likely adopted the new role identity and the new way of thinking, making training less time-consuming.

Good collaboration with colleagues is important because it makes the workday easier. Traditionally, physicians and nurses handle new challenges differently. While medical education highlights independence, responsibility, and confidence to rely on oneself, nursing education is more focused on care, communication, and cooperation [25]. If something proved difficult, the nurses handled this by discussing the problem with a fellow nurse. This team-oriented culture can encourage the nurses to take on untraditional responsibilities and increase the chances of a successful task shift [24]. The nurses experienced that they had to rely on teamwork to a greater extent in the injection room, which led to a new way of cooperating with fellow nurses, in contrast to the more traditional physician–nurse team.

The nurses mentioned several factors that motivated them to complete the training, including having a more varied workweek and making a difference in patients' lives. These factors have previously been reported to influence the motivation to learn [26–28]. Another motivator was the pride and respect the nurses felt in mastering a new task. Taking responsibility for running the injection clinic may have initiated a desire in the nurses to learn more about ophthalmic diseases. Having to disappoint patients who have questions and refer them to a physician for answers may have taken away some of that pride. A study concluded that patients were less satisfied with the information provided by nurses about disease and prognosis [29].

The nurses mentioned eyelid infections as a source of insecurity and a common reason to turn to a physician for advice. Shifting tasks could lead to diffuse limits of liability [5]. Who will have the legal liability if malpractice occurs? This question is one concern considering the ethics and legislation around task shifting [30]. It may therefore be important to establish pre-defined limits of liability prior to a task shift.

The nurses in our study gained self-esteem and believed the way they administered the injections kept the patients calm and comfortable. Patient satisfaction has been recognized as an important factor for quality of care [31, 32]. The literature has shown that patients are satisfied with nurses delivering IVIs [33]. It is conceivable that shifting the administration of the injections to nurses ensures better continuity and that this makes the patients feel more satisfied [34, 35].

The suggested alterations to the training program that emerged during the interviews gave the department an opportunity to improve and adjust the training and the injection clinic [36]. As a result, a specific physician was designated to answer questions from the nurses. As more nurses were trained, it became clear that 10 days of intensive training was sufficient. At their own request, the nurses have a re-certification once a year to ensure quality and adherence to the procedures.

Methodological considerations

This study adhered to the COREQ guidelines, which ensured transparency and trustworthiness of the findings and the interpretation of the data [23]. Our study included both individual interviews and a group interview. The safety and confidentiality of an individual interview differs from the dynamics in a focus group interview, where a common agreement will be highlighted [18, 19]. We experienced that the group dynamics brought broader perspectives and revealed new aspects of the training and the new task. The combination of interview methods strengthened the study, and the combination of different analysing tools visualized the data from a range of perspectives [21]. Further, a total sampling strategy was used, and none of the participants declined.

Conducting interviews came from a desire to learn from the trained nurses because an interview can give in-depth information on participants' attitudes, thoughts, and actions [37]. This qualitative study is an important supplement to our previous RCT [10]. This mixing of methods can act complementarily and provide a richer and deeper understanding of the task shift concept [38], and it is in line with recommendations for training needs assessment [36].

Recruiting only highly motivated nurses who volunteered may have introduced a selection bias in that the most motivated nurses learn faster and may evaluate the training program in a more positive way [39]. However, utilizing dedicated and motivated nurses was most likely a criterion for success.

The first author had limited experience with the interview technique, and being inexperienced can make it more challenging to avoid being influenced by one's own experience in interpreting the data [18]. However, the last author monitored the focus group interview and worked closely with the first author in interpreting the transcripts. Working at the department, the participants might have had a personal interest in the injection clinic becoming a success, which could have biased the feedback. On the other hand, the nurses seemed very communicative and gave both positive and negative feedback. The interviews were relatively short. However, the interviewer was familiar with the context, setting and participants, which ensured prolonged engagement, an important criterion for rigor in qualitative research [40].

Conclusions

The nurses certified to inject anti-VEGF intravitreally expressed satisfaction with the training and the new task. Suggestions to improve the training were identified, which should be considered before it is implemented in other departments.

Abbreviations

Anti-VEGF: anti-vascular endothelial growth factor; DA: Dordi Austeng, second author; IVI: intravitreal injections; KHG: Kari Hanne Gjeilo, last author; SB: Stine Bolme, first author; RCT: randomized controlled trial

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Authors' contributions

Conception and design: SB, DA, KHG. Analysis and interpretation: SB, DA, KHG. Data collection: SB, KHG. Overall responsibility: SB, DA, KHG. The author(s) read and approved the final manuscript.

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Availability of data and materials

The dataset analysed during the current study is available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study followed the declaration of Helsinki [41] and was approved by the Regional Committee for Medical and Health Research Ethics, South-Eastern Norway (2014/1719). Written informed consent was obtained from the nurses. To ensure confidentiality, participants are not described in detail.

Consent for publication

Not applicable.

Competing interests

The authors declare no financial and non-financial competing interests.

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References

1. Falavarjani KG, Nguyen QD. Adverse events and complications associated with intravitreal injection of anti-VEGF agents: a review of literature. Eye (Lond). 2013;27:787–94.
2. Grzybowski A, Told R, Sacu S, Bandello F, Moisseiev E, Loewenstein A, et al. 2018 update on intravitreal injections: Euretina expert consensus recommendations. Ophthalmologica. 2018;239(4):181–93. https://doi.org/10.1159/000486145.
3. Petri AS, Boysen K, Cehofski LJ, van Dijk EHC, Dysli C, Fuchs J, et al. Intravitreal injections with vascular endothelial growth factor inhibitors: a practical approach. Ophthalmol Ther. 2020;9(1):191–203. https://doi.org/10.1007/s40123-020-00230-4.
4. World Health Organization. Task shifting: global recommendations and guidelines. World Health Organization. Available at: https://www.who.int/workforcealliance/knowledge/resources/taskshifting_guidelines/en/. Accessed Nov 17th, 2020.
5. Malterud K, Aamland A, Fosse A. How can task shifting put patient safety at risk? A qualitative study of experiences among general practitioners in Norway. Scand J Prim Health Care. 2020;38(1):24–32. https://doi.org/10.1080/02813432.2020.1714143.
6. Schober M. Development of advanced practice nursing (APN): the international context. Enfermería Clínica (English Edition). 2018;29(2):63–6.
7. Browning DJ. Physician assistants and nurse practitioners in ophthalmology-has the time come? Am J Ophthalmol. 2018;186:ix-xi. https://doi.org/10.1016/j.ajo.2017.09.023.
8. Kredo T, Adeniyi FB, Bateganya M, Pienaar ED. Task shifting from doctors to non-doctors for initiation and maintenance of antiretroviral therapy. Cochrane Database Syst Rev. 2014;7:Cd007331.
9. Thotam SM, Buhse M. Patient satisfaction with physicians and nurse practitioners in multiple sclerosis centers. Int J MS Care. 2020;22(3):129–35. https://doi.org/10.7224/1537-2073.2018-042.
10. Bolme S, Morken TS, Follestad T, Sørensen TL, Austeng D. Task shifting of intraocular injections from physicians to nurses: a randomized single-masked noninferiority study. Acta Ophthalmol (Copenh). 2020;98:139–44.
11. Mohr DC, Young GJ, Meterko M, Stolzmann KL, White B. Job satisfaction of primary care team members and quality of care. Am J Med Qual. 2011;26(1):18–25. https://doi.org/10.1177/1062860610373378.
12. Purdy N, Spence Laschinger HK, Finegan J, Kerr M, Olivera F. Effects of work environments on nurse and patient outcomes. J Nurs Manag. 2010;18(8):901–13. https://doi.org/10.1111/j.1365-2834.2010.01172.x.
13. Kvist T, Voutilainen A, Mäntynen R, Vehviläinen-Julkunen K. The relationship between patients' perceptions of care quality and three factors: nursing staff job satisfaction, organizational characteristics and patient age. BMC Health Serv Res. 2014;14(1):466. https://doi.org/10.1186/1472-6963-14-466.
14. Perry SJ, Richter JP, Beauvais B. The effects of nursing satisfaction and turnover cognitions on patient attitudes and outcomes: a three-level multisource study. Health Serv Res. 2018;53(6):4943–69. https://doi.org/10.1111/1475-6773.12997.

15. Iwu EN, Holzemer WL. Task shifting of HIV management from doctors to nurses in Africa: clinical outcomes and evidence on nurse self-efficacy and job satisfaction. AIDS Care. 2014;26(1):42–52. https://doi.org/10.1080/09540121.2013.793278.
16. McCay R, Lyles AA, Larkey L. Nurse leadership style, nurse satisfaction, and patient satisfaction: a systematic review. J Nurs Care Qual. 2018;33(4):361–7. https://doi.org/10.1097/NCQ.0000000000000317.
17. Lu H, Zhao Y, While A. Job satisfaction among hospital nurses: a literature review. Int J Nurs Stud. 2019;94:21–31. https://doi.org/10.1016/j.ijnurstu.2019.01.011.
18. Polit DF. Beck CT nursing research : generating and assessing evidence for nursing practice, eleventh edition.; international edition. Edn. Philadelphia: Lippincott Williams & Wilkins; 2020.
19. Schaufel MA, Nordrehaug JE, Malterud K. Hope in action-facing cardiac death: a qualitative study of patients with life-threatening disease. Int J Qual Stud Health Well-being. 2011;6(1). https://doi.org/10.3402/qhw.v6i1.5917.
20. Graneheim UH, Lundman B. Qualitative content analysis in nursing research: concepts, procedures and measures to achieve trustworthiness. Nurse Educ Today. 2004;24(2):105–12. https://doi.org/10.1016/j.nedt.2003.10.001.
21. Maher C, Hadfield M, Hutchings M, de Eyto A. Ensuring rigor in qualitative data analysis: a design research approach to coding combining NVivo with traditional material methods. Int J Qual Methods. 2018;17(1):1609406918786362. https://doi.org/10.1177/1609406918786362.
22. Malterud K, Siersma VD, Guassora AD. Sample size in qualitative interview studies: guided by information power. Qual Health Res. 2016;26(13):1753–60. https://doi.org/10.1177/1049732315617444.
23. Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. Int J Qual Health Care. 2007;19(6):349–57. https://doi.org/10.1093/intqhc/mzm042.
24. Feiring E, Lie AE. Factors perceived to influence implementation of task shifting in highly specialised healthcare: a theory-based qualitative approach. BMC Health Serv Res. 2018;18(1):899. https://doi.org/10.1186/s12913-018-3719-0.
25. Davies C. Getting health professionals to work together. BMJ. 2000;320(7241):1021–2. https://doi.org/10.1136/bmj.320.7241.1021.
26. Pelaccia T, Viau R. Motivation in medical education. Med Teach. 2017;39(2):136–40. https://doi.org/10.1080/0142159X.2016.1248924.
27. Riisgaard H, Søndergaard J, Munch M, Le JV, Ledderer L, Pedersen LB, et al. Work motivation, task delegation and job satisfaction of general practice staff: a cross-sectional study. Fam Pract. 2017;34(2):188–93. https://doi.org/10.1093/fampra/cmw142.
28. Zwijnenberg NC, Bours GJ. Nurse practitioners and physician assistants in Dutch hospitals: their role, extent of substitution and facilitators and barriers experienced in the reallocation of tasks. J Adv Nurs. 2012;68(6):1235–46. https://doi.org/10.1111/j.1365-2648.2011.05823.x.
29. Abdel Maqsood AS, Oweis AI, Hasna FS. Differences between patients' expectations and satisfaction with nursing care in a private hospital in Jordan. Int J Nurs Pract. 2012;18(2):140–6. https://doi.org/10.1111/j.1440-172X.2012.02008.x.
30. Delamaire M-L, Lafortune G. Nurses in advanced roles; 2010.
31. World Health Organization. Client Satisfaction Evaluations. World Health Organization Available at: https://apps.who.int/iris/bitstream/handle/10665/66584/WHO_MSD_MSB_00.2g.pdf;jsessionid=963AC1D30052A1D625DB8E67334DBB6B?sequence=7. Accessed Feb 26th, 2021.
32. Bleich SN, Ozaltin E, Murray CK. How does satisfaction with the health-care system relate to patient experience? Bull World Health Organ. 2009;87(4):271–8. https://doi.org/10.2471/BLT.07.050401.
33. DaCosta J, Hamilton R, Nago J, Mapani A, Kennedy E, Luckett T, et al. Implementation of a nurse-delivered intravitreal injection service. Eye (Lond). 2014;28:734–40.
34. Hammerstrøm J. Patients' experiences with a hospital outpatient clinic. Is lack of continuity in the physician-patient relationship an important quality problem? Tidsskr Nor Laegeforen. 1993;113(13):1600–2.
35. Fan VS, Burman M, McDonell MB, Fihn SD. Continuity of care and other determinants of patient satisfaction with primary care. J Gen Intern Med. 2005;20(3):226–33. https://doi.org/10.1111/j.1525-1497.2005.40135.x.
36. Brown J. Training needs assessment: a must for developing an effective training program. Public Pers Manage. 2002;31(4):569–78. https://doi.org/10.1177/009102600203100412.
37. Dicicco-Bloom B, Crabtree BF. The qualitative research interview. Med Educ. 2006;40(4):314–21. https://doi.org/10.1111/j.1365-2929.2006.02418.x.
38. Zhang W, Creswell J. The use of "mixing" procedure of mixed methods in health services research. Med Care. 2013;51(8):e51–e7. https://doi.org/10.1097/MLR.0b013e31824642fd.
39. Orsini C, Binnie VI, Wilson SL. Determinants and outcomes of motivation in health professions education: a systematic review based on self-determination theory. J Educ Eval Health Prof. 2016;13:19. https://doi.org/10.3352/jeehp.2016.13.19.
40. Morse JM. Critical analysis of strategies for determining rigor in qualitative inquiry. Qual Health Res. 2015;25(9):1212–22. https://doi.org/10.1177/1049732315588501.
41. World Medical Association. Declaration of Helsinki The World Medical Association. Available at: https://www.wma.net/what-we-do/medical-ethics/declaration-of-helsinki/doh-oct2008/. Accessed Oct 28th, 2020.

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