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

Stine Bolme, <sup>1,2</sup> Tora Sund Morken, <sup>1,2</sup> Turid Follestad, <sup>3</sup> Torben Lykke Sørensen <sup>4,5</sup> and Dordi Austeng <sup>1,2</sup>

# 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 bestvisual acuity 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

<sup>&</sup>lt;sup>1</sup>Department of Ophthalmology, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway

<sup>&</sup>lt;sup>2</sup>Department of Neuromedicine and Movement Science, Norwegian University of Science and Technology, Trondheim, Norway

<sup>&</sup>lt;sup>3</sup>Department of Public Health and Nursing, Norwegian University of Science and Technology, Trondheim, Norway

<sup>&</sup>lt;sup>4</sup>Department of Ophthalmology, Zealand University Hospital, Roskilde, Denmark

<sup>&</sup>lt;sup>5</sup>Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

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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  $12 \pm 2$  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 Treatment the Early 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  $12 \pm 2$  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 twoway 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

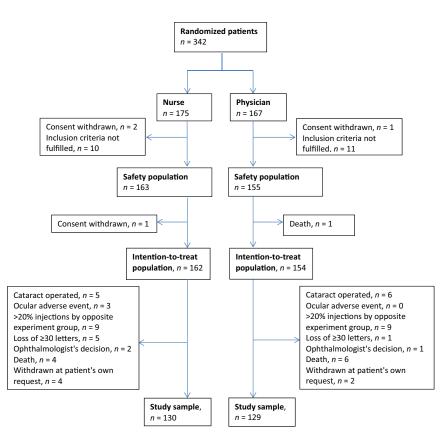


Fig. 1. Flow chart.

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.

#### Primary outcome

Nurse-administered intraocular injections were noninferior to physicianadministered 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: -2.9to + 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 (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-administere 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 equi	valent	
$\leq$ 37 letters, $\leq$ 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)
$\geq$ 78 letters, $\geq$ 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

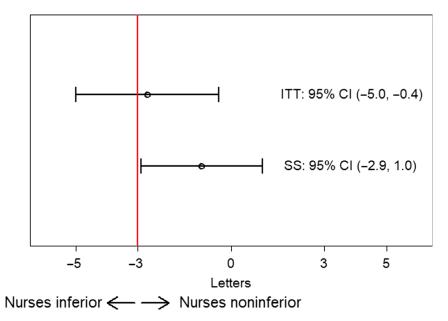
injections from the opposite experiment group were excluded. Fifteen participants treated with anti-VEGF in both eyes were also excluded since they received injections from the other profession in the non-study eye. Survey data on another 22 participants were missing. When asked if they assumed to belong 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 $\geq 5$ 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 <sup>†</sup>	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 (%).

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.

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Correspondence:
Dordi Austeng
Department of Ophthalmology
St. Olavs Hospital
Trondheim University Hospital
7006 Trondheim
Norway
Cell phone number: +47 47352135

Fax: +47 72575765 Email: dordi.austeng@ntnu.no

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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.

<sup>&</sup>lt;sup>†</sup>No patient with lens damage, retinal detachment or intraocular haemorrhage was observed.