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# Incidence of Endophthalmitis after Intravitreal Injections with and without Prophylactic Antibiotics

# Incidência de Endoftalmite após Injeções Intravítreas com e sem Profilaxia Antibiótica

**março, 2019**

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DESIGNAÇÃO DA ÁREA DO PROJECTO

Oftalmologia

TÍTULO DISSERTAÇÃO/~~MONOGRAFIA~~ (riscar o que não interessa)

Incidence of Endophthalmitis after intravitreal injections with and without prophylactic antibiotics

ORIENTADOR

Manuel Alberto de Almeida e Sousa Falcão

COORIENTADOR (se aplicável)

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## Dedicatória

Aos meus pais, José Luís da Silva Ramos e Maria da Conceição Santos Dias Ramos, que todos os dias fazem dos meus sonhos os seus próprios e me mostram que com amor, dedicação e trabalho tudo se consegue atingir. Obrigado por acreditarem em mim, mesmo nos momentos em que não acredito em mim mesmo.

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**Title**

Incidence of Endophthalmitis after Intravitreal Injections with and without Prophylactic Antibiotics

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**Abbreviations/ Acronyms**

IVI – Intravitreal Injections; Anti-VEGF – Anti-Vascular Endothelial Growth Factor; AMD – age-related macular degeneration; DME – diabetic macular edema; RVO – retinal vein occlusion; PPV – pars plana vitrectomy; VA – Visual Acuity; logMAR – logarithm of the minimal angle of resolution; CF – count fingers; HM – hand motion; OR – operating room

# ABSTRACT

**Purpose:** To assess the effect of topical antibiotic prophylaxis on the rate of post-operative endophthalmitis after intravitreal injection (IVI) of anti-vascular endothelial growth factor agents (VEGF) and corticosteroids and to describe the clinical characteristics, management, and visual outcomes of patients with acute endophthalmitis.

**Design:** Retrospective, single-center study.

**Participants:** All patients treated with intravitreal injections for a variety of retinal pathologies between 1 October 2014 and 30 November 2018 were included.

**Methods:** The intravitreal injections performed during a two-year period in which topical antibiotic prophylaxis was used was compared to the number of injections performed over a two-year period without antibiotic prophylaxis.

**Main Outcome Measure:** Incidence of clinical endophthalmitis in the two different groups.

**Results:** Between 1 October 2014 and 30 November 2018, 33515 IVI were performed. During this period, 13 cases of post-IVI endophthalmitis were identified (incidence rate of 0.0388%; 95% CI, 0.0217-0.0644%) or approximately 1 case for every 2578 IVI performed. Between 1 October 2014 and 31 October 2016, when post-operative topical antibiotic prophylaxis was used 14828 IVI were performed and 5 cases of endophthalmitis were reported (0.0337%; 95% CI, 0.0129-0.0739%); between 1 November 2016 and 30 November 2018, when no prophylaxis was used, 18687 IVI were performed and 8 cases of endophthalmitis were identified (0.0428%; 95% CI, 0.0202-0.0808%). There were no statistical differences in the incidence rates between the two groups (p=0.675). The median number of days from injection to presentation was 7.0 (range 2-24 days).

**Conclusions:** The incidence of endophthalmitis after IVI of anti-vascular endothelial growth factors or corticosteroids was low. Post-IVI antibiotic prophylaxis did not reduce the rate of endophthalmitis. Changing the policy from antibiotic prophylaxis to no antibiotic prophylaxis was safe.



**Keywords:** endophthalmitis, antibiotic prophylaxis, intravitreal injection, anti-vascular endothelial growth factor.

## INTRODUCTION

The number of intravitreal injections (IVI) performed has grown exponentially in the past decade, becoming the most commonly performed invasive ophthalmic procedure.[1,2] In the USA alone, there was an estimated 5.9 million IVI performed in 2016.[3]

With the institution of intravitreal anti-vascular endothelial growth factor (anti-VEGF) and corticosteroids for the treatment of wet age-related macular degeneration (AMD), diabetic macular edema (DME) and macular edema secondary to retinal vein occlusions (RVO) an exponential increase in the number of IVI was observed. IVI became the standard of care for the mentioned diseases.[4–7] However, it is important to state that all these diseases are chronic diseases that require frequent retreatments. IVI of anti-VEGF agents are usually started on a monthly basis. As time elapses, different treatment strategies such as *pro re nata* or "Treat and Extend" strategies have been employed to try and reduce the number of injections. Nonetheless, some patients may have up to twelve injections each year.

IVI may induce complications, including endophthalmitis, retinal detachment, and cataract.[8] Infectious endophthalmitis is the most preoccupying complication after IVI because of its poor prognosis resulting in severe and irreversible vision loss.[9] Although the risk is low, with the largest meta-analysis reporting a frequency of 0.056% (197/350.535 injections)[10], since we are talking about chronic macular pathologies with repeated IVI being required, the cumulative risk after 2 years is often more than 1%.[11]

By 2004, IVI was a fairly uncommon procedure and, as such, guidelines at that time mentioned the use of pre- and/or post-injection topical antibiotics.[12,13] Despite the lack of evidence showing any efficacy in preventing post-injection endophthalmitis, it was always an accepted practice to use topical antibiotics since many clinical trial protocols for intravitreal agents required them.[14,15] Using topical antibiotics for prophylaxis up to twelve weeks in one year can potentially lead to the selection of resistant microbiologic strains.[16–18] The widespread use of IVI has considerably increased the body of evidence regarding post-injection endophthalmitis.

Many studies have identified modifiable risk factors to prevent endophthalmitis following IVI, and guidelines based on current best evidence and practices have been published in different countries.[12,19] However, while some have been applied in present clinical practice, no consensus was established about the use of topical prophylaxis with antibiotics.

Povidone-iodine with strict antisepsis rules is the only prophylaxis that was proven to have an effect against endophthalmitis after intra-ocular surgery.[13,20,21] Some studies are starting to suggest the lack of role of topical antibiotics in the prevention of post-injection endophthalmitis.[22–24] In fact, recent studies even suggested that topical prophylaxis with antibiotics may be harmful and increase the risk of endophthalmitis.[16,18,25]

The purpose of this study is to assess the effect of topical antibiotic prophylaxis on the rate of post-operative endophthalmitis after IVI of anti–VEGF agents or corticosteroids and to describe the clinical characteristics, management, and visual outcomes of patients with acute endophthalmitis following IVI.

## PATIENTS AND METHODS

**STUDY DESIGN:** This is a retrospective study of endophthalmitis after intravitreal injections (IVI) given from 1 October 2014 and 30 November 2018 performed at Centro Hospitalar Universitário de São João, Oporto, Portugal.

We compared the 25-month prior to the suspension of the antibiotic prophylaxis (from 1 October 2014 to 31 October 2016) to the immediately following 25-month period (from 1 November 2016 to 30 November 2018) during which no prophylaxis was prescribed.

This study was approved by the local Ethics Committee of Centro Hospitalar Universitário de São João. Medical records were used to identify the total number of intravitreal injections and the setting in which intravitreal injections were performed.

The treatments included in this study were ranibizumab (0.5 mg/0.05 mL; Lucentis; Novartis Pharma SAS; Basel, Switzerland), bevacizumab (1.25 mg/ 0.05 mL; Avastin; Roche, Basel, Switzerland), aflibercept (2 mg/0.05mL; Eylea; Bayer Pharma AG; Berlin, Germany), triamcinolone acetonide (2mg/0,1mL and 4 mg/0.1 mL; Kenalog; Bristol-Myers Squibb, New York, New York, USA), dexamethasone implant (0.7 mg; Ozurdex; Allergan SAS, Irvine, CA, USA), and the fluocinolone acetonide implant (0.19mg; Iluvien; Alimera Sciences Inc; Hampshire, UK).

Indications for intravitreal injection included macular edema secondary to diabetic retinopathy, retinal vein occlusion and uveitis, retinal neovascularization secondary to diabetic retinopathy and venous occlusion and choroidal neovascularization from age-related macular degeneration (AMD), pathologic myopia, angioid streaks, and neovascular glaucoma.

Presumed endophthalmitis was defined as any acute intraocular inflammation occurring within 4 weeks after IVI and requiring intravitreal antibiotics and sometimes vitrectomy.

Other causes of endophthalmitis (postsurgical endophthalmitis cases other than IVI, bleb-associated endophthalmitis, endogenous endophthalmitis, and infection secondary to trauma or corneal ulceration) were excluded.

International Classification of Diseases, 9th and 10th Edition (ICD-9 and ICD-10) codes for endophthalmitis were used to electronically identify cases of endophthalmitis. All possible cases of endophthalmitis from this electronic search were individually reviewed to confirm a diagnosis of presumed infectious endophthalmitis after IVI.

Patient demographics, indication for IVI, clinical presentation symptoms and ophthalmological examination, visual acuity (before infection, at presentation, and posttreatment), the number of injections preceding endophthalmitis, the type of medication used in the injection, the treatment indication, the number of days from IVI to presentation were collected. The management of the endophthalmitis, including intravitreal and systemic antibiotic, pars plana vitrectomy, microbiology results from aqueous and vitreous humor taps and complications were reviewed.

In our department, until the 31st of October 2016, patients were instructed to perform post-injection antibiotic prophylaxis with topical levofloxacin (0.5% eye drops (5mg/mL), 5 times daily for 7 days. The levofloxacin was provided by the institution. From that date, due to new arising evidence in the literature questioning the role of topical antibiotics in endophthalmitis, prophylaxis was suspended.

**INTRAVITREAL INJECTION TECHNIQUE:** All injections were performed in the operating room by a trained ophthalmologist or ophthalmology resident.

All eyes were prepared using a standardized procedure. There were no differences in these procedures before and after the decision to stop antibiotic prophylaxis. Briefly, before injection, local anesthesia was applied with 1 drop of Oxybuprocaine Hydrochloride (4mg/mL). Five percent periocular and conjunctival povidone-iodine was applied for 2 minutes and then a fenestrated self-adhesive sterile drape large enough to mask the patient's nose and mouth was used. Drapes were used to isolate the cilia. A lid speculum was used. Injections were administered via pars plana 3.5 or 4 mm in pseudophakic or phakic eyes, respectively. A 30-gauge needle was for the injections of anti-VEGF and triamcinolone. The dexamethasone implant is a disposable injection device, containing a

rod-shaped implant which is not visible. The dexamethasone implant applicator with TSK needle is 22 gauge and features a coating designed to facilitate glide of the needle through the sclera and into the posterior chamber. The fluocinolone acetonide is administered via a custom applicator with a 25 gauge needle.

All surgeons wore a face mask, a surgical hat, and sterile gloves. All patients wore a disposable cap. At the end of the procedure, the ability of the patient to see light was assessed in all cases.

**ENDOPHTHALMITIS MANAGEMENT:** All eyes in which presumed infectious endophthalmitis developed began treatment according to a previously designed protocol. Immediately, in the emergency room, all patients received antibiotic IVI of vancomycin (1 mg/0.1 mL) and ceftazidime (2 mg/0.1 mL). All patients were admitted to hospital and received a systemic broad-spectrum antibiotic regimen for 10 days including intravenous vancomycin 1g every 12/12h combined with ceftazidime 2g every 12/12h and oral prednisolone adjusted to the body weight and topical atropine 10mg/ml 1 drop 8/8h during a variable period according to patients' needs.

Patients were evaluated daily. According to clinical status evolution, a pars plana vitrectomy (PPV) could be performed and samples from vitreous and aqueous humor were collected during surgical procedure.

**OUTCOMES:**

Our primary outcome measure was the occurrence of post-injection endophthalmitis after IVI with and without topical antibiotic prophylaxis as reported by physicians.

Secondary outcomes were to record the overall profile of patients that developed endophthalmitis as well as their symptoms at presentation, to evaluate clinical outcomes such as final visual acuity or the return to baseline visual acuity, and to report microbiology results.

**VISUAL OUTCOME:** Visual acuity (VA) was measured with Snellen charts and secondarily converted to the logarithm of the minimal angle of resolution (logMAR) values for all statistical analysis. According to Holladay, visual acuity equal to count fingers (CF) and hand motion (HM) corresponds to logMAR 2.0 and logMAR 3.0, respectively.[26] Baseline VA was measured at presentation. Previous VA was defined as the last visual acuity

reported in ophthalmologic examinations prior to the diagnosis of endophthalmitis. Final VA was defined as the last follow-up where visual acuity was measured.

Light perception is not actually a visual acuity measurement but simply a detection of stimulus and, therefore, these cases were excluded from the analysis.[26]

**STATISTICAL ANALYSIS:** Statistical analysis was performed using the SPSS® statistical software (version 25.0 for Windows; SPSS Inc., Chicago, IL., USA).

The Kolmogorov–Smirnov test and normal probability plots were used to confirm the normal distribution of the data. Statistical significance for all the analyses were set at a p value less than 0.05.

Categoric variables were compared using a chi squared test or, for low count variables, Fisher exact test. Continuous variables following a normal distribution were compared using an independent sample t test, and if not following this criteria were compared using a nonparametric Mann-Whitney test.

# RESULTS

**INCIDENCE OF ENDOPHTHALMITIS (Table 1.):** Between 1 October 2014 and 30 November 2018, a total number of 33515 IVI were performed. During this study period, 13 cases of post-IVI endophthalmitis were identified, yielding a rate of 0.0388% (95% CI, 0.0217-0.0644%) or approximately 1 case for every 2578 IVI.

Between 1 October 2014 and 31 October 2016, when topical antibiotic prophylaxis was used, 14828 IVI were performed and 5 cases of endophthalmitis were reported. Between 1 November 2016 and 30 November 2018, when no prophylaxis was used, 18687 IVI were performed and 8 cases of endophthalmitis were identified. The incidence rate on the first period was 0.0337%; 95% CI, 0.0129-0.0739% and in the second period was 0.0428%; 95% CI, 0.0202-0.0808%. No statistical difference was found between the two periods (p=0.675).

**CHARACTERISTICS OF PATIENTS WITH ENDOPHTHALMITIS (Table 2.):** Mean patient age was 71 years (range, 28-94 years) with 3 male patients (23.1%) and 9 right eyes (69.2%). Of all systemic disease, hypertension and diabetes mellitus were the most common with 9 (69.2%) and 6 (46.2%) affected patients, respectively. 4 were phakic (30.8%) and 9

were pseudophakic (69.2%). In patients with endophthalmitis, indications for IVI were neovascular age-related macular degeneration (n = 4, 30.7%), diabetic macular edema (n = 3, 23.1%), macular edema after retinal vein occlusion (n = 1, 7.7%), myopic neovascularization (n = 1, 7.7%), multifocal choroiditis (n=1, 7.7%), idiopathic macular edema (n=2, 15.4%) and macular edema following a vitrectomy for subluxated intraocular lens (n=1, 7.7%). There were no statistical differences detected in any of the characteristics of patients with endophthalmitis with or without the use of topical antibiotics.

**ENDOPHTHALMITIS PRESENTATION (Table 2.):** Median number of IVI before endophthalmitis diagnosis was 9.0 (range, 1-38 injections). Median time from causative injection to endophthalmitis presentation was 7.0 (range, 2-24 days), with 3 patients (23.08%) presenting within 3 days or less and 6 (46.15%) presenting after a week. Clinical presentation was similar between those patients who did and those who did not receive prophylactic topical antibiotics. At initial presentation, 12 of the 13 patients (92.3%) noted diminished visual acuity with only 4 of them (30.8%) presenting with pain. Median visual acuity at presentation was 3.0 (range, 1.0-3.0). Principal signs detected were tyndall in 92.3% and 46.2% had hypopyon. In 10 cases the ocular fundus was not visible by routine indirect ophthalmoscopy (76.9%) and in 1 case there was no information available. Median intraocular pressure (IOP) at presentation was 12.0 (range, 7.0-50.0).

At clinical presentation, all 13 patients initially underwent intravitreal vancomycin (1 mg/0.1 mL) and ceftazidime (2 mg/0.1 mL). 11 patients (84.6%) subsequently underwent PPV.

**MICROBIOLOGY (Table 2.):** Positive microbial cultures were obtained in 2 of 13 (15.4%) cases, 10 cases (84.6%) were culture negative and 1 case did not collect any sample. 12 eyes (92.3%) underwent aqueous and/or vitreous sampling. Of these, 2 (16.7%) had a positive intraocular culture from either aqueous or vitreous sample, and 10 (83.3%) had negative cultures from both aqueous and vitreous samples. Two of 5 eyes (40%) with prophylactic topical antibiotic use had positive cultures, whereas no eyes without prophylactic topical antibiotic use had positive cultures (p = 0.268).

The only organisms isolated were coagulase-negative staphylococci (2 of 13, 15.4%), followed by Streptococcus mitis (1 of 13, 7.7%). All other microbiology performed of either the aqueous or vitreous samples came out as negative results.

**VISUAL ACUITY OUTCOMES (Table 3.):** The median visual acuity before the causative intravitreal injection was 0.70 (range, 0.0-2.0). Median visual acuity at presentation was 3.0 (Hand Motion - range, 1.0-3.0) and the median final visual acuity was 1.30 (range, 0.0-3.0). There were no statistical differences between any of the visual acuity (Previous VA, Baseline VA or Final VA) among the two studied periods.

In this study, 3 patients (23.1%) after presentation returned to their previous values of VA, 2 patients (15.4%) had a decrease in final logMAR value less or equal to 0.1 and 2 patients (15.4%) improved their visual acuity, probably related with posterior cataract surgery. All the other patients had final logMAR values worse than 1.20.

## DISCUSSION

This single-center retrospective study of Portuguese population detected 13 cases of endophthalmitis after 33515 intravitreal injections (IVI) demonstrating a low overall rate (0.0388%) of endophthalmitis following anti-VEGF and corticosteroids IVI. This is broadly consistent with much of the previously published literature from large, retrospective studies.[10,27–29] Our major outcome was to compare the rate of endophthalmitis during a 25-month period when topical antibiotic prophylaxis post-IVI were prescribed with that during a 25-month period when no antibiotic prophylaxis was prescribed. Our findings verified that the incidence of endophthalmitis was not significantly different between both periods. Therefore, our study adds to the idea that no benefits come from the use of antibiotic prophylaxis and that recent guidelines published by the American Academy of Ophthalmology that discourage post-IVI prophylaxis are, to date, the best current practice.[30–32]

Furthermore, it is important to notice that, in our department, the IVI procedure takes place, at all times, in an operating room (OR). In spite of being a more sterile environment than the office setting, our study did not find differences in the incidence of endophthalmitis in comparison with most studies that took place in office.[33–36] A lower rate should be expected but this was not a reality leading us to believe that an operating room might not result in advantages with regard to endophthalmitis' incidence. In fact, given that most times the IVI procedure doesn't occur on the same day of the appointment and the need for an operating room, there are higher costs for both the hospital (surgical team, staff, OR time, material), patient (trips to the hospital, many times from family members) and state (absence

from work activity from both patient and family). However, our study was not designed to evaluate this specifically.

As the use of IVI continues to grow, efforts to validate practice patterns that improve efficiency for both patients and providers are essential and prevention of endophthalmitis should be a main concern because of the numerous sources of contamination. The main sources of ocular infection during the IVI procedure are pathogens of the lid margin and conjunctiva with a possible bacterial inoculation into the vitreous cavity.[37] To date, the only proven endophthalmitis prophylaxis for intra-ocular surgeries remains topical povidone-iodine.[13,20] In contrast, the benefit of post-IVI topical antibiotics in preventing endophthalmitis remains controversial.[20,25,35,38,39] Previous studies have even shown that the repeated use of topical antibiotic prophylaxis could lead to an increase of antibiotic-resistant organisms resulting in more aggressive treatments and worse prognosis.[18,40,41]

Endophthalmitis is usually diagnosed on clinical features such as pain, diminished visual acuity, hypopyon and posterior segment inflammation being rather commonly underestimated by culture tests.[42] In accordance with the literature, the most common symptom reported was reduced vision (92.3%).[43]

In this study, we considered all cases of post-IVI endophthalmitis to be presumed infectious receiving immediate intravitreal antibiotics. Our study achieved culture-positive bacterial identification in 15.4%, which is rather low when compared to other series which report an identification between 30% and 60%.[9,25,44] These bacterial identification results are low mostly due to, in most cases, only performing aqueous and vitreous samples at the beginning of the pars plana vitrectomy (PPV) procedure, which typically occurs hours after the initial administration of IVI antibiotics and possibly after the death of infective bacteria. For this reason, we can conjecture about the tremendous value of harvesting both aqueous and vitreous samples at the time of presentation.

As suggested by our study and general literature, the prognosis of patients that develop endophthalmitis is poor usually resulting in severe vision loss. When analyzing VA values we found that the clinical presentation and visual outcomes of patients with suspected endophthalmitis were similar despite the use or not of post-IVI topical antibiotics.

This study has some limitations. First, it is a retrospective study with, inevitably, missing data since this is collected from medical records. As with any retrospective study of endophthalmitis, it is possible that some cases of endophthalmitis may not have been

captured owing to errors in coding or cases not reported underestimating its incidence, but it also has the benefit of detailed chart patient review to confirm endophthalmitis' cases instead of relying on billing codes alone. Second, the retrospective nature of this study made it impossible for us to control for confounding factors. However, this last should not be a significant limitation since endophthalmitis cannot be foreseen by patients or physicians and we believe selection bias with respect to antibiotic prophylaxis use is improbable to occur.

Despite these limitations, this study has several strengths. First, we included a large number of IVI performed in a single center over a fairly short period. Second, as this involved a single institution, no difference in the standardized preparation, institution or even physician injection protocol interfered with differences in endophthalmitis rates. Third, the management of endophthalmitis after IVI was homogeneous especially in terms of antibiotic IVI, systemic antibiotic regimen and PPV.

Centro Hospitalar de São João performs IVI in an operating room environment and the use of a sterile drape, face mask, surgical hat and sterile gloves is universal. Therefore, extrapolation can be made to other centers and countries with similar conditions but extrapolation for countries using different techniques requires careful consideration.

In conclusion, our retrospective study of over 33515 IVI found a low rate of endophthalmitis comparable to prior studies without differences between patients that received and didn't receive prophylaxis. These results lend support to the safety of stopping topical antibiotic prophylaxis for this common ophthalmic procedure.

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# Tables

**TABLE 1.** Incidence of Presumed Endophthalmitis Cases after Intravitreal Injections (IVI) of Corticosteroids or Anti-Vascular Endothelium Growth Factor.

| | All | Topical Antibiotic Prophylaxis | |
|---|---|---|---|
| | | Yes | No |
| **Number of Cases** | 13 | 5 | 8 |
| **Number of IVI** | 33515 | 14828 | 18687 |
| **Incidence** | 0.0388 (0.0217-0.0644) | 0.0337 (0.0129-0.0739) | 0.0428 (0.0202-0.0808) |
| ***p*** | | 0.675 | |

Values are displayed as absolute frequencies. Incidence is presented in % (95% CI)
Comparisons were made with the chi squared test for dichotomous data; the level of statistical significance was set at P < .05.

**TABLE 2.** Demographics, Management and Bacteriology of Presumed Endophthalmitis Cases (n=13) after Intravitreal Injections (IVI), in Centro Hospitalar Universitário de São João.

| | All (n=13) | Topical Antibiotic Prophylaxis | | *p* |
|---|---|---|---|---|
| | | Yes (n=5) | No (n=8) | |
| **Demography** | | | | |
| **Sex (F/M)** | 10/3 | 4/1 | 6/2 | 1.0 |
| **Age* (y)** | 71 (28-94) | 61 (28-85) | 78 (61-94) | 0.092 |
| **Systemic Diseases** | | | | |
| Diabetes | 6 (46.15) | 2 (40) | 4 (50) | 1.0 |
| Hypertension | 9 (69.23) | 2 (40) | 7 (87.5) | 0.217 |
| Dyslipidemia | 4 (30.77) | 0 | 4 (50) | 0.105 |
| Cardiac | 4 (30.77) | 2 (40) | 2 (25) | 1.0 |
| Renal | 3 (23.08) | 2 (40) | 1 (12.5) | 0.510 |
| Thyroid | 3 (23.08) | 2 (40) | 1 (12.5) | 0.510 |
| **Ocular Antecedents** | | | | |
| Iridocyclitis | 1 (7.69) | 1 (20) | 0 | 0.385 |
| PHACO | 9 (69.23) | 4 (80) | 5 (62.5) | 1.0 |
| **Indications** | | | | |
| NAMD | 4 (30.77) | 0 | 4 (50) | 0.171 |
| DME | 3 (23.08) | 1 (20) | 2 (25) | 0.943 |
| Macular edema after RVO | 1 (7.69) | 1 (20) | 0 | 0.622 |
| Myopic neovascularization | 1 (7.69) | 1 (20) | 0 | 0.622 |
| Multifocal choroiditis | 1 (7.69) | 1 (20) | 0 | 0.622 |
| Unknown macular edema | 2 (15.38) | 1 (20) | 1 (12.5) | 0.833 |
| Macular edema post-VPP for subluxated LIO | 1 (7.69) | 0 | 1 (12.5) | 0.724 |
| **Agents** | | | | |
| Ranibizumab | 0 | 0 | 0 | ND |
| Bevacizumab | 7 (53.85) | 3 (60) | 4 (50) | ND |
| Aflibercept | 3 (23.08) | 1 (20) | 2 (25) | ND |
| Triamcinolone acetonide | 2 (15.38) | 1 (20) | 1 (12.5) | ND |
| Dexamethasone implant | 1 (7.69) | 0 | 1 (12.5) | ND |
| Fluocinolone acetonide implant | 0 | 0 | 0 | ND |
| **Number of IVI before endophthalmitis** | 9 (1-38) | 4 (3-25) | 11 (1-38) | 0.724 |
| **Initial Presentation** | | | | |
| Right/ Left eye affected | 9/4 | 3/2 | 6/2 | 1.0 |
| Days to presentation | 7 (2-24) | 4 (2-16) | 16.5 (2-24) | 0.171 |
| Vision loss | 12 (92.31) | 5 (100) | 7 (87.5) | ND |
| Pain | 4 (30.77) | 3 (60) | 1 (12.5) | ND |
| Redness | 6 (46.15) | 3 (60) | 3 (37.5) | ND |
| Tyndall | 12 (92.31) | 4 (80) | 8 (100) | 0.385 |
| Hypopyon | 6 (46.15) | 2 (40) | 4 (50) | 1.0 |
| Corneal Oedema | 4 (30.77) | 1 (20) | 3 (37.5) | 1.0 |
| Ocular fundus not visible | 10 (76.92) | 3 (60) | 7 (87.5) | 1.0 |
| IOP (mmHg) | 12.0 (7.0-50.0) | 15.0 (10.0-50.0) | 12.0 (7.0-17.0) | 0.432 |
| **Management** | | | | |
| Intravitreal antibiotics[a] | 13 (100) | 5 (100) | 8 (100) | ND |
| Intravenous antibiotics[b] | 13 (100) | 5 (100) | 8 (100) | ND |
| PPV | 11 (84.6) | 5 (100) | 6 (75) | 0.487 |
| **Bacteriology** | | | | |
| **Vitreous and Aqueous Samples** | 12 (92.31) | 5 (100) | 7 (87.5) | 1.0 |
| Bacterial identification (culture positive) | 2 (16.67) | 2 (40) | 0 | 0.268 |
| Coagulase-negative Staphylococci | 2 (16.67) | 2 (40) | 0 | ND |
| Streptococcus mitis | 1 (8.33) | 1 (20) | 0 | ND |

PHACO= phacoemulsification; NAMD=Neovascular age-related macular degeneration; DME= Diabetic Macular Edema; RVO= Retinal Vein Occlusion; LIO= intraocular lens; IVI= Intravitreal Injections; IOP= Intraocular Pressure; PPV= pars plana vitrectomy
Values are displayed as median (range) for continuous variables and number (%) for categorical variables; *mean (range) was considered in this variables.

[a] Vancomycin 1mg and Ceftazidime 2mg.

[b] Vancomycin 1g every 12/12h combined with Ceftazidime 2g every 12/12h for ten days.

Comparisons were made with the Fisher exact test for dichotomous data. An independent sample t test was used for continuous variable following a normal distribution and if non-normal a nonparametric Mann-Whitney test was used; ND= Not Determined; the level of statistical significance was set at $P < .05$;

**TABLE 3.** Visual Acuity (VA) Values and Analysis of Presumed Endophthalmitis Cases (n=13) after Intravitreal Injections, in Centro Hospitalar Universitário de São João.

| | Visual Acuity (logMAR) | | |
|---|---|---|---|
| | **Previous VA** | **VA at presentation** | **Final VA** |
| **All** (n=13) | 0.70 (0.0-2.0) | 3.0 (1.0-3.0)[a] | 1.3 (0.0-3.0) |
| **Topical Antibiotic Prophylaxis** | | | |
| Yes (n=5) | 0.40 (0.0-2.0) | 3.0 (1.0-3.0) | 1.3 (0.0-3.0) |
| No (n=8) | 0.90 (0.3-2.0) | 3.0 (2.0-3.0)[b] | 1.3 (0.4-2.0) |
| ***p*** | 0.171 | 0.548 | 1.0 |

LogMAR = logarithm of the minimal angle of resolution; VA = Visual Acuity
Values are displayed as median (range) for continuous variables and number (%) for categorical variables;
[a] Limited to n=10 (2 cases of light perception and 1 case without information were excluded)
[b] Limited to n=5 (2 cases of light perception and 1 case without information were excluded)
Comparisons were made with the nonparametric Mann-Whitney test, used for continuous variables; the level of statistical significance was set at $P < .05$.

# ANEXOS

**Unidade de Investigação**

Tomei conhecimento. Nada a opor.

03 de Janeiro de 2019

A Coordenadora da Unidade de Investigação

(Prof.ª Doutora Ana Azevedo)

n.º 375/18

SÃO JOÃO

DIRECÇÃO CLÍNICA

Aprovado. Ao CA. 4/01/2019

(Prof.ª Doutora Ana Azevedo)

PEDIDO DE AUTORIZAÇÃO

# Realização de Investigação

*Exmo. Senhor Presidente do Conselho de Administração*
*do Centro Hospitalar de São João*

**AUTORIZADO**

CONSELHO DE ADMINISTRAÇÃO REUNIÃO DE 09 JAN 2019

Presidente do Conselho de Administração

Prof. Dr. António Oliveira e Silva

Diretor Clínico — Prof. Dr. José Artur Paiva

Enfermeira Diretora — (Dr.ª Piedade Cardoso)

Vogal Executivo — (Dr. Luís Porto Correia)

Vogal Executivo — (Dr. Ricardo G. Matos)

*Nome do Investigador Principal:*

Diogo Dias Ramos

*Título da Investigação:*

Differences in the incidence of Endophthalmitis after Intravitreal Injections (IVT) with and without topical antibiotic prophylaxis.

*Pretendendo realizar no(s) Serviço(s) de:*

Oftalmologia

*a investigação em epígrafe, solicito a V. Exa., na qualidade de Investigador/Promotor, autorização para a sua efetivação.*

*Para o efeito, anexo toda a documentação referida no dossier da Comissão de Ética do Centro Hospitalar de São João/ Faculdade de Medicina da Universidade do Porto respeitante à investigação, à qual enderecei pedido de apreciação e parecer.*

*Com os melhores cumprimentos.*

*O Investigador/ Promotor*

*Porto,* 30 *de* Novembro *de* 2018 .

*assinatura*

Centro Hospitalar São João
Centro de Epidemiologia Hospitalar
26/12/2018

CES-IM005-0

SÃO JOÃO

U.PORTO
FMUP FACULDADE DE MEDICINA UNIVERSIDADE DO PORTO

# Questionário para submissão de Investigação

*Exmo. Sr. Presidente da Comissão de Ética do Centro Hospitalar de São João/ Faculdade de Medicina da Universidade do Porto,*

*Pretendendo realizar a investigação infracitada, solicito a V. Exa., na qualidade de Investigador, a sua apreciação e a elaboração do respetivo parecer. Para o efeito, anexo toda a documentação requerida.*

## IDENTIFICAÇÃO DO ESTUDO

**Título da investigação:** Differences in the incidence of Endophthalmitis after Intravitreal Injections (IVT) with and without topic

**Nome do investigador:** Diogo Dias Ramos

**Endereço eletrónico:** diogo.dias.ramos@gmail.com **Contacto telefónico:** 913282740

**Caracterização da investigação:**

☒ Estudo retrospetivo ☐ Estudo observacional ☐ Estudo prospetivo

☐ Inquérito ☐ Outro. Qual? _____

**Tipo de investigação:**

☐ Com intervenção ☒ Sem intervenção

**Formação do investigador em boas práticas clínicas *(GCP)*:** ☐ Sim ☒ Não

**Promotor** *(se aplicável)*: _____

**Nome do orientador de dissertação/tese** *(se aplicável)*: Manuel Alberto de Almeida e Sousa Falcão

**Endereço eletrónico:** falcao@med.up.pt

**Local/locais onde se realiza a investigação:** Serviço de Oftalmologia

Data prevista para início: 01 / 11 / 2018 Data prevista para o término: 01 / 02 / 2019

## PROTOCOLO DO ESTUDO

**Síntese dos objetivos:**

O estudo pretende realizar uma análise retrospectiva com o intuito de avaliar o papel da profilaxia antibiótica em pacientes submetidos a injeções intravitreas. Nesse sentido, será avaliado como outcome primário a incidência de endoftalmite em 2 períodos (Outubro 2014 a Outubro 2016; Novembro 2016 a Novembro 2018) em pacientes submetidos ao procedimento em causa.

**Fundamentação ética (ganhos em conhecimento/inovação; ponderação benefícios/riscos):**

Este estudo permite distinguir os dois protocolos de tratamento relativamente a perspectivas de maior benefício para o doente em termos de necessidade ou não da profilaxia antibiótica e a possibilidade da diminuição da incidência de casos resistentes à antibioterapia.

## CONFIDENCIALIDADE

**De que forma é garantida a anonimização dos dados recolhidos de toda a informação?**
???????????

**O investigador necessita ter acesso a dados do processo clínico?** ☒ Sim ☐ Não

**Está previsto o registo de imagem ou som dos participantes?** ☐ Sim ☒ Não

**Se sim, está prevista a destruição deste registo após o sua utilização?** ☐ Sim ☐ Não

## CONSENTIMENTO

**O estudo implica recrutamento de:**

Doentes: ☐ Sim ☒ Não Voluntários saudáveis: ☐ Sim ☒ Não

Menores de 18 anos: ☐ Sim ☒ Não

Outras pessoas sem capacidade do exercício de autonomia: ☐ Sim ☒ Não

**A investigação prevê a obtenção de Consentimento Informado:** ☐ Sim ☒ Não

**Se não, referir qual o fundamento para a isenção:**
O estudo presente é retrospetivo.

**Existe informação escrita aos participantes:** ☐ Sim ☒ Não

## PROPRIEDADE DOS DADOS

**A investigação e os seus resultados são propriedade intelectual de:**

☒ Investigador ☐ Promotor ☐ Ambos ☐ Serviço onde é realizado

☐ Não aplicável Outro: _____

## BENEFÍCIOS, RISCOS E CONTRAPARTIDAS PARA OS PARTICIPANTES

**Benefícios previsíveis:**
Permitir estabelecer qual o protocolo de tratamento mais adequado em pacientes submetidos a Injeções Intravitreas.

**Riscos/incómodos previsíveis:**
Riscos/incómodos não previsíveis.

**São dadas contrapartidas aos participantes:**

- *pela participação* ☐ Sim ☐ Não ☒ Não aplicável
- *pelas deslocações* ☐ Sim ☐ Não ☒ Não aplicável
- *pelas faltas ao emprego* ☐ Sim ☐ Não ☒ Não aplicável
- *por outras perdas e danos* ☐ Sim ☐ Não ☒ Não aplicável

## CUSTOS / PLANO FINANCEIRO

**Os custos da investigação são suportados por:**

☐ Investigador ☐ Promotor ☐ Serviço onde é realizado

☒ Não aplicável Outro: _____

**Existe protocolo financeiro?** ☐ Sim ☒ Não

## LISTA DE DOCUMENTOS ANEXOS

excluir

- [x] Pedido de autorização ao Presidente do Conselho de Administração do Centro Hospitalar de São João *(se aplicável)*
- [ ] Pedido de autorização à Diretora da Faculdade de Medicina da Universidade do Porto *(se aplicável)*
- [x] Protocolo do estudo
- [x] Declaração do Diretor de Serviço onde decorre o estudo
  *(sendo um estudo na área de enfermagem deve anexar também a concordância da chefia de enfermagem)*
- [x] Profissional de ligação
- [ ] Informação dos orientadores
- [ ] Informação ao participante
- [ ] Modelo de consentimento
- [ ] Instrumentos a utilizar *(inquéritos, questionários,escalas, p.ex.)*: _____
- [x] Curriculum Vitae abreviado *(máx. 3 páginas)*
- [ ] Protocolo financeiro
- [ ] Outros:

## COMPROMISSO DE HONRA E DECLARAÇÃO DE INTERESSES

*Declaro por minha honra que as informações prestadas neste questionário são verdadeiras. Mais declaro que, durante o estudo, serão respeitadas as recomendações constantes da Declaração de Helsínquia (1960 e respetivas emendas), e da Organização Mundial da Saúde, Convenção de Oviedo e das "Boas Práticas Clínicas" (GCP/ICH) no que se refere à experimentação que envolve seres humanos. Aceito, também, a recomendação da CES de que o recrutamento para este estudo se fará junto de doentes que não tenham participado em outro estudo, nos últimos três meses. Comprometo-me a entregar à CES o relatório final da investigação, assim que concluído.*

Porto, 30 de Novembro de 2018

Nome legível: Diogo Dias Ramos

Diogo Dias Ramos
assinatura

**Parecer da Comissão de Ética do Centro Hospitalar de São João/ FMUP** Emitido na reunião plenária da CE de 14 / 12 / 18

A CES aguarda o esclarecimento das questões expendidas no parecer.

Prof. Doutor Filipe Almeida
Presidente da Comissão de Ética

Centro Hospitalar **São João**.

CONSIDERADOS QUE FORAM COMO SATISFATÓRIOS OS ESCLARECIMENTOS PRESTADOS PELO(A) INVESTIGADOR(A), A CES APROVA POR UNANIMIDADE O PARECER DO RELATOR, PELO QUE NADA TEM A OPOR À REALIZAÇÃO DESTE PROJETO DE INVESTIGAÇÃO.

19, 12, 18

Prof. Doutor Filipe Almeida
Presidente da Comissão de Ética

RESPONSÁVEL PELO ACESSO À INFORMAÇÃO

SÃO JOÃO

# Pedido de Reutilização de Registos Clínicos para Investigação e Desenvolvimento (I&D)

Número do Pedido
4|8|0|1|6|0|3|5|
*(A preencher pelo Gabinete de Apoio ao RAI)*

Exmo. Senhor
*Responsável pelo Acesso à Informação*
*(Artigo 9.º da Lei n.º 26/2016, de 22 de agosto)*
Dr. Rui de Vasconcellos Guimarães

SÃO JOÃO

AUTORIZADO
RAI - Responsável pelo Acesso à Informação no Centro Hospitalar de São João
(Art. 9º, Lei 26/2016, de 22/8)
21/12/18

## 1. Identificação do(s) Investigador(es) *Preenchimento Obrigatório*

### 1.1. Investigador Principal

Nome Diogo Dias Ramos
Contacto telefónico +|3|5|1|9|1|3|2|8|2|7|4|0|
Endereço eletrónico diogo.dias.ramos @ gmail.com

### 1.2. Investigador(es) Associado(s)

**Número Total:** 3

Nome Manuel Alberto de Almeida e Sousa Falcão
Contacto telefónico +|3|5|1|9|1|9|2|1|6|5|1|0|
Endereço eletrónico falcao @ med.up.pt

Nome Sónia Cristina Torres da Costa
Contacto telefónico +|3|5|1|9|1|8|8|5|3|6|4|3|
Endereço eletrónico sonia.torres.costa @ gmail.com

Nome Mariana Leuzinger Dias
Contacto telefónico
Endereço eletrónico mariana.ldias @ gmail.com

### 1.3. Afiliação Institucional do Investigador Principal

#### 1.3.1. Grupo Profissional

☐ Médico(a) ☐ Enfermeiro(a) ☐ Docente ☒ Estudante
☐ Outro. Qual?

#### 1.3.2. Documento de identificação pessoal ou profissional

☐ Cartão de Cidadão ☐ Bilhete de Identidade ☐ Célula Profissional
☐ Cartão de Docente ☒ Cartão de Estudante ☐ Outro. Qual?
Número de Documento 2|0|1|3|0|3|3|8|0|

## 2. Enquadramento e Identificação do Trabalho de Investigação e Desenvolvimento *Preenchimento Obrigatório*

### 2.1. Enquadramento da investigação

☒ Trabalho académico de investigação e desenvolvimento:
☐ Não conferidor de grau
☐ Conferidor de grau: ☐ Licenciatura ☒ Mestrado ☐ Doutoramento
☐ Projeto de investigação e desenvolvimento

RAI-IM002-0

**2.2. Entidade(s) que tutela(m) a investigação**

☒ Centro Hospitalar de São João

*Serviço:* Oftalmologia

☒ Universidade do Porto

*Faculdade / Instituto:* Faculdade de Medicina da Universidade do Porto

☐ Outra Instituição. *Qual?* _____

**Há alguma parceria entre instituições?**

☒ Não ☐ Sim. Qual(is)? _____

**2.3. Orientador** *Se Aplicável*

Contacto telefónico | + | 3 | 5 | 1 | 9 | 1 | 9 | 2 | 1 | 6 | 5 | 1 | 0 |

Endereço eletrónico falcao @ med.up.pt

**2.4. Título provisório**

Differences in the incidence of Endophthalmitis after Intravitreal Injections (IVT) with and without topical antibiotic prophylaxis.

*Deverá posteriormente indicar o título definitivo para emissão do Certificado de Reutilização pelo RAI – DAta REuse Certificate for Research – DARE através dos contactos disponíveis no fim deste formulário.*

**2.5. Acesso requerido**

☒ Ficheiro

*Descrição do património informacional a que pretende ter acesso, identificando a informação a obter, i.e. nome, morada, diagnóstico, idade, códigos dos distritos, entre outros.*

Dados demográficos como idade, sexo do doente. Informação clínica relevante como número de injeções que o doente fez, qual a indicação do tratamento, acuidade visual antes da endoftalmite, durante a apresentação do episódio e 3 meses depois, tipo de tratamento efetuado e resultados, compli

☐ Consulta de processos clínicos em ambiente papel:

☐ Bloco ☐ Consulta Externa ☐ Hospital de Dia ☐ Internamento ☐ MCDT ☐ Urgência

*Deverá anexar ficheiro(s) contendo a identificação do pretendido, i.e. números de processos, episódios, números de utente, entre outros.*

Anexar ficheiro no ato de envio

☒ Consulta de registos clínicos eletrónicos

*Especificar os Sistemas de Informação:*

SClínico

Data previsível de fim de utilização das credenciais de acesso | 2 | 0 | 1 | 9 | - | 0 | 2 | - | 0 | 1 |

☐ Outro Acesso. Qual?

**2.3. Pareceres e Autorizações**

☐ Autorização da Hierarquia

☐ Protocolo Científico Aprovado [1]

☐ Parecer da Comissão de Ética para a Saúde (CES) [1]

☐ Parecer do Centro de Epidemiologia Hospitalar [1]

*Deverá anexar ficheiro(s) contendo cópia dos documentos referentes às opções selecionadas.*

Anexar ficheiro no ato de envio

[1] *Obrigatório quando aplicável.*

## 3. Observações *Preenchimento Facultativo*

## 4. Aceitação dos Termos e Condições da Reutilização

Cumulativamente com as obrigações decorrentes da lei já citada *(n.º 2 e 3 do artigo 21 e o n.º 1 e 2 do artigo 12, ambos da Lei n.º 26/2016, de 22 de agosto)* ao submeter o presente pedido concordo e fico ainda vinculado aos seguintes termos e condições:

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- Não vou elaborar, nem ficar na posse, de cópias de bases de dados utilizadas na recolha de informação;
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- Comprometo-me a devolver ao Centro Hospitalar de São João, na pessoa do seu Diretor Clínico, as bases de dados e o resultado da investigação;
- Comprometo-me a ocultar os elementos de identificação da(s) pessoa(s) a quem os registos digam respeito, em futuras e eventuais publicações de resultados;
- Comprometo-me a consultar os processos clínicos nas instalações que me forem indicadas para o efeito;
- Comprometo-me a obter os necessários pareceres, quer da Comissão de Ética do Hospital, quer do Centro de Epidemiologia Hospitalar, sempre que necessário;
- Comprometo-me a citar as fontes sempre que publicitar o trabalho de investigação independentemente de requerer a Certidão de Reutilização (DAta REuse Certificate for Research – DARE);
- Tomei conhecimento, que a violação de qualquer dos compromissos aqui assumidos, resultará no apuramento de responsabilidades disciplinares, civis e penais e ainda, à impossibilidade futura de aceder a informação de saúde para fins de investigação.

## 5. Decisão do investigador sobre requerer a DAta REuse Certificate for Research – DARE *Preenchimento Obrigatório*

☒ Pretendo desde já requerer a Certidão de Reutilização (DARE) cujo sentido, valor e significado consultei em *http://portal-chsj.min-saude.pt/pages/710.*

☐ Não pretendo requerer a Certidão de Reutilização (DARE) cujo sentido, valor e significado consultei em *http://portal-chsj.min-saude.pt/pages/710.*

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*Nota 2: Se o presente pedido for entregue presencialmente, assina e exibe o documento de identificação a quem recebe o pedido.*

Data 2018 - 11 - 30

Diogo Dias Ramos

***Investigador Principal***

**Em caso de dúvida no preenchimento contacte através dos endereços eletrónicos**
rai.reutilizacao.id@chsj.min-saude.pt **ou** ruiguimaraes@chsj.min-saude.pt
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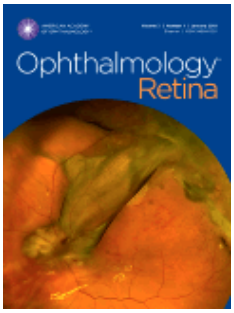
SUBMETER

# OPHTHALMOLOGY RETINA

AUTHOR INFORMATION PACK

## TABLE OF CONTENTS


- **Description** **p.1**
- **Editorial Board** **p.1**
- **Guide for Authors** **p.2**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For details of the Alpins methodology and graphical reporting, please consult the following resources: Alpins N. Astigmatism analysis by the Alpins method. J Cataract Refract Surg 2001;27:31-49. Alpins NA. Vector analysis of astigmatism changes by flattening, steepening, and torque. J Cataract Refract Surg 1997;23:1503-14. Alpins NA. A new method of analyzing vectors for changes in astigmatism. J Cataract Refract Surg 1993;19:524-33. Reinstein DZ, Archer TJ, Randleman JB. JRS standard for reporting astigmatism outcomes of refractive surgery. J Refract Surg 2014;30:654-9.

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## Cancer Classifications

We encourage authors to use the American Joint Commission on Cancer TNM Classification scheme when describing patients with ophthalmic malignancies. AJCC Cancer Staging Manual. (7th ed. New York, NY: Springer; 2009). The classification scheme can also be found at https://cancerstaging.org/references-tools/Pages/What-is-Cancer-Staging.aspx.

## Clinical Trials and Clinical Trial Registration

A clinical trial is defined as any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes. With regards to the reporting of clinical trials, Ophthalmology's policies are similar to the policies of The New England Journal of Medicine (NEJM), and The Journal of the American Medical Association (JAMA) which can be viewed at http://jama.ama-assn.org/misc/authors.dtl.

Consistent with these policies, prospective clinical trial registration is required. Please state in the Methods section where the clinical trial registration information is publicly available. Satisfactory public databases include the NIH's http://www.clinicaltrials.gov and the site from the International Standard Randomized Controlled Trials at http://www.controlled-trials.com.

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Liesegang TJ, Bartley GB. Toward transparency of financial disclosure. Ophthalmology 2014;121:2077-9.

Liesegang TJ, Bartley GB. Footnotes, acknowledgments, and authorship: toward greater responsibility, accountability, and transparency. Ophthalmology 2014;121:2297-8.

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*Examples:*

Reference to a journal publication:
1. Van der Geer J, Hanraads JAJ, Lupton RA. The art of writing a scientific article. *J Sci Commun.* 2010;163:51-59.

Reference to a book:
2. Strunk W Jr, White EB. The Elements of Style. 4th ed. New York, NY: Longman; 2000.

Reference to a chapter in an edited book:
3. Mettam GR, Adams LB. How to prepare an electronic version of your article. In: Jones BS, Smith RZ, eds. Introduction to the Electronic Age. New York, NY: E-Publishing Inc; 2009:281-304.

Reference to a website:
4. Cancer Research UK. Cancer statistics reports for the UK. http://www.cancerresearchuk.org/aboutcancer/statistics/cancerstatsreport/; 2003 Accessed 13.03.03.

Dataset:
5. Oguro M, Imahiro S, Saito S, Nakashizuka T. Mortality data for Japanese oak wilt disease and surrounding forest compositions, Mendeley Data, v1; 2015. http://dx.doi.org/10.17632/xwj98nb39r.1

## Reporting Refractive Surgery Outcomes and Astigmatism

Astigmatism_Reporting_links_to_Reporting_Refractive_Surgery_Outcomes_and_AstigmatismWhen reporting refractive surgery outcomes, please include 6 graphs to illustrate the following (references 1-3): Uncorrected distance visual acuity Change in corrected distance visual acuity Spherical equivalent (attempted versus achieved) Spherical equivalent refractive accuracy Spherical equivalent refraction stability Refractive astigmatism

Descriptions of astigmatism should adhere to terminology and graphical representations originally described by Alpins (references 4-6). An editorial by Reinstein et al (reference 7) presents the argument for standardization.

Waring GO III, Reinstein DZ, Dupps WJ, Kohnen T, Mamalis N, Rosen ES, Koch DD, Obstbaum SA, Stulting RD. Standardized graphs and terms for refractive surgery results. J Refract Surg 2011;27:7-Erratum in J Refract Surg 2011;27:88. Reinstein DZ, Waring GO III. Graphic reporting of outcomes of refractive surgery. J Refract Surg 2009;5:975-8. Waring GO III. Standard graphs for reporting refractive surgery. J Refract Surg 2000;16:459-66. Erratum in J Refract Surg 2001;17:following table of contents. Alpins N. Astigmatism analysis by the Alpins method. J Cataract Refract Surg 2001;27:31-49. Alpins NA. Vector analysis of astigmatism changes by flattening, steepening, and torque. J Cataract Refract Surg 1997;23:1503-14. Alpins NA. A new method of analyzing vectors for changes in astigmatism. J Cataract Refract Surg 1993;19:524-33. Reinstein DZ, Archer TJ, Randleman JB. JRS standard for reporting astigmatism outcomes of refractive surgery. J Refract Surg 2014;30:654-9. Erratum in: J Refract Surg 2015;3:129.

## Reports

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## Review Articles

*Systematic Reviews and Meta-analysis*

Systematic reviews seek to collect and critically assess all evidence that fits pre-specified criteria to answer a clinical question pertaining to the cause, diagnosis, prognosis, prevention, or therapy for a condition. A systematic review may contain a meta-analysis, which uses statistical methods to combine results from similar but independent studies.

Features of a systematic review include "a clearly stated set of objectives with pre-defined eligibility criteria for studies; an explicit, reproducible methodology; a systematic search that attempts to identify all studies that would meet the eligibility criteria; an assessment of the validity of the findings of the included studies, for example through the assessment of risk of bias; and a systematic presentation, and synthesis of the characteristics and findings of the included studies (Higgins JPT, Green S (editors). Chapter 1. *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011).

It is possible to conduct a systematic review and meta-analysis of the evidence supporting any type of research question, whether the question is about intervention effectiveness or harm, etiology, prognosis, diagnostic accuracy, toxicity, incidence, or prevalence. Where intervention effectiveness questions are typically addressed by randomized controlled trials, most other questions are addressed using observational studies. Systematic reviews may be conducted for human or animal studies, in vivo or in vitro.

For standards and classic references in conducting systematic reviews and meta-analyses, please refer to: Institute of Medicine. *Finding what works in health care: standards for systematic reviews.* 2011.Chandler J, Churchill R, Higgins J, Tovey D. *Methodological standards for the conduct of new Cochrane Intervention Reviews.* Version 2.2. 17 December 2012.Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. *Handbook for Diagnostic Accuracy Reviews* [Draft]Little J, Higgins JPT (editors). *The HuGENE™ HuGE Review Handbook*, version 1.0. Guidelines for systematic review and meta-analysis of gene disease association studies (see also Systematic Reviews of Genetic Association Studies, PLoS Medicine 2009;6(3):e1000028)*Systematic Reviews.* CRD's guidance for undertaking reviews in health care. Centre for Reviews and Dissemination, University of York, 2009

For reporting systematic reviews and meta-analyses, if you are submitting a report ofA systematic review and/or meta-analysis of randomized controlled trials, please follow the PRISMA guidelines for reporting; A systematic review and/or meta-analysis of observational studies, please follow the MOOSE guidelines for reporting.

A complete list of guidelines for reporting systematic reviews and meta-analyses can be found at the Enhancing the QUAlity and Transparency Of health Research (EQUATOR) network's website. We strongly recommend you visit the EQUATOR's website for reporting guidelines for systematic reviews and meta-analyses of other study designs (e.g., individual participant data, health equity, genetic association studies). The Cochrane Collaboration also has developed Standards for the Reporting of Cochrane Intervention Reviews.

**Title Page:**

The title should clearly describe the research question and identify the report as a systematic review, meta-analysis, or both in the subtitle. (Example: Anti-vascular endothelial growth factor for neovascular age-related macular degeneration - A systematic review and meta-analysis.)

**Prcis:**

The prcis should indicate a new insight the article offers or a principal controversy that is addressed.

**Structured Abstracts:**

Abstracts for systematic reviews and meta-analysis must be limited to 350 words and include five sections following the PRISMA guidelines: Topic: provide an explicit statement of the specific clinical question being addressed with reference to a brief description of the participants, interventions (or exposures), comparators, and outcomes examined. Clinical relevance: characterize the magnitude and importance of the condition; when relevant, define the current standard of care. Methods: describe the key eligibility criteria for including studies in the systematic review, key databases searched and search dates, methods of assessing the risk of bias in the individual studies. Results: summarize the number and type of included studies and participants, and relevant characteristics of studies; describe the results of main outcomes (benefits and harms), preferably indicating the number of studies and participants for each. If a meta-analysis was done, include summary measures and confidence intervals; report the direction of the effect or association (i.e., which group is favored) and size of the effect using language meaningful to clinicians and patients. Conclusion: summarize the strengths and limitations of the evidence, your general interpretation of the results, and important implications.

Note that the abstract content and conclusions should agree with what is in the manuscript text.

**Manuscript text**

The text should use standard journal formatting and be divided into four distinct sections. The brief descriptions below are gathered from the PRISMA, the MOOSE guidelines, and the Standards for the Reporting of Cochrane Intervention Reviews. The text should report institutional review board approval or exemption, financial disclosures and potential conflicts of interest of the authors, and funding sources of the review.

1. **Introduction** (unlabeled) should provide a concise description of the condition or clinical problem addressed by the review question, provide perspectives on the importance of its management to patient well-being and quality of life, and why it is important to do the review. Always end the introduction with a clear and concise statement of the study's main objectives or hypotheses.

2. **Methods**: The methods section should include the following subheadings: *Eligibility criteria for considering studies for this review*: state eligibility criteria for participants, interventions (or exposures) and comparators, and eligible study design(s) if applicable. Define primary and secondary outcomes of the review and state whether an article had to report measurement of at least one of the outcomes to be eligible. If so, provide rationale. *Search methods for identifying studies*: list all information sources searched, including databases, trial registries, websites, difficult-to-access literature (e.g., grey literature, conference proceedings), reference lists of included studies, and whether individuals or organizations were contacted. For all searches, provide the date of the last search and whether there was any time period or language restriction. Present the exact full search strategy (or strategies) used for at least one database in an Appendix with sufficient detail to permit replication. Report which software was used to manage the records identified and eligibility status. *Study selection*: describe the process for selecting studies, how many people were involved at each step of the review, whether any steps were done by more than one person, and if so whether they worked independently and how different opinions were resolved. D*ata collection and risk of bias assessment*: List and define data items extracted from the reports of included studies. Describe methods used for assessing risk of bias of included studies (risk of bias is a formal assessment of what is often considered study "quality"), and how this information was used in any data synthesis. Describe the process for data extraction and risk of bias assessment, how many people were involved at each step, whether any steps were done by more than one person, and if so whether they worked independently and how different opinions were resolved. Report the software used for data collection and management. *Data synthesis and analysis*: state the methods for combining results across studies, which include qualitative synthesis (see Chapter 4, section on "Qualitative Synthesis of the Body of Evidence; *Finding what works in health care: standards for systematic reviews*) and quantitative synthesis (i.e., meta-analysis). State the summary measures used to quantify the treatment effect or association such as risk ratio, odds ratio, and difference in means. Describe methods for assessing clinical, methodological, and statistical heterogeneity (e.g., I2 statistic, tau-squared, statistical test). Describe methods for additional analyses such as meta-regression, subgroup analysis, and sensitivity analysis, if done, indicate which were pre-specified. State the statistical software used for analysis. Indicate whether a systematic review protocol exists, if so, where and how it can be accessed; and if available, provide systematic review registration information including registration number.

3. **Results**: Provide numbers of studies retrieved, screened, assessed in full for eligibility, included in the review, and included in the meta-analysis, with reasons for exclusion at each stage, ideally with a flow diagram. Present characteristics of included studies including information on the study design, participants, interventions (or exposures) and comparators, outcomes, and source of funding, ideally in a table. Present domain-based risk of bias assessment of each study, ideally in a table or a figure. Composite quality scores and scales are discouraged. For all outcomes considered, irrespective of the direction or strength of the results, present, (1) simple summary data for each group, and (2) estimates of treatment effect (or association) between groups with a measure of statistical uncertainty (e.g., confidence intervals). If meta-analysis was done, report meta-analytical results ideally with a forest plot, number of studies and participants for each meta-analysis, as well as measures of statistical heterogeneity. Present results of any additional analyses (such as meta-regression, subgroup analysis, and sensitivity analysis) if done. Provide a thoughtful qualitative synthesis by analyzing the nature, strengths, and weaknesses of the evidence, and developing a deeper understanding of how an intervention might work (or not), or whether a true association exists, for whom and under what circumstances.

4.**Discussion**: Summarizes the main findings including the strength of evidence for each main outcome. Provide a general interpretation of the evidence considering their relevance to key stakeholders, including patients, healthcare providers, researchers, payers, and policy makers. A Summary of Findings or GRADE table is optional. Discuss limitations at study and outcome level

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