Aus dem

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The quality of reporting of randomized controlled trials of intravitreal anti-VEGF therapy based on CONSORT statement

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Abbreviations

AI	artificial intelligence
AMD	age-related macular degeneration
ANCHOR	Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration
CATT	Comparison of Age-Related Macular Degeneration Treatments Trials
CONSORT	Consolidated Standards of Reporting Trials
DME	diabetic macular edema
EBM	evidence-based medicine
FDA	U.S. Food and Drug Administration
GCP	good clinical practice
GDP	gross domestic product
GPP	good publication practice
JIF	Journal Impact Factor
MARINA	Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration
nAMD	neovascular age-related macular degeneration
MNV	macular neovascularization
NVG	neovascular glaucoma
OCT	optical coherence tomography
PDR	proliferative diabetic retinopathy
RCT	randomized controlled trial
ROP	retinopathy of prematurity
RPE	retinal pigment epithelium
RVO	retinal vein occlusion
SD	standard deviation
SEM	standard error of the mean
STEM	science, technology, engineering, and mathematics
uCME	uveitic cystoid macular edema
VEGF	vascular endothelial growth factor

1. Introduction

Age-related macular degeneration (AMD) is one of the leading causes of permanent vision impairment, leading to a loss of reading ability among people aged 65 years and older in high income countries (Steinmetz et al., 2021).The protein *vascular endothelial growth factor* (VEGF) was identified to play a key role in the permeability of pathological retinal vessels (Keck et al., 1989). Already in 1956 George Wise speculated about an hypothetical unknown factor X, which might develop during retinal anoxia (Wise, 1956). In 1989 two independent groups reported the factor. One author extracted the protein from pituitary follicular cells which was found able to activate angiogenesis (Leung et al., 1989). The other group independently reported a vascular permeability factor (VPF) (Keck et al., 1989). After sequencing the protein, it became clear, that both factors were identic. In 1994, elevated Vascular Endothelial Growth Factor (VEGF) has been identified in hypoxic retina showing its role in the development of ocular neovascularization. The impact on retinal vessels was demonstrated in a primate model (Miller et al., 1994). At the end of 1994, Aiello et al. published a trial with 163 patients. They collected specimens of the vitreous body using sterile tubes and detected VEGF in the samples (Aiello et al., 1994).

Bevacizumab was approved by the FDA (US Food and Drug Administration) for the first line therapy of patients with metastatic colorectal carcinoma in 2004 (US Food and Drug Administration and Research, 2004a) (Hurwitz et al., 2004, Ferrara et al., 2004). 2004 the first approved anti-VEGF therapy in ophthalmology for neovascular AMD (nAMD) was Pegaptanib (US Food and Drug Administration and Research, 2004b).

In 2005 a small study showed that systemic bevacizumab achieved a significant gain in visual acuity, reduction of retinal thickness on optical coherence tomography (OCT) and beneficial outcomes in angiography (Michels et al., 2005). After a successful single treatment attempt (by MD P.J. Rosenfeld administering bevacizumab in the vitreous body), the drug became increasingly popular to

prevent patients from going blind who could previously only be treated with PDT or pegaptanib (Rosenfeld, 2009)

The antibody fragment ranibizumab (Lucentis) had the theoretical advantage of better tissue penetration. MARINA (Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD) and ANCHOR (Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in AMD) in 2006 were the first phase 3 trials to show improvement in visual outcomes in neovascular AMD with ranibizumab (Rosenfeld 2006) (Brown 2006).

Consequently, Ranibizumab was approved by the FDA on June 30, 2006 for the treatment of neovascular age related macular degeneration (US Food and Drug Administration and Research, 2006). The Comparison of Age-Related MACULAR Degeneration Treatment Trials (CATT) showed equal effects of the two drugs bevacizumab or ranibizumab (Martin et al., 2011). In the following years ranibizumab received FDA approvals for the treatment of diabetic macular edema (DME), diabetic retinopathy, macular edema due to retinal vein occlusion (RVO) and myopic choroidal neovascularization (US Food and Drug Administration and Research, 2017).

In 2002 a new drug, aflibercept (2mg dosing), was developed. The fusion protein was developed by Regeneron as a decoy receptor with high affinity to VEGF. Phase 3 results from the VIEW trials revealed that 2 mg of aflibercept every 2 months was not inferior to ranibizumab dosed monthly (Heier et al., 2012). Aflibercept was approved by the FDA on November 18, 2011 (US Food and Drug Administration and Research, 2011).

Brolucizumab has been approved by the FDA for the treatment of nAMD and DME in 2019. A certain rate of vasculitis has been observed in a post approval monitoring (Monés et al., 2021). The advantage of this agent is a dosing interval of 12 weeks in 50% of the patients with nAMD (Dugel et al., 2020) and with DME (Brown et al., 2022).

In 2022, faricimab received the FDA approval as therapy of nAMD and DME. The uniqueness of this drug is the bispecific molecule, that targets VEGF and angiopoietin-2. It reaches 16 weeks in the dosing schedule in 50% of the patients

with nAMD (Heier et al., 2022) and DME (Wykoff et al., 2022). The safety and the efficacy of the treatment of macular edema caused by RVO with faricimab were proved in the BALATON and COMINO trials and in 2023 faricimab has been approved by the FDA for the treatment of Retinal vein occlusion (RVO) (US Food and Drug Administration and Research, 2023, Tadayoni et al., 2024).

Recently, high-dose aflibercept received the FDA approval. High-dose aflibercept (8mg dosing) was frequently used with a 16-weeks dosing interval possible for patients with nAMD (Lanzetta et al., 2024). There might be a reduction of the treatment burden without disadvantages for the central retinal thickness compared to aflibercept (2mg). In the DME, the longer dosing interval did not lead to a detrimental effect on the average outcome (Brown et al., 2024).

VEGF in retinal disease

VEGF plays a major role in the pathogenesis of neovascular AMD, macular edema and diabetic retinopathy and other retinal disease like retinal vein occlusion. Retinal disease are often related to chronic inflammation (Wong et al., 2022). VEGF is a disulfide-bond homodimer glycoprotein with a selective mitogenic activity (Muller et al., 1997). Several retinal cells can secrete VEGF due to the inflammatory mediators (Amadio et al., 2016). VEGF is expressed in endothelial cells as well as in pericytes, monocytes and neural cells. A complex of different VEGF types elevates vascular permeability, causes vascular leakage and macular edema. In the angiogenesis induced by VEGF leak vessels grow and lead to fluid in the macula or in other parts of the retina. In consequence the layer of the photoreceptor gets damaged. (Ferris et al., 2013).

For example, the physiological autophagy in the retinal pigment epithelium (RPE) is impaired and so the chronic inflammation proceeds to neovascular AMD (Liu et al., 2016).nAMD can start with neovascularization in the retina or in the choroid. The latest nomenclature distinguishes different subtypes of macular neovascularization. The definitions of these types take into account the origin of new abnormal vessels, such as the retina or the choroid (Spaide et al., 2020). Neovascular AMD causes the majority of severe central vision loss by AMD (Ambati et al., 2003).

Diabetic retinopathy is a microangiopathy. Hyperglycaemia can induce via multiple metabolic pathways a microvascular damage in the different layers and cells of the retina. For example, a high glucose level in the blood causes an apoptosis of the pericyte in the vessels. In early stages of DR microaneurysm develop consequently. The impaired vessels due to the loss of endothelial cells and pericytes lead to occlusion in vessels and hypoxia in the retina. (Miller and Fortun, 2018). VEGF is upregulated under hypoxia and leads to an abnormal vessel growth (Shweiki et al., 1992).
Proliferative diabetic retinopathy (PDR) can be seen as a progressed state of the diabetic retinopathy with neovascularization. That abnormal growth of new vessels can lead to bleeding in the vitreous body or can cause a tractional retinal detachment (Wang and Lo, 2018).Hyperglycemia also induces inflammatory factors e.g. VEGF and leads to hypoxia in the retina, which leads to hyperpermeability of the retinal capillaries and edema e.g. DME (Wang and Lo, 2018).DME is the most common cause of visual impairment in patients with type 2 diabetes (Browning et al., 2018).

RVO is an occlusion of the branch or central vein in the retina. The blockage causes a high pressure in the capillaries, which can result in leakage of fluid or blood in the retina or macula. Hypoxia may be present as well. As a result of those mechanism VEGF in retina is elevated after a RVO. Consequently macular edema and neovascularization may develop. Macular edema is the main cause of vision loss after a RVO (Fraenkl et al., 2010).
Intravitreal anti-VEGF therapy is one of the most often used therapy in ophthalmology. Anti-VEGF therapy has changed ophthalmology: Conditions which were untreatable became treatable in a manner that blindness could prevented with it (Kent 2019). According to a large scale meta-analysis of Steinmetz et. al. the prevalence of blindness due to age-related macular degeneration declined worldwide from 1990 to 2020 (Steinmetz et al., 2021).

Clinical studies and knowledge transfer

Especially for innovative drugs and new therapy options, the presentation of relevant data should take place in medical journals, however drug promotion can be found as well within advertisements and educational events. The type of presentation and the structured peer review process are intended to ensure that certain requirements for good clinical practice (GCP), ethical standards and scientific structures were met. Cochrane - an organization that provides independently systematic reviews for healthcare specialists worldwide, is important for developing guidelines in specific managements of diseases. In the 1990s a lot of journals started to publish articles online. In the following years an open access movement gained more impact on scientific journals. The basic idea of the open access to journals was that peer-reviewed journals and articles could be read and copied freely (Laakso et al., 2011). In the last years a rising number of scientific articles published by so called “predatory journals” became an issue in research generally. In these journals the focus is on the business of instant publishing after a brief review once the authors paid a fee. These articles hence only receive a superficial review with only a small number of them not being validated (Boulos et al., 2022). In 2010 “Beall`s list” were published with possibly predatory-unethical and questionable- journals.

For these reasons it is more and more important to have tools and parameters to identify good quality of reporting. Boulos et. al. described the database CENTRAL to provide questionable articles. In consequence, authors and reviewers have to be aware of it. “doaj.org” provides is a whitelist of criteria that are typical for predatory journals.

An attribute to differentiate from predatory journals could be the adherence to reporting standards like the CONSORT statement (Hayden, 2020). The Consort statements get discussed in detail below. Consequently, valuable publication of the different trials is also very important to set apart from predatory journals and to enable good clinical practice.

In the large number of publications there was a need of tools to choose the right publication or journal with a high quality. The Journal impact factor (JIF) is an

index that demonstrates the mean number of citations of a journal in a year compared in the last two years (Formula: JIF $_y = \frac{Citations\ y}{publications\ y-1 + publications\ y-2}$). The Journal Impact factor is the first tool to rank them. The impact factor was originally invented in the 1960s to help librarians rate adequate academic journals for the library, but these days the impact factor is misunderstood as a factor of the reputation of a journal (Garfield, 2006).
The mean JIF is different in the diverse scientific fields. Hence the JIF should not be compared among different scientific fields (Scully and Lodge, 2005).

Background of controlled clinical trials

In 1753 James Lind released the first controlled trial about the treatment of scurvy. In this trial he selected twelve sailors, that suffered from scurvy, and divided them in groups of a pair. Each group became different treatment, e.g. cider, vinegar, oranges/lemons, sea water. Lind observed that the sailors who had eaten oranges and lemons were fit again and able to work after six days (Lind, 1753). It took more than 40 years for the Royal navy to have lemons aboard obligatory. The reason for it might be found in Lind´s vague conclusion in his publication as he did not give a clear recommendation for the treatment with oranges/lemons in his publication (Milne, 2012).
The first randomized clinical trial took place in 1948. It was arranged by Professor Austin Bradford Hill. He was known because of the handbook “Principle of Medical Statistics” that he had published about a decade before (Bothwell and Podolsky, 2016). A randomized controlled trial (RCT) is a prospective, comparative, quantitative trial performed under defined conditions with random allocation of interventions. RCTs measure the effectiveness of a new intervention or treatment. Participants were randomly assigned in a control and experimental group. Randomization can reduce bias, because the act of randomization aims to balance the characteristics of the participants (Bhide et al., 2018). RCTs are essential in the evidence- based medicine. The definition of the evidence- based medicine (EBM) as “the conscientious, explicit and judicious use of current best evidence in making decisions about the care of the individual patient” means “integrating individual clinical expertise with the best available external clinical

evidence from systematic research" (Sackett et al., 1996). EBM is a major part of the current clinical practice, aiming to achieve the best available evidence from research to make individual decision for patients' treatment (Smith et al., 2006). In the evidence-based medicine pyramid, systematic reviews and meta-analysis are at the top, below are RCTs and at the bottom case reports. RCTs have a high level of evidence accordingly to the evidence-based medicine pyramid (Murad et al., 2016).

In 1996, editors of journals, researchers and epidemiologists published the first CONSORT (Consolidated Standards of Reporting Trials) statement (Moher et al., 2010). Two groups (SORT group and the Asilomar working group) had met independently (1993 and 1994). They wanted to improve the quality of reporting RCTs, in order to enable the reader an informed judgement about the validity of the study. The transparent communication of study design, treatment allocation, outcome as well as adverse events should result in a comprehensive picture, which patients might benefit from (Begg et al., 1996).The two groups decided to meet and review their checklist. The joint discussion resulted in the published version of the CONSORT (Consolidated Standards of Reporting Trials) statements in 1996 (Moher et al., 2001).

The CONSORT statement represents a guideline that is internationally established to improve the reporting of RCTs. The items of the CONSORT Checklist 2010 (used in this work) are divided into the following topics:

- Title and abstract
- Methods
- Results
- Discussion and
- other information.

The CONSORT statement is a continuous initiative that aims to minimize inadequate reporting of RCTs (Moher et al., 2010). The CONSORT statement is revised regularly. In 2008, Hopewell et. al. released an extension of the CONSORT criteria for abstracts (Hopewell et al., 2008). In 2010, a second revision of the CONSORT statements has been released (Moher et al., 2010). It

included explanations to each CONSORT items and the CONSORT item list has been completed with a few sub-items (in total 37 items).
In 2020, the CONSORT-AI extension has been released, because more trials with artificial intelligence (AI) were conducted (Liu et al., 2020). In 2022, an extension of the Checklist 2010 has been elaborated (Butcher et al., 2022).

In 2001, Sánchez-Thorin et. al. published an article in which the adherence of reported RCTs to the CONSORT criteria within the journal “Ophthalmology” Volume 106 in 1999 were explored. The score (33.42 of 57 possible CONSORT items) was significantly higher compared to the score 15.8 of 56 possible CONSORT items found in RCTs as displayed in the journal “Ophthalmology” in the period of 1991 to 1994 (Scherer and Crawley, 1998); (Sánchez-Thorin et al., 2001).
Before the second revision of the CONSORT Statement in 2010 a systematic review of Fung et.al. worked out that the mean CONSORT score was 83% in all RCTs about the therapy of neovascular AMD published before 31st of October 2007 (Fung et al., 2009).
Yao et. al. reported in a systematic review of a low mean CONSORT score of 39% in RCTs about ophthalmic surgery in the whole year 2011.
Only 47% of RCTs (with a JIF higher than 5) about AMD in the time period from 1st of January 2004 to 31st of December 2013 reported a sample size planning according to an investigation of Tulka et. al. (Tulka et al., 2020). Knippschild et. al. investigated the documentation of the baseline characteristics in a table (CONSORT statement criteria number 15) in the same indication. In only 51%, the baseline characteristics were documented correctly (Knippschild et al., 2020).
In a pilot study, six trials about cataract surgery were evaluated. The median adherence to 37 CONSORT items was 65% (Baulig et al., 2018). Rikos et. al. reported that articles about RCTs of multiple sclerosis with >75% adherence of CONSORT items had an significant increase during the period from 2000 to 2016 (Rikos et al., 2016).

In 2006, Balasubramanian et. al. reported that the CONSORT score was significantly related with a higher number of authors, the Journal Impact factor and multicentric trials in general surgery (Balasubramanian et al., 2006).
All published RCTs in the year 2006 in the four top journals (New England Journal of Medicine (NEJM), Journal of the American Medical Association (JAMA), British Medical Journal (BMJ) and The Lancet) were analyzed in Berwanger et.al. according to the previous CONSORT checklist. The randomization was named in the title in 54.6 % (98.7% in the abstract). In contrast, methods like blinding (in 9.3%) or losses to follow-up (14.1%) were rarely reported (Berwanger et al., 2009).
In 2010 Ghimire et. al. analyzed the implementation of CONSORT for the abstracts of RCTs in four high-impact medical journals, such as The NEW England Journals of Medicine (NEJM), The Lancet, The Journal of American Medical Association (JAMA) and the British Medical Journal (BMJ): In 58.7% the randomization was named in the abstract, only 21% of papers described the methodology of blinding (Ghimire et al., 2012).

A detailed investigation can clarify the quality of the documentation and thus of the trial itself.
The CONSORT statement has been previously discussed as a tool of quality appraisal. The protocol can serve as a guide for reporting of RCTs. When evaluating the main RCTs of intravitreally administered therapies in different indications, the analysis can promise an assessment of which evidence for the treatment was found.

Title and abstract	
1a	Identification as a randomized trial in title
1b	Structured summary of trial design, methods, results, and conclusions
Introduction	
2a	Scientific background and explanation of rationale
2b	Specific objectives or hypotheses
Methods	
3a	Description of trial design (such as parallel, factorial) including allocation ratio
3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons
4a	Eligibility criteria for participants
4b	Settings and locations where the data were collected
5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered
6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed
6b	Any changes to trial outcomes after the trial commenced, with reasons
7a	How sample size was determined
7b	When applicable, explanation of any interim analyses and stopping guidelines
Randomization	
8a	Method used to generate the random allocation sequence
8b	Type of randomization; details of any restriction (such as blocking and block size)
9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned
10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions
11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how
11b	If relevant, description of the similarity of interventions
12a	Statistical methods used to compare groups for primary and secondary outcomes
12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses
Results	
13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome
13b	For each group, losses and exclusions after randomization, together with reasons
14a	Dates defining the periods of recruitment and follow-up
14b	Why the trial ended or was stopped

15	A table showing baseline demographic and clinical characteristics for each group
16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups
17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)
17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended
18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory
19	All important harms or unintended effects in each group
Discussion	
20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses
21	Generalizability (external validity, applicability) of the trial findings
22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence
Other information	
23	Registration number and name of trial registry
24	Where the full trial protocol can be accessed, if available
25	Sources of funding and other support (such as supply of drugs), role of funders

Table 1: CONSORT 2010 checklist, based on Moher et. al, 2010

Question in focus: studies with intravitreal therapeutics and publication standards

After intravitreal treatment became established in 2005 as a completely new therapeutic modality and revolutionized ophthalmology, the question arose as to what extent the approval studies of more costly agents on the one hand and clinical studies looking at off-label therapy on the other hand were reported in accordance with the requirements of the CONSORT group. With regard to the dimension of drug costs and the number of patients treated this study investigated differences in accuracy in reporting of RCT with intravitreal Anti-VEGF. This study intended to clarify whether different standards might be observed in ophthalmology journals.

After the approval of anti-VEGF therapy more than a decade ago, the systematic assessment was developed to find out how the quality of reporting changed over time and whether the number of complied CONSORT criteria was associated with

the number of subsequent uptakes in the literature, measured by the number of citations. The analysis was started to clarify the influence of a comparatively smaller readership, the impact factors and the sample size.

The hypothesis of whether RCTs in journals with a higher JIF were also published with a higher score regarding the CONSORT statements was tested.

This study aimed to evaluate if there might be a gender bias in the retinal subspecialty with intravitreal injections compared to the field of ophthalmology in general.

It was investigated whether the CONSORT score is associated with parameters like “total citations”, “distribution of the publication years” and “average number of citations per year”.

The expectation was that a higher CONSORT score is associated with a higher number of randomized patients and another quality parameter of RCTs, like blinding. It was investigated whether the number of authors was related to a higher CONSORT score or a higher JIF.

It was of interest whether industry-sponsored trials were published with a higher CONSORT score compared to independent research and whether the multicentric trials were published with a higher CONSORT score.

This work gives an overview of the reporting of the classical intravitreal anti-VEGF therapy (aflibercept, ranibizumab, bevacizumab) in ophthalmology. So far there are few evaluations of the quality of reporting of RCTs in ophthalmology, especially regarding the therapy with intravitreal injection - one of the most common invasive therapy in ophthalmology. It was explored if there were differences in the RCTs of the respective classical anti-VEGF in the association to the CONSORT score and the JIF:

This work is intended to clarify the importance of reporting standards in consideration of the selection or publication bias.

2. Material and methods

2.1. Data sources and search strategies

As part of a systematic review, PubMed was used to search for randomized controlled trials on anti-VEGF.

The search request at PubMed had the following keywords:

“intravitreal”, “intravitreous”
“anti-vegf”
“bevacizumab”, “ranibizumab”, “aflibercept
“humans”

Table 2: search strategy keywords

The publication type and the period were not specified/limited. PubMed was searched for RCTs at the 6th of June 2017 at 16:26 pm CET using the following Boolean operators:

intravitreal[All Fields] OR (intravitreous[All Fields] AND ("bevacizumab"[MeSH Terms] OR "bevacizumab"[All Fields] OR ("anti"[All Fields] AND "vegf"[All Fields]) OR "anti vegf"[All Fields]) AND ("bevacizumab"[MeSH Terms] OR "bevacizumab"[All Fields]) AND ("ranibizumab"[MeSH Terms] OR "ranibizumab"[All Fields]) AND ("aflibercept"[Supplementary Concept] OR "aflibercept"[All Fields]) AND ("humans"[MeSH Terms] OR "humans"[All Fields])

As a result of the first search 2.827 publications were identified. The open- source software PubMed2XL (version 2.01, by Nitin Arora and Roman V. Kiseloiv) was used to govern the data (Microsoft office 365) (Isaak, 2016). The evaluation of the inclusion and exclusion criteria was based on the title and abstracts (Fig. 1).

2.2. Eligibility criteria

The inclusion criteria were RCT including Anti-VEGF (bevacizumab, aflibercept, ranibizumab) that were administered intravitreally. English language of the publication was mandatory.

77 publications were included by reviewing title and abstract.

The remaining publications were analyzed on a full text basis, if the language was English (not English: 2) and the treatment included anti-VEGF drugs (trial about other medication than anti-VEGF: 2); there was no redundancy.

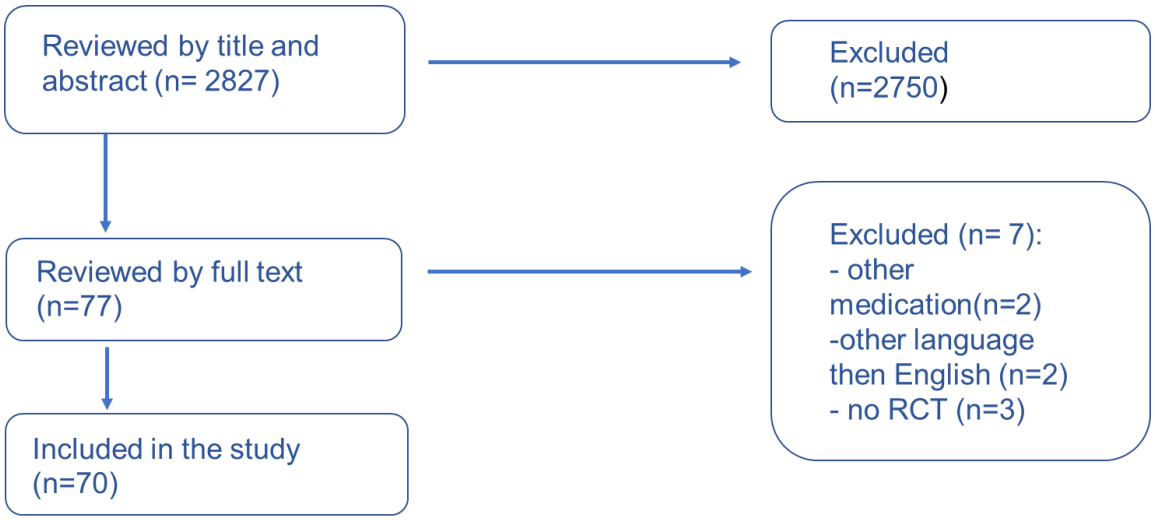


Figure 1 Flow diagram for study inclusion

70 RCTs were finally evaluated concerning the criteria of the CONSORT 2010 checklist (Moher et al., 2010). The number of citations, the journal and its JIF of the year of publication were added (accessed at the web of science: https://jcr.clarivate.com/jcr/browse-journals).

The evaluation was completed with additional criteria such as mono- or multicentric trial, gender of the author, duration of trial, country/continent, in which the trial took place and industry sponsored trial.

The gender of the first author was listed with the following abbreviations: f =(female), m (=male), n (=not specified).

The category “gender” was defined by the given name or a photograph of the author in the publication if available or not specified.

The category “country” was defined as the site where the trial was conducted, in international multicentric trials the country in which the corresponding author resides was used as a reference.

2.3. Scoring

The full text publications of the RCTs were evaluated using the CONSORT 2010 checklist (http://www.CONSORT-statement.org). The list consisted of 25 items including few sub-items (total 37 items). One additional item (to No.13) was included in order to assess whether an article included a participant flow diagram (1=yes/0=no). In addition to No. 4a, the papers were checked for eligibility criteria being listed in a table (y/n). Meeting the requirements with detailed information, as explained in the "CONSORT 2010 Explanation and Elaboration: updates guidelines for reporting parallel group randomized trials" (Moher et al.,2010), criteria were scored in a binary fashion (1: fulfilled, 0: not met).

2.4.Statistical analysis

In the exploratory data analysis using the Software JMP (Cary (North Carolina), USA) the dependent variable was the mean CONSORT score and JIF.

Bar charts, grouped bar charts, scatter plots, box plots and frequency distribution graphs were used to get an overview of the data and trends. Scatter plot matrix was used to explore if there are possible relationships between the variables.

As a measure of central tendency, median or mean were used. As measures of variability the interquartile range, the standard deviation (SD) and the standard error of the mean were used.

Because of strong outliers in the total number of citation, number of randomized patients and the CONSORT score median was presented as it is proved to be more robust to outliers than the mean.

Non-parametric tests (Wilcoxon rank sum test and the Spearman´s rho test) were performed. $P < 0.05$ was considered to be statistically significant.

The Wilcoxon rank sum test was performed to compare the CONSORT score, JIF, duration of trial and the affiliation of authors and the number of randomized patients in the dichotomic groups (industry/non-industry trial, mono-/multicentric and with or without blinding).

The Spearman rho test was used to evaluate the correlation between the CONSORT score and the JIF with the parameters "year of publication", "average

number of citations” (per year), “total number of authors”, “number of randomized patients”, “duration of trial”.
Pearson´s Chi Square test was performed to compare the categorial variables non-industry/industry trial, gender and mono-/multicentric trial.
The Cramer V test was performed to check effect size of the relation between continents and industry trial.

Statistical analysis has been done with Microsoft Excel © for Microsoft 365 (Version 2401 Build 16.0.17231.20194- 32 Bit, Redmond, WA, USA)- and JMP © software, (SAS Institute, version 16/16.2, Cary, NC, USA)

3. Results

As a result of the search on PubMed 2.827 publications were identified. 2.753 publications have been excluded by title and abstract.

70 publications about RCTs on anti-VEGF (classical anti-VEGF: aflibercept, ranibizumab, bevacizumab) met the inclusion criteria and were published before the cutoff date (6th of June 2017- day of the search request at PubMed).

Most of these 70 publications were published in 2013 and 2015 (see Figure 2), the first RCTs using anti-VEGF drugs were published in 2006. Most trials appeared in the years 2013 and 2015. In 2010, the second most common trials were released.

3.1. Trends in publications of RCTs covering anti-VEGF therapy

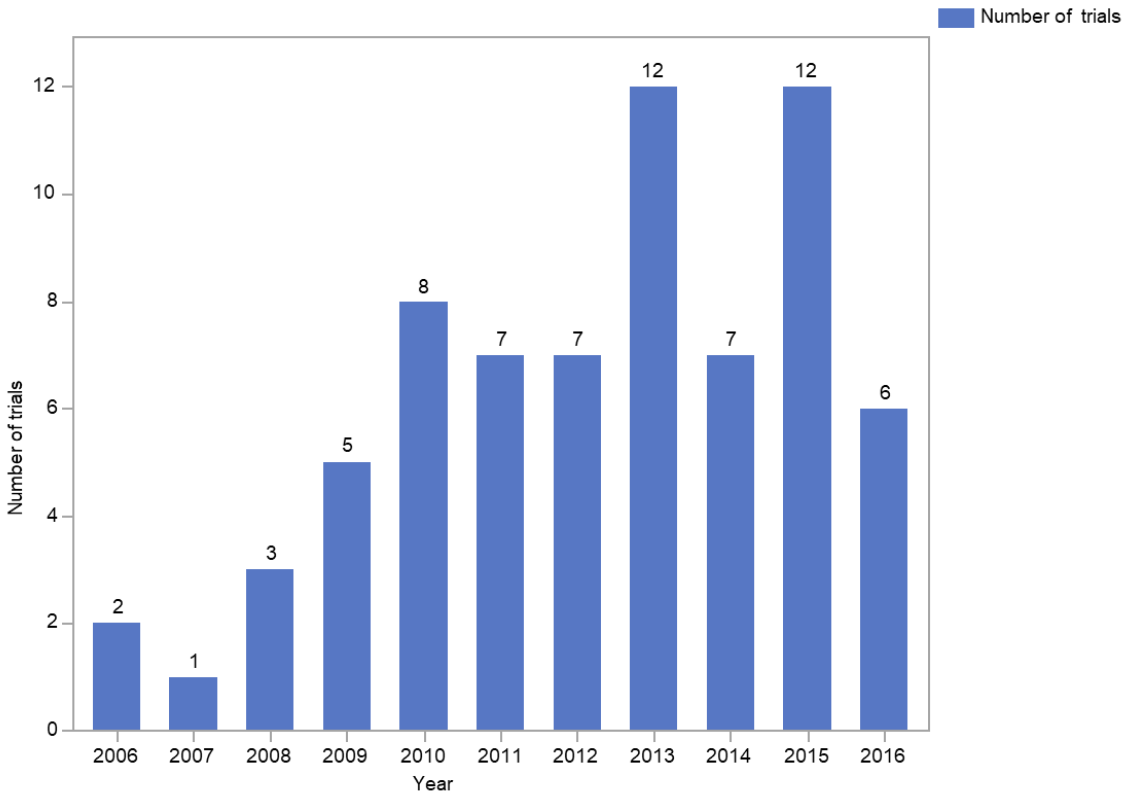


Figure 2 number of publications per year before 6th June of 2017- date of the search request in PubMed

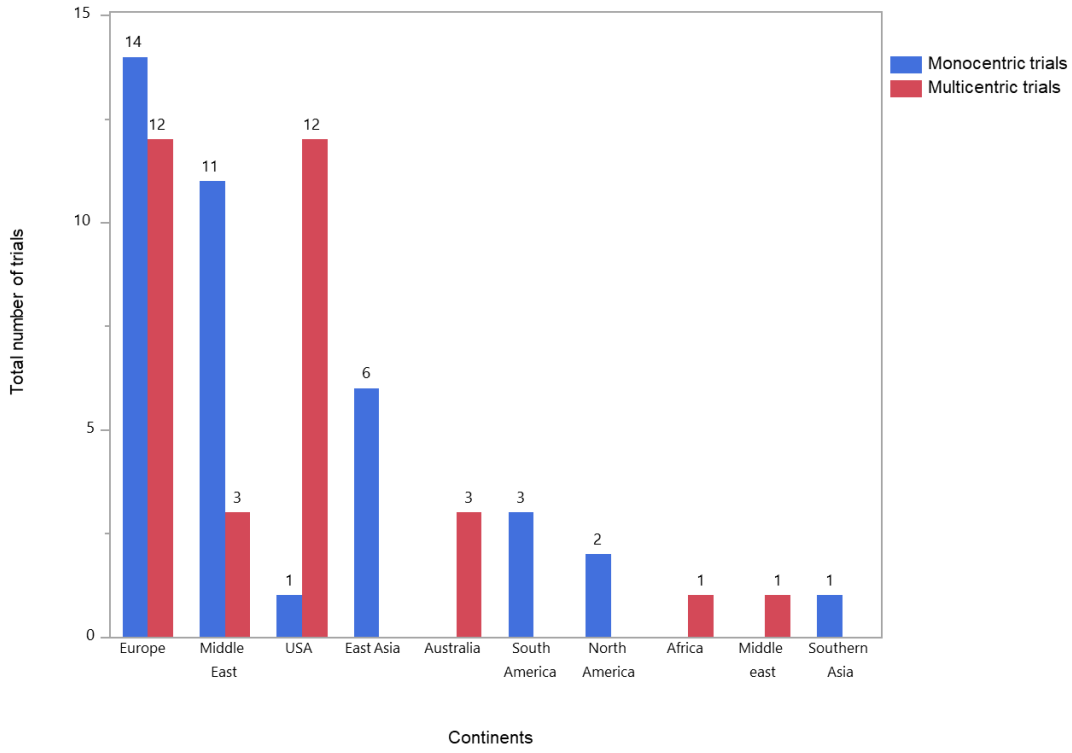


Figure 3 continents in which the RCTs (multi-, monocentric) were conducted

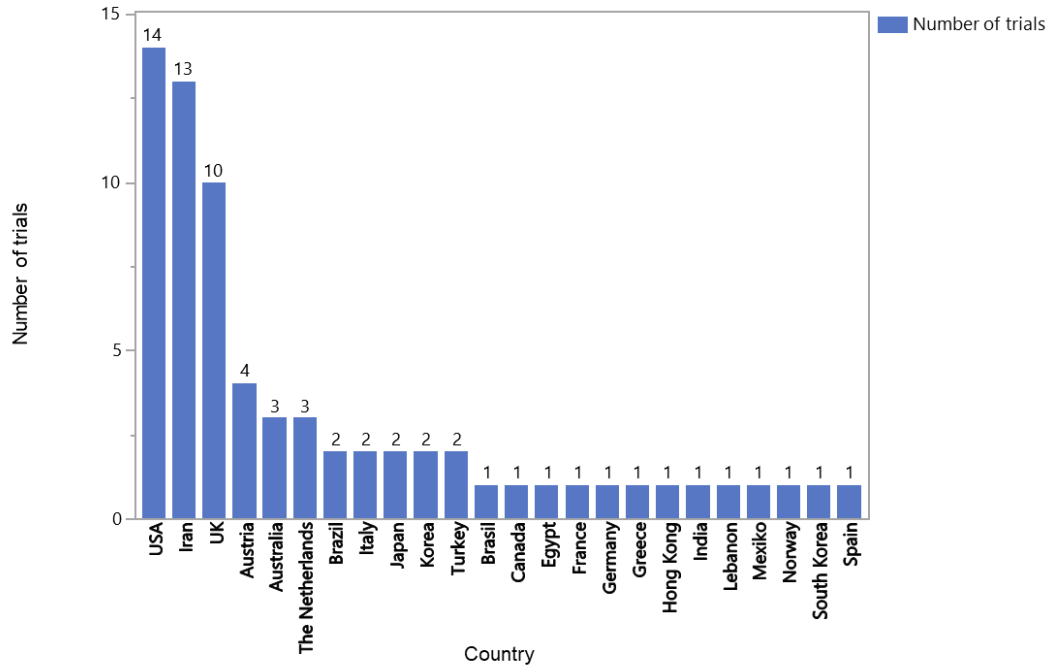


Figure 4 country of RCTs

Most RCTs were published in the USA, second most in Iran and the UK ranks third (see Figure 5).

In Europe and in the USA most multicentric trials were conducted (see Figure 3).

Most of the RCTs were realized in Europe, followed by the Middle East and on the third rank is North America. The fewest RCTs took place in Africa or South Asia (see Fig 3).

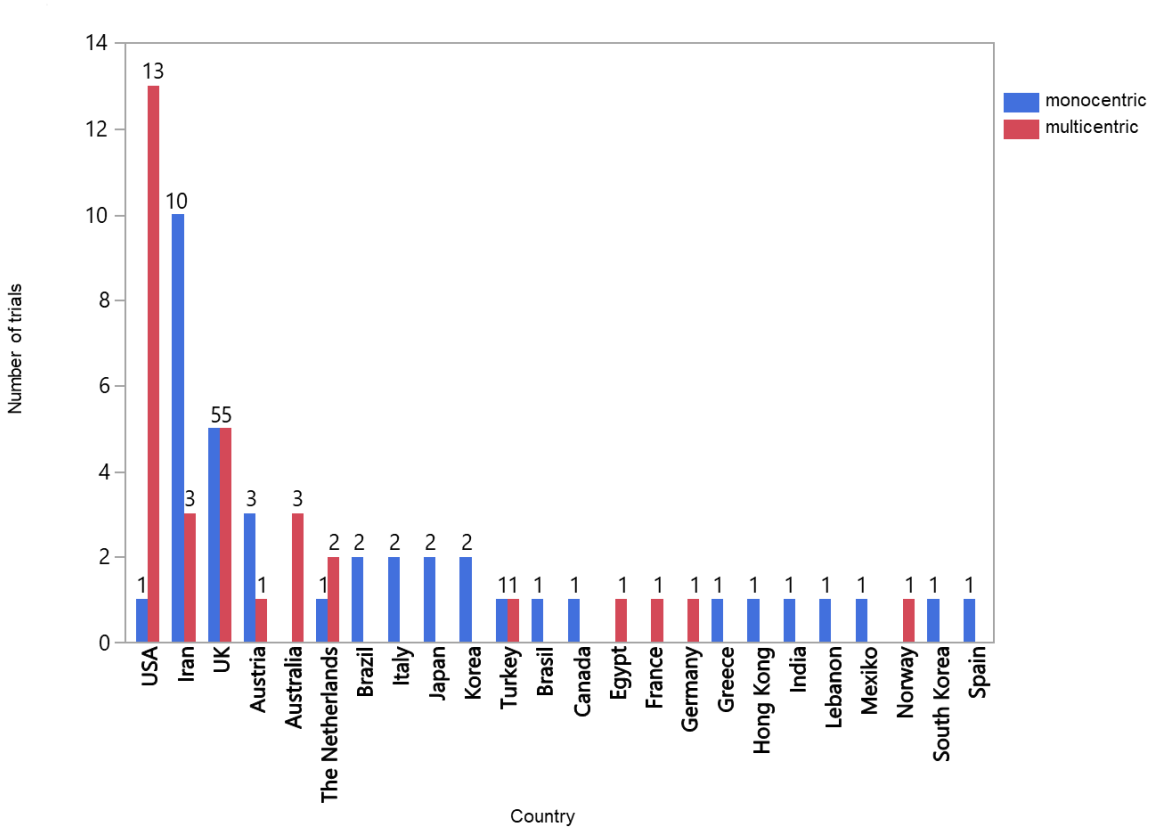


Figure 5 country in which the trials were conducted; in multicentric trials the country of the corresponding author is named.

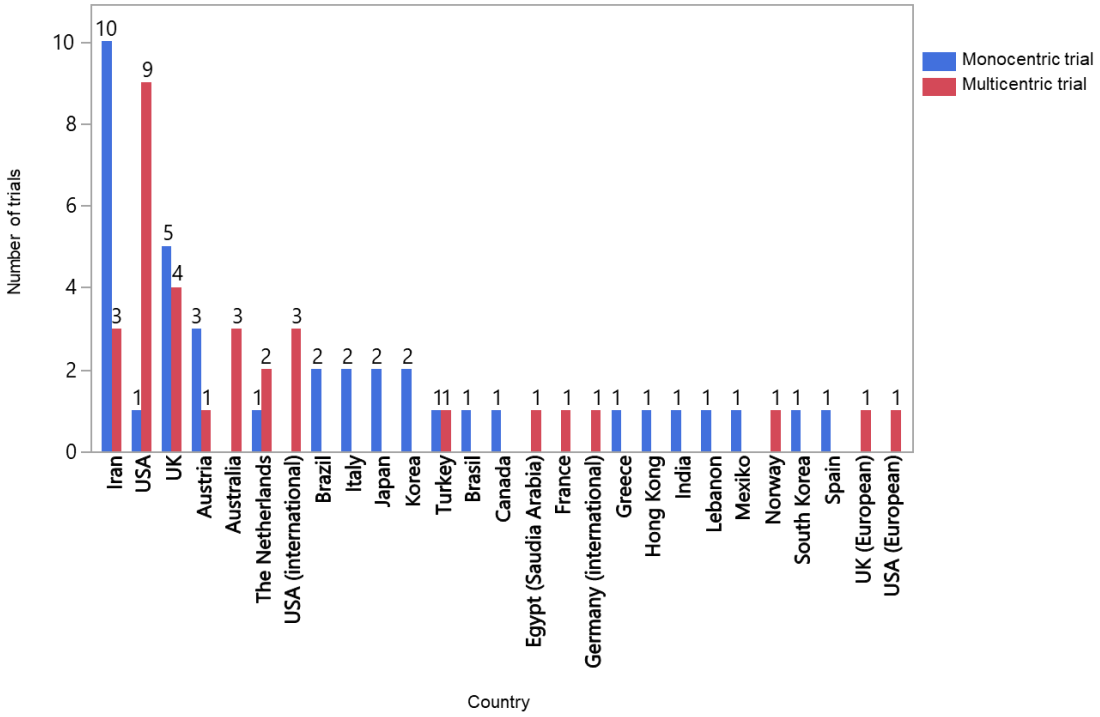
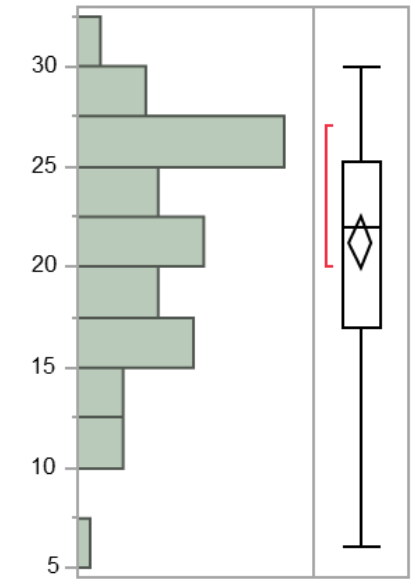


Figure 6 number of trials (multi-or monocentric) per country; trial sites in brackets.

In this graph international multicentric trials were indicated separately and not counted as multicentric trials that were conducted in one country. That is the reason why Iran is on the top of the ranking of the highest number of trials per country.

Distribution of CONSORT score



Quantile

100.0%	Maximum	30
99.5%		30
97.5%		30
90.0%		28
75.0%	Quartile	25.25
50.0%	Median	22
25.0%	Quartile	17
10.0%		13
2.5%		9.875
0.5%		6
0.0%	Minimum	6

Statistic parameters

Mean	21.2
Standard deviation	5.5235989
Std.-error mean	0.6601963
95% CI above mean	22.517056
95% KC below mean	19.882944
N	70

Figure 7 frequency distribution of CONSORT score

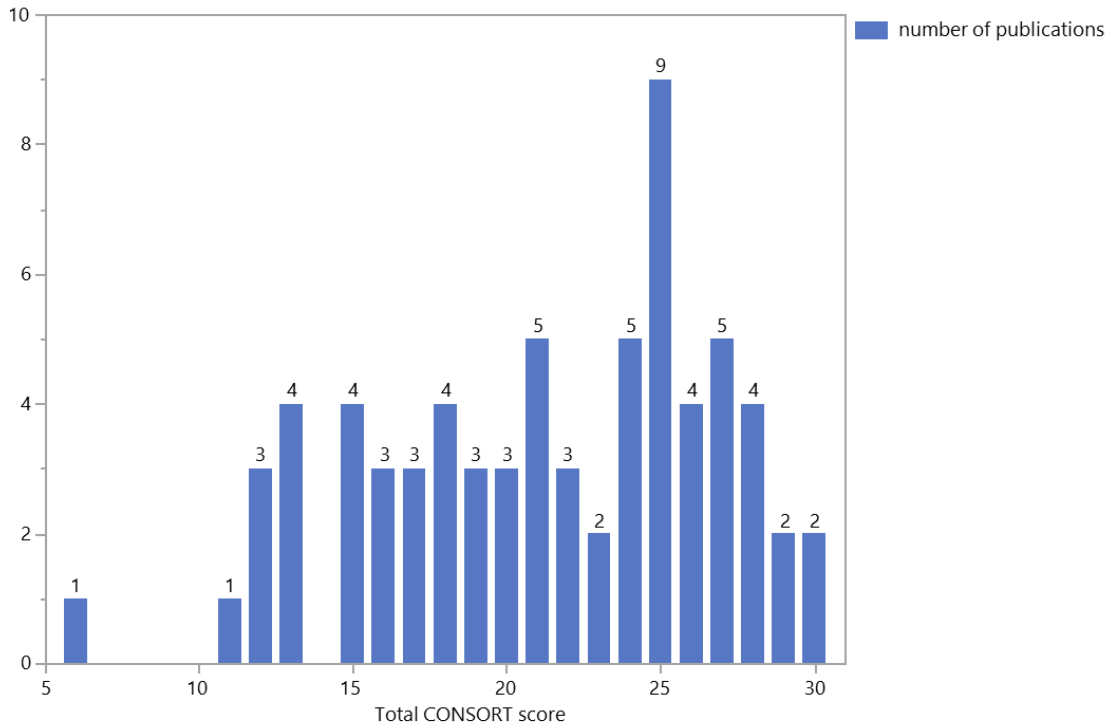


Figure 8 total CONSORT score in the publications

3.2. Adherence of CONSORT items

First section “title and abstracts”:

Item	**Adherence (number of articles (%))**
1a Identification as a randomized trial in title	**34 (48.57)**
1b Structured summary of trial design, methods, results, and conclusions	**70 (100)**

Second section “Introduction”:

2a Scientific background and explanation of rationale	**70 (100)**
2b Specific objectives or hypotheses	**70 (100)**

Third section “Methods”:

3a Trial design	**70 (100)**
3b Important changes	**4 (5.71)**
4a Eligibility criteria for participants	**69 (98.57)**
4b Settings and locations where the data were collected	**44 (62.86)**
5 The interventions for each group with sufficient details to allow replication	**69 (98.57)**
6a Pre-specified primary and secondary outcome measures	**32 (45.71)**
6b Any changes to trial outcomes after the trial commenced	**2 (2.86)**
7a Sample Size	**37 (52.86)**
7b Explanation of any interim analyses and stopping guidelines	**0 (0)**
8a Method used to generate the random allocation sequence	**50 (71.43)**
8b Type of randomization	**40 (57.14)**
9 Mechanism used to implement the random allocation sequence	**15 (21.43)**
10 Random allocation sequence	**13 (18.57)**
11a Blinding	**48 (68.57)**
11b If relevant, description of the similarity of interventions	**23 (32.86)**
12a Statistical methods	**40 (57.14)**
12b Methods for additional analyses	**20 (28.57)**

Fourth section “Results”:

13a For each group ,the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome	**44 (44)**
13b Losses and exclusions after randomization, together with reasons	**26 (37.14)**
14a Dates defining the periods of recruitment & follow-up	**48 (68.57)**

14b Why the trial ended or was stopped	**0 (0)**
15 A table showing baseline demographic and clinical characteristics for each group	**51 (72,86)**
16 Number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	**34 (48.57)**
17a Primary and secondary outcome	**51 (72.86)**
17b For binary outcomes, presentation of both absolute and relative effect sizes is recommended	**0 (0)**
18 Results of any other analyses performed, including subgroups	**22 (31.43)**
19 Harms	**34 (48.57)**

Fifth section “Discussion”:

20 Trial limitations	**60 (85.71)**
21 Generalizability	**56 (80)**
22 Interpretation	**67 (95.71)**

Sixth section “Other information”:

23 Registration	**45 (64.29)**
24 Full trial protocol can be accessed	**7 (5.71)**
25 Funding	**57 (81.43)**

Table 3 adherence of RCT to CONSORT items

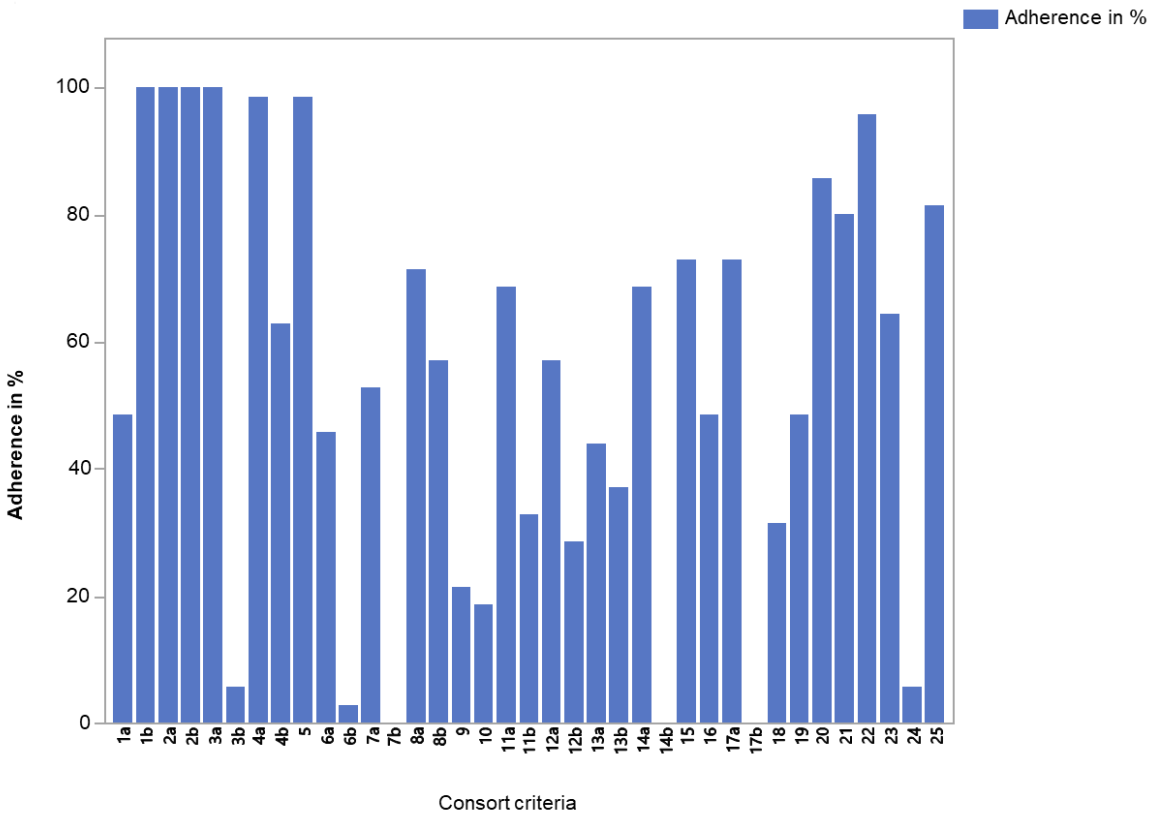


Figure 9 adherence in % per CONSORT Criteria

The mean CONSORT score was 21 (57.3% of the total CONSORT score) for the selected 70 publications.
The lowest score with only 6 of 37 items was found in one publication, the highest score with 30 of 37 items was found in two publications. 9 publications had a score of 25 (Figure 7).

All studies featured a description of the scientific background and justification why the trials were conducted (CONSORT item 2a), the objectives or hypothesis (CONSORT item 2b) and the trial design (CONSORT item 3a) was named in all 70 studies.
Criteria 1b, 2a, 2b and 3a were fulfilled in all studies. These items can be found in the sections “Title and abstract”, ”Introduction” and “Methods”.

No publication gave details to CONSORT item 7b (“explanation of interim analysis”), 14b (“why the trial ended/was stopped”) an 17b (“for binary outcomes,

absolute and relative effect size recommended"). These criteria are found in the section "methods" and "results".

An adherence of 98,57% was found in the section of eligibility criteria (CONSORT item 4a) and the interventions for each group (CONSORT item 5):
In 69 of 70 studies eligibility criteria were named. If at least the eligible criteria were mentioned, the CONSORT item 4a was rated as fulfilled.
In 10 of 70 studies the eligibility criteria were displayed in a table. 69 of 70 studies (98.57%) gave sufficient details about the intervention for each group (CONSORT item 5). 69 studies came with a detailed description of the interventions concerning drug name, administration and the conditions under which the intervention were executed. 62 of 70 trials reported an exact dose in a scale unit.
Trial limitations (item 20), generalizability (item 21), interpretation (item 22) and funding (item 25) were mentioned in over 80% of the publications.

The majority of the publications (over 60%) reported the settings and location (item 4b), methods to generate random allocation (item 8a), blinding (item 11a), dates defining the recruitment and follow up (item 14a), a table with baseline characteristics (items 15), primary and secondary outcomes (item 17a) and registration (item 23).
Most publications mentioned a register number and some indicated the national and/or international trial register. Most trials had an NCT number. Some had EUDRACT or ISRCTN numbers (CONSORT item 23). Only 7 of 70 studies declared where the full protocol can be accessed (CONSORT item 24). Only 4 full protocols were found to be available.

The type of randomization (item 8b) and the statistical methods (12a) were described in 57.14% of the publications. The sample size (item 7a) was reported in 37 of 70 publications.
Slightly less than 50% of the publications mentioned pre-specified primary and secondary outcomes (CONSORT item 6a), the number of participants that were

randomized and analyzed (CONSORT item 13a), the number of participants in each analysis (CONSORT item 16) and harms (CONSORT item19).

44 of 70 studies gave numbers of participants (CONSORT item 13a). On average, 197 participants have been randomized across all studies.
Only 24 RCTs included a participant flow diagram, though it is strongly recommended. 26 of 70 studies give information about losses and exclusions after randomization (CONSORT item 13b)
In 4 of 70 studies changes have been described (CONSORT item 3b). It is hard to say if there were no changes respective the methods after the trail had commenced (see Table 1) in all other 66 studies, because only for a few studies a protocol could be accessed to compare the results.

2 of 70 trials mentioned changes to trial outcomes after the trial commenced (CONSORT item 6b)(see Figure 10).
According to website *clinicaltrials.gov*, there were more changes listed under the NCT number: 22 of 70 studies reported of changes in trial after the commencement of a trail.

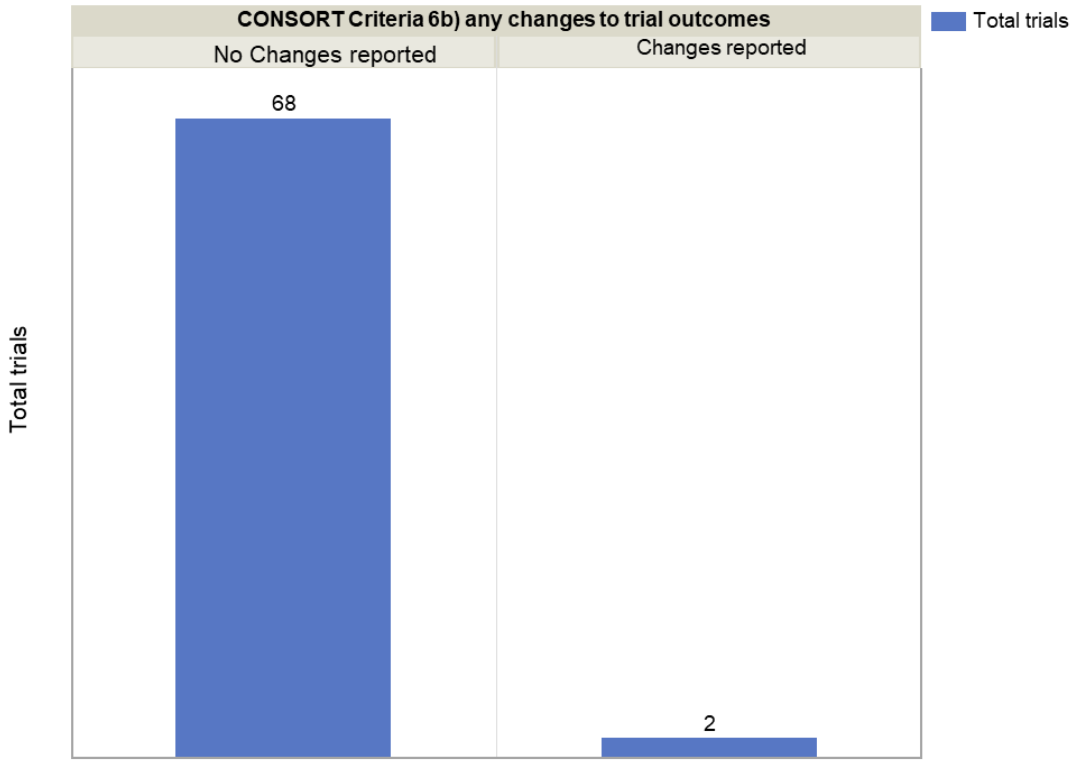


Figure 10 reported changes to trial outcomes in the publications

3.3. Citation distribution

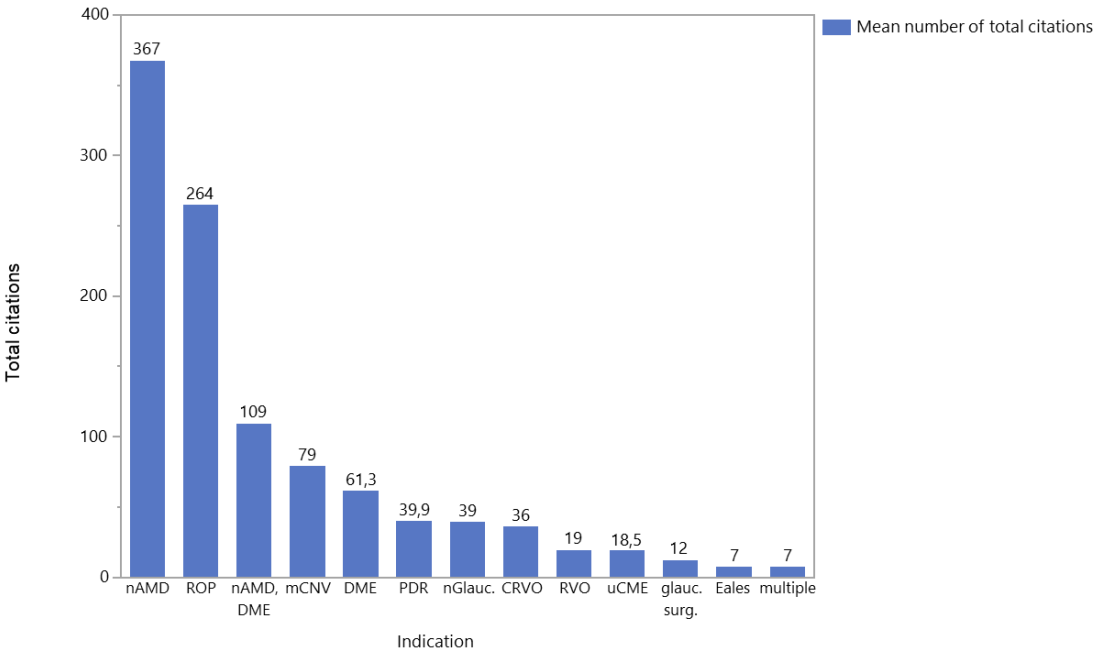
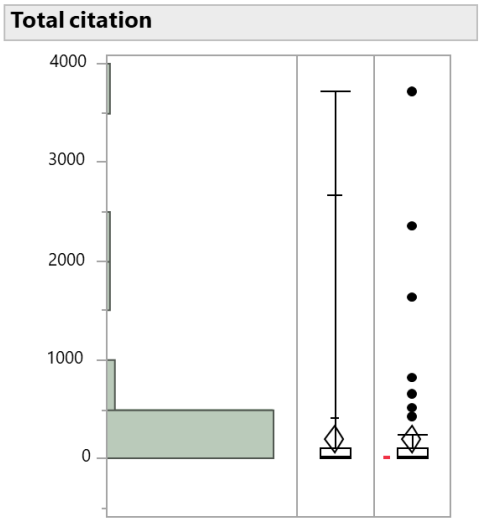


Figure 11 mean total citations and indications

Trials with the indication nAMD were most frequently cited, followed by the indication ROP, the double indication of neovascular AMD and DME (see Figure 11).



Quantile

100.0%	Maximum	3713
99.5%		3713
97.5%		2660.55
90.0%		409,1
75.0%	Quartile	104.5
50.0%	Median	31.5
25.0%	Quartile	14
10.0%		10
2.5%		5,775
0.5%		5
0.0%	Minimum	5

Statistic parameter

Mean	188
Std.-dev.	556.9416
Std.-error mean	66.567253
95% KI above Mean	320.79804
95% KI below Mean	55.201964
N	70

Figure 12 frequency distribution of total citations

Outliers with a maximum of 3.712 citations and minimum of 5 citations were found in the frequency distribution of the total number of citations.

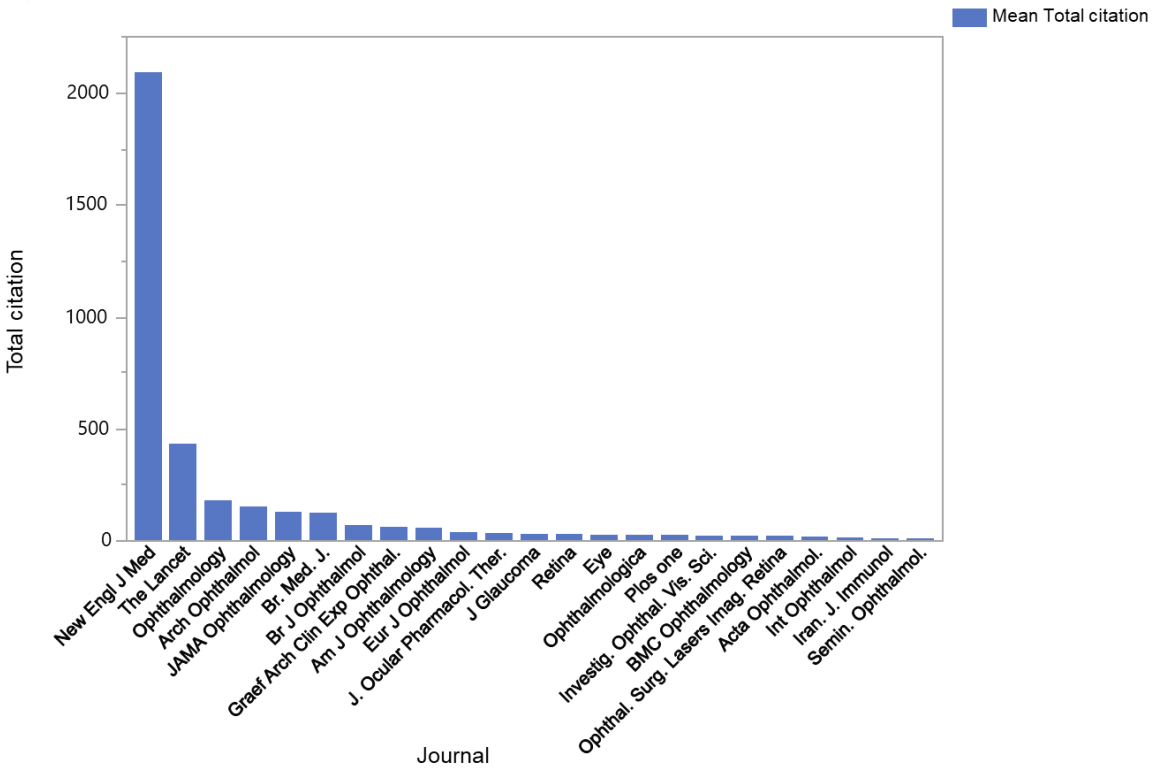


Figure 13 mean total citations of the different journals

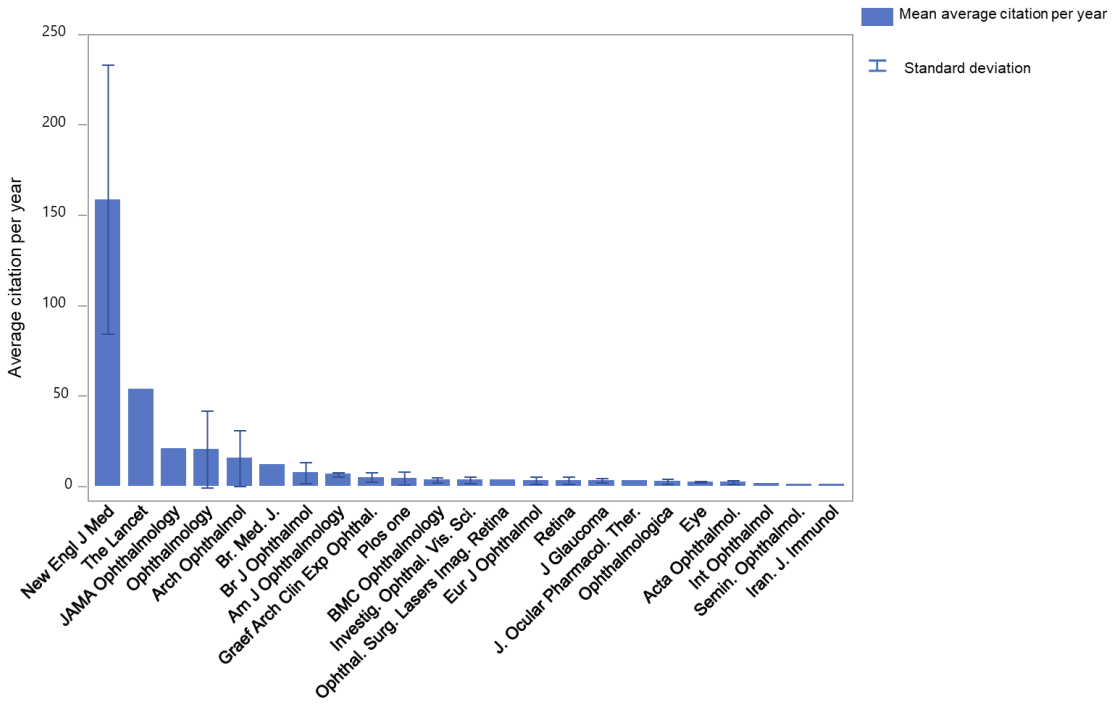


Figure 14 average citation in the different journals

Two multidisciplinary journals (the “New England Journal of Medicine” and the “Lancet”) had the highest total number of citation for the included trials.

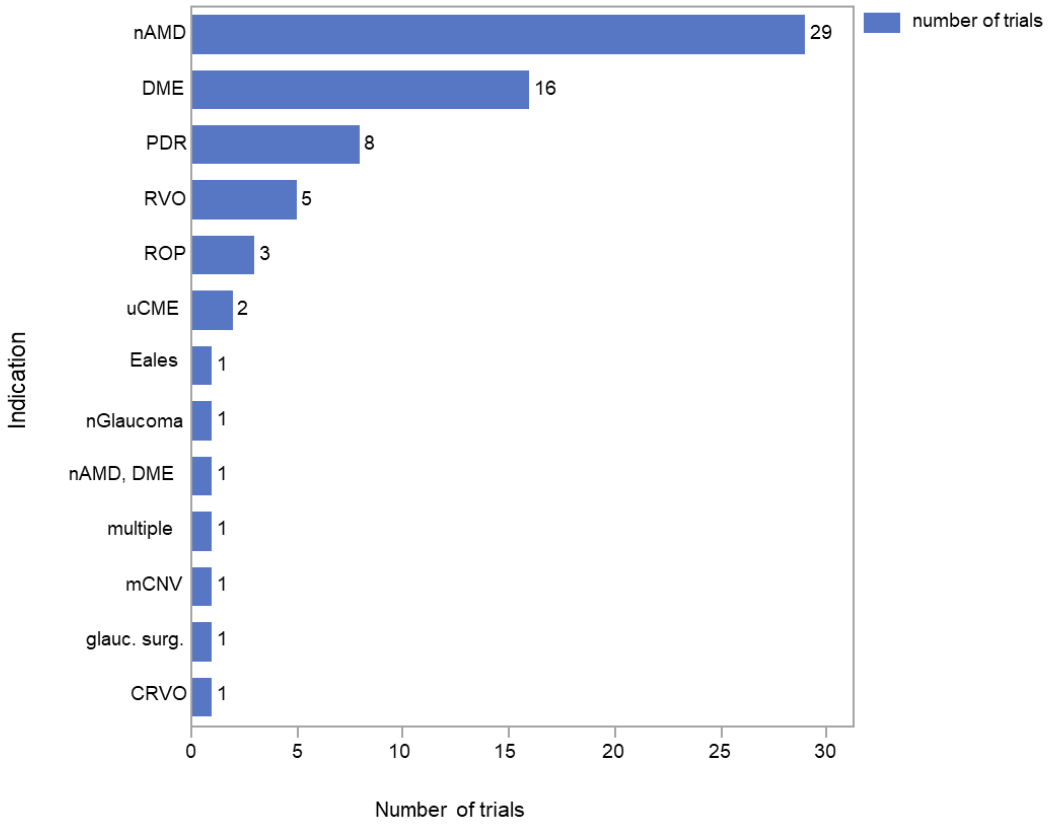


Figure 15 number of publication in the different indications

The distribution of the number of trials per disease indicated 41% of all trials to deal with neovascular AMD. 23% of trials covered the treatment of DME. 11% of trials described treatment of PDR.

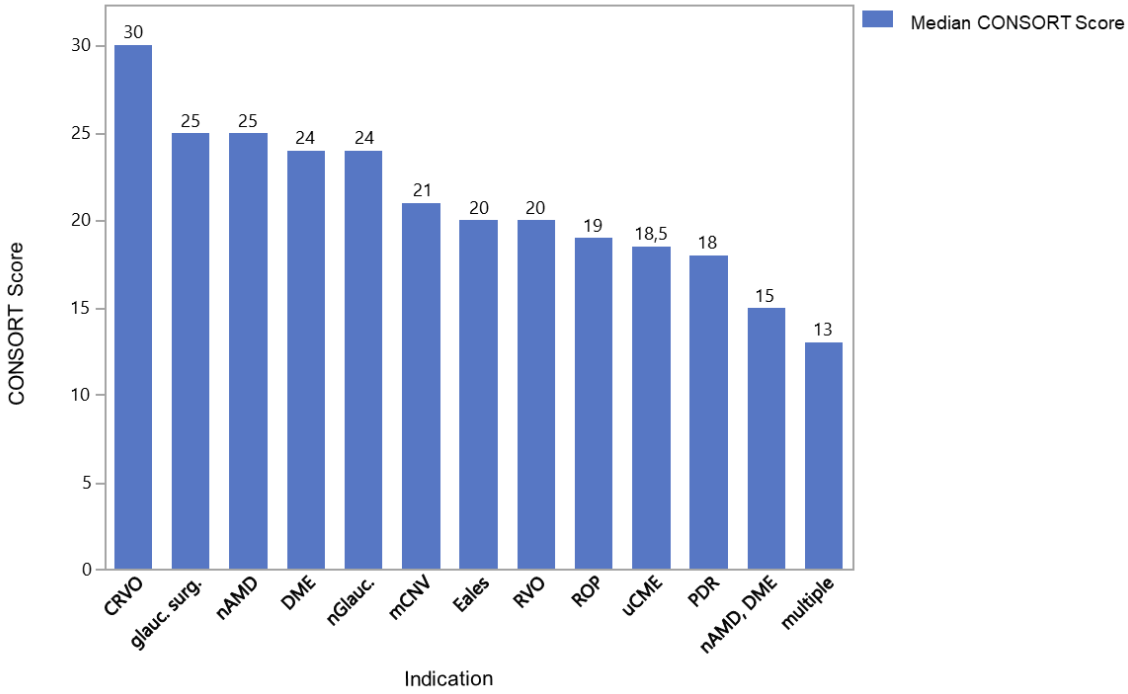


Figure 16 median CONSORT Score in the pooled data of indications

The highest median score was found in a trial about CRVO. A trial about glaucoma surgery as well as trials about nAMD ranked second equally (see Figure 15 and 16).

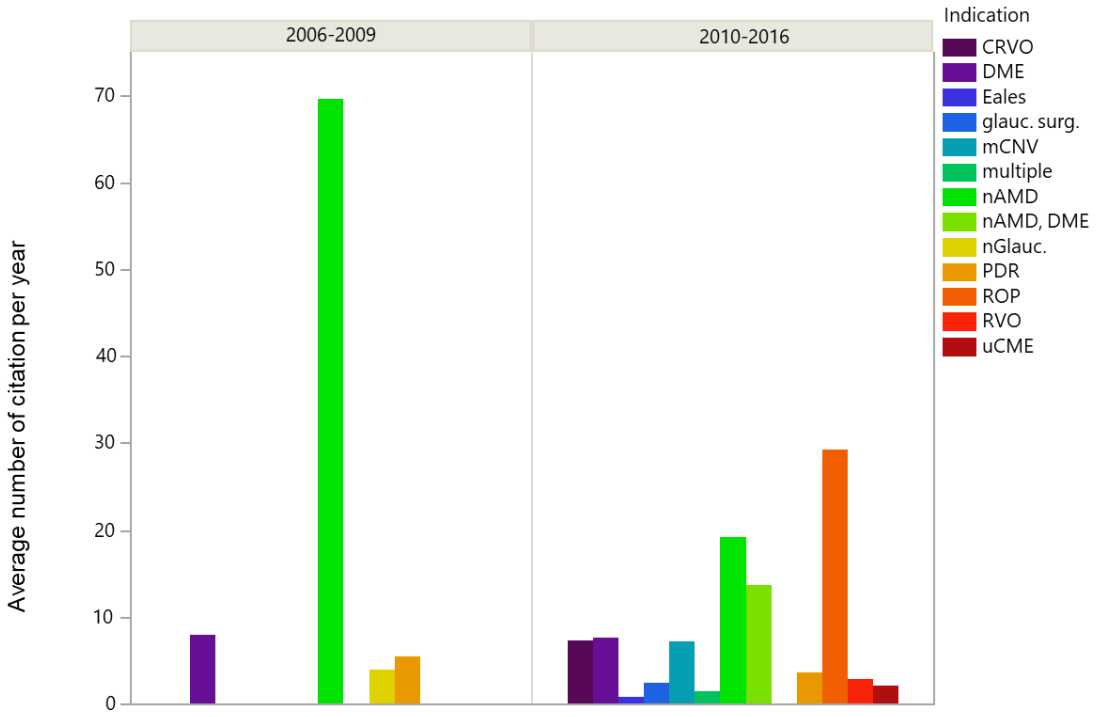


Figure 17 average number of citations per year in the different indications

The major indication of the intravitreal therapy with Anti-VEGF was nAMD in the time period from 2006 to 2009.

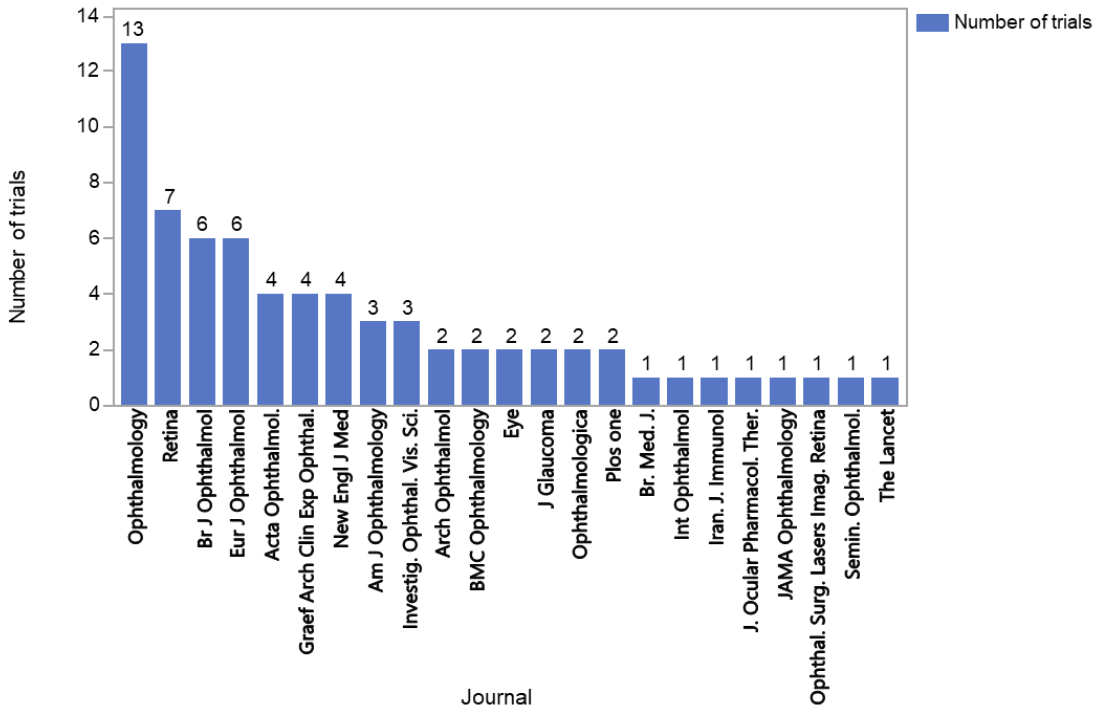


Figure 18 number of trials per journal

Most publications about Anti-VEGF therapy (13) were released in “Ophthalmology”. The journal “Retina” ranked second with seven publications and the third rank is to the “British Journal of Ophthalmology” with six publications. Four trials were published in the “New England Journal of Medicine” as a non-ophthalmological journal (see Figure 17).

The CONSORT score and the average number of citations (per year) were moderately correlated, Spearman´s ρ=0,3132, p= 0,0083.
The year of publication and the CONSORT score were not significantly related, Spearman´s ρ=0,1099, p=0,3651.

3.4. Number of randomized patients

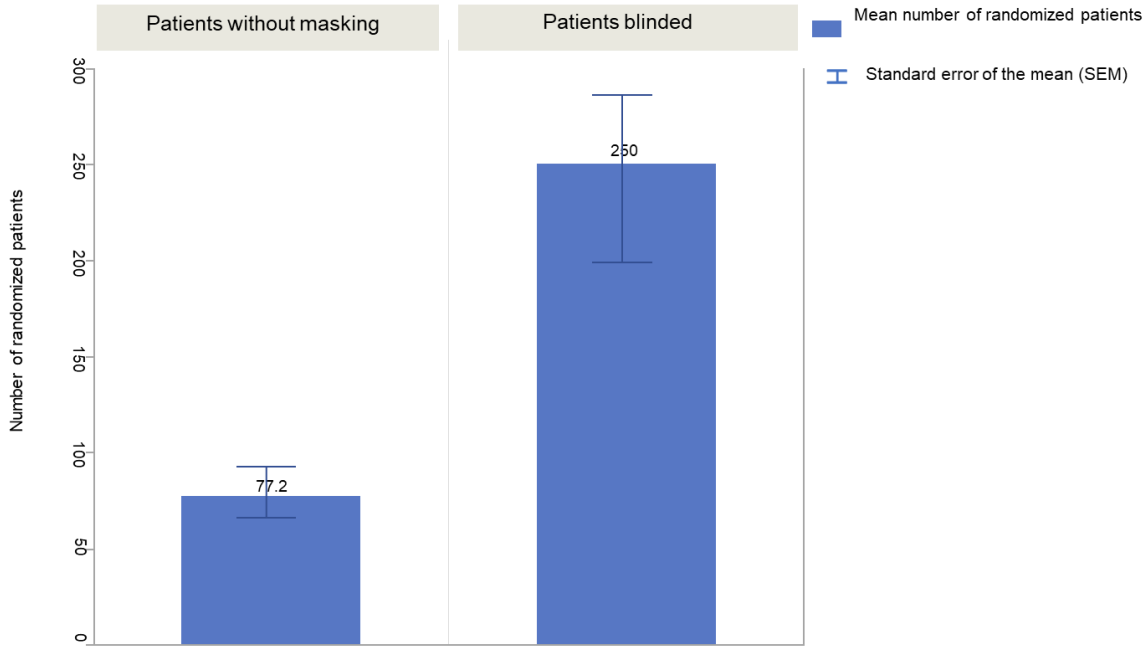
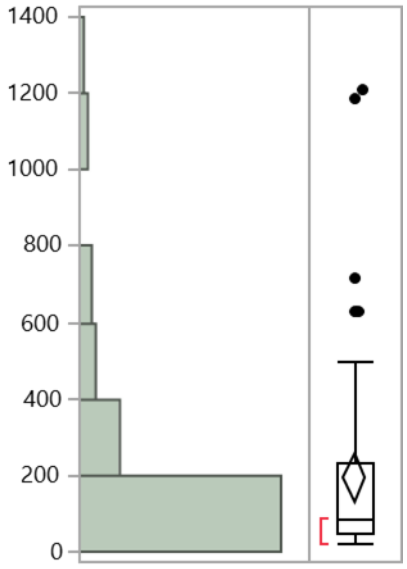


Figure 19 mean number of randomized patients in trial with masking or without masking

The highest number of randomized patients was found in RCTs with masking.

Distribution of randomized patients



Quantile

100.0%	Maximum	1208
99.5%		1208
97.5%		1190.175
90.0%		495
75.0%	Quartile	233.25
50.0%	Median	87
25.0%	Quartile	48
10.0%		32.2
2.5%		23.1
0.5%		20
0.0%	Minimum	20

Statistic parameters

Mean	195,72857
Std.-Deviation	264,50155
Std.-error mean	31,613982
95% KI above mean	258,79674
95% KI below mean	132,6604
N	70

Figure 20 frequency distribution of randomized patients

A significantly higher number of patients was included in RCTs with masking than in trials without masking (Wilcoxon rank sum test: Z=-2.82207, p= 0.0048).

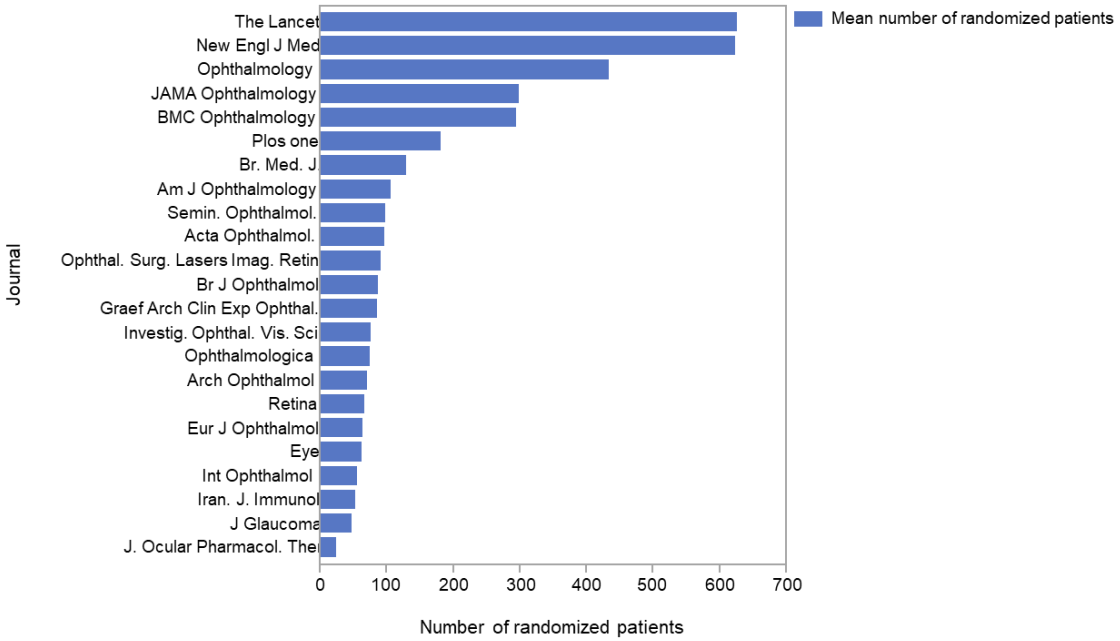


Figure 21 mean number of randomized patients in the different journals

Trails with the highest average number of randomized patients were published in “The Lancet” and the “New England Journal of Medicine”.

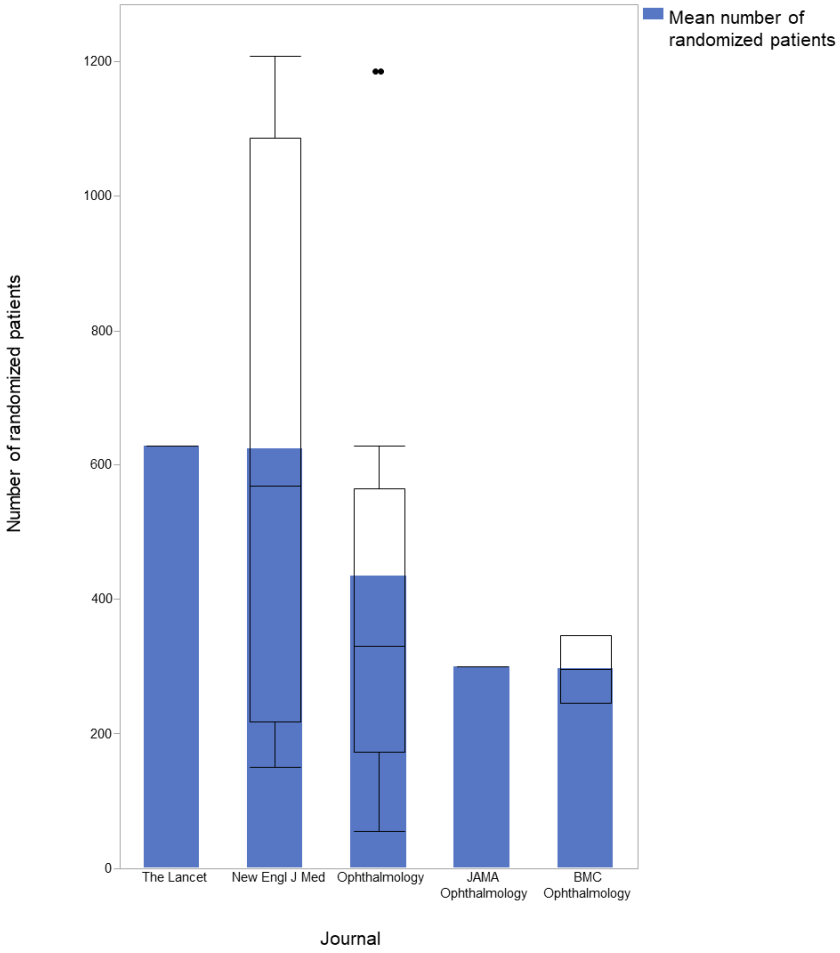


Figure 22 boxplots of the top five journals with the highest number of randomized patients

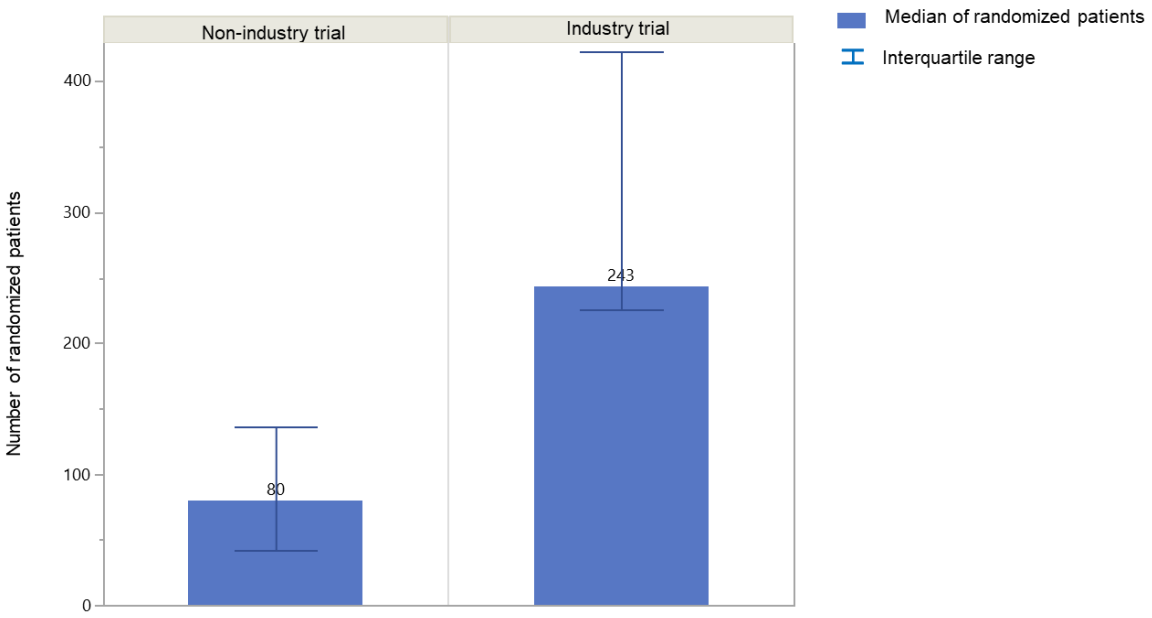


Figure 23 median of randomized patients in Industry and Non-Industry trial

The number of (randomized) patients was significantly higher in industry sponsored trials than in independent trials (Wilcoxon rank sum test Z=3.115, p=0.0018).

There was a strong correlation between the number of randomized patients and the CONSORT score (Spearman´s ρ=0,4245, p=0,002), respectively the JIF (Spearman´s ρ=0,4757, p=0,001).

3.5. Masking

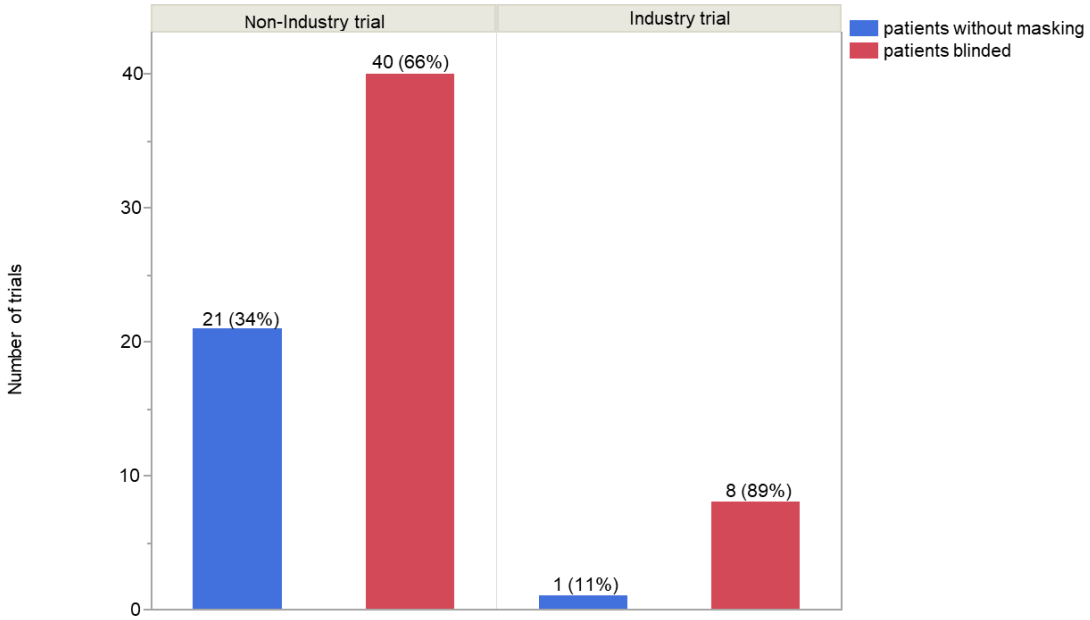


Figure 24 distribution of trials with or without masking; total number (percentage of trials in the particular group: non-industry or industry sponsored)

The ratio of trials with blinded patients and trials without masking was 8:1 in industry-sponsored trials, in contrast to non-industry-sponsored trials with 1,9:1 (see Figure 25). 89% of industry sponsored trials were found to use masking, in 66% of non-industry sponsored trials patients did implement blinded assessment.

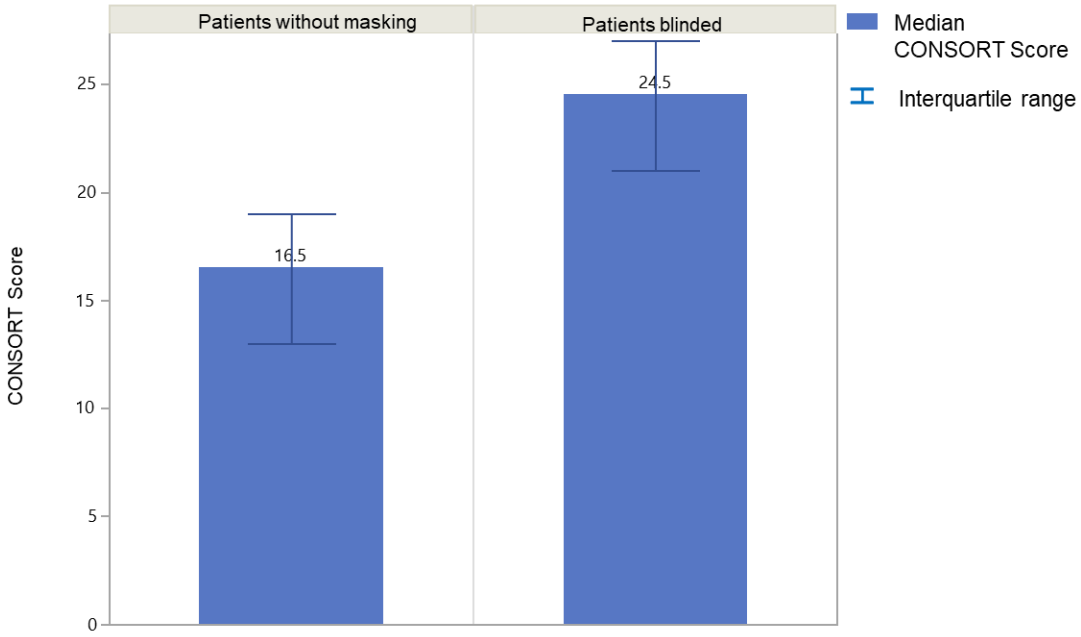


Figure 25 median CONSORT score in trials with or without masking

The CONSORT score was significantly higher in trials with masking (Wilcoxon rank sum test: Z=-4.50762, p= <0.0001). Furthermore, there was no significant relationship between the JIF and presence of blinding in the trial (Wilcoxon rank sum test: Z=-1,82871, p=< 0.0674).

3.6. Industry sponsored trials

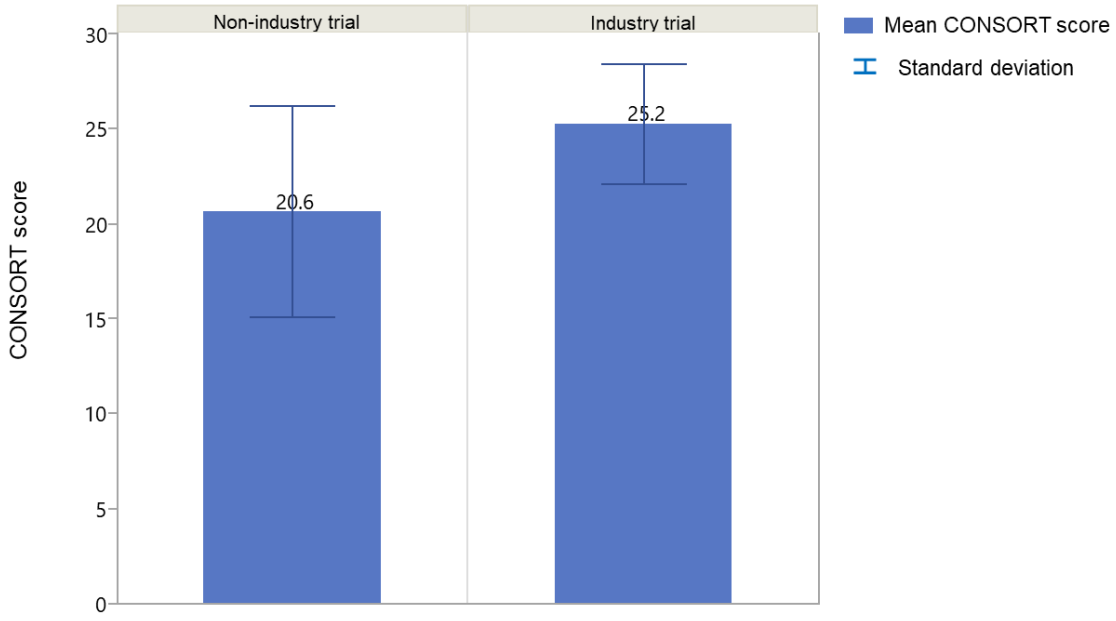


Figure 26 mean CONSORT score in industry or non-industry trial

The CONSORT score was significantly higher in the industry sponsored trials than in the independent trials (Wilcoxon rank sum test: Z=2,2509, p=0,0244).

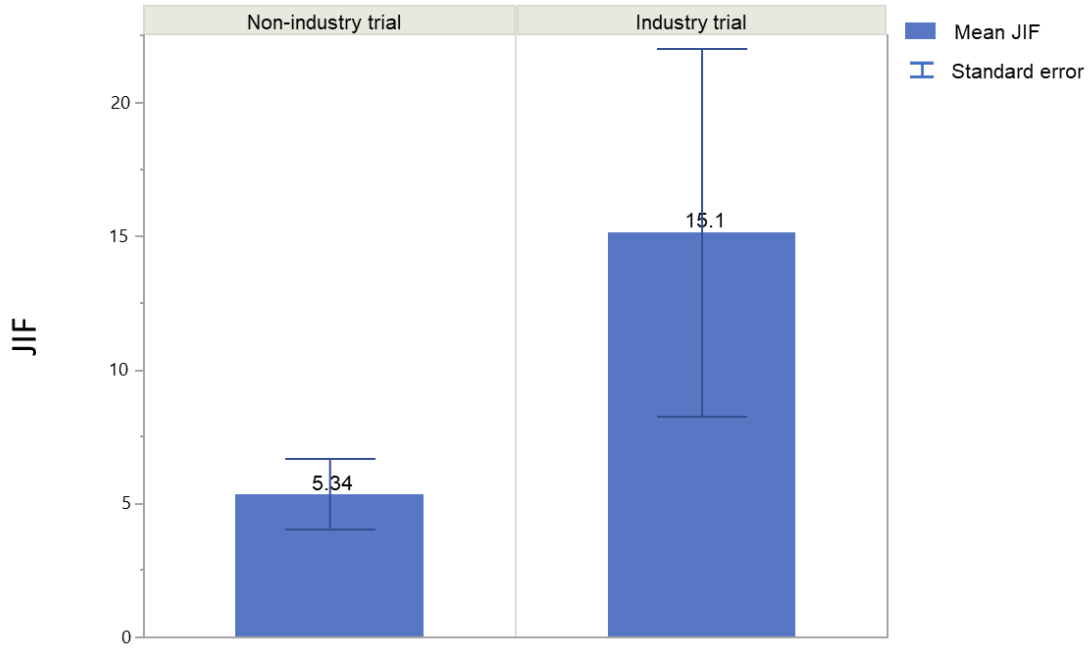


Figure 27 mean JIF in industry and non-industry trials

The JIF of industry sponsored trial was significantly higher than the JIF of independent trials (The Wilcoxon rank sum test Z= 2.527, p= 0.0115).

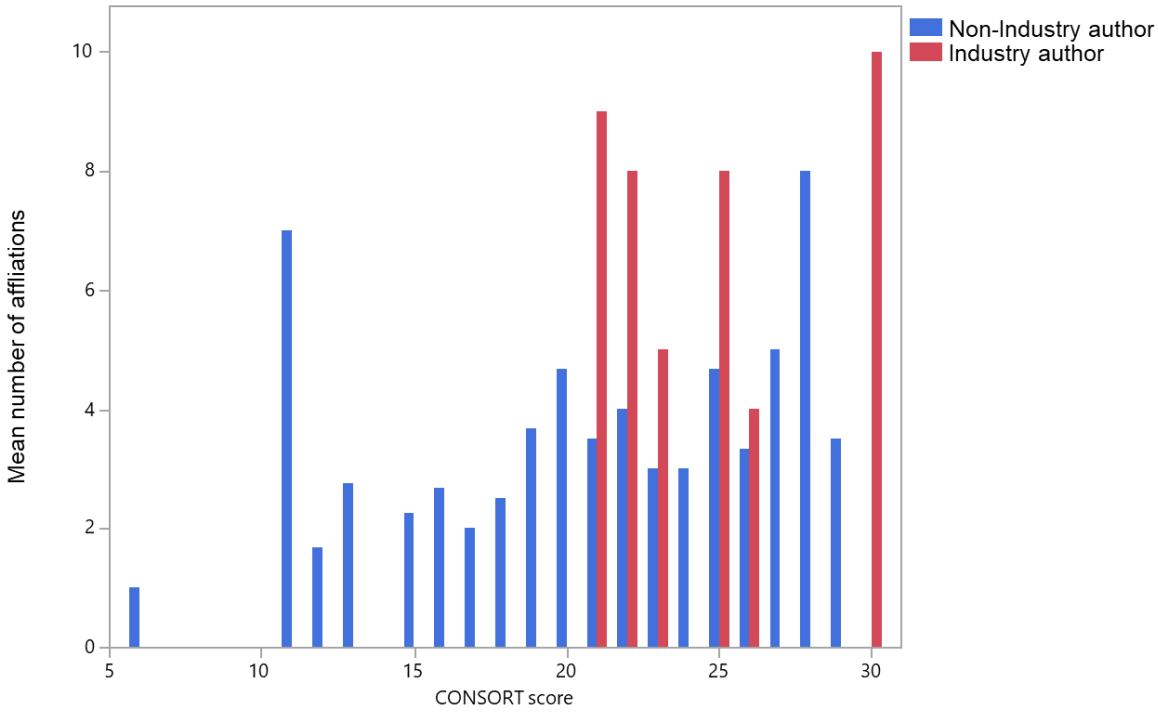


Figure 28 mean CONSORT score compared to the number of affiliations and the distribution of industry sponsored trial

Figure 28 shows that industry sponsored trials had the highest CONSORT score and the highest number of affiliations.

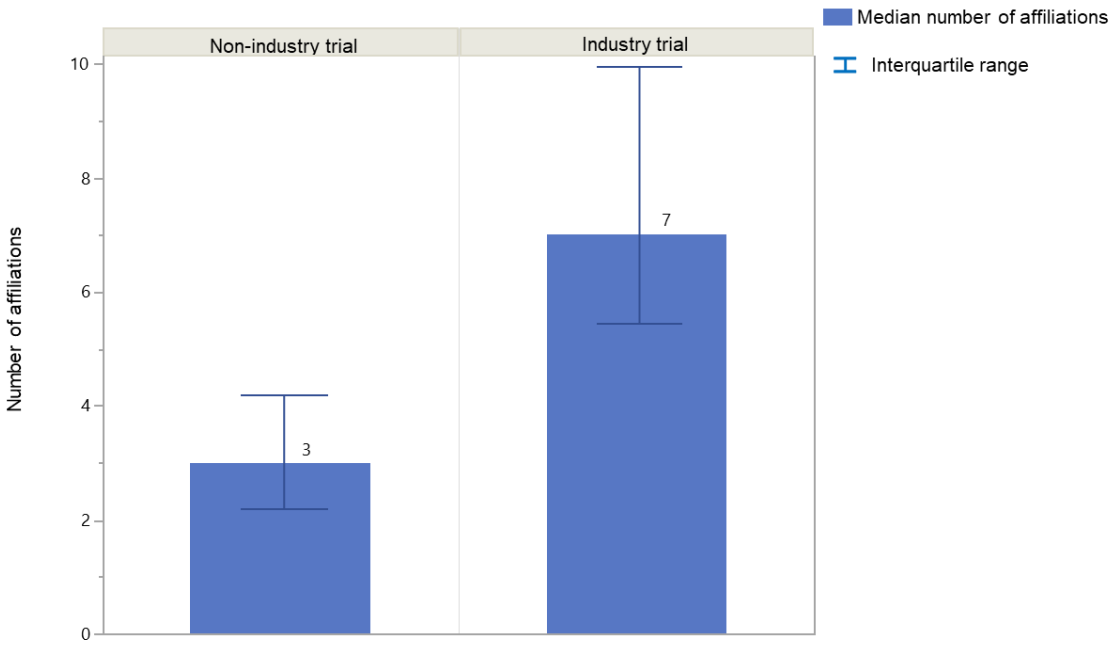


Figure 29 median number of affiliations in industry and non-industry trials

The number of affiliations was significantly higher in industry sponsored trials than in non-industry sponsored trials (Wilcoxon rank sum test Z=3.74451, p=0.0002).

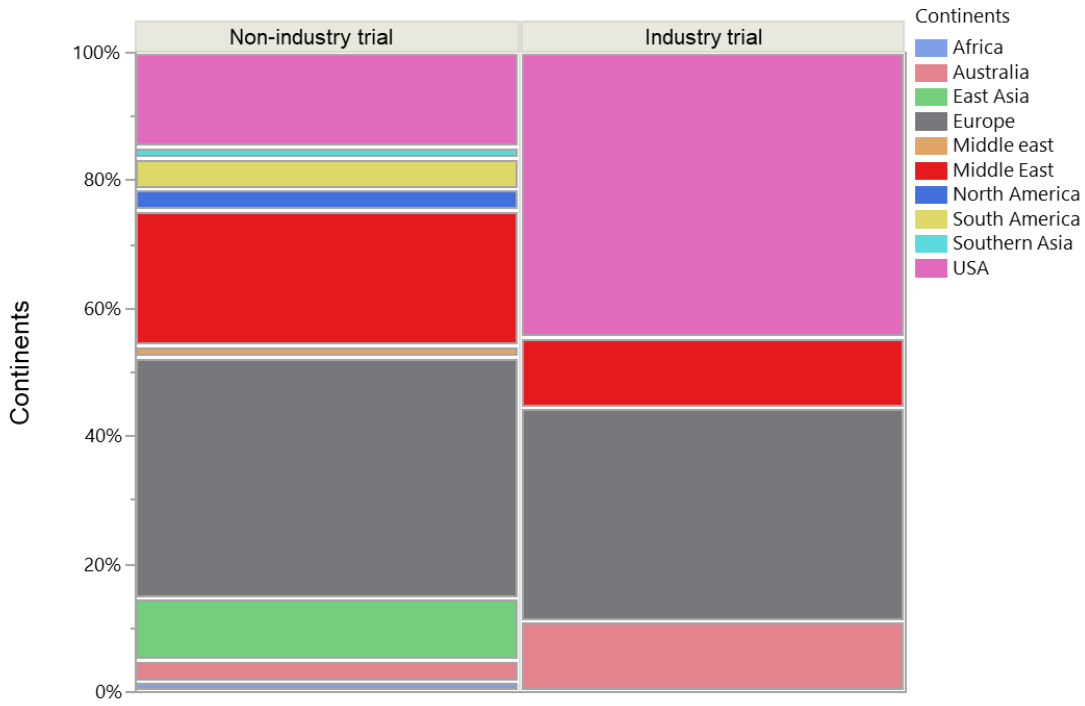


Figure 30 Industry trials and continents

A moderate relation between continents and industry-sponsoring of trials was found (The Cramer V test V=0.3282).

	Industry Author
Journal	**Summe**
Acta Ophthalmol.	1
Am J Ophthalmology	1
Arch Ophthalmol	0
BMC Ophthalmology	1
BMJ	0
Br J Ophthalmol	0
Eur J Ophthalmol	0
Eye	0
Graefes Arch Clin Exp Ophthalmol	0
Int Ophthalmol	0
Investigative Ophthalmology & Visual Science	0
Iran.J.Immunol	0
J Glaucoma	0
JAMA Ophthalmology	0
JOURNAL OF OCULAR PHARMACOLOGY AND THERAPEUTICS	0
New Engl J Med	2
Ophthalmic Surgery, Lasers & Imaging Retina	0
Ophthalmologica	0
Ophthalmology	4
Plos one	0
Retina	0
Seminars in Ophthalmology	0
The Lancet	0

Table 4 number of industry trial in the different journals

Most of the industry-sponsored publications in this survey of 70 publications were published in the journal “Ophthalmology”.

There was a significant relation between industry-sponsoring and the multicentric conduction of the trials (Chi square test: $X^2(1,N=70)=12.263$, $p=0.0005$).

3.7. Multicentric trial

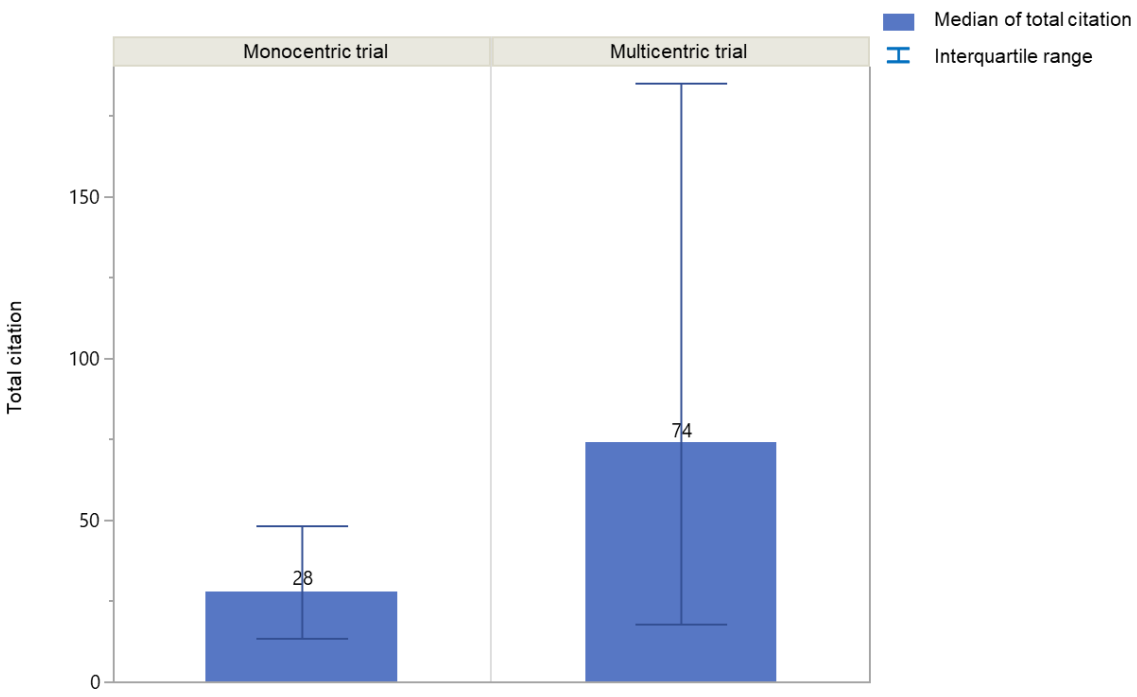


Figure 31 median of total citations in mono- or multicentric trial

The number of total citations was significantly higher in multicentric trials than in monocentric trials (Wilcoxon rank sum test Z=2.69470, p=0.0070).

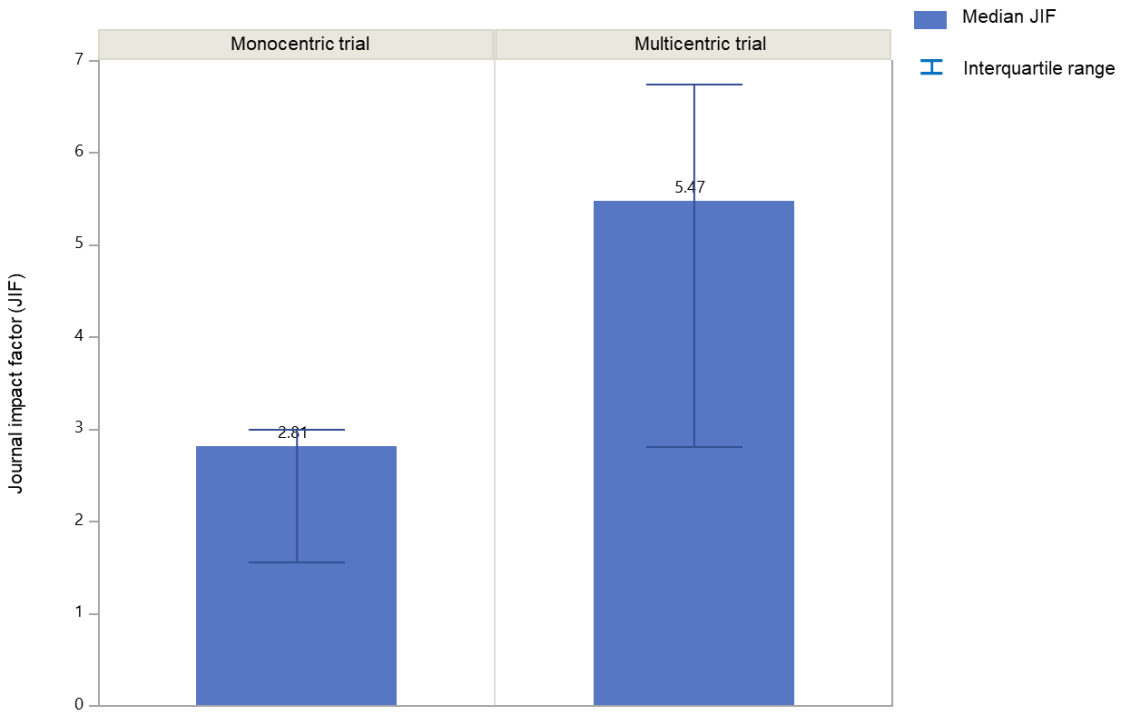


Figure 32 JIFs in the relative year of publication of the trial in mono- and multicentric trials

The JIF was significantly higher in multicentric trials than in monocentric trials (Wilcoxon rank sum test Z=3.76802, p=0.0002).

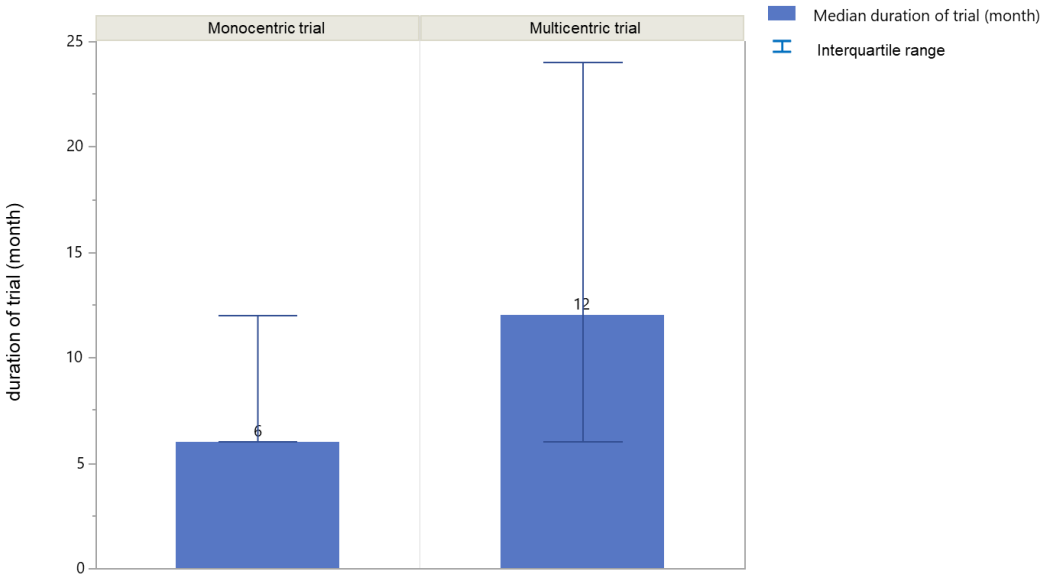


Figure 33 duration of trial in mono- and multicentric trial

The duration of trial was significantly higher in multicentric than in monocentric trials (Wilcoxon rank sum test Z=2.45727, p=0.0140).

The duration of trial was significantly correlated to the JIF (Spearman 0.3345, p=0.0057).

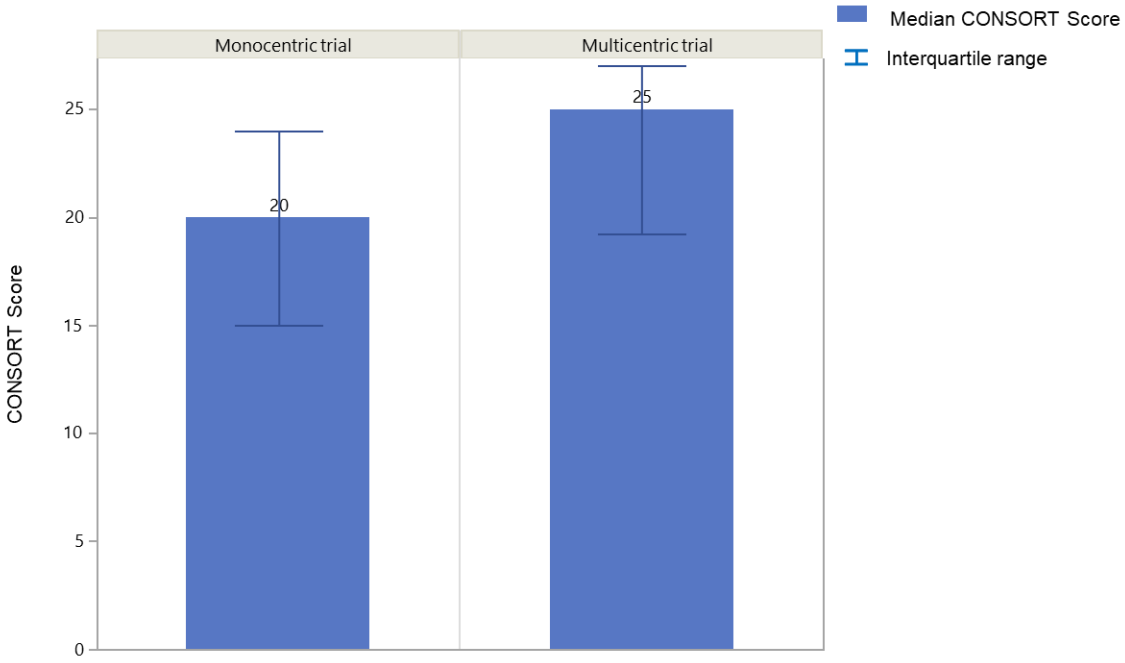


Figure 34 median CONSORT score in mono-/multicentric trial

The CONSORT score was significantly higher in multicentric than in monocentric trials (Wilcoxon rank sum test Z=2.85358, p= 0.0043).

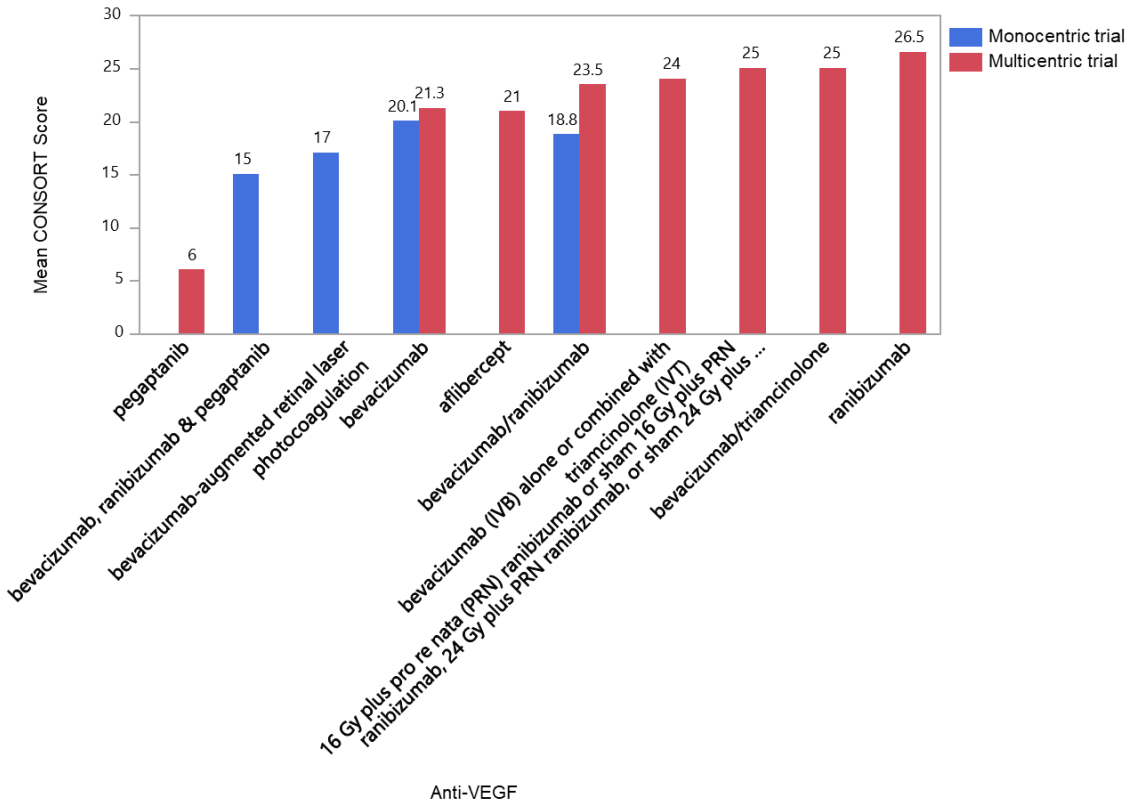


Figure 35 mean CONSORT score and Anti-VEGF in multi-/monocentric trial

The highest mean CONSORT score was found in publications of multicentric trials with ranibizumab.

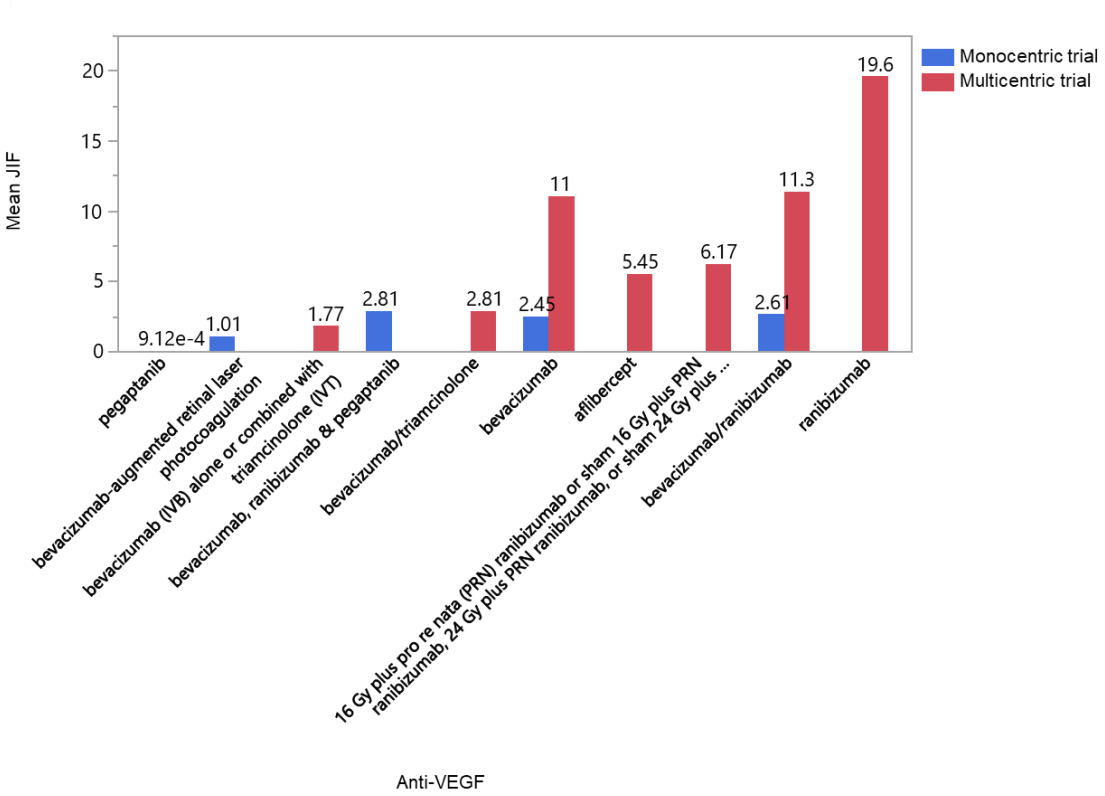


Figure 36 mean JIF and anti-VEGF in multi-/monocentric trial

Multicentric RCTs with ranibizumab were published in journals with the highest mean JIF as in David M. Brown et. al. in 2006 and Philipp J. Rosenfeld in 2006 (Rosenfeld et al., 2006), (Brown et al., 2006).

3.8. Gender distribution

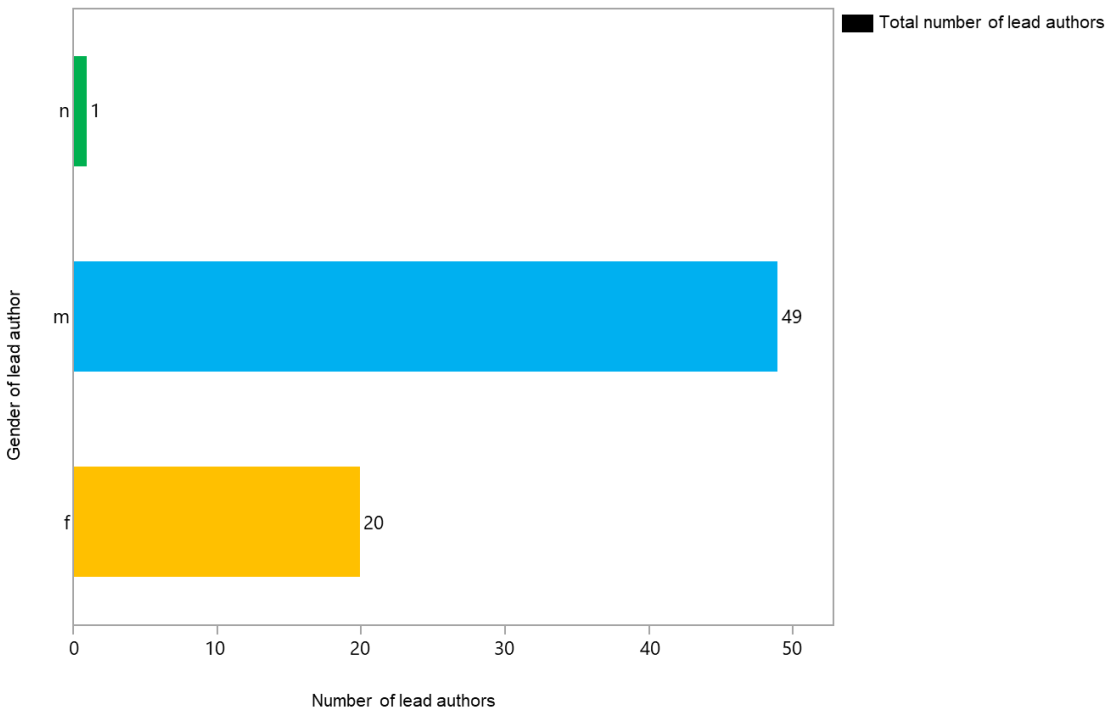


Figure 37 gender of lead author

49 (70%) of lead authors were male and 20 (28.57%) were female. One lead author´s gender could not be specified (Korean unisex given name) (see Fig 37).

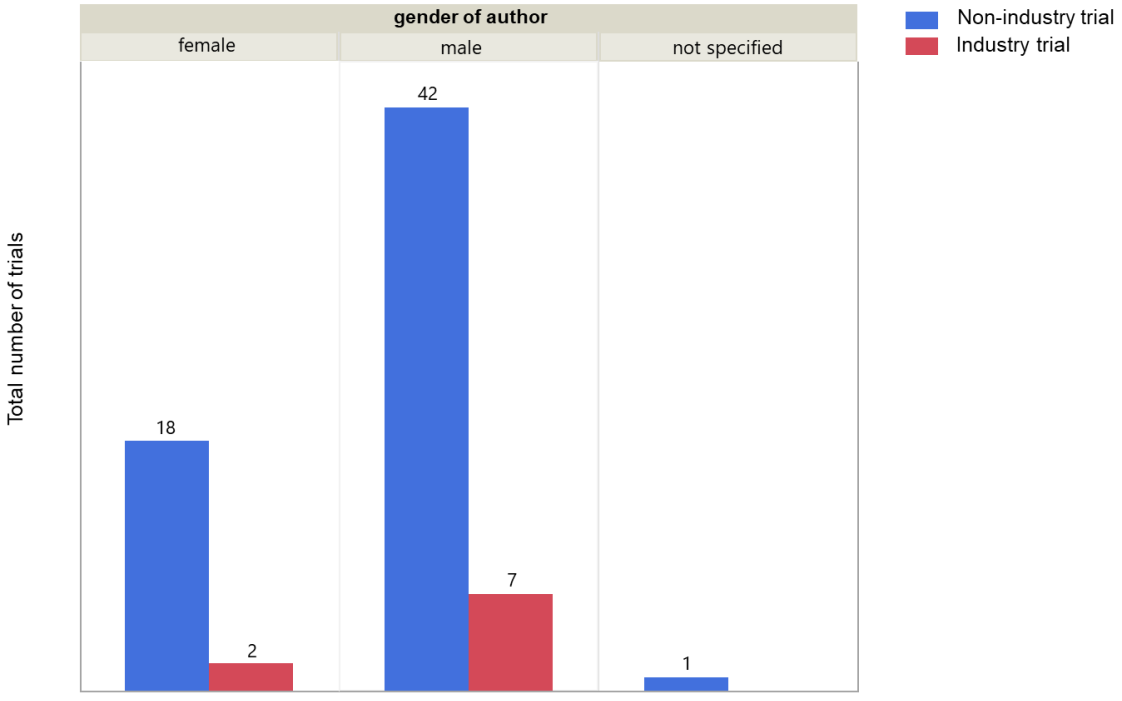


Figure 38 gender and industry trial

7 male industry authors and 2 female industry authors were found in all 70 publications.

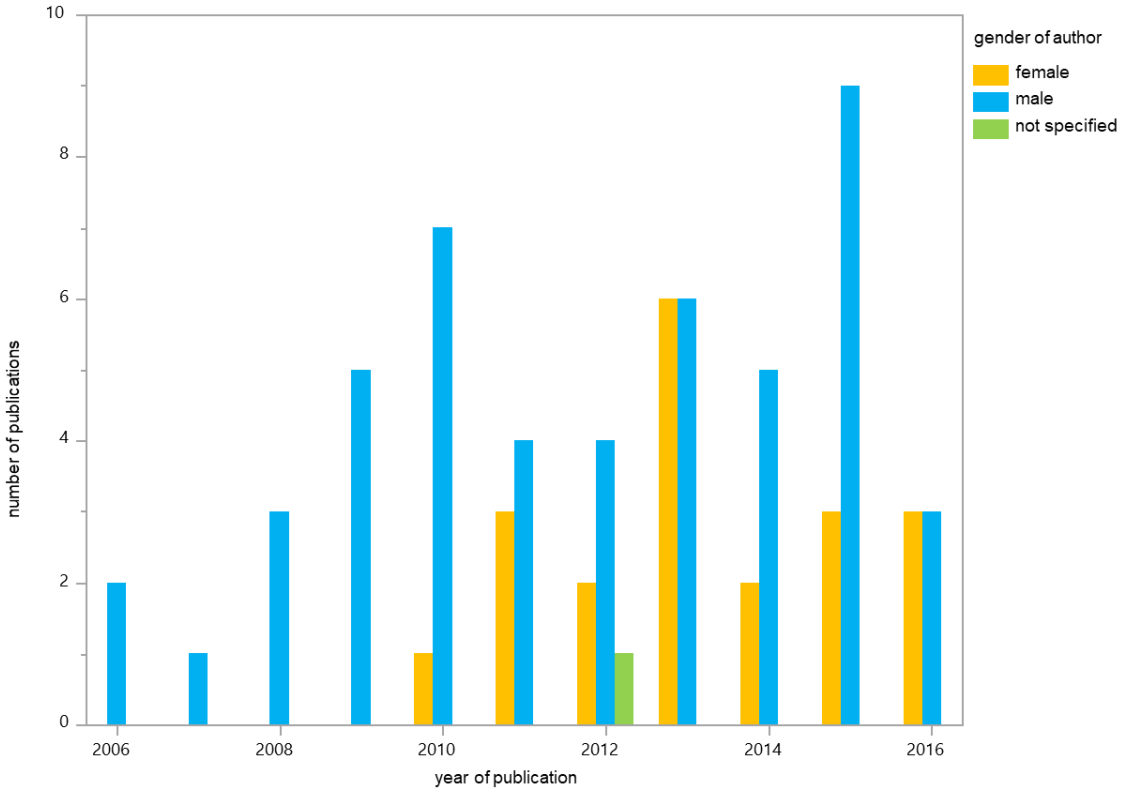


Figure 39 year of publication and gender of author

Female lead authors´ publications were released starting in 2010.

There was no significant relationship between industry sponsored publications and gender (Pearson chi square test: $X^2(1, N=70)=0.383$, $p=0.8259$) and there was no significant correlation between multi-/monocentric trial and gender Pearson chi square test: $X^2(1, N=70) = 2.96$, $p=0.2276$).

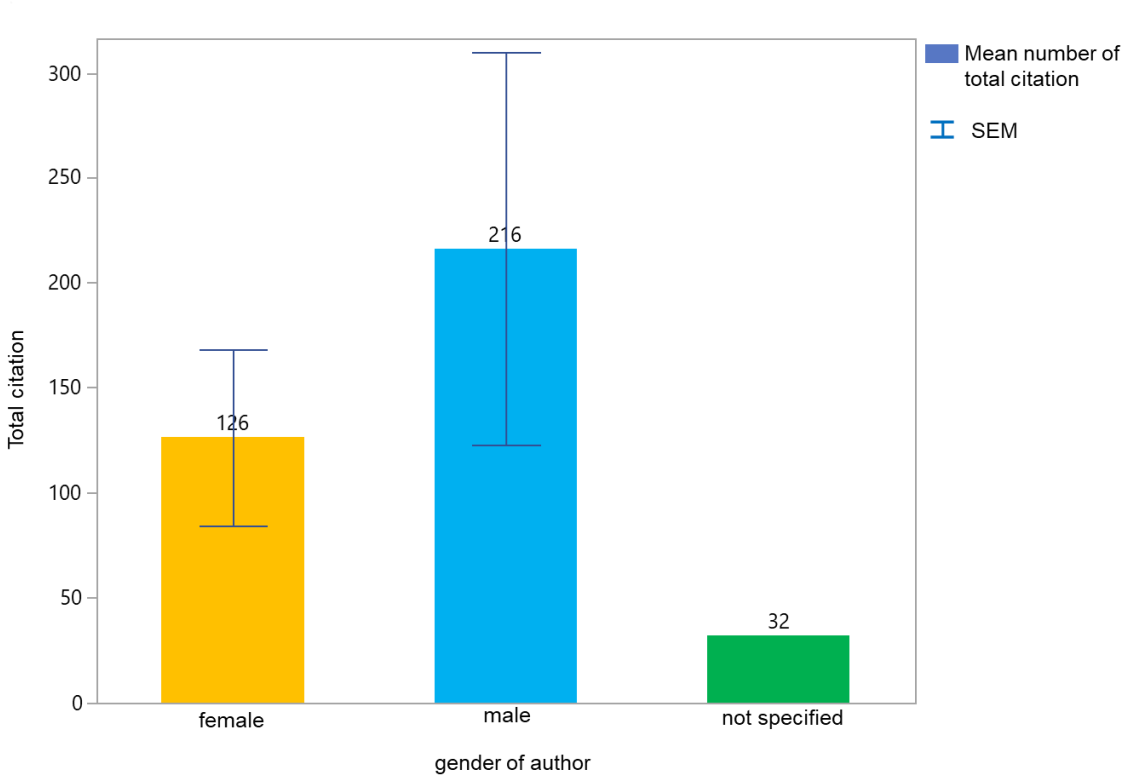


Figure 40 mean total citations and gender

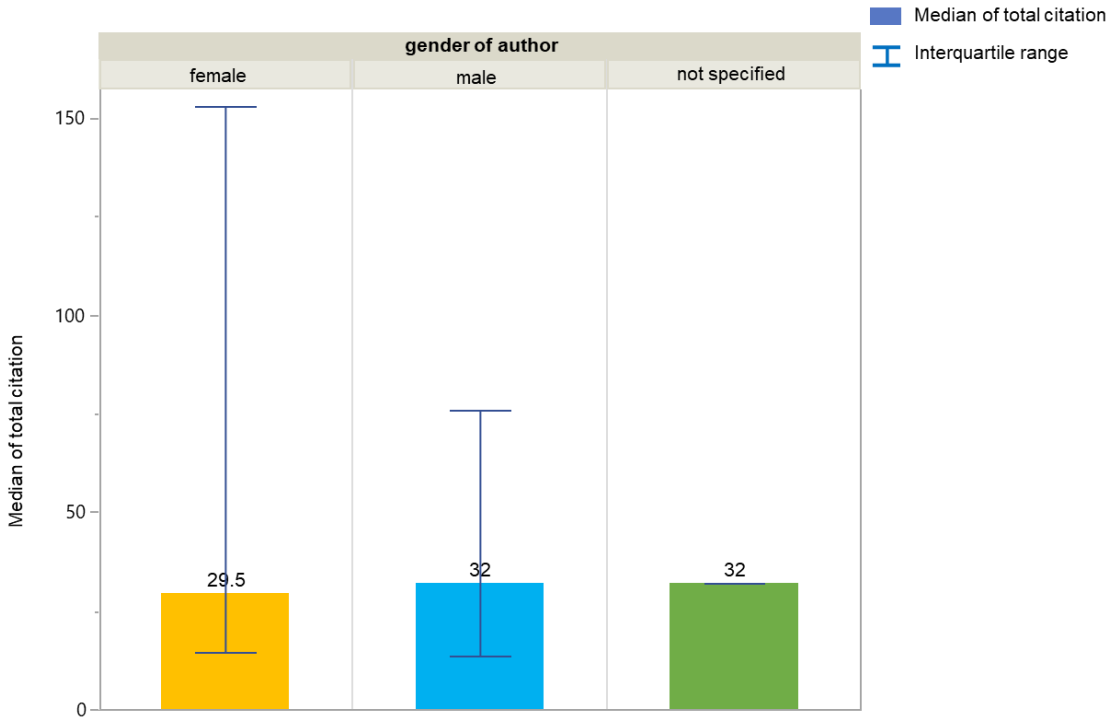
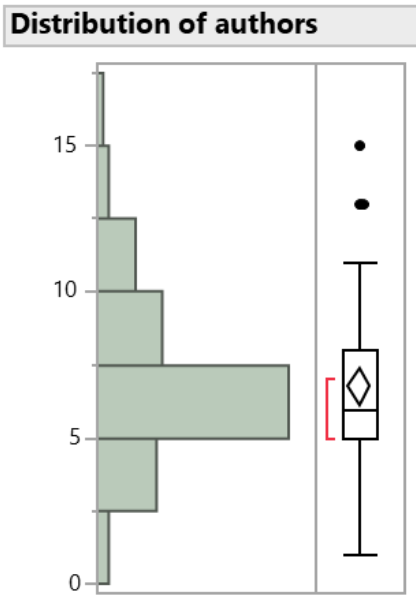


Figure 41 median total citations and gender distribution

The mean total citations of male lead authors was found to be 216 vs. 126 female lead authors. Given the apparent outliers, medians were generated. The more robust median was found to be 29.5 citations for female authors vs. 32 citations for male authors.

Nevertheless, the total citations were not significantly dependant on the authors' gender (Pearson Chi square test: X^2 (2,N=70) =0.3361, p=0.8453.)



quantile

100.0%	maximum	15
99.5%		15
97.5%		13,45
90.0%		10
75.0%	quartil	8
50.0%	median	6
25.0%	quartil	5
10.0%		3,1
2.5%		1,775
0.5%		1
0.0%	minimum	1

Statistic parameters

mean	6,7285714
Standard deviation.	2,6370901
Std.-error mean	0,3151926
95% CI above mean	7,3573634
95% CI below mean	6,0997795
N	70

Figure 42 frequency distribution of the number of authors per trial

The mean number of authors was 6.73 authors per publication. The maximum of authors per publication included was 15.

The number of authors was correlated with the CONSORT score (Spearman´s ρ=0,327, p=0,005) and the JIF (Spearman´s ρ=0,3041, p=0,0105), (see Table 5).

3.9. Relation of CONSORT and JIF with other parameter

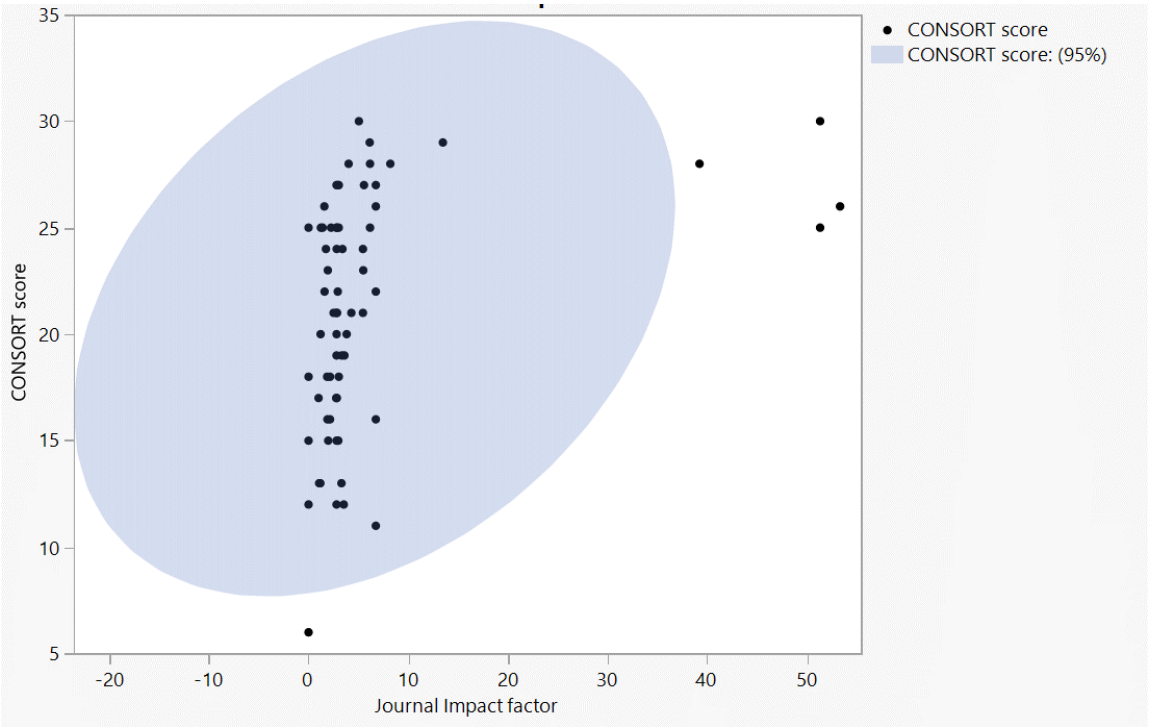


Figure 43 correlation between CONSORT score and JIF

The CONSORT score and the JIF of the corresponding publication were found to be strongly correlated, Spearman´s ρ =0.4899, p=<0.0001.

Criteria	**parameter**	**Spearman´s ρ**	**Significance**
CONSORT score	year of Publication	0.1099	n.s.
CONSORT score	average number of citations (per year)	0.3132	p= 0.0083

CONSORT score	number of authors	0.327	p= 0.005
CONSORT score	number of randomized patients	0.4245	p=0.002
CONSORT score	duration of trial	0.0583	n.s.
JIF	CONSORT score	0.4899	p<0.0001
JIF	number of randomized patients	0.4757	p=0.0001
JIF	total number of authors	0.3041	p=0.0105
JIF	duration of trial	0.3345	p=0.0057

Table 5: Correlation of CONSORT/ JIF with different parameters

4. Discussion

4.1. Distribution of publications

In the survey of Catalá-López et. al., in which RCTs published in forty highly ranked journals in the period 1965-2017 were analyzed, most RCTs were published in the USA, followed by the UK in second rank and Canada in third rank (Catalá-López et al., 2020).

In a current study of Wang et. al. about ophthalmic RCTs (from 2020 until 2022) most RCTs were conducted in the USA, followed by the UK and China, subsequently.

The results of this survey, in which most trials were published in the USA, the second most in Iran and the third most in the UK, fit partly to the results of Catalá-Lopez and Wang. In Wang et.al. Iran was in the 8th rank. It remains unclear why Iran ranked second in this study. A group of researchers might have been very productive and interested in different RCTs about anti-VEGF in Teheran. Compared to Rikos et. al. the year of publication and the adherence of CONSORT score were not significantly related. The reason for it could be the small cohort of this survey.

In the years 2013 and 2015 most trials were published. This observation partly fits the result of the article of AlRyalat et. al. In this observational study of RCTs in ophthalmology it was found that in 2015 the most RCTs were published. Further in retinal disease the most RCTs were conducted (AlRyalat et al., 2019).

4.2. Adherence of CONSORT statements

In this systematic review, 21 of 37 CONSORT items (56.75%) were fulfilled on an average.

The results of this overview was in the range of Fung et. al. with 65-96% CONSORT items fulfilled (in RCTs about neovascular AMD until October, 31

2007) and the result of Yao et. al. with 39% of CONSORT items (RCTs about ophthalmic surgery in the year 2011), (Fung et al., 2009, Yao et al., 2014).

Important criteria were found to be ignored by the majority of study authors. For example, CONSORT criterion 1a “Identification as randomized trial in title” helps scientists and physicians to easily identify a study as randomized. Randomization is a major prerequisite in order to control confounding factors. If trials are not clearly marked as randomized (not named in the title or abstract), it is harder to generate meta-analyses.

In only 34 of 70 articles (48.57%) the randomization of the trials were named in the title.

This number is inferior to the findings of Berwanger et. al., who identified the randomization within the title in 54.6 % of published RCTs in 2006, in the top four journals: “the New England Journal of Medicine” (NEJM), “Journal of the American Medical Association” (JAMA), “British Medical Journal” (BMJ), and “the Lancet” (Berwanger et al., 2009).

The specific objectives or hypotheses (CONSORT item 2b) were named in all publications of RCTs in this overview, this is contrary to the results of Ghimire et. al. who found that only 72.7% of publications named the specific objectives.

CONSORT items 4 and 5 were meanwhile supplemented in the CONSORT- AI Extension. CONSORT item 4 is about eligibility for participants and item 5 is about interventions. According to Liu et. al. in these two parts of a trial AI gets evermore involved. CONSORT item 6b) “any changes to trial outcomes after the trial commenced with reasons” showed an adherence of only 2.85%.

The Publication of Mintz-Hittner was the only one to name an amendment in all selected trials in this systematic review: “Before the date on which the data were first analyzed, we changed the primary outcome to treatment failure: the recurrence of neovascularization in one or both eyes arising from the retinal vessels and requiring retreatment by 54 weeks’ postmenstrual age (with ascertainment performed between 50 and 70 week)” (Mintz-Hittner et al., 2011).

The CONSORT item 7a for the sample size planning has been fulfilled in 52.86% of the publications considered in this work - in contrast to the results of Tulka

et.al. According to Tulka et. al. only 47% of the publications of AMD (all publications before 2010) reported of sample size planning. This might indicate a slight improvement in the reporting of trials in AMD.

Hence, an improvement in reporting of the sample size and the objectives is apparent.

No paper named interim analyses (CONSORT item 7b). This result cannot be exactly compared with the results of Yao et. al. and Fung et. al. because in the CONSORT statement of 2001 criterion 7b did not exist. In criterion 7 of the CONSORT statement of 2001, sample size, interim analyses, stopping rules were summarized in the previous version of the CONSORT statement. The CONSORT item 8a “methods used to generate the random allocation sequence” was found in 71.43% of all selected publications in this survey.

40 of 70 studies (57.14% of the studies) included a detailed description of the type of randomization and details of any restriction (CONSORT item 8b).

15 of 70 trials (21.43%) featured descriptions of the mechanism to implement the random allocation sequence (CONSORT item 9). The descriptions varied from vague wordings like “A random allocation sequence was performed by a biostatistician” (Ahmadieh et al., 2008) to a more precise “After the randomization, the random series was put in sealed envelopes that were labeled only with the name of the hospital and a number indicating the sequence of iterance of subjects into the study within each center” (Moradian et al., 2011).

56 of 70 papers gave detailed descriptions of how the trial findings might be applicable (CONSORT item 21). In most trials, the results were summarized in a phrase as a conclusion in the discussion part.

According to Kane et. al., which evaluated RCTs in the Journal of the American Medical Association (JAMA) and in the New England Journal of Medicine (NEJM) in the period of 1993-1995 (pre-CONSORT) and 1999-2002 (post-CONSORT), the quality of reporting improved after the first publication of CONSORT statement (Kane et al., 2007).

4.3. Masking

48 of 70 studies, which are categorized as “masked” or “blinded”, gave a description of the blinding methods (CONSORT item 11a) in this study. A very high significance found in this work is between the reporting of blinding and the mean number of CONSORT score.

Blinding is a very important method to reduce a potential bias in any study. Detection and performance bias can be reduced via masking. The performance bias especially in ophthalmology`s vital parameters like visual acuity can be confounded by the patient or the examiner, if aware of the treatment modality (Higgins JPT, 2023).

The report of blinding was not higher in journals with a higher JIF. The blinding was not verified by an independent database.

4.4. Adverse events

Only 34 of 70 trials (48.57%) reported adverse events, although each adverse event should be documented in clinical trials. Phillips et. al. detected a rate of 62% in a systemic review of in 184 RCTs in the four top rank journals (the “British Medical Journal”, the “Journal of the American Medical Association”, the “Lancet“ and the “New England Journal of Medicine”, time interval from September 2015 to September 2016) (Phillips et al., 2019). Scharf et. al. compared the reported adverse events in the scientific articles to the adverse events that were listed in the database of the clinical trials. 27% of high grade events could not be matched with the adverse events in the database of the National Cancer Institute (Scharf and Colevas, 2006).

Underreporting of adverse events is an issue that could be solved with statistical models like the Bayesian hierarchical model (Barmaz and Ménard, 2021). Such statistical model can help to compare reported adverse events to statistically predicted adverse events.

4.5. Industry-sponsored trials

A positive significant coherence between the JIF and industry sponsored trials was demonstrated in the selected publications. Furthermore, the total number of randomized patients was significantly higher in industry-sponsored trials.

The main reason for this association could be the fact that the trials with industry sponsorship/authorship were well-funded approval trials.

Multicentric trials were published by various authors with different affiliations: In this studies, affiliations in industry-sponsored trials were significantly higher.

The New England Journal of medicine is one of the top-ranked multidisciplinary journals. Not so many interventions in ophthalmology were published in such a prestigious journal. Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration (ANCHOR)-Trial, the Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration (MARINA)-Trial and the Comparison of Age-Related Macular Degeneration Treatments (CATT)-Trials (Rosenfeld et al., 2006, Brown et al., 2006, Martin et al., 2011) are very important RCTs and were published in the New England Journal of medicine. According to AlRyalat et. al., only 18% of RCTs within ophthalmology have been released in ophthalmological journals (AlRyalat et al., 2019).

4.6. Gender bias

In this study, 70% of the lead authors of the included RCTs are male, while at least 20% are female in the corresponding time period between 2006 and 2016. This result deviates only slightly from the publication of Steren et. al., which analysed the gender distribution of all certified ophthalmologist of the American Board of ophthalmology between 1992 and 2020: 65.4% were male ophthalmologist. In the subspecialty ‘medical retina’, however, 52% were female and 48% male physicians (Steren et al., 2023).

In all subspecialties the number of certified ophthalmologists of the American Board of ophthalmology increased from 1992 to 2020. The number of female ophthalmologist increased faster than compared to its male counterpart. This

result shows a similar direction to the result of this study in which the number of publications of female authors rose faster than the males authors´ publications.
In 2020, Huang et. al. investigated the gender bias in science, technology, engineering, and mathematics (STEM) fields. In all fields, 27% of authors were female in the period from 1900 to 2016. In health science 30.4% of authors were found to be female. There was a significant discrepancy by country: for example only 28% were female in Germany compared to 50% female authors in Russia. This publication focused also on the number of citations (accumulated 10 years after the publication) of the authors as a parameter of the impact in the course of the career as a scientist: male authors got 30% more citations than female authors. However the annual productivity was almost the same: female authors published 1.33 papers and male authors 1.32 papers per year on an average (Huang et al., 2020). In this survey, no significant correlation between gender and the number of citations was found. The median of total citations was only slightly different. The reason could be the relatively low number of cases in this study.
To close the gender gap, mentoring programs and organizations, e.g. AWIS (Association for Women in Science) in the USA that helps women to network and develop as professional scientists, are needed.
Further role models for female students as well as young researchers and physicians are essential.

4.7. CONSORT statement in journals with a high JIF

More than 600 biomedical journals formally endorsed the CONSORT statements. Articles might have a higher adherence to the CONSORT statements if publishers made this a formal requirement (Shamseer et al., 2016). In 2003, Good publication practice (GPP) has been released as a guideline to improve the publication in the pharmaceutical industry. These guidelines also recommended the CONSORT statements to all authors.
These facts fit the result of this systematic review: The CONSORT score was significantly higher in industry-sponsored trials. In this observation, the CONSORT score was also clearly associated with articles with a higher JIF.

This is a similar result to the publication of Balasubramanian et. al. in which a higher CONSORT score was related to a higher JIF, to a higher number of authors and to multicentric trials (Balasubramanian et al., 2006).
The CONSORT statements can serve as guidelines for authors to improve the reporting of trials. Clear communication is an important part in the evidence-based medicine. Systematic reviews and meta-analyses contribute to the current body of evidence. With a clear orientation, physicians can provide each individual patient with the best therapy.

4.8. Limitations

It is necessary to mention that the studies were in the first round selected according to abstract and title. Hence, the validity of the CONSORT item 1a and 1b implies some weakness. CONSORT Item 1b ”Structured summary of trial design, method, results and conclusions” had the best adherence: All studies gave sufficient details in their abstracts to maintain a good overview of the trial.
In 2008, a specific guidance “CONSORT for abstracts” (Hopewell et al., 2008) was published. “Items to include when reporting a randomized trial in a journal abstract” are listed in “CONSORT 2010 Explanation and Elaboration: updated guidelines for reporting parallel group randomized trials” (Moher et al., 2010). Only one trial did not mention the numbers of patients in the abstract (Sivaprasad et al., 2013).
The scoring based on the CONSORT checklist was binary without distinguishing how a criterion was met. So the minimum of each criterion was classified as “fulfilled”. There was no assessment how the criteria were met. So slight differences in the type and quality of reporting were not in account in this study.
A relatively small sample size in this survey limits the generalizability of the results.
A classification regarding the degree of fulfillment of the CONSORT Checklist would be helpful in the evaluation of RCTs for some criteria, for example as to the “mechanism to implement the random allocation sequence” (CONSORT Criterion 9).

In summary, the CONSORT recommendations, as well as other parameters such as the number of randomized patients, multicenter conduct and masking, were an essential prerequisite for a high JIF. Further research is needed to analyze and further improve the reporting of RCTs and adherence to the CONSORT checklist. Considering the unequal gender distribution, improved structures are needed.

Investigators, readers and authors should be aware of the importance of guidelines for a certain standard of trial reporting.

5. Summary

Introduction:

Randomized controlled trials (RCTs) are critical in evidence-based medicine, particularly for conditions like age-related macular degeneration (AMD), a leading cause of permanent vision impairment. The advent of anti-VEGF for neovascular AMD revolutionized ophthalmology. Consequently, the reporting quality of these RCTs is of significant interest. The CONSORT (Consolidated Standards of Reporting Trials) statements serve as guidelines for RCT reporting. This study evaluated the adherence to the 2010 CONSORT guidelines in 70 RCTs on anti-VEGF therapy. Additionally, correlations between the CONSORT score and other parameters such as publication year, journal impact factor (JIF), total citations, number of randomized patients, number of authors and blinding were explored.

Differences in CONSORT score between industry-sponsored and independently conducted trials, as well as multicenter and single-center studies, were also analyzed.

Furthermore, the study investigated potential gender bias in the authorship of retina therapy trials compared to general ophthalmology.

Methods:

In June 2017, PubMed was searched for trials on intravitreal anti-VEGF therapy. The articles were evaluated using the 2010 CONSORT statement checklist, and various parameters of the RCTs were assessed.

Results:

Seventy publications met the inclusion criteria covering RCTs conducted from 2006 to 2016. The mean was 21.2, representing 57.3% of the total CONSORT score (37 items). No significant correlation was found between the CONSORT score and the year of publication. However, there was a strong correlation between the CONSORT score and JIF (Spearman's $\rho = 0.4899$, $p < 0.0001$). Gender distribution among lead authors was unequal, with 70% male and 28.57% female. Peaks in RCT publications on anti-VEGF were observed in 2013 and 2015.

Discussion:

Most trials were conducted in Europe, with groundbreaking trials published in top-ranked multidisciplinary journals. Compared to previous studies, there has been an improvement in adherence to CONSORT guidelines, notably in reporting sample size and specific objectives. Industry-sponsored trials had significantly higher JIFs compared to non-industry trials.

Conclusion:

The study demonstrated a significant relationship between the CONSORT score and JIF, as well as other parameters like the number of randomized patients and multicentric trial status. Further research is necessary to enhance the reporting quality of RCTs and adherence to CONSORT guidelines, ensuring the production of high-quality publications which are essential for evidence-based medicine.

Summary in German

Einführung:

Randomisierte kontrollierte Studien (RCTs) sind in der evidenzbasierten Medizin von entscheidender Bedeutung, insbesondere bei Erkrankungen wie der altersbedingten Makuladegeneration (AMD), einer der Hauptursachen für dauerhafte Sehstörungen. Das Aufkommen von Anti-VEGF gegen neovaskuläre AMD revolutionierte die Augenheilkunde. Daher ist die Qualität der Berichterstattung dieser RCTs von erheblichem Interesse. Das CONSORT (Consolidated Standards of Reporting Trials) -Statement dient als Richtlinie für die Berichterstattung von randomisierten kontrollierten Studien. In dieser Studie wurde die Einhaltung des CONSORT-Statements von 2010 in 70 RCTs zur Anti-VEGF-Therapie bewertet. Darüber hinaus wurden Korrelationen zwischen CONSORT-Scores und anderen Parametern wie dem Veröffentlichungsjahr, dem Journal Impact Factor (JIF), der Gesamtzitationen, der Anzahl randomisierter Patienten, der Anzahl der Autoren und der Verblindung untersucht.

Es wurden auch Unterschiede in den CONSORT-Scores zwischen Industrie-gesponserten und unabhängigen Studien sowie multizentrischen und monozentrischen Studien analysiert.

Darüber hinaus untersuchte diese Studie einen möglichen Gender Bias bei der Autorenschaft von Studien zur Netzhauttherapie im Vergleich zur allgemeinen Augenheilkunde.

Methoden:

Im Juni 2017 wurde PubMed nach Studien zur intravitrealen Anti-VEGF-Therapie durchsucht. Die Artikel wurden anhand der CONSORT-Statement-Checkliste 2010 bewertet, wobei verschiedene Parameter der RCTs beurteilt wurden.

Ergebnisse:

Siebzig Publikationen erfüllten die Einschlusskriterien für RCTs, die zwischen 2006 und 2016 durchgeführt wurden. Der mittlere CONSORT-Score betrug 21,2, das entspricht 57,3 % des gesamten CONSORT-Scores (37 Punkte). Zwischen dem CONSORT-Score und dem Erscheinungsjahr konnte kein signifikanter

Zusammenhang festgestellt werden. Es bestand jedoch eine starke Korrelation zwischen dem CONSORT-Score und dem JIF (Spearman's ρ = 0,4899, p < 0,0001). Die Geschlechterverteilung unter den HauptautorInnen war ungleich: 70 % Männer und 28,57 % Frauen. In den Jahren 2013 und 2015 wurden Spitzenwerte in RCT-Veröffentlichungen zu Anti-VEGF beobachtet.

Diskussion:

Die meisten Studien wurden in Europa durchgeführt, wobei bahnbrechende Studien in erstklassigen multidisziplinären Fachzeitschriften veröffentlicht wurden. Im Vergleich zu früheren Studien gab es eine Verbesserung bei der Einhaltung des CONSORT-Statements, insbesondere bei der Berichterstattung über die Stichprobengröße und bestimmter Studienziele. Industrie-gesponserte Studien hatten im Vergleich zu unabhängigen Studien deutlich höhere JIFs.

Schlussfolgerung:

Die Studie zeigte einen signifikanten Zusammenhang zwischen dem CONSORT-Score und dem JIF sowie anderen Parametern, wie der Anzahl randomisierter Patienten und dem Status einer multizentrischen Studie. Weitere Forschung ist erforderlich, um die Berichterstattungsqualität von RCTs und die Einhaltung der CONSORT-Richtlinien zu verbessern und die Produktion hochwertiger Publikationen sicherzustellen, die für die evidenzbasierte Medizin unerlässlich sind.

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7. Declaration regarding my own contribution

Erklärungen zum Eigenanteil:

Die Arbeit wurde in der Universitäts-Augenklinik Tübingen unter Betreuung von Prof. Dr. med. Focke Ziemssen durchgeführt.
Die Konzeption der Studie erfolgte durch mich in Zusammenarbeit mit Prof. Dr. med. Focke Ziemssen.
Die Datenerhebung wurde von mir eigenständig (exklusive der Angaben zur Anzahl der Zitationen und des JIF, welche von Prof. Dr. med. Focke Ziemssen hinzugefügt worden sind) durchgeführt.
Die statistische Auswertung erfolgte nach einer Einführung durch Prof. Dr. med. Focke Ziemssen durch mich.
Ich versichere, das Manuskript selbständig verfasst zu haben und keine weiteren als die von mir angegebenen Quellen verwendet zu haben.

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