ΠΑΝΕΠΙΣΤΗΜΙΟ ΘΕΣΣΑΛΙΑΣ
ΣΧΟΛΗ ΕΠΙΣΤΗΜΩΝ ΥΓΕΙΑΣ
ΤΜΗΜΑ ΙΑΤΡΙΚΗΣ
ΠΡΟΓΡΑΜΜΑ ΜΕΤΑΠΤΥΧΙΑΚΩΝ ΣΠΟΥΔΩΝ

ΜΕΘΟΔΟΛΟΓΙΑ ΒΙΟΪΑΤΡΙΚΗΣ ΕΡΕΥΝΑΣ, ΒΙΟΣΤΑΤΙΣΤΙΚΗ ΚΑΙ ΚΛΙΝΙΚΗ ΒΙΟΠΛΗΡΟΦΟΡΙΚΗ

Μεταπτυχιακή Διπλωματική Εργασία

«ΑΞΙΟΛΟΓΗΣΗ ΤΗΣ ΠΟΙΟΤΗΤΑΣ ΑΝΑΦΟΡΑΣ ΤΩΝ ΤΥΧΑΙΟΠΟΙΗΜΕΝΩΝ ΕΛΕΓΧΟΜΕΝΩΝ ΚΛΙΝΙΚΩΝ ΔΟΚΙΜΩΝ ΓΙΑ ΤΗ ΘΕΡΑΠΕΙΑ ΜΕ Anti-VEGF ΣΤΗΝ ΝΕΟΑΓΓΕΙΑΚΗ ΗΛΙΚΙΑΚΗ ΕΚΦΥΛΙΣΗ ΩΧΡΑΣ ΚΗΛΙΔΑΣ ΜΕ ΒΑΣΗ ΤΗ ΔΗΛΩΣΗ CONSORT"

"ASSESSMENT OF THE REPORTING QUALITY OF RANDOMIZED CONTROLLED TRIALS FOR Anti-VEGF THERAPY IN NEOVASCULAR AGE-RELATED MACULAR DEGENERATION BASED ON THE CONSORT STATEMENT"

ΠΑΠΑΒΑΣΙΛΕΙΟΥ Δ. ΜΑΡΙΑ-ΕΛΕΝΗ

Ειδικευόμενη Ιατρός Οφθαλμολογίας

Επιβλέπων καθηγητής:

***Ζιντζαράς Ηλίας**, MSc, PhD*

Τριμελής Συμβουλευτική Επιτροπή:

Ζιντζαράς Ηλίας
Δοξάνη Χρυσούλα, MD, MSc, PhD
Δαρδιώτης Ευθύμιος, MD, MSc, PhD

ΛΑΡΙΣΑ, 2022

Abstract

Background: Randomized controlled trials (RCTs) provide the most reliable evidence of effectiveness of health interventions. The Consolidated Standards of Reporting Trials (CONSORT) statement improves the quality of RCT reporting in an evidence-based approach.

Objective: To assess the quality of reporting RCTs for anti-VEGF therapy in patients with nAMD, based on the 2010-CONSORT Statement.

Methods: Electronic research was conducted using the MEDLINE/PupMed to identify all English-language RCTs involving patients with nAMD who received anti-VEGF therapy published from 2010 to 2022. Inclusion criteria were as follows: included patients who randomly received at least one of the four anti-VEGF medications for nAMD and they were randomly assigned to at least two interventions groups. An overall CONSORT compliance metric was calculated using a 38-item checklist based on the CONSORT 2010 statement. Adherence ≥75% was defined as a good reporting quality. Two different publication periods were assessed for reporting quality (2010-2016 and 2017-2022). The determination of compliance of each item separately and control of potential determinants in relation to the quality of reporting of RCTs, have also been assessed.

Results: A total of 23 articles, published in 12 different medical journals, were considered eligible. The average CONSORT compliance score was 67.35% with SD=11.09. The RCTs that presented an adequate reporting (≥75% of items) were 8 (34.79%), while the remaining 15 studies (65.21%) had not the optimal compliance with Consort statement (<75%). Of the 38 items of the CONSORT list only 15 (39.47%) were reported adequately (≥75%), with 9 of them (23.69%) having the optimum reporting (100%), whereas the rest 23 items (60.53%) presented a suboptimal reporting (<75%).

Conclusions: Reporting quality of RCTs for anti-VEGF therapy in patients with nAMD remains unsatisfactory. Adherence to the CONSORT statement should be further encouraged and included in each journal's instructions to authors.

Keywords CONSORT, Randomized Controlled Trials, RCTs, anti-VEGF, Neovascular age-related macular degeneration

Περίληψη

Εισαγωγή: Οι Τυχαιοποιημένες Ελεγχόμενες Κλινικές δοκιμές (RCTs) μας δίνουν τα πιο αξιόπιστα αποτελέσματα σχετικά με την αποτελεσματικότητα των ιατρικών παρεμβάσεων. Η δήλωση CONSORT βελτιώνει την ποιότητα αναφοράς των RCTs, βασιζόμενη σε αποδεικτικά στοιχεία.

Στόχοι: Η αξιολόγηση της ποιότητας αναφοράς των RCTs για θεραπεία με αντι-VEGF σε άτομα με νεοαγγειακή ηλικιακή-εκφύλιση της ωχράς κηλίδας, με βάση τη δήλωση CONSORT 2010.

Μέθοδοι: Διεξήχθη ηλεκτρονική έρευνα με τη χρήση του MEDLINE/PubMed για τον εντοπισμό όλων των RCTs που αφορούσαν ασθενείς με νεοαγγειακή εκφύλιση της ωχράς κηλίδας που έλαβαν θεραπεία με anti-VEGF παράγοντες, δημοσιευμένες από το 2010 έως το 2022 στην αγγλική γλώσσα. Τα κριτήρια καταλληλότητας ήταν τα εξής: περιλάμβαναν ασθενείς που έλαβαν τυχαία τουλάχιστον μία από τις τέσσερις anti-VEGF ενδουαλοειδικές ενέσεις για τη νεοαγγειακή ηλικιακή εκφύλιση ωχράς κηλίδας και τυχαιοποιήθηκαν σε τουλάχιστον δύο ομάδες παρέμβασης. Υπολογίστηκε μία συνολική μέτρηση της συμμόρφωσης με τη δήλωση CONSORT, χρησιμοποιώντας ένα ερωτηματολόγιο 38 στοιχείων ελέγχου που βασίζεται στη λίστα ελέγχου CONSORT 2010. Η συμμόρφωση ≥75% ορίστηκε ως καλή ποιότητα αναφοράς. Οι αναφορές αξιολογήθηκαν σε δύο περιόδους δημοσίευσης (2010-2016 και 2017-2022). Ο προσδιορισμός της συμμόρφωσης του κάθε στοιχείου ελέγχου της λίστας ξεχωριστά και ο έλεγχος των πιθανών καθοριστικών παραγόντων σε σχέση με την ποιότητα αναφοράς εξετάστηκε.

Αποτελέσματα: Συνολικά 23 άρθρα θεωρήθηκαν κατάλληλα, τα οποία ήταν δημοσιευμένα σε 12 διαφορετικά περιοδικά. Η μέση βαθμολογία συμφωνίας με τη δήλωση CONSORT υπολογίστηκε 67.35% με τυπική απόκλιση 11.09. Οι RCTs που παρουσίασαν επαρκή αναφορά των στοιχείων (≥75%) ήταν 8 (34.79%), ενώ οι υπόλοιπες 15 μελέτες (65.21%) δεν είχαν τη βέλτιστη συμμόρφωση με τη δήλωση CONSORT. Μόνο 15 από τα 38 στοιχεία της λίστας ελέγχου (39.47%) αναφέρθηκαν επαρκώς (≥75%), με 9 από αυτά (23.69%) να παρουσιάζουν τη βέλτιστη αναφορά (100%), ενώ τα υπόλοιπα 23 στοιχεία (60.53%) παρουσίασαν υποβέλτιστη αναφορά (<75%).

Συμπεράσματα: Η ποιότητα αναφοράς των RCTs για τη θεραπεία με anti-VEGF σε ασθενείς με νεοαγγειακή ηλικιακή εκφύλιση ωχράς κηλίδας παραμένει μη ικανοποιητική. Η καλύτερη συμμόρφωση με τη δήλωση CONSORT θα πρέπει να υποστηρίζεται περαιτέρω και να ενσωματώνεται στις οδηγίες κάθε περιοδικού ως προς τους συγγραφείς.

Λέξεις κλειδιά CONSORT, Τυχαιοποιημένες ελεγχόμενες κλινικές δοκιμές, RCTs, anti-VEGF, νεοαγγειακή ηλικιακή εκφύλιση ωχράς κηλίδας

Introduction

Randomized Controlled Trials (RCTs) are the cornerstone of evidence-based approach and are considered the optimum study design for the evaluation of causal associations in clinical research [1, 2]. When RCTs are designed in the right way and are properly conducted, they can offer the most trustworthy data on the effectiveness of health care interventions, since proper blinding and randomization eliminate selection and confounding bias [3].

Nevertheless, a various number of RCTs are characterized by methodological distortions, which may result to biased calculations [4]. Respectively inaccurate reporting may yield misguided conclusions and decision misleading in all facets of healthcare [5, 6]. It is crucial that the planning, execution and analysis of RCTs are clearly and accurate analyzed in the full text, so that readers and reviewers can critical appraisal the validity of the results. Transparent reporting of RCTs limits exaggerated treatment effects and facilitates reader's appreciation of trial findings [7,8].

Taking into consideration these concerns about poor reporting of clinical trials a team of editors and scientists, created the CONsolidated Standards Of Reporting Trials (CONSORT) statement. It's first publication was in 1996 [9] and revised twice since then, in 2001 and 2010 [10, 11]. This statement is an evidence-based approach, which includes a checklist of 25 items and a flowchart [12] and is going along with a comprehensive explanation and elaboration document [13]. It is very important, that detailed information concern the title, introduction, methods, results, discussion and other information should be reported thoroughly and transparent as possible, covering all aspects of a trial. Authors can use it as a guidance tool, ensuring transparent reporting and avoiding omission of important information. Therefore, over time, many high-ranked journals are advocating for their implementation of improved reporting standards. [14].

Age-related macular degeneration (AMD) is the leading cause of non-reversible central vision loss among individuals over the age of 50 in developed countries [15], leading to blindness in about 32.4 million people all around the world and moderate-to-severe visual impairment in another 191 million [16]. Until 2050, the new cases of early AMD would be 39.05 million and 6.41 million for late AMD [17]. The basic characteristic of the disease is the progressive degeneration of RPE and photoreceptors in the retina. AMD is divided into two main categories, the dry form (non-neovascular), which progressively can lead to geographic atrophy and the wet form (neovascular) [18]. The last one, is more aggressive, with rapid progression since it is characterized by choroidal neovascularization (CNV) affecting the foveal center [19]. Until mid-200s nAMD had a poor prognosis. With the advent of intravitreal administration of anti-vascular endothelial growth factor (VEGF) drugs that block the action of all isoforms of VEGF-A. There are, currently, four anti-vascular endothelial growth factor (VEGF) drugs with indication for the treatment of neovascular AMD. Ranibizumab (Lucentis), bevacizumab (Avastin), brolucizumab (Beovu) and aflibercept (Eylea) [20].

Given the above reasons, the need for therapeutic interventions that are effective concerning anti-VEGF treatment in nAMD is of the utmost importance. To the best of knowledge, this is the first study conducted, to examine the reporting quality of RCTs for anti-VEGF therapy in nAMD based on the CONSORT 2010 statement, covering a period from 2010 to 2022, allowing the interpretation of results in regard to the transparency of the reporting RCTs in the field of Ophthalmology.

Methods

The present study evaluates retrospectively the RCTs for anti-VEGF therapy in nAMD.

Search Strategies

A meticulous electronic research using the MEDLINE/Pubmed was conducted to find all applicable RCTs, from January 2010 to August 2022. The subsequent term combinations were used:

((((((((((((((((anti-VEGF) OR (Anti-vascular endothelial growth factor)) OR (Ranibizumab)) OR (Aflibercept)) OR (Bevacizumab)) OR (Brolucizumab)) OR (Lucentis)) OR (Eylea)) OR (Avastin)) OR (Beovu)) AND (Neovascular age related macular degeneration)) OR (nAMD)) OR (Wet age related macular degeneration)) OR (wAMD)) OR (Exudative age related macular degeneration)) OR (ARMD)) OR (Age related macular degeneration) OR (Choroidal Neovascularization)

The following filters were additionally used: the type of the article : “Randomized Controlled Trial”, language :“English” and for species :“Humans”

Eligibility criteria

Studies were eligible if they fulfilled the subsequent criteria:

- They were designed as RCTs, in which participants were randomly assigned to at least 2 intervention groups
- Patients were included, who randomly received at least 1 of the 4 anti-VEGFs - ranibizumab, aflibercept, bevacizumab, brolucizumab- no matter the administration regimen, treatment duration and comparators
- The recruited arms were participants with Neovascular Age-Related Macular Degeneration
- They had publication date before August 2022
-

Studies were excluded per the subsequent criteria:

- Non-randomized studies
- Non-human studies
- Articles using information from a previously conducted studies (post-hoc analyses, sub-group analysis, sub-studies)
- Other study designs (reviews, systematic reviews, meta-analyses, small pilot studies, dose comparison studies, economic analysis, abstracts, study protocols, editorials)
- Articles not published in English

First screening of the title of the study, followed by the abstract and then by the whole text was conducted to identify all studies who met the eligibility criteria.

Reporting Assessment Tool and Data Extraction

As a tool for the assessment of the reporting quality was used the revised CONSORT 2010 checklist, which includes 25 items, 12 of them are divided into two sections (37 items in total) [Table 1, Supplementary file]. The existence of the participant flow chart (item 13) was evaluated as a further item (38 items in total), since it's strongly recommended in the Consort explanation and elaboration document [21].
All items of the CONSORT checklist were analyzed and evaluated, only if they had a transparent reference on the trial and they were not taken into consideration if they were just performed during the trial. More specific, each item separately was appraised equally by one point when it had a clear and adequate reference, zero when it was absent, or the reference was unclear, and as not applicable in step with specific features of the trial. Items with reference over once in several sections of the studies were rated as 0 if they were not consistent.

Items that were reported in a different section of the trial (Title, Abstract, Introduction, Methods, Results and Discussion) were evaluated as zero, with the exception of the "Other Information" section (Registration, Protocol, Funding) and item 14a "dates defining periods of recruitment and follow-up" (either methods or results section) which were evaluated as one irrespective of where they were described. Supplementary data were evaluated as one, just in case they had a relevant reference within the main body of the paper. Ecxeption of this rule, was item 8a, since according to the CONSORT Explanation and Elaboration document "information on the process of randomization is included in the body of the main article and not as a separate supplementary file; where it will be missed by the reader".

Specific items on the CONSORT checklist statements like 3b (Changes to methods), 6b (Changes to trial outcomes), 7b (When applicable), 11b (If relevant), 12b (Methods of additional analyses), 14b (Why the trial ended or was stopped), 18 (Results of any other analyses performed) were not evaluated in case of non-applicability but were assessed accordingly if the answer was definite yes or not. Overall compliance to the CONSORT statement was calculated without considering non applicable items.

The additional information concerning the journal and article characteristics were also collected: year of publication, sample size, journal ranking according to the Journal Impact Factor -IF- published in 2021 by Clarivate Analytics via Journal Citation Reports, possible commercial funding and also the existence of participant flowchart, which is strongly recommended as directed by the CONSORT 2010 Explanation and Elaboration document.

Outcomes

The primary endpoint of this investigation was to evaluate the average compliance of RCTs for anti-VEGF treatment in nAMD according to the CONSORT statement. Secondary endpoints were the determination of compliance of each item separately and control of potential determinants in relation to the quality of reporting of RCTs. To provide maximum scientific evidence, all existing articles were evaluated to provide a complete sensus of all available studies.

Evaluation and Statistical Analysis

The mean adherence to the CONSORT Statement of RCTs for anti-VEGF therapy concerning patients with nAMD was calculated and described with statistic measures of central tendency and variance. CONSORT adherence above 75% was determined as good reporting quality and below 75% as suboptimal reporting [22, 23]. It was calculated, also, the percentage of the studies that had an adequate reporting quality (≥75% of the 38 checklist items) overall and by time period.

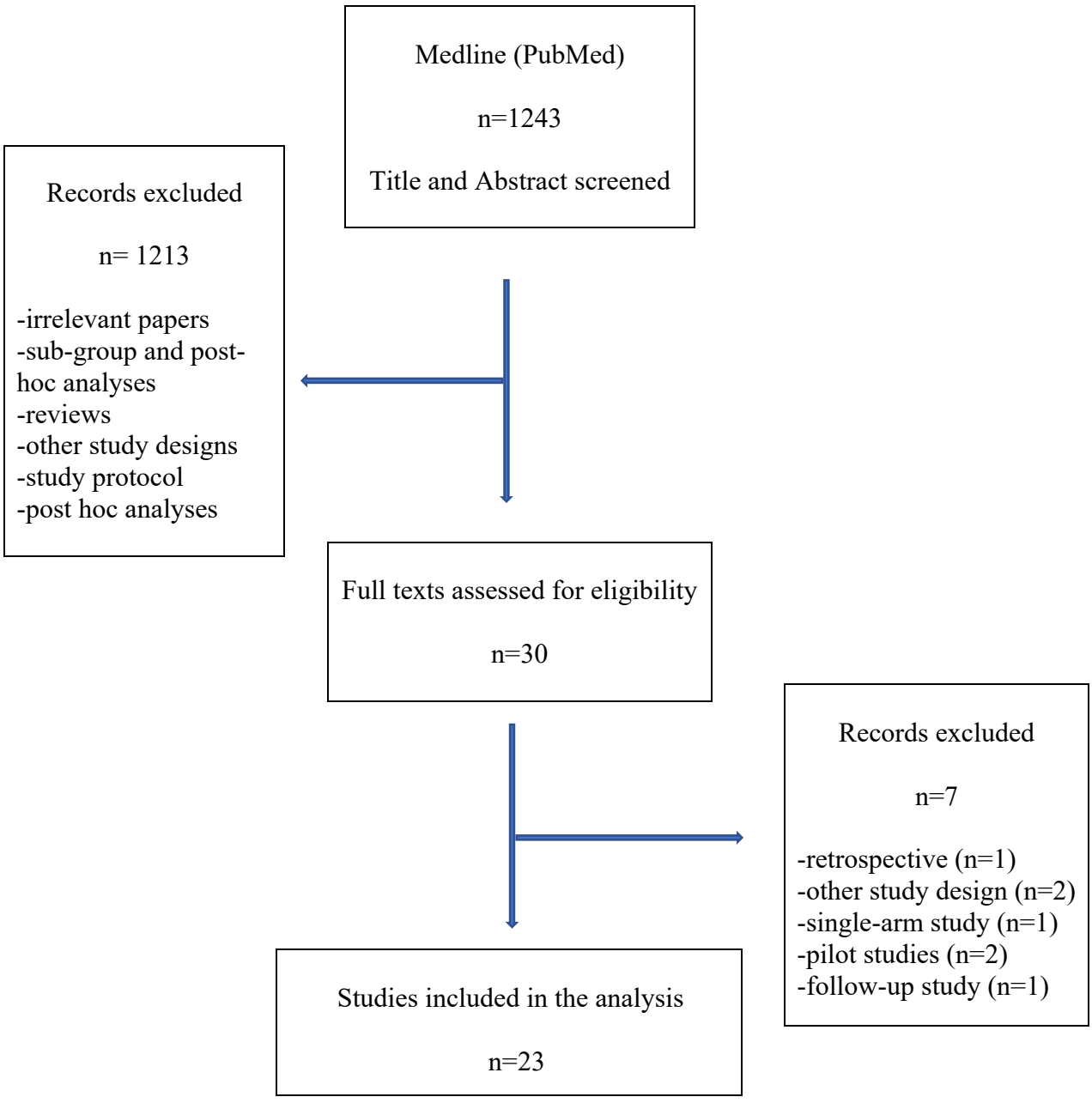
Additionally, it was calculated the adherence to the CONSORT statement per item (items reported in ≥75% of the studies, were defined as adequately or <75% of the studies were defined as inadequately reported) and comparison of different time periods for each item was carried out by using the Pearson's chi-square test in order to identify improvements over time.

Univariate analysis for possible determinants was performed. According to the impact factor (IF) list of each journal, based on the ISI (Institute for Scientific Information) impact factor (IF) list for 2021, articles were spited into 2 groups. High impact factor medical journals (IF>10) and low impact factor medical journals (IF<10). The choice of IF=10 as a switch off-point was arbitrary. It was calculated the mean CONSORT adherence score of the articles published in low ranked (IF<10) and in high ranked medical journals (IF>10) and performed a Mann-Whitney U nonparametric test to compare these groups. Comparison between >75% compliance among different parameters (categorical variables) was performed. Two different time periods (2010-2016 and 2017-2022), sample size (derived from the mean of our sample, <532 vs ≥532 randomized patients), existence of participation flowchart (yes/no) and reporting of funding (yes/no) were analyzed, using Person's chi-square test for trend or Fisher's exact test. All statistical analyses were made on the IBM SPSS Statistics 26. For statistical significance a cut-off point was set at the two-sided 0.05 level. Odds Ratios (ORs) and 95% Confidence Intervals (95% CIs) are presented. Binary logistic regression was performed in order to search for possible associations between the parameters and reporting quality. For the regression analysis a value of 0.05 was set to be significant.

Results

Evaluation process was performed in three steps as shown in the flow diagram (Fig. 1). The initial literature search yielded 1243 related articles. After screening of the title and abstract 1213 studies were excluded, since they were eligible. The remaining 30 studies were full text searched, 7 of which were not met the inclusion criteria and finally 23 articles were evaluated as eligible [24-45]. Among them 11 were published between 2010 and 2016 and 12 between 2017 and 2022.

Fig. 1. Flow diagram of the literature search



CONSORT compliance

The average Consort compliance score for studies published the publication period from 2010 to 2022 (n=23) was 67.35% with SD=11.09 (Median=67.64%, Minimum Adherence=50 % and Maximum Adherence=82.86% ,with Range=32.86%). The RCTs that presented an adequate reporting (≥75% of items) were 8 (34.79%), while the remaining 15 studies (65.21%) had not the optimal compliance with Consort statement (<75%). Specifically, 4 studies (33.34%) presented adequate reporting in period 2010-2016 and 4 studies (36.23%) the period 2017-2022.

Twelve different medical journals hosted the retrieved articles. Six of them are currently support CONSORT, corresponding to 73.91% of the articles (17 articles) with an average CONSORT adherence of these articles 69.95%. The rest 6 articles (26.09%) were published in 6 non endorsing journals and their average CONSORT adherence reached 59.94%. This difference among endorsing and non-endorsing journals was not statistically significant (p-value=0.087, U=26.500, z=-1.720, Mann Whitney U test).

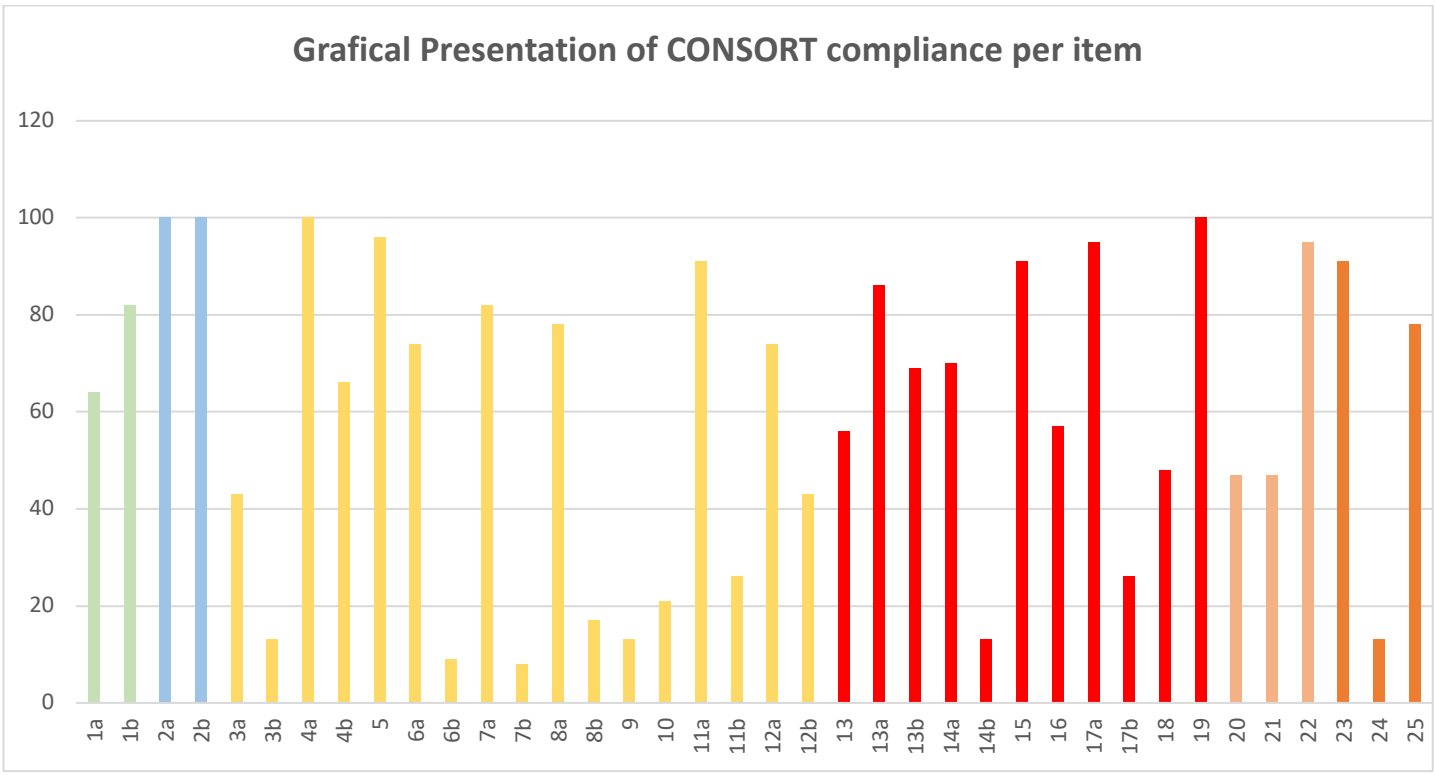
Secondary endpoint, among others, was the determination of adherence of each item separately. Table 2, shows the percentages of articles that reported each individual item for the two publication periods and for the combined period Fig 2. Taking into account the whole period, only 15 of the 38 items of the checklist (39.47%) were reported adequately (≥75%), with 4 of them (26.67%) having the optimum reporting (100%), whereas the rest 23 items (60.53%) presented a suboptimal reporting (<75%). Particularly, among the retrieved articles 64% identified the trial as “randomized” in the Title (item 1a), while the Introduction sections (items 2a and 2b), Eligibility criteria for participants (item 4a) and Harms or unintended effects (item 19) registered an excellent reporting (100%). Among items with insufficient reporting was the Method section, specifically Randomization and Blinding items, with regard to allocation concealment mechanism (item 9) and implementation (item 10), which were described in 13% and 21% of the studies respectively. Although 91% of the articles recorded who was blinded (item 11a), only 26% of them described the similarity of interventions (item 11b). As for the Results, they were assessed in more than half of the studies (64.63%), whereas solely 56% of them included a participant flow diagram (item 13), which is strongly recommended by the CONSORT Explanation and Elaboration document. Most of the rest section items, Discussion and Other Information, were generally adequately reported, except for limitations (item 20) and generalizability (item 21) which recorded a low rate (47%), whereas only 3 articles in total reported where the Full Trial Protocol can be found. Comparing the two different periods to identify improvements over time for each item separately, found that 16 of 38 items of the CONSORT checklist showed an insignificant increase (p-value>0.05) (Supplementary file, Table 3).

Table 2
Adherence with Consort checklist per Item and Time Period

Data Item	Compliance (2010-2022) (%) n=23	2010-2016 (%) n=11	2017-2022 (%) n=12	P-value
1a	64	45	**83**	0.05
1b	**82**	**90**	**75**	0.31
2a	**100**	**100**	**100**	1
2b	**100**	**100**	**100**	1
3a	43	36	50	0.51
3b	13	18	10	0.48
4a	**100**	**100**	**100**	1
4b	66	82	50	0.11
5	**96**	**100**	**92**	0.32
6a	74	73	**75**	0.90
6b	9	18	0	0.12
7a	**82**	**90**	**75**	0.31
7b	08	0	17	0.15
8a	**78**	64	**92**	0.10
8b	17	18	17	0.92
9	13	9	17	0.59
10	21	18	25	0.69
11a	**91**	**82**	**100**	0.12
11b	26	36	17	0.28
12a	74	73	**75**	0.90
12b	43	45	42	0.85
13	56	45	67	0.30
13a	**86**	73	**100**	0.05
13b	69	64	75	0.55
14a	70	73	67	0.75
14b	13	9	17	0.59
15	**91**	**100**	**83**	0.15
16	57	64	50	0.51
17a	**95**	**90**	**100**	0.28
17b	26	27	25	0.90
18	48	55	42	0.53
19	**100**	**100**	**100**	1
20	47	36	58	0.29
21	47	63	58	0.79
22	**95**	**90**	**100**	0.28
23	**91**	**100**	**83**	0.15
24	13	18	08	0.48
25	**78**	**81**	**75**	0.69

Item 13 corresponds to the participant flowchart
Bold corresponds to good reporting (75% or higher) for each item

Fig. 2.



Potential determinants of the reporting quality

Potential associated factors were analyzed univariately, and one significant association was revealed. The average adherence of studies to the CONSORT Statement published in low (IF<10) Impact Factor medical journals was 60.75% and high (IF>10) Impact Factor medical journals was 70.87%. This difference between high vs low ranked medical journals was found to be statistically significant [p-value<0.05, U=29.50, Z=-1.975, Mann-Whitney test], showing that high-ranked medical journals have better compliance with the CONSORT Statement. Every other analysis performed, for the comparison between >75% compliance among different parameters, including publication period [p-value =1.000, OR=0.875, 95%CI = (0.157, 4.874)], funding [p-value=1.000, OR=0.750, 95%CI = (0.098, 5.768)], existence of participant flow-chart [p-value=0.204, OR=4.000, 95%CI = (0.587, 27.248)] and sample size larger than 532 [p-value=0.621, OR=2.400, 95%CI = (0.355, 16.213)], failed to demonstrate statistical significance.

Multivariate analysis included all the aforementioned parameters. Publication period, higher IF, sample size greater than 532, reporting of funding and persistence of participant flowchart provided insignificant results (Table 4).

Table 4

Multivariate analysis of potential associated factors of reporting quality

Parameter	OR	95%CI lower limit	95%CI upper limit	P-value
IF	0.998	0.972	1.025	0.880
Publication period	1.336	0.200	8.916	0.765
Participant flow-chart	3.573	0.402	31.780	0.253
funding	0.982	0.087	11.074	0.988
Sample size greater than 532	0.998	0.291	25.294	0.380

95% Confidence Interval (CI), Odds Ratio (OR), Impact Factor (IF)

Discussion

This study tried to assess the quality of reporting of RCTs for anti-VEGF therapy in patients with nAMD based on the CONSORT 2010 statement, taking into consideration all the 38 checklist items and masking a duration of at least 12 years. Only 8 (34.79%) form the total 23 articles that included int the analysis, registered an adequate reporting (≥75%). The limit for good reporting was defined as ≥75%. The rest 13 (65.21%) had not the optimal CONSORT compliance. Taking into account the whole period, only 15 of the 38 items of the checklist (39.47%) were analyzed adequately (≥75%). Unsatisfactory reporting seems to concern Methods section, where item 3a (description of trial design) was reported in 43% of the articles, due to the absence of reporting not only the type of the trial also the conceptual framework of the trial. A similar underreporting was observed by Chen et al. where clear statements of trial design were missing [46]. Item 9 (Mechanism used to implement the random allocation sequence) and item 10 (Who generated the random allocation sequence, Who enrolled participants and Who assigned participants to interventions) were described in 13% and 21% of the articles, respectively. However incomplete reporting of these items it appears to be a general affliction [47]. Item 13 (participant flow diagram), which was evaluated as an extra item according to the explanation and elaboration document, was reported in over the half of the studies (56%), with insignificant improvement between the two time periods. Item 24 (where the full trial protocol can be assessed, if available), which constitutes a new checklist item of the 2010 CONSORT version found to be underreported (13%). Some of the reporting items, like item 3b (Important changes to methods), 6b (Any changes to trial outcomes after the trial commenced, with reasons), 7b (When applicable, explanation of any interim analyses and stopping guidelines), 8b (Type of randomization; details of any restriction), 11b (If relevant, description of the similarity of interventions), 14b (Why the trial ended or was stopped) and 18 (Results of any other analyses performed) were in general terms not reported adequately, since some them were not applicable to most studies. It is worth mentioning that item 1a (Identification as randomized trial in the title) shows improvement over time (45% of the articles in period 2010-2016 versus 83% of the articles in period 2017-2022), while item 1b (abstract) was reported in 82% of the studies.

The quality of reporting of the RCTs abstracts for the AMD study, indicated that there is a significant room for improvement to mmet the CONSORT recommendations for abstract reporting as indicated by Baulig et al.
Reporting of RCT abstracts is of the utmost importance as there is evidence that many clinicians will change their clinical decisions based on RCT abstracts [48]. Nevertheless, it is quite satisfactory that information about Scientific Background, Specific objectives or hypotheses, Eligibility criteria for participants and All-important harms or unintended effects in each group, were analyzed in all studies (100%).

In our study articles that were published in lower-ranked medical journals (IF<10), presented lower compliance with CONSORT statement, whereas studies published in higher-ranked medical journals (IF>10) had better adherence. This difference found statistically significant and can be explained by the fact that high-ranked medical journals select RCTs with the greatest quality. Univariate and multivariate analysis of possible determinants for reporting quality, including publication year, sample size, existence of participation flowchart and reporting of commercial funding (yes/no) failed to reach statistical significance.

The present study suggests that CONSORT statement is a very helpful tool for investigators and others to write or appraise trial reports. Because CONSORT is a document that is constantly evolving, it demands an active process of continuous evaluation, refinement and if necessary, revise, in order to succeed the utmost transparent on reporting clinical trials and validation of clinical research. This is evidenced by the improved quality of reporting of RCTs in journals that have endorsed it [49]. It is crucial that journals endorse CONSORT Statement to optimize the validity of RCTs and the interpretation of their results.

This study has its strengths. The literature search involved PubMed database and all relative articles were evaluated for eligibility. So, this study represents the whole body of scientific evidence in the field of Ophthalmology, regarding nAMD. In addition, the reproducibility of the results of this study is easy, since the tools that were used for the evaluation are free for access.

Limitations of this study have to be presented. First, the exclusion criteria (English language, specific time period) and search strategy including only one database, may conceal bias. Furthermore, the response of each item separately as positive or negative, was not always straightforward, making it susceptible to subjectivity. And finally, the CONSORT 2010 checklist was used for all articles, since they were published after 2010, allowing no comparison with the CONSORT checklist and reporting quality before revision.

To the best of our knowledge this is the first study to evaluate the reporting quality of RCTs in anti-VEGF therapy for nAMD. The results indicate moderate compliance with CONSORT statement and show that there is a significant room for improvement in meeting the recommendations of the CONSORT report . Since AMD is one of the most common ocular diseases with a growing need for research in recent years, CONSORT tool is will help both researchers (well-designed clinical trials) and reviewers (critical appraise the results and validity of trials). Transparent reporting and reliable estimation of treatment effects are critical for the formulation of national health policy.

Declaration of interest

None

Funding

This research received no specific funding from public, commercial, or non-profit sector funding agencies.

Acknowledgments

Professor Zintzaras Elias, Dr Doxani Chrysoula and Professor Dardiotis Efthimios of the supervisory board provided valuable guidance and educational contributions in the completion of this paper. A special thank to my family for their spiritual encouragement and continued support throughout my life.

References

1. Hariton, E., & Locascio, J. J. (2018). Randomised controlled trials - the gold standard for effectiveness research: Study design: randomised controlled trials. *BJOG: an international journal of obstetrics and gynaecology*, *125*(13), 1716. https://doi.org/10.1111/1471-0528.15199
2. Agha, R., Cooper, D., & Muir, G. (2007). The reporting quality of randomised controlled trials in surgery: a systematic review. *International journal of surgery (London, England)*, *5*(6), 413–422. https://doi.org/10.1016/j.ijsu.2007.06.002
3. Burns, P. B., Rohrich, R. J., & Chung, K. C. (2011). The levels of evidence and their role in evidence-based medicine. *Plastic and reconstructive surgery*, *128*(1), 305–310. https://doi.org/10.1097/PRS.0b013e318219c171
4. Wood, L., Egger, M., Gluud, L. L., Schulz, K. F., Jüni, P., Altman, D. G., Gluud, C., Martin, R. M., Wood, A. J., & Sterne, J. A. (2008). Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. *BMJ (Clinical research ed.)*, *336*(7644), 601–605. https://doi.org/10.1136/bmj.39465.451748.AD
5. Moher, D., Pham, B., Jones, A., Cook, D. J., Jadad, A. R., Moher, M., Tugwell, P., & Klassen, T. P. (1998). Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? *Lancet (London, England)*, *352*(9128), 609–613. https://doi.org/10.1016/S0140-6736(98)01085-X
6. Pildal, J., Hróbjartsson, A., Jørgensen, K. J., Hilden, J., Altman, D. G., & Gøtzsche, P. C. (2007). Impact of allocation concealment on conclusions drawn from meta-analyses of randomized trials. *International journal of epidemiology*, *36*(4), 847–857. https://doi.org/10.1093/ije/dym087

7. Schulz, K. F., & Grimes, D. A. (2002). Allocation concealment in randomised trials: defending against deciphering. *Lancet (London, England)*, *359*(9306), 614–618. https://doi.org/10.1016/S0140-6736(02)07750-4
8. Schulz, K. F., Chalmers, I., Hayes, R. J., & Altman, D. G. (1995). Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA*, *273*(5), 408–412. https://doi.org/10.1001/jama.273.5.408
9. Begg, C., Cho, M., Eastwood, S., Horton, R., Moher, D., Olkin, I., Pitkin, R., Rennie, D., Schulz, K. F., Simel, D., & Stroup, D. F. (1996). Improving the quality of reporting of randomized controlled trials. The CONSORT statements. *JAMA*, *276*(8), 637–639. https://doi.org/10.1001/jama.276.8.637
10. Moher, D., Schulz, K. F., Altman, D., & CONSORT Group (Consolidated Standards of Reporting Trials) (2001). The CONSORT statement: revised recommendations for improving the quality of reports of parallel group randomized trials. *JAMA*, *285*(15), 1987–1991. https://doi.org/10.1001/jama.285.15.1987
11. Schulz, K. F., Altman, D. G., Moher, D., & CONSORT Group (2010). CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ (Clinical research ed.)*, *340*, c332. https://doi.org/10.1136/bmj.c332
12. Egger, M., Jüni, P., Bartlett, C., & CONSORT Group (Consolidated Standards of Reporting of Trials) (2001). Value of flow diagrams in reports of randomized controlled trials. *JAMA*, *285*(15), 1996–1999. https://doi.org/10.1001/jama.285.15.1996
13. Moher, D., Hopewell, S., Schulz, K. F., Montori, V., Gøtzsche, P. C., Devereaux, P. J., Elbourne, D., Egger, M., Altman, D. G., & CONSORT (2012). CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *International journal of surgery (London, England)*, *10*(1), 28–55. https://doi.org/10.1016/j.ijsu.2011.10.001
14. Shamseer, L., Hopewell, S., Altman, D. G., Moher, D., & Schulz, K. F. (2016). Update on the endorsement of CONSORT by high impact factor journals: a survey of journal "Instructions to Authors" in 2014. *Trials*, *17*(1), 301. https://doi.org/10.1186/s13063-016-1408-z
15. Bressler N. M. (2004). Age-related macular degeneration is the leading cause of blindness... *JAMA*, *291*(15), 1900–1901. https://doi.org/10.1001/jama.291.15.1900
16. Wong, W. L., Su, X., Li, X., Cheung, C. M., Klein, R., Cheng, C. Y., & Wong, T. Y. (2014). Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. *The Lancet. Global health*, *2*(2), e106–e116. https://doi.org/10.1016/S2214-109X(13)70145-1
17. Wang, Y., Zhong, Y., Zhang, L., Wu, Q., Tham, Y., Rim, T. H., Kithinji, D. M., Wu, J., Cheng, C., Liang, H., Yu, H., Yang, X., & Liu, L. (2022). Global Incidence, Progression, and Risk Factors of Age-Related Macular Degeneration and Projection of Disease Statistics in 30 Years: A Modeling Study. *Gerontology*, *68*(7), 721–735. https://doi.org/10.1159/000518822
18. Yonekawa, Y., & Kim, I. K. (2014). Clinical characteristics and current treatment of age-related macular degeneration. *Cold Spring Harbor perspectives in medicine*, *5*(1), a017178. https://doi.org/10.1101/cshperspect.a017178
19. Ng, E. W., & Adamis, A. P. (2005). Targeting angiogenesis, the underlying disorder in neovascular age-related macular degeneration. *Canadian journal of ophthalmology. Journal canadien d'ophtalmologie*, *40*(3), 352–368. https://doi.org/10.1016/S0008-4182(05)80078-X
20. Kim, L. A., & D'Amore, P. A. (2012). A brief history of anti-VEGF for the treatment of ocular angiogenesis. *The American journal of pathology*, *181*(2), 376–379. https://doi.org/10.1016/j.ajpath.2012.06.006
21. Moher, D., Hopewell, S., Schulz, K. F., Montori, V., Gøtzsche, P. C., Devereaux, P. J., Elbourne, D., Egger, M., Altman, D. G., & Consolidated Standards of Reporting Trials Group (2010).

CONSORT 2010 Explanation and Elaboration: Updated guidelines for reporting parallel group randomised trials. *Journal of clinical epidemiology*, *63*(8), e1–e37. https://doi.org/10.1016/j.jclinepi.2010.03.004

22. Lai, T. Y., Wong, V. W., Lam, R. F., Cheng, A. C., Lam, D. S., & Leung, G. M. (2007). Quality of reporting of key methodological items of randomized controlled trials in clinical ophthalmic journals. *Ophthalmic epidemiology*, *14*(6), 390–398. https://doi.org/10.1080/09286580701344399
23. D.C. Ziogas, E. Zintzaras (2009) Analysis of the quality of reporting of randomized con- trolled trials in acute and chronic myeloid leukemia, and myelodysplastic syndromes as governed by the CONSORT statement, Ann. Epidemiol. 19 (7) 494–500, https://doi.org/10.1016/j.annepidem.2009.03.018.
24. Dugel, P. U., Koh, A., Ogura, Y., Jaffe, G. J., Schmidt-Erfurth, U., Brown, D. M., Gomes, A. V., Warburton, J., Weichselberger, A., Holz, F. G., & HAWK and HARRIER Study Investigators (2020). HAWK and HARRIER: Phase 3, Multicenter, Randomized, Double-Masked Trials of Brolucizumab for Neovascular Age-Related Macular Degeneration. *Ophthalmology*, *127*(1), 72–84. https://doi.org/10.1016/j.ophtha.2019.04.017
25. Dugel, P. U., Jaffe, G. J., Sallstig, P., Warburton, J., Weichselberger, A., Wieland, M., & Singerman, L. (2017). Brolucizumab Versus Aflibercept in Participants with Neovascular Age-Related Macular Degeneration: A Randomized Trial. *Ophthalmology*, *124*(9), 1296–1304. https://doi.org/10.1016/j.ophtha.2017.03.057
26. Heier, J. S., Brown, D. M., Chong, V., Korobelnik, J. F., Kaiser, P. K., Nguyen, Q. D., Kirchhof, B., Ho, A., Ogura, Y., Yancopoulos, G. D., Stahl, N., Vitti, R., Berliner, A. J., Soo, Y., Anderesi, M., Groetzbach, G., Sommerauer, B., Sandbrink, R., Simader, C., Schmidt-Erfurth, U., … VIEW 1 and VIEW 2 Study Groups (2012). Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. *Ophthalmology*, *119*(12), 2537–2548. https://doi.org/10.1016/j.ophtha.2012.09.006
27. CATT Research Group, Martin, D. F., Maguire, M. G., Ying, G. S., Grunwald, J. E., Fine, S. L., & Jaffe, G. J. (2011). Ranibizumab and bevacizumab for neovascular age-related macular degeneration. *The New England journal of medicine*, *364*(20), 1897–1908. https://doi.org/10.1056/NEJMoa1102673
28. Kodjikian, L., Souied, E. H., Mimoun, G., Mauget-Faÿsse, M., Behar-Cohen, F., Decullier, E., Huot, L., Aulagner, G., & GEFAL Study Group (2013). Ranibizumab versus Bevacizumab for Neovascular Age-related Macular Degeneration: Results from the GEFAL Noninferiority Randomized Trial. *Ophthalmology*, *120*(11), 2300–2309. https://doi.org/10.1016/j.ophtha.2013.06.020
29. Woo, S. J., Veith, M., Hamouz, J., Ernest, J., Zalewski, D., Studnicka, J., Vajas, A., Papp, A., Gabor, V., Luu, J., Matuskova, V., Yoon, Y. H., Pregun, T., Kim, T., Shin, D., & Bressler, N. M. (2021). Efficacy and Safety of a Proposed Ranibizumab Biosimilar Product vs a Reference Ranibizumab Product for Patients With Neovascular Age-Related Macular Degeneration: A Randomized Clinical Trial. *JAMA ophthalmology*, *139*(1), 68–76. https://doi.org/10.1001/jamaophthalmol.2020.5053
30. D'Souza, H. S., Kapoor, K. G., & Wagner, A. L. (2021). Ziv-aflibercept for Better Regulating Neovascular Age-Related Macular Degeneration (ZEBRA): A Prospective, Randomized Trial. *Seminars in ophthalmology*, *36*(1-2), 28–34. https://doi.org/10.1080/08820538.2021.1884269
31. Tufail, A., Patel, P. J., Egan, C., Hykin, P., da Cruz, L., Gregor, Z., Dowler, J., Majid, M. A., Bailey, C., Mohamed, Q., Johnston, R., Bunce, C., Xing, W., & ABC Trial Investigators (2010). Bevacizumab for neovascular age related macular degeneration (ABC Trial): multicentre

randomised double masked study. *BMJ (Clinical research ed.)*, *340*, c2459. https://doi.org/10.1136/bmj.c2459
32. Krebs, I., Vécsei Marlovits, V., Bodenstorfer, J., Glittenberg, C., Ansari Shahrezaei, S., Ristl, R., & Binder, S. (2013). Comparison of Ranibizumab monotherapy versus combination of Ranibizumab with photodynamic therapy with neovascular age-related macular degeneration. *Acta ophthalmologica*, *91*(3), e178–e183. https://doi.org/10.1111/aos.12018
33. Krebs, I., Schmetterer, L., Boltz, A., Told, R., Vécsei-Marlovits, V., Egger, S., Schönherr, U., Haas, A., Ansari-Shahrezaei, S., Binder, S., & MANTA Research Group (2013). A randomised double-masked trial comparing the visual outcome after treatment with ranibizumab or bevacizumab in patients with neovascular age-related macular degeneration. *The British journal of ophthalmology*, *97*(3), 266–271. https://doi.org/10.1136/bjophthalmol-2012-302391
34. Chakravarthy, U., Harding, S. P., Rogers, C. A., Downes, S. M., Lotery, A. J., Culliford, L. A., Reeves, B. C., & IVAN study investigators (2013). Alternative treatments to inhibit VEGF in age-related choroidal neovascularisation: 2-year findings of the IVAN randomised controlled trial. *Lancet (London, England)*, *382*(9900), 1258–1267. https://doi.org/10.1016/S0140-6736(13)61501-9
35. Kunimoto, D., Ohji, M., Maturi, R. K., Sekiryu, T., Wang, Y., Pan, G., Li, X. Y., Schneider, S., & BAMBOO and CYPRESS Study Groups (2019). Evaluation of Abicipar Pegol (an Anti-VEGF DARPin Therapeutic) in Patients with Neovascular Age-Related Macular Degeneration: Studies in Japan and the United States. *Ophthalmic surgery, lasers & imaging retina*, *50*(2), e10–e22. https://doi.org/10.3928/23258160-20190129-13
36. Callanan, D., Kunimoto, D., Maturi, R. K., Patel, S. S., Staurenghi, G., Wolf, S., Cheetham, J. K., Hohman, T. C., Kim, K., López, F. J., & Schneider, S. (2018). Double-Masked, Randomized, Phase 2 Evaluation of Abicipar Pegol (an Anti-VEGF DARPin Therapeutic) in Neovascular Age-Related Macular Degeneration. *Journal of ocular pharmacology and therapeutics: the official journal of the Association for Ocular Pharmacology and Therapeutics*, *34*(10), 700–709. https://doi.org/10.1089/jop.2018.0062
37. Kunimoto, D., Yoon, Y. H., Wykoff, C. C., Chang, A., Khurana, R. N., Maturi, R. K., Agostini, H., Souied, E., Chow, D. R., Lotery, A. J., Ohji, M., Bandello, F., Belfort, R., Jr, Li, X. Y., Jiao, J., Le, G., Schmidt, W., Hashad, Y., & CEDAR and SEQUOIA Study Groups (2020). Efficacy and Safety of Abicipar in Neovascular Age-Related Macular Degeneration: 52-Week Results of Phase 3 Randomized Controlled Study. *Ophthalmology*, *127*(10), 1331–1344. https://doi.org/10.1016/j.ophtha.2020.03.035
38. Subramanian, M. L., Abedi, G., Ness, S., Ahmed, E., Fenberg, M., Daly, M. K., Houranieh, A., & Feinberg, E. B. (2010). Bevacizumab vs ranibizumab for age-related macular degeneration: 1-year outcomes of a prospective, double-masked randomised clinical trial. *Eye (London, England)*, *24*(11), 1708–1715. https://doi.org/10.1038/eye.2010.147
39. Larsen, M., Schmidt-Erfurth, U., Lanzetta, P., Wolf, S., Simader, C., Tokaji, E., Pilz, S., Weisberger, A., & MONT BLANC Study Group (2012). Verteporfin plus ranibizumab for choroidal neovascularization in age-related macular degeneration: twelve-month MONT BLANC study results. *Ophthalmology*, *119*(5), 992–1000. https://doi.org/10.1016/j.ophtha.2012.02.002
40. Kaiser, P. K., Boyer, D. S., Cruess, A. F., Slakter, J. S., Pilz, S., Weisberger, A., & DENALI Study Group (2012). Verteporfin plus ranibizumab for choroidal neovascularization in age-related macular degeneration: twelve-month results of the DENALI study. *Ophthalmology*, *119*(5), 1001–1010. https://doi.org/10.1016/j.ophtha.2012.02.003
41. Motarjemizadeh, Q., Aidenloo, N. S., Abbaszadeh, M., & Sadrinia, V. (2018). Intravitreal Bevacizumab with or without Triamcinolone for Wet Age-related Macular Degeneration:

Twelve-month Results of a Prospective, Randomized Investigation. *Middle East African journal of ophthalmology*, *25*(1), 1–7. https://doi.org/10.4103/meajo.MEAJO_292_16
42. Berg, K., Pedersen, T. R., Sandvik, L., & Bragadóttir, R. (2015). Comparison of ranibizumab and bevacizumab for neovascular age-related macular degeneration according to LUCAS treat-and-extend protocol. *Ophthalmology*, *122*(1), 146–152. https://doi.org/10.1016/j.ophtha.2014.07.041
43. Holz, F. G., Oleksy, P., Ricci, F., Kaiser, P. K., Kiefer, J., Schmitz-Valckenberg, S., & COLUMBUS-AMD Study Group (2022). Efficacy and Safety of Biosimilar FYB201 Compared with Ranibizumab in Neovascular Age-Related Macular Degeneration. *Ophthalmology*, *129*(1), 54–63. https://doi.org/10.1016/j.ophtha.2021.04.031
44. Abraham, P., Yue, H., & Wilson, L. (2010). Randomized, double-masked, sham-controlled trial of ranibizumab for neovascular age-related macular degeneration: PIER study year 2. *American journal of ophthalmology*, *150*(3), 315–324.e1. https://doi.org/10.1016/j.ajo.2010.04.011
45. Singh, R., Chauhan, R., Saxena, A., Shah, A., Mondal, L., Bakhle, D., Shah, C., Shah, A., Deoghare, S., Krishnan, N., & Godse, N. (2022). A prospective, randomized, parallel group, double blind, multicenter study to compare the efficacy, safety and immunogenicity of Lupin's Ranibizumab with Lucentis® in patients with neovascular age-related macular degeneration. *Indian journal of ophthalmology*, *70*(8), 3008–3014. https://doi.org/10.4103/ijo.IJO_2118_21
46. Chen, M., Cui, J., Zhang, A. L., Sze, D. M., Xue, C. C., & May, B. H. (2018). Adherence to CONSORT Items in Randomized Controlled Trials of Integrative Medicine for Colorectal Cancer Published in Chinese Journals. *Journal of alternative and complementary medicine (New York, N.Y.)*, *24*(2), 115–124. https://doi.org/10.1089/acm.2017.0065
47. Chan, A. W., & Altman, D. G. (2005). Epidemiology and reporting of randomised trials published in PubMed journals. *Lancet (London, England)*, *365*(9465), 1159–1162. https://doi.org/10.1016/S0140-6736(05)71879-1
48. Baulig, C., Krummenauer, F., Geis, B., Tulka, S., & Knippschild, S. (2018). Reporting quality of randomised controlled trial abstracts on age-related macular degeneration health care: a cross-sectional quantification of the adherence to CONSORT abstract reporting recommendations. *BMJ open*, *8*(5), e021912. https://doi.org/10.1136/bmjopen-2018-021912
49. Plint, A. C., Moher, D., Morrison, A., Schulz, K., Altman, D. G., Hill, C., & Gaboury, I. (2006). Does the CONSORT checklist improve the quality of reports of randomised controlled trials? A systematic review. *The Medical journal of Australia*, *185*(5), 263–267. https://doi.org/10.5694/j.1326-5377.2006.tb00557.x

Supplementary file

Table 1

Section/Topic	**Item**	**Description**
Trial and abstract	1a	Identification as a randomised trial in the title
	1b	Structured summary of a trial design, methods, results and conclusions
Introduction		
Background and objectives	2a	Scientific background and explanation of rationale Specific objectives or hypotheses
	2b	
Methods		
Trial design	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
Participants	4a	Eligibility criteria for participants
	4b	Settings and locations where the data were collected
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered
Outcomes	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
Sample size	7a	How sample size was determined
	7b	When applicable, explanation of any interim analyses and stopping guidelines
Randomisation:		
Sequence generation	8a	Method used to generate the random allocation sequence
	8b	Type of randomisation; details of any restriction (such as blocking and block size)
Allocation concealment mechanism	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
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions

Blinding	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
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes Methods for additional analyses, such as subgroup analyses and adjusted analyses
	12b	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome
Participant flow diagram Participant flow	13	Flow diagram
	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome
	13b	For each group, losses and exclusions after randomisation, together with reasons
Recruitment	14a	Dates defining the periods of recruitment and follow-up
	14b	Why the trial ended or was stopped
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups
Outcomes and estimation	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
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms) Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses
Discussion		
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses
Generalisability	21	Generalisability (external validity, applicability) of the trial findings

Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant ecidence
Other information		
Registration	23	Registration number and name of trial registry
Protocol	24	Where the full trial protocol can be accessed, if available
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders

Table 4.
List of the CONSORT item with improvement over time

CONSORT item	P-value
1a. Identification as a randomised trial in the title	0.05
3a. Description of trial design (such as parallel, factorial) including allocation ratio	0.51
6a. Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	0.90
7b. When applicable, explanation of any interim analyses and stopping guidelines	0.15
8a. Method used to generate the random allocation sequence	0.10
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	0.59
10. Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	0.69
11a.If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	0.12
12a.Statistical methods used to compare groups for primary and secondary outcomes	0.90
13. Participant flowchart	0.30
13a.For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	0.05
13b.For each group, losses and exclusions after randomisation, together with reasons	0.55
14b.Why the trial ended or was stopped	0.59
17a.For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	0.28
20. Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	0.29
22. Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	0.28