RESEARCH ARTICLE

META-ANALYSIS TO ESTIMATE EXPECTABLE DROPOUT RATES IN RANDOMIZED CONTROLLED CLINICAL TRIALS ON AGE-RELATED MACULAR DEGENERATION - SUPPORTING FOR OPTIMIZED SAMPLE SIZE CALCULATION

Stephanie Knippschild, Frank Krummenauer and Christine Baulig.
Institute for Medical Biometry and Epidemiology, Faculty of Health, Witten/Herdecke University, Witten Germany.

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Abstract

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Topic: Over- or underestimation of participants in clinical trials may lead to serious problems regarding ethics, economics or significance of results. A realistic net sample size calculation is essential for planning; which also includes an expectable dropout profile to ensure sufficient number of subjects for statistical analysis. This meta-analysis determine dropout rates in randomized and controlled clinical trials (RCTs) on age-related macular degeneration (AMD), to optimize sample size calculation according to the requirements of the current guidelines (BGBI (2004), Moher et al., 2010).

Methods: A meta-analysis was conducted to estimate the dropout rate in RCTs of AMD. Data collection was performed by a full text handsearch in six subject-specific journals of the Anglo-American language area with peer review system and high impact factors (publication period 01/2004 - 12/2013). Raw data extraction on reported dropout rates was performed by two independent parallel readers. Meta-estimation of the reported 12 and 24-month dropout rates was based on the random effects model.

Results: 45 RCTs (16,555 patients) out of 1,062 publications were included in the analysis after 12-month follow-up, and 22 RCTs (7,845 patients) met the inclusion criteria for the 24-month follow-up period. The meta-dropout rate for the primary endpoint was estimated as 9.2% [95% CI 7.1% - 11.9%] and increased up to 19.0% [95% CI 14.2% - 25.0%] after 24 months.

Conclusion: Sample size calculation in clinical trials for AMD should account for dropouts of at least 10% during a 12-month follow-up and of at least 20% during a 24-month follow-up period.

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Introduction:

Clinical trials are the most important tool to improve medical knowledge. The increasing number of randomized controlled clinical trials (RCTs) and their publication counts reflect this every year. Together with this trend, the required resources such as participants, trial staff, medication and facilities for carrying out clinical trials also increase. In summary, the expenses for clinical research are already very high and will continue to increase in future. Therefore, every investigation should primarily aim for meaningful results. In 1994, however, D. Altman reported serious deficiencies in the planning, conduction and analysis of clinical trials. He pointed out that the use of

Corresponding Author: Stephanie Knippschild.
Address: Institute for Medical Biometry and Epidemiology, Faculty of Health, Witten/Herdecke University, Witten Germany.

inappropriate designs, unrepresentative samples, small samples, incorrect methods of analysis and faulty interpretation has often been observed in publications (Altman 1994). Today, these deficiencies can still be observed in publications and the high relevanz of invalid and useless, published data is as topical today as it was 20 years ago. In 2014 the Lancet published an article series on the growing research waste to highlight this problem. Ioannidis reported that "information obtained" from publications "might not be useful or important, and statistical precision or power is often too low or used in a misleading way" (Ioannidis et al., 2014). He traced this problem back to poor trial protocols and designs among other reasons.

The focus of this paper is on an important part within the designing phase of a clinical trial: the calculation of an appropriate sample size. Neither too few nor too many patients should be included within a clinical trial for ethical or economic reasons. The sample size should therefore be big enough to achieve valid (i.e. statistically significant) results referring to the primary endpoint but small enough to avoid ethical problems. This balancing act can only be achieved with a realistic sample size calculation which also includes the specification of a realistic dropout rate. This rate presents an increase of the net number of trial participants necessary for statistical analysis; the resulting increased number of trial participants "to be expected for recruitment" therefore takes dropout patterns during the observation period of a trial into account. Its pre-specification seeks to ensure the availability of the net number of patients by nominal "over-recruitment". Accounting for dropouts is also recommended by the ICH guidelines E6 "Guideline For Good Clinical Practice" (Agency 2002), E9 "Statistical Principles for Clinical Trials" (Agency 1998) and by the CONSORT Statement (Moher et al. 2010). The importance of this factor is frequently described (Julious 2010, Schumacher M. 2008) in literature, but unfortunately only little information is available on dropouts in clinical trials (Baulig et al., 2016a, Baulig et al., 2016b, Knippschild et al., 2014). In particular for studies of the treatment for age-related macular degeneration, there is no data accessible concerning withdrawals so far. Consequently, the sample size has to be calculated by using information from a pilot study or has to be specified on the basis of published trials providing this information. This limited information, however, may be crucially biased (although unintended) as being drawn from only a single or very few trial reports and lacking representativity. At the same time, there is a high risk of incorrect assumptions, which may impact the quality of study results as well as ethical aspects of planning.

Objectives:
The aim of this meta-analysis was to estimate meta-dropout rates in RCTs on the treatment of AMD for the typical follow-up periods of 12 and 24 months in order to enable optimized trail planning for this high volume research segment. These meta-dropout rates may serve to support further investigations in research regarding both from an ethical and economical perspective as well as facilitate transparent reporting.

Methods:
The primary endpoint of the meta-analysis was the total dropout rate in RCTs on AMD treatment after a 12-month individual follow-up. A key secondary endpoint was the corresponding total dropout rate after a 24-month follow-up.

Search strategy and inclusion criteria:
In contrast to clinical outcome measurements, the dropout rate in medical trials represents a methodological endpoint. To achieve a maximum of sensitivity in data collection, this analysis was therefore based on a full text handsearch in six pre-selected journals. The journals were consented by statistical and ophthalmological trialists: American Journal of Ophthalmology (IF 4.021), Archives of Ophthalmology (IF 4.488), British Journal of Ophthalmology (IF 2.809), Graefe's Archive for Clinical and Experimental Ophthalmology (IF 2.333), Ophthalmology (IF 6.170) and Retina (IF 3.177). For the sake of completeness, data from the most known clinical trials in age-related macular degeneration were added to this pool: CATT, IVAN and MARINA study (Chakravarthy et al., 2013, Chakravarthy et al., 2012, Comparison of Age-related Macular Degeneration Treatments Trials Research et al., 2012, Rosenfeld et al., 2006).

The search was restricted to publication dates between 01/2004 and 12/2013; all RCTs on treatment of AMD were included without consideration of various treatments. Trials on other forms of macular degeneration (e.g. diabetic retinopathy, diabetic macular edema, retinal vein occlusion or polypoidal choroidal vasculopathy) were excluded from this analysis.

Data extraction and data management:
First one author screened suitable publications by reviewing all titles and abstracts of each study. All clinical trials which address the treatment of AMD were documented and stored for further processing. The results for the primary and secondary key endpoint and validation of all RCTs were extracted independently by two parallel readers as recommended by the Cochrane Institute (Higgins JPT). Data collection included trial specifications such as title of the study, authors, journal and year of publication and raw data such as number of patients randomized into the study and number of patients not available for final analysis / missing after a follow-up period of 12 and 24 months respectively. In addition, dropout rates for subgroups were determined, whereby subgroups were defined according to the actual patterns. This classification was based on the randomization sequences and addressed different therapy options in AMD RCTs:

➤ "treatment group": application of inhibitors for vascular endothelial growth factor (VEGF), dietary supplements, photodynamic, medical, biogenetic, radiation and surgical/laser therapy,
➤ "placebo group": application of a sham treatment as sham injection, sham medication etc.
➤ "observation group": patients were only observed and did not receive any treatment.

Furthermore, the two independent readers evaluated information about trial design and report determinants (evidence of cooperation partners such as methodological core facilities or evidence of industrial partners), the methodological quality of the study (randomization, masking level) and patients' health status (multimorbidity besides the AMD indication e.g. diabetes etc.).

To evaluate the previously estimated meta-dropout rates in the subgroups and to achieve a maximum sensitivity for these results, the difference in dropout rates between the "active-therapy group (only VEGF therapy) in comparison to the "placebo group" after a study duration of 12 months (primary end point) was examined. Therefore, all trials were extracted, which offer exactly this study design from the dataset to maintain the randomization sequenz and to evaluate an inter-trial wise effect-estimator.

Documentation of the raw data was carried out with the software Excel® (Office 2010 release for Windows®).

Statistical Analysis:
All analyses were carried out with the software Comprehensive Meta Analysis (CMA®) release 2.2.064, Biostat, Englewood 2011 (M 2011). Based on the reported number of patients randomized and of patients available at the 12-month follow-up evaluation of the trial, the total dropout rate was estimated by means of an exact 95% confidence interval based on the binomial distribution. For meta estimation of the total 12-month dropout rate a random effects model assumption was made and the DerSimonian-Laird estimator was used to estimate τ^2; the meta-dropout rate was then again presented by means of its 95% confidence interval and the underlying total number of patients at recall. Statistical heterogeneity was explored by means of forest plots as well as I² statistics (iterative Paule-Mandel method to estimate the between-study variance); an I² value above 75% was considered to indicate a high heterogeneity. The software "R" (R Core Team (2013): A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria) (R Core Team 2013) was used to generate the graphics. To illustrate a possible publication bias for the present meta-analysis, funnel plots were created by plotting the dropout rates (in logit scale) in relation to the respective trial size (in standard error scale). It can be expected that the dropout profile from the included publications shifts towards clinical trials with low or moderate dropout rates, which generates an asymmetry as studies with high dropout rates are published lesslikely. In this case the Duval and Tweedie trim and fill method was applied to adjust the dropout rates for such underreporting by again using the random effects model to derive conservative meta-dropout rate estimates.

Assessment of risk of bias in individual studies:
We noticed that the evaluation of a putative risk of bias basically depends on a transparent description within the publication. Only details listed in the publication can finally be documented and analysed. These may not necessarily contain a secure reference to a correctly conducted clinical trial of a high quality, but give an indication which authors prepare their publications in accordance with the CONSORT Statement which suggests a standard performance in study publication. Provided with this information, we assessed the risk of bias of the included clinical trials in accordance with the Cochrane Handbook (Julian PT Higgins 2011) by verifying transparent reporting of the following items: concealment of randomization and blinding (patients, healthcare providers, data collectors and/or outcome assessors), statistical sample size calculation, availability of a CONSORT flow chart in

the trial report (Moher et al. 2010), whether this trial was stopped earlier or not and whether it was a multicenter trial.

Results:
Study Selection:
Screening of publication titles and abstracts in the six journals specified above identified 1,062 study reports on treatment of age-related macular degeneration (Figure 1). 79 papers which published randomized controlled trials met all eligibility criteria. Therefrom 45 studies reported dropout rates for the primary endpoint (Arias et al., 2006, Azab et al., 2005, Beatty et al., 2013, Boyer et al., 2009, Bressler et al., 2004, Brown et al., 2009, Busbee et al., 2013, Chakravarthy et al. 2013, Chang et al., 2010, Chaudhary et al., 2007, Comparison of Age-related Macular Degeneration Treatments Trials Research et al. 2012, Costagliola et al., 2010, Dawczynski et al., 2013, El-Mollayess et al., 2012, Flaxel et al., 2012, Friberg et al., 2006, Gelisken et al., 2007, Gillies et al., 2004, Group et al., 2006, Hawkins et al., 2004, Heier et al., 2006, Jaakkola et al., 2005, Jackson et al., 2013, Kaiser et al., 2012, Kodjikian et al., 2013, Krebs et al., 2013, Larsen et al., 2012, Lee et al., 2007, Li et al., 2012, Ma et al., 2012, Maberley and Canadian Retinal Trials 2009, Macugen et al., 2007, Marcus et al., 2004, Michels et al., 2005, Nguyen et al., 2012, Odergren et al., 2008, Piermarocchi et al., 2008, Ranchod et al., 2013, Regillo et al., 2008, Rosenfeld et al., 2007, Rosenfeld et al. 2006, Schmidt-Erfurth et al., 2011, Slakter et al., 2006, Souied et al., 2013, Zambarakji et al., 2006) (16,555 participants) after a 12-month study duration and 22 trials (Abraham et al., 2010, Antoszyk et al., 2008, Azab et al. 2005, Beatty et al. 2013, Bressler et al. 2004, Brown et al. 2009, Chakravarthy et al. 2013, Comparison of Age-related Macular Degeneration Treatments Trials Research et al. 2012, Dugel et al., 2013, Friberg et al. 2006, Gillies et al. 2004, Group et al. 2006, Hawkins et al. 2004, Jaakkola et al. 2005, Luke et al., 2009, Mata et al., 2013, Piermarocchi et al. 2008, Rosenfeld et al. 2006, Schmidt-Erfurth et al., 2008, Soderberg et al., 2012, Souied et al. 2013, Zambarakji et al. 2006) (7,845 participants) reported dropout rates for the secondary endpoint after a 24-month study duration (figure 1). For the subgroup analysis, nine clinical trial reports (1,160 study participants) were available for the estimation of dropout rates in the "placebo group", four (559 study participants) for the estimation of dropout rates in the "observation group" and 44 e.g. 63 study arms (14,748 study participants) for estimation of dropout rates in the "treatment group" after a 12-month study duration. Within the "treatment group" the following therapy arms were considered: medical therapy (one study arm), surgical/Laser treatment (four study arms), radiation therapy (four study arms), VEGF therapy (23 study arms) and PDT treatment – also in addition with cortisone (11 study arms), combination of VEGF in addition with PDT (one study arm), biogenetic therapy (one study arm) and treatment with dietary supplements (3 study arms). Also study arms with patients receiving a standard therapy in addition with sham were numbered among the "treatment subgroup" (6 study arms). After a follow-up of 24 months, seven (701 study participants) clinical trial reports were included for the analysis of the estimation of dropout rates in the "placebo group", five (7,412 study participants) for the estimation of dropout rates in the "observation group" and 21 e.g. 29 study arms (2,173 study participants) for the estimation of dropout rates in the "treatment group". Within the "treatment group" for the estimation of the dropout rate after 24 months study duration the following therapy arms were considered: surgical/Laser treatment (4 study arms), radiation therapy (2 study arms), VEGF therapy (7 study arms) and PDT treatment – also in addition with cortisone (7 study arms), combination of VEGF in addition with PDT (2 study arms), treatment with dietary supplements (3 study arms) and study arms with patients receiving a standard therapy in addition with sham (3 study arms).

Primary endpoint:
Considering all exclusion criteria, 45 study reports (16,555 participants) were included in this analysis after a 12-month study duration: the number of participants varied from N=7 (Chang et al. 2010) to N=4,300 (Boyer et al. 2009); the respective dropout rates varied from 0 % [95% CI 0.0% – 1.8%] (Michels et al. 2005) to 32.5% [95% CI 31.1% – 33.4%] (Boyer et al. 2009). Random effects model estimation revealed a total dropout rate of 9.2 % [95% CI 7.1%– 11.9%], but was due to significant heterogeneity ($I^2 = 96.3\%$; $\tau^2 = 0.7$). The associated forest plot is shown in figure 2 and indicated evidence of asymmetric reporting. By adjusting the dropout rate using the Duval and Tweedie trim and fill method, ten publications had to be imputed, resulting in an adjusted 12-month dropout rate of 11.6% [95% CI 9.1%-14.6%].

Secondary endpoint:
Considering the 22 study reports (7,845 participants) included after 24-month follow-up the number of participants varied from N=50 (Luke et al. 2009) to N = 1,185 (Comparison of Age-related Macular Degeneration Treatments Trials Research et al. 2012) and the respective dropout rates from 0 % [95% CI 0.0% -4.3 %] (Michels et al. 2005)

to 56.8% [95% CI 52.0% -61.5 %] (Beatty et al. 2013). The meta estimate for the dropout rate after a 24-month follow-up revealed a value of 19.0% [95% CI 14.2% - 25.0%]. The forest plot in figure 3 displays the dropout rates for all studies included in this analysis. According to a considerable heterogeneity (I^2 = 96.8%, τ^2 = 0.6), the adjustment by using the Duval and Tweedie trim and fill method imputed three publications and estimated an adjusted dropout rate of 21.6% [95% CI 20.6%-22.6%].

Subgroup analysis:
For the analysis of subgroups, 14,748 participants in the "treatment group", 1,160 participants in the "placebo group", and "only" 559 patients in the "observation group" were included after a 12-month study duration; 7,412 /2,173 and 701 participants were available, respectively, up to a 24-month study duration. Table 1 indicates the meta-dropout estimates stratified by therapy. A dropout rate of 8.4% [95% CI 6.4% - 11.1%] was estimated for the "treatment group" after a 12-month follow-up. A dropout rate of 12.3% [95% CI 9.0% - 16.5%] resulted for the "placebo group", and of 12.9% for the "observation group" [95% CI 8.3% - 19.5%]. The dropout rates after 24 months were estimated as 14.2% in the "treatment group" [95% CI 7.8% - 22.4%], 19.9% [95% CI 14.6% - 26.5%] in the "placebo group", and 18.0% [95% CI 14.2% - 22.5%] in the "observation group".

For the analysis of the dropout rate difference (VEGF versus placebo) three publications (Group et al. 2006, Regillo et al. 2008, Rosenfeld et al. 2006) (605 participants in the "placebo group" and 1,503 participants in the "VEGF-treatment group") were included in the analysis. Random effects model estimation revealed a rate difference for dropouts of 4.0% [95% CI -2.0% - 10.0%] after a 12-months study duration, but was due to significant heterogeneity (I^2=74.6%, τ^2 = 0.0021).

Risk of bias / study quality:
The risk of bias for the included studies was assessed as shown in table 2. Only one publication was identified as reporting 100% of the previously specified quality indicators for the RCT reports and for this reason was included in this analysis as a study report of maximum quality. Furthermore, 28 publications (54%) were included which reported less than 50% of the factors. Only 20 (39%) of 52 publications reported an implemented randomization scheme and clearly described an appropriate concealment strategy. A blinded study design was reported in 39 (75%) of 52 publications. In 25 clinical trials (48%) participants were blinded, healthcare providers in 19% of the analyzed trials (10 studies), and outcome assessors in 46% (24 clinical trials). The data collectors were unaware of the applied therapy in 54% (28 studies) of the analyzed trials. The number of patients and accordingly the dropout rate were documented via flowchart in 35% (18 studies) and a sample size calculation was reported in 50% (26 clinical trials) of the analyzed publications. 36 (69%) of the studies were multicenter trials.

Discussion:
Summary of main results:
The dropout rate is an important factor with respect to study planning and analysis of clinical trials in view of ethically and statistically relevant results and the aim to avoid „research waste". Despite this importance there are very few recommendations regarding this issue especially in terms of the number of dropouts to be expected in multifarious indications. For this reason, this meta-analysis sought to quantify the expectable dropout rate in clinical trials on age-related macular degeneration. It was found to be 9.2% [95% CI 7.1%-11.9%] during a study duration of 12 months and rose to 19.0% [95% CI 14.2%-25.0%], depending on the study duration after 24 months. This important information of rather low dropouts was not easy to obtain without thorough research. In view of the severity of this disease and the possibility of stopping its development, a low dropout rate may have been expected, but an increase of a moderate amount of withdrawals has to be assumed with regard to the age of AMD study participants and the age-related comorbidity patterns. From this point of view, a dropout rate below 10% might already surprise.

Limitation:
Finding clinical trials (RCTs) of high quality is essential for the outcome of meta-analyses. This requires a complete search and the identification of possibly unbiased publications. The decision on the optimal process (handsearch or electronic searches) for data collection is a key step of analyses. Hopewell et al. investigated the question whether handsearch identifies more randomized controlled trials than electronic searching (Hopewell S 2008). They found that handsearching alone will miss a small proportion of studies and that a combination of handsearching and electronic searching is the most comprehensive approach in identifying reports of randomized trials". In contrast to other investigations, we addressed a methodological end point ("dropout rate"), which is not accessible by means of

standard tools such as the MeSH term approach in PubMed®. This was the main reason why we favored a handsearch. To lower the selection bias of included journals, two experts were asked to consent the journals', regarding high impact as outlets for RCTs in age-related macular degeneration. For all that, we were aware that a small percentage of all possible journals were represented within our data collection due to the selected years of 2004-2013.

Another limitation of our analysis arises from heterogeneity in the reported data. A considerable heterogeneity was as curtailed both for the primary and the secondary endpoint. A Q =1,204.239, I^2=96.346 and τ^2=0.723 was shown for the study duration of 12 months, and a Q =660.960, I^2=96.823 τ^2=0.639 after a 24-month study duration. The trim and fill method by Duval and Tweedie was applied to explain this high heterogeneity and to adjust the effect estimates. The funnel plots (figures 4 and 5) reveal that most of the included studies have many participants and relatively low dropout rates. The expected symmetry shifts to the top and left side of the diagram. For this reason, it may be assumed that there is a lack of publications due to missing publications of small trials on the one hand and to trials with (too) high dropout rates on the other hand. In case of high dropout rates, studies possibly were not published due to problems during analysis caused by the reduced sample size or to appropriate stopping rules in the statistical analysis plan of these trials. "The trim and fill method uses an iterative procedure to remove the most extreme small studies from one side of the funnel plot, re-computing the effect size at each iteration until the funnel plot is symmetric concerning the (new) effect size". "In theory, this will yield an unbiased estimate for the effect size" (Borenstein M 2009). However, the trim and fill approach does not correspond to its usual interpretation of bias reduction in the recent setting, but rather provides a conservative rate adjustment. The resulting rate estimates have to be reconsidered from the practical perspective:

➢ In the recent setting, trim and fill accounts for possible unpublished trials with "too large" dropout rates, since such trials would hardly be considered valid and representative.
➢ The adjusted rate estimate accounting for such trials might introduce a different kind of bias leading to an unethical overestimation of gross sample sizes.

Application of the Duval and Tweedie trim and fill method resulted in an increased adjusted dropout rate of 11.6 % [95% CI 9.1 - 14.6 %]. In comparison to the primary calculated rate of 9.2 % [95% CI 7.1 - 11.9%], both point estimates are of comparable order ("expect about 10% dropouts for a 12-month observational period!"). In consideration of the upper confidence limits, an expectable rate up to 15% has to be taken into account.
Hence, the authors recommend the unadjusted estimate sample size calculation of RCTs in age-related macular degeneration.

Stratification for study groups reveals a higher dropout rate of 12% [95% CI 9.0%-16.5%] for the "placebo group" and 13% [95% CI 8.3%-19.5%] for the "observation group", as opposed to the "treatment group" with 8% [95% CI 6.4%-11.1%]. These results obviously show a difference in dropout rates between subgroups in this investigation, which might lead to the assumption that some patients become aware of their treatment allocation and withdraw participation. A distortion within the results is possible, caused by the small number of cases within the "observation- and placebo group". Note that, the analysis is limited as these subgroup meta estimators were evaluated not "intra-trial" but "inter-trial" wise. This means that any study arms of each RCT were used for the analysis of subgroups, as assigned to the respective subgroups. To gain more information about the estimated dropout rate in between the subgroups - the authors performed an additional meta-analysis of the risk difference between therapy groups. For this, only those studies were included which had at least one VEGF-therapy arm and one placebo arm. However, only three studies (Gillies et al. 2004, Group et al. 2006, Rosenfeld et al. 2006) were identified that met these criteria - all three studies included a VEGF therapy among therapy groups. These three RCTs included 1,503 study participants in VEGF and 605 in the placebo group after 12 months. In order to reveal the intra-trial dropout rate-differences the risk-difference was chosen as target parameter for this special evaluation. The 12 months dropout rate was estimated to be 4.0% [95% CI -2.0% - 10.0%] higher in the "placebo group" than in the" (VEGF-) treatment group" (Baulig et al. 2016b). This result was very surprising since a higher difference in dropouts between these groups was expected. The rationale behind this result may be the maximum attention paid to patients during treatment with VEGF inhibitors as well as placebo VEGF injections. This result may be biased due to the very small number of studies available for this analysis, but further research is limited to the ethical aspect of such RCTs.

Review and comparison of current literature:
Three research groups already published results for dropout rates in clinical trials. Gehling et al. analyzed the implication of withdrawals of opioid studies in patients with chronic pain due to osteoarthritis by a high dropout rate (Gehling et al., 2011). Therefore, they calculated dropout rates and odds ratios according to different risk factors such as adverse events and lack of analgesic efficacy. In this investigation Gehling et al. found a dropout rate of 38% in the placebo group. Independent of the reasons for dropouts, the study group found an increased risk for dropouts (OR=1.32) in the treatment group compared to the placebo group (Gehling et al. 2011). Given the intention and also the study design, this meta-analysis is not directly comparable to the investigation from Gehling et al. In summary, our analysis showed different results for overall dropout rates and group comparison (Baulig et al. 2016b). At this point, the number of dropouts to be expected in various medical disciplines appears to depend on the indication.

The second study was published by Makatsori et al. (Makatsori et al., 2014) who examined an overall dropout rate and dropout profiles in sublingual allergen immunotherapy. Their publication considered several characteristics: size of the study, duration, allergen preparation, age of participants, number of study sites, type of respiratory disease being treated and the treatment schedule employed. In addition, the authors examined whether dropout rates differ between the active and the placebo-treated group. As a result, Makatsori found an overall dropout rate of 14% in the placebo group after a study duration of one year, and 16% in the active treatment group (Makatsori et al. 2014), which is higher than the dropout rate found in our investigation. However, the outcome from Makatsori showed only minor differences in dropout rates between study groups in comparison to our results.

A meta-analysis performed by our research group investigated the influence of comorbidities to drop out rates in cataract surgery (Baulig et al. 2016a) supporting sample size calculation for this indication: 41 RCTs without comorbidities (n=3.384) and 7 RCTs allowing for comorbidities (n=1.082) were identified for the 12 months follow-up evaluation. The 12 months meta-dropout rate of 16.3% [95% CI 13.2 – 20.0%] were estimated from RCTs without comorbidities. RCTs allowing for comorbidity by design demonstrated lower drop out estimate with 6.7% [95% CI 3.9 – 11.2%] after 12 months. Thus the results of the both ophthalmological meta-analyzes show comparable, low dropout rates.

Study quality / Risk of bias:
As mentioned in the Methods section, the assessment of study quality is a characteristic which may be addressed only with a high risk of false statement based on the documentation. In those cases where the defined aspects to assess study quality were not evident in a publication, this is not necessarily an indication of low trial quality. Primarily it would indicate poor documentation and low transparency. Therefore we cannot guarantee that this assessment is absolutely objective. Based on our documentation and analysis, we found less than 50% of the predefined factors documented in 46% of the included studies (24 out of 52) and a documentation rate of under 30% in 35% (18 out of 52) of included publications. At first glance, these findings might suggest a moderate study quality. In addition to these findings, the funnel plots show that a big part of included studies hold many participants, which may indicate a standard conduction with relatively high quality in processes of these trials. In summary, the authors were not able to rule out a poor study quality underlying some trials which were used in this analysis and should therefore be taken into account when results are interpreted.

Conclusion:
This investigation sought to quantify the expectable dropout rates in RCTs on age-related macular degeneration for the sake of optimized clinical trial planning both from a methodological and an ethical perspective. These results show that sample size calculations should account for dropouts of at least 10% during a 12-month follow-up and of at least 20% during a 24-month follow-up period. In addition, it was observed, that placebo patients showed an only moderately increased dropout rate compared to active treatment (placebo 12%, active treatment 8% and observation 13%).

Figures and Legendes:
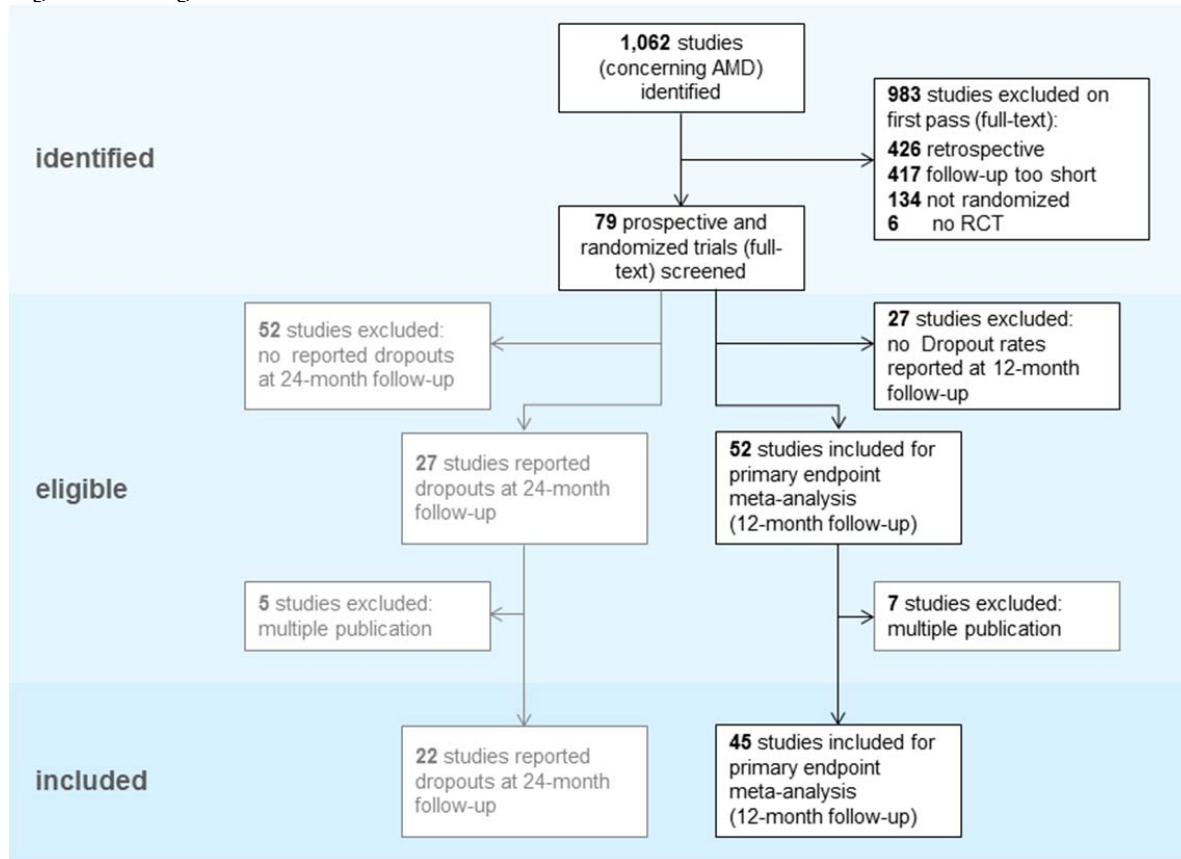
Figure 1: Flow diagram for the inclusion/exclusion process of RCTs in AMD with reported 12 and / or 24-month follow-up: documentation of absolute numbers of eligible publications including stratification for the follow-up period and through the different phases of a review.

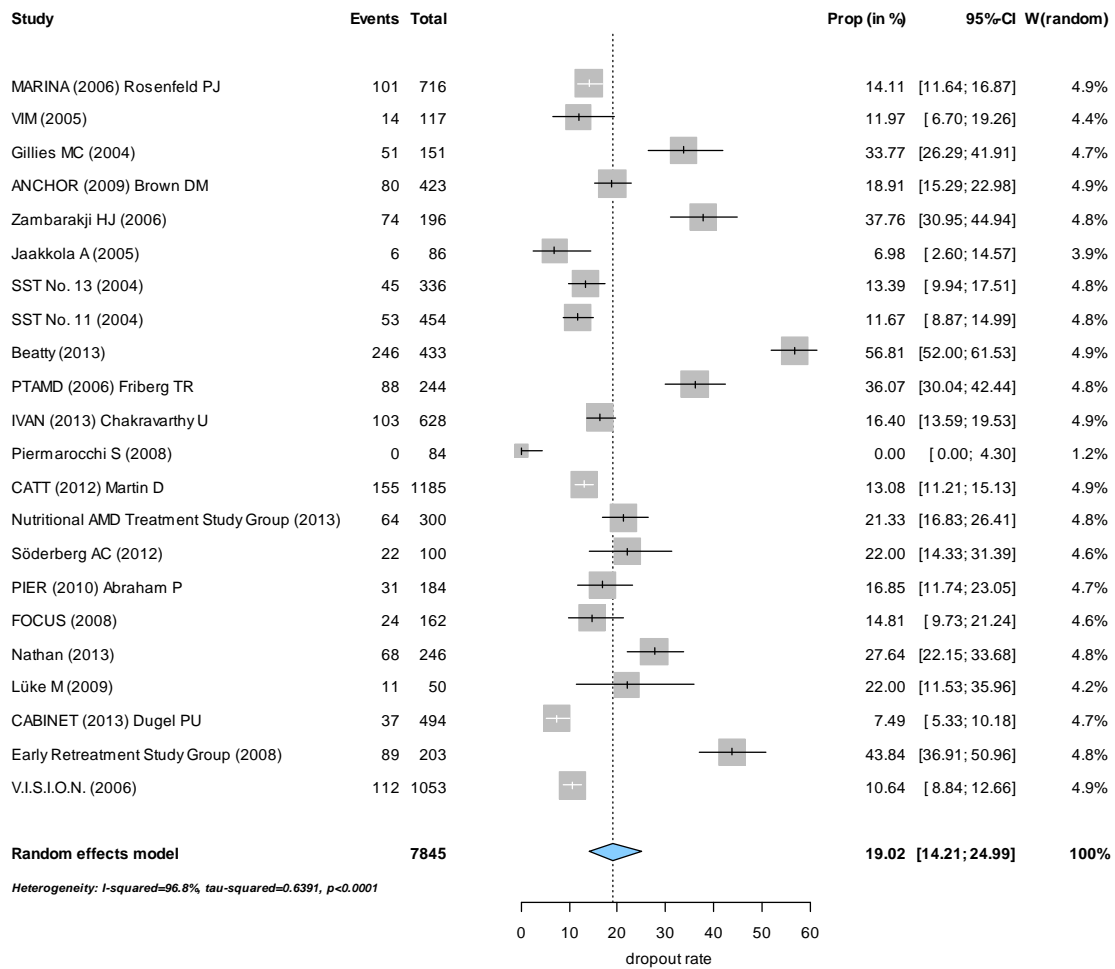| Study	Events	Total		Prop (in %)	95%-CI	W(random)
MARINA (2006) Rosenfeld PJ	52	716		7.26	[5.47; 9.42]	2.8%
Krebs I (2013)	73	321		22.74	[18.27; 27.72]	2.8%
Odergren A (2008)	3	98		3.06	[0.64; 8.69]	1.9%
El-Mollayess GM (2012)	0	120		0.00	[0.00; 3.03]	0.8%
PIER (2008) Regillo CD	13	184		7.07	[3.82; 11.78]	2.6%
VALIO (2007) Rosenfeld PJ	11	60		18.33	[9.52; 30.44]	2.5%
Flaxel C (2012)	0	30		0.00	[0.00; 11.57]	0.7%
Chang MA (2010)	1	7		14.29	[0.36; 57.87]	1.1%
Lee (J (2007)	1	37		2.70	[0.07; 14.16]	1.2%
FOKUS (2006) Heier JS	10	162		6.17	[3.00; 11.06]	2.5%
VIM (2005)	7	117		5.98	[2.44; 11.94]	2.4%
Gillies MC (2004)	9	151		5.96	[2.76; 11.01]	2.4%
Gelisken F (2007)	5	50		10.00	[3.33; 21.81]	2.2%
GEFAL (2013) Kodjikian L	127	501		25.35	[21.60; 29.40]	2.8%
INTREPID (2013) Jackson TL	5	230		2.17	[0.71; 5.00]	2.2%
HABOR (2013) Busbee BG	61	1098		5.56	[4.28; 7.08]	2.8%
Ma L (2012)	1	108		0.93	[0.02; 5.05]	1.2%
MONET (2012) Nguyen QD	17	152		11.18	[6.65; 17.30]	2.6%
DENALI (2012) Kaiser PK	35	321		10.90	[7.71; 14.84]	2.7%
EXCITE (2011) Schmidt-Erfurth U	49	353		13.88	[10.45; 17.93]	2.8%
Canadian Retinal Trials Group (2009) Maberley D	7	100		7.00	[2.86; 13.89]	2.3%
ANCHOR (2009) Brown DM	37	423		8.75	[6.23; 11.86]	2.7%
Chaudhary V (2007)	0	30		0.00	[0.00; 11.57]	0.7%
Macugen AMD Study Group (2007)	0	110		0.00	[0.00; 3.30]	0.8%
Arias L (2006)	4	61		6.56	[1.82; 15.95]	2.1%
Zambarakji HJ (2006)	62	196		31.63	[25.19; 38.64]	2.8%
Slakter JS (2006)	96	530		18.11	[14.93; 21.66]	2.8%
Michels S (2005)	0	203		0.00	[0.00; 1.80]	0.8%
Jaakkola A (2005)	4	86		4.65	[1.28; 11.48]	2.1%
SST No. 13	45	336		13.39	[9.94; 17.51]	2.7%
SST No. 11	30	454		6.61	[4.50; 9.30]	2.7%
Ranchod TM (2013)	3	40		7.50	[1.57; 20.39]	1.9%
Beatty S (2013)	88	433		20.32	[16.63; 24.43]	2.8%
MONT BLANC (2012) Larsen M	15	255		5.88	[3.33; 9.52]	2.6%
PTAMD (2006) FribergTR	60	244		24.59	[19.32; 30.49]	2.8%
SAILOR (2009) Boyer DS	1398	4300		32.51	[31.11; 33.93]	2.8%
V.I.S.I.O.N. (2006)	123	1208		10.18	[8.53; 12.03]	2.8%
IVAN (2013) Chakravarthy U	64	628		10.19	[7.94; 12.83]	2.8%
Costagliola C (2010)	3	88		3.41	[0.71; 9.64]	1.9%
THE AMDRT RESEARCH GROUP (2004)	26	88		29.55	[20.29; 40.22]	2.6%
Piermarocchi S (2008)	0	84		0.00	[0.00; 4.30]	0.8%
CATT (2012) Martin D	80	1185		6.75	[5.39; 8.33]	2.8%
Nutritional AMD Treatment Study Group (2013)	46	300		15.33	[11.45; 19.92]	2.7%
LUTEGA (2013) Dawczynski J	27	172		15.70	[10.61; 22.01]	2.7%
NATTB (2012) Li X	24	185		12.97	[8.49; 18.69]	2.7%
Random effects model		**16555**		**9.24**	**[7.13; 11.88]**	**100%**

Heterogeneity: I-squared=96.3%, tau-squared=0.7227, p<0.0001

0   10   20   30   40   50
dropout rate

Figure 2: Forest plot for the meta estimation of dropout rates after 12-month study duration. Forty-five publications (16,555 patients) with documented dropout rates and a minimum of 12-month follow-up were available for this analysis. The "R®" software was used for graphical presentation of the results.

Study	Events	Total		Prop (in %)	95%-CI	W(random)
MARINA (2006) Rosenfeld PJ	101	716		14.11	[11.64; 16.87]	4.9%
VIM (2005)	14	117		11.97	[6.70; 19.26]	4.4%
Gillies MC (2004)	51	151		33.77	[26.29; 41.91]	4.7%
ANCHOR (2009) Brown DM	80	423		18.91	[15.29; 22.98]	4.9%
Zambarakji HJ (2006)	74	196		37.76	[30.95; 44.94]	4.8%
Jaakkola A (2005)	6	86		6.98	[2.60; 14.57]	3.9%
SST No. 13 (2004)	45	336		13.39	[9.94; 17.51]	4.8%
SST No. 11 (2004)	53	454		11.67	[8.87; 14.99]	4.8%
Beatty (2013)	246	433		56.81	[52.00; 61.53]	4.9%
PTAMD (2006) Friberg TR	88	244		36.07	[30.04; 42.44]	4.8%
IVAN (2013) Chakravarthy U	103	628		16.40	[13.59; 19.53]	4.9%
Piermarocchi S (2008)	0	84		0.00	[0.00; 4.30]	1.2%
CATT (2012) Martin D	155	1185		13.08	[11.21; 15.13]	4.9%
Nutritional AMD Treatment Study Group (2013)	64	300		21.33	[16.83; 26.41]	4.8%
Söderberg AC (2012)	22	100		22.00	[14.33; 31.39]	4.6%
PIER (2010) Abraham P	31	184		16.85	[11.74; 23.05]	4.7%
FOCUS (2008)	24	162		14.81	[9.73; 21.24]	4.6%
Nathan (2013)	68	246		27.64	[22.15; 33.68]	4.8%
Lüke M (2009)	11	50		22.00	[11.53; 35.96]	4.2%
CABINET (2013) Dugel PU	37	494		7.49	[5.33; 10.18]	4.7%
Early Retreatment Study Group (2008)	89	203		43.84	[36.91; 50.96]	4.8%
V.I.S.I.O.N. (2006)	112	1053		10.64	[8.84; 12.66]	4.9%
Random effects model		**7845**		**19.02**	**[14.21; 24.99]**	**100%**

Heterogeneity: I-squared=96.8%, tau-squared=0.6391, p<0.0001

```
   0   10   20   30   40   50   60
            dropout rate
```

Figure 3: Forest plot for the meta estimation of dropout rates after 24-month study duration. Twenty-two publications (7,845 patients) with documented dropout rates and a minimum of 24-month follow-up were available for this analysis. The "R®" software was used for graphical presentation of the results.
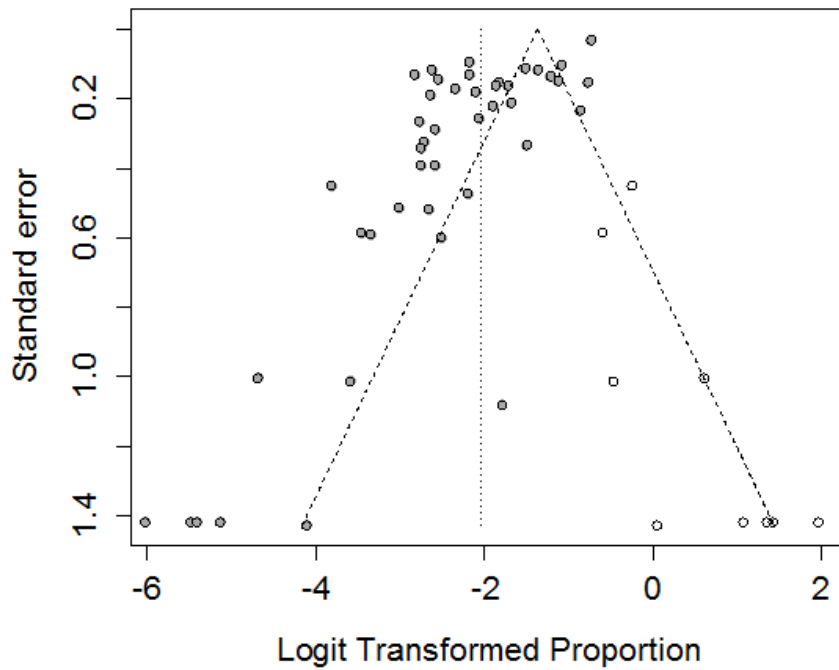
Figure 4: Funnel plot for the meta estimation of reported 12-month dropout rates in RCTs on AMD treatment. 45 observed studies (filled circles) and ten imputed studies (open circles) were used for analysis. The software Comprehensive Meta Analysis (CMA®) was used for graphical presentation of the results.
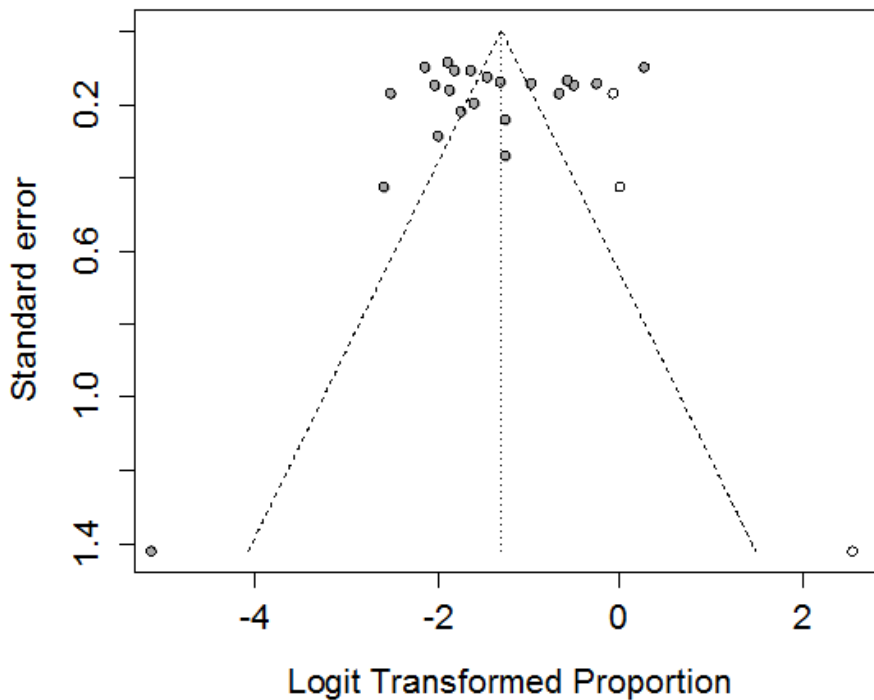
Figure 5: Funnel plot for the meta estimation of reported 24-month dropout rate in RCTs on AMD treatment. Twenty-two observed studies (filled circles) and 3 imputed studies (open circles) were used for analysis. The software Comprehensive Meta Analysis (CMA®) was used for graphical presentation of the results.

Table 1: Dropout rates and number of included studies for analyses, stratified by subgroups ("placebo", "active therapy" and "observation" group) and study duration. (CI=Confidence Interval, N=Number of included studies).

subgroup	12-month study duration		24-month study duration	
	number of studies [N]	dropout rate [%] [95% CI]	number of studies [N]	dropout rate [%] [95% CI]
placebo	9	**12.3** [9.0-16.5]	7	**19.9**[14.6-26.5]
active therapy	44	**8.4** [6.4-11.1]	21	**14.2**[7.8-22.4]
observation	4	**12.9** [8.3-19.5]	5	**18.0**[14.2-22.5]

Table 2: Documentation of study design and characteristics of included RCTs with reported 12-month and/or 24-month follow-ups to illustrate the quality of studies used for these analyses. (RCT=Randomized Controlled Trial).

Trial/Author (Year)	Follow-up period (12 months)	Follow-up period (24 months)	Concealment of Randomization	RCT stopped early	Patients blinded	Healthcare providers blinded	Data collectors blinded	Outcome assessors blinded	CONSORT Flow chart presented	Sample size calculation reported	Multicentric
MARINA (2006)	x	x	No	No	Yes	No	Yes	Yes	No	Yes	Yes
Krebs I (2013)	x		No	No	Yes	No	Yes	Yes	No	Yes	Yes
Odergren A (2008)	x		No	No	No	No	No	No	No	Yes	No
El-Mollayess (2012)	x		Yes	No	No	No	Yes	No	No	Yes	No
PIER (2008), Regillo CD	x		Yes	No	Yes	No	Yes	Yes	No	Yes	Yes
VALIO (2007)	x		No	No	No	No	Yes	Yes	Yes	No	Yes
Flaxel C (2012)	x		No	No	No	No	No	No	No	No	No
Chang MA (2010)	x		No	No	No	No	No	No	No	No	No
Lee J (2007)	x		Yes	No	No	No	Yes	Yes	No	No	No
FOCUS (2006), Heier JS	x		Yes	No	Yes	No	Yes	Yes	No	Yes	Yes
VIM (2005)	x	x	No	No	Yes	No	Yes	Yes	Yes	No	Yes
Gillies MC (2004)	x	x	Yes	No	No	No	No	No	Yes	No	No
Gelisken F (2007)	x		Yes	No	No	No	No	No	Yes	No	No
GEFAL (2013)	x		Yes	No	Yes	Yes	No	No	Yes	Yes	Yes
INTREPID (2013)	x		Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
HARBOR (2013)	x		Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes
Ma L (2012)	x		Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No
MONET (2012)	x		No	No	No	No	Yes	Yes	No	No	Yes
DENALI (2012)	x		No	No	Yes	No	Yes	Yes	No	Yes	Yes
EXCITE (2011)	x		No	No	Yes	No	No	Yes	Yes	Yes	Yes
Canadian Retinal Trials Group (2009) Maberley D	x		Yes	No	Yes	No	Yes	No	No	Yes	Yes
ANCHOR (2009)	x	x	No	No	No	No	No	No	No	No	Yes
Chaudhary V (2007)	x		No	No	No	No	Yes	No	No	No	No
Macugen AMD Study (2007)	x		Yes	No	Yes	Yes	Yes	No	No	No	Yes
Arias L (2006)	x		No	No	No	No	Yes	No	Yes	Yes	Yes
Zambarakji HJ (2006)	x	x	No	No	No	No	No	No	No	No	No

Slakter JS (2006) Anecortave Acetate Clinical Study Group	x		No	No	Yes	No	Yes	No	No	Yes	Yes
Michels S (2005)	x		No	No	No	No	No	No	No	No	Yes
Jaakkola A (2005)	x	x	Yes	No	No	No	Yes	Yes	Yes	Yes	Yes
Submacular Surgery Trials No. 11 (2004)	x	x	Yes	No	No	No	Yes	Yes	No	Yes	Yes
Submacular Surgery Trials No. 13 (2004)	x	x	No	No	No	No	Yes	Yes	No	Yes	Yes
SAILOR (2009)	x		No	No	Yes	No	No	No	No	No	Yes
V.I.S.I.O.N. (2006)	x	x	No	No	Yes	Yes	No	No	Yes	No	Yes
IVAN (2013)	x	x	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes
Costagliola C (2010)	x		No	No	No	No	No	No	No	No	Yes
AMDRT (2004)	x		Yes	No	No	No	Yes	Yes	No	No	No
Piermarocchi S (2008)	x	x	No	No	No	No	No	No	No	No	No
CATT (2012)	x	x	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
LUTEGA (2013)	x		No	No	No	No	No	No	Yes	No	No
NATTB (2012)	x		No	No	No	No	No	No	No	No	Yes
Söderberg AC (2012)		x	Yes	No	No	No	No	Yes	No	Yes	No
PIER (2010), Abraham P		x	No	No	Yes	No	No	No	Yes	Yes	Yes
FOCUS (2008), Antroszyc AN		x	No	No	Yes	No	No	No	No	No	Yes
Mata NL (2013)		x	No	No	No	No	No	Yes	No	No	Yes
Lüke M (2009)		x	No	No	Yes	No	No	Yes	No	No	Yes
CABERNET (2013)		x	No	No	No	No	Yes	Yes	Yes	Yes	Yes
Ranchod (2013)	x		No	No	No	No	No	Yes	No	No	No
Beatty (2013)	x	x	Yes	No	Yes	Yes	No	No	Yes	No	Yes
Larsen (2012)	x		No	No	Yes	No	Yes	No	No	Yes	Yes
Friberg (2006)	x	x	Yes	No	Yes	Yes	Yes	No	No	Yes	Yes
Souied (2013)	x	x	Yes	No	Yes	Yes	Yes	No	Yes	Yes	No
Schmidt-Erfurth U (2008)		x	No	No	No	No	No	No	No	No	Yes

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