Randomized controlled trials in ophthalmology: a bibliometric study [version 1; peer review: 2 approved]

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Abstract

Background: Randomized controlled trials (RCTs) are situated at the top of hierarchy of evidence-based medicine, where its number and quality are important in the assessment of quality of evidence in a medical field. In this study, we aim to assess the status of RCTs in Ophthalmology.

Methods: On 15th of May 2019, we performed a PubMed search for randomized controlled trials published in the field of ophthalmology using relevant filters and search terms. We categorized the results into specific topics in ophthalmology according to Medical Subject Heading (MeSH) database classification system. We used Altmetric explorer to identify journals and articles with the highest number of RCTs and highest citations.

Results: We found a total of 540,427 publications in the field of ophthalmology, of which only 11,634 (2.15%) of them were RCTs. 'Retinal diseases' was the topic with the highest number of RCTs, followed by 'glaucoma' and 'conjunctival diseases'. The trial with highest number of citations was on retinal diseases. Only around 18% of all ophthalmology RCTs are published in the top 10 ophthalmology journals, with a maximum percentage of RCTs was (5.53%) published in Ophthalmology.

Conclusion: RCTs in ophthalmology primarily concern the retina, glaucoma, and a few other sub-topics, with little focus on sclera, orbit, and the eyelids. Most of the high impact RCTs are published in non-ophthalmology journals.

Keywords
Ophthalmology; Randomized Controlled Trials; PubMed; Retina; Journals; Bibliometrics.
Introduction
Since the conception of the term “evidence-based medicine” in clinical practice in 1992, where well-conducted randomized controlled trials (RCTs) are situated at the top of hierarchy of evidence, there has been an emphasis on accepting high quality evidence in terms of RCTs in clinical practice. Moreover, previous reports showed that RCTs have generally higher methodological rigor than observational studies. However, despite the rapid growth in ophthalmology literature in the recent years, this growth has not been paralleled by a growth in the quality of evidence. This is evident by the number of Cochrane reviews that don’t include any RCTs (i.e. empty review), which were estimated to be half of the total reviews on Cochrane Eyes and Vision in 2013. In this study, we aim to assess the status of RCTs in ophthalmology, and will focus on publishing trends for RCTs in ophthalmology in the recent years with regards to different ophthalmology topics.

Methods
PubMed search strategy
On 15th of May 2019, we performed a PubMed search for randomized controlled trials published in the field of ophthalmology. We used the following search filters:

- Ophthalmology studies: eye diseases [MeSH Terms]
- RCT: Randomized Controlled Trial [Publication Type]

To categorize the results into specific topics in ophthalmology, we used the Medical Subject Heading (MeSH) database to identify the topics within ophthalmology, where the following were included:

- Orbital Diseases
- Conjunctival Diseases
- Corneal Diseases
- Eyelid Diseases
- Lacrimal Apparatus Diseases
- Lens Diseases
- Glaucoma
- Refractive Errors
- Scleral Diseases
- Uveal Diseases
- Retinal Diseases

For each topic, we added the query as a MeSH term to the search to identify relevant articles (e.g. Orbital diseases[Mesh Terms]. It is worth noting that trials might be categorized in more than one topic.

To identify journals with the highest number of RCTs and top articles with highest citations, we used Altmetric database, where we inputted the PubMed query we used in the PubMed search in the search field; the database yielded citation information about searched articles along with information about the journals these articles published previously.

Variables
For each RCT, we extracted data regarding the topic of the study and categorized them into the following: RCTs per year, percentage of each sub-specialty. Articles per sub-specialty per year, Top 10 journals with their respective data, Top 10 articles with highest dimensions citations

Results
Ophthalmology RCTs
A total of 540,427 publications in the field of ophthalmology were identified, of which only 11,634 (2.15%) of them were RCTs. There was a total of 482,791 RCT identified in all disciplines, of which only 2.4% are in the field of ophthalmology. Of these trials, 124 were phase 1 trials, 270 were phase 2 trials, 380 were phase 3 trials, and 42 phase 4 trials; all others did not have phases. Number of RCTs peaked in 2015 with a total of 583 trials. Figure 1 shows the trend in number of RCTs in the field of ophthalmology.

RCTs in each ophthalmology topic
‘Retinal diseases’ is the topic with the highest number of RCTs, with a total of 2915 trials, followed by ‘glaucoma’, with 2118 trials, and ‘conjunctival diseases’, with 1230 trials. Figure 2 details the number of trials for each topic.

Top RCTs and ophthalmology journals publishing RCTs
The trial with highest number of citations discussed retinal complications of diabetes mellitus entitled “The Effect of Intensive Treatment of Diabetes on the Development and Progression of Long-Term Complications in Insulin-Dependent Diabetes Mellitus”, published in The New England Journal of Medicine. Table 1 details the top 10 RCTs with highest citations. A total of 2090 (18%) of the RCTs were published in 10 journals, with “Ophthalmology” being the top journal with highest number of RCT published in it (643 RCTs). Table 2 details the top 10 journals with highest number of RCTs published in them.

Discussion
In the current study, we observed a peak in the annual number of RCTs on 2015, after which a steady decrease observed till 2018. Retinal diseases is the topic with the highest number of RCTs, followed by glaucoma and conjunctival diseases. The trial with highest citation was on retinal diseases and was published in The New England Journal of Medicine, where also other top cited trials were published in general non-ophthalmology journals. The total RCTs published in top 100 ophthalmology journals was only 2090 (17.96%).

In general, there has been an increase in the number of RCTs in ophthalmology since the late 1990s. In a study assessing the frequency of prospective studies published in the American Journal of Ophthalmology and British Journal of Ophthalmology,
they found an increase from 1% to 12% during the years 1980 to 1999. We observed a low number of RCTs among the ophthalmology literature, a percentage that didn’t exceed 2.5% of the overall ophthalmology literature. In a previous study assessing the frequency of RCTs published in the major four ophthalmology journals, they found that only around 3.5% of their annual publications are RCTs. Moreover, we found that only around 18% of all ophthalmology RCTs are published in the top 10 ophthalmology journals, with the most RCTs (5.53%) published in *Ophthalmology*. In a study that reviewed risk of bias in RCTs published in major ophthalmology journals found that a risk of bias was observed in 29.4% of published RCTs. In another study that assessed fragility of RCT’s that included the comparison between two groups found a high proportion of fragile results in ophthalmology RCTs. In a study that assessed types of articles published in core pediatric journals, they found that only 0.3% were RCTs, which supports our findings that a large proportion of RCTs were published in high-impact general medical journals.

One of the main limitations in this study is that it didn’t assess the quality of RCTs, so we included RCTs from our
Table 1. The 10 randomized controlled trials with the highest number of citations.

<table>
<thead>
<tr>
<th>Number</th>
<th>Citations</th>
<th>Title</th>
<th>Journal</th>
<th>Publication Date</th>
<th>Reference</th>
<th>OA Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>16741</td>
<td>The Effect of Intensive Treatment of Diabetes on the Development and Progression of Long-Term Complications in Insulin-Dependent Diabetes Mellitus</td>
<td>New England Journal of Medicine</td>
<td>1993</td>
<td>6</td>
<td>FALSE</td>
</tr>
<tr>
<td>2</td>
<td>5177</td>
<td>Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38</td>
<td>British Medical Journal</td>
<td>1998</td>
<td>12</td>
<td>TRUE</td>
</tr>
<tr>
<td>3</td>
<td>3623</td>
<td>Ranibizumab for Neovascular Age-Related Macular Degeneration</td>
<td>New England Journal of Medicine</td>
<td>2006</td>
<td>13</td>
<td>FALSE</td>
</tr>
<tr>
<td>4</td>
<td>2343</td>
<td>Ranibizumab versus Verteporfin for Neovascular Age-Related Macular Degeneration</td>
<td>New England Journal of Medicine</td>
<td>2006</td>
<td>14</td>
<td>FALSE</td>
</tr>
<tr>
<td>5</td>
<td>2239</td>
<td>The Ocular Hypertension Treatment Study</td>
<td>Archives of Ophthalmology</td>
<td>2002</td>
<td>15</td>
<td>TRUE</td>
</tr>
<tr>
<td>6</td>
<td>1736</td>
<td>Pegaptanib for Neovascular Age-Related Macular Degeneration</td>
<td>New England Journal of Medicine</td>
<td>2004</td>
<td>16</td>
<td>TRUE</td>
</tr>
<tr>
<td>7</td>
<td>1683</td>
<td>The advanced glaucoma intervention study (AGIS): 7. the relationship between control of intraocular pressure and visual field deterioration</td>
<td>American Journal of Ophthalmology</td>
<td>2000</td>
<td>17</td>
<td>FALSE</td>
</tr>
<tr>
<td>8</td>
<td>1641</td>
<td>The Ocular Hypertension Treatment Study</td>
<td>Archives of Ophthalmology</td>
<td>2002</td>
<td>18</td>
<td>TRUE</td>
</tr>
<tr>
<td>10</td>
<td>1526</td>
<td>Grading Diabetic Retinopathy from Stereoscopic Color Fundus Photographs - An Extension of the Modified Airlie House Classification</td>
<td>Ophthalmology</td>
<td>1991</td>
<td>20</td>
<td>FALSE</td>
</tr>
</tbody>
</table>

OA, open access.

Table 2. The 10 ophthalmology journals with the highest number of randomized controlled trials (RCTs) and proportion of RCTs of total ophthalmology RCTs published in each.

<table>
<thead>
<tr>
<th>Journal</th>
<th>Number of RCTs</th>
<th>Percentage from total ophthalmology RCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ophthalmology</td>
<td>643</td>
<td>5.53%</td>
</tr>
<tr>
<td>American Journal of Ophthalmology</td>
<td>333</td>
<td>2.86%</td>
</tr>
<tr>
<td>British Journal of Ophthalmology</td>
<td>246</td>
<td>2.11%</td>
</tr>
<tr>
<td>Investigative Ophthalmology &amp; Visual Science</td>
<td>163</td>
<td>1.40%</td>
</tr>
<tr>
<td>Archives of Ophthalmology</td>
<td>157</td>
<td>1.35%</td>
</tr>
<tr>
<td>Journal of Cataract &amp; Refractive Surgery</td>
<td>149</td>
<td>1.28%</td>
</tr>
<tr>
<td>Retina</td>
<td>106</td>
<td>0.91%</td>
</tr>
<tr>
<td>JAMA Ophthalmology</td>
<td>103</td>
<td>0.89%</td>
</tr>
<tr>
<td>Optometry and Vision Science</td>
<td>97</td>
<td>0.83%</td>
</tr>
<tr>
<td>Journal of Glaucoma</td>
<td>93</td>
<td>0.80%</td>
</tr>
<tr>
<td>Total</td>
<td>2090</td>
<td>17.96%</td>
</tr>
</tbody>
</table>
PubMed search regardless of their quality. Recent studies have stated that ophthalmology literature is of questionable methodological robustness, where RCTs become the center of the scope when methodological robustness is assessed, as they are the source of the highest level of evidence\textsuperscript{10,21}. Future studies should focus on assessing quality of RCTs rather than the quantity (which was the scope of this study), where the Cochrane Eyes and Vision library criteria for RCT robustness can be utilized\textsuperscript{22}.

### References

Open Peer Review

Current Peer Review Status: ✔️ ✔️

Version 1

Reviewer Report 08 April 2020

https://doi.org/10.5256/f1000research.22737.r61423

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Sa'ed H. Zyoud

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I would like to congratulate you on the work done. This helps to analyze the most active researchers in the subject, facilitating future collaborations. I would like to ask some questions that were not very clear for me in the paper.

1. Why did you only use PubMed to survey data?

2. How did you consider collaborations?

3. You could have done more interesting things, such as a heat map (VOSViewer has a great one and is free to use - but have used it in a previous bibliometric analysis).

4. Bibliometric is an aid in the characterization of a field, but scholarly communication is too complex to explain the history, status, and development of any field of science. Bibliometric has a lot of limitations that should be recognized in order to avoid a simplistic misuse of the indicators and methodologies.


Without further comments or questions, I congratulate again the initiative.

References

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Toxicology, bibliometric

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Peter Y Chang
Massachusetts Eye Research & Surgery Institution (MERSI), Waltham, MA, USA

I applaud the authors' efforts in sifting through the large volume of data in determining the proportion of ophthalmology publications that are categorized as RCTs. The authors also found that most of the RCTs concern retinal diseases. This makes sense, as one of the most dramatic therapeutic advancements since early 2000s - not just in Ophthalmology but all of medicine - is the employment of anti-VEGF therapy in the treatment of age-related macular degeneration and diabetic retinopathy. These two conditions, along with glaucoma, are perhaps the 3 most common ophthalmic conditions for which many newer therapeutics are being developed. It is also encouraging to see that the number of RCT published annually in Ophthalmology has generally
trended upward, and that they are published in well-regarded peer-reviewed journals. Overall, though, there remains a lack of RCTs in Ophthalmology, with majority of published works being presumably retrospective in nature.

**Is the work clearly and accurately presented and does it cite the current literature?**
Yes

**Is the study design appropriate and is the work technically sound?**
Yes

**Are sufficient details of methods and analysis provided to allow replication by others?**
Yes

**If applicable, is the statistical analysis and its interpretation appropriate?**
Yes

**Are all the source data underlying the results available to ensure full reproducibility?**
Yes

**Are the conclusions drawn adequately supported by the results?**
Yes

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Ocular inflammatory diseases, vitreoretinal surgery

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

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