THE APPLICABILITY AND UTILIZATION OF SYSTEMATIC REVIEWS FOR CLINICAL PRACTICE

Kristina Lindsley

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The applicability and utilization of systematic reviews for clinical practice

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Kristina Boyd Lindsley

geboren op 16 juli 1979
te El Paso, Texas, Verenigde Staten

Promotoren:

Prof. dr. L. Hooft

Prof. dr. R.J.P.M. Scholten

Copromotor:

Dr. T. Li

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Chapter 2
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Chapter 3
Lindsley K, Hutfless S, Hawkins BS, Blim JF, Roberts D, Olsen TW, Lum F, Dickersin K. Evaluation of Clinical Questions and Patient-Important Outcomes Associated With the Treatment of Age-Related Macular Degeneration. JAMA Ophthalmol. 2018 Nov 1;136(11):1217-1225. doi: 10.1001/jamaophthalmol.2018.3456. PMID: 30128539; PMCID: PMC6248173.

Chapter 4
Saldanha IJ, **Lindsley K**, Do DV, Chuck RS, Meyerle C, Jones LS, Coleman AL, Jampel HD, Dickersin K, Virgili G. Comparison of Clinical Trial and Systematic Review Outcomes for the 4 Most Prevalent Eye Diseases. JAMA Ophthalmol. 2017 Sep 1;135(9):933-940. doi: 10.1001/jamaophthalmol.2017.2583. PMID: 28772305; PMCID: PMC5625342.

Chapter 5
Saldanha IJ, **Lindsley K**, Money S, Kimmel HJ, Smith BT, Dickersin K. Outcome choice and definition in systematic reviews leads to few eligible studies included in meta-analyses: a case study. BMC Med Res Methodol. 2020 Feb 11;20(1):30. doi: 10.1186/s12874-020-0898-2. PMID: 32046643; PMCID: PMC7014938.

Chapter 6
Lindsley K, Fusco N, Teeuw H, Mooij E, Scholten R, Hooft L. Poor compliance of clinical trial registration among trials included in systematic reviews: a cohort study. J Clin Epidemiol. 2021 Apr;132:79-87. doi: 10.1016/j.jclinepi.2020.12.016. PMID: 33333165.

Chapter 7
Lindsley K, Fusco N, Li T, Scholten R, Hooft L. Clinical trial registration was associated with lower risk of bias compared with non-registered trials among trials included in systematic reviews. J Clin Epidemiol. 2022 Jan 23;145:164-173. doi: 10.1016/j.jclinepi.2022.01.012. PMID: 35081449.

Contents

CHAPTER 1

General introduction

For those involved in systematic reviews, there is a strong desire to accurately synthesize the evidence and for the results of their research to be applied in practice. To have one without the other misses the mark. Evidence synthesis research does not and should not occur in a silo. Rather, systematic reviews provide a critical link between primary studies and decision-makers. This intersection of information is the crux of evidence-based medicine (EBM). It takes place when the best available evidence, clinical expertise, and patient values are all brought together to improve the health and lives of people.

EBM is defined as "the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients."[1] It is not intended to restrict clinical practice to only what the evidence shows, but to ensure that the evidence is considered in the clinical decision-making process. Much of this process depends on identifying the relevant information, accurately and appropriately interpreting the evidence, and generating results in a timely manner to inform practice. There are multiple stakeholders engaged throughout the process; however, the ultimate goal of EBM is to deliver "the right care at the right time to the right patient for the right price."[2] To determine what is "right" is a matter of context, but can be supported by a well-functioning evidence ecosystem.

Ecosystems refer to complex and interconnected networks. The term evidence ecosystem has been used to describe the "distinctly different but related stages of evidence generation, evidence synthesis, formulation of policy and practice guidelines informed by evidence, and evidence implementation."[3] When running efficiently, data generated from primary research flows seamlessly into evidence synthesis research, such as systematic reviews. The findings from evidence synthesis research can then be used to inform clinical decision-making and be put into practice. To complete the cycle, questions or evidence gaps that arise from evidence synthesis or from practice feed back into primary research. However, there can be disruptions within the system that lead to inefficiencies and breaks in knowledge transfer. This type of loss of information is termed research waste. Research waste can occur at any stage of research, including question generation, study design and methods, conduct, reporting, and dissemination.[4,5]

A variety of initiatives have been undertaken in past years to prevent or minimize research waste across all stages of research. Priority-setting methods have been developed to identify important questions for research to answer based on input from multiple stakeholders.[6–9] Core outcome sets have been proposed to standardize and align data collected and reported for specific diseases areas.[10–12] Study registries, such as ClinicalTrials.gov for interventional

studies and PROSPERO for systematic reviews, have been created to record study objectives and methods in order to reduce duplication of research and discourage reporting bias.[13–16] Multiple reporting guidelines have been produced to establish minimum standards across various types of research, such as the Consolidated Standards of Reporting Trials (CONSORT), the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), and Standards for Reporting of Diagnostic Accuracy (STARD) to name a few.[17–19] There also has been a push towards making research findings publicly available (i.e., open access) rather than blocked by paywalls.[20–22] These initiatives combined with data sharing reduce research waste by making research available and useable to others. Finally, partnership networks have been formed to facilitate transparency and collaboration among different members of the evidence ecosystem, including primary researchers, systematic reviewers, clinical practice guideline developers, and end users (e.g., health care professionals, patients, consumers).[23–27]

Another way to reduce research waste, with respect to evidence synthesis specifically, is for systematic reviews to be both applicable and usable to health care decision makers. In 1972, Archie Cochrane noted that there were "strong suggestions of inefficient use of effective therapies, and considerable use of ineffective ones."[28] Since then systematic reviews have come a long way in terms of both methodological rigor and as a tool to address diverse types of important clinical questions. Systematic reviews have evolved not only to identify the most effective (or ineffective) treatment for a specific disease, but to determine efficient prevention methods, reduce costs and health care resource utilization, establish optimal diagnostic tests and screening procedures, and predict the prognosis of individuals with a specific disease.[29,30] Their output can be used to inform clinical decisions from personalized (or precision) medicine to population-based health care. The issue at hand is to what degree systematic reviews are currently meeting the needs of clinical decision makers.

Aims and outline of this thesis

The aims of this thesis are to examine the applicability and utilization of systematic reviews in health care, and to identify barriers and provide insights for integrating systematic reviews more effectively into clinical practice in order to positively affect the health of patients. For the purposes of this thesis, applicability refers to whether a systematic review is relevant or appropriate for clinical decision-making. Utilization is defined as the actual use of systematic reviews in practice.

The first part of this thesis assesses the extent to which systematic reviews are being used to inform clinical practice guidelines (Chapter 2). Subsequent

chapters investigate specific challenges and potential solutions for incorporating systematic reviews, or evidence synthesis research generally, into health care decision-making (Chapters 3-7). The final chapter summarizes the work presented in this thesis and provides implications for practice and research (Chapter 8).

Clinical practice guidelines and priority-setting

Chapter 2 examines the applicability and utilization of systematic reviews in clinical practice guidelines for the treatment of age-related macular degeneration (AMD). We assess the reliability of systematic reviews of AMD that have been published and determine whether reliable systematic reviews could be used to support the treatment recommendations provided in the clinical practice guidelines. In Chapter 3, we survey four stakeholder groups in a priority-setting exercise to identify important clinical questions and patient-important outcomes for AMD.

Outcome selection in clinical trials and systematic reviews

In Chapter 4, we conduct a cross-sectional examination of the most frequently reported outcomes used in clinical trials and systematic reviews for the most prevalent eye diseases: AMD, cataract, diabetic retinopathy, and glaucoma. We then compare the overlap between outcomes used in clinical trials versus those used in systematic reviews. Chapter 5 is a case study of 175 systematic reviews published by Cochrane Eyes and Vision to evaluate the impact of outcome choice and definition on conducting meta-analysis, and to investigate reasons why included studies were not included in meta-analysis.

Clinical trial registration and risk of bias

Chapter 6 describes a sample of 100 systematic reviews published by the Cochrane Musculoskeletal, Oral, Skin and Sensory (MOSS) Network. From the sample of reviews, we assess whether the trials included in the reviews had been registered or not, as well as investigate characteristics of registered versus non-registered trials and trends over time. In **Chapter 7**, we use the same sample of reviews to assess the association between clinical trial registration and risk of bias in the trials that were included in the reviews.

Finally, in **Chapter 8**, we provide a summary of key findings from each chapter and implications for practice and research. The discussion focuses on three main issues for systematic reviewers: 1) asking the right questions, 2) selecting the right outcomes, and 3) strengthening the evidence base.

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CHAPTER 2

Interventions for age-related macular degeneration: are practice guidelines based on systematic reviews?

Kristina Lindsley
Tianjing Li
Elizabeth Ssemanda
Gianni Virgili
Kay Dickersin

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ABSTRACT

Purpose:
Are existing systematic reviews of interventions for age-related macular degeneration incorporated into clinical practice guidelines?

Design:
High-quality systematic reviews should be used to underpin evidence-based clinical practice guidelines and clinical care. We examined the reliability of systematic reviews of interventions for age-related macular degeneration (AMD) and described the main findings of reliable reviews in relation to clinical practice guidelines.

Methods:
Eligible publications were systematic reviews of the effectiveness of treatment interventions for AMD. We searched a database of systematic reviews in eyes and vision without language or date restrictions; the database was up to date as of May 6, 2014. Two authors independently screened records for eligibility and abstracted and assessed the characteristics and methods of each review. We classified reviews as reliable when they reported eligibility criteria, comprehensive searches, methodologic quality of included studies, appropriate statistical methods for meta-analysis, and conclusions based on results. We mapped treatment recommendations from the American Academy of Ophthalmology (AAO) Preferred Practice Patterns (PPPs) for AMD to systematic reviews and citations of reliable systematic reviews to support each treatment recommendation.

Results:
Of 1570 systematic reviews in our database, 47 met inclusion criteria; most targeted neovascular AMD and investigated anti-vascular endothelial growth factor (VEGF) interventions, dietary supplements, or photodynamic therapy. We classified 33 (70%) reviews as reliable. The quality of reporting varied, with criteria for reliable reporting met more often by Cochrane reviews and reviews whose authors disclosed conflicts of interest. Anti-VEGF agents and photodynamic therapy were the only interventions identified as effective by reliable reviews. Of 35 treatment recommendations extracted from the PPPs, 15 could have been supported with reliable systematic reviews; however, only 1 recommendation cited a reliable intervention systematic review. No reliable systematic review was identified for 20 treatment recommendations, highlighting areas of evidence gaps.

Conclusions:
For AMD, reliable systematic reviews exist for many treatment recommendations in the AAO PPPs and should be cited to support these recommendations. We also identified areas where no high-level evidence exists. Mapping clinical practice guidelines to existing systematic reviews is one way to highlight areas where evidence generation or evidence synthesis is either available or needed.

BACKGROUND

Age-related macular degeneration (AMD) is the leading cause of severe vision loss among people older than 65 years in industrialized countries.[1,2] This disease can be divided into 2 basic subtypes: neovascular (wet) AMD and non-neovascular (dry) AMD. Neovascular AMD is characterized by choroidal neovascularization, in which formation of abnormal blood vessels leads to subretinal and intraretinal macular edema, hemorrhage, fibrosis, or a combination thereof causing rapid central vision loss. In non-neovascular AMD, because of the gradual loss of photoreceptors and development of geographic atrophy, vision decreases slowly over many years. With no effective treatment available, patients with non-neovascular AMD are usually followed up to detect and treat complications, such as development of neovascular AMD.

For decades, laser photocoagulation was the only available treatment for neovascular AMD, yet other treatments have been the subject of research, including radiotherapy, interferon α, and photodynamic therapy; of these, photodynamic therapy received regulatory approval in April 2000.[3] More recently, treatments focusing on the neutralization of vascular endothelial growth factor (VEGF) by injecting antibodies (bevacizumab), antibody fragments (ranibizumab), or fusion proteins (aflibercept) into the vitreous of the eye have become the current standard of care for neovascular AMD.[4]

Systematic reviews are summaries of the best research evidence available to address a specific question and follow explicit eligibility criteria and methods.[5] Because systematic reviews underpin evidence-based clinical practice guidelines, it is important that they are trustworthy and at low risk for bias, yet we know that this is not always the case.[6] For example, an author who has a potential conflict of interest may influence research conclusions,[7] or multiple reviews of the same topic may represent unnecessary duplication of effort and prove confusing if the review authors reach different conclusions. Some reasons for differing conclusions are understandable, for example, when the studies synthesized in systematic reviews were conducted during dissimilar periods or included different types of study designs.[8] But sometimes differing conclusions can be ascribed to the use of systematic review methods that potentially are subject to bias.[9]

The best practice for the development of clinical practice guidelines involves the integration of high-quality systematic reviews.[6] To accomplish this goal, guideline developers can elect to undertake a systematic review in house, commission a third party to conduct a systematic review, use results from previously completed systematic reviews, or implement a combination of

these methods. The objectives of this study were (1) to identify all published systematic reviews in the area of eyes and vision that had examined the treatment of AMD, (2) to assess the reliability of existing reviews, and (3) to map clinical practice guideline recommendations to reliable systematic reviews to encourage the integration of reliable systematic reviews and clinical practice guideline recommendations.

METHODS

Identification of Systematic Reviews of Interventions for Age-Related Macular Degeneration

The search strategies and definition used for systematic reviews have been published.[10,11] Our searches used no language or date restrictions and were up to date as of May 6, 2014. Systematic reviews eligible for this study had examined interventions for AMD; we excluded reviews concerned only with AMD etiology diagnosis, prognosis, and cost-effectiveness of treatment. Furthermore, to be eligible, reports of systematic reviews had to be full-text journal articles representing "a scientific investigation that addressed a focused question and used explicit, pre-specified scientific methods to identify, select, assess, and summarize similar but separate studies."[5,12] Systematic reviews were eligible regardless of whether meta-analyses were performed; however, we considered articles that described a meta-analysis only, without a systematic review component, to be ineligible because we could not be sure they were based on a systematic review. For eligible reviews with multiple published versions, such as updated or copublished Cochrane reviews, we included the most recent publication.

We used a 2-stage screening process to identify eligible systematic reviews. First, 2 individuals independently screened the titles and abstracts of all 1570 reviews listed in our database of systematic reviews in eyes and vision as of May 6, 2014. Next, for all records classified as potentially relevant, 2 individuals independently reviewed each full-text report for eligibility. We resolved discrepancies at each stage through discussion.

Assessment of Systematic Reviews of Interventions for Age-Related Macular Degeneration

For each eligible systematic review, 2 individuals independently abstracted data from the review onto an electronic data collection form developed, pilot tested, and maintained in the Systematic Review Data Repository.[13] This form was adapted from components of the Critical Appraisal Skills Programme,[14] the Assessment of Multiple Systematic Reviews,[15] and the Preferred Reporting Items for Systematic

Reviews and Meta-Analyses; [16] we have used the form in other studies.[9,17] We extracted data related to review objectives, populations, interventions, outcomes, methods (e.g., eligibility criteria for selection of studies for the systematic review, search strategies for eligible studies, assessment of risk of bias in included studies), results, conclusions, and financial support. When a meta-analysis was conducted, we also abstracted data on the statistical methods used. We resolved any discrepancy in data abstraction through discussion.

Based on previously published criteria9 and standard systematic review methodology,[5,6,14-16] we classified reviews as reliable when they reported (1) defined criteria for selection of studies, (2) comprehensive searches for eligible studies, (3) assessment of risk of bias in included studies, (4) appropriate statistical methods for meta-analysis, and (5) agreement between the results and conclusions. We considered searches to be comprehensive when 3 or more bibliographic databases were searched, at least 1 method of other searching was used (e.g., handsearching conference abstracts, identifying ongoing trials, screening reference lists of included studies), and search results were not limited to English language only.[5] When 1 or more of these criteria were not met, we classified reviews as being unreliable.

We conducted descriptive analyses of review characteristics and estimated proportions of reliable reviews. We conducted a prespecified subgroup analysis by whether the systematic review was a Cochrane review. Furthermore, we explored characteristics of systematic reviews when more than 1 addressed the same research question.

Mapping Clinical Practice Guideline Recommendations to Systematic Review Evidence

We extracted treatment recommendations from the 2015 American Academy of Ophthalmology (AAO) Preferred Practice Patterns (PPPs) on management of AMD.[18] We included only recommendations related to the effectiveness of treatment interventions (i.e., recommendations related to diagnosis and follow-up were excluded) and recorded the section of the AAO PPP where we found each recommendation.

We mapped the treatment recommendations to systematic reviews identified by our study and assessed whether reliable systematic reviews were available to address each treatment recommendation and, if so, whether they were cited by the AAO PPP. We also assessed whether sources of evidence were provided with each treatment recommendation and, when provided, categorized each cited reference as a systematic review, randomized controlled trial, or other study type.

RESULTS

Description of Search Results

Of 1570 systematic reviews in our database as of May 6, 2014, 47 systematic reviews met our eligibility criteria (Fig 1).[19–65]

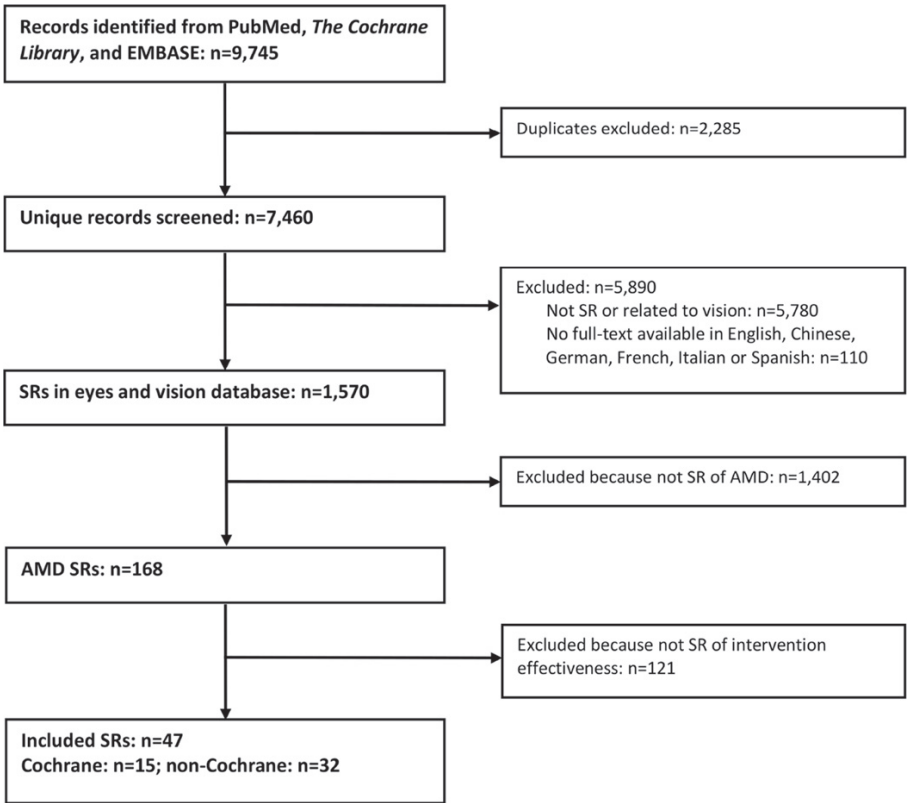

Figure 1. Flow chart showing the identification of systematic reviews (SRs) of interventions for age-related macular degeneration (AMD) as of May 6, 2014.

Table 1. Characteristics of systematic reviews of interventions for age-related macular degeneration

	Reliability of review					
	All Systematic Reviews (n = 47)		*Reliable (n = 33)*		*Unreliable (n = 14)*	
Characteristics	*No.*	*%*	*No.*	*%*	*No.*	*%*
Year(s) published, median (range)	2009 (2001–2014)		2009 (2001–2014)		2009 (2001–2013)	
Eligibility criteria						
Participants						
Neovascular AMD	26	55.3	20	60.6	6	42.9
Any AMD	11	23.4	6	18.2	5	35.7
General population	8	17.0	5	15.2	3	21.4
Nonneovascular AMD	1	2.1	1	3.0	0	0.0
Early AMD	1	2.1	1	3.0	0	0.0
Interventions examined						
Anti-VEGF vs. anti-VEGF or PDT or placebo	15	31.9	10	30.3	5	35.7
Dietary supplement vs. dietary supplement or placebo	9	19.1	7	21.2	2	14.3
PDT vs. placebo or no treatment	6	12.8	5	15.2	1	7.1
Submacular surgery vs. no treatment	3	6.4	2	6.1	1	7.1
Health or rehabilitation intervention vs. no intervention	3	6.4	1	3	2	14.3
Other comparison	11	23.4	8	24.2	3	21.4
Outcomes examined*						
Visual acuity	32	68.1	25	75.8	7	50.0
Safety (e.g., cardiovascular events)	37	78.7	28	84.8	9	64.3
Quality of life	23	48.9	20	60.6	3	21.4
Contrast sensitivity	14	29.8	13	39.4	1	7.1
Visual function	8	17.0	7	21.2	1	7.1
Cost	11	23.4	7	21.2	4	28.6
Development or progression of AMD	10	21.3	7	21.2	3	21.4
Study designs examined*						
Randomized controlled trials	40	85.1	32	97.0	8	57.1
Controlled clinical trials	10	21.3	8	24.2	2	14.3
Other study designs	15	31.9	7	21.2	8	57.1

	Reliability of review					
	All Systematic Reviews (n = 47)		*Reliable (n = 33)*		*Unreliable (n = 14)*	
Characteristics	*No.*	*%*	*No.*	*%*	*No.*	*%*
Systematic review publication characteristics						
Publication type						
Cochrane Library	15	31.9	15	45.5	0	0.0
Other peer-reviewed journal	25	53.2	14	42.4	11	78.6
Government or insurance agency report	7	14.9	4	12.1	3	21.4
Language						
English	41	87.2	31	93.9	10	71.4
Non-English	6	12.8	2	6.1	4	28.6
No. of authors						
1	4	8.5	3	9.1	1	7.1
2	9	19.1	7	21.2	2	14.3
3 or more	34	72.3	23	69.7	11	78.6
Search for studies						
Databases searched*						
MEDLINE (PubMed)	47	100.0	33	100.0	14	100.0
Cochrane Central Register	40	85.1	31	93.9	9	64.3
EMBASE	38	80.9	32	97.0	6	42.9
LILACS	11	23.4	11	33.3	0	0.0
Other databases	27	57.4	18	54.5	9	64.3
Median no. of databases searched (IQR)	4 (3-5)		4 (3-5)		3 (1.75-5)	
Search restrictions						
No restriction in language of studies	28	59.6	23	69.7	5	35.7
No restriction in years searched for at least 1 database	31	66.0	25	75.8	6	42.9
Other sources searched*						
Reference lists, reports that cited the study, or both	36	76.6	30	90.9	6	42.9
Experts in the field and/or study authors	22	46.8	17	51.5	5	35.7
Hard-to-access or unpublished studies	24	51.1	20	60.6	4	28.6
Ongoing studies	19	40.4	19	57.6	0	0.0

	Reliability of review					
	All Systematic Reviews (n = 47)		*Reliable (n = 33)*		*Unreliable (n = 14)*	
Characteristics	*No.*	*%*	*No.*	*%*	*No.*	*%*
Results of systematic reviews*						
Median no. of studies included (IQR)	7 (2–14)		5 (2–12.75)		11 (7.25–35)	
Median no. of participants included (IQR)	1480 (505–4414)		948 (339–2505)		4052 (1560–82,941)	
Qualitative synthesis performed†	38	88.4	28	96.6	10	71.4
One or more meta-analysis presented†	22	51.2	16	55.2	6	42.9
Statistical heterogeneity assessed‡	19	86.4	16	100.0	3	50.0
Funding and conflicts of interest						
Funding sources						
Funding reported*	31	66.0	22	66.7	9	64.3
Government	18	58.1	13	39.4	5	35.7
Department/institution	10	32.3	9	27.3	1	7.1
Industry	4	12.9	0	0.0	4	28.6
Foundation	3	9.7	3	9.1	0	0.0
Other sources	2	6.5	2	6.1	0	0.0
Explicitly stated no funding	1	3.2	1	3.0	0	0.0
Funding not reported	16	34.0	11	33.3	5	35.7
Conflict of interest						
Conflict of interest reported	31	66.0	25	75.8	6	42.9
Explicitly stated no conflict of interest	19	40.4	19	57.6	0	0.0
Any conflict of interest reported	12	25.5	6	18.2	6	42.9
Conflict of interest not reported	16	34.0	8	24.2	8	57.1

AMD = age-related macular degeneration; PDT = photodynamic therapy; VEGF = vascular endothelial growth factor.
*Systematic reviews may be counted in more than 1 category, so totals may add to more than 100%.
†Denominator = 43 systematic reviews with ≥2 included studies (4 reliable reviews included fewer than 2 studies).
‡Denominator = 22 systematic reviews that performed ≥1 quantitative synthesis (i.e., meta-analysis).

Characteristics of Systematic Reviews of Age-Related Macular Degeneration

The earliest eligible AMD systematic review identified was published in 2001 (Table 1). More than half (26/47; 55%) of the AMD systematic reviews focused on neovascular disease. The most commonly investigated interventions were anti-VEGF agents (15/47; 32%), dietary supplements (9/47; 19%), and photodynamic therapy (6/47; 13%). Most systematic reviews examined the effect of treatment on visual acuity (32/47; 68%) and safety (37/47; 79%); almost half assessed quality of life as outcomes of interest (23/47; 49%).

Approximately one third (15/47; 32%) of AMD systematic reviews were published in The Cochrane Library,[19-33] with 25 of 47 (53%) published in other journals,[34-58] and 7 of 47 (15%) as agency reports (e.g., French National Authority for Health).[59-65] Most systematic reviews had at least 2 authors (43/47; 91%). The median number of bibliographic databases searched for systematic reviews was 4; 31 of 47 (66%) groups of authors searched all possible years of at least 1 database. Only 28 of 47 (60%) review groups searched for non-English language articles. The number of included intervention studies in each systematic review ranged from 0 to 88 (median, 7). Of the 43 systematic reviews that included 2 or more studies, review findings were synthesized qualitatively in most (38; 88%) and quantitatively (i.e., meta-analyses) in approximately half (22; 51%).

Almost two thirds of AMD systematic reviews provided information on funding (31/47; 66%), with government (18/31; 58%) and department or institution (10/31; 32%) as the most common funding sources. Fewer than half of systematic review author teams stated that they had no conflicts of interest (19/47; 40%), with 12 of 47 (26%) disclosing that at least 1 author had a potential conflict of interest; 16 of 47 (34%) did not report information on conflicts of interest.

Assessment of the Reliability of Age-Related Macular Degeneration Systematic Reviews

We classified most (33/47; 70%) AMD systematic reviews as reliable (Fig 2). The most common reason for classifying a review as unreliable was not reporting a comprehensive search for eligible studies (Table 2, available at www.aaojournal.org). Compared with unreliable systematic reviews, reliable systematic reviews were more likely to have been funded by departments or institutions and to have been produced by review authors who explicitly stated they had no conflicts of interest; all 4 systematic reviews that reported industry funding were assessed as unreliable (Table 2, available at www.aaojournal.org). Areas needing improvement across all reviews were the need for explicit statements regarding (1) pre-specification of eligibility criteria for studies to be

included and (2) limitations of the review. In addition, review authors seldom performed independent evaluation of study eligibility and methodologic quality or independent data abstraction by 2 or more reviewers (Fig 2).

All 15 Cochrane systematic reviews were classified as reliable compared with 18 of 32 (56%) non-Cochrane systematic reviews (Fig 3). All 15 Cochrane systematic reviews specified predefined eligibility, compared with 16 of 32 (50%) non-Cochrane systematic reviews, and were more likely to have reported independent selection of studies by 2 or more review authors, assessment of risk of bias, and extraction of data compared with non-Cochrane systematic reviews. However, fewer Cochrane systematic reviews (27%) discussed limitations at the review level (e.g., incomplete retrieval of relevant studies, the potential effect of reporting bias on the review findings) than non-Cochrane systematic reviews (53%).

Main Findings of Reliable Age-Related Macular Degeneration Systematic Reviews

Reliable AMD systematic reviews of anti-VEGF agents and photodynamic therapy reported favorable results (Table 3, available at www.aaojournal.org). For other interventions—including antioxidant vitamins, minerals, or both; complement inhibitors; interferon α; laser photocoagulation; radiotherapy; Rheopheresis; statins; submacular surgery; and steroids—reliable AMD systematic reviews reported findings that were either inconclusive or that demonstrated no evidence of an intervention effect.

Among reliable AMD systematic reviews that had addressed the same research question, the conclusions were in good agreement with the exception of the comparative effectiveness and safety of ranibizumab versus bevacizumab for neovascular AMD. Ten reliable systematic reviews published between 2007 and 2014 included 17 distinct randomized controlled trials published between 2004 and 2011[66-82] (Fig 4). Reasons for discordance among systematic reviews all related to the studies included, which in turn were the result of variations in search dates, eligibility criteria, and minimum lengths of follow-up time. Authors of earlier systematic reviews that had compared ranibizumab versus bevacizumab cautioned against using bevacizumab as an off-label alternative to ranibizumab,[41-43] whereas the more recent reviews, which included additional randomized controlled trials, suggested no appreciable difference between the anti-VEGF agents in terms of effectiveness or safety.[34,38] The eligibility criteria of the systematic reviews changed over time, in accordance with completion and publication of findings from new randomized controlled trials. For example, earlier systematic reviews evaluated pegaptanib or ranibizumab versus sham treatment, but more recent systematic reviews evaluated head-to-head comparison of bevacizumab versus ranibizumab.

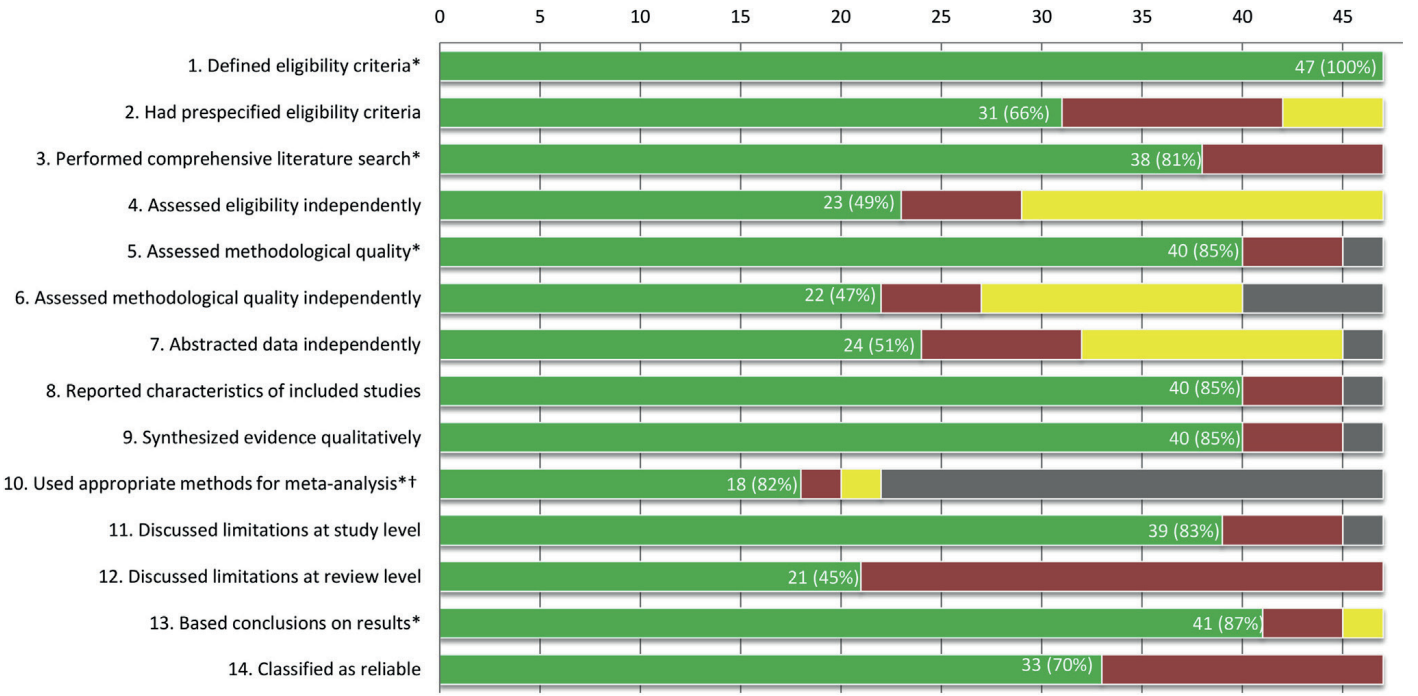

Figure 2. Graph showing the assessment of reliability criteria for 47 systematic reviews of interventions for age-related macular degeneration. Green = yes; red = no; yellow = can't tell/not reported; gray = not applicable. *Five criteria used for classifying reliability of systematic reviews. †Denominator = 22 systematic reviews with 1 or more quantitative synthesis.

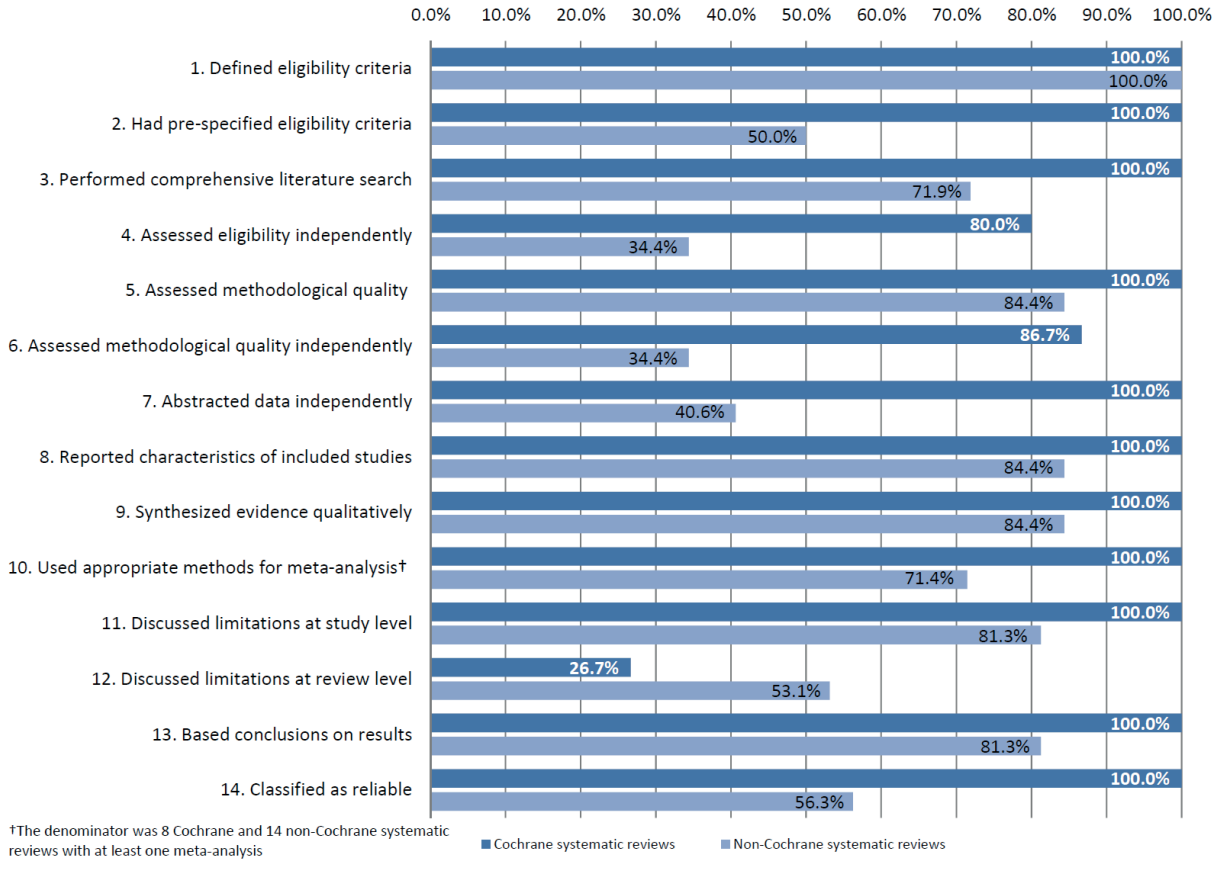

Figure 3. The proportion satisfying each reliability criterion for Cochrane (n = 15) vs. non-Cochrane systematic reviews (n = 32).

Mapping of Clinical Practice Guidelines to Existing Systematic Review Evidence

We extracted 35 treatment recommendations from the 2015 AAO PPP for AMD (Table 4). Treatment recommendations appeared in 5 sections of the AAO PPP document: (1) highlighted findings and recommendations for care table, (2) background text, (3) care process text, (4) treatment recommendations and follow-up for AMD (see Table 4 in the PPP article[18]), and (5) PPP recommendation grading section. Twenty-five of 35 recommendations were reported within the section of the PPP specific to the management of AMD, and 4 of the 35 recommendations were stated in all 5 sections of the PPP that reported recommendations. Most evidence cited by the AAO PPP to support recommendations were randomized controlled trials rather than systematic reviews: 18 of 35 recommendations were accompanied by citations to randomized controlled trials, whereas 1 of 35 recommendations was accompanied by citation to a reliable systematic review (Table 5, available at www.aaojournal.org). The PPP cited one other reliable systematic review identified by our study, but it was cited in the background section and not in direct support of a recommendation. No citation was provided to support 12 of 35 recommendations, and 4 of 35 recommendations cited other reference types (e.g., AAO policy statements, insurance company documents, non-AMD intervention systematic reviews).

We identified existing reliable systematic reviews of interventions for AMD for 15 of the 35 treatment recommendations (Table 4). For example, additional reliable systematic reviews of anti-VEGF agents, vitamins and minerals, photodynamic therapy, laser photocoagulation, submacular surgery, and radiotherapy could have been referenced by the AAO PPP guideline to inform their recommendations but were not (Table 4). We identified no existing reliable systematic review for 20 treatment recommendations, which highlights evidence gaps. The treatment recommendations and findings from reliable systematic reviews generally were consistent (Table 3, available at www.aaojournal.org).

Randomized controlled trial (RCT) ID	Date of first publication	Interventions compared	Length of follow-up	Systematic reviews of anti-vascular endothelial growth factor treatments for age-related macular degeneration (n = 10)									
				Author Year	Takeda 2007	Colquitt 2008	Vedula 2008 (Cochrane)	Schouten 2009	Ziemssen 2009	Schmucker 2010	Schmucker 2011	Schmucker 2012	Cheng 2012	Jiang 2014
				Date of search	SEPTEMBER 2006	SEPTEMBER 2006	FEBRUARY 2008	MARCH 2008	JULY 2008	AUGUST 2009	AUGUST 2009	MAY 2011	OCTOBER 2011	MARCH 2013
				Interventions assessed	PEGAPTANIB RANIBIZUMAB	PEGAPTANIB RANIBIZUMAB	PEGAPTANIB RANIBIZUMAB	BEVACIZUMAB	BEVACIZUMAB	RANIBIZUMAB BEVACIZUMAB	RANIBIZUMAB BEVACIZUMAB	RANIBIZUMAB BEVACIZUMAB	PEGAPTANIB RANIBIZUMAB BEVACIZUMAB	RANIBIZUMAB BEVACIZUMAB
				Minimum follow-up	12 months	12 months	12 months	None	None	None	None	12 months	12 months	12 months
1. VISION	Dec 2004	Pegaptanib vs sham	> 1 year		+	+	+						+	
2. Heier	Feb 2006	Ranibizumab vs usual care	6 months							+	+			
3. MARINA	Oct 2006	Ranibizumab vs sham	> 1 year		+	+	+			+	+	+	+	+
4. ANCHOR	Oct 2006	Ranibizumab vs PDT	> 1 year		+	+	+			+	+	+	+	+
5. FOCUS	Nov 2006	Ranibizumab+PDT vs PDT	> 1 year		+	+	+			-	-	-	+	+
6. Lazic	Jan 2007	Bevacizumab vs PDT vs both	3 months					+	+	+	+			
7. Hahn	Jul 2007	Bevacizumab vs PDT+triamcinolone	3 months					+	-	+	+			
8. Bashur	Oct 2007	Bevacizumab vs PDT	6 months					+	+	+	+			
9. PIER	Feb 2008	Ranibizumab vs sham	> 1 year			+				+	+	+	+	+
10. Weigert	Mar 2008	Bevacizumab vs PDT+triamcinolone	1 year						+	+	+	+	-	-
11. SAILOR	Sep 2009	0.3 mg vs 0.5 mg ranibizumab	1 year									+		+
12. Costagliola	Dec 2009	Bevacizumab vs PDT+bevacizumab	1 year									+		-
13. Subramanian	Dec 2009	Ranibizumab vs bevacizumab	1 year									+		+
14. ABC	Jun 2010	Bevacizumab vs standard care	1 year									+	+	-
15. CATT	April 2011	Ranibizumab vs bevacizumab	> 1 year									+		+
16. Biswas	May 2011	Ranibizumab vs bevacizumab	> 1 year									+		-
17. EXCITE	May 2011	0.3 mg quarterly vs. monthly vs 0.5 mg ranibizumab	> 1 year									+		+

+ RCT included in the SR

- RCT eligible, but not included in SR

RCT not eligible for the SR

RCT published after search date of the SR

Figure 4. Inclusion of randomized controlled trials in systematic reviews of anti-vascular endothelial growth factor treatments for age-related macular degeneration.

DISCUSSION

Reliability of Systematic Reviews

We classified 14 of 47 (30%) systematic reviews describing intervention effectiveness for AMD as unreliable according to standard methodologic criteria. Lack of reporting a comprehensive search strategy was the most common reason for classifying a review as unreliable. We found that Cochrane reviews comprise approximately one third of all AMD systematic reviews. We assessed all 15 Cochrane reviews as reliable compared with 18 of 32 (56%) non–Cochrane reviews. This finding is in keeping with other investigations that have shown the high quality of Cochrane reviews and methodology.[83–90] Because we are affiliated with the Cochrane Eyes and Vision Group, the criteria we set for assessing review methods and reporting are Cochrane oriented. Our perspectives partially may explain the judgements we made and the discrepancies we found.

Studies evaluating the reporting quality of systematic reviews of other topics have found systematic reviews to be of disappointing quality, many finding 20% to 65% of the systematic reviews as being poor or low quality.[83,84,91–95] Yet with the availability and promotion of methodologic and reporting standards for systematic reviews,[16,96–98] we expect reliable conduct and reporting of systematic reviews published in the literature to increase. Well-reported methods may not accord with methods actually used to conduct the review, however. For example, an investigation of studies described as randomized controlled trials in Chinese-language journals found that 93% (95% confidence interval, 92.3%–94.1%) of the studies actually used nonrandom methods to allocate treatment groups.[99] A limitation of our study is that we evaluated systematic review reporting and did not contact review authors for supplemental information when methods were not reported or were reported unclearly. Furthermore, authors of reports from studies included in systematic reviews may not report methods clearly and accurately.

The uncoordinated fashion in which many systematic reviews currently are conducted and reported seems to result in unnecessary duplication of effort and varying results.[100,101] In some cases, existing reviews were unreliable because of the lack of adherence to reporting standards and use of systematic review methodology aimed at minimizing selection and reporting biases. Publication of unreliable reviews represents a waste of resources. Journal editors should set standards for systematic reviews they publish and refer authors and peer reviewers to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses reporting standards.[96,97] To conserve resources, we recommend that future systematic reviews address unanswered clinical questions. Furthermore, systematic reviews should be undertaken by individuals trained in systematic review methodology. Manuscripts that report systematic reviews should be

reviewed by editors and peer reviewers knowledgeable in methodologic and reporting standards to produce reliable research that can be used by guideline developers, patients, clinicians, and others.

Usefulness of Systematic Reviews for Informing Clinical Practice Guidelines

The risk of producing reviews that are not relevant to clinical users is made tangible by the fact that many treatments for AMD summarized in reliable reviews included in our study were not mentioned in the 2015 AAO PPPs. Many systematic reviews, including Cochrane reviews, undergo a long publication process that on one hand ensures high quality, but on the other hand may render them out of date or unavailable to users and guidelines producers in a rapidly emerging therapeutic area, such as anti-VEGF therapy for neovascular AMD. Collaboration between systematic reviewers and guideline developers could facilitate relevancy of topics and communication of results in a timely manner.

Six types of treatments for AMD were evaluated by 2 or more systematic reviews. In the case of 5 types of interventions (antioxidants, omega-3 fatty acids, photodynamic therapy, laser photocoagulation, and submacular surgery), reviews addressing the same topic yielded the same conclusions and initially seemed to indicate a waste of resources. However, in the case of anti-VEGF therapy, the research question and eligibility criteria addressed by the systematic reviews changed over time as treatment availability and potential outcomes changed. The first systematic reviews included only randomized controlled trials that compared pegaptanib or ranibizumab treatment with a control group. The more recent systematic reviews of anti-VEGF therapy also included case series and nonrandomized studies specifically to address the issue of effectiveness and safety of the off-label drug bevacizumab. Since the time the searches were conducted for this study, Cochrane authors have updated an earlier review of anti-VEGF effectiveness and also have published a review comparing the systemic safety of ranibizumab versus bevacizumab.[102,103] Unlike other research that has found duplication of systematic reviews of the same topic to be wasteful[101,104] or to lead to discordant findings,[8,105] we conclude that sequential systematic reviews that at first glance seem to cover similar topics instead may represent evolution in the research question with increased clinical experience and serve as an indication of a rapidly developing field.

Despite summarizing the available evidence, systematic reviews may not meet the needs of clinicians, patients, and guideline panels. Reviews with narrow scopes, that is, those that split a clinician's real-world question into answerable research questions, may not provide all information needed by guidelines panelists. Nor

do traditional pairwise comparisons address the question of what works best. Multiple treatment comparisons use network meta-analysis methodology and increasingly are used when head-to-head trials of multiple interventions are not available or are insufficient to address the research question.[106]

Integration of Systematic Reviews in Clinical Practice Guidelines

Literature searches for the 2015 AAO PPP on AMD were updated on June 11, 2013. The AAO PPP cited 2 systematic reviews that were rated as reliable in our study, with many recommendations citing evidence only from individual studies or no citation at all; the AAO PPP did not cite any unreliable systematic review. However, evidence from 22 additional reliable systematic reviews underpinning 15 of the 35 recommendations could have been incorporated into the AAO PPP. Nine existing Cochrane reviews directly supported 12 of the treatment recommendations. In accordance with best practice standards outlined by the Institute of Medicine,[6] we suggest that interaction between systematic review teams and clinical practice guideline groups be encouraged to provide a comprehensive view of the evidence at a point in time and to illuminate evidence gaps. For example, the AAO PPP panel for AMD could collaborate with the Cochrane Eyes and Vision Group to identify existing Cochrane reviews for their guidelines and highlight evidence gaps where Cochrane reviews should be given high priority. Cochrane authors would need to act promptly to provide timely development or updating of reviews.

Most treatment recommendations in the AAO PPP for AMD were supported by evidence from only randomized controlled trials or nonrandomized studies. We acknowledge that a number of studies supporting some recommendations of treatments for AMD were well-designed, landmark randomized controlled trials, and these studies may have been well known to experts preparing recommendations. However, by transparently filtering and summarizing evidence in one place, systematic reviews provide an evidence base more extensive and comprehensive than looking at individual studies alone; they include structured assessment of trial methodology and the overall certainty of the evidence, providing the opportunity to evaluate all the evidence addressing a question to determine the current best answer. Systematic reviews and meta-analyses also are likely to be more useful than individual studies for providing information about rare adverse events, because even large randomized controlled trials often are not powered adequately to detect differences between treatments for infrequently observed outcomes.[107]

Although systematic reviews are important underpinnings of trustworthy treatment recommendations, they are not intended to serve in place of clinical practice guidelines. Clinical practice guidelines should be clear in stating unambiguously what is recommended, or not recommended, and should provide the evidence in support of each recommendation. In fact, frameworks such as the Grading of Recommendations Assessment, Development and Evaluation (GRADE) (www.gradeworkinggroup.org) have tools that use complementary methods and presentation graphics to support the work of both guideline developers and systematic reviewers. These are especially important for recommendations for which no high-quality evidence exists so that guideline developers must rely on lower-level sources of evidence and clinical expertise. For clarity, when preparing clinical practice guidelines, it would be helpful to have all recommendations with supporting citations clearly reported in one place in the guideline document.

In conclusion, ideally, reliable systematic reviews underpin evidence-based clinical practice guidelines. For AMD, reliable systematic reviews exist for many treatment recommendations in the AAO PPP and should be used to support these recommendations. Mapping clinical practice guidelines to existing systematic reviews is a useful way to highlight areas where evidence generation or evidence synthesis is either available or needed.

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Table 4. Treatment recommendations from the American Academy of Ophthalmology (AAO) Preferred Practice Pattern (PPP) Guideline Statement (2015) and systematic reviews (SRs) of age-related macular degeneration (AMD)

		Relevant and eligible SRs identified in our study		*Intervention SRs cited with recommendation in AAO PPP*	
	Recommendation made	**Any SRs**	**Reliable SRs**	**Any SRs**	**Reliable SRs**
1	"Patients who are currently smoking should be advised to stop."	Sin[55]	None	None	N/A
2	"In light of all the available information on the subject of aspirin use and AMD, the current preferred practice is for patients who have been instructed to use aspirin by a physician to continue their aspirin therapy as prescribed."	None	N/A	None	N/A
3	"The routine use of genetic testing is not supported by the existing literature and is not recommended at this time."	None	N/A	None	N/A
4	"Patients with early AMD and/or a family history of AMD should be encouraged to assess their own visual acuity using monocular vision testing (i.e., Amsler grid) and have scheduled dilated eye examinations for detecting the intermediate stage of AMD."	None	N/A	None	N/A
5	"Patients with a high-risk AMD phenotype are at increased risk of progression to advanced AMD and should be educated about methods of detecting new symptoms of CNV, including self-monitoring. They should also be educated about the need for promptly reporting new symptoms to an ophthalmologist who can confirm if the new symptoms are from CNV and who can begin any necessary treatment."	None	N/A	None	N/A
6	"The risks, benefits, complications, and alternatives of the treatment should be discussed with the patient and informed consent obtained."	None	N/A	None	N/A

		Relevant and eligible SRs identified in our study		*Intervention SRs cited with recommendation in AAO PPP*	
	Recommendation made	**Any SRs**	**Reliable SRs**	**Any SRs**	**Reliable SRs**
Antioxidants and minerals					
7	"Treatment with antioxidants and minerals as described previously in the original AREDS and AREDS2 trials is recommended for patients who have progressed to intermediate or advanced AMD in at least one eye."	Evans[22]; Evans[36]	Evans[22]; Evans[36]	None	N/A
8	"There is no evidence to support the use of these supplements for patients who have less than intermediate AMD."	Chong[35]; Evans[21]; Evans[36]	Chong[35]; Evans[21]; Evans[36]	None	N/A
9	"Additional vitamin E supplementation above the AREDS levels should be avoided."	Evans[36]	Evans[36]	None	N/A
10	"A lower zinc dose (25 mg) in the AREDS2 formulation could be considered"	Vishwanathan[56]	None	None	N/A
11	"The final results of AREDS2 support the recommendation for substitution of beta-carotene with lutein (10 mg) and zeaxanthin (2 mg)."	Zhang[57]	None	None	N/A
12	"When considering long-term supplementation, some people may have reason to avoid one of more of the supplements evaluated in the original AREDS or AREDS2. Because of the potential adverse effects, such as increased rate of genitourinary conditions that may require hospitalizations, the high doses of antioxidant vitamins and minerals recommended by the original AREDS and AREDS2 should be reviewed by the patient's primary care physician."	Evans[21]; Evans[36]	Evans[21]; Evans[36]	None	N/A

		Relevant and eligible SRs identified in our study		*Intervention SRs cited with recommendation in AAO PPP*	
	Recommendation made	**Any SRs**	**Reliable SRs**	**Any SRs**	**Reliable SRs**
Anti-VEGF therapy					
13	"Intravitreal injection therapy using anti-vascular endothelial growth factor (VEGF) agents (e.g., aflibercept, bevacizumab, and ranibizumab) is the most effective way to manage neovascular AMD and represents the first line of treatment."	Brown[59]; Colquitt[62]; Ip[52]; Jiang[38]; Lanzetta[53]; Oliva[61]; Schouten[44]; Takeda[45]; Vedula[30]; Ziemssen[47]	Colquitt[62]; Jiang[38]; Schouten[44]; Takeda[45]; Vedula[30]; Ziemssen[47]	Vedula 2008	Vedula 2008
14	"Current practice patterns support the use of anti-VEGF monotherapy for patients with newly diagnosed neovascular AMD, and suggest that these other therapies [verteporfin PDT and thermal laser photocoagulation surgery] are rarely needed yet may be used in unresponsive cases."	Brown[59]; Colquitt[62]; Ip[52]; Jiang[38]; Lanzetta[53]; Oliva[61]; Schouten[44]; Takeda[45]; Vedula[30]; Ziemssen[47]	Colquitt[62]; Jiang[38]; Schouten[44]; Takeda[45]; Vedula[30]; Ziemssen[47]	None	N/A
15	"Aflibercept intravitreal injection 2.0 mg as described in published reports"	None	N/A	None	N/A
16	"Bevacizumab intravitreal injection 1.25 mg as described in published reports"	Jiang[38]; Lanzetta[53]; Mitchell[54]; Schouten[44]; Ziemssen[47]	Jiang[38]; Schouten[44]; Ziemssen[47]	None	N/A
17	"The ophthalmologist should provide appropriate informed consent with respect to the off-label status"	Schmucker[41]; Schmucker[42]; Schmucker[43]	Schmucker[41]; Schmucker[42]; Schmucker[43]	None	N/A
18	"Caution should be used when dosing PRN bevacizumab, as it may be slightly less effective than other monthly anti-VEGF regimens."	Lanzetta[53]	N/A	None	N/A
19	"Ranibizumab intravitreal injection 0.5 mg as recommended in literature"	Brown[59]; Colquitt[62]; Ip[52]; Jiang[38]; Lanzetta[53]; Mitchell[54]; Oliva[61]; Takeda[45]; Vedula[30]	Colquitt[62]; Jiang[38]; Takeda[45]; Vedula[30]	None	N/A

		Relevant and eligible SRs identified in our study		*Intervention SRs cited with recommendation in AAO PPP*	
	Recommendation made	**Any SRs**	**Reliable SRs**	**Any SRs**	**Reliable SRs**
20	"Small retinal hemorrhages are a sign of active CNV or polypoidal choroidal vasculopathy and may be managed with anti-VEGF therapy."	None	N/A	None	N/A
21	"Most juxtafoveal lesions that may have been previously treated using laser photocoagulation are currently managed using the anti-VEGF agents."	None	N/A	None	N/A
22	"The current trend is to use anti-VEGF agents in preference to laser photocoagulation" for extrafoveal lesions	None	N/A	None	N/A
23	"Symptoms suggestive of postinjection endophthalmitis or retinal detachment require prompt evaluation."	None	N/A	None	N/A
Verteporfin photodynamic therapy					
24	"PDT with verteporfin as recommended in the TAP and VIP reports"	Cruess[49]; Husereau[63]; Oliva[61]; Oliva[65]; Meads[40]; Meads[64]; Wormald[33]	Husereau[63]; Oliva[65]; Meads[40]; Meads[64]; Wormald[33]	None	N/A
25	"Photosensitivity reaction (<3% of patients)…The stated, current recommendations are to avoid direct sunlight for the first 5 days after a treatment."	None	N/A	None	N/A
26	"Careful consideration should be given to patients with liver dysfunction and to patients who are pregnant, breast-feeding, or of pediatric age, because these patients were not studied in published reports."	None	N/A	None	N/A
27	"Patients with juxtafoveal lesions may also be considered eligible for the off-label use of PDT with verteporfin."	Husereau[63]; Oliva[65]; Meads[40]; Meads[64]; Wormald[33]	Husereau[63]; Oliva[65]; Meads[40]; Meads[64]; Wormald[33]	None	N/A

	Recommendation made	*Relevant and eligible SRs identified in our study*		*Intervention SRs cited with recommendation in AAO PPP*	
		Any SRs	**Reliable SRs**	**Any SRs**	**Reliable SRs**
Thermal laser photocoagulation surgery					
28	"Thermal laser photocoagulation surgery as recommended in the MPS reports"	Parodi[28]; Virgili[31]	Parodi[28]; Virgili[31]	None	N/A
29	Thermal laser photocoagulation surgery: "These realities must be emphasized to the patient and family before treatment." These realities = "Introduction or enlargement of pre-existing scotoma, with or without visual acuity loss, is not a complication of thermal laser photocoagulation; rather, it is an anticipated side effect of the treatment. Similarly, recurrence or persistence of CNV, or the development of new CNV and further visual deterioration after adequate thermal laser surgery, is usually a result of the disease process and is not a complication."	Parodi[28]; Virgili[31]	Parodi[28]; Virgili[31]	None	N/A
30	"Thermal laser photocoagulation surgery is no longer recommended for subfoveal CNV treatment."	Parodi[28]; Virgili[31]	Parodi[28]; Virgili[31]	None	N/A
31	"Laser surgery for extrafoveal lesions remains a less-commonly used, yet reasonable, therapy."	None	N/A	None	N/A
Other treatment recommendations					
32	"The data do not currently support the use of combination therapy [intravitreal corticosteroids and/or anti-VEGF agents in various drug combinations or with verteporfin PDT] at this time, especially with the long-term side effects of glaucoma and cataract that are associated with corticosteroid use."	Zhou[58]	N/A	None	N/A
33	"Observation with no medical or surgical therapies" recommended for early, non-neovascular AMD	None	N/A	None	N/A
34	"Current therapies that have insufficient data to demonstrate clinical efficacy include radiation therapy, acupuncture, electrical stimulation, macular translocation surgery, and adjunctive use of intravitreal corticosteroids with verteporfin PDT. Therefore, at this time, these therapies are not recommended."	Eandi[19]; Evans[23]; Falkner[50]; Giansanti[26]	Eandi[19]; Evans[23]; Giansanti[26]	None	N/A
35	"The data on management of these larger [submacular] hemorrhages are inadequate to make a recommendation at this time."	None	N/A	None	N/A

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ADDITIONAL FILES

Supplementary materials

Table 2. Reliability assessments for 47 systematic reviews of age-related macular degeneration

Study ID	Publication Source (Language)	Types of interventions evaluated	Number of included studies	Direction of main finding	Defined criteria for selection of studies	Comprehensive searches for eligible studies	Assessment of risk of bias in included studies	Appropriate statistical methods for meta-analysis	Concordance between results and conclusions
Reviews classified as reliable based on five criteria (n = 33)									
Cheng 2012	Journal (English)	Anti-VEGFs	6	Effective	Yes	Yes	Yes	Yes	Yes
Chong 2007	Journal (English)	Dietary supplements	12	Inconclusive	Yes	Yes	Yes	Yes	Yes
Colquitt 2008	Agency (English)	Anti-VEGFs	6	Effective	Yes	Yes	Yes	Not applicable	Yes
Eandi 2008	Cochrane (English)	Submacular surgery	1	Inconclusive	Yes	Yes	Yes	Not applicable	Yes
Evans 2008	Journal (English)	Dietary supplements	10	Inconclusive	Yes	Yes	Yes	Yes	Yes
Evans 2013	Cochrane (English)	Dietary supplements	2	Inconclusive	Yes	Yes	Yes	Not applicable	Yes
Evans 2012	Cochrane (English)	Dietary supplements	4	Ineffective	Yes	Yes	Yes	Yes	Yes
Evans 2010	Cochrane (English)	Other	14	Inconclusive	Yes	Yes	Yes	Yes	Yes
Evans 2012	Cochrane (English)	Dietary supplements	13	Effective	Yes	Yes	Yes	Yes	Yes
Gehlbach 2012	Cochrane (English)	Statins	2	Inconclusive	Yes	Yes	Yes	Not applicable	Yes
Geltzer 2013	Cochrane (English)	Other	3	Ineffective	Yes	Yes	Yes	Not applicable	Yes
Giansanti 2009	Cochrane (English)	Submacular surgery	3	Ineffective	Yes	Yes	Yes	Yes	Yes
Hodge 2007	Journal (English)	Dietary supplements	2	Inconclusive	Yes	Yes	Yes	Not applicable	Yes
Husereau 2002	Agency (English)	Photodynamic therapy	3	Effective	Yes	Yes	Yes	Not applicable	Yes
Jiang 2014	Journal (English)	Anti-VEGFs	8	Effective	Yes	Yes	Yes	Yes	Yes
Lawrenson 2012	Cochrane (English)	Dietary supplements	0	Inconclusive	Yes	Yes	Not applicable	Not applicable	Yes
Lee 2008	Journal (English)	Health or rehabilitation	not reported	Effective	Yes	Yes	Yes	Not applicable	Yes
Meads 2004	Journal (English)	Photodynamic therapy	2	Inconclusive	Yes	Yes	Yes	Yes	Yes
Meads 2003	Agency (English)	Photodynamic therapy	2	Inconclusive	Yes	Yes	Yes	Yes	Yes
Oliva 2002	Agency (Spanish)	Photodynamic therapy	2	Effective	Yes	Yes	Yes	Not applicable	Yes
Parodi 2009	Cochrane (English)	Laser photocoagulation	9	Inconclusive	Yes	Yes	Yes	Yes	Yes
Reddy 2006	Cochrane (English)	Other	1	Ineffective	Yes	Yes	Yes	Not applicable	Yes
Schmucker 2012	Journal (English)	Anti-VEGFs	11	Ineffective	Yes	Yes	Yes	Yes	Yes
Schmucker 2010	Journal (English)	Anti-VEGFs	33	Ineffective	Yes	Yes	Yes	Not applicable	Yes
Schmucker 2011	Journal (English)	Anti-VEGFs	25	Inconclusive	Yes	Yes	Yes	Yes	Yes
Schouten 2009	Journal (English)	Anti-VEGFs	26	Effective	Yes	Yes	Yes	Not applicable	Yes
Takeda 2007	Journal (English)	Anti-VEGFs	5	Effective	Yes	Yes	Yes	Not applicable	Yes
Vedula 2008	Cochrane (English)	Anti-VEGFs	5	Effective	Yes	Yes	Yes	Yes	Yes
Virgili 2007	Cochrane (English)	Laser photocoagulation	15	Effective	Yes	Yes	Yes	Yes	Yes
Wild 2009	Journal (German)	Other	2	Ineffective	Yes	Yes	Yes	Not applicable	Yes
Williams 2014	Cochrane (English)	Other	0	Inconclusive	Yes	Yes	Not applicable	Not applicable	Yes
Wormald 2005	Cochrane (English)	Photodynamic therapy	6	Effective	Yes	Yes	Yes	Yes	Yes
Ziemssen 2009	Journal (English)	Anti-VEGFs	33	Effective	Yes	Yes	Yes	Not applicable	Yes

Table 2. Continued

Study ID	Publication Source (Language)	Types of interventions evaluated	Number of included studies	Direction of main finding	Defined criteria for selection of studies	Comprehensive searches for eligible studies	Assessment of risk of bias in included studies	Appropriate statistical methods for meta-analysis	Concordance between results and conclusions
Reviews classified as unreliable based on five criteria (n = 14)									
Brown 2008	Agency (English)	Anti-VEGFs	12	Effective	Yes	Yes	Yes	Can't tell	Yes
Chuo 2007	Journal (English)	Statins	8	Inconclusive	Yes	Yes	No	Yes	Yes
Cruess 2009	Journal (English)	Photodynamic therapy	36	Effective	Yes	No	No	Not applicable	No
Falkner 2007	Journal (English)	Submacular surgery	88	Effective	Yes	No	Yes	No	No
Haute 2001	Agency (French)	Multiple treatments	not reported	Effective	Yes	Yes	Yes	Not applicable	Can't tell
Hooper 2008	Journal (English)	Health or rehabilitation	32	Inconclusive	Yes	No	Yes	Not applicable	Yes
Ip 2008	Journal (English)	Anti-VEGFs	54	Effective	Yes	No	Yes	Not applicable	Yes
Lanzetta 2013	Journal (English)	Anti-VEGFs	7	Effective	Yes	No	No	Not applicable	No
Mitchell 2011	Journal (English)	Anti-VEGFs	20	Inconclusive	Yes	No	No	Not applicable	Yes
Oliva 2009	Agency (Spanish)	Multiple treatments	6	Effective	Yes	Yes	Yes	Can't tell	Yes
Sin 2013	Journal (English)	Health or rehabilitation	not reported	Effective	Yes	No	No	Not applicable	Can't tell
Vishwanathan 2013	Journal (English)	Dietary supplements	10	Inconclusive	Yes	No	Yes	Not applicable	Yes
Zhang 2010	Journal (Chinese)	Dietary supplements	9	Effective	Yes	Yes	Yes	No	No
Zhou 2012	Journal (Chinese)	Anti-VEGFs	7	Effective	Yes	No	Yes	Yes	Yes

Examples of inappropriate statistical methods included combining results from different study designes (e.g., cohort and case-control studies), analyzed within group data only (i.e., not using between group estimates), and using case-control studies to assess incidence

Table 3. Main findings from 33 reliable systematic reviews and mapping to clinical practice guidelines

Author	Year	Main findings of the systematic review	American Academy of Ophthalmology (AAO) Preferred Practice Pattern (PPP) Guideline Statement (2015)
Anti-vascular endothelial growth factor (anti-VEGF) agents (n = 10)			
Takeda, et al[45]	2007	"Pegaptanib and ranibizumab appear to slow or stop the progression of neovascular AMD. Uncertainty remains over the relative benefits of pegaptanib compared with ranibizumab and other unlicensed drugs (eg, Avastin), due to the nature of the evidence. Head-to-head RCTs and economic evaluations comparing these alternatives are needed."	Intravitreal injection therapy using anti-vascular endothelial growth factor (VEGF) agents (e.g., aflibercept, bevacizumab, and ranibizumab) is the most effective way to manage neovascular AMD and represents the first line of treatment.
Colquitt, et al[62]	2008	"Patients with AMD of any lesion type benefit from treatment with pegaptanib or ranibizumab on measures of visual acuity when compared with sham injection and/or PDT. Patients who continued treatment with either drug appeared to maintain benefits after 2 years of follow-up. When comparing pegaptanib and ranibizumab, the evidence was less clear due to the lack of direct comparison through head-to-head trials and the lack of opportunity for indirect statistical comparison due to heterogeneity."	Intravitreal injection therapy using anti-vascular endothelial growth factor (VEGF) agents (e.g., aflibercept, bevacizumab, and ranibizumab) is the most effective way to manage neovascular AMD and represents the first line of treatment.
Vedula, et al[30]	2008	"Pegaptanib and ranibizumab reduce the risk of visual acuity loss in patients with neovascular AMD. Ranibizumab causes gains in visual acuity in many eyes. Quality of life and cost will be important for treatment decisions. Other agents blocking VEGF are being tested in ongoing trials."	Intravitreal injection therapy using anti-vascular endothelial growth factor (VEGF) agents (e.g., aflibercept, bevacizumab, and ranibizumab) is the most effective way to manage neovascular AMD and represents the first line of treatment.
Schouten, et al[44]	2009	"Visual acuity improves and central retinal thickness decreases in patients with exudative AMD after bevacizumab. There is no reasonable doubt that this is caused by bevacizumab. It is likely that a randomized controlled trial will show that bevacizumab is equivalent in effect to ranibizumab, which showed a change in ETDRS of +5.9 letters for occult or minimally classic CNVand +9.8 letters for classic CNV after three monthly injections in two large RCTs."	Intravitreal injection therapy using anti-vascular endothelial growth factor (VEGF) agents (e.g., aflibercept, bevacizumab, and ranibizumab) is the most effective way to manage neovascular AMD and represents the first line of treatment.
Ziemssen, et al[47]	2009	"In 33 studies, there was consistent and clear evidence for the efficacy of bevacizumab in neovascular AMD."	Intravitreal injection therapy using anti-vascular endothelial growth factor (VEGF) agents (e.g., aflibercept, bevacizumab, and ranibizumab) is the most effective way to manage neovascular AMD and represents the first line of treatment.

Table 3. Continued

Schmucker, et al[42]	2010	"Given the lack of controlled data, the widespread off-label use of bevacizumab is not justified in clinical practice. On the other hand, a major challenge in the management of patients who require repeated antivascular endothelial growth factor injections is the high cost of ranibizumab. This dilemma underlines the need for head-to-head studies comparing both vascular endothelial growth factor antibodies, or, at least, well conducted randomized controlled trials evaluating intravitreal bevacizumab."	Intravitreal injection therapy using anti-vascular endothelial growth factor (VEGF) agents (e.g., aflibercept, bevacizumab, and ranibizumab) is the most effective way to manage neovascular AMD and represents the first line of treatment.
Jiang, et al[38]	2014	"Ranibizumab 0 .3 or 0. 5 mg monthly treatment was more effective for neovascular AMD than non-anti-VEGF treatments but is no better than bevacizumab."	Intravitreal injection therapy using anti-vascular endothelial growth factor (VEGF) agents (e.g., aflibercept, bevacizumab, and ranibizumab) is the most effective way to manage neovascular AMD and represents the first line of treatment.
Schmucker, et al[42]	2011	"The bevacizumab studies show too many methodological limitations to rule out any major safety concerns. Higher evidence from ranibizumab trials suggests signals for an increased ocular and systemic vascular and haemorrhagic risk which warrants investigation."	Intravitreal anti-VEGF therapy is generally well tolerated and rarely associated with serious adverse events such as infectious endophthalmitis or retinal detachment. Symptoms suggestive of postinjection endophthalmitis or retinal detachment require prompt evaluation.
Cheng, et al[34]	2012	"The strength evidence suggests that the intravitreal use of anti-VEGF antibodies is not associated with an increased risk of arterial thromboembolic events."	Intravitreal anti-VEGF therapy is generally well tolerated and rarely associated with serious adverse events such as infectious endophthalmitis or retinal detachment. Symptoms suggestive of postinjection endophthalmitis or retinal detachment require prompt evaluation.
Schmucker, et al[41]	2012	"Evidence from head-to-head trials raises concern about an increased risk of ocular and multiple systemic AE with bevacizumab."	Intravitreal anti-VEGF therapy is generally well tolerated and rarely associated with serious adverse events such as infectious endophthalmitis or retinal detachment. Symptoms suggestive of postinjection endophthalmitis or retinal detachment require prompt evaluation.

Table 3. Continued

Vitamins and/or minerals (n = 7)			
Chong, et al[35]	2007	"There is insufficient evidence to support the role of dietary antioxidants, including the use of dietary antioxidant supplements, for the primary prevention of early AMD."	Antioxidant vitamin and mineral supplementation as per the original AREDS and AREDS2 trials should be considered in patients with intermediate or advanced age-related macular degeneration (AMD). There is no evidence to support the use of these supplements for patients who have less than intermediate AMD.
Evans[36]	2008	"Current evidence does not support the use of antioxidant vitamin supplements to prevent AMD. People with AMD, or early signs of the disease, may experience some benefit from taking supplements as used in the AREDS trial. Potential harms of high-dose antioxidant supplementation must be considered. These may include an increased risk of lung cancer in smokers (b-carotene), heart failure in people with vascular disease or diabetes (vitamin E) and hospitalisation for genitourinary conditions (zinc)."	Antioxidant vitamin and mineral supplementation as per the original AREDS and AREDS2 trials should be considered in patients with intermediate or advanced age-related macular degeneration (AMD). There is no evidence to support the use of these supplements for patients who have less than intermediate AMD.
Evans, et al[21]	2012	"There is accumulating evidence that taking vitamin E or beta-carotene supplements will not prevent or delay the onset of AMD. There is no evidence with respect to other antioxidant supplements, such as vitamin C, lutein and zeaxanthin, or any of the commonly marketed multivitamin combinations. Although generally regarded as safe, vitamin supplements may have harmful effects and clear evidence of benefit is needed before they can be recommended."	Antioxidant vitamin and mineral supplementation as per the original AREDS and AREDS2 trials should be considered in patients with intermediate or advanced age-related macular degeneration (AMD). There is no evidence to support the use of these supplements for patients who have less than intermediate AMD.
Evans, et al[22]	2012	"People with AMD may experience delay in progression of the disease with antioxidant vitamin and mineral supplementation."	Antioxidant vitamin and mineral supplementation as per the original AREDS and AREDS2 trials should be considered in patients with intermediate or advanced age-related macular degeneration (AMD). There is no evidence to support the use of these supplements for patients who have less than intermediate AMD.
Hodge, et al[37]	2007	"Clinical research on this topic is scarce. Only two studies were eligible to be included in this review. Although one study result indicated efficacy of [omega-3 fatty acids] preventing AMD progression to its advanced form, this result needs to be duplicated and supported by future research."	The addition of omega-3 supplementation (DHA and EPA) had no further benefit.

Table 3. Continued

Lawrenson, et al[27]	2012	"Until data from RCTs become available for analysis, there is currently no evidence to support increasing levels of omega 3 LCPUFA inthe diet for the explicit purpose of preventing or slowing the progression of AMD."	The addition of omega-3 supplementation (DHA and EPA) had no further benefit.
Evans[20]	2013	"The question as to whether people with AMD should take Ginkgo biloba extract to prevent progression of the disease has not been answered by research to date."	Not addressed in guideline
Photodynamic therapy (n = 5)			
Husereau, et al[62]	2002	"The evidence from three high-quality RCTs suggested that verteporfin PDT treatment for 2 years reduces the number of cases of central blindness, compared with placebo, by slowing disease progression. However, this treatment is not aimed at restoring vision and the majority of treated patients will continue to lose visual acuity. Verteporfin treatment did not increase serious adverse events compared with placebo (angiography and sham treatment), however, some adverse events occurred with greater frequency in individuals treated with verteporfin. The authors stated that these results relate to a study population with subfoveal neovascularisation from AMD, of which only a minority would be likely to qualify for treatment after diagnosis and angiographic assessment."	PDT with verteporfin is rarely needed yet may be used in unresponsive cases with subfoveal CNV. Patients with juxtafoveal lesions may also be considered eligible for the off-label use of PDT with verteporfin.
Oliva[65]	2002	"The scientific evidence suggests that PDT may be effective and safe for subfoveal CNV secondary to AMD."	PDT with verteporfin is rarely needed yet may be used in unresponsive cases with subfoveal CNV. Patients with juxtafoveal lesions may also be considered eligible for the off-label use of PDT with verteporfin.
Meads, et al[64]	2003	"There is a need to conduct a large, multicentre, publicly funded pragmatic double-blind RCT with parallel health economic evaluation to assess not just the impact of PDT on visual acuity and adverse events, but also directly measured global quality of life and survival. There is no indication of the relationship between benefits and costs where wet AMD affects the worse-seeing eye first. Treatment of wet AMD, with verteporfin, other types of PDT, and other new technologies is an area under very active investigation, so this technology should be kept under close review."	PDT with verteporfin is rarely needed yet may be used in unresponsive cases with subfoveal CNV. Patients with juxtafoveal lesions may also be considered eligible for the off-label use of PDT with verteporfin.
Meads, et al[60]	2004	"For several reasons it was considered that the most likely estimate of the predominantly classic subgroup effect size was the whole trial result. This has implications for the relationship between cost and benefit, the subject of intense debate. Results of the ongoing trials should help to clarify this subgroup effect size issue."	PDT with verteporfin is rarely needed yet may be used in unresponsive cases with subfoveal CNV. Patients with juxtafoveal lesions may also be considered eligible for the off-label use of PDT with verteporfin.

Table 3. Continued

Wormald, et al[33]	2007	"Photodynamic therapy in people with choroidal neovascularisation due to AMD is effective in preventing clinically significant visual loss with a relative risk reduction of approximately 20%.Modified treatment regimens have not convincingly shown increased effectiveness. There was no evidence on quality of life and little on cost."	PDT with verteporfin is rarely needed yet may be used in unresponsive cases with subfoveal CNV. Patients with juxtafoveal lesions may also be considered eligible for the off-label use of PDT with verteporfin.
Laser photocoagulation (n = 2)			
Virgili, et al[31]	2007	"In the medium to long term laser photocoagulation of CNV slows the progression of visual loss in people with neovascular AMD. However, it is associated with an increased risk of visual loss immediately after treatment and this period may be longer in people with subfoveal AMD. With the advent of modern pharmacological therapies, and concern for the impact of iatrogenic scotoma in subfoveal CNV, laser photocoagulation of subfoveal CNV is not recommended. No studies have compared photocoagulation with modern pharmacological agents for AMD for non-subfoveal CNV."	Thermal laser photocoagulation surgery is no longer recommended for subfoveal CNV treatment. Laser surgery for extrafoveal lesions remains a less-commonly used, yet reasonable, therapy.
Parodi, et al[28]	2009	"The trials included in this review confirm the clinical observation that laser photocoagulation of drusen leads to their disappearance. However, there is no evidence that this subsequently results in a reduction in the risk of developing CNV, geographic atrophy or visual acuity loss."	Thermal laser photocoagulation surgery is no longer recommended for subfoveal CNV treatment. Laser surgery for extrafoveal lesions remains a less-commonly used, yet reasonable, therapy.
Submacular surgery (n = 2)			
Eandi, et al[19]	2008	"There is insufficient evidence from randomised controlled trials on the effectiveness of macular translocation, which is also not free of important risks. Furthermore, this technique is difficult to perform and a long surgical training is required. Future studies might include patients with small neovascular lesions that failed to respond to current pharmacological therapies and are willing to accept the risks associated with surgery to try to improve visual acuity."	Radiation therapy, acupuncture, electrical stimulation, macular translocation surgery, and adjunctive use of intravitreal steroids with verteporfin PDT are not recommended.
Giansanti, et al[26]	2009	"There is no benefit with submacular surgery in most people with subfoveal choroidal neovascularisation due to AMD in terms of prevention of visual loss. Furthermore, the risk of developing cataract and retinal detachment increases after surgery."	Radiation therapy, acupuncture, electrical stimulation, macular translocation surgery, and adjunctive use of intravitreal steroids with verteporfin PDT are not recommended.
Complement inhibitors (n = 1)			
Williams, et al[32]	2014	"There is insufficient information at present to generate evidence-based recommendations on the potential safety and efficacy of complement inhibitors for prevention or treatment of AMD. However we anticipate the results of ongoing trials."	Not addressed in guideline

Table 3. Continued

Interferon alpha (n = 1)			
Reddy, et al[29]	2006	"At present there is not enough evidence to recommend the use of interferon alfa-2a for the treatment of age-related macular degeneration."	Not addressed in guideline
Radiotherapy (n = 1)			
Evans, et al[23]	2010	"This review currently does not provide convincing evidence that radiotherapy is an effective treatment for neovascular AMD. If further trials are to be considered to evaluate radiotherapy in AMD then adequate masking of the control group must be considered."	Radiation therapy, acupuncture, electrical stimulation, macular translocation surgery, and adjunctive use of intravitreal steroids with verteporfin PDT are not recommended.
Rheophoresis (n = 1)			
Wild, et al[46]	2009	"No evidence for the efficacy of rheophoresis in the treatment of patients with dry AMD."	Not addressed in guideline
Statins (n = 1)			
Gehlbach, et al[24]	2012	"Evidence from currently available RCTs was insufficient to conclude that statins have any role in preventing or delaying the onset or progression of AMD."	Not addressed in guideline
Steroids (n = 1)			
Geltzer, et al[25]	2013	"Based on the included trials, we found no evidence that antiangiogenic steroids prevent visual loss in patients with neovascular AMD."	Not addressed in guideline
Self-management programs (n = 1)			
Lee, et al[39]	2008	"Self-management programs appear effective for older adults with AMD. Small sample size, use of nontraditional statistics and methodological quality meant only a narrative analysis was possible. Future studies with more robust methodology including intent-to-treat analysis are still required."	Not addressed in guideline

Table 5. Treatment recommendations extracted from the American Academy of Ophthalmology (AAO) Preferred Practice Pattern Guideline Statement (2015) for age-related macular degeneration (AMD)

	Section of PPP where recommendation appears					Systematic reviews cited	Randomized controlled trials cited	Other citations
	Management sections of PPP		Other sections of PPP					
	Care process (pp 19-23)	Table 4. Treatment recommendations (pp 20-21)	Highlighted findings and recommendations for care (page 4)	Background (pp 7-16)	Appendix 3. Grading of recommendations (pp 30-35)			
1	"Patients who are currently smoking should be advised to stop." (page 19)	Not mentioned	"Smoking cessation is strongly recommended when advising patients who have AMD or are at risk for AMD."	"Smoking cessation is strongly recommended when advising patients" (page 7)	I++; Good; Strong	1 non-AMD intervention SR cited	None	2 NRSs; 1 CPG cited
2	Not mentioned	Not mentioned	"Patients who have been instructed to use aspirin by a physician should continue to use it as prescribed."	"In light of all the available information on the subject of aspirin use and AMD, the current preferred practice is for patients who have been instructed to use aspirin by a physician to continue their aspirin therapy as prescribed." (page 8)	II++; Good; Strong	1 non-AMD intervention SR cited	1 RCT cited	1 NRS cited
3	Not mentioned	Not mentioned	Not mentioned	"The routine use of genetic testing is not supported by the existing literature and is not recommended at this time." (page 8)	III; Insufficient; Discretionary	None	1 RCT cited	1 NRS cited
4	"Patients with early AMD and/or a family history of AMD should be encouraged to assess their own visual acuity using monocular vision testing (i.e., Amsler grid) and have scheduled dilated eye examinations for detecting the intermediate stage of AMD." (page 19)	"Monitoring of monocular near vision (reading/Amsler grid)"; "Fundus photos, fluorescein angiography, or OCT as appropriate"	Not mentioned	Not mentioned	III; Good; Strong	None	None	None
5	"Patients with a high-risk AMD phenotype are at increased risk of progression to advanced AMD and should be educated about methods of detecting new symptoms of CNV, including self-monitoring. They should also be educated about the need for promptly reporting new symptoms to an ophthalmologist who can confirm if the new symptoms are from CNV and who can begin any necessary treatment." (page 19)	Not mentioned	Not mentioned	Not mentioned	III; Good; Stong	None	None	None

Table 5. Continued

	Section of PPP where recommendation appears					Systematic reviews cited	Randomized controlled trials cited	Other citations
	Management sections of PPP		Other sections of PPP					
	Care process (pp 19-23)	Table 4. Treatment recommendations (pp 20-21)	Highlighted findings and recommendations for care (page 4)	Background (pp 7-16)	Appendix 3. Grading of recommendations (pp 30-35)			
6	"The risks, benefits, complications, and alternatives of the treatment should be discussed with the patient and informed consent obtained." (page 22)	Not mentioned	Not mentioned	Not mentioned	III; Good; Strong	None	None	1 AAO policy statement cited
7	"Treatment with antioxidants and minerals as described previously in the original AREDS and AREDS2 trials is recommended for patients who have progressed to intermediate or advanced AMD in at least one eye." (page 19)	"Antioxidant vitamin and mineral supplements as recommended in the original AREDS and AREDS2 reports"	"Antioxidant vitamin and mineral supplementation as per the original AREDS and AREDS2 trials should be considered in patients with intermediate or advanced age-related macular degeneration."	"The original AREDS results demonstrate a beneficial effect for the use of high-dose oral antioxidant vitamins (vitamins C, E, beta-carotene) and zinc supplementation in reducing progression of intermediate AMD or advanced AMD in the fellow eye to advanced AMD by 25%." (page 7)	I++; Good; Discretionary	None	2 RCTs cited	1 NRS; 1 textbook cited
8	Not mentioned	Early AMD not listed as diagnosis eligible for treatment	"There is no evidence to support the use of these supplements for patients who have less than intermediate AMD."	"There is no evidence to support the use of these supplements for patients who have less than intermediate AMD." (page 10)	I++; Good; Discretionary	None	None	None
9	Not mentioned	Not mentioned	Not mentioned	"Additional vitamin E supplementation above the AREDS levels should be avoided." (page 7)	Not mentioned	1 non-AMD intervention SR cited	None	None
10	Unclear	Not mentioned	Not mentioned	Unclear	"A lower zinc dose (25 mg) in the AREDS2 formulation could be considered"; I++; Good; Discretionary	None	None	None

Table 5. Continued

	Section of PPP where recommendation appears					Systematic reviews cited	Randomized controlled trials cited	Other citations
	Management sections of PPP		Other sections of PPP					
	Care process (pp 19-23)	Table 4. Treatment recommendations (pp 20-21)	Highlighted findings and recommendations for care (page 4)	Background (pp 7-16)	Appendix 3. Grading of recommendations (pp 30-35)			
11	Unclear	Not mentioned	"Replacement of the beta-carotene from the original AREDS formulation with lutein/zeaxanthin in the AREDS2 supplements may decrease the risk of lung cancer in smokers."	"Results of AREDS2 support the replacement of beta-carotene (from the original AREDS) with lutein/zeaxanthin in the new AREDS2 supplements." (page 7); "The final results of AREDS2 support the recommendation for substitution of beta-carotene with lutein (10 mg) and zeaxanthin (2 mg)." (page 11)	Not mentioned	None	4 RCTs cited	None
12	" Because of the potential adverse effects, such as increased rate of genitourinary conditions that may require hospitalizations, the high doses of antioxidant vitamins and minerals recommended by the original AREDS and AREDS2 should be reviewed by the patient's primary care physician." (page 23)	Not mentioned	Not mentioned	Not mentioned	III; Good; Strong	None	4 RCTs cited	None
13	Unclear	Unclear	"Intravitreal injection therapy using anti-vascular endothelial growth factor (VEGF) agents (e.g., aflibercept, bevacizumab, and ranibizumab) is the most effective way to manage neovascular AMD and represents the first line of treatment."	"Anti-VEGF therapies have become first-line therapy for treating and stabilizing most cases of neovascular AMD." (page 12)	I++; Good; Strong	1 reliable SR (Vedula 2008)	None	None

Table 5. Continued

	Section of PPP where recommendation appears					Systematic reviews cited	Randomized controlled trials cited	Other citations
	Management sections of PPP		Other sections of PPP					
	Care process (pp 19-23)	Table 4. Treatment recommendations (pp 20-21)	Highlighted findings and recommendations for care (page 4)	Background (pp 7-16)	Appendix 3. Grading of recommendations (pp 30-35)			
14	Unclear	"Less commonly used treatments for neovascular AMD" are PDT with verteporfin and thermal laser photocoagulation surgery	Not mentioned	"Current practice patterns support the use of anti-VEGF monotherapy for patients with newly diagnosed neovascular AMD, and suggest that these other therapies [verteporfin PDT and thermal laser photocoagulation surgery] are rarely needed yet may be used in unresponsive cases." (page 13)	III; Good; Strong	None	None	None
15	"Assessment and treatment plans for non-neovascular and neovascular AMD are listed in Table 4." (page 19)	"Aflibercept intravitreal injection 2.0 mg as described in published reports"	"Intravitreal injection therapy using anti-vascular endothelial growth factor (VEGF) agents (e.g., aflibercept, bevacizumab, and ranibizumab) is the most effective way to manage neovascular AMD and represents the first line of treatment."	"Anti-VEGF therapies have become first-line therapy for treating and stabilizing most cases of neovascular AMD." (page 12)	III; Good; Strong	None	2 RCTs cited	None
16	"Assessment and treatment plans for non-neovascular and neovascular AMD are listed in Table 4." (page 19)	"Bevacizumab intravitreal injection 1.25 mg as described in published reports"	"Intravitreal injection therapy using anti-vascular endothelial growth factor (VEGF) agents (e.g., aflibercept, bevacizumab, and ranibizumab) is the most effective way to manage neovascular AMD and represents the first line of treatment."	"Anti-VEGF therapies have become first-line therapy for treating and stabilizing most cases of neovascular AMD." (page 12)	III; Good; Strong	None	6 RCTs cited	2 NRSs; 1 AAO policy statement cited
17	Not mentioned	"The ophthalmologist should provide appropriate informed consent with respect to the off-label status"	Not mentioned	Not mentioned	III; Good; Strong	None	None	1 insurance company document cited
18	"Caution should be used when dosing PRN bevacizumab, as it may be slightly less effective than other monthly anti-VEGF regimens." (page 22)	Not mentioned	Not mentioned	Not mentioned	I+; Moderate; Discretionary	None	None	None

Table 5. Continued

	Section of PPP where recommendation appears					Systematic reviews cited	Randomized controlled trials cited	Other citations
	Management sections of PPP		Other sections of PPP					
	Care process (pp 19-23)	Table 4. Treatment recommendations (pp 20-21)	Highlighted findings and recommendations for care (page 4)	Background (pp 7-16)	Appendix 3. Grading of recommendations (pp 30-35)			
19	"Assessment and treatment plans for non-neovascular and neovascular AMD are listed in Table 4." (page 19)	"Ranibizumab intravitreal injection 0.5 mg as recommended in literature"	"Intravitreal injection therapy using anti-vascular endothelial growth factor (VEGF) agents (e.g., aflibercept, bevacizumab, and ranibizumab) is the most effective way to manage neovascular AMD and represents the first line of treatment."	"Anti-VEGF therapies have become first-line therapy for treating and stabilizing most cases of neovascular AMD." (page 12)	III; Good; Strong	None	4 RCTs cited	4 NRSs; 1 FDA document cited
20	"Small subretinal hemorrhages are a sign of active CNV or polypoidal choroidal vasculopathy and may be managed with anti-VEGF therapy. (page 22)	Not mentioned	Not mentioned	Not mentioned	Not mentioned	None	None	None
21	Unclear	Not mentioned	Not mentioned	"Most juxtafoveal lesions that may have been previously treated using laser photocoagulation are currently managed using the anti-VEGF agents." (page 14)	III; Good; Strong	None	1 RCT cited	None
22	Unclear	Not mentioned	Not mentioned	"The current trend is to use anti-VEGF agents in preference to laser photocoagulation" for extrafoveal lesions" (page 14)	III; Good; Strong	None	1 RCT cited	None
23	Not mentioned	"Patients should be instructed to promptly report symptoms suggestive of endophthalmitis"	"Symptoms suggestive of postinjection endophthalmitis or retinal detachment require prompt evaluation."	Not mentioned	III; Good; Strong	None	None	None
24	"Assessment and treatment plans for non-neovascular and neovascular AMD are listed in Table 4." (page 19)	"PDT with verteporfin as recommended in the TAP and VIP reports"	Not mentioned	Not mentioned	III; Good; Discretionary	None	2 RCTs cited	None
25	"Photosensitivity reaction (<3% of patients)...The stated, current recommendations are to avoid direct sunlight for the first 5 days after a treatment." (page 23)	Not mentioned	Not mentioned	Not mentioned	Not mentioned	None	2 RCTs cited	None

Table 5. Continued

	Section of PPP where recommendation appears					Systematic reviews cited	Randomized controlled trials cited	Other citations
	Management sections of PPP		Other sections of PPP					
	Care process (pp 19-23)	Table 4. Treatment recommendations (pp 20-21)	Highlighted findings and recommendations for care (page 4)	Background (pp 7-16)	Appendix 3. Grading of recommendations (pp 30-35)			
26	"Careful consideration should be given to patients with liver dysfunction and to patients who are pregnant, breast-feeding, or of pediatric age, because these patients were not studied in published reports." (page 23)	Not mentioned	Not mentioned	Not mentioned	III; Good; Strong	None	None	None
27	"Assessment and treatment plans for non-neovascular and neovascular AMD are listed in Table 4." (page 19)	"Juxtafoveal CNV is an off-label indication for PDT but may be considered in select cases"	Not mentioned	"Patients with juxtafoveal lesions may also be considered eligible for the off-label use of PDT with verteporfin." (page 14)	III; Good; Discretionary	None	1 RCT cited	None
28	"Assessment and treatment plans for non-neovascular and neovascular AMD are listed in Table 4." (page 19)	"Thermal laser photocoagulation surgery as recommended in the MPS reports"	Not mentioned	"There still remains a possible role for thermal laser surgery treatment in eyes with extrafoveal and peripapillary CNV lesions as defined by the MPS." (page 14)	III; Moderate; Strong	None	1 RCT cited	None
29	Thermal laser photocoagulation surgery: "These realities must be emphasized to the patient and family before treatment." These realities = "Introduction or enlargement of pre-existing scotoma, with or without visual acuity loss, is not a complication of thermal laser photocoagulation; rather, it is an anticipated side effect of the treatment. Similarly, recurrence or persistence of CNV, or the development of new CNV and further visual deterioration after adequate thermal laser surgery, is usually a result of the disease process and is not a complication." (page 23)	Not mentioned	Not mentioned	Not mentioned	III; Good; Strong	None	None	None
30	"Assessment and treatment plans for non-neovascular and neovascular AMD are listed in Table 4." (page 19)	Macular CNV not listed as diagnosis eligible for treatment	Not mentioned	"Thermal laser photocoagulation surgery is no longer recommended for subfoveal CNV treatment." (page 13)	None	None	1 RCT cited	None

Table 5. Continued

	Section of PPP where recommendation appears					Systematic reviews cited	Randomized controlled trials cited	Other citations
	Management sections of PPP		Other sections of PPP					
	Care process (pp 19-23)	Table 4. Treatment recommendations (pp 20-21)	Highlighted findings and recommendations for care (page 4)	Background (pp 7-16)	Appendix 3. Grading of recommendations (pp 30-35)			
31	"Assessment and treatment plans for non-neovascular and neovascular AMD are listed in Table 4." (page 19)	Thermal laser photocoagulation surgery "may be considered for extrafoveal classic CNV, new or recurrent"	Not mentioned	"Laser surgery for extrafoveal lesions remains a less-commonly used, yet reasonable, therapy." (page 14)	III; Good; Strong	None	1 RCT cited	None
32	Not mentioned	Not mentioned	Not mentioned	"The data do not currently support the use of combination therapy [intravitreal corticosteroids and/or anti-VEGF agents in various drug combinations or with verteporfin PDT] at this time, especially with the long-term side effects of glaucoma and cataract that are associated with corticosteroid use." (page 13)	None	None	4 RCTs cited	2 NRSs cited
33	"Assessment and treatment plans for non-neovascular and neovascular AMD are listed in Table 4." (page 19)	"Observation with no medical or surgical therapies" recommended for early, non-neovascular AMD	Not mentioned	Not mentioned	III; Good; Strong	None	2 RCTs cited	1 NRS cited
34	Not mentioned	Not mentioned	Not mentioned	"Current therapies that have insufficient data to demonstrate clinical efficacy include radiation therapy, acupuncture, electrical stimulation, macular translocation surgery, and adjunctive use of intravitreal corticosteroids with verteporfin PDT. Therefore, at this time, these theapies are not recommended." (page 14)	III; Moderate; Strong	None	None	None
35	"The data on management of larger [submacular] hemorrhages are inadequate to make a recommendation at this time." (page 22)	Not mentioned	Not mentioned	Not mentioned	None	None	None	None

CHAPTER 3

Evaluation of clinical questions and patient-important outcomes associated with the treatment of age-related macular degeneration

Kristina Lindsley
Susan Hutfless
Barbara S Hawkins
Jill F Blim
Dan Roberts
Timothy W Olsen
Flora Lum
Kay Dickersin

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ABSTRACT

Importance:
Identifying and prioritizing unanswered clinical questions may help to best allocate limited resources for research associated with the treatment of age-related macular degeneration (AMD).

Objective:
To identify and prioritize clinical questions and outcomes for research associated with the treatment of AMD through engagement with professional and patient stakeholders.

Design, setting, and participants:
Multiple cross-sectional survey questions were used in a modified Delphi process for panel members of US and international organizations, the American Academy of Ophthalmology (AAO) Retina/Vitreous Panel (n=7), health care professionals from the American Society of Retinal Specialists (ASRS) (n=90), Atlantic Coast Retina Conference (ACRC) and Macula 2017 meeting (n=34); and patients from MD (Macular Degeneration) Support (n=46). Data were collected from January 20, 2015, to January 9, 2017.

Main outcomes and measures:
The prioritizing of clinical questions and patient-important outcomes for AMD.

Results:
Seventy clinical questions were derived from the AAO Preferred Practice Patterns for AMD and suggestions by the AAO Retina/Vitreous Panel. The AAO Retina/Vitreous Panel assessed all 70 clinical questions and rated 17 of 70 questions (24%) as highly important. Health care professionals assessed the 17 highly important clinical questions and rated 12 of 17 questions (71%) as high priority for research to answer; 9 of 12 high-priority clinical questions were associated with aspects of anti–vascular endothelial growth factor agents. Patients assessed the 17 highly important clinical questions and rated all as high priority. Additionally, patients identified 6 of 33 outcomes (18%) as most important to them (choroidal neovascularization, development of advanced AMD, retinal hemorrhage, gain of vision, slowing vision loss, and serious ocular events).

Conclusions and relevance:
Input from 4 stakeholder groups suggests good agreement on which 12 priority clinical questions can be used to underpin research related to the treatment of AMD. The 6 most important outcomes identified by patients were balanced between intended effects of AMD treatment (eg, slowing vision loss) and adverse events. Consideration of these patient-important outcomesmay help to guide clinical care and future areas of research.

BACKGROUND

Age-related macular degeneration (AMD) is the leading cause of uncorrectable vision loss in adults 50 years and older in the UnitedStates.[1] Vision loss due to AMD, which ultimately affects central vision, is associated with poor quality of life and a decreased sense of independence in affected individuals.[2] Similar to clinical measures, outcomes that have been named as important by patients should be validated through research.[3] Patient perspective, clinical expertise, and scientific evidence form the triad of evidence-based medicine; thus these viewpoints should be considered together when setting a research agenda and determining outcomes to be examined in research.[4]

Randomized clinical trials (RCTs) and systematic reviews of RCTs are considered to provide the highest level of evidence to determine the effectiveness of clinical interventions.[5] Resources are insufficient to conduct RCTs and systematic reviews on all possible research questions.[6] Thus, establishing a framework for identifying important unanswered clinical questions would help funders and researchers to prioritize trials and systematic reviews to be conducted.

The overall objective of this study was to identify and prioritize clinical questions and patient-important outcomes associated with the treatment of AMD by adapting a priority-setting framework used for other eye conditions.[7-11] The process begins by identifying treatment recommendations from clinical practice guidelines and translating each treatment recommendation into an answerable clinical question. In a previous study,[12] evidence gaps were identified by assessing the evidence cited to support each treatment recommendation and mapping the clinical questions to existing reliable systematic reviews for treatment recommendations extracted from the 2015 American Academy of Ophthalmology (AAO) Preferred Practice Pattern (PPP) for the management of AMD.[13] In this study, multiple stakeholders, including clinical practice guideline developers, health care professionals, and patients, prioritized the importance of research to answer each clinical question in light of the available evidence.

METHODS

This study used a modified Delphi process to identify and prioritize clinical research questions and patient-important outcomes associated with the treatment of AMD in 4 steps: (1) derive clinical questions from clinical practice guidelines and specialists in AMD; (2) survey clinical practice guideline developers to identify the most important clinical questions for research to answer; (3) survey retina experts and health care professionals to prioritize the order in which the most important clinical questions should be addressed by research; and (4) survey patients to prioritize the most important clinical questions and outcomes from their perspective (Figure).

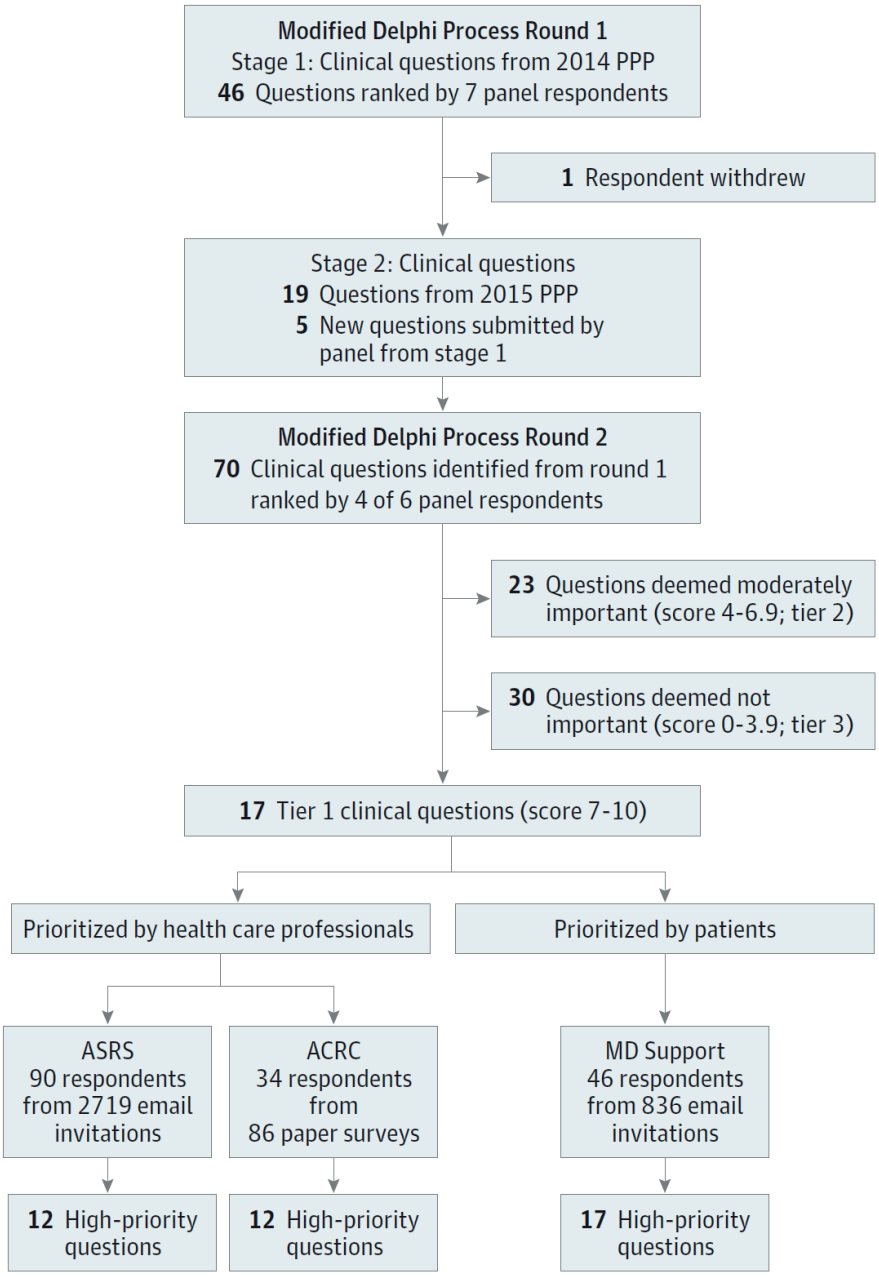

Figure. Flowchart for Identification and Prioritization of Clinical Questions. ACRC indicates Atlantic Coast Retina Conference; ASRS, American Society of Retinal Specialists; MD, macular degeneration; and PPP, preferred practice pattern.

This study was approved by the Johns Hopkins Bloomberg School of Public Health Institutional Review Board, Baltimore, Maryland. Per direction from the institutional review board, the survey included the statement that completing the survey was also providing informed consent. We did not collect identifiable data from any survey participant and all responses remain anonymous. eAppendix 1 in the Supplement includes protocol and amendments.

Step 1: Derive Clinical Questions From Clinical Practice Guidelines and Specialists in AMD

We identified treatment recommendations in the 2014 and 2015 AAO clinical practice guidelines, known as Preferred Practice Pattern (PPP), for management of AMD.[13,14] Two individuals (B.S.H. and K.B.L. for 2014 PPP and K.B.L. and S.H. for 2015 PPP) independently reviewed and extracted every statement that could be considered a treatment recommendation published in the PPP guideline. We formulated each recommendation into an answerable clinical question using the PICO (participant, intervention, comparison, and outcome) format. We consulted with AMD specialists (1 member of ACRC and Macula 2017, Neil M. Bressler, MD, and 1 of us, T.W.O.) who had expertise both in the management of AMD and in forming answerable clinical questions to confirm that our restatements were accurate and adding other clinical questions that were not addressed directly in the PPP guideline.

Step 2: Identify Highly Important Clinical Questions

We conducted a 2-round, web-based, cross-sectional, modified Delphi consensus survey.[15] We asked each panel member to assign a rating to each clinical question derived from the PPP on a scale of 0 to 10, with 10 indicating highly important and 0 indicating not important at all. Panel members also had an option to assign a score of "no judgment." At each round, panel members could enter comments and suggest new clinical questions.

We administered the first round of the survey in 2 stages because the AAO PPP published an update during the first survey period (January 2015). From January to February 2015, the 7-member panel rated 46 clinical questions derived from the 2014 AAO PPP on the management of AMD. We used Survey Monkey (http://www.surveymonkey.com) in the first part of round 1; we used Qualtrics (http://www.qualtrics.com) for all subsequent online surveys. One panel member withdrew from the panel between the first and second part of round 1 and was not replaced. In the second part of round 1 (March 2016), the 6-member panel rated 24 additional clinical questions as a continuation of the first round of the survey, 19 derived from the 2015 AAO PPP and 5 contributed by the panel members in the first stage. In the 2 parts of round 1, panel members prioritized a total of 70 clinical questions.

In round 2 of the survey, conducted from June through August 2016, we provided the 6 panel members the median score for each clinical question from the first round of the survey. We asked them to rate the 70 clinical questions again, taking into account the median scores from the first round.

After the second round was completed, we grouped clinical questions into 3 prespecified tiers based on the median scores after the second round (tier 1, median score of 7-10; tier 2, median score of 4-6.9, and tier 3, median score of 0 to 3.9). We considered tier 1 questions to represent highly important clinical research questions. The rationale for asking the panel to identify the most important clinical questions was to reduce the number of clinical questions so that the prioritization surveys could be completed in 15 minutes or less.

Step 3: Prioritize Clinical Questions by Health Care Professionals

To prioritize the tier 1 clinical questions, we surveyed members of the American Society of Retinal Specialists (ASRS) and attendees of the Atlantic Coast Retina Conference (ACRC) and Macula 2017 meetings. Survey participants rated each tier 1 clinical question on a scale of 0 to 10, with 10 indicating the highest priority and 0 indicating not a priority at all (eAppendix 3 in the Supplement). Survey participants also had an option to assign a score of "no judgment" and to submit additional clinical questions important to them. Additionally, we asked survey participants to provide demographic and professional information.

In partnership with ASRS, the survey was announced and first made available at the ASRS exhibitor booth on Retina Subspecialty Day at the AAO Annual Meeting in Chicago, Illinois, on October 14, 2016. The survey was available online via ASRS listserv until December 19, 2016; invitations and reminders to complete the survey were sent to the membership via ASRS's Retina FYI monthly e-newsletter (October, November, and December 2016). The ASRS listserv included 2719 email addresses.

We surveyed attendees of the ACRC and Macula 2017 meeting, held January 5-7, 2017, in Baltimore, Maryland. The survey, administered on paper, included the same questions as those posed to ASRS, with an additional question that asked whether the participant had completed the online survey. We distributed 86 surveys to attendees from the registration table. We collected completed surveys through January 9, 2017.

Step 4: Prioritize Clinical Questions and Outcomes by Patients

The online MD (Macular Degeneration) Support is a nonprofit organization established to educate and support individuals affected by macular degeneration. Survey participants rated each tier 1 clinical question on a scale of 0 to 10, with 10

indicating the highest priority and 0 indicating not a priority at all. In addition to rating the tier 1 clinical questions, survey participants ranked the importance of outcomes related to the management of AMD using 4 categories: most important, moderately important, least important, and unsure (no judgment). We identified the outcomes to be ranked based on common AMD-related outcomes assessed in published RCTs and systematic reviews.[16,17] We considered outcomes ranked as "most important" by 70% or more respondents as highly important and those scored as "most important" by 15% or fewer respondents as not highly important.[18] We asked participants to record any clinical questions or outcomes of importance to them that were not included in the survey. We also asked broad, nonidentifying questions about the respondents' AMD status, such as stage of AMD.

The patient survey was available online from October 13, 2016, until December 19, 2016. The MD Support online forum consists of 385 listserv members and 451 people registered for automatic notices on the website. An unknown number of people are registered to both lists; thus, we considered the forum to include a maximum of 836 unique email addresses.

We calculated the median and interquartile range for each clinical question from each prioritization survey. We considered clinical questions with a median score of 7 or higher to represent high-priority clinical questions for research to answer. We compared scores by cohort of stakeholders (ie, ASRS, ACRC and Macula 2017, and MD Support). Data were collected from January 20, 2015, to January 9, 2017.

RESULTS

In total, we identified 70 clinical questions associated with the management of AMD (eAppendix 1 in the Supplement). Of the 70 clinical questions, 17 involved anti–vascular endothelial growth factor (anti-VEGF) agents; 13 photodynamic therapy; 8 laser photocoagulation; 8 antioxidant vitamin and mineral supplements; and 24 were related to other treatment modalities.

The AAO Retina/Vitreous Panel rated 17 of 70 clinical questions (24%) as tier 1 (ie, highly important) (Figure; eAppendix 2 in the Supplement). No clinical question changed tiers between round 1 and round 2 of the survey. Nine of the 17 tier 1 clinical questions (53%) related to anti-VEGF agents, 4 to antioxidant vitamin and mineral supplements (24%), and 1 each to photodynamic therapy, smoking cessation, self-monitoring, and surgery for cataract in eyes with AMD (Table 1). Six of the 7 panel members reported no conflicts of interest.

Table 1. Prioritization of 17 highly important clinical questions associated with the management of age-related macular degeneration (AMD)

Clinical Questions Scored as Highly Important by the AAO Retina/Vitreous Panel	ASRS	ACRC and Macula 2017	MD Support
Are intravitreous injections of anti-VEGF agents effective treatments for neovascular AMD?	High priority	High priority	High priority
Is aflibercept effective for the treatment of AMD?	High priority	High priority	High priority
Is aflibercept safe for the treatment of AMD?	High priority	High priority	High priority
Is bevacizumab effective for the treatment of AMD?	High priority	High priority	High priority
Is bevacizumab safe for the treatment of AMD?	High priority	High priority	High priority
Is ranibizumab effective for the treatment of AMD?	High priority	High priority	High priority
Is ranibizumab safe for the treatment of AMD?	High priority	High priority	High priority
Are intravitreous injections of anti-VEGF agents effective as a primary treatment for AMD with juxtafoveal lesions?	High priority	High priority	High priority
Are anti-VEGF agents safe to inject during pregnancy?	High priority	High priority	High priority
Are antioxidant vitamin and mineral supplements an effective treatment for intermediate AMD?	Not high priority	High priority	High priority
Are antioxidant vitamin and mineral supplements an effective treatment for advanced AMD in only 1 eye?	Not high priority	Not high priority	High priority
Is long-term supplementation with high-dose antioxidants safe for the general patient with AMD?	High priority	High priority	High priority
Is long-term supplementation with high-dose antioxidants safe for smokers with AMD?	Not high priority	Not high priority	High priority
Does smoking cessation prevent progression of AMD?	High priority	Not high priority	High priority
Is self-monitoring by patients at high-risk effective in preventing progression of advanced AMD?	High priority	High priority	High priority
Does avoiding sunlight after verteporfin photodynamic therapy prevent or reduce photosensitivity reactions?	Not high priority	Not high priority	High priority
Is surgery for cataracts in people with AMD safe?	High priority	High priority	High priority

Abbreviations: AAO, American Academy of Ophthalmology; ACRC, Atlantic Coast Retina Conference; ASRS, American Society of Retina Specialists; MD, macular degeneration; VEGF, vascular endothelial growth factor.

From invitations sent to 2719 email addresses in the ASRS listserv, 106 ASRS members (4%) accessed the online prioritization survey and 90 of 106 members (85%) participated in the survey. Health care professionals assessed the 17 highly important clinical questions and rated 12 of 17 questions (71%) as high priority for research to answer. Nine of the 12 high-priority clinical questions were associated with aspects of anti-VEGF agents. We distributed 86 paper surveys to ACRC and Macula 2017 attendees and 34 of 86 surveys (40%) were returned. None of the ACRC and Macula 2017 respondents reported completing the online survey. In total, the prioritization surveys we reviewed by 192 health care professionals and 124 of 192 professionals (65%) responded to at least 1 survey question.

There were similarities and differences among participants in the ASRS and ACRC and Macula 2017 cohorts (Table 2). Most respondents were US-based ophthalmologists specializing in the retina, had affiliation with at least one professional society, had experience working on RCTs, used systematic reviews for making treatment decisions, and reported no conflicts of interest. Many ASRS participants (61 of 90 [68%]) were self-employed or in private practice, whereas most ACRC and Macula 2017 participants (22 of 34 [65%]) were affiliated with academic centers. Eleven percent of ASRS participants (10 of 90) reported that 1% to 25%of their patients had AMD compared with 44% of ACRC and Macula 2017 participants (15 of 34); 54% of ASRS participants (49 of 90) reported that 26%to 50% of their patients had AMD compared with 18% of ACRC and Macula 2017 participants (6 of 34). Among ASRS respondents, 57% (51 of 90) were not members of any formal research group compared with 74% of ACRC and Macula 2017 respondents (25 of 34).

Of the 17 tier 1 clinical questions, there was general agreement among respondents from the health care professional groups surveyed (Table 1). Both groups rated all 9 of the tier 1 clinical questions associated with anti-VEGF treatments as high priority. Two additional clinical questions were suggested by survey participants: (1) Which types of drug delivery systems are effective and safe? (2) Which interventions are effective and safe for treating or preventing geographic atrophy?

Of the 836 email addresses in the MD Support forum, 56 patients (7%) accessed the online prioritization survey and 46 of 56 patients (82%) participated in the survey. Half of the patients who responded had wet AMD (Table 3). Of 35 respondents with AMD, most had been diagnosed at least 1 year earlier, were women, were aged 70 years or older, and lived in the United States.

Table 2. Characteristics of the clinical survey respondents

Characteristic	No. (%)	
	ASRS (n = 90)	ACRC and Macula (n = 34)
Area of expertise[a]		
Retina	84 (93)	26 (77)
Anterior segment or cornea	6 (7)	1 (3)
Glaucoma	4 (4)	0
Neuro-ophthalmology	3 (3)	1 (3)
Pediatric ophthalmology	2 (2)	0
Oculoplastics	0	1 (3)
Optometry	1 (1)	1 (3)
General ophthalmology	9 (10)	4 (12)
No response	6 (7)	3 (9)
Type of practice		
Self-employed or private practice	61 (68)	9 (27)
Academic medical center or university	18 (20)	22 (65)
Government hospital or organization	3 (3)	2 (6)
For-profit hospital	2 (2)	1 (3)
No response	6 (7)	0
Country of practice		
United States	63 (70)	28 (82)
Outside the United States	18 (20)	2 (6)
No response	9 (10)	4 (12)
Patients with AMD		
1%-25%	10 (11)	15 (44)
26%-50%	49 (54)	6 (18)
>50%	25 (28)	9 (27)
Do not see patients	0	3 (9)
No response	6 (7)	1 (3)
Primary professional affiliation		
Ophthalmologist	84 (93)	28 (82)
Other	0	5 (15)
No response	6 (7)	1 (3)

Table 2. Continued.

Characteristic	No. (%)	
	ASRS (n = 90)	ACRC and Macula (n = 34)
Professional society affiliations[a]		
ASRS	83 (92)	18 (53)
AAO	77 (86)	24 (71)
ARVO	30 (33)	16 (47)
ASCRS	6 (7)	3 (9)
Macula Society	12 (13)	7 (21)
Other	10 (11)	5 (15)
No response	6 (7)	1 (3)
Research group affiliations		
Cochrane Collaborative	2 (2)	0
DRCRnet	19 (21)	4 (12)
None	51 (57)	25 (74)
No response	19 (21)	5 (15)
Randomized clinical trial experience		
None	14 (16)	13 (38)
At least 1 clinical trial	67 (74)	19 (56)
1-3	8 (9)	6 (18)
4-6	10 (11	2 (6)
≥7	11 (12)	7 (21)
Not specified	37 (41)	4 (12)
If at least 1, level of involvement[a]		
Designed a multisite or single-site randomized clinical trial	10 (11)	7 (21)
Site participant for a multicenter randomized clinical trial	56 (62)	11 (32)
Other	8 (9)	4 (12)
No response	9 (10)	2 (6)
Systematic review publications		
None	54 (60)	23 (68)
At least 1	16 (18)	8 (24)
No response	20 (22)	3 (9)
Use systematic reviews to make treatment decisions		
No	3 (3)	2 (6)
Yes	77 (86)	29 (85)
No response	10 (11)	3 (9)

Table 2. Continued.

Characteristic	No. (%)	
	ASRS (n = 90)	ACRC and Macula (n = 34)
Clinical practice guideline experience		
No	53 (59)	26 (77)
Yes	27 (30)	7 (21)
No response	10 (11)	1 (3)
Potential conflicts of interest relevant to AMD research		
No	71 (79)	32 (94)
Yes	7 (8)	1 (3)
No response	12 (13)	1 (3)
Sex		
Male	76 (84)	24 (71)
Female	4 (4)	9 (27)
No response	10 (11)	1 (3)
Decade of birth		
1950s or earlier	27 (30)	10 (29)
1960s	26 (29)	4 (12)
1970s	15 (17)	1 (3)
1980s or later	10 (11)	7 (21)
Race/ethnicity[a]		
White	68 (76)	22 (65)
Other	14 (16)	12 (35)
No response	12 (13)	1 (3)
Hispanic origin		
No	65 (72)	32 (94)
Yes	9 (10)	1 (3)
No response	16 (18)	1 (3)

Abbreviations: AAO, American Academy of Ophthalmology; ACRC, Atlantic Coast Retina Conference; AMD, age-related macular degeneration; ARVO, Association for Research in Vision and Ophthalmology, ASCRS, American Society of Cataract and Refractive Surgery; ASRS, American Society of Retina Specialists; DCRCNet, Diabetic Retinopathy Clinical Research Network.

[a]Multiple answers allowed; total percentages may not add to 100.

Table 3. Characteristics of patient survey respondents

Characteristic	MD Support (n = 46), No. (%)
AMD diagnosis	
Yes	35 (76)
Dry (nonexudative, nonneovascular) AMD	12 (26)
Wet (exudative, neovascular) AMD	23 (50)
None/no response	11 (24)
Time since AMD diagnosis,[a] years	
<1	3 (7)
1–5	9 (20)
5–10	9 (20)
>10	14 (30)
Sex[b]	
Female	28 (61)
Male	9 (20)
Age, y[b]	
<70	11 (24)
70 to <80	17 (37)
≥80	9 (20)
Race/ethnicity[b,c]	
White	37 (80)
American Indian or Alaska Native	1 (2)
Hispanic origin[b]	
No	37 (80)
Yes	0
Country of residence[b,c]	
United States	35 (76)
Outside the United States	7 (15)
Highest level of education[b]	
No 4-y college degree	11 (24)
Bachelor's degree	14 (30)
Graduate or professional degree	12 (26)

Characteristic	MD Support (n = 46), No. (%)
Participation in a randomized clinical trial[d]	
None	31 (67)
At least 1	5 (11)
Use systematic reviews to make treatment decisions[d]	
No	14 (30)
Yes	18 (39)
Not sure	4 (9)

Abbreviation: AMD, age-related macular degeneration.
[a]No response for 11 of 46 survey participants.
[b]No response for 9 of 46 survey participants.
[c]Multiple answers allowed; total percentages may add to more than 100.
[d]No response for 10 of 46 survey participants.

Table 4. Prioritization of patient-important outcomes for research in age-related macular degeneration (AMD)

Clinical Outcomes Categorized by Members of MD Support	No. (%)			
	Highly Important	Moderately Important	Least Important	Unsure (No Judgment)
Cataract	8 (33)	9 (38)	4 (17)	3 (13)
Choroidal neovascularization[a]	24 (86)	2 (7)	1 (4)	1 (4)
Copper deficiency anemia[b]	0	7 (28)	10 (40)	8 (32)
Cornea problems	12 (52)	4 (17)	4 (17)	3 (13)
Cosmetic effects (eg, yellowing of skin)[b]	0	3 (13)	19 (79)	2 (8)
Death	12 (48)	2 (8)	6 (24)	5 (20)
Depression[b]	3 (13)	13 (57)	6 (26)	1 (4)
Development of advanced AMD[a]	24 (83)	4 (14)	1 (3)	0
Development of blind spots	14 (50)	10 (36)	4 (14)	0
Eye bleeding or discharge	11 (50)	7 (32)	2 (9)	2 (9)
Eye pain	7 (28)	12 (48)	4 (16)	2 (8)
Falls[b]	2 (9)	9 (39)	7 (30)	5 (22)
Gain of vision[a]	19 (70)	5 (19)	2 (7)	1 (4)
Hemorrhage in the retina or inside of the eye[a]	20 (74)	7 (26)	0	0

Clinical Outcomes Categorized by Members of MD Support	No. (%)			
	Highly Important	Moderately Important	Least Important	Unsure (No Judgment)
Hospitalizations[b]	2 (9)	9 (39)	7 (30)	5 (22)
Increased intraocular pressure	11 (50)	9 (41)	2 (9)	0
Increased sensitivity to light	5 (20	15 (60	5 (20	0
Inflammation of the eye	5 (21)	13 (54)	2 (8)	4 (17)
Lung cancer among current and former smokers[b]	2 (7)	7 (26)	8 (30)	10 (37)
Eye pain	7 (28)	12 (48)	4 (16)	2 (8)
Near vision tasks such as reading	11 (44)	11 (44)	3 (12)	0
Patient independence	7 (28)	12 (48)	4 (16)	2 (8)
Quality of life (eg, activities of daily living)	11 (42)	11 (42)	4 (15)	0
Retinal pigment epithelium rips (tears)	9 (38)	6 (25)	4 (17)	5 (21)
Retinal scarring	16 (67)	3 (13)	3 (13)	2 (8)
Retinal thickness	7 (29)	7 (29)	1 (4)	9 (38)
Serious ocular adverse events (eg, endophthalmitis[a])	19 (76)	3 (12)	1 (4)	2 (8)
Serious systemic adverse events (eg, stroke, heart attack)	14 (52)	4 (15)	4 (15)	5 (19)
Traumatic injury to the lens	8 (32	5 (20	4 (16)	8 (32)
Vision loss[a]	21 (72)	4 (14)	2 (7)	2 (7)
Visual acuity	13 (57)	6 (26)	4 (17)	0
Visual function	16 (64)	4 (16)	5 (20)	0
Visual hallucination (eg, Charles Bonnet syndrome)[b]	2 (8)	8 (33)	8 (33)	6 (25)
Vitreous floaters	2 (8)	11 (46)	10 (42)	1 (4)

Abbreviation: MD, macular degeneration.

[a] The outcome was rated "most important" by at least 70% of respondents.

[b] The outcome was rated "most important" by fewer than 15%of respondents.

Participants from MD Support rated all 17 tier 1 clinical questions as high priority (Figure), with 12 of 17 questions given a median score of 10 (eAppendix2 in the Supplement). Survey participants suggested 4 additional clinical questions that were not included in the survey:

1. Is gene therapy (or stem cell therapy) effective in treating AMD?
2. Is the intraocular miniature telescope an effective treatment for AMD?
3. Are cholesterol-lowering diets effective in preventing or reducing AMD-related drusen?
4. What types of education improve living with AMD (eg, online support groups, communication with health care professionals)?

Six of 33 outcomes were identified as most important: choroidal neovascularization, development of advanced AMD, any retinal hemorrhage occurring with choroidal neurovascularization, gain of vision, vision loss, and serious ocular events (eg, endophthalmitis). Eight outcomes were scored as not highly important: copper deficiency anemia, cosmetic effects (eg, yellowing of skin), depression, falls, hospitalizations, lung cancer among smokers, visual hallucination, and vitreous floaters (Table 4). No additional outcomes were suggested by survey participants.

DISCUSSION

The results of this priority-setting study suggest that research related to anti-VEGF treatments for AMD remains a key area of interest for multiple stakeholder groups. Nine of 17 highly important clinical questions identified by the AAO Retina/Vitreous Panel were associated with aspects of anti-VEGF treatments, all of which were rated as high priority by all prioritization survey cohorts. Previous research evaluating the reliability of systematic reviews of interventions for AMD also showed that anti-VEGF agents were the most common treatment modality evaluated by systematic reviewers.[12] Although many high-quality RCTs and systematic reviews have addressed the effectiveness and safety of intravitreous anti-VEGF injections for AMD, new questions have emerged now that they have become the standard of care for neovascular AMD, concerning how frequently injections should be administered, the long-term (≥10years) effects of these injections, and other possible drug delivery options.

Health care professionals and patients rated clinical questions addressing both effectiveness and safety as highly important. Furthermore, the highly important outcomes identified by patients in this study were balanced between intended effects of AMD treatment (eg, slowing vision loss) and adverse events (eg, retinal hemorrhage). This balance suggests research that examines potential benefits and harms together (eg, trade-off analysis) as an area for future investigation.

Methodologic Considerations

In this study, we evaluated a single method for prioritizing clinical research; another method may have led to other topics given priority. A priority-setting project in the United Kingdom that used a focus group format identified 29 priority questions related to AMD.[19] However, their questions included question types not limited to treatment, such as "What is the cause of AMD?" and questions too broad for an RCT to address, such as "Can a treatment to stop dry AMD progressing and/or developing into the wet form be devised?" Our project was designed to include and prioritize only clinical questions for specific treatments.

As part of the study design, we asked the AAO Retina/Vitreous Panel to narrow the list of 70 clinical questions that we identified to a shortened list of highly important (tier 1) clinical questions. The rationale was to reduce the number of clinical questions for the larger groups to prioritize. However, even with a shortened survey, the response rate was low for all groups surveyed.

Patients rated all 17 clinical questions identified as highly important by the AAO Retina/Vitreous Panel as high priority, compared with 12 of 17 rated as high priority by both health care professional groups. When asked to rank the importance of outcomes by allocating outcomes into 1 of 4 categories, patients distinguished 6 highly important outcomes and 8 not so important outcomes among 33 outcomes assessed. Other patient-focused research has shown that patients tend to score all items as high priority when using rating scales, such as Likert scales.[20] For prioritization research, asking participants to rank items rather than rating them independently may elicit clear patient preferences.

We identified at least 12 high-priority clinical research questions. Survey participants suggested additional areas of interest, such as alternative drug delivery systems, interventions for treating or preventing geographic atrophy, and effects of gene therapy. In a 2015 study of evidence used to underpin clinical practice guidelines, reliable systematic reviews were cited to support 15 of 35 treatment recommendations in the 2015 AAO PPP for AMD.[12] Nine of the high-priority clinical questions identified by this prioritization project map to the 15 treatment recommendations with reliable systematic reviews available, suggesting that even with existing high-quality evidence, some uncertainty may remain as to whether a clinical question has been answered. For the remaining 8 highly important clinical questions identified by the AAO Retina/Vitreous Panel, no reliable systematic review had been identified, suggesting research areas with evidence gaps.

Limitations

A potential limitation to our framework is that we derived our initial set of clinical questions from clinical practice guidelines concurrently with the request for new clinical questions. Although evidence-based clinical practice guidelines may reflect the current state of prevention, screening and therapy from multiple stakeholder groups,[4] they may not anticipate new treatments or areas of research. To address this issue, we consulted with members of the AAO Retina/Vitreous Panel to add relevant clinical questions to our initial set and provided survey participants opportunities to suggest additional research questions at each stage of the process.

CONCLUSIONS

The 6 highly important outcomes targeted by patients should be considered in the discussion of core outcome sets for studies that evaluate the treatment of AMD. Choroidal neovascularization and visual acuity are outcomes that have been noted frequently in outcome research related to AMD; however, retinal hemorrhage has been considered less frequently by clinicians and researchers.[17,21,22] While we cannot assume that patients understand the AMD process, all patient participants were members of MD Support, an education-oriented support community for individuals with AMD. Further research could survey AMD patients more generally to see if there are different priorities or outcome concerns based on different levels of understanding of AMD.

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ADDITIONAL FILES

Supplementary materials

Appendix 1. Study Protocol

Research Aims:

The overall aim of this study is to test a framework for setting priorities for systematic reviews and RCTs related to treatment of age-related macular degeneration (AMD). In this study, we will translate statements in the American Academy of Ophthalmology (AAO) clinical practice guideline for management of AMD into answerable clinical questions and map the questions to existing, reliable systematic reviews. We will partner with clinical practice guideline developers, retina experts, healthcare professionals, and patients to prioritize a research agenda for AMD.

By identifying and assessing the available evidence, and the important clinical questions, we aim to provide reliable information to clinicians, researchers, and policymakers; identify where evidence gaps exist; and prioritize important clinical questions for research to answer.

Methods:

1) Extraction of guideline recommendations

Two individuals will independently review and extract every statement that could be considered a recommendation, published in the AAO's Preferred Practice Patterns (PPPs) related to the management of AMD (AAO 2015). We will restate each recommendation as an answerable clinical question. We will consult with AMD specialists who have expertise both in the management of AMD and in forming answerable clinical questions to confirm that our restatements are accurate. The restated clinical questions will constitute a preliminary list of priorities for systematic reviews and clinical trials to address. We will refine this list in subsequent cross-sectional surveys.

2) Survey to identify highly important clinical questions: Survey of the American Academy of Ophthalmology Retina/Vitreous Panel

The purpose of surveying the AAO Retina/Vitreous Panel will be to identify highly important clinical questions to be prioritized. Initial discussions with professional associations and patient groups suggested that their membership would be more likely to respond and complete the surveys if the number of questions could be reduced so that the survey could be completed in 15 minutes or fewer. Members of the AAO Retina/Vitreous Panel will score all clinical questions derived in the first step and we will use their responses to form the shortened list of highly important clinical questions to be prioritized.

We will conduct a two-round web-based cross-sectional modified "Delphi" consensus survey (Custer 1999). We will ask survey participants electronically, using email and the Internet, to score the list of research questions we derived from the AAO's PPP on the management of AMD. The invitation to participate will be sent by an AAO designee and will include the consent to participate (see "Description of the Consent Process"). We will ask participants to score each clinical question on a scale of 0 to 10, with a score of 10 indicating that they view the clinical question as highly important; a score of 0 indicates that they view the clinical question as not important at all. If the participant feels unqualified to rate a particular clinical question, they may select 'no judgment'. There will be space for comments, questions and nomination of items not included in the list. Respondents will be given 4 weeks total to respond to Round One of the survey. After the initial request, an email reminder will be sent at the end of week 1, week 2, week 3, and 2 days prior to the end of week 4.

In Round Two of the survey we will provide each respondent with the group summary measure (median) for each clinical question asked in Round One and ask the Panel to score additional clinical questions suggested by respondents in Round One. Respondents will be given the opportunity to re-score each item in light of ratings and comments from the previous round. Respondents will be given 4 weeks total to respond to this round of the survey. After the initial request, an email reminder will be sent at the end of week 1, week 2, week 3, and 2 days prior to the end of week 4.

The highest scored clinical questions will represent the highly important clinical questions to be prioritized. We will include the highest scored 10-15 clinical questions, with median scores of at least 7 or higher, in the prioritization surveys. Lower scored clinical questions, considered as moderately important (median at least 4) or not important (median less than 4), will not be included in the prioritization surveys.

3) Survey of healthcare professionals to prioritize clinical questions: Survey of the American Society of Retina Specialists

Using the survey results from the AAO Retina/Vitreous Panel, we will ask members of the American Society of Retinal Specialists (ASRS) to prioritize the order in which the highly important clinical questions should be answered.

The invitation to participate in the survey will be sent by an ASRS designee and will include the consent to participate (see "Description of the Consent"). We will ask participants to score each clinical question on a scale of 0 to 10, with a score of 10 indicating that they view the clinical question as high priority; a score of 0 indicates that they view the clinical question as not a priority. If the participant

feels unqualified to score a particular clinical question, they may select 'no judgment'. There will be space for comments, questions and nomination of items not included in the list. Respondents will be given 4 weeks total to respond to the survey. After the initial request, an email reminder will be sent at the end of week 1, week 2, week 3, and 2 days prior to the end of week 4.

Additionally, we will request survey participants to provide demographic and other information such as occupation/field, specialty, and place of employment (e.g. government, industry, academia, other), experience in clinical trials/systematic reviews (see draft survey). These data will be examined for possible association with the level of importance assigned if sufficient data are available. We will not collect identifiable data and expect that all responses will remain anonymous.

4) Survey of patients to prioritize clinical questions and outcomes: Survey of MD Support
We will ask members of MD Support (www.mdsupport.org), an online patient group for macular degeneration, to prioritize the order in which the highly important clinical questions should be answered by research. The clinical questions will be reworded to lay language, in collaboration with the Director of MD Support, and we will include definitions of clinical terms to make the survey questions clear to nonhealthcare professionals. Additionally, we will ask for their assistance in identifying patient-important outcomes for systematic reviews and RCTs related to management of AMD. We will derive the list of outcomes for patients to assess from common outcomes assessed in research related to AMD (Saldanha 2014). We will ask each survey participant demographic and other information, such as having early or advanced stage AMD (i.e. advanced stage = previously received laser or injections in the eye to treat AMD).

5) Sample size

a. Survey of the American Academy of Ophthalmology's Retina/Vitreous Panel
   The size of the AAO Retina/Vitreous Panel varies from 6 to 8 individuals. Because this effort has full collaboration with the AAO, we estimate that all active Panel members will participate in each of the two rounds of the survey.
b. Survey of the American Society of Retina Specialists
   We aim to invite about 400 ASRS members. We estimate that a minimum of 25% will participate in the online surveys.
c. Survey of patient and consumer panels
   MD Support's online forum consists of about 400 members. We will invite all members with active email addresses to participate in the online survey and estimate that a minimum of 25% with AMD will participate in the online survey.

6) Analysis and Reporting

a. Statistical Plan
   We will calculate summary statistics (mean, standard deviation, median, and inter-quartile range) of scores for each clinical question for each survey. We will compare scores by groups of stakeholders, for example healthcare professionals versus patients.
b. Dissemination
   We will report our results in a journal article as well as other methods of dissemination (email to survey partners, Twitter, etc.). We will assess the utility of the project by obtaining feedback from CEV editors and authors conducting systematic reviews.

7) Ethical considerations (IRB #2709; exemption status)

a. Inclusion and Exclusion Criteria
   The inclusion criterion is to be a member of the respective group that is being asked to complete each specific survey (AAO Retina/Vitreous Panel, ASRS, or MD Support). Consumer patient stakeholders from MD Support will have self-reported AMD or care for a person with AMD to be eligible for analysis.
b. Gender, Age and Locale
   We will not exclude participants on the basis of gender, age, or nationality.
c. Recruitment Process
   For all surveys, our collaborating partners (AAO, ASRS, and MD Support) will invite participation by email.
d. Risk/Benefits
   Description of Risks: There is no foreseeable physical risk to survey participants. Participation in the survey may involve a loss of privacy and a commitment of time.
   Description of Measures to Minimize Risks: We will pilot test each round of the survey to provide participants with an estimate of the time it will take to complete. We will ensure participant anonymity and confidentially of responses. Only survey moderators will have access to the anonymous individual survey results. We will report results in an aggregate form without personal identifiers (see "Confidentiality Assurance").
   Description of Potential Benefits: By providing their opinions on the importance of a series of clinical questions about AMD, survey participants will contribute to establishing a framework for setting priorities for new systematic reviews and RCTs.
   Description of Level of Research Burden: We anticipate that the time commitment for each survey will vary, decreasing with each round. No survey should take more than 30 minutes to complete.

e. Compensation
   There will be no monetary compensation for participating in any survey, although each group participating will be thanked and acknowledged in publications and on the CEV website.
f. Description of the Consent Process
   For all surveys, the initial invitation will contain a description of the research we are conducting. Invitees will be given a total of 4 weeks to consider whether they will participate. An email reminder will be sent at the end of each of the 4 weeks that the survey is active. We will consider a response to the survey as evidence of consent to participate. We will consider the invitee as declining participation if s/he sends a declining email or if s/he does not respond to the survey after four weeks.
g. Data Security
   All survey invitations and reminders will be sent by the partnering groups; none by CEV.
   CEV will not solicit the contact information of members from our partner groups; however, email, mail, or phone correspondence from a survey participant to CEV moderators may include information that would enable the moderators to know who the participant is. In any case, participant names will not be used on any survey instrument or data file. We will report results in an aggregate form without personal identifiers.
   We will store paper forms in an office building that has very good external security (615 N. Wolfe Street Baltimore, MD 21205). The building has a 24-hour manned security desk, and photo ID is required to get in. We will store the electronic data file on a password-protected server. We will back up data files on a regular basis with a CD-ROM version stored off-site.

8) Protocol amendments

In August 2016, after receiving the Panel's Round 2 survey responses, we increased the number of highly important clinical questions to be prioritized from 10-15 to 17 based on the median score of 7 or higher.

In December 2016, after observing low response rates to the online surveys, we decided to survey another group of healthcare professionals to increase the absolute number of respondents. We printed paper copies of the prioritization surveys and distributed them at the registration table during the Atlantic Coast Retina Conference and Macula meetings held in Baltimore, Maryland in January 2017.

9) References

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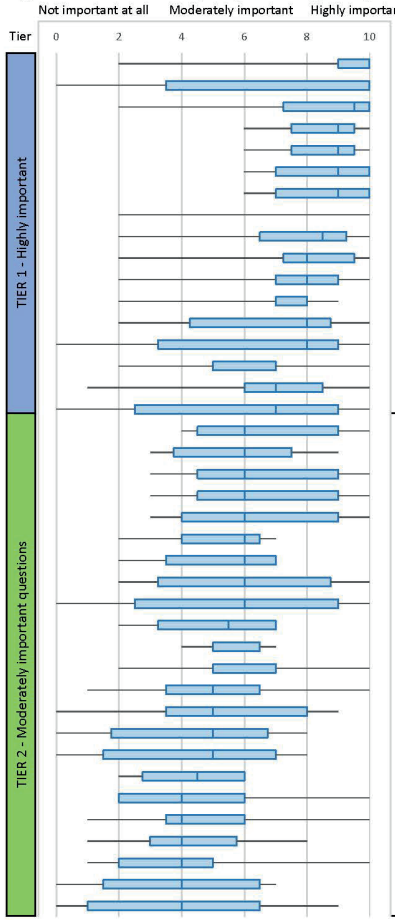
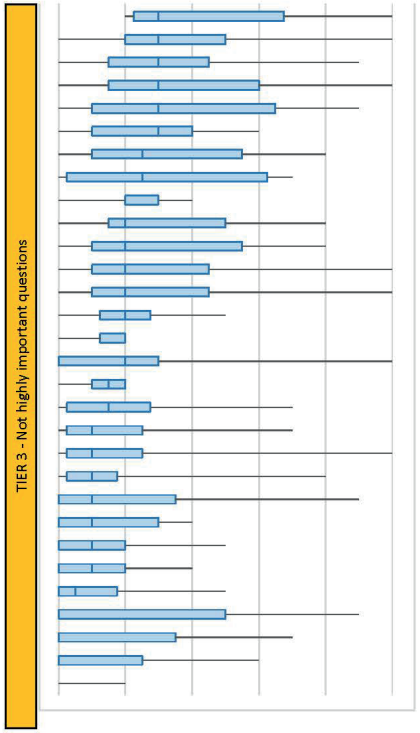
Appendix 2. American Academy of Ophthalmology Retina/Vitreous Panel scoring of importance of clinical questions related to the treatment of age-related macular degeneration (AMD)

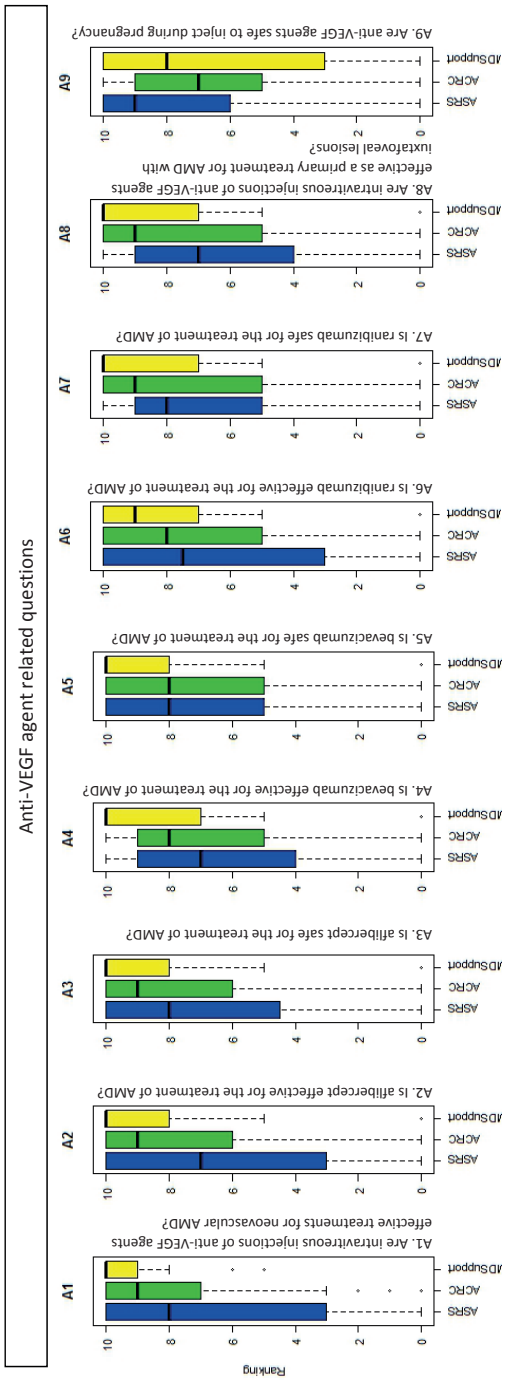


	Clinical question
1	Is aflibercept effective for the treatment of AMD?
2	Are intravitreous injections of anti-VEGF agents effective treatments for neovascular AMD?
3	Is ranibizumab effective for the treatment of AMD?
4	Is long-term supplementation with high-dose antioxidants safe for the general patient with AMD?
5	Is long-term supplementation with high-dose antioxidants safe for smokers with AMD?
6	Are antioxidant vitamin and mineral supplements an effective treatment for intermediate AMD?
7	Are antioxidant vitamin and mineral supplements an effective treatment for advanced AMD in only one eye?
8	Is aflibercept safe for the treatment of AMD?
9	Is ranibizumab safe for the treatment of AMD?
10	Is self-monitoring by patients at high-risk effective in preventing progression of advanced AMD?
11	Is bevacizumab effective for the treatment of AMD?
12	Is bevacizumab safe for the treatment of AMD?
13	Is surgery for cataracts in people with AMD safe?
14	Does avoiding sunlight after verteporfin photodynamic therapy prevent or reduce photosensitivity reactions?
15	Are anti-VEGF agents safe to inject during pregnancy?
16	Does smoking cessation prevent progression of AMD?
17	Are intravitreous injections of anti-VEGF agents effective as a primary treatment for AMD with juxtafoveal lesions?
18	Does the effectiveness of anti-VEGF agents differ by agent, treatment regimen or the combination of agent and treatment regimen?
19	Is verteporfin photodynamic therapy effective for polypoidal choroidal vasculopathy?
20	Are intravitreous injections of anti-VEGF agents for AMD safe in terms of acute inflammation?
21	Are intravitreous injections of anti-VEGF agents for AMD safe systemically (i.e., cardiovascular events)?
22	Are intravitreous injections of anti-VEGF agents for AMD safe overall?
23	Are zinc supplements for AMD safe?
24	Are implantable miniature telescopes (IMT) for vision loss due to end-stage AMD effective?
25	Are antioxidant vitamin and mineral supplements an effective treatment for patients who have less than intermediate AMD?
26	Are intravitreous injections of anti-VEGF agents for AMD safe for the eye (i.e., endophthalmitis, infection)?
27	Do omega 3 fatty acids prevent or slow the progression of AMD?
28	Is vitamin E supplementation above the AREDS levels safe in patients with AMD?
29	Are intravitreous injections of anti-VEGF agents more effective than laser photocoagulation for extrafoveal neovascular lesions?
30	Is observation without medicine, surgery or repeat testing an effective treatment strategy for advanced AMD with bilateral disciform scars?
31	Is thermal laser photocoagulation surgery an effective treatment for AMD with juxtapapillary CNV?
32	Is verteporfin photodynamic therapy effective for patients with AMD who are pregnant or breast-feeding?
33	Is submacular surgery (e.g., vitrectomy) an effective treatment for AMD with large submacular hemorrhage?
34	Are intravitreous injections of anti-VEGF agents effective treatments for polypoidal choroidal vasculopathy (PCV)?
35	Does genetic testing improve the effectiveness of interventions used to treat AMD?
36	Is observation without medicine, surgery or repeat testing an effective treatment strategy for advanced AMD with bilateral subfoveal geographic atrophy or disciform scars?
37	Are complement inhibitors effective for AMD?
38	Is observation without medicine, surgery or repeat testing an effective treatment strategy for asymptomatic non-neovascular AMD?
39	Are intravitreous injections of corticosteroids for AMD safe?
40	Are intravitreous injections of corticosteroids an effective treatment for AMD?



41 Is aspirin safe to use in patients being treated for AMD?
42 Is thermal laser photocoagulation surgery for AMD safe?
43 What is the incidence of a new scotoma or enlargement of a pre-existing scotoma with or without visual acuity loss after thermal laser photocoagulation surgery for AMD?
44 Is radiotherapy (e.g., with strontium) an effective treatment for AMD?
45 Is thermal laser photocoagulation surgery an effective treatment fornew extrafoveal classic CNV?
46 How long does thermal laser surgery for AMD prevent recurrence, persistence or new choroidal neovascularization (CNV)?
47 Is radiotherapy (e.g., with strontium) for AMD safe?
48 Is verteporfin photodynamic therapy safe for patients with AMD who are pregnant or breast-feeding?
49 Is verteporfin photodynamic therapy effective for treating juxtafoveal CNV in AMD?
50 Is verteporfin photodynamic therapy combined with pharmacologic therapy an effective treatment for AMD?
51 Is the combination of intravitreous injections of anti-VEGF agents with other treatments (e.g., transpupillary thermotherapy) more effective than anti-VEGF agents alone for advanced AMD?
52 Is verteporfin photodynamic therapy effective for occult CNV when PDT with vision 20/50?
53 Is verteporfin photodynamic therapy effective for new or recurrent subfoveal CNV where the classic component is >50% of the lesion and the entire lesion is <=5400 microns in greatest linear diameter?
54 Is adjunctive use of intravitreous injections of corticosteroids with verteporfin photodynamic therapy an effective treatment for AMD?
55 Is acupuncture an effective treatment for AMD?
56 Is verteporfin photodynamic therapy safe for the general patient with AMD?
57 Is electrical stimulation an effective treatment for AMD?
58 Is verteporfin photodynamic therapy safe for patients with AMD and liver dysfunction?
59 Is macular translocation surgery for AMD safe?
60 Is macular translocation surgery an effective treatment for AMD?
61 Is verteporfin photodynamic therapy effective for patients with AMD and liver dysfunction?
62 Is interferon for advanced AMD safe?
63 Is verteporfin photodynamic therapy effective for the general patient with AMD?
64 Is thermal laser photocoagulation surgery a more or similarly effective treatment than intravitreous injections of anti-VEGF agents for subfoveal CNV in AMD?
65 Is rheopheresis for advanced AMD safe?
66 Is rheopheresis an effective treatment for advanced AMD?
67 Is thermal laser photocoagulation surgery an effective treatment for recurrent extrafoveal classic CNV?
68 Are intravitreous injections of anti-VEGF agents effective treatments for the general patient with AMD?
69 Is interferon an effective treatment for advanced AMD?
70 Is thermal laser photocoagulation surgery an effective treatment for the general patient with AMD?

Appendix 3. Results of prioritization of Tier 1 clinical questions (n=17) by healthcare professionals and patients



Antioxidant related questions
Other treatment modality related questions
Ranking
A10
A10. Are antioxidant vitamin and mineral supplements an effective treatment for intermediate AMD?
A11
A11. Are antioxidant vitamin and mineral supplements an effective treatment for advanced AMD in only one eye?
A12
A12. Is long-term supplementation with high-dose antioxidants safe for the general patient with AMD?
A13
A13. Is long-term supplementation with high-dose antioxidants safe for smokers with AMD?
A14
A14. Does smoking cessation prevent progression of AMD?
A15
A15. Is self-monitoring by patients at high-risk effective in preventing progression of advanced AMD?
A16
A16. Does avoiding sunlight after verteporfin photodynamic therapy prevent or reduce photosensitivity reactions?
A17
A17. Is surgery for cataracts in people with AMD safe?
ASRS
ACRC
AUSupport
0
2
4
6
8
10

CHAPTER 4

Comparison of clinical trial and systematic review outcomes for the 4 most prevalent eye diseases

Ian J Saldanha
Kristina Lindsley
Diana V Do
Roy S Chuck
Catherine Meyerle
Leslie S Jones
Anne L Coleman
Henry D Jampel
Kay Dickersin
Gianni Virgili

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ABSTRACT

Importance:
Suboptimal overlap in outcomes reported in clinical trials and systematic reviews compromises efforts to compare and summarize results across these studies.

Objective:
To examine the most frequent outcomes used in trials and reviews of the 4 most prevalent eye diseases (age-related macular degeneration [AMD], cataract, diabetic retinopathy [DR], and glaucoma) and the overlap between outcomes in the reviews and the trials included in the reviews.

Design, setting, and participants:
This cross-sectional study examined all Cochrane reviews that addressed AMD, cataract, DR, and glaucoma; were published as of July 20, 2016; and included at least 1 trial and the trials included in the reviews. For each disease, a pair of clinical experts independently classified all outcomes and resolved discrepancies. Outcomes (outcome domains) were then compared separately for each disease.

Main outcomes and measures:
Proportion of review outcomes also reported in trials and vice versa.

Results:
This study included 56 reviews that comprised 414 trials. Although the median number of outcomes per trial and per review was the same (n = 5) for each disease, the trials included a greater number of outcomes overall than did the reviews, ranging from 2.9 times greater (89 vs 30 outcomes for glaucoma) to 4.9 times greater (107 vs 22 outcomes for AMD). Most review outcomes, ranging from 14 of 19 outcomes (73.7%) (for DR) to 27 of 29 outcomes (93.1%) (for cataract), were also reported in the trials. For trial outcomes, however, the proportion also named in reviews was low, ranging from 19 of 107 outcomes (17.8%) (for AMD) to 24 of 89 outcomes (27.0%) (for glaucoma). Only 1 outcome (visual acuity) was consistently reported in greater than half the trials and greater than half the reviews.

Conclusions and relevance:
Although most review outcomes were reported in the trials, most trial outcomes were not reported in the reviews. The current analysis focused on outcome domains, which might underestimate the problem of inconsistent outcomes. Other important elements of an outcome (ie, specific measurement, specific metric, method of aggregation, and time points) might have differed even though the domains overlapped. Inconsistency in trial outcomes may impede research synthesis and indicates the need for disease-specific core outcome sets in ophthalmology.

BACKGROUND

Outcomes are measures or events used to assess the effectiveness and/or safety of clinical interventions.[1] In clinical trials and systematic reviews, researchers use outcomes as a basis for conclusions about whether interventions being tested will be effective and safe.

Worldwide, the 4 most prevalent eye diseases are age-related macular degeneration (AMD), cataract, diabetic retinopathy (DR), and glaucoma.[2] To improve the conditions of patients with these diseases, clinicians and patients should use evidence from trials and reviews to identify effective and safe interventions and treatment strategies. Determining which interventions and treatment strategies are the most effective and safe involves making comparisons across trials and reviews. However, suboptimal overlap in outcomes among these studies[3–5] compromises such comparisons. A systematic review[6] has documented the problem of inconsistency in outcome use in various fields.

An example of this problem in ophthalmology was demonstrated in a Cochrane review[7] of trials that compared nonsteroidal anti-inflammatory drugs with corticosteroids for controlling inflammation after uncomplicated cataract surgery. Although the review authors[7] included 48 trials, none of the trials reported data for the review's prespecified primary outcome: proportion of patients with intraocular inflammation at 1-week follow-up after surgery. Modifying the outcome to include mean amount of inflammation at 1-week follow-up would have allowed only 7 trials to be eligible. Including other follow-up time points would have allowed only 4 additional studies to be eligible.[7] Studies have demonstrated that inconsistent outcome use is also a problem in AMD,[8] glaucoma,[9] uveitis,[10] allergic conjunctivitis,[11] and intermittent exotropia.[12]

Inconsistent outcome use is also a problem in reviews in ophthalmology. A previous study[3] examined all Cochrane reviews that addressed the 4 most prevalent eye diseases and found that researchers who evaluated interventions for the same disease considered different outcomes to be important, and when researchers considered the same outcome to be important, they usually used different measurements or analyzed the data differently or at different time points. Similarly, Ismail and colleagues[13] identified inconsistency in outcomes examined in reviews that addressed glaucoma.

Our goal was to assess the extent of overlap in outcomes in reviews of the 4 most prevalent eye diseases and in the trials included in the reviews. Specifically, for each disease, our objectives were to examine the most frequent outcomes used in trials and reviews and the overlap between outcomes in the reviews and the trials included in the reviews.

METHODS

In the present study, we identified the current versions of all Cochrane reviews that addressed AMD, cataract, DR, and glaucoma. We compared the outcomes in these reviews with the outcomes reported in the trials included in the reviews.

Definition of Outcomes

A completely specified outcome includes 5 elements: domain, specific measurement, specific metric, method of aggregation, and time points of interest.[3,14] We focused on the domain (eg, visual acuity, intraocular pressure). An example would be that measuring visual acuity using the Snellen chart or the Early Treatment Diabetic Retinopathy Study chart pertains to the outcome domain visual acuity. Similarly, we counted an outcome reported at multiple timepoints as pertaining to a single outcome domain. We classified outcome domains as specifically as possible (eg, we considered photopic contrast sensitivity and mesopic contrast sensitivity as 2 separate outcome domains).

Reviews Examined and Data Abstracted From Reviews

We included all Cochrane reviews that addressed at least 1 of the 4 most prevalent eye diseases (AMD, DR, glaucoma, and cataract) and were published by Cochrane Eyes and Vision in the Cochrane Database of Systematic Reviews as of July 20, 2016. Because we were interested in the overlap in review and trial outcomes, we restricted this study to completed reviews (ie, we excluded reviews in the protocol stage) that included at least 1 trial (ie, we excluded reviews that did not include any studies, the so-called empty reviews). We assessed the overlap in outcomes within subgroups defined by disease. For each review, we abstracted all outcomes reported in the Methods section irrespective of whether they were also presented in the Results section.

Trials Examined

We examined each trial that each eligible review included if the trial (1) compared at least 2 groups to which participants were randomly allocated and (2) was published as a peer-reviewed journal article (ie, we excluded conference abstracts).For each trial, we identified 1 journal article defined by the review authors as that trial's primary publication, as conventionally indicated by an asterisk next to the citation information in the References to Studies Included in this Review section of Cochrane reviews.

Data Abstraction From Trials

We developed a data abstraction form in the Systematic Review Data Repository (https://srdr.ahrq.gov), an open repository of review data.[15,16] We conducted a pilot test of the form by using 10 trials and 10 reviews. The form included check-box items for predefined outcomes and free-text items for additional outcomes not previously identified. Two of us (I.J.S., K.L.) and a Cochrane eyes and vision methodologist (Sueko Ng, MHS) conducted data abstraction; 2 individuals independently abstracted data from each trial and review, resolving discrepancies through discussion.

From each trial's primary publication, we abstracted all outcomes for which results were reported. We defined results as any quantitative data, including from statistical testing, that compared 2 or more interventions for efficacy or safety after trial baseline reported anywhere in the article's text, tables, or figures.

Classification of Outcomes

We classified outcomes into specific domains by using a 2-step process. In step1, the outcomes in the trials and reviews were initially coded (by 2 of us [I.J.S., K.L.] and Sueko Ng), and a prior classification system of outcomes in Cochrane reviews that addressed the same 4 eye diseases was updated.[3] In step 2, for each disease, 2 clinician coauthors (D.D. and C.M. for AMD, R.S.C. and L.S.J. for cataract, D.V.D. and G.V. for DR, and A.L.C. and H.D.J. for glaucoma) with expertise in that disease verified the initial coding of abstracted outcomes. Within each pair, masked to each other's and to the initial coding, each expert coded the reported outcomes in the trials and reviews. For each reported outcome, the expert (1) coded the outcome as an exact match to an existing outcome in the updated classification system of Saldanha et al[3] or (2) suggested a new outcome to which the outcome pertained. After independent coding by the experts, disagreements were resolved through discussion. We considered the agreed-on classification by the experts as the final classification for each outcome.

Overlap Between Outcomes in Trials and Reviews

For each disease, we adopted the following 3 approaches to examine the overlap of outcomes in trials and reviews. First, we constructed Venn diagrams for the number of outcomes in both trials and reviews and the numbers uniquely in each. Second, we constructed scatterplots of the proportion of trials and the proportion of reviews that examined each outcome (hypothetical scenarios explained in Figure 1). Third, we examined the overlap in the 7 most frequent outcomes in the trials and reviews. We chose 7 because Cochrane recommends including up to 7 outcomes in summary of findings tables in reviews.[17]

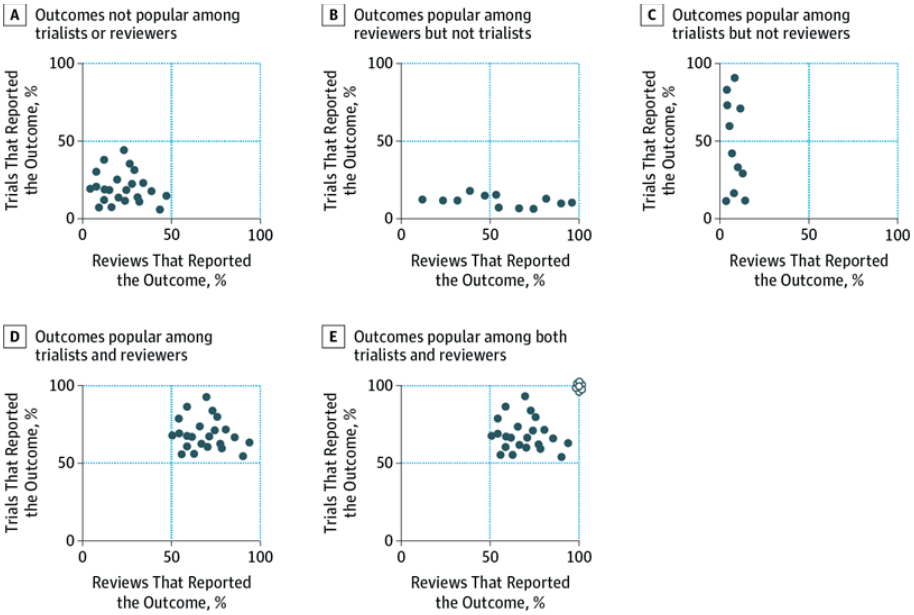

Figure 1. Hypothetical Scenarios Showing Proportion of Trials Reporting and Proportion of Reviews Naming Each Outcome. Each dot refers to 1 outcome. White dots indicate outcomes measured by all trialists and reviewers.

RESULTS

Reviews Examined

Among the 65 Cochrane reviews of AMD, cataract, DR, and glaucoma published as of July 2016, a total of 61 were completed (ie, 4 were in protocol stages), and 56 of these completed reviews included at least 1 trial (eFigure in the Supplement). A total of 54 of the 56 eligible and included reviews (96.4%) were published in 2008 or later (Table 1).

Trials Examined

Overall, the 56 included reviews comprised 445 unique trials. We excluded 31 trials reported only as conference abstracts, thereby including 414 unique trials. Reviews incorporated a median of 5.0 trials each (interquartile range [IQR], 2.0–10.5; range 1.0–60.0). Most trials were in reviews that addressed glaucoma (142 of 414 [34.3%]) or cataract (138 of 414 [33.3%]).

Table 1. Characteristics of the trials and Cochrane reviews examined

Characteristic	No. (%) of Publications	
	Trials (n = 414)	Reviews (n = 56)
Year of publication		
1987 or earlier	16 (3.9)	0
1988–1992	36 (8.7)	0
1993–1997	45 (10.9)	0
1998–2002	99 (23.9)	0
2003–2007	99 (23.9)	2 (3.6)
2008–2012	96 (23.2)	22 (39.3)
2013 or later	23 (5.6)	32 (57.1)
Disease addressed		
Age-related macular degeneration	79 (19.1)	15 (26.8)
Cataract	138 (33.3)	15 (26.8)
Diabetic retinopathy	55 (13.3)	6 (10.7)
Glaucoma	142 (34.3)	20 (35.7)

Outcomes Identified

We identified 262 total unique outcomes in the trials and reviews. Overall, the trials and reviews reported measuring similar numbers of outcomes (trials: median, 5.0 outcomes per trial; IQR, 3.0–8.0; range, 1.0–24.0; reviews: median, 5.0 outcomes per review; IQR, 4.0–6.0; range, 2.0–10.0).

Overlap Analysis for All Outcomes

For each disease, the trials included a greater number of outcomes than did the reviews, ranging from 2.9 times (89 vs 30 outcomes for glaucoma) to 4.9 times greater (107 vs 22 outcomes for AMD) (Figure 2). When considering all outcomes across trials and reviews that addressed a disease, the overlap between the outcomes measured in trials and reviews was limited, ranging from 19 of 110 outcomes (17.3%) (for AMD) to 24 of 95 outcomes (25.3%) (for glaucoma). For review outcomes, most outcomes were also reported in the trials, ranging from 14 of 19 outcomes (73.7%) (for DR) to 27 of 29 outcomes (93.1%) (for cataract). For trial outcomes, the overlap was small, ranging from19 of 107 outcomes (17.8%) (for AMD) to 24 of 89 outcomes (27.0%) (for glaucoma).

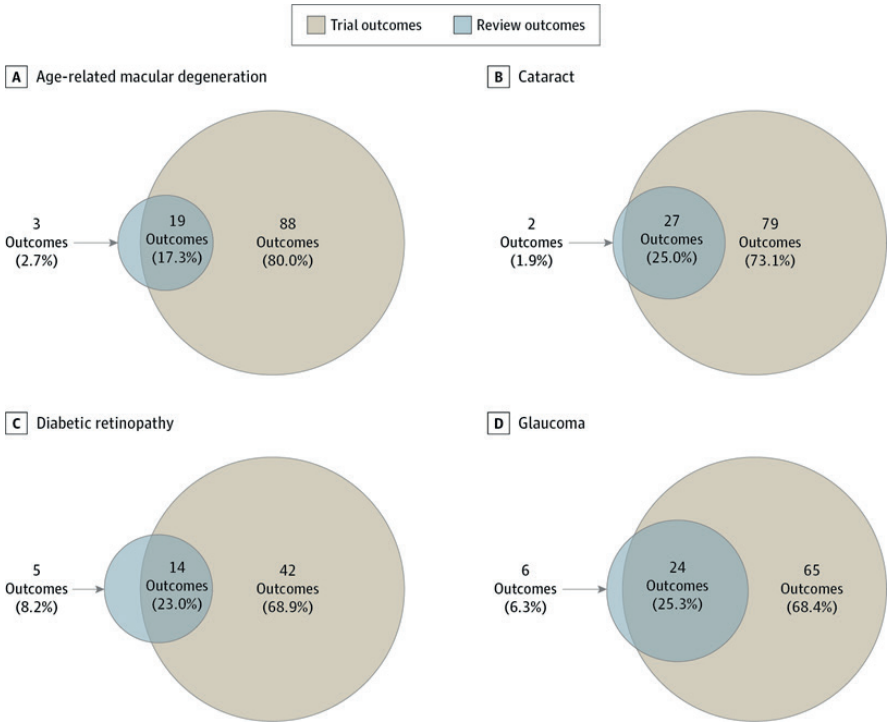

Figure 2. Overlap Between Outcomes in Reviews and Trials by Disease. Outcomes in 15 reviews and 79 trials of age-related macular degeneration (A), 15 reviews and 138 trials of cataract (B), 6 reviews and 55 trials of diabetic retinopathy (C), and 20 reviews and 142 trials of glaucoma (D).

Overlap Analysis for Proportions Reporting Each Outcome

In each scatterplot (Figure 3), most outcomes clustered in the lower left quadrant, indicating that, for each disease, most outcomes were reported in fewer than half the trials and fewer than half the reviews. Across the 4 diseases, only 1 outcome (visual acuity) was consistently named in greater than half the trials and greater than half the reviews.

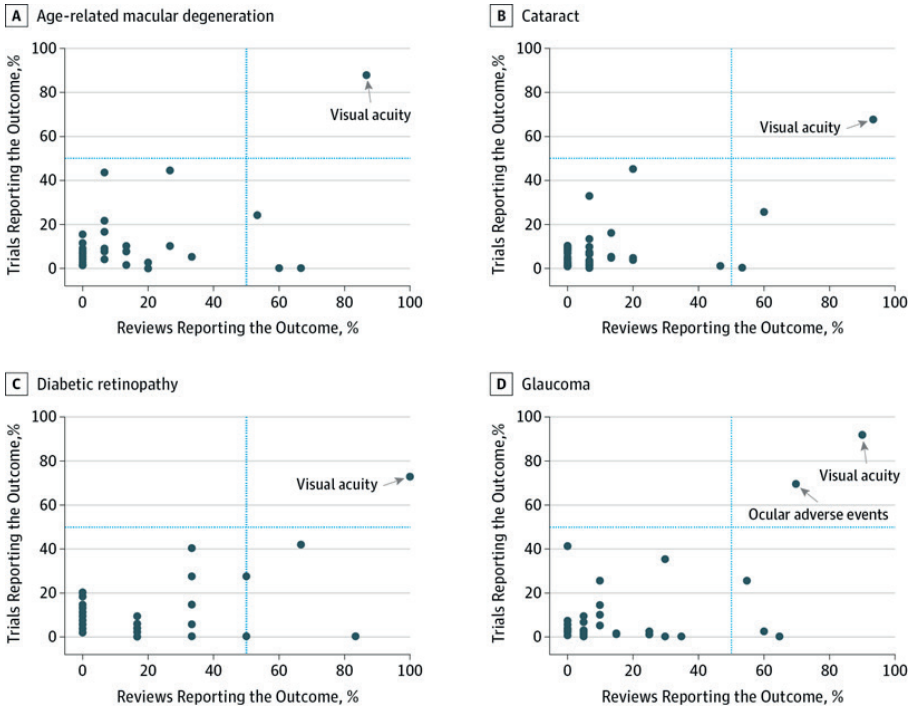

Figure 3. Scatterplot Showing Proportion of Trials Reporting and Proportion of Reviews Naming Each Outcome by Disease. For age-related macular degeneration, 110 outcomes were reported in 79 trials and 15 reviews (A); cataract, 108 outcomes in 138 trials and 15 reviews (B); diabetic retinopathy, 61 outcomes in 55 trials and 6 reviews (C); and glaucoma, 96 outcomes in 142 trials and 20 reviews (D). Each dot refers to 1 outcome.

Overlap Analysis for the 7 Most Frequent Outcomes

For each disease, there was limited overlap in the 7 most frequent outcomes in the trials and reviews, with some noticeable differences (Table 2). For trials and reviews, visual acuity was the most frequent outcome for 3 diseases (AMD, cataract, and DR), whereas for glaucoma, it was among the 7 most frequent outcomes. Ocular adverse events also were among the 7 most frequent outcomes for trials and reviews except for reviews that addressed AMD. Some frequent review outcomes were not often reported in the trials. For example, general quality of life was among the 7 most frequent review outcomes for each disease but never among the 7 most frequent trial outcomes. Similarly, costs were among the 7 most frequent review outcomes for cataract, DR, and glaucoma but not among the 7 most frequent trial outcomes.

Table 2 examines whether certain outcomes may be frequently used by trialists and reviewers. None of the common outcomes were reported in all trials and reviews.

Table 2. Comparison of the 7 most frequent outcomes in trials and reviews by disease.

Most Frequent Outcomes in Trials		Most Frequent Outcomes in Reviews		Overlapping Outcomes Between the Most Frequent Outcomes in Trials and Reviews
Outcome	**Trials, No. (%)**	**Outcome**	**Reviews, No. (%)**	
Age-Related Macular Degeneration (79 Trials and 15 Reviews)				
Visual acuity	69 (87.3)	Visual acuity	13 (86.7)	Visual acuity
Choroidal neovascularization	35 (44.3)	Adverse events (unspecified)	10 (66.7)	Choroidal neovascularization
Ocular adverse events	34 (43.0)	General quality of life	9 (60.0)	Contrast sensitivity
Contrast sensitivity	19 (24.1)	Contrast sensitivity	8 (53.3)	
All-cause mortality	17 (21.5)	Vision-related quality-of-life	5 (33.3)	
Systemic adverse events	13 (16.5)	Choroidal neovascularization	4 (26.7)	
Choroidal neovascular membrane size	13 (16.5)	Progression of AMD	4 (26.7)	
Cataract (138 Trials and 15 Reviews)				
Visual acuity	93 (67.4)	Visual acuity	14 (93.3)	Visual acuity
Posterior capsule opacification	62 (44.9)	Ocular adverse events	9 (60.0)	Posterior capsule opacification
Need for Nd:YAG laser capsulotomy	45 (32.6)	General quality-of-life	8 (53.3)	Ocular adverse events
Ocular adverse events	35 (25.4)	Costs	7 (46.7)	
Contrast sensitivity	22 (15.9)	Posterior capsule opacification	3 (20.0)	
Intraocular pressure	18 (13.0)	Adverse events (unspecified)	3 (20.0)	
Anterior chamber cells or flare	14 (10.2)	Vision-related quality of life	3 (20.0)	
Diabetic Retinopathy (55 Trials and 6 Reviews)				
Visual acuity	40 (72.7)	Visual acuity	6 (100)	Visual acuity
Ocular adverse events	23 (41.8)	General quality of life	5 (83.3)	Ocular adverse events
Retinal or macular thickness	22 (40.0)	Ocular adverse events	4 (66.7)	Systemic adverse events

Most Frequent Outcomes in Trials		Most Frequent Outcomes in Reviews		Overlapping Outcomes Between the Most Frequent Outcomes in Trials and Reviews
Outcome	**Trials, No. (%)**	**Outcome**	**Reviews, No. (%)**	
Systemic adverse events	15 (27.3)	Adverse events (unspecified)	3 (50.0)	
Vitreous hemorrhage	15 (27.3)	Systemic adverse events	3 (50.0)	
Blood pressure	11 (20.0)	Costs	2 (33.3)	
Glycosylated hemoglobin	10 (18.2)	Progression of diabetic retinopathy	2 (33.3)	
Glaucoma (142 Trials and 20 Reviews)				
Intraocular pressure	131 (92.3)	Intraocular pressure	19 (95.0)	Intraocular pressure
Ocular adverse events	98 (69.0)	Ocular adverse events	14 (70.0)	Ocular adverse events
Visual acuity	57 (40.1)	General quality of life	13 (65.0)	Visual acuity
No. of medications	55 (38.7)	Visual acuity	12 (60.0)	Visual field
Visual field	36 (25.4)	Visual field	11 (55.0)	No. of medications
Adherence to interventions	14 (9.9)	Costs	7 (35.0)	
Pulse or heart rate	14 (9.9)	No. of medications	7 (35.0)	

DISCUSSION

In this study, which focused on outcome domains, we found that trials included in Cochrane reviews of the 4 most prevalent eye diseases reported a greater number of outcomes than did the reviews. Although large proportions of review outcomes, ranging from 73.7% to 93.1%, were reported in the trials, smaller proportions of trial outcomes, ranging from 17.8% to 27.0%, were reported in the reviews.

Implications for Ophthalmology

Visual acuity was the most frequent outcome in trials and reviews for all diseases in our study. Visual acuity directly measures vision, the eye's primary function and a mechanism that most eye diseases eventually affect. The measurement of visual acuity is relatively insensitive to the patient's language fluency and educational level and is important because of its correlations with general and vision-related quality of life[18] and activities of daily living.[19] In addition, measurement of visual acuity is generally inexpensive and minimally invasive.

For each disease, the 7 most frequent outcomes in trials never included general quality of life, vision-related quality of life, or costs, outcomes recommended for Cochrane reviews.[16] However, almost half (47.3%) the trials included in our sample were published before or during 2002; outcome selection for these trials likely occurred years earlier. Widespread recognition of the importance of quality of life as an outcome for clinical research is a more recent phenomenon. In recent trials, a possible reason for omission might be the additional resources and expertise needed to rigorously collect and analyze quality-of-life data compared with less subjective outcomes.[20,21]

Ocular adverse events were frequent outcomes in trials and reviews that addressed cataract, DR, and glaucoma. Systemic adverse events were common in trials and reviews of DR but only in trials of AMD. However, in the Methods sections of AMD, cataract, and DR reviews, the authors mentioned the intention to examine adverse events without providing further detail; we therefore denoted these as adverse events (unspecified). Adverse events might be approached differently in trials and reviews. Trialists are often subject to strict regulations regarding reporting of individual adverse events, especially if the adverse events are severe and even if unrelated to the treatment. However, reviewers might consider specific adverse events to be of little interest if they are not a priori known to be associated with the treatment. Moreover, in ophthalmology, reviews generally have identified few trials, and the included trials often have small sample sizes and/or short follow-up durations; thus, low numbers of detected adverse events are reported.[22] Reviews and meta-analyses in this field consequently do not often achieve sufficient power to make conclusions regarding specific adverse events.[22]

Many of the 7 most frequent outcomes in trials but not in reviews were anatomical outcomes, such as retinal thickness and vitreous hemorrhage (in DR), choroidal neovascular membrane size (in AMD), and posterior capsular opacification (in cataract). Although Cochrane reviewers are encouraged to include patient-centered and functional outcomes, there may still be a need to continue examining anatomical outcomes in reviews.

Comparison With Other Studies

Our current findings in ophthalmology are consistent with recent findings of small overlap in outcomes between Cochrane reviews that address human immunodeficiency virus (HIV) infection and AIDS and the trials included in those reviews.[23] These findings reflect discord among reviewers and trialists addressing the same disease, in addition to the increasing evidence of the inconsistency in outcome use among trials. Other systematic investigations of trials that addressed HIV infection and AIDS,[23] tinnitus,[24] cardiac arrest,[25]

and critical care[26] have also demonstrated the absence of a single outcome that was reported across all trials. The proportion of outcomes reported in only 1 trial each has been reported to be high, ranging from 41% to 70%, for HIV infection and AIDS,[23] glaucoma,[13] cardiothoracic surgery,[27] and audiology.[28] Multiplicity in outcomes can serve a purpose. It may represent the intention of trialists to capture nontraditional outcomes and can lead to new hypotheses and deeper understanding of potential effects of interventions on disease processes. However, when multiplicity in outcomes occurs to an extent that precludes reviews from achieving their goal (ie, combining results from trials), as in the example of the review[12] comparing nonsteroidal anti-inflammatory drugs with corticosteroids for patients with uncomplicated cataract surgery, evidence-based medicine may be undermined.

Implications for Core Outcome Sets in Ophthalmology

The small overlap in outcomes in trials and reviews highlights the urgent need to harmonize outcomes in ophthalmology. The Core Outcome Measures for Effectiveness Trials (COMET) and Outcome Measures in Rheumatology (OMERACT) initiatives have promoted consistency in outcome use, thereby aiming to facilitate meaningful comparisons across studies within specific disease areas.[29,30] These efforts have fostered core outcome set development in various fields.[6] Core outcome sets refer to the minimum set of outcomes that must be measured in all clinical trials that address a given topic.[29]

In ophthalmology, we are aware of available core outcome sets for AMD,[31,32] cataract,[33] cataract surgery,[34] glaucoma,[35] juvenile idiopathic arthritis–associated uveitis,[36] and thyroid eye disease.[37] The 7 most frequent outcomes in our sample of AMD trials and reviews include 3 outcomes (visual acuity, ocular adverse events, and vision-related quality of life) in common with one of the available AMD core outcome sets[31] and 2 outcomes (visual acuity and ocular adverse events) in common with the other.[32] For cataract, the available core outcome set includes 4 outcomes,[33] of which 3 (visual acuity, ocular adverse events, and vision-related quality of life) are common to the 7 most frequent outcomes in our sample of trials and reviews. Similarly, for glaucoma, the available core outcome set includes 4 outcomes,[35] of which 3 (intraocular pressure, visual field, and ocular adverse events) are common to the 7 most frequent outcomes in our sample of trials and reviews. In addition to published core outcome sets, core outcome sets are being developed for AMD, uveitis, DR, visual impairment after stroke, amblyopia, strabismus, and ocular motility.[29] To achieve greater consistency in outcomes, those developing core outcome sets should consider the views and priorities of all relevant stakeholders, including patients, clinicians, and others.

COMET suggests that core outcome set development should begin with a comprehensive review of the literature, including trials and reviews.[4] We previously tested a framework for this approach for outcomes in trials and reviews that addressed HIV infection and AIDS.[23,38] Macefield and colleagues[39] also used a similar framework while identifying patient-reported core outcomes for esophageal cancer.

Limitations

Our study has some limitations. First, we focused on 1 of the 5 elements of an outcome (ie, the domain). Therefore, the identification of overlap in outcomes that we found implies only that various researchers examining the same disease might be performing similar assessments and not that the reported results can be combined in meta-analyses. In ongoing work, we are exploring the specific overlapping outcome domains to establish whether the overlap represents the same outcome measured using the same measurement and with data aggregation and analyses performed in the same way at the same time point. If such overlap is not present, the inconsistency of outcomes may be greater than we have reported. Second, we excluded trials only reported in conference abstracts; therefore, some outcomes from unpublished trials may have been missed. Third, our study focused on Cochrane reviews. It is possible that the overlap in outcomes between trials and non-Cochrane reviews might be systematically different from the overlap reported in this article.

CONCLUSIONS

We compared all outcomes in all Cochrane reviews that addressed the 4 most prevalent eye diseases with outcomes in the trials included in those reviews. Although most review outcomes were reported in the trials, most trial outcomes were not reported in the reviews. Inconsistency in trial outcomes may impede research synthesis efforts and indicates the need for disease-specific core outcome sets in ophthalmology.

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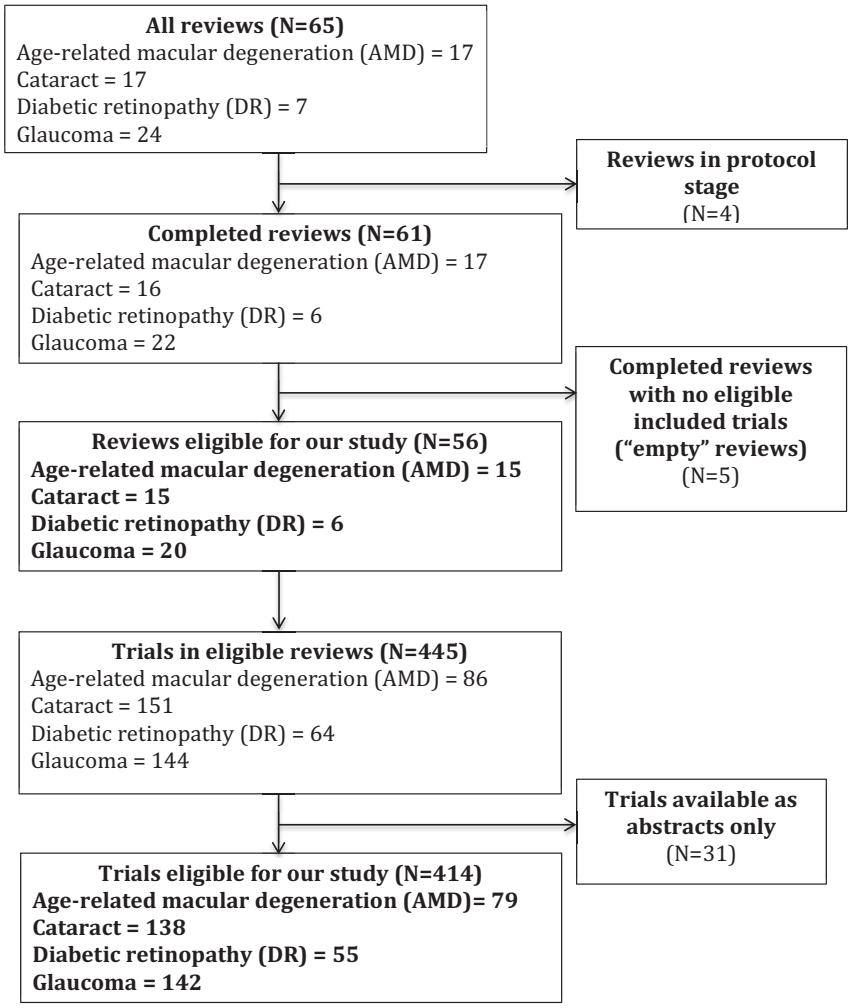
ADDITIONAL FILES

Supplementary materials

eFigure. Selection of reviews and trials for this study.



CHAPTER 5

Outcome choice and definition in systematic reviews leads to few eligible studies included in meta-analyses: a case study

Ian J Saldanha
Kristina Lindsley
Sarah Money
Hannah J Kimmel
Bryant T Smith
Kay Dickersin

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ABSTRACT

Background:
There is broad recognition of the importance of evidence in informing clinical decisions. When information from all studies included in a systematic review ("review") does not contribute to a meta-analysis, decision-makers can be frustrated. Our objectives were to use the field of eyes and vision as a case study and examine the extent to which authors of Cochrane reviews conducted meta-analyses for their review's pre-specified main outcome domain and the reasons that some otherwise eligible studies were not incorporated into meta-analyses.

Methods:
We examined all completed systematic reviews published by Cochrane Eyes and Vision, as of August 11, 2017. We extracted information about each review's outcomes and, using an algorithm, categorized one outcome as its "main" outcome. We calculated the percentage of included studies incorporated into meta-analyses for any outcome and for the main outcome. We examined reasons for non-inclusion of studies into the meta-analysis for the main outcome.

Results:
We identified 175 completed reviews, of which 125 reviews included two or more studies. Across these 125 reviews, the median proportions of studies incorporated into at least one meta-analysis for any outcome and for the main outcome were 74% (interquartile range [IQR] 0–100%) and 28% (IQR 0–71%), respectively. Fifty-one reviews (41%) could not conduct a meta-analysis for the main outcome, mostly because fewer than two included studies measured the outcome (21/51 reviews) or the specific measurements for the outcome were inconsistent (16/51 reviews).

Conclusions:
Outcome choice during systematic reviews can lead to few eligible studies included in meta-analyses. Core outcome sets and improved reporting of outcomes can help solve some of these problems.

BACKGROUND

There is broad recognition of the importance of evidence in determining clinical decision-making.[1] For evidence-based healthcare, decision-makers (e.g., patients, clinicians, guideline developers) increasingly rely on systematic reviews ("reviews").[1] Reviews identify primary studies, such as clinical trials and observational studies, that have addressed the research question of interest. This research question typically defines the population, interventions, and comparators; these defined aspects in turn help delineate the primary studies eligible for the review.

Reviews may or may not include quantitative syntheses of data across studies ("meta-analyses"). When appropriately conducted, meta-analyses provide decision-makers with summary estimates (e.g., relative risks) and accompanying estimates of uncertainty (e.g., 95% confidence intervals) that convey information about treatment effectiveness or safety succinctly.[2] Often, however, meta-analyses cannot be conducted because the studies address somewhat different clinical questions, assess different outcomes than the systematic reviewer ("reviewer") had pre-specified, are methodologically heterogeneous, or are poorly-reported (e.g., inadequate information about results). In these circumstances, a study may be eligible for the review, but may not contribute to a meta-analysis.[3] When a review includes multiple studies, but these studies cannot be included in the meta-analysis, both doers (i.e., reviewers) and users of reviews (i.e., decision-makers) can be frustrated. Decision-makers want to know how treatments compare quantitatively; they may not be able to get reliable information about this when only some included studies contribute data to the meta-analysis or when no meta-analysis is possible.[4]

Outcomes are measures or events used to assess the effectiveness and/or safety of clinical interventions.[5] A frequent reason for non-conduct of meta-analyses is that the studies assess different outcomes or assess the same outcomes, but do so differently. These scenarios can occur even among high-quality studies.

Although outcomes are fundamental to reviews of interventions, outcomes are typically not considered when determining the eligibility of a primary study in such reviews.[6] This is because outcomes inform meta-analyses, not whether the primary study is eligible for the review. Consistent with guidance in the Cochrane Handbook for Systematic Reviews of Interventions,[6] we believe that studies that address the population, interventions, and comparators of interest should be included and cataloged in systematic reviews even if they do not report outcomes of interest. Outcome choice in a review is crucial because: (1) outcomes serve as yardsticks for basing conclusions about treatments; and (2)

which outcomes are chosen and how they are defined can impact how many meta-analyses can be done and how many studies can be included in them.[7-11]

Outcomes may be assessed differently in different studies because an "outcome" (a seemingly monolithic entity) actually comprises five elements: domain, e.g., visual acuity; specific measurement, e.g., Snellen chart; specific metric, e.g., ≥3 lines of vision lost; method of aggregation, e.g., proportion; and time-points, e.g., 6 months.[9,12] Another example of the application of this five-element framework to clearly specify a particular data point of interest related to the outcome of "anxiety" is mean (method of aggregation) change (specific metric) in anxiety (domain) measured through the Hamilton Anxiety Rating Scale (specific measurement) from baseline to 1 year (time-point).[9,12]

We previously demonstrated, through case studies in the fields of eyes and vision[11] and HIV/AIDS,[10] that reviewers and clinical trialists addressing the same research question often examine different outcomes. In addition, inconsistency in outcome reporting across eligible studies prevents incorporation of all eligible studies into meta-analyses. For instance, a 2017 Cochrane systematic review comparing non-steroidal anti-inflammatory drugs (NSAIDs) with corticosteroids for inflammation after cataract surgery[13] included 48 trials, none of which reported data for the review's prespecified primary outcome, "proportion of patients with intraocular inflammation at 1 week after surgery."

To document the extent and determinants of this problem, we embarked on the current case study in the field of eyes and vision. Our objectives were to examine the extent to which Cochrane reviews in eyes and vision conducted meta-analyses for the main outcome domain and the reasons why some otherwise eligible studies were not incorporated into meta-analyses.

METHODS

Reviews examined

We examined all completed systematic reviews published by Cochrane Eyes and Vision in the Cochrane Database of Systematic Reviews as of August 11, 2017. We excluded reviews that were still in the protocol stage.

Data extraction

We developed a data extraction form in the Systematic Review Data Repository (SRDR), an open-source platform for extracting and archiving data.[14,15] Using a pilot-tested form, two individuals (from among SM, HK, BTS, and IJS) independently extracted data, resolving discrepancies through discussion. We

extracted the following data: year published, population (i.e., eye function/region affected), and types of interventions and comparators. We extracted the numbers of primary, secondary, and other, i.e., non-primary and non-secondary, outcome domains. We also extracted the number of studies included in the review and in ≥1 meta-analysis for any, any primary, any secondary, and any other domain.

"Main" outcome domains

We categorized one domain from each review as its "main" outcome domain (Table 1). For reviews that named only one primary outcome domain, we categorized it as the main outcome domain; for reviews that named more than one primary outcome domain (or named more than one secondary outcome domain), we categorized the primary outcome domain (or secondary outcome domain) with the highest number of included studies as the main outcome domain. For reviews that did not name any primary or secondary outcome domains, we categorized the "other", i.e., nonprimary and non-secondary, outcome domain with the highest number of included studies as the main outcome domain.

For each main outcome domain, we extracted the other four elements specified: specific measurement, specific metric, method of aggregation, and time-points. For the main outcome domain, we also extracted the numbers of studies that reported measuring it, reported any data, reported any meta-analyzable data, and were incorporated into ≥1 meta-analysis. We considered data for a given outcome from a given study to be "meta-analyzable" if the study reported adequate information so that it could be incorporated into a meta-analysis. For categorical outcomes, meta-analyzable meant that either of these conditions were met: (1) total number of participants and number of participants with the outcome were reported for each study arm; and (2) the between-group treatment effect (e.g., relative risk) and an uncertainty estimate (e.g., 95% confidence interval) were reported. For continuous and time-to-event outcomes, meta-analyzable meant that either of these conditions were met: (1) mean and uncertainty estimates were reported for each study arm; and (2) the between-group treatment effect (e.g., mean difference) and an uncertainty estimate were reported.

Table 1. Algorithm for categorizing the "main" outcome domain for each systematic review.

Scenario	If	Then	Number of systematic reviews (N = 175)
			n (%)
1	The review named only 1 primary outcome domain	we categorized that outcome domain as the main outcome domain.	131 (75)
2	The review named >1 primary outcome domain	we categorized the primary outcome domain with the highest number of included studies as the main outcome domain.	41 (23)
3	The review did not name any primary outcome domain, but named ≥1 secondary outcome domain	we categorized the secondary outcome domain with the highest number of included studies as the main outcome domain.	0 (0)
4	If the review did not name any primary or secondary outcome domains	we categorized the "other" (i.e., non-primary and non-secondary) outcome domain with the highest number of included studies as the main outcome domain.	3 (2)

Note: In scenarios 2, 3, and 4, if there were two or more possible outcome domains that had the same number of included studies ("Then" column), we categorized the first outcome listed in the Methods section as the main outcome domain

RESULTS

Reviews examined

We identified 175 completed systematic reviews published by Cochrane Eyes and Vision in the Cochrane Database of Systematic Reviews (Table 2). The reviews were published between January 1, 2005 and August 11, 2017 (median = 2014). The most common populations were patients with retinal/choroidal disease (35 reviews; 20%) and visual impairment/ low vision (33 reviews; 19%). The most common types of interventions/comparators were drugs (74 reviews; 42%) and surgeries (67 reviews; 38%).

Incorporation of studies into meta-analyses for any outcome domain

The 175 included reviews examined a median of 6 total outcome domains, including a median of 1 primary outcome domain, 4 secondary outcome domains, and 1 other outcome domain.

The 175 reviews included a median of 3 studies (IQR 1–9); 125 reviews (71%) included ≥2 studies. For these 125 reviews, Fig. 2 plots the percentage of

studies incorporated into a meta-analysis for any outcome domain (blue line) and for the main outcome domain (red bars). Among these reviews, 44/125 reviews (35%) incorporated every included study into ≥1 meta-analysis (for any outcome domain). Conversely, 33/125 reviews (26%) did not incorporate any study into any meta-analysis for any outcome, i.e., they did not conduct any meta-analysis. The remaining 48/125 reviews (38%) incorporated only a subset of their studies into ≥1 meta-analysis. These 48 reviews included a median of 12.5 studies (IQR 6–22), and the meta-analyses in these reviews incorporated a median of 6.5 studies (IQR 4–13).

Among the 125 reviews that could have conducted a meta-analysis, i.e., those including ≥2 studies, the median proportion of studies incorporated into ≥1 meta-analysis for any outcome was 74% (IQR 0–100%). Among the 92 reviews that conducted a meta-analysis, the median proportion of studies incorporated into ≥1 meta-analysis for any outcome was 93% (IQR 64–100%).

Characteristics of main outcome domains

Almost all reviews (172/175 reviews; 98%) named ≥1 primary outcome domain (Table 1). Three in four reviews (131/175 reviews; 75%) each named exactly one primary outcome domain, which we categorized as their main outcome domain. The most frequent main outcome domains across the 175 reviews were visual acuity (31%) and intraocular pressure (6%) (Table 3). Thirty-eight outcome domains were main outcome domains in just one review each. The main outcome was categorical in 70% and continuous in 29% of reviews. Most main outcome domains (98%) were efficacy outcomes, i.e., not safety outcomes.

Incorporation of studies into meta-analyses for the main outcome domain

Among the 125 reviews including ≥2 studies, only 18 reviews (14%) incorporated all their studies into a meta-analysis for the main outcome domain. Conversely, 51/125 reviews (41%) did not incorporate any study into the meta-analysis for the main outcome domain, i.e., they did not conduct any meta-analysis for the main outcome domain. The remaining 56/125 reviews (45%) incorporated only a subset of their studies into the meta-analysis for the main outcome domain. These 56 reviews included a median of 12 studies each, and the meta-analyses for the main outcome domain in these reviews incorporated a median of 4 studies each.

Among the 125 reviews that could have conducted a meta-analysis, i.e., those including ≥2 studies, the median proportion of studies incorporated into ≥1 meta-analysis for the main outcome domain was 28% (IQR 0–71%). Among the 74 reviews that conducted meta-analyses for the main outcome domain, the median proportion of studies incorporated was 67% (IQR 39–91%).

Meta-analysis conduct for the main outcome domain

Figure 1 illustrates a cascading effect of loss of information as regards the main outcome domain in the 175 reviews. Thirty-five reviews (20%) included no studies, i.e., were empty reviews, and 15 (9%) included one study each (Fig. 1). Of the 125 reviews including ≥2 studies, i.e., those in which a meta-analysis could theoretically be done for the main outcome if ≥2 studies reported meta-analyzable data, only 74 reviews (59%) conducted a meta-analysis for the main outcome.

Table 2. Characteristics of systematic reviews examined.

Characteristic	Number of systematic reviews (N = 175)
	n (%)
Year published	
2003–2005	3 (2)
2006–2008	12 (7)
2009–2011	15 (9)
2012–2014	68 (39)
2015–2017	77 (44)
Population (function/region of eye) addressed	
Retinal/choroidal disease	35 (20)
Visual impairment/low vision	33 (19)
Optic nerve, including glaucoma	32 (18)
Ocular surface	31 (18)
Lens	18 (10)
Ocular vasculature	5 (3)
Other	21 (12)
Interventions and comparators examined[a]	
Drug	74 (42)
Surgery	67 (38)
Other procedure	31 (18)
Device	15 (9)
Supplements	6 (3)
Screening/testing	5 (3)
Other intervention	26 (15)
Number of outcome domains examined	

Characteristic	Number of systematic reviews (N = 175)
	n (%)
Median	6
Interquartile range	5 to 8
Range	1 to 19
Number of primary outcome domains examined	
Median	1
Interquartile range	1 to 1
Range	0 to 5
Number of secondary outcome domain examined	
Median	4
Interquartile range	3 to 6
Range	0 to 12
Number of other outcome domains examined	
Median	1
Interquartile range	0 to 2
Range	0 to 6
Number of studies included	
Median	3
Interquartile range	1 to 9
Range	0 to 137

[a]More than one category could apply

Table 3. Characteristics of main outcome domains in all 175 systematic reviews examined.

Characteristic	Number of systematic reviews (N = 175)
	n (%)
Main outcome domain	
Visual acuity	55 (31)
Intraocular pressure	11 (6)
Visual field	7 (4)
Visual impairment/vision loss	5 (3)
Success of surgery/procedure	5 (3)
Failure of trabeculectomy	4 (2)
Progression of age-related macular degeneration	3 (2)
Reading speed	3 (2)
Ocular symptoms (unspecified)	3 (2)
Symptoms of dry eye	3 (2)
Vision-related quality of life	3 (2)
Resolution of infection	3 (2)
Active trachoma	3 (2)
Healing of keratitis	3 (2)
Other	64 (37)
Type of main outcome domain	
Categorical	122 (70)
Continuous	50 (29)
Other (i.e., time-to-event)	2 (1)
Not reported	1 (0)
Goal of main outcome domain	
Efficacy	172 (98)
Safety	3 (2)

Reasons for non-conduct of meta-analyses for the main outcome domain

Among the 125 reviews including ≥2 studies, 51 reviews (41%) did not conduct a meta-analysis for the main outcome domain. For 21/51 reviews (41%), fewer than two studies measured the review's main outcome (Table 4). When ≥2 studies reported meta-analyzable data, there were numerous reasons why reviewers did not conduct a meta-analysis, most frequently due to inconsistency in outcome

elements among the included studies. Specifically, data could not be meta-analyzed because the specific measurements used (16/51 reviews; 31%) and time-points examined (9/51 reviews; 18%) were inconsistent among studies. Figure 2 demonstrates that the loss of information for the main outcome domain (red bars) was similar in pattern to the loss of information when considering any outcome domain (blue line).

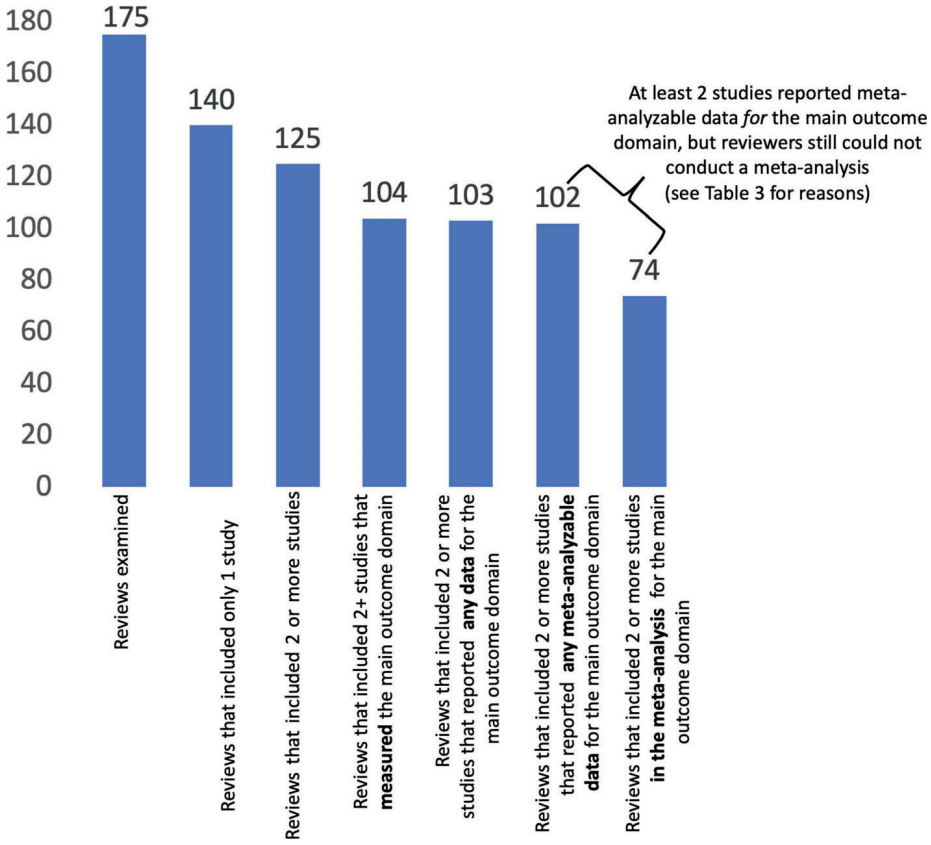

Figure 1. Conduct of meta-analyses for the main outcome domain.

Table 4. Reasons for non-conduct of a meta-analysis for the systematic review's main outcome even when ≥2 studies were included in the systematic review (N = 51 of 125 reviews that included ≥2 studies)

Reason	Number of systematic reviews (N = 51)	
	n	(%)
When meta-analyzable data[1] for the review's main outcome domain were NOT REPORTED by ≥2 studies (n = 23 reviews)		
<2 studies measured the review's main outcome	21	(41)
<2 studies reported any data for the review's main outcome	1	(2)
<2 studies reported any meta-analyzable data1for the review's main outcome	1	(2)
When meta-analyzable data[1] for the review's main outcome domain were REPORTED by ≥2 studies (n = 28 reviews)[2]		
Reasons related to inconsistencies in outcome elements		
Studies used inconsistent specific measurements	16	(31)
Studies used inconsistent specific metrics	0	(0)
Studies used inconsistent methods of aggregation	0	(0)
Studies reported data at inconsistent time-points	9	(18)
Reasons related to heterogeneity		
Studies were clinically heterogeneous	7	(14)
Studies were methodologically heterogeneous	2	(4)
Studies were statistically heterogeneous	0	(0)

[1]For categorical outcomes, we considered data to be meta-analyzable if either of the following scenarios were met [1]: total number of participants and number of participants with the outcome of interest were reported for each study arm; and [2] the between-group treatment effect (e.g., relative risk, odds ratio) and an estimate of uncertainty (e.g., 95% confidence interval) were reported. For continuous and time-to-event outcomes, we considered data to be meta-analyzable if either of the following scenarios were met [1]: mean and estimate of uncertainty (e.g., standard deviation) were reported for each study arm; and [2] the between-group treatment effect (e.g., mean difference) and an estimate of uncertainty (e.g., 95% confidence interval) were reported.

[2]More than one reason could apply.

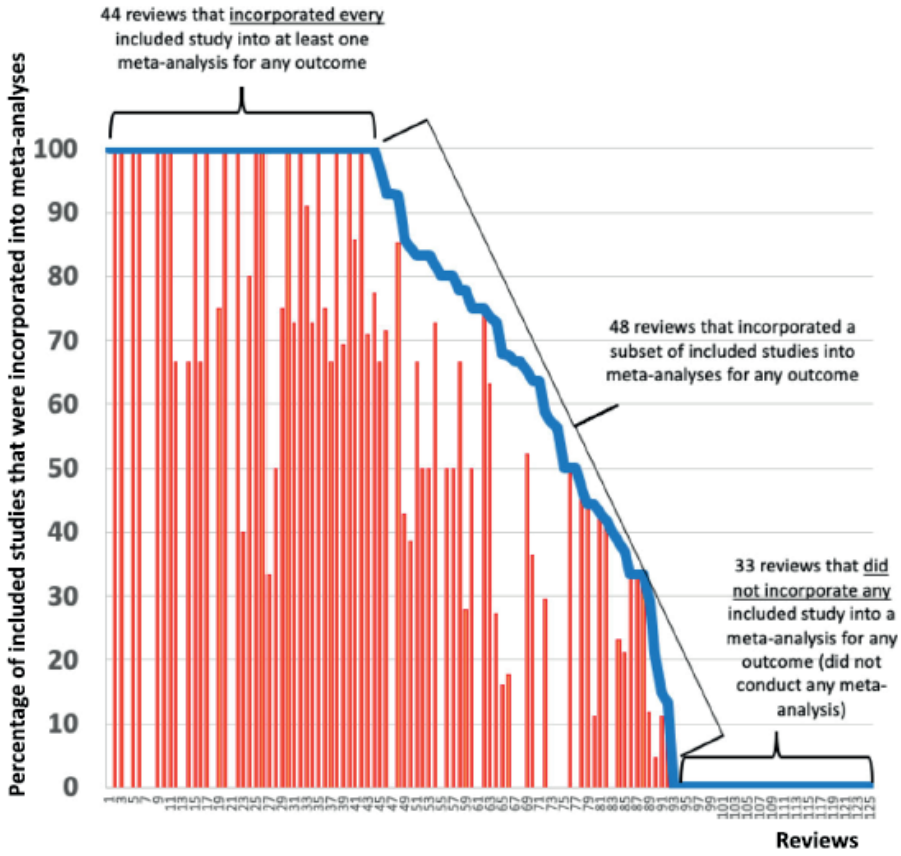

Figure 2. Percentage of studies included in the review that were incorporated into a meta-analysis for any outcome (blue line) and for the review's main outcome (red bars). Notes: This Figure excludes the 50 systematic reviews in whom a meta-analysis was not possible: 35 systematic reviews that each included 0 studies (i.e., "empty reviews") and 15 systematic reviews included that each included only 1 study. When the blue line is non-0 but the red bars are 0, it implies that the systematic review did not conduct a meta-analysis for the main outcome, but did so for ≥1 of the remaining outcomes.

DISCUSSION

Through a case study of all Cochrane reviews in the field of eyes and vision, the current work demonstrates three major areas that need improvement.

First, primary studies addressing similar research questions should align their outcomes better. Studies often could not be incorporated into meta-analyses because the outcomes were not aligned, either because the domains or ≥1 of the other four outcome elements did not overlap. Among the reviews including ≥2 studies, only 59 and 74% could conduct a meta-analysis for the main outcome and for any outcome, respectively. In other words, even when reviews included ≥2 studies, 41 and 26% of reviews missed opportunities to conduct a meta-analysis to succinctly convey information regarding the main outcome and any outcome, respectively.

Second, reviews and primary studies should align their outcomes better. When looking at reviews that could have conducted a meta-analysis, i.e., those including ≥2 studies, the median percentages of included studies incorporated into the meta-analysis for the main outcome and for any outcome were 28 and 74%, respectively. This suggests that, approximately 7 in 10 studies that reviewers include are not incorporated into the meta-analysis for the main outcome, and 1 in 4 studies are not incorporated into the meta-analysis for any outcome. In previous work, we demonstrated poor overlap between outcomes in clinical trials and reviews, and possible differences in the types of outcomes they examine.[10, 11] For HIV/AIDS, we demonstrated that reviewers examined more long-term clinical outcomes and patient-centered outcomes than did clinical trialists. Such differences may arise because: (1) reviews may more directly inform clinical practice guidelines, and (2) reviewers may be less affected by common constraints faced by clinical trialists, e.g., costs and sample size.[10]

Our findings beg the question of who should prioritize outcomes for measurement and reporting in research. It has aptly been stated that achieving consensus in outcome use across research "cannot be left to serendipity."[16] One deliberate and fundamental aspect of the solution to the problem of outcome inconsistency is the development of "core outcome sets." A core outcome set is a minimum set of outcomes that should be measured and reported in all clinical trials addressing a given condition.[17] Core outcome sets are increasingly common in various health fields; a 2018 systematic review identified 307 core outcomes sets.[18] However, outcome inconsistency remains widespread; 40% of recent (2019) published Cochrane reviews explicitly noted this problem.[19]

We[10, 11] and others[20] have argued that, as stakeholders in a given field, systematic

reviewers should both participate in the development of and adopt core outcome sets for that field. By broadening the participation in outcome prioritization efforts, this could potentially help ensure that the outcomes that are measured and reported in research are widely relevant and important. Two aspects of core outcome sets are worthy of clarification. First, core outcome sets do not stifle innovation; they are simply meant to represent a minimum set of outcomes that should be reported. Once a core outcome set exists for a given topic, clinical trialists working in that topic area should explicitly specify the intention to measure and report the outcomes in the set. Second, core outcome sets are not static; they can and should be updated as the field advances and new knowledge emerges.

The third major area in need of improvement that our study demonstrates is the reporting of outcomes in primary studies. Results data from primary studies were often not meta-analyzable even when outcomes might have been aligned. In addition, outcome domains were frequently not reported in primary studies or ≥1 of the outcome elements were frequently missing or inadequately reported (e.g., "worsening of disease" without clarification of how "worsening" was defined). It is possible that the studies measured these outcomes, but did not report measuring them or reported them inadequately. If such selective reporting, either non-reporting or inadequate reporting, of outcomes in the included studies occurred as a function of the direction of the outcome's results, it would be suggestive of outcome reporting bias.[21] In this case study, we relied on the reviewers' reporting of the extent to which the primary studies reported the outcomes. Because we did not examine the reports of the primary studies (or their protocols), we are unable to comment definitively on whether non-reporting of the outcomes indicates outcome reporting bias. However, outcome reporting bias in primary studies has been documented to be a widespread problem across reviews,[22-26] and, as such, is a likely explanation for some outcomes not being reported.

Implications

For the evidence-based medicine paradigm to work, decision-makers must be able to rely on systematic reviews, which in turn rely on the results of primary studies. For results of primary studies to be actionable, there (1) needs to be alignment in outcomes considered important to both primary study researchers and reviewers, and (2) those outcomes need to be reported completely. Important discussions need to be had regarding who should choose outcomes for the field and how such choices should be made. We, in conjunction with others, suggest that these discussions should include, at the least, clinicians, patients, clinical trialists, systematic reviewers, regulators, and other decision-makers.[27]

We have demonstrated that the choice of outcomes for systematic reviews may have led to loss of information through non-incorporation of results from included studies into meta-analyses. The most substantial drops in the percentage of reviews conducting meta-analyses for the main outcome domain appeared to be due to inadequate numbers of studies reporting the outcome and, when there were adequate numbers of studies for a meta-analysis (i.e., ≥2 studies), differences in the specific measurements and time-points used.

Our findings also demonstrate that even when focusing on reviews that conducted meta-analyses for their main outcome domain, only about 2 in 3 studies were incorporated into those meta-analyses. As such, non-incorporation of included studies into meta-analyses represents two main problems. First, it represents missed opportunities for using research to inform decision-making through evidence synthesis. This contributes considerably towards research waste.[28–30] Second, non-incorporation of included studies into meta-analyses represents a failed obligation on the part of the researchers (both trialists and reviewers).[31] As a community of researchers, both parties have a solemn obligation to research participants to ensure that their participation will lead to a useful contribution to science; failing to agree upon outcomes that should be collected and adequately reported likely violates this obligation.

Other solutions

Core outcome sets are integral to solving the problems this study illustrates. Other parts of the solution are worth discussing. We agree with existing recommendations against studies being excluded from systematic reviews solely on the basis of the lack of relevant outcome data.[3] Thankfully, such recommendations have been associated with a reduction in the number of reviews excluding studies solely on the basis of outcome data.[32] As the current study demonstrates, the review team's choice of outcomes may not align with that of the primary studies. This may be particularly true for eyes and vision, a field with few core outcome sets.[4,18] We also encourage reviewers to report an outcome matrix,[23,24] a transparent and simple way to indicate all fully-reported, partially-reported, or non-reported outcomes in each included study.

Large numbers of empty reviews and reviews including only one study

Twenty-percent of the reviews we examined were empty and 9% included only one study each. While such reviews are useful in driving primary research, the possible reasons for the paucity of studies in them are worth exploring. One possibility is that these represent topics that primary researchers have not yet studied. Another is that only observational studies addressing these topics

may exist; Cochrane reviews typically include only randomized trials. It also is possible that these topics reflect the priorities of Cochrane Eyes and Vision and the authors of these reviews, rather than of the field at-large.

Limitations

Our study has certain limitations. First, we focused on Cochrane reviews within one field. Loss of information due to the choice of review outcomes could be a bigger, similar, or smaller problem in non-Cochrane systematic reviews in eyes and vision or systematic reviews in other fields. Second, we analyzed in-depth the extent of incorporation of included studies into meta-analyses only for the main outcome domain. Meta-analyses of other primary, secondary, and other outcome domains may have incorporated higher percentages of included studies. However, Fig. 2 suggests that this is likely not the case. It is possible that our algorithm for categorizing the "main" outcome for each review could have impacted our findings. But, in reviews where more than one outcome domain could have served as the main outcome, we categorized as the main outcome the outcome that the highest number of included studies had reported. Our results thus represent the best-case scenario. Third, most outcome domains (98%) were efficacy outcomes. Selective outcome reporting has also been reported to be a problem for safety outcomes.[33] Fourth, we relied on the reviews to determine whether or not each included study did the following for the main outcome domain: reported measuring it, reported any results for it, and reported meta-analyzable data for it. Related to this, we did not examine the appropriateness or feasibility of the reviewers' being able to conduct meta-analyses when the included studies reported data in a format different from what the reviewers were interested. As such, our results document what was actually done in the reviews.

CONCLUSIONS

This case study of all Cochrane systematic reviews addressing an entire field (eyes and vision) demonstrates that only 59 and 74% of the reviews including ≥2 studies could conduct a meta-analysis for the main outcome and for any outcome, respectively. In evidence-based healthcare, such loss of information represents missed opportunities and a failed obligation by researchers to research participants to ensure that their participation will lead to a useful contribution to science. Core outcome sets and improved outcome reporting can help solve some of these problems.

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CHAPTER 6

Poor compliance of clinical trial registration among trials included in systematic reviews: a cohort study

Kristina Lindsley
Nicole Fusco
Hannah Teeuw
Eva Mooij
Rob Scholten
Lotty Hooft

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ABSTRACT

Objectives:
The objective of the study was to examine whether clinical trials that have been included in systematic reviews have been registered in clinical trial registers and, when they have, whether results of the trials were included in the clinical trial register.

Study design and setting:
This study used a sample of 100 systematic reviews published by the Cochrane Musculoskeletal, Oral, Skin and Sensory Network between 2014 and 2019.

Results:
We identified 2,000 trials (369,778 participants) from a sample of 100 systematic reviews. The median year of trial publication was 2007. Of 1,177 trials published in 2005 or later, a clinical trial registration record was identified for 368 (31%). Of these registered trials, 135 (37%) were registered prospectively and results were posted for 114 (31%); most registered trials evaluated pharmaceutical interventions (62%). Of trials published in the last 10 years, the proportion of registered trials increased to 38% (261 of 682).

Conclusion:
Although some improvement in clinical trial registration has been observed in recent years, the proportion of registered clinical trials included in recently published systematic reviews remains less than desirable. Prospective clinical trial registration provides an essential role in assessing the risk of bias and judging the quality of evidence in systematic reviews of intervention safety and effectiveness.

INTRODUCTION

Systematic reviews of randomized clinical trials produce the highest level of evidence for informing the effectiveness of health care interventions.[1] The quality of evidence relies on the credibility of the trials included and whether the trials were likely to be at risk of potential bias. To minimize bias, the methods of trials should be outlined before conducting the trial, and deviations should be documented. Clinical trial registers allow trial investigators to prospectively register their intention to conduct a trial and the main methods and outcomes of the trial before enrolling the first trial participant.

In addition to registering trials to minimize methodological biases and maximize transparency, there are also ethical implications. Research participants who volunteer and consent for their information to be used do so with an understanding that their participation will contribute to medical research and further scientific knowledge. If trials are not made known to the public and their results are not disseminated, the implicit agreement between the study participant and researcher is broken. Furthermore, this is a form of research waste which may result in duplicate studies being conducted to examine research questions which may already have been answered by previously conducted studies.

In 2004, the International Committee of Medical Journal Editors (ICMJE) recommended that journals consider publishing articles reporting clinical trials of health care interventions only when the trial had been registered prospectively.[2] ICMJE recognizes six clinical trial registries in addition to 10 other primary registries included in the World Health Organization (WHO) International Clinical Trials Registry Portal (ICTRP). As of September 27, 2007, US law charges the US Food and Drug Administration (FDA) with overseeing clinical trial registration as a requirement for all 'applicable clinical trials' of drugs, biologics, and devices (FDAAA 801).[3] The law requires that in addition to registering the trial before enrolling the first participant, the trial investigators are required to submit results for trials that investigated an FDA-approved drug, biologic, or device within 12 months of the completion date of the trial. Similar requirements for posting clinical trial results were outlined by the European Medicines Agency in 2014.[4] In 2013, the international AllTrials campaign was launched, calling for all trials to be registered and the results reported in accordance with the Declaration of Helsinki principles.[5] Specifically, the campaign lists four areas of reporting for each trial: 1) registration, 2) summary of trial results in the same place as the registration, 3) details of study methods and results (e.g., full report in compliance with Consolidated Standards of Reporting Trials (CONSORT)), and 4) individual patient data, of which the first three areas should be made available in the public domain.

OBJECTIVES

The objectives of the study were to examine whether clinical trials that have been included in systematic reviews have been registered in clinical trial registers (e.g., ClinicalTrials.gov) and, when they have, whether results of the trials were included in the clinical trial register. We also assessed whether trial results published in journal articles were made available in the public domain (i.e., open access) and describe trial characteristics (e.g., year of publication, number of participants).

METHODS

Data source

We identified clinical trials from systematic reviews published by the Cochrane Musculoskeletal, Oral, Skin and Sensory (MOSS) Network from 2014 to 2019. We used Cochrane reviews because they are limited to clinical trials, which are the type of study design of interest for this project (i.e., studies required to be registered in a clinical trial registry) and they search trial registers in addition to bibliographic databases. The MOSS network includes eight topic-specific review groups: 1) back and neck; 2) ear, nose, and throat; 3) eyes and vision; 4) musculoskeletal; 5) oral health; 6) pain, palliative and supportive care; 7) skin; and 8) wounds.

Eligible reviews were intervention reviews published within the past 5 years (September 2014 to September 2019) that included at least five trials (n 5 618). Reviews that had been withdrawn, overviews of reviews, reviews of diagnostic test accuracy, reviews of prognosis, and protocols of reviews were not eligible. We used a random number generator in Microsoft Excel to select 10 reviews meeting the eligibility criteria from each of the eight review groups (except for Eyes and Vision, for which 30 reviews were selected as part of the initial pilot study). In all, 100 out of the 618 eligible reviews were included (citations of included reviews are listed in Appendix A).

Data collection

We designed and pilot tested a data extraction form in DistillerSR (Evidence Partners, evidencepartners.com) to collect data from each of the 100 randomly selected reviews. In addition to hierarchical data extraction (i.e., compatible for extracting data on multiple trials included in a single review), DistillerSR allows for serial review of data extraction. One person extracted data for each review, and a second person verified the data extracted. Any discrepancy between the two reviewers was resolved by discussion.

Data collection included review characteristics, such as the condition under investigation, the type of interventions being examined, the number of included trials, whether meta-analysis was performed, and the review authors' conclusions. We also collected data on the characteristics of each trial included in each review, such as when the trial was published, the number of participants randomized, the country of the trial, whether a trial registration record was reported by the review authors, whether the trial provided data for meta-analysis, and whether the full published study report was available open access.

If no trial registration record was reported by the review authors and the trial was published in 2000, when ClinicalTrials.gov became publicly available, or more recently, we searched study reports and trial registers to determine if the trial was registered. In the first searching phase, we reviewed the abstracts of trial references and, when the full-text report was available open access, we searched the full report for a trial registration ID. If no trial registration ID was found from the study reports, we used condition and intervention terms to search the two clinical trial registry databases that are endorsed by the ICMJE: ClinicalTrials.gov (www.clinicaltrials.gov) and the WHO ICTRP (www.who.int/ictrp/en/). We confirmed trial registration matching by comparing the study investigators and/or institutions and sponsors, the number of participants, the study period, and the study design.

When a trial registration record was identified, from either the review authors or our own searching, we recorded whether the trial was registered prospectively or retrospectively (registration submitted more than 1 month after study start date) and documented whether the trial results were posted within the trial registration record. We classified posted results as efficacy outcomes only, safety outcomes only, or both efficacy and safety outcomes. Acknowledging that some investigators may consider linking the trial registry record to a journal publication with trial results, we also assessed whether trial results published in full journal articles referenced by the review authors were available in the public domain; we searched PubMed, Google Scholar, and Google for an open access article or document (i.e., the full-text report was available free of cost).

Data analysis

We summarized descriptive statistics (medians, ranges, and proportions) for review level and trial level data using RStudio (R version 3.6.1). Because Cochrane requires reviews to be registered with the editorial group to prevent duplicate review topics, analyses were based on an assumption of independence (i.e., no trial was included in more than one review).

The primary outcome of this study was the proportion of trials included in systematic reviews of interventions with an identifiable clinical trial registration record. Eligible trials for the primary outcome were published in 2005, the first full calendar year that the ICMJE criteria for trial registration came into effect, or later. We also examined potential factors that may be associated with clinical trial registration based on the following criteria: condition (review group), type of intervention (pharmaceutical; medical device; surgical; behavioral, including physiotherapy, diet, and self-care programs; and combined interventions), number of participants (<100; 100 or more), trial date (before 2007; 2007 and after, based on the Food and Drug Administration Amendments Act of 2007 [FDAAA]), and the review authors' conclusions (favors intervention, favors comparator, inconclusive). Between-group differences were compared using the chi-square test, with $P < 0.05$ indicating statistical significance.

Secondary outcomes included the proportion of trials with a clinical trial registration that posted trial results and the proportion of all trials with an open access report. Based on feedback from editorial and peer review, we also analyzed data for trials that were published in the last 10 years (2010—2020) to provide additional insight into more recent trends in clinical trial registration.

RESULTS

Review level characteristics

Among 100 randomly selected reviews from the Cochrane MOSS Network, the majority of reviews evaluated pharmaceutical interventions (56%), performed meta-analysis (93%), and concluded that the test interventions were favorable to comparison interventions (52%) (Table 1). Within specific review groups, these trends were the similar, with the following exceptions: the Back and Neck group evaluated more behavioral interventions (60%; five of which were physiotherapy) than other types; the Oral Health group evaluated more device interventions (60%) than other types, and the review authors' conclusions were inconclusive in a majority of Oral health and Wounds reviews (60%). There were 2,000 trials included across all reviews (median number of trials included per review was 13, range 5 to 137).

Table 1. Review characteristics overall and by review group (n = 100)

Review group:	Included trials: total number; median (range) per review	Intervention type: pharmaceutical; device; surgical; behavioral; combination*	Meta-analysis: number (%)	Review authors' conclusions: favors intervention; favors comparator; no difference between groups; inconclusive
Overall (n=100)	2000; 13 (5-137)	56; 33; 23; 26; 12	93 (93%)	52; 3; 6; 39
Back and Neck (n=10)	197; 18 (10-41)	2; 0; 2; 6; 0	10 (100%)	6; 0; 1; 3
Ear, Nose and Throat (n=10)	98; 7.5 (5-25)	5; 3; 1; 1; 0	10 (100%)	6; 0; 0; 4
Eyes and Vision (n=30)	586; 12.5 (5-137)	18; 10; 14; 5; 3	27 (90%)	15; 0; 4; 11
Musculoskeletal (n=10)	250; 21.5 (7-54)	5; 1; 0; 4; 0	9 (90%)	8; 0; 0; 2
Oral Health (n=10)	166; 12.5 (6-32)	3; 6; 3; 2; 3	10 (100%)	3; 1; 0; 6
Pain, Palliative and Supportive Care (n=10)	244; 16.5 (7-62)	8; 4; 2; 2; 2	8 (80%)	6; 1; 0; 3
Skin (n=10)	334; 25 (6-77)	8; 5; 0; 6; 3	9 (90%)	5; 0; 1; 4
Wounds (n=10)	125; 11.5 (7-20)	7; 4; 1; 0; 1	10 (100%)	3; 1; 0; 6

*total percentage >100 as reviews may have evaluated more than one type of intervention

Trial level characteristics

The median year of trial publication was 2007, with 823 trials published before 2005, 1,177 trials published in 2005 or after, and 682 trials published in 2010 or after (Table 2). There were 367,137 participants included in 2,000 trials across all reviews (median number of participants per trial was 63, range 1 to 77,015). Most trials used a randomized parallel-group design overall, before and after 2005 (1,704 of 2,000; 85%). Three review groups (musculoskeletal; pain, palliative and supportive care; and skin) included proportionally more trials than three other review groups (ear, nose, and throat; oral health; and wounds). Most trials, especially those published before 2005, were conducted in Europe and North America. In 2005 and after, the proportion of trials conducted in Africa and the Middle East, Asia and the Pacific, South America, and multiple regions increased compared with trials published before 2005. There were more publicly available full-text reports published in 2005 or after (583 of 1,177 trials; 50%) than published before 2005 (241 of 823 trials; 29%). Of 682 trials published in 2010 or after, 352 (52%) had publicly available full-text reports.

Registered vs. nonregistered trials

We identified a clinical trial registry record for 379 of 1,432 (26%) of trials published since 2000, when ClinicalTrials.gov became publicly available, most of which (97%; 368 of 379) were published since 2005, when the ICMJE criteria for trial registration requirements came into effect. As of 2005, the proportion of trial registration increased to 31% (368 of 1,177 trials), and as of 2010, the proportion of trial registration increased to 38% (261 of 682 trials). Two review groups, musculoskeletal and pain, palliative and supportive care, had proportionally more registered trials than nonregistered trials compared with other review groups (Table 3; Table 4). The majority of registered trials evaluated pharmaceutical interventions (62%); 46% of nonregistered trials evaluated pharmaceutical interventions as of 2005 (44% as of 2010). Registered trials included a median of 120 participants (105,192 overall), compared with a median of 60 (80,499 overall) in nonregistered trials as of 2005 (Table 3). Ninety-three percent of registered trials were published in 2007 or later (median year of publication 2011); 82% of nonregistered trials were published in 2007 or later (median year of publication 2010). Trials from reviews favoring the intervention group were more likely to be registered than nonregistered, whereas trials from reviews with inconclusive results were more likely to be nonregistered than registered as of both 2005 and 2010. Slightly more registered trials had an open access full-text report available (59%) than not available, whereas slightly fewer nonregistered trials had an open access full-text report available (45% as of 2005; 47% as of 2010) than not available.

As of 2005, about one-third of registered trials (114 of 368; 31%) provided results for at least one outcome within the registry record. Most trials were retrospectively registered (233 of 368; 63%); 135 of 368 (37%) were registered prospectively before the enrollment of the first participant. As of 2010, one-third of registered trials (87 of 261; 33%) provided results for at least one outcome within the registry record. Still, most trials were retrospectively registered (151 of 261; 58%), but some improvement was seen with 110 of 261 (42%) trials registered prospectively before the enrollment of the first participant.

Table 2. Characteristics of clinical trials included in systematic reviews

	Total trials (n=2000)	Trials published before 2005 (n=823)	Trials published in 2005 or after (n=1177)	Trials published in 2010 or after (n=682)
Publication year, median (range)	2007 1958-2018	1995 1958-2004	2010 2005-2018	2012 2010-2018
Trial participants				
Total	367,137	181,446	230,161	90,072
Median per trial (range)	63 (1-77,015)	58 (1-77,015)	68 (4-16,603)	68 (4-4,203)
Trial design, number (percent)				
Parallel-group randomized trial	1704 (85%)	668 (81%)	1036 (88%)	608 (89%)
Cluster randomized trial	5 (<1%)	1 (<1%)	4 (<1%)	1 (<1%)
Cross-over randomized trial	105 (5%)	74 (9%)	31 (3%)	19 (3%)
Within-person randomized trial	126 (6%)	32 (4%)	94 (8%)	45 (7%)
Quasi-randomized trial/unclear	60 (3%)	48 (6%)	12 (1%)	9 (1%)
Clinical topic area, number (percent)				
Back and neck	197 (10%)	56 (7%)	141 (12%)	77 (11%)
Ear, nose, and throat	98 (5%)	45 (5%)	53 (5%)	40 (6%)
Eyes and vision	586 (29%)	256 (31%)	330 (28%)	200 (29%)
Musculoskeletal	250 (13%)	120 (15%)	130 (11%)	62 (9%)
Oral health	166 (8%)	68 (8%)	98 (8%)	59 (9%)
Pain, palliative, supportive care	244 (12%)	100 (12%)	144 (12%)	89 (13%)
Skin	334 (17%)	125 (15%)	209 (18%)	117 (17%)
Wounds	125 (6%)	53 (6%)	72 (6%)	38 (6%)
Geographic region, number (percent)				
Africa/Middle East	230 (12%)	48 (6%)	182 (15%)	126 (18%)
Asia/Pacific	435 (22%)	93 (11%)	342 (29%)	216 (32%)
Europe	732 (37%)	399 (48%)	333 (28%)	174 (26%)
North America	430 (22%)	237 (29%)	193 (16%)	102 (15%)
South America	69 (3%)	13 (2%)	56 (5%)	29 (4%)
Multiple regions	95 (5%)	26 (3%)	69 (6%)	35 (5%)
Not reported	9 (<1%)	7 (1%)	2 (<1%)	0

Table 3. Characteristics of clinical trials published 2005 or later with versus without clinical trial registration

	Trials with a clinical trial registration (n=368)	Trials without a clinical trial registration (n=809)
Clinical topic area, number (percent)*		
Back and neck	36 (10%)	105 (13%)
Ear, nose, and throat	14 (4%)	39 (5%)
Eyes and vision	100 (27%)	230 (28%)
Musculoskeletal	56 (15%)	74 (9%)
Oral health	15 (4%)	83 (10%)
Pain, palliative and supportive care	78 (21%)	66 (8%)
Skin	49 (13%)	160 (20%)
Wounds	20 (5%)	52 (6%)
Review intervention type, number (percent)**		
Pharmaceutical	229 (62%)	370 (46%)
Device	107 (29%)	344 (43%)
Surgical	73 (20%)	259 (32%)
Behavioral	96 (26%)	253 (31%)
Combination	40 (11%)	154 (19%)
Trial participants*		
Total (median per trial)	105,192 (120)	80,499 (60)
Less than 100 participants, number (percent)	158 (43%)	593 (73%)
100 or more participants, number (percent)	210 (57%)	216 (27%)
Date of publication*		
Median (range)	2011 (2005-2018)	2010 (2005-2018)
Published before 2007, number (percent)	27 (7%)	147 (18%)
Published 2007 or later, number (percent)	341 (93%)	662 (82%)
Review authors' conclusions, number (percent)*		
Favors intervention	224 (61%)	451 (56%)
Favors comparator	15 (4%)	11 (1%)
No difference between groups	16 (4%)	51 (6%)
Inconclusive	113 (31%)	296 (37%)
Publicly available full text report (available free of charge), number (percent)*		
Yes	216 (59%)	367 (45%)
No	152 (41%)	442 (55%)

*Chi-square test P<0.05 comparing registered versus non-registered trials
**total percentage >100 as reviews may have evaluated more than one type of intervention

Table 4. Characteristics of clinical trials published 2010 or later with versus without clinical trial registration

	Trials with a clinical trial registration (n=261)	Trials without a clinical trial registration (n=421)
Clinical topic area, number (percent)*		
Back and neck	26 (10%)	51 (12%)
Ear, nose, and throat	12 (5%)	28 (7%)
Eyes and vision	78 (30%)	122 (29%)
Musculoskeletal	30 (11%)	32 (8%)
Oral health	14 (5%)	45 (11%)
Pain, palliative and supportive care	55 (21%)	34 (8%)
Skin	34 (13%)	83 (20%)
Wounds	12 (5%)	26 (6%)
Review intervention type, number (percent)**		
Pharmaceutical	161 (62%)	186 (44%)
Device	82 (31%)	189 (45%)
Surgical	61 (23%)	138 (33%)
Behavioral	66 (25%)	126 (30%)
Combination	30 (11%)	85 (20%)
Trial participants*		
Total (median per trial)	59,331 (109)	30,741 (60)
Less than 100 participants, number (percent)	119 (46%)	326 (77%)
100 or more participants, number (percent)	142 (54%)	95 (23%)
Date of publication		
Median (range)	2013 (2010-2018)	2012 (2010-2018)
Review authors' conclusions, number (percent)*		
Favors intervention	155 (59%)	224 (53%)
Favors comparator	10 (4%)	3 (1%)
No difference between groups	10 (4%)	14 (3%)
Inconclusive	86 (33%)	180 (43%)
Publicly available full text report (available free of charge), number (percent)*		
Yes	155 (59%)	197 (47%)
No	106 (41%)	224 (53%)

*Chi-square test P<0.05 comparing registered versus non-registered trials
**total percentage >100 as reviews may have evaluated more than one type of intervention

Trial registration by year of publication

Overall, there is an increasing trend in the number of registered trials since 2005 and 2010, although for only 2 years, 2015 (n = 65) and 2018 (n = 4), was the percent of registration more than 50% of trials published in those years (Fig. 1). The cumulative percentage of trials registered increased between 2005 and 2015 but remains less than one-third of all trials identified in this project (Fig. 2). There were slight increases in the number of trial registrations with results posted from 2008 to 2013; however, the cumulative percentage of registered trials included in recently published systematic reviews still remains very low at less than 10%.

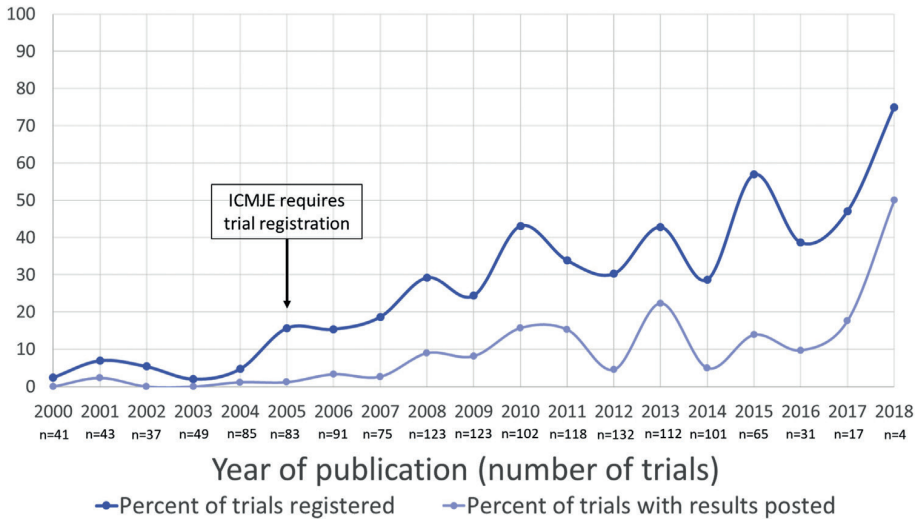

Figure 1. Percent of clinical trials with clinical trial registration and with results posted by year of publication.

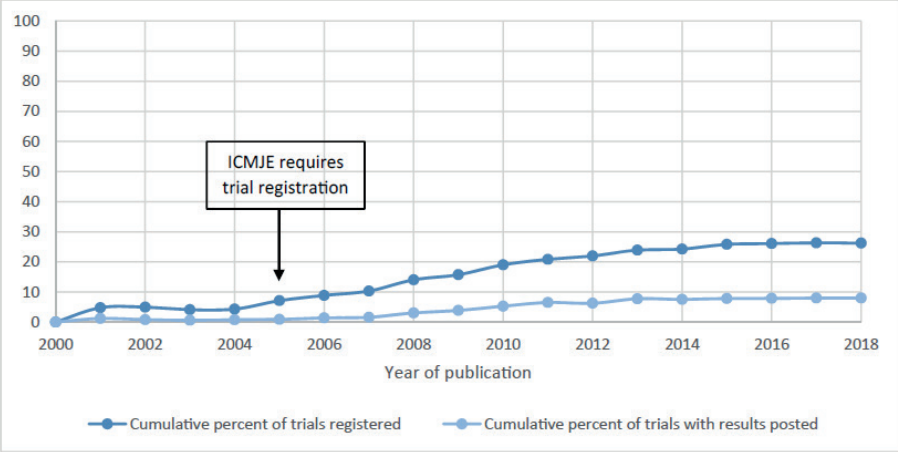

Figure 2. Cumulative percent of clinical trials with clinical trial registration and with results posted by year of publication.

DISCUSSION

Although we observed some improvement in the registration of clinical trials since 2000, especially after 2005 when trial registration was endorsed by the ICMJE (change from 25% to 31%), there does not seem to be strong consistency of trial registration in practice within the topic areas evaluated in our sample of systematic reviews. Fewer than one-third of trials identified in this study had an accessible clinical trial registration record, even when conducting in-depth searches of multiple sources and allowing retrospective registration. Even fewer, less than 10%, provided efficacy or safety results as part of the trial registration record. These deficiencies in clinical trial registration and reporting negatively affect the confidence and reliability of the evidence ecosystem which they underpin.

Previous studies have reported poor compliance with clinical trial registration requirements in both ClinicalTrials.gov[6–8] and the EU Clinical Trials Register[8–10] in the range of 39% to 50%. The lower proportion found in this study (31% as of 2005) is likely due to the time needed to conduct a systematic review after the included trials have been completed and lags in publication. Even so, by reviewing the status of trial registration without time restrictions, our results represent an overestimate of the proportion of trials included in systematic reviews that adhered to trial registration guidelines. Although trials should be registered before enrollment of the first participant, most of the trials identified in our study were registered retrospectively (63%). Furthermore, trial results for interventions requiring regulatory approval should be made available within 12 months of the study conclusion. We accepted any posted trial result regardless

of when the results were posted and still found only 10% with trial results. Finally, we searched for trial registration records more recently (as of March 1, 2020) than when the original systematic review authors conducted searches for their reviews, all of which were published between 2014 and 2019.

Of all registered trials, 93% were published in 2007, the year FDAAA was enacted, or later. We also found pharmaceutical interventions made up the most common type of intervention among registered trials included in systematic reviews (62%). These findings are consistent with other studies that suggest better compliance with both ICMJE and FDAAA trial registration requirements for trials conducted for the specific purpose of new drug approvals, with up to 100% compliance for specific drugs.[11,12] However, although also regulated by FDAAA, only 24% of device trials in our study were registered as of 2005 and 30% as of 2010.

The Final Rule of FDAAA, developed in 2016, set out to clarify which trials are required to comply with federal trial registration and reporting regulations in the United States.[13] Based on a study by DeVito et al., complete compliance plateaued from July 2018 to September 2019 at around 40%,[7] suggesting that, even in the era of the Final Rule, reporting of clinical trial results still falls short. In the context of the evidence ecosystem, more time is required to fully assess the impact of the Final Rule on clinical trial compliance and the reliability of systematic reviews. What also remains unclear is how to address the lack of oversight of trial registration and reporting for trials that influence patient care, but not covered by FDAAA and other regulatory agencies, especially with respect to surgical and behavioral (including physiotherapy) trials.

The scientific community at large also has an important role in better enforcing clinical trial registration. A study by Cook et al.[14] found that dermatology journals that required or recommended trial registration when considering articles for publication had higher rates of trial registration reporting (72%) than those without formal trial registration policies (38%). Similar studies in other disease areas also have shown increased reporting of trial registration among journals with policies that require or recommend trial registration compared with those that do not.[15–17] These differences in reporting provide evidence that, by imposing policies at the level of journal publication, the percentage of trials published with registration information can be improved. Professional societies can also adopt the CONSORT Statement extension for abstracts[18] and require clinical trial registration information to be reported as part of the abstract submission and acceptance process for conferences. Likewise, internal review boards and ethic committees could require trial registration before approving the start of patient enrollment. Even though it is not a formal part of the Preferred Reporting Items

for Systematic Reviews and Meta-Analyses checklist,[19] systematic reviewers often document clinical trial registration of studies included in their reviews and use the information provided in the trial registration to assess for selective outcome reporting and other sources of bias. Although not ideal, an approach of implementing clinical trial registration requirements at various stages of the evidence ecosystem seems the only feasible way to ensure that these standards will be met as no one method seems capable of ensuring clinical trial registration for all trials.

CONCLUSIONS

In this study, we systematically examined the proportion of clinical trial registration among trials included in recently published systematic reviews of interventions. Although some improvement in clinical trial registration has been observed in recent years, the proportion of registered clinical trials included in recently published systematic reviews remains less than desirable. Systematic reviews, to provide the best level of evidence for decision makers, should be based on properly conducted and completely reported clinical trials. Access to unbiased and complete trial information needed to adequately judge the quality and strength of evidence plays a critical role in the evidence-based health care ecosystem and trustworthiness of medical research.

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ADDITIONAL FILES

Supplementary materials

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CHAPTER 7

Clinical trial registration was associated with lower risk of bias compared with non-registered trials among trials included in systematic reviews

Kristina Lindsley
Nicole Fusco
Tianjing Li
Rob Scholten
Lotty Hooft

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ABSTRACT

Objectives:
To examine the association between clinical trial registration and risk of bias in clinical trials that have been included in systematic reviews. As a secondary objective, we evaluated the risk of bias among trials registered prospectively vs. retrospectively.

Method:
Clinical trials published in 2005 or after included in a sample of 100 Cochrane systematic reviews published from 2014-2019.

Results:
Of 1,177 clinical trials identified, we verified 368 (31%) had been registered, of which 135 (36.7%) were registered prospectively (i.e., before or up to 1 month after enrollment of the first participant). Across the bias domains (one bias assessment for each domain per trial), the percentage of trials at low risk ranged from 29% to 58%; unclear risk ranged from to 26% to 61% and high risk ranged from 2% to 38%. Trials that had been registered had less high or unclear risk of bias in five domains: random sequence generation (univariate risk ratio [RR] 0.69, 95% confidence interval [95% CI] 0.58-0.81), allocation concealment (RR 0.64, 95% CI 0.57-0.72), performance bias (RR 0.65, 95% CI 0.58-0.72), detection bias (RR 0.70, 95% CI 0.62-0.78), and reporting bias (RR 0.62, 95% CI 0.53-0.73). An association between clinical trial registration and high or unclear risk of attrition bias could not be demonstrated nor refuted (RR 1.02, 95% CI 0.89-1.17). It also was observed in terms of overall risk of bias, that registered trials had less high or unclear overall risk of bias than trials that had not been registered (univariate RR 0.29, 95% CI 0.19-0.46). Prospective clinical trial registration was associated with low risks of selection bias due to inadequate allocation concealment, performance bias, and detection bias compared with retrospective clinical trial registration.

Conclusion:
In a large sample of clinical trials included in recently published systematic reviews of interventions, clinical trial registration was associated with low risk of bias for five of the six domains examined.

INTRODUCTION

In 2004, the International Committee of Medical Jour- nal Editors (ICMJE) published the recommendation that any clinical trial being submitted for publication should be registered in a publicly accessible clinical trial register.[1] The online clinical trial register ClinicalTrials.gov, which was made available to the public in 2000, saw a substantial increase in the number of trial registrations following ICMJE's recommendation, and even more after the Food and Drug Administration Amendment Act of 2007,[2] which required that clinical trials used for regulatory approval of pharmaceuticals in the United States be registered.[3,4] Furthermore, the Consolidated Standards of Reporting Trials (CONSORT) guideline also includes trial registration number and name of trial registry as part of their reporting checklist.[5]

Much research has been conducted on the utility of clinical trial registration records in evidence synthesis.[6–11] A key advantage of trial registration in research, beyond the creation of a public record indicating that the trial has taken place, is that trial registry records may also serve as trial protocol repositories, establishing the intended methods and outcomes of a clinical trial before results are known. This additional source of trial information may fill in gaps about the methods and results of trials that may not make it into journal publications or conference abstracts due to space limitations and other reasons, and thus facilitate systematic reviewers in assessing the risk of bias of included trials.

Risk of bias assessment is a critical step when performing a systematic review as it provides the confidence that the review findings can be trusted and applied to health care decision making. There have many advances in the understanding of bias in clinical research, as reflected in the updated Cochrane Risk of Bias tool.[12] This study aims to evaluate the relationship between clinical trial registration and risk of bias among clinical trials included in recently published systematic reviews.

OBJECTIVES

To examine the association between trial registration and risk of bias among clinical trials included in systematic reviews of healthcare interventions. Specifically, we assessed whether clinical trials (published in 2005 and after) that were included in systematic reviews had been registered in clinical trial registers and the relationship with risk of bias (high, low, or unclear) for each domain according to the Cochrane Risk of Bias tool used by the systematic reviewers (v1; 2011).[13] Secondary objectives were to evaluate the overall risk of bias and risk of bias among trials registered prospectively vs. retrospectively.

METHODS

Data source

This research was conducted in accordance with a protocol that included prespecified objectives, variable definitions, and analysis plan; methods for data collection have been described previously.[14] Briefly, we selected a sample of systematic reviews of intervention effectiveness from the Cochrane Musculoskeletal, Oral, Skin and Sensory (MOSS) network portfolio of reviews published from September 2014 to September 2019. Between 2019 and 2020, Cochrane began recommending using a second version of their Risk of Bias Tool (Sterne et al, 2020); thus, this research includes only reviews that used the first version for consistency of results. The MOSS network includes eight topic-specific review groups: (1) Back and Neck; ((2) Ear, Nose and Throat; (3) Eyes and Vision; (4) Musculoskeletal; (5) Oral Health; (6) Pain, Palliative and Supportive Care; (7) Skin; and (8) Wounds. From seven of the eight topic-specific review groups, we selected a random sample of 10 intervention reviews that included at least five clinical trials; we selected 30 Eyes and Vision reviews as part of the initial pilot project. Thus, we included a total of 100 Cochrane systematic reviews in our sample (references supplied in Appendix A). These 100 reviews included 2000 trials, 1177 of which were published in 2005 or after. We selected the date of 2005 based on when the ICMJE criteria for trial registration came into effect. Any trial design (e.g., parallel group trial, cross-over trial) was eligible for inclusion.

Data collection

Two individuals independently extracted data, including review characteristics, such as the condition under investigation, the interventions and comparisons being examined, and the number of included trials, as well as the characteristics of the trials included in each review, such as when the trial was conducted, the number of participants randomized, and whether a trial registration ID was reported by the review authors. DistillerSR (Evidence Partners) was used for data extraction. We verified all trial registration IDs provided by the review authors. When no trial registration number was reported by the review authors and the trial was published in 2005 or more recently, we first searched the original study reports. Then, if no trial registration number was provided in the reports, we searched trial registers to determine if the trial was registered. Two individuals searched ClinicalTrials.gov (www.clinicaltrials.gov) and the WHO ICTRP (www.who.int/ ictrp/ en/), the two clinical trial registry databases that are endorsed by the ICMJE, using a combination of condition and intervention terms. We confirmed trial registration matching by comparing the study investigators and/or institutions and sponsors, the number of participants, the study period, and

the study design. We developed an algorithm in Python (PyCharm; JetBrains s.r.o. 2020) to automatically extract the risk of bias assessments (domains and judgements of high, low, or unclear risk of bias) from an html file for each included Cochrane review. We checked the reliability of the data collected by the algorithm against the risk of bias tables in the reviews.

Data analysis for primary objective

We summarized review and trial level characteristics descriptively (medians, ranges, and proportions) using RStudio (R version 3.6.1) with an assumption of independence by checking that no trial was included in more than one review. Between group differences were compared using the Chi-squared test, with $P < 0.05$ indicating statistical significance.

The primary association of interest was between clinical trial registration and risk of bias among trials that were included in systematic reviews of interventions and published in 2005 or more recently (N = 1,177). The independent variable or determinant was trial registration, and the outcome was high or unclear risk of bias. Thus risk ratios (RR) greater than 1 suggest an association between clinical trial registration and high or unclear risk of bias and RRs less than 1 suggest that clinical trial registration is associated with low risk of bias.

We analyzed each of the following main risk of bias domains individually: random sequence generation, allocation concealment, performance bias, detection bias, attrition bias, and reporting bias. We employed a complete case analysis such that risk of bias domains not assessed by review authors were excluded from the analysis; however, as a mandatory requirement, few reviews did not assess all risk of bias domains. One risk of bias assessment per domain was analyzed per trial. We used the assessments as reported by the review authors regardless of study design. In cases where review authors assessed the risk of bias for multiple outcomes, the assessment of the primary review outcome was selected for that domain. In cases where re- view authors used variations in wording, we classified the assessment according to the appropriate risk of bias domain.

We performed univariate analysis and examined the following covariates of interest using multivariable logistic regression (glm function in RStudio): year of publication (continuous), number of participants (continuous), type of intervention (pharmaceutical vs. non-pharmaceutical), study design (parallel-group RCT vs. others), geographical region (Europe, North America, and multiregional vs others), and availability of an open access full-text publication (yes vs. no). Non-pharmaceutical interventions comprised devices, surgery, and behavioral interventions, including physiotherapy, diet, and self-care programs.

For the primary analyses, risk of bias per domain was dichotomized as high or unclear vs. low. We conducted sensitivity analyses (1) comparing high risk of bias vs. low or unclear and (2) excluding assessments of unclear risk of bias from the analysis (high vs. low risk of bias).

Data analysis for secondary objectives

We followed the recommendation from the Cochrane Risk of Bias tool to classify an overall risk of bias for each trial as follows: overall low risk of bias when low risk of bias was assessed for all key domains, overall unclear risk of bias when unclear risk of bias was assessed for one or more key domains, and overall high risk of bias when high risk of bias was assessed for one or more key domains.[13] We performed univariate analysis, multivariable analysis, and sensitivity analyses according the same methods as with the primary objective; however, due to the small number of studies with overall low risk of bias ("non-exposed" group), the analyses were performed using the inverse estimates.

Secondary analysis also compared the risk of bias among trials registered prospectively vs. retrospectively. Prospective registration was considered a first posting date prior to, or up to 1 month after, the date of when the first participant was enrolled. Any registration first registered more than 1 month after the date of participant enrollment was classified as retrospective registration. In the analysis prospective registration was considered the determinant and high/unclear risk of bias was the outcome.

RESULTS

Characteristics of included trials

We identified 1,177 trials from a sample of 100 recently published reviews (median: 9 trials per review) from the Cochrane MOSS Network and published as of 2005, the first full calendar year in which the ICMJE recommended trial registration for publication. The median year of publication was 2010 (range 2005-2018) and the trials included 230,161 total participants (median 68 per trial). The most common study design was the randomized parallel-group trial (1036, 88%). Most trials were conducted in Asia/Pacific and Europe, followed by North America and Africa/Middle East. Half of the trials had full text reports available free of charge to the public. Clinical trial registration was found for 368 (31%) trials; of those 135 (36.7%) were registered prospectively. Of note, trial registration numbers were reported by review authors for only 180 trials; we identified the remaining 188 trial registrations by manually searching the clinical trial registers. Compared with trials with no clinical trial registration, registered trials were less likely to have been published before 2015 and more likely to

include 100 or more participants, examine pharmaceutical interventions, and have an open access publication (Table 1).

Risk of bias of included trials

We examined each of the predefined risk of bias domains individually across all studies and for trials that were registered (n = 368) compared with trials that were not registered (n = 809). All reviews assessed random sequence generation, allocation concealment, and attrition bias. Seven reviews (71 trials, 6%) did not provide assessments for performance bias, three reviews (18 trials, 2%) did not assess detection bias, and six reviews (91 trials, 8%) did not assess reporting bias. Most review authors (94 reviews) reported that the risk of bias assessments were performed independently by at least two individuals; for five reviews it was reported only that assessments were done according to standard Cochrane methods;[15–19] and one review was conducted by a single author.[20]

Overall, three domains were assessed as low risk for 45% or more trials: random sequence generation, attrition bias, and reporting bias (Fig. 1). The majority of studies were assessed as having unclear risk of bias for allocation concealment (61%). Performance and detection biases were assessed as high risk for more than one third of trials (38% and 34%, respectively). In terms of overall risk of bias, 74 trials (6%) were at low risk, 402 trials (34%) were at unclear risk, and 701 (60%) were at high risk.

Table 1. Characteristics of included trials (n = 1,177)

Trial characteristics	Total trials n=1,177	Registered trials n=368 (31%)	Non-registered trials n=809 (69%)
Date of publication, median (range)	2010 (2005-2018)	2011 (2005-2018)	2010 (2005-2018)
Date of publication, number (%)*			
Published 2005 to before 2010	495	107 (22%)	388 (78%)
Published 2010 to before 2015	565	201 (36%)	364 (64%)
Published 2015 to before 2019	117	60 (51%)	57 (49%)
Trial participants, total (median per trial)	185,691 (68)	105,192 (120)	80,499 (60)
Trial participants, number (%)*			
Less than 100 participants	751	158 (21%)	593 (79%)
100 or more participants	426	210 (49%)	216 (51%)
Clinical topic area, number (%)*			
Back and neck	141	36 (26%)	105 (74%)
Ear, nose, and throat	53	14 (26%)	39 (74%)
Eyes and vision	330	100 (30%)	230 (70%)
Musculoskeletal	130	56 (43%)	74 (57%)
Oral health	98	15 (15%)	83 (85%)
Pain, palliative and supportive care	144	78 (54%)	66 (46%)
Skin	209	49 (23%)	160 (77%)
Wounds	72	20 (28%)	52 (72%)
Review intervention type, number (%)*			
Pharmaceutical	599	229 (38%)	370 (62%)
Non-pharmaceutical**	578	139 (24%)	439 (76%)
Trial design, number (%)*			
Parallel-group randomized trial	1036	339 (33%)	697 (67%)
Cluster randomized trial	4	0	4 (100%)
Cross-over randomized trial	31	10 (32%)	21 (68%)
Within-person randomized trial	94	19 (20%)	75 (80%)
Quasi-randomized trial or unclear	12	0	12 (100%)
Geographic region, number (%)*			
Africa/Middle East	182	29 (16%)	153 (84%)
Asia/Pacific	342	57 (17%)	285 (83%)
Europe	333	106 (32%)	227 (68%)

Trial characteristics	Total trials n=1,177	Registered trials n=368 (31%)	Non-registered trials n=809 (69%)
North America	193	101 (52%)	92 (48%)
South America	56	20 (36%)	36 (64%)
Multiple regions	69	55 (80%)	14 (20%)
Not reported	2	0	2 (100%)
Full text report available free of charge, number (%)*			
Yes	583	216 (37%)	367 (63%)
No	594	152 (26%)	442 (74%)

*Chi-square test P<0.005 comparing registered versus non-registered trials
**Non-pharmaceutical interventions comprised devices, surgery, and behavioral interventions, including physiotherapy, diet, and self-care programs

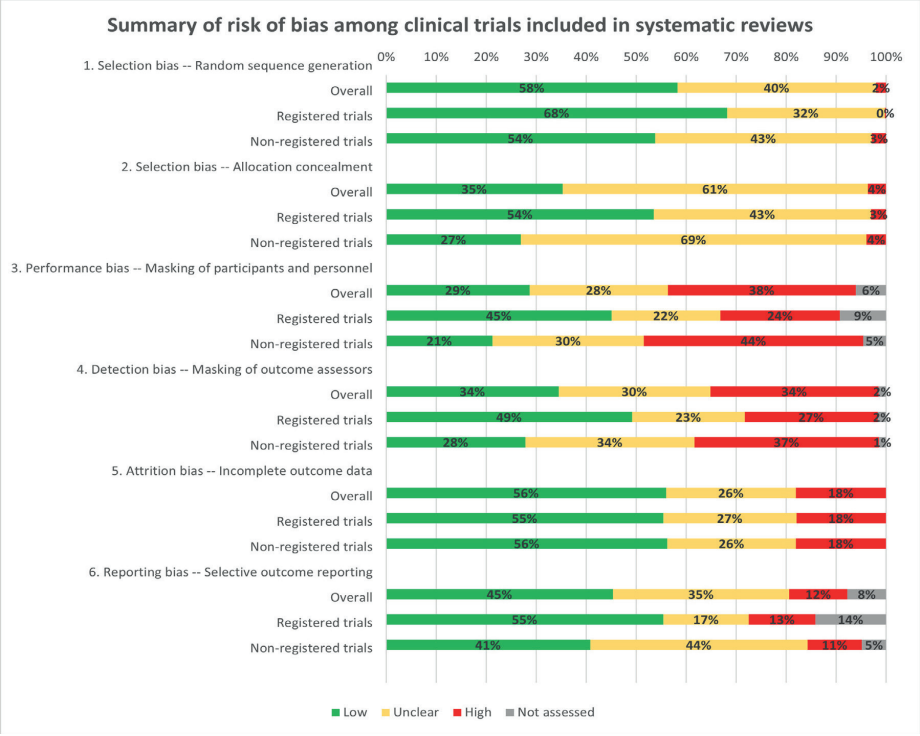

Figure 1. Summary of risk of bias among clinical trials included in systematic reviews. *All risk of bias domains, except for attrition bias, were significantly associated with clinical trial registration. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Table 2. Risk ratios (RRs) for the presence of risk of bias of having been registered vs. not having been registered

Random sequence generation (selection bias)	**Number**	**RR[a] (95% CI)**
Primary, univariate analysis (high/unclear vs low ROB)	1,177	0.69 (0.58–0.81)
Multivariable analysis* (high/unclear vs low ROB)	1,177	0.71 (0.53–0.95)
Sensitivity analysis 1 (high vs low/unclear ROB)	1,177	0.10 (0.01–0.70)
Sensitivity analysis 2 (high vs low ROB)	710	0.08 (0.01–0.58)
Allocation concealment (selection bias)	**Number**	**RR (95% CI)**
Primary, univariate analysis (high/unclear vs low ROB)	1,177	0.64 (0.57–0.72)
Multivariable analysis* (high/unclear vs low ROB)	1,177	0.45 (0.34–0.61)
Sensitivity analysis 1 (high vs low/unclear ROB)	1,177	0.76 (0.39–1.48)
Sensitivity analysis 2 (high vs low ROB)	458	0.41 (0.21–0.80)
Blinding of participants and personnel (performance bias)	**Number**	**RR (95% CI)**
Primary, univariate analysis (high/unclear vs low ROB)	1,106	0.65 (0.58–0.72)
Multivariable analysis* (high/unclear vs low ROB)	1,106	0.39 (0.28–0.53)
Sensitivity analysis 1 (high vs low/unclear ROB)	1,106	0.57 (0.47–0.70)
Sensitivity analysis 2 (high vs low ROB)	781	0.51 (0.43–0.62)
Blinding of outcome assessment (detection bias)	**Number**	**RR (95% CI)**
Primary, univariate analysis (high/unclear vs low ROB)	1,159	0.70 (0.62–0.78)
Multivariable analysis* (high/unclear vs low ROB)	1,159	0.53 (0.40–0.72)
Sensitivity analysis 1 (high vs low/unclear ROB)	1,159	0.72 (0.60–0.88)
Sensitivity analysis 2 (high vs low ROB)	802	0.62 (0.52–0.74)
Incomplete outcome data (attrition bias)	**Number**	**RR (95% CI)**
Primary, univariate analysis (high/unclear vs low ROB)	1,177	1.02 (0.89–1.17)
Multivariable analysis* (high/unclear vs low ROB)	1,177	1.11 (0.84–1.47)
Sensitivity analysis 1 (high vs low/unclear ROB)	1,177	0.99 (0.76–1.29)
Sensitivity analysis 2 (high vs low ROB)	871	1.01 (0.78–1.30)
Selective reporting (reporting bias)	**Number**	**RR (95% CI)**
Primary, univariate analysis (high/unclear vs low ROB)	1,086	0.62 (0.53–0.73)
Multivariable analysis* (high/unclear vs low ROB)	1,086	0.45 (0.34–0.61)
Sensitivity analysis 1 (high vs low/unclear ROB)	1,086	1.36 (0.98–1.88)
Sensitivity analysis 2 (high vs low ROB)	671	0.92 (0.67–1.26)

95% CI: 95% confidence interval; ROB: risk of bias; RR: risk ratio
[a]High or unclear risk of bias compared with low risk; RR < 1 indicates low risk associated with trial registration, RR > 1 indicates high/unclear risk associated with trial registration
*Full multivariable model included the following: year of publication (continuous), number

of participants (continuous), type of intervention (pharmaceutical vs non-pharmaceutical), study design (parallel-group RCT vs others), geographical region (Europe, North America, and multiregional vs others), and availability of an open access full-text publication (yes vs no); all sensitivity analyses are univariate.

Association of clinical trial registration and risk of bias

All risk of bias domains, with the exception of attrition bias, were significantly associated with clinical trial registration in that registered trials were more likely to have been assessed as having low risk of bias, in both univariate and multivariable analyses (Table 2). The direction of association changed for one risk of bias domain in sensitivity analysis: grouping unclear with low risk of reporting bias resulted with trial registration favoring a high risk of bias, most likely a result of the smaller proportion of unclear trials in the registered group (17%) than the unregistered group (44%). Similarly, in sensitivity analysis excluding unclear risk, no association between clinical trial registration and risk of reporting bias was observed. For all other domains, excluding unclear assessments strengthened the associations. Primary, multivariable, and sensitivity analyses suggest evidence of no association between clinical trial registration and risk of attrition bias.

Secondary analysis – Association of clinical trial registration and overall risk of bias

Of 368 registered trials, 45 (12%) were at overall low risk, 141 trials (38%) were at overall unclear risk, and 182 (49%) were at overall high risk. Of 809 trials that were not registered, 29 (4%) were at overall low risk, 261 trials (32%) were at overall unclear risk, and 519 (64%) were at overall high risk. The analyses suggest that clinical trial registration may be associated with overall low risk bias as observed with univariate, multivariable, and sensitivity analyses (Table 3).

Table 3. Risk ratios (RRs) for the presence of overall risk of bias of having been registered vs. not having been registered

Overall risk of bias	Number	RR[a] (95% CI)
Primary, univariate analysis (high/unclear vs low ROB)	1,177	0.29 (0.19–0.46)
Multivariable analysis* (high/unclear vs low ROB)	1,177	0.31 (0.18–0.54)
Sensitivity analysis 1 (high vs low/unclear ROB)	1,177	0.71 (0.62–0.81)
Sensitivity analysis 2 (high vs low ROB)	775	0.27 (0.17–0.41)

95% CI: 95% confidence interval; ROB: risk of bias; RR: risk ratio
[a]High or unclear risk of bias compared with low risk; RR < 1 indicates low risk associated with trial registration, RR > 1 indicates high/unclear risk associated with trial registration

*Full multivariable model included the following: year of publication (continuous), number of participants (continuous), type of intervention (pharmaceutical vs non-pharmaceutical), study design (parallel-group RCT vs others), geographical region (Europe, North America, and multiregional vs others), and availability of an open access full-text publication (yes vs no); all sensitivity analyses are univariate.

Secondary analysis – Association of prospective or retrospective clinical trial registration and risk of bias

Of 368 registered trials, 135 (36.7%) were registered prospectively and 233 (63.3%) retrospectively. Secondary analyses suggest that prospective clinical trial registration may be associated with low risks of selection bias from inadequate allocation concealment, performance bias, and detection bias compared with retrospective clinical trial registration (Table 4). The association of prospective clinical trial registration also favored low risks of selection bias due to inadequate random sequence generation and reporting bias, but these were not statistically significant. As with the primary analyses, no association was observed with attrition bias, although the confidence interval was imprecise (95% CI 0.85 to 1.36).

Table 4. Secondary analyses: Risk ratios for the presence of high or unclear risk of bias of prospective versus retrospective registration

Registered trials (n=368)	**High or unclear ROB, proportion (%)**		
	Prospective	**Retrospective**	**RR[a] (95% CI)**
Random sequence generation (selection bias)	39/135 (29%)	78/233 (33%)	0.86 (0.63-1.19)
Allocation concealment (selection bias)	48/135 (36%)	123/233 (53%)	**0.67 (0.52-0.87)**
Blinding of participants and personnel (performance bias)	43/126 (34%)	125/208 (60%)	**0.57 (0.43-0.74)**
Blinding of outcome assessment (detection bias)	52/133 (39%)	129/229 (56%)	**0.69 (0.55-0.88)**
Incomplete outcome data (attrition bias)	63/135 (47%)	101/233 (43%)	1.08 (0.85-1.36)
Selective reporting (reporting bias)	33/101 (33%)	79/215 (37%)	0.89 (0.64-1.24)

95% CI: 95% confidence interval (bold indicates the 95% CI does not cross null); ROB: risk of bias; RR: risk ratio

[a]High or unclear risk of bias compared with low risk; RR < 1 indicates low risk associated with prospective trial registration, RR > 1 indicates high/unclear risk associated with prospective trial registration

DISCUSSION

Summary of main findings

Among a large sample of clinical trials included in recently published (2015-2019) systematic reviews of interventions, this study found that clinical trial registration was associated with low risk of bias for all bias domains examined except for attrition bias, and for overall risk of bias. These findings were consistent using both univariate and multivariable regression models. For three bias domains – random sequence generation, performance bias, and detection bias – grouping unclear risk with low risk or excluding trials with unclear risk altogether did not impact the direction or significance of the associations. Evidence of no association between clinical trial registration and attrition bias was observed; however, imprecise estimates preclude a definitive conclusion of no association.

Comparing prospectively vs. retrospectively registered trials, prospectively registered trials were more likely to have low risks of selection bias due to inadequate allocation concealment, performance bias, and detection bias; no associations were noted for selection bias due to inadequate random sequence generation, attrition bias, or reporting bias; however, imprecise estimates preclude a definitive conclusion for these domains.

Our findings are in line with prior research investigating clinical trial registration and risk of bias. In a study of fertility treatment trials, 44% of 693 randomized controlled trials published between 2010 and 2014 had been registered and significant differences were observed between registered and non-registered trials for random sequence generation, allocation concealment, and selective outcome reporting.[10] Similarly, in a study of randomized controlled trials conducted in Latin America and the Caribbean and published in 2010, 17% of 526 trials had been registered in ICTRP, of which registered trials were a lower risk of overall bias than non-registered trials.[21] Because trials may be initiated for reasons other than regulatory approval or publication, examining trials included in systematic reviews may shed light more directly on the impact to evidence-based decision-making.

Methods for minimizing bias in clinical trials and ascertaining the impact of potential bias

Although not unexpected, clinical trial registration was associated with low risk of bias for many domains. The causes of these associations are unclear, but they could be influenced by the review authors having additional sources of information when assessing risk of bias and improved reporting of methods

(such as compliance with CONSORT recommendations). It could also be that registered trials may be more likely to involve a multidisciplinary team of investigators who are aware of both methods for minimizing the risks of bias during the conduct of the trial and standard trial registration and reporting requirements.

By definition, many aspects of the design and conduct of an experimental study are directly controlled by the investigators. With respect to clinical trials, how the randomization sequence is generated, how allocation of participants is concealed, whether blinding is done, and how and which outcomes are reported are fully under to the control of investigators from the protocol stage and throughout the clinical trial lifecycle. All these methods are encompassed within the risk of bias domains that were associated with clinical trial registration in this study. For the remaining risk of bias domain examined – attrition bias – the association with clinical trial registration was inconclusive. As with all bias domains, attrition bias involves multiple factors; however, missing data, a key contributor to attrition bias, cannot be completely controlled. Although trialists can apply methods aimed at preventing participant attrition, such as compensating patients, using a run-in period, or employing a flexible treatment and follow-up schedule,[22] some reasons for missing data are outside the hands of the investigators, such as death, participants missing follow-up visits, or participants withdrawing consent. Thus, given that study attrition cannot always be controlled, the presence of missing data could be distributed evenly across studies to explain why the proportion of trials with unclear and high risk of attrition bias were the same regardless of trial registration status.

In addition to research dedicated to reducing missing data, much work has been put into improving the quality of clinical trials overall, especially with respect to the transparent reporting of trial methods and findings. In our sample of trials, all domains had a high percentage of trials assessed at high or unclear risk of bias (42%-65%). Although these data are limited to the clinical topic areas covered by the Cochrane MOSS network, prior research has reported similar percentages of high or unclear risk of bias across many different clinical areas.[23,24] It is important to note that risk of bias assessments are driven by two factors – the reporting of methods and the actual methods – and interpretation of unclear or high risk may conflate the two. Another possibility for the high number of unclear and high risk of bias assessments could be the misinterpretation of the first version of the Cochrane Risk of Bias tool.[25] Reviewers could complete their assessment driven by single, strict yes/no responses (e.g., Were any participants lost to follow-up?) and not necessarily consider how these factors would influence (i.e., bias) the effect estimates. The second version of the Risk of Bias tool,[12] which was incorporated in the 2020 update of the Cochrane

Handbook,[26] addresses this issue by incorporating signaling questions for each domain and applying an algorithm to help reviewers navigate through their assessments. Study design specific versions (e.g., cross-over trials, cluster-randomized trials) also have been developed for the second version. As uptake of the new tool enters the evidence synthesis ecosystem, it will be interesting to see if the proportion of studies with unclear risk of bias assessments decreases.

The state of clinical trial registration and the evidence synthesis ecosystem

It has been more than 15 years since the ICMJE recommended that journals publish manuscripts of trial results only when the trial had been registered in a public trials registry. Although there was a trend of improved registration in more recent years, the overall number of registered trials in our sample was low (31% overall and 38% since 2010). Even more, of registered trials, only 37% had been registered prospectively. Other studies examining trends in clinical trial registration have also reported low rates (50% or less) of prospective trial registration.[27–30] It is important to note that the trials included in this study were identified from recently published systematic reviews of interventions (2014-2019), and thus impact current day evidence-based decision making.

The two bias domains with the largest percentage difference in unclear assessments between registered and non-registered trials were allocation concealment and reporting bias. Sensitivity analysis grouping unclear with low risk of bias impacted allocation concealment and reporting bias; excluding unclear risk of bias impacted only reporting bias. Overall, allocation concealment had the highest percentage of unclear risk of bias (61%). Currently, allocation concealment is not an explicit data element captured in the clinical trial registration record; however, it is an item on the CONSORT checklist.

A major advantage of clinical trial registries is the opportunity to compare the planned outcomes in the trial registration record with the outcomes reported in the trial publications. Even when trials had been registered retrospectively, more than one-third had issues with selective outcome reporting. In the updated Cochrane Risk of bias tool, selective outcome reporting has been replaced by assessing the bias in selection of the reported results and the assessment of selective outcome reporting is recommended to be done for the review level rather than at the trial level.[12] As switching of clinical trial outcomes remains problematic in the published literature,[31,32] the clinical trial registration record is a useful resource to identify both potential reporting bias and bias in the selection of the reported results when trials have been registered.

Also notable was that more than half of the trial registration numbers in our sample were not cited by the systematic review authors as recommended by the Methodological Expectations of Cochrane Intervention Reviews (MECIR Standards);[33] we identified 51% of trial registrations by manually searching the clinical trial registers. We also observed that, when reported, the trial registration numbers were reported in various places across reviews—most frequently in the table of characteristics of included studies or the risk of bias tables, and sometimes in the main text or as a reference to the study. It is uncertain the extent that trial registries, if searched at all, are being utilized by review authors and incorporated into the evidence ecosystem.

CONCLUSIONS AND IMPLICATIONS FOR RESEARCH

This study found that clinical trial registration was associated with low risk of bias for five of the six domains examined, using both univariate and multivariable regression models, for a large sample of clinical trials included in systematic reviews of interventions within eight clinical topic areas. In addition to following best practice standards for registering trials prospectively, trialists should also take care to implement, and clearly report, methods for minimizing the risk of bias. Systematic reviewers should also follow guidelines (Cochrane, PRISMA 2020) for incorporating searches of the clinical trial registries and employing trial registry records when assessing the study's risk of bias, especially as relates to selective outcome reporting and publication bias. In systematic reviews with meta- analysis, trial registration could serve as a relevant single variable for conducting sensitivity analysis to examine the impact on results.

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ADDITIONAL FILES

Supplementary materials

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Python code for extracting risk of bias data from Cochrane reviews

```
import os
import xlsxwriter
import collections
from bs4 import BeautifulSoup

ReviewDataRow = collections.namedtuple('ReviewDataRow', 'group_name
review_name study_id bias authors_judgment')

def extract_data(input_dir):
    review_data = []
    for subdir, dirs, files in os.walk(input_dir):
        group_name = os.path.basename(subdir)
        for file_name in files:
            review_name = file_name.replace('.html', '')
            full_path = os.path.join(subdir, file_name)
            with open(full_path, 'r', encoding='utf-8') as f:
                html_text = f.read()
                soup = BeautifulSoup(html_text, 'html.parser')

                                included_studies_section = soup.find("section",
class_="characteristicIncludedStudiesContent")

                if not included_studies_section:
                    raise Exception('Could not find included studies section.')

                    study_ids = [title.text for title in included_studies_section.find_
all("span", class_="table-title")]
                tables = included_studies_section.find_all("table")

                if not tables:
                    raise Exception('Could not find review study tables.')

                if len(study_ids) != len(tables):
                raise Exception('Number of titles and number of tables must match.')

                study_num = 0
                for table in tables:
                    study_id = study_ids[study_num]
                    in_rob_section = False
                    for row in table.find_all("tr"):
                        if 'Bias' in row.td.text:
```

```
                    in_rob_section = True
                    continue
                if in_rob_section:
                    cells = row.find_all("td")
                    bias = cells[0].text.strip()
                    authors_judgment = cells[1].text.strip()
                     review_data.append(ReviewDataRow(group_name, review_
name, study_id, bias, authors_judgment))
            study_num = study_num + 1
            if not in_rob_section:
                raise Exception('Unable to find risk of bias section.')

    return review_data

def write_to_excel(review_data):
    # Create an new Excel file and add a worksheet.
     workbook = xlsxwriter.Workbook(r'C:\projects\sandbox\output\extracted_
data.xlsx')
    bold = workbook.add_format({'bold': True})

    worksheet = workbook.add_worksheet()

    # Widen the first column to make the text clearer.
    # worksheet.set_column('A:A', 20)

    worksheet.write('A1', 'Group', bold)
    worksheet.write('B1', 'Review', bold)
    worksheet.write('C1', 'Study ID', bold)
    worksheet.write('D1', 'Bias', bold)
    worksheet.write('E1', "Author's Judgment", bold)

    for tup in enumerate(review_data):
        row = tup[0] + 1
        row_data = tup[1]

        worksheet.write(row, 0, row_data.group_name)
        worksheet.write(row, 1, row_data.review_name)
        worksheet.write(row, 2, row_data.study_id)
        worksheet.write(row, 3, row_data.bias)
        worksheet.write(row, 4, row_data.authors_judgment)

    workbook.close()

data = extract_data(r'C:\projects\sandbox\input\Reviews')
write_to_excel(data)
```

CHAPTER 8

General discussion

The term evidence ecosystem refers to the dynamic interconnectedness of primary research, evidence synthesis, clinical practice guidelines, and health care decision-making.[1,2] Within an ideal system, evidence is generated from primary research, which is then gathered and synthesized into meaningful insights in which to support the development of clinical practice guidelines and to inform evidence-based medicine. There are several beneficiaries of a well-functioning evidence ecosystem including, but not limited to, patients and caregivers, clinicians, health care systems, regulatory and reimbursement agencies, and research funders.

There, however, exists disjunction in the evidence ecosystem such that information generated from patients (primary research) may not contribute to the synthesis of available evidence (systematic reviews), and the synthesis of available evidence may not feed into health care decision making (clinical practice guidelines). Thus, the loss of information within the evidence ecosystem reduces the capacity and efficiency of evidence-based medicine at the ultimate cost to patient care.

This thesis investigated the applicability and utilization of systematic reviews in clinical practice by assessing potential barriers and providing potential solutions for better incorporating systematic reviews into clinical decision making. Chapters 2-3 were set in the context of clinical practice guidelines and provided a snapshot of the extent to which systematic reviews were being incorporated into clinical practice guidelines and perspectives from multiple stakeholders on rating clinically important research questions. Chapters 4-5 presented a deeper dive into key differences and loss of information in the measurement and reporting of outcomes within the evidence ecosystem and highlighted ways forward. Chapters 6-7 reviewed the reliability of evidence in the context of clinical trial registration and risk of bias.

Summary of key findings

Chapter 2 presented an example of the use, or non-use, of systematic reviews in informing evidence-based clinical practice guidelines for age-related macular degeneration (AMD). The absence of systematic reviews cited to underpin recommendations that was observed in the study can be classified in two ways – lack of applicability and lack of utilization.

- ***First***, guideline authors may have been unaware or simply chose not to include systematic reviews as supporting evidence for their recommendations. Although multiple, reliable systematic reviews (i.e., reviews that reported eligibility criteria, comprehensive searches, methodologic quality of included studies, appropriate statistical methods for meta-analysis, and conclusions based on results) were available to underpin 15 of the 35 (43%)

treatment recommendations in the guidelines, only one recommendation in the guideline was supported by a systematic review by the guideline authors. Furthermore, certain systematic reviews may not have been cited in the guidelines as citing these may have been considered weaker than citing the clinical trials directly or because it may have been believed that the users of the guideline would be more familiar with the trials than with the systematic review. A sizable proportion (30%) of published systematic reviews in this sample were deemed unreliable as they did not employ standard methodology.

- ***Second***, no reliable systematic review was available to inform the remaining 20 of 35 (57%) treatment recommendations in the guidelines, suggesting a vast evidence gap in the management of patients with AMD.

Thus, the potential barriers to the application and use of systematic reviews in clinical practice were found to be two-fold: there was a disruption in the evidence ecosystem such that 1) reliable systematic reviews were not being integrated into health care decision making and 2) the available systematic reviews did not address many of the questions for which decision makers needed answers. Priority setting-exercises are an example of setting a research agenda when multiple clinical questions are unanswered.

Chapter 3 described a priority-setting exercise in which multiple stakeholders were surveyed to rate the importance of clinical questions for research to answer and to identify patient-important outcomes for AMD. The clinical questions were derived from the treatment recommendations provided in the clinical practice guidelines and evidence gaps observed in Chapter 2. The results of the surveys yielded notable agreement among the stakeholders and implications for prioritizing future evidence synthesis research.

- ***First***, of the 17 highly important clinical questions prioritized by the American Academy of Ophthalmology (AAO) Retina/Vitreous Panel (the AMD clinical practice guideline developers), health care professionals rated 12 as high priority and patients with AMD rated all 17 as high priority clinical questions for research to answer, suggesting good agreement.
- ***Second***, clinical questions related to anti-vascular endothelial growth factor (anti-VEGF) therapy comprised more than half (9) of all clinical questions rated as highly important by all stakeholders. At the time of the surveys, anti-VEGF therapy was becoming the new standard of care for AMD, and the importance of these questions to patients, health care professionals, and clinical practice guideline developers were reflective of current clinical practice.

- ***Third***, in prioritizing clinical questions and patient-important outcomes, it was clear that a balance between the effectiveness (clinical improvement) and safety (minimization of adverse events) of treatment was seen as highly important amongst all stakeholders.

Thus, the observed agreement amongst various stakeholders within the evidence ecosystem may be viewed positively and leveraged to align evidence synthesis research with priority questions and to facilitate the uptake of systematic reviews in clinical practice guideline development. In addition, research addressing questions and outcomes related to safety should not be neglected in favor of effectiveness.

Chapter 4 compared outcomes frequently measured and reported in clinical trials and Cochrane systematic reviews for the four most prevalent eye diseases (AMD, cataract, diabetic retinopathy, and glaucoma). The study showed differences in outcomes assessed in systematic reviews versus those collected from primary research.

- ***First***, the total number of outcomes assessed in systematic reviews represented only a fraction (17–25%) of the total number of outcomes reported in clinical trials.
- ***Second***, some outcomes of interest in systematic reviews (2–8%) were not assessed in any clinical trial on the same eye disease topic.
- ***Third***, when limiting to the seven most frequently reported outcomes, there was an overlap of only 3 to 5 outcomes between clinical trials and systematic reviews.

Thus, there is a mismatch in outcomes of interest and a substantial loss of information within the evidence ecosystem such that most outcomes measured in clinical trials are not synthesized in systematic reviews. Although the selection of outcomes included in systematic reviews can be independent of the data collected from primary research, there should be consistency between evidence generation and evidence synthesis to minimize research waste at all levels. Core outcome sets by disease topic area have been proposed as a potential solution to this type of loss of information to ensure that outcomes important for decision making are captured at both levels of evidence generation and evidence synthesis.

Chapter 5 builds on the findings gathered from Chapter 4 by examining specific outcomes that were selected and how they were defined in systematic reviews compared with the primary studies included in the reviews. The results suggested that the research question and specific definition of outcomes selected by review authors may limit the number of studies contributing to meta-analysis or preclude meta-analysis altogether.

- ***First***, of 175 eligible Cochrane reviews 23% did not identify a sufficient number of primary studies to inform the research question (i.e., 0 or 1 studies were included in these reviews).
- ***Second***, among 125 Cochrane reviews with two or more included studies, only 59% could conduct a meta-analysis for the main outcome.
- ***Third***, the median proportion of clinical trials included in the primary meta-analysis was 28% (range 0–71%) per review; the median proportion of clinical trials included in any meta-analysis increased to 74% (range 0–100%) per review.
- ***Fourth***, in some instances when outcome domains were the same between clinical trials and reviews (e.g., visual acuity), clinical trial data did not meet the review outcome definition (e.g., reported as a mean change instead of proportion who changed) and were not included in meta-analysis.

Thus, based on the research question and choice of outcome definition in the systematic review, the effort put in to completing the review may lead to non-informative results or information loss. In light of limited resources, research questions and outcomes selected for systematic reviews should address clinical uncertainties in treatment decisions and maximize information available from primary research.

Chapter 6 investigated clinical trial registration among trials included in recently conducted systematic reviews and found that the status of clinical trial registration is less than ideal. The value in clinical trial registration, in addition to documenting the existence of the research, is to maximize transparency of methods and minimize potential reporting biases. Ultimately, the reliability and credibility of primary research impacts the trustworthiness of evidence synthesis.

- ***First***, fewer than a third (31%) of clinical trials that were published after the International Committee of Medical Journal Editors' (ICMJE) recommendation that clinical trials be registered as a requirement for publication and were included in a sample of 100 Cochrane reviews had been registered. Of those that had been registered, only 37% were registered prospectively and 31% had posted trial results.
- ***Second***, in a subgroup of clinical trials published within the last 10 years, well after the 2004 ICMJE statement[3] recommending clinical trial registration for publication and the 2007 US Food and Drug Administration (FDA) law requiring clinical trial registration for drug approval,[4] the proportion of registered trials increased slightly to 38%.

Thus, although some improvement in clinical trial registration has been observed over time, the status is not yet ideal. Not only is clinical trial registration

required for regulatory approval, but it is also a critical step to building trust and reliability within the evidence ecosystem. Clinical trial registration serves to reduce research waste, improve study designs, discourage reporting bias, and increase dissemination.

Chapter 7 expands on the research reported in Chapter 6 by extending the analysis of clinical trial registration among studies included in systematic reviews to the association of clinical trial registration with risk of bias. Domain-specific risk of bias assessments shed light on the certainty of evidence of trial results as well as overall review findings.

- ***First***, clinical trials that had been registered were associated with low risk of bias for five of the domains assessed: random sequence generation, allocation concealment, performance bias, detection bias, and reporting bias. No association was observed for attrition bias.
- ***Second***, based on multivariable analysis, eight study characteristics were associated with clinical trial registration: allocation concealment; low risk of performance bias; low risk of reporting bias; more recent publication; 100 or more participants; pharmaceutical interventions; study conducted in Europe, North America, or multiregional; and having an open access publication.
- ***Third***, compared with retrospective registration, prospective clinical trial registration was associated with low risks of selection bias due to inadequate allocation concealment, performance bias, and detection bias.

Thus, among recently published systematic reviews, clinical trial registration was shown to be associated with low risk of bias. The reasons for this association are hypothetical but could be related to the availability of information provided in the trial registration record when assessing risk of bias, or it could be that registered trials are likely to be conducted by investigators who are familiar with and follow best practice methods which include standard trial registration and reporting requirements. Nevertheless, clinical trial registration should be encouraged for all trials to improve the reliability and transparency of data throughout the evidence ecosystem.

Implications for practice and research

1. Asking the right questions

For systematic reviews to be incorporated into clinical practice, they must address relevant research questions and provide useful evidence to inform clinical decision-making. This is not always the case as sometimes there is no reliable systematic review available to address a specific treatment recommendation (Chapter 2) or systematic reviews that have been conducted may not provide key findings

(Chapter 5). Before any systematic review is undertaken, the clinical uncertainty that the research aims to answer should be fully identified and a rationale provided. Taking it a step further, the investigators should collaborate closely with multiple stakeholders to both 1) determine what clinical answers are needed and 2) plan how the results will be disseminated and used for clinical decision-making.

An example of the evidence ecosystem in action was presented in Chapter 3. We started with actual treatment recommendations to derive clinical questions and worked with multiple stakeholders to rate the importance of finding the answers to each clinical question. As a practical follow-up, the study findings were cycled back to the American Academy of Ophthalmology (AAO) to inform an update of their guidelines. A research plan was made to address all clinical questions that mapped to a treatment recommendation such that:

1. If a reliable systematic review was available and provided answers to a research question, the systematic review was shared with the clinical practice guideline developers to support their treatment recommendations.
2. If no reliable systematic review was available or a systematic review had been conducted but did not provide conclusive answers (e.g., no eligible studies were identified, results were unclear or imprecise), a systematic review on the topic was registered with Cochrane or the existing review was updated.
3. If no reliable systematic review was available as it was known that there had been no primary studies on the topic, the clinical questions were shared with trial investigators.

The partnership with the AAO in updating their guidelines was replicated across other eye diseases to support all of their 23 Preferred Practice Patterns (PPPs);[5-9] however, limitations with this approach should be noted. In an already intense and time sensitive process of developing clinical practice guidelines, integrating the additional steps of translating treatment recommendations to answerable clinical questions, surveying multiple stakeholders, and creating a research plan for each topic may not be feasible or resources may not be available. Additionally, the speed at which evidence is being generated in some areas (COVID-19 is a relevant example) may outpace this type of question-deriving method. One way to mitigate resources and speed up the process, but retain the core characteristics of our approach, would be to build a multidisciplinary review team representing key stakeholders (clinical practice guideline developers, content experts, methods experts, clinical trialists, health care professionals, patients, etc.) to ensure important clinical questions are being addressed in systematic reviews and so that the review findings will be known by these groups. The development and adoption of core outcome sets also could facilitate the process.

Many other frameworks for identifying and prioritizing topics for systematic reviews have been proposed.[10–13] The majority of methods recommend the involvement of a diverse group of stakeholders, and an assessment of the existing literature and evidence gaps before undertaking a systematic review.[14,15] However, although most reported implications for practice, few took actionable steps to directly integrate their findings into clinical decision-making and bridge the evidence ecosystem.

There also must be consideration based on the ideal versus best available evidence. Many reviews focused on only randomized controlled trials fail to make use of real-world evidence or miss out on addressing important questions that are commonly addressed with other study designs (e.g., populations with rare diseases, diagnostic test accuracy, evaluation of harms). Not all clinical decision-making is focused only on intervention effectiveness. Sometimes the question of interest may require novel approaches to find the answer. The development of systematic review methods to assess questions of safety, screening and diagnostic test accuracy, and prognosis in recent years has demonstrated that evidence synthesis research can be relevant yet maintain its methodologic rigor.[16–20] As have methods to incorporate non-traditional systematic review data such as data from preclinical studies and case reports, non-comparative studies or individual patient-data (IPD), and combining data from randomized and non-randomized studies to make use of the existing primary research.[21–25] The expanding toolbox for conducting systematic reviews reduces the barriers to asking the right research question and trusting the answers.

2. Selecting the right outcomes

As described in Chapter 2, the shortcomings of using systematic reviews in clinical practice are at least two-fold – systematic reviews may not address the questions in which decision makers need answers and systematic reviews may not provide the information needed to make decisions. While asking the right questions addresses the former issue, selecting the right outcomes addresses the latter.

In Chapters 4 and 5, we highlighted differences between primary research and systematic reviews in the outcomes selected and how they were defined. Based on the five elements of a clearly defined outcome (domain, measurement, method of aggregation, metric, and time point)[26,27] it is possible that although data are available to address a research question, there may be loss of information during the evidence synthesis process. In a case study of a Cochrane review which included 48 studies addressing its research question, none of the studies reported data related to the primary outcome per the systematic review outcome definition, although 18 studies provided data on the primary outcome domain

using other outcome definitions.[28] By analyzing the outcome as continuous outcome, as it was reported in the primary studies, rather than as a proportion, as was defined by the systematic review authors, 11 studies would have been eligible for meta-analysis, instead of none when analyzing proportions. The choice to use a dichotomous outcome definition instead of a continuous outcome resulted in a missed opportunity to use available data from trials.

It should be noted, however, that for some clinical decisions a dichotomous outcome definition may be of more use than a continuous outcome definition. Dichotomous outcomes can be easily interpreted and understood by patients and other health care decision makers. For example, in the field of eyes and vision, a commonly asked question from patients is, "Will I be able to drive?" To answer this question, visual acuity outcomes are often defined in systematic reviews as the proportion of patients achieving best-corrected visual acuity of 20/40 or better, the current criteria for possessing a driver's license in many countries. However, many clinical trials report visual acuity as a mean value at a timepoint or a mean change from baseline, which provides an imprecise answer for the original question of interest. How information will be disseminated and consumed at different stages of the evidence ecosystem should inform how data are measured and reported at the time of evidence generation. The development and validation of patient-reported outcome measures (PROMs) and the formation of the United States Patient-Centered Outcomes Research Institute (PCORI) are examples of how the scientific community has taken action to include patient-important outcomes in research.[29,30]

There also are many initiatives underway to develop core outcome sets aimed to align outcomes throughout the evidence ecosystem and reduce research waste.[31-34] Since 2010, the COMET (Core Outcome Measures for Effectiveness Trials) Initiative has promoted the uptake of core outcome sets across clinical trials being conducted within a disease area. The four-step process to developing a core outcome set recommended by COMET includes, 1) defining the scope of core outcomes, 2) assessing whether a new or updated core outcome set is needed and, if yes, registering the intent the create one, 3) designing the protocol to develop the core outcome set, and 4) determining the minimal outcomes to be included in the core outcome set.[35] Although there has been wide-spread adoption of the development of core outcome sets, their application has been less successful, with clinical trial investigators not in full agreement with which outcomes are important or outcomes not being aligned with those that are required for regulatory approval or reimbursement.[36] The development of core outcome sets are also forward-facing in that outcomes that were frequently published in the past may be deemed not important and excluded from the core list of outcomes, thus creating another scenario for potential information loss.

Beyond clinical trials, there is also value in systematic reviews adhering to core outcome sets. In a selected sample of 100 Cochrane reviews, review authors for only seven reviews mentioned consulting a core outcome set when choosing the outcomes for their review.[37] Increased uptake of core outcome sets are needed in evidence synthesis not only to minimize research waste, but to facilitate comparisons of results across different reviews (e.g., overview of reviews or umbrella reviews) and conduct network meta-analysis. Systematic review registers, such as PROSPERO, should also be checked to consider outcomes being used in related evidence synthesis research. By selecting the right outcomes that bridge outcomes measured in primary research and those needed to inform clinical decision-makers, core outcome sets developed for use in systematic reviews may remove barriers to the application and utilization of findings by maximizing the synthesis of available evidence and standardizing results across individual yet related systematic reviews.

3. Strengthening the evidence base

The adage goes, "Garbage in, garbage out," meaning that the results from systematic reviews are only as reliable and trustworthy as the primary research being synthesized. In Chapter 6, we found that a disappointingly small proportion of clinical trials that were conducted since the inception of trial registers had been registered. Even fewer had been registered prospectively or provided results within one year of publication as recommended for standard practice. In Chapter 7, we took a closer look and found that although clinical trials that had been registered had lower risk of bias than trials that had not been registered, the overall quality of all the trials was poor.

The explicit agreement the scientific community makes to study participants is that the information gained from their participation in research will be used and applied to society at large. At a minimum, the research should be conducted with sufficient quality as to be a usable and trusted source of information. In addition to ethical considerations, any contribution towards knowledge gain should be taken advantage of fully to avoid research waste. This concept applies to all levels within the evidence ecosystem. There is a responsibility within the scientific community to ensure that participation in research is not wasted or misused. As with other areas of health care, a holistic approach should be adopted, wherein coordination across evidence generation, evidence synthesis, and clinical decision-making is integrated and working together. At each step there should be a clear downstream impact and a plan of how the information will be or should be implemented.

As this thesis focuses on systematic reviews, our main aim is in strengthening the evidence base in the context of evidence synthesis. One major limitation in conducting evidence synthesis research is the overwhelming amount of information being generated on a daily basis, what is termed "information overload." To date, PubMed, the online bibliographic database hosted by the United States National Library of Medicine contains more than 33 million records.[38] It is estimated that the number of scientific publications increases 8-9% each year; these estimates do not include information presented at conferences, shared on social media, or account for the amount of "big data" being accumulated from electronic health records or claims databases.[39,40]

In order to process the massive amount of data being generated, some pragmatic approaches may be considered without compromising the methodologic rigor of systematic reviews. One proposed method is to incorporate natural language processing (NLP) into the systematic review process.[41-44] Although there is apprehension to perform steps using NLP only, there is general agreement that NLP can supplement traditional review methods such as by applying machine learning to search algorithms, serving as second reviewer or rescreening excluded records for quality control, annotating records to facilitate data extraction and risk of bias assessment, and producing standardized text of the results. More research is needed to determine the validity and acceptability of automation in systematic reviews, but there is potential with NLP to significantly reduce the resource burden and time needed to conduct traditional evidence synthesis and correct for human error or biases in the review process.

Another approach to improve the efficiency in completing a systematic review is to apply rapid review methodology, such as reducing the number of databases searched and employing data verification rather than independent data extraction by two individuals.[45] Rapid reviews aim to expedite the review process by relaxing methodological rigor in order to shorten the time and reduce the resources needed to complete the review. The tradeoffs attempt to minimize the impact on the main results and interpretation of the findings. For example, the risk of not identifying a small study that would not affect the overall effect estimate in meta-analysis may offset the effort and time needed to search an additional bibliographic database.

Additionally, although traditional review methods discourage using search date cut-offs as they are seen to compromise the comprehensive and exhaustive purpose of the literature search, in some cases date restrictions can be justified. For example, in the case of ranibizumab for AMD, searching for relevant studies among articles published before ranibizumab was developed would be unproductive. Furthermore, historical patient populations may not

be comparable to current patient populations, and thus studies published 10 or even 5 years ago may not provide suitable evidence to answer today's questions. Advancements in standard of care, such as anti-retroviral therapy for HIV and second generation direct-acting antivirals for chronic hepatitis C infection, have drastically improved health outcomes in affected patients. An evolving understanding of the underlying disease may also shift clinical management, such as the identification of actionable biomarkers in oncology. To compare new treatments under investigation for certain conditions to the treatment landscape before a significant change in clinical practice would not be appropriate. Over time the quality of research has also improved, as reported in Chapter 7. Although older studies may provide historical context, they often do not adequately describe methods to assess risk of bias and, therefore, offer insufficient or uncertain support for clinical decisions. Thus, employing date restrictions can be reasonable for certain situations.

An adaptation of using search restrictions has also been considered when existing systematic reviews are available. For example, if updating a review or conducting an overview of reviews, to avoid duplication of effort, it would be warranted to use the date of the last search, even if the prior review was completed by a different research team. Some of these issues could be absolved by living systematic reviews, or systematic reviews in which the search and screening processes are performing on a rolling basis and the analyses are updated as soon as new data become available.[46] Living systematic reviews also may be enhanced with semi-automation tools to manage search results, prioritize records for screening, and preliminarily extract data using text mining.

The use of pragmatic approaches to evidence synthesis methods to provide reliable, clinically meaningful findings in a timely manner would help to eliminate barriers in the applicability and utilization of systematic reviews in clinical decision-making.

Concluding remarks

The main theme of this thesis was to identify areas for improvement in the applicability and utilization of systematic review in clinical practice. Although numerous guidelines, consensus statements, and manuals have been developed to walk individuals through how to conduct primary research, how to perform evidence synthesis, and how to produce evidence-based clinical practice guidelines, these processes are generally disconnected from each other in practice. This thesis outlined ways in which systematic reviewers can collaborate with clinical practice guideline developers to ensure that the right questions are being asked so that their findings can be used to inform clinical decision-making,

can build from primary research by selecting the right outcomes to minimize research waste and develop core outcome sets, and can strengthen the evidence base with methods to maximize the efficiency in conducting systematic reviews to get relevant answers in a timely manner. An important step at all stages is to intentionally plan how information will be used upstream and downstream within the evidence ecosystem. A well-functioning evidence ecosystem has the potential to benefit multiple stakeholders, most importantly patients.

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8

APPENDICES

Summary
Samenvatting
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Summary

Key goals of a healthy and functional evidence ecosystem are to optimize the value of the evidence and minimize research waste as information flows from one stage to the next. Within the complex evidence ecosystem, evidence synthesis acts as an intermediary between primary studies and clinical practice by identifying and summarizing information generated from primary studies to deliver key insights to underpin clinical decision making. Thus, there are at least two places for potential loss of information and missed opportunities: when moving from (1) evidence generation to evidence synthesis and (2) from evidence synthesis to clinical practice. Herein, we have defined applicability as the appropriateness or suitability of use and utilization as practical usage. The aims of this thesis are to examine the applicability and utilization of systematic reviews in health care and clinical practice in order to positively affect the health of patients.

In **Chapter 2**, we examined the reliability of systematic reviews of treatments for age-related macular degeneration (AMD). We also mapped whether reliable systematic reviews could have been used (applicability) or had been used (utilization) in the American Academy of Ophthalmology (AAO) Preferred Practice Patterns (PPPs) for AMD. Among 47 systematic reviews of AMD, 33 (70%) were classified as reliable based on the following five criteria: defined eligibility criteria, conducted comprehensive searches, assessed methodologic quality of included studies, used appropriate statistical methods for meta-analysis, and based conclusions on results. Of the 33 reliable reviews, 27 (82%) could have been used to support guidelines in the PPPs (applicability). The other six reliable reviews investigated interventions not covered in the PPPs. Of 35 treatment recommendations provided in the PPPs, only one recommendation (3%) was supported by a systematic review (utilization) when 15 could have been supported by at least one reliable systematic review. Evidence gaps also were noted. For 20 treatment recommendations no reliable systematic review was available. The methods employed in this chapter presented one way to assess the applicability and utilization of systematic reviews in clinical decision-making. Our findings suggested more could be done on both sides to incorporate systematic reviews into clinical practice guidelines.

Based on the findings and evidence gaps identified in Chapter 2, we completed a priority-setting exercise. In **Chapter 3**, diverse sets of stakeholders completed questionnaires to prioritize clinical questions and outcomes for research associated with the treatment of AMD. The groups surveyed included:

- Clinical practice guideline developers: AAO Retina/Vitreous Panel
- Health care professionals: American Society of Retinal Specialists, meeting attendees from the Atlantic Coast Retina Conference and Macula 2017
- Patients: Macular Degeneration Support group

The AAO Retina/Vitreous Panel rated 17 of 70 clinical questions (24%) as highly important. Of those 17 clinical questions, health care professionals rated 12 as high priority clinical questions for research. Patients assessed all 17 clinical questions as high priority. Additionally, patients identified 6 outcomes as the most important AMD outcomes for patients. Both the high priority clinical questions and the patient-important outcomes included topics of clinical effectiveness and safety. Findings from multidisciplinary priority-setting exercises such as this may be helpful to inform future research and clinical care. In **Chapter 4**, we investigated the flow of information from primary research to systematic reviews. We compared outcomes reported in trials versus reviews for the four most prevalent eye diseases: AMD, cataract, diabetic retinopathy, and glaucoma. In a cross-sectional evaluation of 56 systematic reviews that included 414 trials, the median number of outcomes was the same for individual trials and reviews (5 outcomes). However, depending on disease area trials reported 3 to 5 times more unique outcomes than systematic reviews. Only one outcome, visual acuity, was reported in more than half of all trials and reviews. Most of the outcomes included in the systematic reviews were the same as those reported in the trials. However, depending on disease area the systematic reviews included only 17% to 25% of all reported trial outcomes. Thus, there are many outcomes measured and reported by trials that do not get incorporated into systematic reviews. The development of disease-specific core outcome sets may help with consistency between systematic reviews and trials in capturing clinically relevant outcomes and to facilitate the comparison of outcomes across trials and reviews.

As an extension of the work presented in Chapter 4, we undertook a closer evaluation of the outcomes assessed by systematic reviews in eyes and vision. In **Chapter 5**, we investigated how the outcome definitions impacted the inclusion of trial data in meta-analysis. Among 125 systematic reviews that included at least two studies, and thus theoretically qualified for conducting meta-analysis, 75% of the included trials were included in meta-analysis for any outcome (28% were included in meta-analysis of the main review outcome). However, 26% of the systematic reviews did not conduct any meta-analysis for any outcome and 41% did not conduct meta-analysis for the main review outcome. Reasons for not performing a meta-analysis were summarized as either 1) not having a sufficient number of included trials that reported quantitative data for analysis or 2) inconsistency in outcome definitions among the included studies and review. Examples of inconsistent outcome definitions included using different metrics (e.g., means versus proportions) or timepoints (e.g., six months versus one year). These findings suggest that although individual trials and reviews appear to address the same research question, differences in outcome choice and definition may lead to loss of information within the evidence ecosystem. Disease-specific

core outcome sets could provide one way to better align outcome definitions across evidence generation and evidence synthesis research. Reporting guidelines should also be followed to improve complete data reporting for analysis.

In **Chapter 6**, we examined another potential area of information loss between trials and reviews. We assessed whether clinical trials that had been included in systematic reviews had been registered in a clinical trial register. In the past, clinical trial registration was developed to document the existence of a trial, prespecify key methods of the trial, and make the trial results publicly available. With clinical trial registries, researchers and the community at large would have a central place to know about planned, ongoing, and completed clinical trials; appraise prespecified trial methods, such as patient eligibility, intervention descriptions, and outcome definitions; and access key trial results and data. These factors play an important role in evidence synthesis for facilitating the identification of relevant trials, assessing potential biases from what gets reported in trial publications, and as a potential source of supplementary information for review authors. In this chapter, we identified a cross-sectional sample of 100 systematic reviews from Cochrane's Musculoskeletal, Oral, Skin and Sensory Network published between 2014 and 2019. There were 1,177 trials included across all the reviews that were published in 2005 or later. We used 2005 as a cut-off date because it was the year when the International Committee of Medical Journal Editors' (ICMJE) recommendation that all clinical trials be registered as a prerequisite for publication was initiated. Less than one third (31%) of the trials had been registered, and even fewer had been registered prospectively or provided trial results with the registration record as recommended. More stringent enforcement of clinical trial registration is needed so that complete trial information is available to adequately assess the quality and strength of evidence.

In **Chapter 7**, we examined the association between clinical trial registration and risk of bias by using the same set of 1,177 clinical trials as in Chapter 6. We assessed the following bias domains: random sequence generation, allocation concealment, performance bias, detection bias, attrition bias, and reporting bias. There were two domains with at least half of the trials at low risk of bias: random sequence generation and attrition bias. The remaining domains were assessed at high or unclear risk of bias for the majority of trials. As such, only a small proportion of trials were judged to be at low risk of bias overall (12%) according to the Cochrane algorithm ("overall low risk of bias when low risk of bias was assessed for all key domains, overall unclear risk of bias when unclear risk of bias was assessed for one or more key domains, and overall high risk of bias when high risk of bias was assessed for one or more key domains"). Using univariate logistic regression analysis, clinical trial registration was associated with low risk of bias overall and for all individual domains except for attrition

bias. Multivariable analyses and sensitivity analyses were also performed, and the results supported the primary univariate analysis. In secondary analyses, we compared *prospective* clinical trial registration (i.e., trial registration before enrollment of the first study participant) with *retrospective* clinical trial registration. Prospective registration was associated with low risk of bias for three domains: selection bias due to inadequate allocation concealment, performance bias, and detection bias. The findings from this chapter suggest that the design, conduct, and reporting of clinical trials are connected. It should also be noted that both the appropriate conduct and complete reporting of clinical trials are needed to effectively inform downstream evidence synthesis.

Lastly, in **Chapter 8**, we presented a general discussion of the research and key findings from each chapter and we provided implications for future research and practice. The themes discussed centered on three issues for evidence synthesis: 1) asking the right questions, 2) selecting the right outcomes, and 3) strengthening the evidence base. All three of these areas play an important role for minimizing the loss of information within the evidence ecosystem and optimizing actionable insights for clinical practice decision-making. In terms of asking the right questions, systematic review authors should coordinate with clinical practice guideline developers in order to identify what evidence is relevant to inform treatment recommendations and where evidence gaps may exist.

Priority-setting exercises with diverse stakeholders may be beneficial to ensure that important questions and outcomes are being addressed to facilitate uptake (applicability) and to allocate resources to research that will be incorporated into clinical decision-making (utilization). In terms of selecting the right outcomes, systematic review authors should coordinate not only with clinical decision-makers, but also with primary investigators to increase the value of trial data for evidence synthesis. Patients should also play a critical role in setting the research agenda to ensure that their questions are addressed. Disease-specific core outcomes sets have been proposed as a possible solution to minimize research waste by defining standard outcomes for primary research to measure and report. Systematic reviewer authors should also use these core outcome sets when selecting and defining the outcomes for their review. In terms of strengthening the evidence base, the work of evidence synthesis is moving uphill in regards to the volume of information being generated on a daily basis and compounded by slower improvements in quality.

Novel applications of technology, such as natural language processing, and novel methods, such as rapid reviews and living reviews, may provide a sustainable way forward for providing meaningful answers to inform clinical practice in a timely manner.

Collaboration across all steps of the evidence ecosystem is key for improving the applicability and utilization of systematic reviews in clinical practice. Although dynamic and complex, a healthy evidence ecosystem offers the most value in research and, hopefully, the best outcomes for patients.

Summary in Dutch (Nederlandse samenvatting)

De belangrijkste doelstellingen van een gezond en functioneel *evidence* ecosysteem zijn het optimaliseren van de toepasbaarheid van evidence en het minimaliseren van onderzoeksverspilling (*research waste*) wanneer informatie van de ene naar de volgende fase van het ecosysteem gaat. Binnen het complexe evidence-ecosysteem vormt evidence-synthese de overgang tussen primaire onderzoeken en de klinische praktijk. Alle informatie die is gegenereerd in primaire onderzoeken, wordt geïdentificeerd en daarna samengevat om belangrijke inzichten te geven ter ondersteuning van klinische besluitvorming. Op tenminste twee momenten kan er dus mogelijk verlies van informatie ontstaan en kunnen kansen gemist worden: bij de overgang van (1) het genereren van evidence naar het samenvatten ervan (evidence-synthese) en (2) van evidence-synthese naar de klinische praktijk. In dit proefschrift gebruiken we twee begrippen: 'toepasbaarheid' en 'gebruik'. Toepasbaarheid hebben we gedefinieerd als geschiktheid voor gebruik in de klinische praktijk en 'gebruik' als het daadwerkelijke gebruik van systematische reviews in de praktijk. De doelstellingen van dit proefschrift zijn om de toepasbaarheid en het daadwerkelijke gebruik van systematische reviews in de gezondheidszorg en de klinische praktijk te onderzoeken teneinde uiteindelijk de gezondheid van patiënten positief te beïnvloeden.

In **Hoofdstuk 2** onderzochten we de geschiktheid van systematische reviews bij de keuze van verschillende behandelingen voor maculadegeneratie. We brachten ook in kaart of betrouwbare systematische reviews gebruikt hadden kunnen worden (toepasbaarheid) of waren gebruikt (gebruik) in de *Preferred Practice Patterns (PPP's) for age-related macular degeneration* van de *American Academy of Ophthalmology (AAO)*. Van de 47 systematische reviews werden 33 (70%) als geschikt geclassificeerd volgens de volgende vijf criteria: goede definitie van de in- en exclusiecriteria, uitvoering van uitgebreide zoekacties, het beoordeeld hebben van de methodologische kwaliteit van de geïdentificeerde primaire onderzoeken, gebruikmaking van geschikte statistische methoden voor meta-analyse en conclusies gebaseerd op de resultaten. Van de 33 geschikte reviews hadden er 27 (82%) gebruikt kunnen worden ter ondersteuning van richtlijnen in de PPP's (toepasbaarheid). De overige zes geschikte reviews onderzochten behandelingen die niet in de PPP's aan de orde waren. Van de 35 behandelaanbevelingen die in de PPP's werden gegeven, werd slechts één aanbeveling (3%) ondersteund door een systematische review ('gebruik'), terwijl 15 ondersteund hadden kunnen worden door ten minste één betrouwbare systematische review (toepasbaarheid). Er werden ook evidence-lacunes gevonden: voor 20 behandelaanbevelingen was geen betrouwbare systematische review beschikbaar. De methoden die in dit hoofdstuk werden gebruikt, bieden een manier om de toepasbaarheid en het gebruik van systematische reviews bij

klinische besluitvorming in kaart te brengen. De bevindingen suggereren dat op beide fronten meer zou kunnen worden gedaan om systematische reviews op te nemen in klinische richtlijnen.

Op grond van de bevindingen in Hoofdstuk 2 en de daarin vastgestelde evidence-lacunes voerden wij een prioriteitsstellingsprocedure uit. In **Hoofdstuk 3** vulden diverse groepen belanghebbenden vragenlijsten in om prioriteit te geven aan klinische vragen en uitkomstmaten voor onderzoek betreffende de behandeling van maculadegeneratie. De onderzochte groepen bestonden uit de volgende personen:

- Richtlijnontwikkelaars (*Retina/Vitreous Panel* van de AAO);
- Professionals uit de gezondheidszorg (*American Society of Retinal Specialists*, deelnemers aan de *Atlantic Coast Retina Conference and Macula 2017* meeting);
- Patiënten (*Macular Degeneration Support group*).

Het AAO Retina/Vitreous Panel vond 17 van de 70 klinische vraagstellingen (24%) 'zeer belangrijk'. Van die 17 klinische vraagstellingen vonden gezondheids-zorgprofessionals dat er 12 een hoge prioriteit hadden om onderzocht te worden. Patiënten kenden aan alle 17 klinische vraagstellingen een hoge prioriteit toe. Daarnaast kozen patiënten zes uitkomsten als de belangrijkste voor patiënten met maculadegeneratie. Zowel de klinische vraagstellingen met hoge prioriteit als de uitkomsten die door de patiënten als belangrijk werden beoordeeld betroffen klinische effectiviteit en veiligheid. Multidisciplinaire prioriteitstellingsprocedures zoals deze kunnen helpen bij het sturen van toekomstig onderzoek en de zorg.

In **Hoofdstuk 4** onderzochten we de informatieovergang van primair onderzoek naar systematische reviews. We vergeleken de uitkomsten die in primaire onderzoeken gerapporteerd waren met die van systematische reviews voor de vier meest voorkomende oogziekten: maculadegeneratie, cataract, diabetische retinopathie en glaucoom. In een cross-sectionele evaluatie van 56 systematische reviews met in totaal 414 primaire onderzoeken was het mediane aantal uitkomsten hetzelfde voor primaire onderzoeken als voor reviews (5 uitkomsten). Echter, afhankelijk van de oogziekte rapporteerden primaire onderzoeken 3 tot 5 keer meer unieke uitkomsten dan systematische reviews. Slechts één uitkomst (gezichtsscherpte) werd gerapporteerd in meer dan de helft van alle primaire onderzoeken en systematische reviews. De meeste uitkomsten die in de systematische reviews gerapporteerd werden, waren dezelfde als in de primaire onderzoeken. Afhankelijk van de oogziekte echter betrokken de systematische reviews slechts 17% tot 25% van alle in de primaire onderzoeken gerapporteerde uitkomsten in hun review. Kortom, er zijn veel uitkomsten gemeten en gerapporteerd in primaire onderzoeken die niet worden opgenomen in systematische reviews. Het definiëren van een minimumset van

relevante uitkomsten (*core outcome sets*) kan de consistentie met betrekking tot het bestuderen van klinisch relevante uitkomsten tussen systematische reviews en primaire onderzoeken bevorderen en de vergelijking van uitkomsten tussen onderzoeken en reviews vergemakkelijken.

Ter aanvulling van het in hoofdstuk 4 gepresenteerde onderzoek ondernamen we een meer diepgaande evaluatie van de uitkomsten die in oogheelkundige systematische reviews werden beschouwd. In **Hoofdstuk 5** onderzochten we de invloed van de definitie van uitkomsten op de opname van de resultaten van de primaire onderzoeken in meta-analyses. Onder de 125 systematische reviews die ten minste twee onderzoeken omvatten en dus theoretisch een meta-analyse konden uitvoeren, werd 75% van de geïncludeerde onderzoeken voor tenminste één uitkomst opgenomen in een meta-analyse (28% werd opgenomen in de meta-analyse van de primaire reviewuitkomst). Echter, 26% van de systematische reviews voerde voor geen enkele uitkomst een meta-analyse uit en 41% voerde geen meta-analyse uit voor de primaire uitkomst van de review. Redenen voor het niet uitvoeren van een meta-analyse waren 1) het ontbreken van een voldoende aantal geïncludeerde onderzoeken die kwantitatieve resultaten rapporteerden of 2) verschillen in de uitkomstdefinities tussen de opgenomen onderzoeken en de review. Voorbeelden van dergelijke verschillen waren het gebruik van verschillende samenvattende effectmaten (bijv. gemiddelden versus proporties) of verschillende meetmomenten (bijv. zes maanden versus 1 jaar). Deze bevindingen wijzen erop, dat verschillen in de keuze en definitie van de uitkomsten kunnen leiden tot verlies aan informatie binnen het evidence-ecosysteem, ook al lijken primaire onderzoeken en reviews dezelfde onderzoeksvraag te hebben bestudeerd. Ziektespecifieke kernuitkomstensets zouden een manier kunnen zijn om uitkomstdefinities in primair onderzoek (*evidence generation*) en systematische reviews (*evidence synthesis*) beter op elkaar af te stemmen. Richtlijnen voor rapportage van onderzoeksgegevens zouden ook moeten worden toegepast zodat de rapportage van resultaten geschikt is voor verdere (meta-)analyse.

In **Hoofdstuk 6** onderzochten we een ander potentiële bron van informatieverlies tussen onderzoeken en systematische reviews. We gingen na of de in systematische reviews opgenomen onderzoeken waren geregistreerd in een erkend klinisch trialregister. De trialregistratie werd in het verleden in het leven geroepen om het bestaan van een onderzoek kenbaar te maken. Daarnaast worden In het trialregister de belangrijkste methoden van een onderzoek vooraf vastgelegd en dient het om de onderzoeksresultaten openbaar beschikbaar te maken. Klinische trialregisters zouden onderzoekers en het algemene publiek een centrale plek bieden om (1) geplande, lopende en afgeronde klinische onderzoeken te identificeren, (2) vooraf gespecificeerde onderzoeksmethoden

te beoordelen (zoals criteria voor insluiting van patiënten, beschrijvingen van de interventies en definities van de uitkomsten) en (3) toegang te krijgen tot de belangrijkste onderzoeksresultaten en onderzoeksgegevens. Deze onderdelen spelen een belangrijke rol bij de synthese van evidence door de identificatie van relevante onderzoeken te vergemakkelijken en mogelijke selectieve rapportage van uitkomsten op het spoor te komen. Bovendien vormen zij een potentiële bron van aanvullende informatie voor review-auteurs. In dit hoofdstuk selecteerden wij een cross-sectionele steekproef van 100 systematische reviews van het *Musculoskeletal, Oral, Skin and Sensory Network* van Cochrane, welke reviews waren gepubliceerd tussen 2014 en 2019. In die reviews warn 1.177 primaire onderzoeken opgenomen die in 2005 of later waren gepubliceerd. We kozen 2005 als uiterste jaar omdat dat het jaar was waarin het beleid van het *International Committee of Medical Journal Editors (ICMJE)* om alle klinische onderzoeken te registreren als voorwaarde voor publicatie tot stand is gekomen. Minder dan een derde (31%) van de onderzoeken was geregistreerd en nog minder onderzoeken waren prospectief geregistreerd of hadden, zoals aanbevolen, de onderzoeksresultaten in het registratiedocument gepubliceerd. Registratie van onderzoeken dient strikter gehandhaafd te worden, zodat de volledige informatie van een onderzoek beschikbaar is waardoor de kwaliteit en de sterkte van de evidence adequaat kunnen worden beoordeeld.

In **Hoofdstuk 7** onderzochten we de associatie tussen registratie van klinische onderzoeken in een erkend trial register en de kans op vertekening (*bias*). We maakten gebruik van dezelfde set van 1177 onderzoeken als in Hoofdstuk 6. We beoordeelden de volgende domeinen van vertekening: randomisatie, *concealment of allocation* (het verborgen houden van de toewijzing van onderzoekdeelnemers aan de interventiegroepen), *performance bias* (gebrek aan blindering van de patiënt, behandelaar of beiden), detectiebias (gebrek aan blindering van de persoon die de uitkomstmeting deed), selectieve uitval (*attrition bias*) en selectieve rapportage van uitkomsten (*reporting bias*). In de domeinen 'randomisatie' en 'selectieve uitval' scoorde ten minste de helft van de onderzoeken een lage kans op vertekening. In de overige domeinen scoorden de meeste onderzoeken een hoge of onduidelijke kans op vertekening. Op onderzoeksniveau (dat wil zeggen rekening houdend met alle domeinen) werd volgens het Cochrane-algoritme slechts een klein deel van de onderzoeken beoordeeld als hebbende een lage kans op vertekening (12%) ('lage kans op vertekening voor een onderzoek, indien die kans voor alle domeinen laag was, onduidelijke kans op vertekening indien die kans voor een of meer domeinen onduidelijk was, en een hoge kans op vertekening, indien die kans voor een of meer domeinen hoog was'). In univariabele logistische regressieanalyses was registratie van onderzoeken in een trial-register geassocieerd met een lage kans op vertekening, zowel op onderzoeksniveau als voor alle individuele domeinen, behalve voor selectieve

uitval. Er werden ook multivariabele analyses en sensitiviteitsanalyses uitgevoerd en de resultaten ondersteunden de primaire univariabele analyses. In secundaire analyses werd prospectieve registratie van onderzoeken (d.w.z. registratie van een onderzoek vóórdat de eerste deelnemer werd ingesloten) vergeleken met retrospectieve registratie. Prospectieve registratie was geassocieerd met een lage kans op vertekening voor drie domeinen: selectiebias vanwege ontoereikende *concealment of allocation*, *performance bias* en *detectiebias*. De bevindingen uit dit hoofdstuk suggereren dat de opzet, uitvoering en rapportage van onderzoeken met elkaar samenhangen. Ook dient opgemerkt te worden dat zowel een juiste uitvoering als een volledige rapportage van klinische onderzoeken nodig zijn om achteraf de synthese van evidence op een adequate wijze mogelijk te maken.

In **hoofdstuk 8** presenteerden we een algemene discussie over de onderzoeken die we uitgevoerd hebben, en over de belangrijkste bevindingen uit elk hoofdstuk. Ook formuleerden we aanbevelingen voor verder onderzoek en voor de praktijk. De aan de orde gekomen thema's waren gericht op drie vraagstukken rond evidence-synthese: 1) het stellen van de juiste vragen, 2) het selecteren van de juiste uitkomsten en 3) het versterken van het wetenschappelijke fundament (de *evidence base*). Deze drie thema's spelen alle een belangrijke rol bij het beperken van verlies aan informatie binnen het evidence-ecosysteem en bij het optimaliseren van die informatie zodat bruikbare inzichten kunnen worden gegenereerd voor besluitvorming in de klinische praktijk. Om de juiste vragen te kunnen stellen moeten auteurs van systematische reviews afstemmen met richtlijnontwikkelaars: welke evidence is relevant voor het opstellen van aanbevelingen voor de klinische praktijk en waar ontbreekt dergelijke evidence? Prioritering in samenwerking met verschillende belanghebbende groeperingen kan helpen bij de keuze van de belangrijkste vraagstellingen en de meest relevante uitkomsten. Op deze wijze wordt de toepasbaarheid van de evidence bevorderd en kunnen financiële middelen toegewezen worden aan die onderzoeken waarvan de resultaten later daadwerkelijk opgenomen kunnen worden in de klinische besluitvorming (gebruik). Om de toepasbaarheid van de uiteindelijke onderzoeksresultaten voor evidence-synthese te vergroten moeten auteurs van systematische reviews voor de selectie van de juiste uitkomsten niet alleen samenwerken met richtlijnontwikkelaars, maar ook met diegenen die primair onderzoek uitvoeren. Patiënten dienen een cruciale rol te spelen bij het bepalen van de onderzoeksagenda om ervoor te zorgen dat ook hun vragen aan de orde komen. In het verleden is voorgesteld voor iedere aandoening sets van relevante uitkomsten te definiëren (*core outcome sets*). Deze ziekte-specifieke kernuitkomsten zouden in primair onderzoek gemeten en gerapporteerd moeten worden om ook op deze wijze onderzoeksverspilling tot een minimum te beperken. Systematische review auteurs zouden deze kernuitkomstensets ook moeten gebruiken bij het selecteren en definiëren van de uitkomsten voor

hun review. De kennis die wordt verkregen via evidence-synthesen neemt snel toe in kwantitatieve zin (snelgroeiende hoeveelheid informatie), maar de ontwikkelingen in kwalitatieve zin nemen minder snel toe (afnemen van de kans op vertekening).

Nieuwe technologieën zoals automatische taalverwerking (*natural language processing*) en nieuwe review-methoden zoals *rapid reviews* en *living reviews* bieden mogelijk opties om de klinische praktijk tijdig van relevante informatie te voorzien.

Samenwerking in alle fasen van het evidence-ecosysteem is essentieel voor het verbeteren van de toepasbaarheid en het gebruik van systematische reviews in de klinische praktijk. Ook al is het dynamisch en complex, een gezond evidence-ecosysteem leidt tot het meest waardevolle onderzoek en – hopelijk – tot de beste uitkomsten voor patiënten.

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"The world is your oyster."

Like many expressions in our lexicon, this phrase derives from Shakespeare. Over time, it has come to mean that life is full of opportunities for those who go for it. I feel very fortunate to have had the opportunity to "go for it" with this thesis, and even more fortunate to have worked with so many great people along the way.

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"He picked me up, He turned me around, He placed my feet on solid ground."
– Maverick City Music

Curriculum vitae

Kristina Lindsley was born in El Paso, Texas, in the United States, on July 16, 1979. She completed her Bachelor of Science with a double major in Biology and Psychology at the University of Maryland, Baltimore County, in 2001. After graduating, she worked in the Department of Pharmacology and Experimental Therapeutics at the University of Maryland, Baltimore, where her work focused on investigating modulators of developmental cell death. She then enrolled in the graduate program at the University of Maryland, Baltimore.

After obtaining her Master of Science in Epidemiology and Preventive Medicine from the University of Maryland, Baltimore, in 2004, she began her career in Evidence Synthesis research at the Bloomberg School of Public Health at Johns Hopkins University. She served as the Project Coordinator for large-scale systematic reviews on Food, Nutrition, and Physical Activity and the Prevention of Cancer for the World Cancer Research Fund. In 2008, she joined the United States Cochrane Center as a methodologist for the Cochrane Eyes and Vision US Satellite, eventually becoming the Project Director. As the Project Director, she managed a portfolio of more than 100 systematic reviews and partnered with the American Academy of Ophthalmology to produce up-to-date evidence-based clinical practice guidelines. She led successful programs aimed to make healthcare in the United States evidence-based, including the creation of Centers for Evidence-Based Vision Care at top eye care centers, such as the Wilmer Eye Institute at Johns Hopkins, the Byers Eye Institute at Stanford, and the Stein Eye Institute at UCLA. While at Johns Hopkins she also worked with the Johns Hopkins Evidence-based Practice Center on systematic reviews related to the treatment and screening of glaucoma.

In 2016 the opportunity arose to pursue a thesis with Professors Dr. Kay Dickersin from Johns Hopkins University (United States Cochrane Center), and Dr. Rob Scholten and Dr. Lotty Hooft from Utrecht University (Cochrane Netherlands).

In 2018, Kristina began working in consulting—first at IBM Watson Health and literature-based research offerings, and currently at IQVIA as an Associate Principal, overseeing evidence-based research projects. She has published more than 60 papers, presented at numerous conferences, and conducted training workshops on evidence synthesis. In addition she recently became an Associate Editor for the journal *Systematic Reviews*.

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Conference presentations related to this thesis

2020 *Trends in trial registration for randomized clinical trials in eyes and vision*. Presented at the Association for Research in Vision and Ophthalmology (ARVO) annual meeting (virtual presentation).

2020 *Public availability of clinical trial results from a random sample of systematic reviews*. Presented at the Society for Clinical Trials annual meeting (virtual presentation).

2017 *Outcome choice and potential loss of valuable information - an example from a Cochrane Eyes and Vision systematic review*. Presented at the Global Evidence Summit, Cape Town, South Africa (long podium presentation).

2017 *A database of systematic reviews in eyes and vision – a cross-section of the evidence available to underpin clinical practice guidelines and set the research agenda*. Presented at the Global Evidence Summit, Cape Town, South Africa (poster presentation).

2016 *Partnership between Cochrane Eyes and Vision and the American Academy of Ophthalmology to identify systematic review evidence for clinical practice guidelines.* Presented at the 24th Annual Cochrane Colloquium, Seoul, South Korea (short podium presentation).