APPENDIX A. SEARCH STRATEGY

Ovid MEDLINE® and Ovid OLDMEDLINE® 1947 to February Week 1 2011 **-- Date Searched 2011/02/15 - QUESTION 1**			
	Concept	**Search String**	**N**
1	Age-related macular degeneration	Exp macular degeneration/ OR geographic atrophy/ OR macular edema/ OR wet macular degeneration/ OR macular degeneration.mp OR AMD.mp OR ((moderate OR intermediate) ADJ5 (macular degeneration OR AMD OR maculopath$ OR macular dystroph$)).mp OR (age ADJ4 maculopath$).mp OR (age ADJ4 macular).mp OR (retinal ADJ4 degeneration).mp OR macular dystrophy.mp OR Retinal drusen/ OR retinal druse$.mp OR Retinal neovascularization/ OR Retinal Pigment Epithelium/ OR retinal pigment epithelium hyperplasia.mp OR RPE.mp OR retinal pigment epithelium atroph$.mp OR retinal pigment epithelium depigmentation.mp OR geographic atrophy.mp OR Choroidal neovascularization/ OR Choroidal neovascularization.mp OR AREDS stage 1.mp OR AREDS stage 3.mp OR subjacent retinal pigmentation epithelium.mp OR choriocapillaris.mp OR lipofuscin.mp OR neovascular AMD.mp OR CNV.mp OR macular pigment optical density.mp OR MPOD.mp OR (age ADJ1 related ADJ1 eye ADJ1 disease ADJ1 study).mp OR Pigment epithelium of eye/ OR Macula Lutea/ OR fovea centralis/ OR Retinal detachment/	57,272
2	Nutritional supplements, carotenoids, antioxidants, omega 3 fatty acids	Dietary supplements/ OR (dietary ADJ1 supplement$).mp OR (nutritional ADJ1 supplement$).mp OR Vitamins/ OR Carotenoids/ OR carotenoid$.mp OR zeaxanthin.mp OR Lutein/ OR lutein.mp OR Beta carotene/ OR beta-carotene.mp OR beta carotene.mp OR Antioxidants/ OR antioxidant$.mp OR Zinc/ OR zinc.mp OR Vitamin E/ OR (vitamin ADJ1 E).mp OR Ascorbic acid/ OR (vitamin ADJ1 C).mp OR Fatty Acids, Omega-3/ OR omega 3 fatty acids.mp OR alpha-Linolenic Acid/ OR alpha linolenic acid.mp OR Docosahexaenoic Acids/ OR Docosahexaenoic acid.mp OR Eicosapentaenoic Acid/ OR Eicosapentaenoic acid.mp OR tocopherols.mp	268,101
3	Cochrane Reviews Clinical Hedge	(randomized controlled trial OR controlled clinical trial OR meta-analysis).pt OR randomized.ab OR placebo.ab OR drug therapy.fs OR randomly.ab OR trial.ab OR groups.ab OR (systematic ADJ1 review).mp	2,611,405
4	**Q1:**	1 AND 2 AND 3	**523**

EMBASE -- Date Searched 2011/03/17 - QUESTION 1			
	Concept	**Search String**	**N**
1	Age-related macular degeneration	'retina macula age related degeneration'/exp OR 'retina macula degeneration'/exp OR 'retina macula edema'/exp OR 'drusen'/exp OR 'retina neovascularization'/exp OR 'pigment epithelium'/exp OR 'subretinal neovascularization'/exp OR 'retina macula lutea'/exp OR 'retina fovea'/exp OR 'retina detachment'/exp OR 'macular degeneration'/de OR 'macular degeneration' OR 'geographic atrophy' OR 'macular edema'/de OR 'macular edema' OR 'wet macular degeneration' OR 'amd'/de OR amd OR (moderate OR intermediate) NEAR/5 ('macular degeneration' OR amd OR maculopat* OR 'macular dystrophy') OR age NEAR/4 maculopath* OR age NEAR/4 macular OR retinal NEAR/4 degenerat* OR 'macular dystrophy'/de OR 'macular dystrophy' OR rpe OR 'retinal pigment epithelium atrophy' OR 'retinal pigment epithelium depigmentation' OR 'areds stage 1' OR 'areds stage 3' OR 'subjacent retinal pigmentation epithelium' OR 'choriocapillaris'/de OR choriocapillaris OR 'lipofuscin'/de OR lipofuscin OR 'neovascular amd' OR cnv OR 'macular pigment optical density' OR mpod AND [embase]/lim *search also required that the term be a major focus of the article	46,770
2	Nutritional supplements, carotenoids, antioxidants, omega 3 fatty acids	'diet supplementation'/exp OR 'vitamin'/exp OR 'carotenoid'/exp OR 'xanthophyll'/exp OR 'beta carotene'/exp OR 'antioxidant'/exp OR 'zinc'/exp OR 'alpha tocopherol'/exp OR 'ascorbic acid'/exp OR 'omega 3 fatty acid'/exp OR 'linolenic acid'/exp OR 'docosahexaenoic acid'/exp OR 'icosapentaenoic acid'/exp OR 'tocopherol'/exp OR 'zeaxanthin'/exp	538,080

3	Cochrane Reviews Clinical Hedge	'randomized controlled trial'/exp OR 'controlled clinical trial'/exp OR 'meta analysis'/exp OR 'systematic review'/exp *Also searched as keyword and major focus of article	380,031
4	**Q1:**	1 AND 2 AND 3	**146**

COCHRANE (Cochrane Database of Systematic Reviews; Database of Abstracts of Reviews of Effects; Cochrane Central Register of Controlled Trials) -- Date Searched 2011/03/28 - QUESTION 1			
	Concept	**Search String**	**N**
1	Age-related macular degeneration	"macular degeneration" OR "geographic atroph*" OR "macular edema" OR AMD "macular dystroph*" OR "Retinal druse*" OR "Retinal neovascularization" OR "Retinal Pigment Epithelium" OR RPE OR "Choroidal neovascularization" OR AREDS OR choriocapillaris OR lipofuscin OR "neovascular AMD" OR CNV OR "macular pigment optical density" OR MPOD OR "Macula Lutea" OR "fovea centralis" OR "Retinal detachment" (Title, Abstracts, or Keywords search)	28
2	Nutritional supplements, carotenoids, antioxidants, omega 3 fatty acids	Supplement* OR vitamin* OR carotenoid* OR xanthophyll OR beta carotene* OR antioxidant* OR zinc OR tocopherol* OR "ascorbic acid" OR "omega 3 fatty acid*" OR linolenic OR docosahexaenoic OR icosapentaenoic OR zeaxanthin (Title, Abstracts, or Keywords search)	530
4	**Q1:**	1 AND 2	**3**

SCOPUS -- Date Searched 2011/03/28 - QUESTION 1			
	Concept	**Search String**	**N**
1	Age-related macular degeneration	macular degeneration OR geographic atroph* OR macular edema OR AMD macular dystroph* OR Retinal druse* OR Retinal neovascularization OR Retinal Pigment Epithelium OR RPE OR choroidal neovascularization OR AREDS OR choriocapillaris OR lipofuscin OR neovascular AMD OR CNV OR macular pigment optical density OR MPOD OR Macula Lutea OR fovea centralis OR Retinal detachment (Title, Abstracts, or Keywords search)	73,074
2	Nutritional supplements, carotenoids, antioxidants, omega 3 fatty acids	Supplement* OR vitamin* OR carotenoid* OR xanthophyll OR beta carotene* OR antioxidant* OR zinc OR tocopherol* OR "ascorbic acid" OR "omega 3 fatty acid*" OR linolenic OR docosahexaenoic OR icosapentaenoic OR zeaxanthin	4,296
4	**Q1:**	1 AND 2	**73**

Conference Papers Index -- Date Searched 2011/03/28 - QUESTION 1			
	Concept	**Search String**	**N**
1	Age-related macular degeneration	macular degeneration OR geographic atroph* OR macular edema OR AMD macular dystroph* OR Retinal druse* OR Retinal neovascularization OR Retinal Pigment Epithelium OR RPE OR choroidal neovascularization OR AREDS OR choriocapillaris OR lipofuscin OR neovascular AMD OR CNV OR macular pigment optical density OR MPOD OR Macula Lutea OR fovea centralis OR Retinal detachment (Keywords search)	3,832
2	Nutritional supplements, carotenoids, antioxidants, omega 3 fatty acids	Supplement* OR vitamin* OR carotenoid* OR xanthophyll OR beta carotene* OR antioxidant* OR zinc OR tocopherol* OR "ascorbic acid" OR "omega 3 fatty acid*" OR linolenic OR docosahexaenoic OR icosapentaenoic OR zeaxanthin (Keywords search)	22,207
4	**Q1:**	1 AND 2	**68**

Ovid MEDLINE® and Ovid OLDMEDLINE® 1947 to February Week 4 2011 **-- Date Searched 2011/02/15 - QUESTION 2 SEARCH**			
	Concept	**Search String**	**N**
1	Population	Aging/ OR aging.mp. OR ageing.mp. OR Aged/ OR aged.mp. OR "Aged, 80 and over"/ OR frail elderly/ OR Middle aged/ OR middle aged.mp. OR elder$.mp. OR senior$.mp. OR geriatric$.mp OR age-related.mp. OR (age adj1 related).mp.	3,562,146
2	Zeaxanthin, lutein, beta-carotene, zinc, vitamin e, vitamin c, alpha linolenic acid, DHA, EPA	zeaxanthin.mp OR Lutein/ OR lutein.mp OR Beta carotene/ OR beta-carotene.mp OR beta carotene.mp OR Zinc/ OR zinc.mp OR Vitamin E/ OR (vitamin ADJ1 E).mp OR tocopherols.mp OR Ascorbic acid/ OR (vitamin ADJ1 C).mp OR alpha-Linolenic Acid/ OR alpha linolenic acid.mp OR Docosahexaenoic Acids/ OR Docosahexaenoic acid.mp OR Eicosapentaenoic Acid/ OR Eicosapentaenoic acid.mp	160,101
3	Cochrane Reviews Clinical Hedge	(randomized controlled trial OR controlled clinical trial OR meta-analysis).pt OR randomized.ab OR placebo.ab OR drug therapy.fs OR randomly.ab OR trial.ab OR groups.ab OR (systematic ADJ1 review).mp	2,656,105
4	Harms	unsafe.mp OR safety.mp OR harm.mp OR harms.mp OR complication$.mp OR poison$.mp OR risk$.mp OR AE.fs OR MO.fs OR PO.fs OR TO.fs OR CT.fs OR side-effect$.mp OR (undesirable ADJ1 effect$).mp OR (treatment ADJ1 emergent).mp OR tolerab$.mp OR toxic$.mp OR adrs.mp OR (adverse ADJ2 (effect or effects or reaction or reactions or event or events or outcome or outcomes)).mp	3,492,667
5	**Q2:** Population, dietary supplements, study methods, and harms	1 AND 2 AND 3 AND 4	**3,514**

Embase -- Date Searched 2011/03/17 - QUESTION 2			
	Concept	**Search String**	**N**
1	Population	'aged'/mj OR 'frail elderly'/mj OR 'elderly'/mj OR 'very elderly'/mj OR 'aged hospital patient'/mj OR 'middle aged'/mj OR senior* OR geriatric* OR 'age near/1 related' AND [embase]/lim	154,441
2	Zeaxanthin, lutein, beta-carotene, zinc, vitamin e, vitamin c, alpha linolenic acid, DHA, EPA	'diet supplementation'/mj OR 'carotenoid'/mj OR 'xanthophyll'/mj OR 'beta carotene'/mj OR 'antioxidant'/mj OR 'zinc'/mj OR 'alpha tocopherol'/mj OR 'ascorbic acid'/mj OR 'omega 3 fatty acid'/mj OR 'linolenic acid'/mj OR 'docosahexaenoic acid'/mj OR 'icosapentaenoic acid'/mj OR 'tocopherol'/mj OR 'zeaxanthin'/mj AND [embase]/lim	98,250
3	Cochrane Reviews Clinical Hedge	'randomized controlled trial'/mj OR 'randomized controlled trial'/de OR 'randomized controlled trial' OR 'controlled clinical trial'/mj OR 'controlled clinical trial'/de OR 'controlled clinical trial' OR 'meta analysis'/mj OR 'meta analysis'/de OR 'meta analysis' OR 'systematic review'/mj OR 'systematic review'/de OR 'systematic review' AND [embase]/lim *also searched as keyword and main topic of article	380,031
4	Harms	'adverse drug reaction'/mj OR 'adverse drug reaction' OR 'drug induced disease'/mj OR 'drug induced disease' OR 'complication'/mj OR 'complication' OR 'intoxication'/mj OR 'intoxication' OR 'toxicity'/mj OR 'toxicity' OR 'drug hypersensitivity'/mj OR 'drug hypersensitivity' OR unsafe OR 'safety'/mj OR safety OR harm OR harms OR complication* OR poison* OR risk* OR undesirable NEAR/1 effect OR treatment NEAR/1 emergent OR tolerab* OR toxic* OR adrs OR adverse NEAR/2 (effect OR effects OR reaction OR reactions OR event OR events OR outcome OR outcomes) AND [embase]/lim	3,965,190

5	**Q2:** Population, dietary supplements, study methods, and harms	1 AND 2 AND 3 AND 4	**108**

SCOPUS -- Date Searched 2011/03/17 - QUESTION 2			
	Concept	**Search String**	**N**
1	Population	aged OR elderly OR "middle aged" OR senior* OR geriatric* OR "age related" in TITLE-ABS-KEY	3,178,852
2	Zeaxanthin, lutein, beta-carotene, zinc, vitamin e, vitamin c, alpha linolenic acid, DHA, EPA	zeaxanthin OR lutein OR "Beta carotene" OR zinc OR "Vitamin E" OR tocopherol* OR "Ascorbic acid" OR "vitamin C" OR alpha-linolenic OR docosahexaenoic OR eicosapentaenoic in TITLE-ABS-KEY-AUTH	447,672
3	Cochrane Reviews Clinical Hedge	"randomized controlled trial*" OR "controlled clinical trial*" OR "meta analysis" OR "systematic review*" TITLE-ABS-KEY-AUTH	529,484
4	Harms	"adverse drug reaction*" OR "adverse reaction*" OR complication* OR toxic* OR poison* OR harm* OR unsafe OR tolerab* OR adverse outcome* OR adverse event* OR adverse effect* TITLE-ABS-KEY-AUTH	252,917
5	**Q2:** Population, dietary supplements, study methods, and harms	1 AND 2 AND 3 AND 4	**309**

Cochrane Library (Cochrane Database of Systematic Reviews; Database of Abstracts of Reviews of Effects; Cochrane Central Register of Controlled Trials) **-- Date Searched 2011/03/25 - QUESTION 2**			
	Concept	**Search String**	**N**
1	Population	aged OR elderly OR "middle aged" OR senior* OR geriatric* OR "age related" (Title, Abstracts or Keywords search)	1,238
2	Zeaxanthin, lutein, beta-carotene, zinc, vitamin e, vitamin c, alpha linolenic acid, DHA, EPA	zeaxanthin OR lutein OR "Beta carotene" OR zinc OR "Vitamin E" OR tocopherol* OR "Ascorbic acid" OR "vitamin C" OR alpha-linolenic OR docosahexaenoic OR eicosapentaenoic (Title, Abstracts or Keywords search)	79
3	Harms	reaction* OR complication* OR toxic* OR poison* OR harm* OR unsafe OR safety OR tolerab* OR adverse (Title, Abstracts or Keywords search)	4,283
4	**Q2:** Population, dietary supplements, study methods, and harms	1 AND 2 AND 3	**23**

Conference Papers Index -- Date Searched 2011/03/25 - QUESTION 2			
	Concept	**Search String**	**N**
1	Population	aged OR elderly OR "middle aged" OR senior* OR geriatric* OR "age related" (Keyword search)	21,302

2	Zeaxanthin, lutein, beta-carotene, zinc, vitamin e, vitamin c, alpha linolenic acid, DHA, EPA	zeaxanthin OR lutein OR "Beta carotene" OR zinc OR "Vitamin E" OR tocopherol* OR "Ascorbic acid" OR "vitamin C" OR "omega 3 fatty acid*" OR alpha-linolenic OR docosahexaenoic OR eicosapentaenoic (Keyword search)	9,376
3	Harms	reaction* OR complication* OR toxic* OR poison* OR harm* OR unsafe OR safety OR tolerab* OR adverse (Keyword search)	98,395
4	**Q2:** Population, dietary supplements, study methods, and harms	1 AND 2 AND 3	**1**

APPENDIX B. INCLUSION/EXCLUSION CRITERIA

1. Is the full text of the article in English?
   Yes.....Proceed to #2
   No.....Code **X1**. STOP

2. Is the article a controlled clinical trial or a systematic review/meta-analysis of controlled trials comparing the effects of supplemental/non-dietary carotenoids, antioxidants, or omega-3 fatty acids (alone or in combination) with usual care or placebo?
   Yes.....Proceed to #3
   No .....Code **X2**. Go to #6

3. Does the population include adults with age-related macular degeneration?
   Yes.....Proceed to #4
   No.....Proceed to #5

4. Does the study report outcomes that include vision loss, quality of life, functional status, or adverse effects of treatment?
   Yes..... Code **I4**. STOP
   No.....Code **X4**. Go to #6

5. Does the study report the adverse effects of treatment in a population of ≥100 adults without age-related macular degeneration who were observed for >24 weeks?
   Yes..... Code **I5**. STOP
   No.....Code **X5**. Proceed to #6

6. Is the article potentially useful for background, discussion, or reference-mining?
   Yes..... Add Code **B**. STOP
   No..... STOP

PICOTS

Patients: KQ1: Adults with age-related macular degeneration
KQ2: Adults, exclude patients with severe chronic illnesses such as end-stage liver disease, ESRD, severe COPD, metastatic cancer, ALS, severe heart failure

Interventions: Carotenoids – zeaxanthin, lutein, beta-carotene
Antioxidants – zinc, vitamin e, vitamin c
Omega-3 fatty acids – alpha linolenic acid (C18:3n-3), docosahexaenoic acid (DHA; C22:6n-3), eicosapentaenoic acid (EPA; C20:5n-3)

Comparators: Placebo, usual care (usual diet)

Outcomes: Vision loss
Visual impairment in the best eye defined as: ≤ 20/60 by Snellen acuity; or ≤ 6/18 metric acuity; or doubling of the visual angle (e.g. 20/50 to 20/100); or ≥ three lines of loss; or ≥ 15 letters lost; or progression to advanced disease (either geographic atrophy or wet macular degeneration); quality of life; functional status.

APPENDIX C. ASSESSMENT OF METHODOLOGIC QUALITY AND RISK OF BIAS IN RANDOMIZED CONTROLLED TRIALS OF ORAL SUPPLEMENTS FOR AGE-RELATED MACULAR DEGENERATION

Study	Allocation sequence adequately generated	Allocation adequately concealed	Blinding of participants, personnel and outcome assessors	Incomplete outcome data adequately addressed	Absence of selective outcome reporting	Free of other sources of bias	Overall risk of bias	Funding source
AREDS, 2001[10]	Yes; randomization by treatment center then patients assigned with probability to 1/4 to each group.	Yes	Yes; all meds and placebo were coded and concealed from subjects and examiners…codes were kept only in the coordinating center.	Yes; participants were dropped if not photographed or proper visual acuity measurements were not obtained…these dropped subjects were "evenly distributed across the groups". Only 2.4% of subjects were lost to follow-up (missed at least 2 consecutive visits).	Yes; each stated outcome measure was reported in addition to adverse events.	Yes	Low	NIH; Bausch & Lomb Inc.
Feher, 2005[16]	Yes; computer generated randomization sequence.	Yes; staff and subjects were masked.	Yes; all meds and placebos were masked from both subjects and investigators.	Yes; ITT analysis was done; 5/106 failed to complete study and details were reported of each.	Yes; outcomes were reported as indicated.	Yes	Low	Funding NR
Newsome, 1988[11]	Yes	Yes	Yes	Unclear	Yes	Yes	Low	Research Fund Department of Veterinary Science, Utah State University
Newsome, 2008[14]	Yes: randomized with 50% likelihood scheme (Yes; 50% likelihood scheme).	Yes; study coordinator provided supplements but did not complete data collection.	Yes; supplements identical in appearance.	Unclear; did not include data from subjects who dropped out or died.	Yes	Yes	Low	Retinal Disease Research Foundation
Richer, 1996[15]	Yes	Yes	Yes	Unclear: 12 of 71 rate of attrition, but no data provided for those patients, including treatment assignment.	Yes	Yes; 17% loss to follow-up, unclear treatment assignment.	Low	Twin Laboratories, Inc.; Eye Communications, Inc.; Stereo Optical, Inc; Illinois College of Optometry; Pacific University College of Optometry; Ezell Foundation, American Academy of Optometry
Richer, 2004[12]	Yes; random card.	Yes	Yes	Yes	Yes	Yes	Low	DVA Medical Center, North Chicago; Kemin Foods, Vitacost.com; Nutraceutical Sciences Institute; Great Smokies Diagnostic Laboratory
Stur, 1996[13]	Unclear; randomization method not described.	Yes	Yes	Yes	Yes	Yes	Low	Austrian Foundation for the Propagation of Scientific Research

APPENDIX D. PEER REVIEW COMMENTS AND RESPONSES

Reviewer	Comment	Response
Question 1: Are the objectives, scope, and methods for this review clearly described?		
2	It is clear in the Methods section that your literature focuses on patients with ARMD, although in the Background of the Executive Summary and the Introduction, it is noted that "observational studies suggest that people with dietary intakes higher in various nutritional supplements have a lower risk of developing AMD". Yet there is no mention of the data indicating that nutritional supplements may have a role in preventing ARMD. Since the data evaluating prevention of ARMD is not even addressed, perhaps a statement recognizing that prevention data exists, but is outside the realm of this report would be beneficial.	The comment in the background was modified to clarify our purpose. The statement identifies the reason large supplementation trials were initiated to investigate the role of dietary supplements in AMD prevention. We note there is a large body of observational data suggesting dietary antioxidants, carotenoids and/or fish oils may be beneficial. This data is not reviewed here because of the risk of uncontrolled confounding and recall bias in observational cohort studies.
3	Yes; Specific aims of study and methods are clearly described and are appropriate.	Noted, thank you.
4	Yes; Thorough and excellent review	Noted, thank you.
Question 2: Is there any indication of bias in our synthesis of the evidence?		
1	Yes… and this is clearly stated at the very beginning of the report (It should also be stated in the conclusion) On page 3, the authors reject 298 of 335 (89 %) full-text scientific articles (1000+ authors) not meeting the inclusion criteria of EBM; 2) Throughout the entire report, the term "Functional" is used rather than the more precise term "Snellen Visual Acuity"; 3) Key Question 1: Limiting most all discussions of carotenoids to primarily a B carotene and all antioxidants to 1 form of the 8 isomers of vitamin E (i.e. alpha tocopherol) is an oversimplification of nature and known science, (despite the fact that another government agency (NEI / NIH) made this decision to persist in using the same 1990s nutritional components in the "new" AREDS II study). Given the relative lack of information ??? about the effects of xanthophylls, carotenoids and omega III fatty acids, future trials should be considered to assess the effects of these supplements in AMD patients". The term "information" should be replaced with "EBM" to be consistent. There are 1000's of scientific articles concerning n3 fatty acids, and dozens concerning the salutary benefit for AMD patients and people worried about not getting it. I know of only a single negative omega III – AMD study.	The inclusion and exclusion criteria were pre-specified before we undertook the review. The outcomes of interest and interventions of interest were determined based on discussion with a Technical Expert Panel. In the methods section, we defined functional vision loss in a variety of ways using both Snellen and non-Snellen methods. Given the problems inherent with observational data, we included only RCTs and only found one RCT of omega IIIs evaluating the outcomes of interest
2	No.	Noted, thank you.
3	There is no evidence of bias. English only studies were examined, but this is appropriate for age-related macular degeneration as Caucasians are most frequently affected and relevant studies are in English. Appropriate steps were taken to review appropriate studies in a systemic manor with accepted evaluation techniques.	Noted, thank you.
4	No.	Noted, thank you.
Question 3: Are there any published or unpublished studies that we may have overlooked?		
1	The report does not list the 298 rejected studies.	Although we do not list excluded studies in our report, we can provide a list of excluded studies and reasons for exclusion separately upon request.

Reviewer	Comment	Response
1	Lintje Ho, MD et al The Rotterdam Study Reducing the Genetic Risk of AMD with Dietary Antioxidants, Zinc and w3 fatty acids *Arch Ophthalmol. 2011; 129 (6):758-66* (High dietary intake of nutrients with antioxidant properties reduces the risk of early AMD in those at high genetic risk. Therefore, clinicians should provide dietary advice to young susceptible individuals to postpone or prevent the vision-disturbing consequences of AMD).	Thank you for suggesting this study. Our scope and inclusion criteria would exclude this study because the focus of the review is on supplemental rather than dietary intake of antioxidants.
1	*Christen GS et al,* The Women's Health Study - Dietary w3 Fatty Acid and Fish Intake and Incident AMD in Women *Arch Ophthalmol. 2011; 129 (7):921-9* (These prospective data from a large cohort of female health professionals without a diagnosis of AMD at baseline indicate that regular consumption of DHAA and EPA and fish was associated with a significantly decreased risk of incident AMD and may be of benefit in primary prevention of AMD).	Our scope and inclusion criteria would exclude this study as well because the focus of the review is on supplemental rather than dietary intake of antioxidants.
2	Under **Other Adverse Effects**, *Yellowing of the skin*: it only notes that beta-carotene is associated with yellowing of the skin. This effect is also noted with lutein. See ref: Regul Toxicol Pharmacol 2006; 45: 289-298.	We have added this suggested narrative review and references for the two trials it cites regarding lutein supplementation and carotenodermia.
3	No.	Noted, thank you.
4	Not that I am aware.	Noted, thank you.
Question 4: Please write additional suggestions or comments below. If applicable, please indicate the page and line numbers from the draft report.		
1	The 1862 legal term Snellen Visual Acuity throughout the report is used to define both "function" and "stage of disease". However, foveal vision in humans is, more often than not, highly conserved until the patho-physiology of AMD has run its course. It is therefore a poor term to use to describe both functional vision and the stage of disease in either dry or wet AMD. Thus the EBM model adopted within this report is in complete opposition to biology and the patient-doctor encounter. It contradicts the results of both the LAST study 2004 and our recently published ZVF study (FDA #78,973). In both studies patients had better than 20/32 visual acuity yet poor contrast sensitivity and glare recovery…i.e. they had visual disability. If we use an AREDS deterministic legal definition of 15 letter Snellen improvement, your report is correct to assume that ours were negative studies by definition.	The outcomes of interest were determined after discussion with a group of technical experts who felt functional vision loss as we've defined it was the appropriate outcome to evaluate for the systematic review. Evaluation of these more proximal outcome metrics is outside the scope of our review.

Reviewer	Comment	Response
1	In this report, it was stated not once but twice that AMD changes occur slowly over time. I agree, but only if one is younger than 85 – then the changes will occur very quickly. Furthermore, such aged individuals are the fastest growing demographic in the United States. There are 10x the number of patients with AMD between age 85 and 95 compared to ages 75 – 85 (and not double). We are wasting time.	We agree and have added the suggested text to the Discussion section.
2	Excellent report. Thank you for taking the time to develop this document. One suggestion would be to provide references to the studies noted in the Executive Summary Table on page 6.	We have added the study references to the summary table in the Conclusions of the main report, as suggested. We generally do not include citations in the Executive Summary.
2	Under **Study Selection**, it is noted that only those studies with at least 24 weeks of follow-up and sample size of 100 were included, but some of the data is not consistent with that statement. For example, the Newsome, 2008 trial only contained 74 participants.	We have clarified the methods to specify that we did not limit the sample size or duration of treatment of RCTs to answer the question of efficacy. Sample size of 100 or more pertained to included studies of adverse effects.
2	EDRTS is used throughout the document. It should be ETDRS for Early Treatment Diabetic Retinopathy Study	Thank you for this correction. We have changed "EDTRS" to ETDRS" throughout the document.
3	The reviewers did an excellent job of identifying the categories of AMD and incorporating the relative susceptibility as part of their evaluation. For example, studies evaluating patients with Category 1 and 2 AMD are not likely to find a benefit to supplementation given the gradual nature of the disease process as well as the lack of vision loss in these categories. This finding is of crucial importance in determining which patients may benefit from supplementation that does carry some risk.	Noted, thank you.
4	I feel the comment on page 4 that there are not effective therapies is out of sequence. I am not sure this is born out in the grade 3 and 4 AMD patients with the supplements. Overall the paper is correct; clinicians refer to the AREDS trial as an indication of the use of supplements as the only valid trial. As you noted there is additional AREDS2 looking at adding carotenoids in progress. Also, there is a "smokers" AREDS without the antioxidants that may reduce the risk of lung cancer? I think the part that remains difficult is the assessment of the risk. If there were even marginal benefit and no risk then the treatment strategy is clear. I think you have addressed this in as much detail as is currently available	We have deleted the first sentence to improve clarity. We added text to the Discussion section regarding the amendment to the AREDS study in which smokers were offered a chance to change their randomization of treatment supplements to either zinc alone (without the antioxidants) or placebo.
5	Page 3, 4th paragraph: In the AREDS study- please specify AREDS 1 and list the formula components.	Done.
5	Page 4 and through the document: please define "former" smoker if that information is given in the reviewed studies.	We have added definitions for "former" smoker, as suggested.
5	Page 5, 1st paragraph: "Higher doses of vit E have been associated with increased mortality and congestive heart failure among those with high baseline risk". High baseline risk needs to be defined. What constitutes high baseline risk? Also, "carotenoids such as beta-carotene have been associated with an increased risk of lung cancer among smokers. The absolute risk of harm is low." How low is low? please clarify here.	We have added the estimated magnitude of increased risk for each outcome in this paragraph.

Reviewer	Comment	Response
5	Page 6-7: executive summary table. In the Comment Column, it would be nice to have the actual doses listed to help understand what authors mean by High-dose vit E, beta-carotene, etc. Also 'high risk patients" needs to be clarified.	Thank you for this suggestion. We have added the dose range to the Summary Table to better characterize the high-dose and low-dose studies. We have also added a footnote in Table 1 to specify the definition of high vs low risk AMD used in Stur, 1996.
5	Page 9, 1 paragraph, 1 line: The natural history of AMD has not been shown definitely to have been altered by any treatment modality. The authors should specify that they are specifically looking at the *nonexudative* AMD.	Thank you for this suggestion, however, we have decided to delete this sentence to improve clarity in response to another comment.
5	Page 10, under Patients: Adults with age-related macular degeneration - please specify *nonexudative* age-related macular degeneration is being studied here.	Done.
5	Outcomes: It would be nice to point out here that a 3-line change in visual acuity (i.e. +/-15 letters) using the ETDRS chart is equivalent to a doubling or halving of the visual angle regardless of the baseline visual acuity measurement.	We have added the suggested text to the list of outcomes in the Methods section.
5	Page 11, Fig 1. Adult outpatients with (NON-EXUDATIVE- please add) age-related macular degeneration	Done.
5	Page 14, 2nd paragraph: Please add a reference at the end of the sentence that talks about the GRADE working group.	Citation added.
5	Page 18, 2nd paragraph: "In analysis limited to only those with Category 3 or 4 AMD, a reduction in functional visual loss was noted with either supplement alone or in combination." should be clarified by specifying how much improvement was detected with either and with the combination.	Thank you for this suggestion. We have revised the paragraph accordingly.
5	The last sentence" No baseline characteristic differences were noted between the Category 2, 3, or 4 participants." is confusing, since these categories of participants are inherently different from each other. Not sure what the sentence is saying. Please clarify.	We have clarified this sentence to read: "No significant differences in demographics, socioeconomic status, smoking status, or comorbidities were noted between the Category 2, 3 or 4 participants."
5	Page 20-22: Table 1. The 4th-6th columns list outcomes, however no P-values are listed to make sense of numbers listed. Please include P-values (from articles listed) wherever is possible.	Done.
5	Page 23: "Additionally, the treatment arms will evaluate the effects of eliminating beta-carotene for the original AREDS formulation..." should be FROM the original AREDS. Would also be nice to list the ingredients of the AREDS formulation here.	Thank you for this correction. We have specified the ingredients of the original AREDS formulation, as suggested.
5	Page 26, under Lung Cancer: please define what was meant by "former smokers". How many years after quitting tobacco?	We have added definitions for "former" smokers, as suggested.