

APPENDIX 1: LITERATURE SEARCH STRATEGY

OVERVIEW		
Interface:	OVID®	
Databases:	BIOSIS Previews <1989 to 2007 Week 2>; CINAHL - Cumulative Index to Nursing & Allied Health Literature <1982 to December Week 48 2006>; EMBASE <1980 to 2007 Week 3>; Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <Jan 26, 2007>; Ovid MEDLINE(R) <1966 to Jan Week 3 2007> * Note: Subject headings have been customized for each database.	
Date of Search:	January 26, 2007	
Alerts:	Monthly search updates began January 26 2007 and ran to November 2 2007.	
Study Types:	Systematic reviews; meta-analyses; technology assessments; randomized controlled trials; controlled clinical trials; economic.	
Limits:	Humans	
SYNTAX GUIDE		
/	At the end of a phrase, searches the phrase as a subject heading	
.sh	At the end of a phrase, searches the phrase as a subject heading	
MeSH	Medical Subject Heading	
fs	Floating subheading	
exp	Explode a subject heading	
\$	Truncation symbol, or wildcard: retrieves plural or variations of a word	
*	Indicates that the marked subject heading is a primary topic	
?	Truncation symbol for one or no characters only	
ADJ	Requires words are adjacent to each other (in any order)	
ADJ#	Adjacency within # number of words (in any order)	
.ti	Title	
.ab	Abstract	
.hw	Heading Word; usually includes subject headings and controlled vocabulary	
.pt	Publication type	
.rn	CAS registry number	
BIOSIS Previews, CINAHL, EMBASE, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R)		
Line #	Search Strategy	Results
	Main Drug	
1	verteporfin.ti,ab.	1026
2	Visudyne.ti,ab,tn.	441
3	Verteporfin photodynamic therapy.ti,ab.	110

4	VPDT.ti,ab.	2
5	Benzoporphyrin derivati\$.ti,ab.	305
6	Benzoporphyrin derivatitive.sh.	0
7	BPD-MA.ti,ab.	115
8	BPDMA.ti,ab.	8
9	129497-78-5.rm.	625
10	photodynamic therapy.sh.	5523
11	Photochemotherapy.sh.	8244
12	or/1-11	13990
	Indication	
13	((macula\$ or retina\$ or choroid\$) adj3 (degener\$ or neovasc\$)).ti,ab.	19735
14	neovascular age-related macular degeneration.ti,ab.	361
15	AMD.ti,ab.	4551
16	ARMD.ti,ab.	759
17	(Retina Macula Age Related Degeneration or Retina Macula Degeneration or Subretinal Neovascularization or Choroidal Neovascularization or Macular Degeneration).sh.	13229
18	or/13-17	25860
19	12 and 18	1817
	Methodology Filter – Clinical Trials – RCT/Comparative/Observational	
20	exp Controlled Clinical Trials/ or exp Epidemiologic Research Design/ or Multicenter Studies.sh.	1251288
21	(Multicenter Study or Randomized Controlled Trial or Controlled Clinical Trial).pt.	344198
22	(random\$ or sham\$ or placebo\$ or (singl\$ adj (blind\$ or dumm\$ or mask\$)) or (doubl\$ adj (blind\$ or dumm\$ or mask\$))).ti,ab.	775589
23	((tripl\$ adj (blind\$ or dumm\$ or mask\$)) or (trebl\$ adj (blind\$ or dumm\$ or mask\$))).ti,ab.	276
24	((control\$ adj (study or studies or trial\$)) or rct\$).ti,ab.	189252
25	((multicent\$ or multi cent\$) adj (study or studies or trial\$)).ti,ab.	36464
26	or/20-25	1934495
27	(Multicenter Study or Randomized Controlled Trial or Randomized Clinical Trial).mp.	404851
28	(Randomized Trial or Evidence-Based Medicine).mp.	81854
29	(random\$ or sham\$ or placebo\$ or (singl\$ adj (blind\$ or dumm\$ or mask\$)) or (doubl\$ adj (blind\$ or dumm\$ or mask\$))).ti,ab.	775589
30	((tripl\$ adj (blind\$ or dumm\$ or mask\$)) or (trebl\$ adj (blind\$ or dumm\$ or mask\$))).ti,ab.	276
31	((control\$ adj (study or studies or trial\$)) or rct\$).ti,ab.	189252
32	((multicent\$ or multi cent\$) adj (study or studies or trial\$)).ti,ab.	36464
33	or/27-32	1038074
34	(Major Clinical Study or Multicenter Study).sh. or exp Controlled Study/ or	2044298

	Randomized Controlled Trial.sh.	
35	exp Evidence Based Medicine/	226314
36	(random\$ or sham\$ or placebo\$ or (singl\$ adj (blind\$ or dumm\$ or mask\$)) or (doubl\$ adj (blind\$ or dumm\$ or mask\$))).ti,ab.	775589
37	((tripl\$ adj (blind\$ or dumm\$ or mask\$)) or (trebl\$ adj (blind\$ or dumm\$ or mask\$))).ti,ab.	276
38	((control\$ adj (study or studies or trial\$)) or rct\$).ti,ab.	189252
39	((multicent\$ or multi cent\$) adj (study or studies or trial\$)).ti,ab.	36464
40	or/34-39	2786399
41	26 or 33 or 40	3532681
42	19 and 41	755
43	remove duplicates from 42	648
44	limit 43 to human [Limit not valid in: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations; records were retained]	616
	Comparator Drugs	
45	(ranibizumab or lucentis or rhuFab V2).ti,ab,tn.	165
46	347396-82-1.rn.	177
47	Ranibizumab.sh.	181
48	(pegaptanib or macugen or nx 1838 or "EYE 001").ti,ab,tn.	351
49	222716-86-1.rn.	323
50	Pegaptanib.sh.	326
51	(Bevacizumab or rhuMAb-VEGF or Avastin).ti,ab,tn.	2157
52	216974-75-3.rn.	2766
53	Bevacizumab.sh.	2794
54	(anecortave acetate or AL-3789 or Retaane).ti,ab,tn.	114
55	7753-60-8.rn.	121
56	anecortave acetate.sh.	2
57	placebo.ti,ab.	166380
58	or/45-57	170189
59	19 and 58	271
	Methodology Filter - Economic	
60	exp "Costs and Cost Analysis"/	203797
61	(economic value of life or economics, medical or economics, pharmaceutical or models, economic or markov chains or monte carlo method or uncertainty).sh.	29925
62	economics.fs.	219527
63	(quality of life or quality-adjusted life years).sh.	122140
64	((econom\$ or cost or costly or costing or costed or prices or pricing or discount or discounts or discounted or discounting or budget\$ or afford\$ or pharmaco-economic\$ or pharmaco) adj1 economic\$).ti,ab.	123352
65	(decision adj1 (tree\$ or analy\$ or model\$)).ti,ab.	8853
66	((value or values or valuation) adj2 (money or monetary or life or lives)).ti,ab.	2986

67	(QOL or QOLY or QOLYs or HRQOL or QALY or QALYs).ti,ab.	18822
68	(((((quality adj1 life) or (willingness adj1 pay) or (quality adj1 adjusted life year\$) or sensitivity) adj analys?s) or quality adjusted life expectanc\$).ti,ab.	9987
69	economics.sh.	27171
70	(Economic Impact or Economic Value or Pharmacoeconomics or Health Care Cost or Economic Factors or Economics or Cost Analysis or Cost or Economic Analysis or Cost-Effectiveness or Costs or "Quality of Life" or Health Care Cost or Cost Savings or Cost-Benefit Analysis or Hospital Costs or Medical Costs or Quality-of-Life).mp.	578756
71	exp Health economics/ or exp Economic Evaluation/ or exp Pharmacoeconomics/ or exp Economic Aspect/ or Quality Adjusted Life Year.sh. or exp Quality of Life/ or pe.fs.	341911
72	or/60-71	876205
73	41 or 72	4168208
	Methodology Filter – Systematic Review/Meta-analysis	
74	(MEDLINE or systematic review).tw. or meta-analysis.pt.	103295
75	exp Technology Assessment, Biomedical/ or (health technology assessment\$ or HTA or HTAs or biomedical technology assessment\$ or bio-medical technology assessment\$).ti,ab.	13959
76	(Meta analysis or systematic review).ti,ab. use prem or review.ti. use prem	5900
77	or/74-76	121594
78	(Meta Analysis or Systematic Review or Biomedical Technology Assessment).mp.	129876
79	(meta analy\$ or metaanaly\$ or met analy\$ or metanaly\$ or health technology assessment\$ or HTA or HTAs or biomedical technology assessment\$ or bio-medical technology assessment\$).ti,ab.	63113
80	(meta regression\$ or metaregression\$ or mega regression\$).ti,ab.	1527
81	((systematic\$ adj (literature review\$ or review\$ or overview\$)) or (methodologic\$ adj (literature review\$ or review\$ or overview\$))).ti,ab.	44118
82	((quantitative adj (review\$ or overview\$ or synthes\$)) or (research adj (integration\$ or overview\$))).ti,ab.	1541
83	((integrative adj2 (review\$ or overview\$)) or (collaborative adj (review\$ or overview\$)) or (pool\$ adj analy\$)).ti,ab.	6111
84	(data synthes\$ or data extraction\$ or data abstraction\$).ti,ab.	19444
85	(handsearch\$ or hand search\$).ti,ab.	6265
86	(mantel haenszel or peto or der simonian or dersimonian or fixed effect\$ or latin square\$).ti,ab.	6243
87	(mantel haenszel or peto or der simonian or dersimonian or fixed effect\$ or latin square\$).ti,ab.	20054
88	or/78-87	179924
89	(Meta Analysis or Systematic Review).sh.	57736
90	(meta analy\$ or metaanaly\$ or met analy\$ or metanaly\$ or health technology assessment\$ or HTA or HTAs or biomedical technology assessment\$ or bio-medical technology assessment\$).ti,ab.	63113
91	(meta regression\$ or metaregression\$ or mega regression\$).ti,ab.	1527

92	((systematic\$ adj (literature review\$ or review\$ or overview\$)) or (methodologic\$ adj (literature review\$ or review\$ or overview\$))).ti,ab.	44118
93	((quantitative adj (review\$ or overview\$ or syntheses\$)) or (research adj (integration\$ or overview\$))).ti,ab.	1541
94	((integrative adj2 (review\$ or overview\$)) or (collaborative adj (review\$ or overview\$)) or (pool\$ adj analy\$)).ti,ab.	6111
95	(data syntheses\$ or data extraction\$ or data abstraction\$).ti,ab.	19444
96	(handsearch\$ or hand search\$).ti,ab.	6243
97	(mantel haenszel or peto or der simonian or dersimonian or fixed effect\$ or latin square\$).ti,ab.	20054
98	or/89-98	166783
99	77 or 88 or 98	222196
100	73 and 59 and	261
101	remove duplicates from 100	230
102	limit 101 to human [Limit not valid in: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations; records were retained]	229
OTHER DATABASES		
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE® search, with appropriate syntax used.	
Cochrane Library Issue 3, 2006;	Same MeSH, keywords, and date limits used as per MEDLINE® search, excluding study types and Human restrictions. Syntax adjusted for Cochrane Library databases.	

GREY LITERATURE AND HAND SEARCHES

Dates for Search:	January 2007
Keywords:	verteporfin, visudyne, photodynamic therapy, macular degeneration
Limits:	Publication years 1996-present

* **NOTE:** This section lists the main agencies, organizations, and websites searched; **it is not a complete list.** For a complete list of sources searched, contact CADTH (<http://www.cadth.ca>).

Health Technology Assessment Agencies

Alberta Heritage Foundation for Medical Research (AHFMR)
<http://www.ahfmr.ab.ca>

Agence d'Evaluation des Technologies et des Modes d'Intervention en Santé (AETMIS). Québec
<http://www.aetmis.gouv.qc.ca>

Canadian Agency for Drugs and Technologies in Health (CADTH)
<http://www.cadth.ca>

Centre for Evaluation of Medicines (Father Sean O'Sullivan Research Centre,
St. Joseph's Healthcare, Hamilton, and McMaster University, Faculty of Health Sciences, Hamilton, Ontario).
<http://www.thecem.net/>

Centre for Health Services and Policy Research, University of British Columbia.
<http://www.chspr.ubc.ca/cgi-bin/pub>

Health Quality Council of Alberta (HQCA)
<http://www.hqca.ca>

Health Quality Council. Saskatchewan.
<http://www.hqc.sk.ca/>

Institute for Clinical Evaluative Sciences (ICES). Ontario.
<http://www.ices.on.ca/>

Institute of Health Economics (IHE). Alberta.
<http://www.ihe.ab.ca/>

Manitoba Centre for Health Policy (MCHP)
<http://www.umanitoba.ca/centres/mchp/>

Ontario Ministry of Health and Long Term Care. Health Technology Reviews
http://www.health.gov.on.ca/english/providers/program/mas/tech/tech_mn.html

The Technology Assessment Unit of the McGill University Health Centre
<http://www.mcgill.ca/tau/>

Therapeutics Initiative. Evidence-Based Drug Therapy. University of British Columbia.
<http://www.ti.ubc.ca>

Health Technology Assessment International (HTAi)
<http://www.htai.org>

International Network for Agencies for Health Technology Assessment (INAHTA)
<http://www.inahta.org>

WHO Health Evidence Network
<http://www.euro.who.int/HEN>

Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S)
<http://www.surgeons.org/Content/NavigationMenu/Research/ASERNIPS/default.htm>

Centre for Clinical Effectiveness (Monash University)
<http://www.med.monash.edu.au/healthservices/cce/>

Medicare Services Advisory Committee (Department of Health and Aging)
<http://www.msac.gov.au/>

NPS RADAR (National Prescribing Service Ltd)
http://www.npsradar.org.au/site.php?page=1&content=/npsradar%2Fcontent%2Farchive_alpha.html

ITA - Institute of Technology Assessment
<http://www.oeaw.ac.at/ita/index.htm>

Federal Kenniscentrum voor de Gezondheidszorg
<http://www.kenniscentrum.fgov.be>

Danish Centre for Evaluation and Health Technology Assessment (DCEHTA). National Board of Health
<http://www.dihta.dk/>

DSI Danish Institute for Health Services Research and Development
<http://www.dsi.dk/engelsk.html>

Finnish Office for Health Care Technology and Assessment (FinOHTA). National Research and Development Centre for Welfare and Health. <http://finohta.stakes.fi/EN/index.htm>

L'Agence Nationale d'Accréditation et d'Evaluation en Santé (ANAES). Ministère de la Santé, de la Famille, et des Personnes handicapées
<http://www.anaes.fr/anaes/anaesparametrage.nsf/HomePage?ReadForm>

Committee for Evaluation and Diffusion of Innovative Technologies (CEDIT)
http://cedit.aphp.fr/english/index_present.html

German Institute for Medical Documentation and Information (DIMDI). Federal Ministry of Health.
<http://www.dimdi.de/static/de/hta/db/index.htm>

Health Service Executive
<http://www.hebe.ie/ProgrammesProjects/HealthTechnologyAssessment>

College voor Zorgverzekeringen/Health Care Insurance Board (CVZ)
<http://www.cvz.nl>

Health Council of the Netherlands
<http://www.gr.nl>

New Zealand Health Technology Assessment Clearing House for Health Outcomes and Health Technology Assessment (NZHTA)
<http://nzhta.chmeds.ac.nz/>

Norwegian Centre for Health Technology Assessment (SMM)
<http://www.kunnskapssenteret.no/index.php?show=38&expand=14,38>

Agencia de Evaluación de Tecnologías Sanitarias (AETS), Instituto de Salud "Carlos III"/Health Technology Assessment Agency
http://www.isciii.es/htdocs/investigacion/Agencia_quees.jsp

Basque Office for Health Technology Assessment (OSTEBA). Departamento de Sanidad
<http://www.osasun.ejgv.euskadi.net/r52-2536/es/>

Catalan Agency for Health Technology Assessment and Research (CAHTA)
<http://www.aatrm.net/html/en/Du8/doc7850.html>

CMT - Centre for Medical Technology Assessment
<http://www.cmt.liu.se/pub/jsp/polopoly.jsp?d=6199&l=en>

Swedish Council on Technology Assessment in Health Care (SBU)
<http://www.sbu.se/www/index.asp>

Swiss Network for Health Technology Assessment
<http://www.snhta.ch/about/index.php>

European Information Network on New and Changing Health Technologies (EUROSCAN). University of Birmingham. National Horizon Scanning Centre
<http://www.euroscan.bham.ac.uk>

National Horizon Scanning Centre (NHSC)
<http://www.pcpoh.bham.ac.uk/publichealth/horizon>

NHS Health Technology Assessment /National Coordinating Centre for Health Technology Assessment (NCCHTA). Department of Health R&D Division.
<http://www.hta.nhsweb.nhs.uk>

NHS National Institute for Clinical Excellence (NICE)
<http://www.nice.org.uk>

NHS Quality Improvement Scotland
<http://www.nhshealthquality.org>

University of York NHS Centre for Reviews and Dissemination (NHS CRD)
<http://www.york.ac.uk/inst/crd>

The Wessex Institute for Health Research and Development. Succinct and Timely Evaluated Evidence Review (STEER)
<http://www.wihrd.soton.ac.uk/>

West Midlands Health Technology Assessment Collaboration (WMHTAC)
<http://www.publichealth.bham.ac.uk/wmhtac/>

Agency for Healthcare Research and Quality (AHRQ)
<http://www.ahrq.gov/>

Dept. of Veterans Affairs Research & Development, general publications
http://www1.va.gov/resdev/prt/pubs_individual.cfm?webpage=pubs_ta_reports.htm

VA Technology Assessment Program (VATAP)
<http://www.va.gov/vatap/>

ECRI
<http://www.ecri.org/>

Institute for Clinical Systems Improvement
<http://www.icsi.org/index.asp>

Technology Evaluation Center (Tec). BlueCross BlueShield Association.
<http://www.bluecares.com/tec/index.html>

University HealthSystem Consortium (UHC)
<http://www.uhc.edu/>

Health Economic

Bases Codecs. CODECS (COnnaisances et Décision en EConomie de la Santé) Collège des Economistes de la Santé/INSERM
[http://www.inserm.fr/codecs/codecsanglais.nsf/\(Web+English+Startup+Page\)?OpenForm](http://www.inserm.fr/codecs/codecsanglais.nsf/(Web+English+Startup+Page)?OpenForm)

Centre for Health Economics and Policy Analysis (CHEPA). Dept. of Clinical Epidemiology and Biostatistics.
Faculty of Health Sciences. McMaster University, Canada.
<http://www.chepa.org>

Health Economics Research Group (HERG). Brunel University, U.K.
<http://www.brunel.ac.uk/about/acad/herg>

Health Economics Research Unit (HERU). University of Aberdeen.
<http://www.abdn.ac.uk/heru/>

XOHE-IFMPA Database Ltd. (HEED)
<http://www.ohe-heed.com/>

The Hospital for Sick Children (Toronto). PEDE Database.
<http://pede.bioinfo.sickkids.on.ca/pede/index.jsp>

University of Connecticut. Department of Economics. RePEc database.
<http://ideas.repec.org>

Search Engines

Google
<http://www.google.ca/>

Yahoo!
<http://www.yahoo.com>

APPENDIX 1A: CLINICAL DATA EXTRACTION FORM

Study Identification	Methods	Participant Characteristics	Intervention Characteristics	Comparator Characteristics	Covariates	Outcomes
<p>Study ID:</p> <p>Study question addressed:</p> <p>Citation (Author, year):</p> <p>Related publications:</p> <p>Reviewer Initial:</p> <p>Verified by:</p> <p>Other question(s) that this study addresses in this review?</p> <p>Comments:</p>	<p>Study objective:</p> <p>Study design:</p> <p>Site(s):</p> <p>Inclusion criteria:</p> <p>Exclusion criteria:</p> <p>Data collection technique:</p> <p>Date(s) of data collection:</p> <p>Funding source:</p>	<p>N (full) =</p> <p>N (Enrolled/Completed) = IG</p> <p>N (Enrolled/Completed) = IG2</p> <p>N (Enrolled/Completed) = IG3</p> <p>N (Enrolled/Completed) = CG</p> <p>N (Enrolled/Completed) = CG2</p> <p>Refusal to consent: IG CG IG2 IG3 CG2</p> <p>Mean age:</p> <p>% Female:</p> <p>Race/ethnicity:</p> <p>Geographic location:</p> <p>Baseline visual acuity: How measured</p> <p>Baseline lesion size: How measured</p> <p>Baseline QOL: How measured</p> <p>Other:</p>	<p>Intervention (1):</p> <p>Dose (1):</p> <p>Source (1):</p> <p>Intervention (2):</p> <p>Dose (2):</p> <p>Source (2):</p> <p>Intervention (3):</p> <p>Dose (3):</p> <p>Source (3):</p>	<p>Intervention (1):</p> <p>Dose (1):</p> <p>Source (1):</p> <p>Intervention (2):</p> <p>Dose (2):</p> <p>Source (2):</p>	<p>Grade/Severity (cataract):</p> <p>Grade/Severity (other ocular pathology):</p> <p>Type of CNV:</p> <p>Other:</p>	<p>Visual acuity: How measured</p> <p>Lesion size How measured</p> <p>QOL: How measured</p> <p>Adverse events (Ocular):</p> <p>Adverse Events (General):</p> <p>Adverse Events (Systemic):</p> <p>Other:</p>

APPENDIX 1B: RCTS – SUMMARY OF RESULTS

Author, Year; Study Country(s)	Type of CNV	Total Follow-up Period (mos)	Age (yrs)	Intervention (n=), % Female	Comparator (n=), % Female	Main Outcome(s)	Jadad Score; Adequacy of allocation concealment	Industry Funded
TAP & VIP Study Groups, 2003; USA, Canada, Europe ²⁰	Occult with no classic	24	75.4	V-PDT (n=166), 60.8%	Placebo (n=92), 64.1%	ETDRS, MPS disc area	4; Adequate	Yes
Kaiser, 2002; USA, Canada, Europe ²²	NR	NR	NR	V-PDT (n=225), NR	Placebo (n=114), NR	Adverse events	4, Adequate	Yes
Michels, 2005; Europe ²⁴	Predominantly classic	12	IG: 72.7 CG: 75.1	V-PDT: retreatment at 2 months (n=100), NR	V-PDT: retreatment at 3 months (n=103), NR	ETDRS, MPS disc area	1; Unclear	No
Bressler, 2006 ²¹	Predominantly classic	12	NR	Ranibizumab 0.3mg (n=137), Ranibizumab 0.5mg (n=139), NR	V-PDT (n=142), NR	Quality of life	2; Unclear	Yes
Antoszyk, 2006 ²⁵	Predominantly classic	12	NR	V-PDT + Ranibizumab (n=105), NR	V-PDT (n=56), NR	ETDRS	2; Unclear	Yes
Slakter, 2006 ¹⁸	Predominantly classic	12	76.6	Anecortave acetate (n=263), NR	V-PDT (n=267), NR	ETDRS	3; Unclear	Yes
Brown, 2006 ¹⁷	Predominantly classic	12	IG1=77.4 IG2=76.0 CG=77.7	Ranibizumab 0.3mg (n=140) 47.9% Ranibizumab 0.5mg (n=140) 46.4%	V-PDT (n=143), 55.2%	ETDRS, MPS disc area	3; Unclear	Yes
Heier, 2006 ¹³	Predominantly classic, Minimally classic, Occult with no classic	12	IG=74.7 CG=73.0	V-PDT + Ranibizumab (n=106), 56.6%	V-PDT (n=56), 46.4%	ETDRS, MPS disc area, Adverse events	2; Unclear	Yes
VIP Study Group ²³	NR	24	IG=75.0 CG=75.0	V-PDT (n=166), 61%	Placebo (n=92), 64%	ETDRS, MPS disc area	5; Adequate	Yes
Hahn, 2007 ²⁶	Occult, Classic,	3	IG=77.5 CG1=79.5	Bevacizumab (n=10), 30%	SPDT-IVTA (n=10), 30%;	ETDRS, Central retinal	N/A	NR

Author, Year; Study Country(s)	Type of CNV	Total Follow- up Period (mos)	Age (yrs)	Intervention (n=), % Female	Comparator (n=), % Female	Main Outcome(s)	Jadad Score; Adequacy of allocation concealment	Industry Funded
	Minimally classic		CG2=80		RPDT-IVTA (n=10), 10%	thickness		
Lazic, 2007 ¹²	Minimally classic, Occult	3	IG=75.4 CG1=76.1 CG2=75.6	Bevacizumab + V-PDT (n=52), 65%	Bevacizumab alone (n=54), 68%; V-PDT alone (n=50), 70%	ETDRS, Central foveal thickness	3; Inadequate	NR
Bashshur, 2007 ²⁷	Predomin antly classic	6	IG=75.4 CG=74.6	Bevacizumab (n=32), 56%	V-PDT (n=30), 43%	Snellen visual acuity, Central retinal thickness	2; Unclear	NR

mos=Months, yrs=Years, n=Sample size, ITT=Intent-to-treat, V-PDT=Photodynamic therapy with Verteporfin, ETDRS=Early Treatment Diabetic Retinopathy Study visual acuity, MPS=Macular Photocoagulation Study, NR=Not reported, IG=Intervention group, CG=Control group, SPDT-IVTA=Standard light influence PDT with verteporfin and intravitreal triamcinolone, RPDT-IVTA=Reduced light influence PDT with verteporfin and intravitreal triamcinolone, N/A=Not available

APPENDIX 2: NON-RCT COMBINATION THERAPIES

Author, Year; Study Country(s)	Study Design	Type of CNV	Total Follow-up Period (mos)	Age (yrs)	Intervention (n=), % Female	Comparator (n=), % Female	Main Outcome(s)
Chan, 2005; Hong Kong, SAR ³⁰	Non-randomized comparative	Occult with no classic	12	IG=73.9 CG=73.3	V-PDT & IVTA (n=12) 50%	V-PDT (n=13) 26%	ETDRS, MPS disc area
Augustin, 2007; Germany ³¹	Prospective, non-comparative, interventional case series	Predominantly classic, Minimally classic, Occult with no classic	Mean=40* Range=20, 60*	76.5	V-PDT & Bevacizumab & Dexamethasone (n=104); 60.6%		ETDRS, MPS disc area
Dhalla, 2006; USA ²⁹	Retrospective case series	Predominantly classic, Occult with no classic	7	74.0	V-PDT & Bevacizumab(n=24); NR		ETDRS, MPS disc area
Liggett, 2006; USA ²⁸	Retrospective, interventional case series	NR	6	81.5	(No previous treatment) V-PDT & IVTA & Pegaptanib (n=9); NR	(Previously treated with V-PDT and IVTA) V-PDT & IVTA & Pegaptanib (n=13); NR	ETDRS, Macular thickness by OCT
Ahmadiéh, 2007; Iran ¹¹	Prospective interventional case series	Predominantly classic, minimally classic, occult; retinal angiomatous proliferation	Mean= 50.4* Range= 24, 73*	67.7	V-PDT & IVB & IVTA (n=17); 59%	Snellen visual acuity, Macular thickness by OCT	
Ladas, 2007	Retrospective interventional case series	Occult CNV with serious pigment epithelium detachment	9	Range= 52, 75	V-PDT & IVB (n=6); 66%	Snellen visual acuity, Central 1mm retinal thickness by OCT	

* In weeks

mos=Months, yrs=Years, n=Sample size, ITT=Intent-to-treat, V-PDT=Photodynamic therapy with Verteporfin, ETDRS=Early Treatment Diabetic Retinopathy Study visual acuity, MPS=Macular Photocoagulation Study, NR=Not reported, OCT=optical coherence topography; IG=Intervention group, CG=Control group, IVTA=Intravitreal triamcinolone acetonide, IVB=Intravitreal bevacizumab

APPENDIX 3: BASELINE CLINICAL CHARACTERISTICS

Study and Intervention	V-PDT Comparator			
	n=	Mean	n=	Mean
Age (years)				
Heier, 2006 ¹³ : 0.5mg Rb	106	74.7	56	73.0
Brown, 2006 ¹⁷ : 0.3mg Rb	140	77.4	143	77.7
Brown, 2006 ¹⁷ : 0.5mg Rb	140	76.0	143	77.7
Slakter, 2006 ¹⁸ : AA	263	76.6	267	76.6
Combined	649	76.3	609	76.8
% Female				
Heier, 2006 ¹³ : 0.5mg Rb	106	56.6%	56	46.4%
Brown, 2006 ¹⁷ : 0.3mg Rb	140	47.9%	143	55.2%
Brown, 2006 ¹⁷ : 0.5mg Rb	140	46.4%	143	55.2%
Slakter, 2006 ¹⁸ : AA	263	52.0%	267	52.0%
Combined	649	50.7%	609	53.0%
Visual Acuity Score (ETDRS)				
Heier, 2006 ¹³ : 0.5mg Rb	106	45.1	56	48.5
Brown, 2006 ¹⁷ : 0.3mg Rb	140	47.0	143	45.5
Brown, 2006 ¹⁷ : 0.5mg Rb	140	47.1	143	45.5
Slakter, 2006 ¹⁸ : AA	263	49.0	267	48.0
Combined	649	47.5	609	46.9
Lesion size (MPS disc size)				
Heier, 2006 ¹³ : 0.5mg Rb	106	2.0	56	2.2
Brown (2006) ¹⁷ : (0.3mg Rb	140	1.9	143	1.9
Brown (2006) ¹⁷ : (0.5mg Rb	140	1.8	143	1.9
Slakter, 2006 ¹⁸ : AA	263	1.5	267	1.5
Combined	649	1.7	609	1.7
Age (years)				
Lazic, 2007 ¹² : COMB	55	75.4	55	75.6
Lazic, 2007 ¹² : BEV	55	76.1	55	75.6
Bashshur, 2007 ²⁷ : BEV	32	75.4	32	74.6
Combined	142	75.7	142	75.4
% Female				
Lazic, 2007 ¹² : COMB	55	65%	55	70%
Lazic, 2007 ¹² : BEV	55	69%	55	70%
Bashshur, 2007 ²⁷ : BEV	32	56%	32	43%
Combined	142	65%	142	64%
Visual Acuity Score (ETDRS:logMAR)				
Lazic, 2007 ¹² : COMB	55	1.062	55	1.106
Lazic, 2007 ¹² : BEV	55	1.090	55	1.106
Bashshur, 2007 ²⁷ : BEV	0	n.a	0	n.a
Combined	110	1.076	110	1.106

Study and Intervention			V-PDT Comparator	
	n=	Mean	n=	Mean
Visual Acuity Score (Snellen)				
Lazic, 2007 ¹² : COMB	0	n.a	0	n.a
Lazic, 2007 ¹² : BEV	0	n.a	0	n.a
Bashshur, 2007 ²⁷ : BEV	32	20/119	32	20/108
<i>Combined</i>	32	20/119	32	20/108
Retinal Thickness (µm)				
Lazic, 2007 ¹² : COMB	55	349.1	55	356
Lazic, 2007 ¹² : BEV	55	355.1	55	356
Bashshur, 2007 ²⁷ : BEV	32	354.0	32	352.0
<i>Combined</i>	142	352.5	142	355.1

n=sample size, ETDRS=Early Treatment Diabetic Retinopathy Study visual acuity, COMB = Combination of intravitreal bevacizumab with V-PDT, BEV =bevacizumab, MPS=Macular Photocoagulation Study, Rb=Ranibizumab, AA=anecortave acetate, V-PDT=photodynamic therapy plus verteporfin.

Note: Lesion size and ETDRS raw scales not available.

APPENDIX 4: SUMMARY OF CHANGES IN THE NUMBER OF LETTERS IN THE ETDRS SCALE

Study and Intervention	Treatment Group				V-PDT Comparator				Net Benefit
	n=	Baseline ETDRS	Follow-up ETDRS	Δ	n=	Baseline ETDRS	Follow-up ETDRS	Δ	
Monthly Ranibizumab									
Heier, 2006 ¹³ : 0.5mg Rb	106	45.1	50	4.9	56	48.5	40.3	-8.2	13.1
Brown, 2006 ¹⁷ : 0.3mg Rb	140	47	55.5	8.5	143	45.5	36	-9.5	18.0
Brown, 2006 ¹⁷ : 0.5mg Rb	140	47.1	58.4	11.3	143	45.5	36	-9.5	20.8
<i>Overall Benefit - Ranibizumab</i>	386	N/A	N/A	N/A	342	N/A	N/A	N/A	18.00
Anecortave Acetate									
Slakter, 2006 ¹⁸ : AA	214	48	21	-27	220	49	20	-29	3.0
<i>Overall benefit - AA</i>	214	N/A	N/A	N/A	220	N/A	N/A	N/A	7.45

n=sample size, ETDRS=Early Treatment Diabetic Retinopathy Study visual acuity, Rb=Ranibizumab, N/A=not applicable, AA=anecortave acetate, V-PDT=photodynamic therapy plus verteporfin.

APPENDIX 5: SEVERE VISION LOSS FOLLOWING ANECORTAVE ACETATE INTERVENTION

Study and Intervention				V-PDT Comparator			Relative Risk (95% CI)	P-value
	N=	n=	%	N=	n=	%		
Loss of > 4 lines (20 letters) Slakter, 2006 ¹⁸	214	68	31.90%	220	67	30.30%	1.04 (0.789 to 1.381)	0.382

N=total sample size, n=number of severe vision loss, CI=confidence interval, V-PDT=photodynamic therapy plus verteporfin.

APPENDIX 6: QUALITY OF LIFE - NATIONAL EYE INSTITUTE VISUAL FUNCTION QUESTIONNAIRE (NEI-VFQ 25)²¹

Study and Intervention			V-PDT Comparator		Net Benefit
	n=	Mean	n=	Mean	
Mean change in overall score					
Brown, 2006: 0.3mg Rb	140	5.9	143	2.2	3.7
Brown, 2006: 0.5mg Rb	140	8.1	143	2.2	5.9
Mean change in near activities subscale					
Brown, 2006: 0.3mg Rb	140	6.6	143	3.7	2.9
Brown, 2006: 0.5mg Rb	140	9.1	143	3.7	5.4
Mean change in distant activities subscale					
Brown, 2006: 0.3mg Rb	140	6.4	143	1.7	4.7
Brown, 2006: 0.5mg Rb	140	9.3	143	1.7	7.6
Mean change in vision related dependency subscale					
Brown, 2006: 0.3mg Rb	140	7.6	143	-1.4	9.0
Brown, 2006: 0.5mg Rb	140	8.9	143	-1.4	10.3

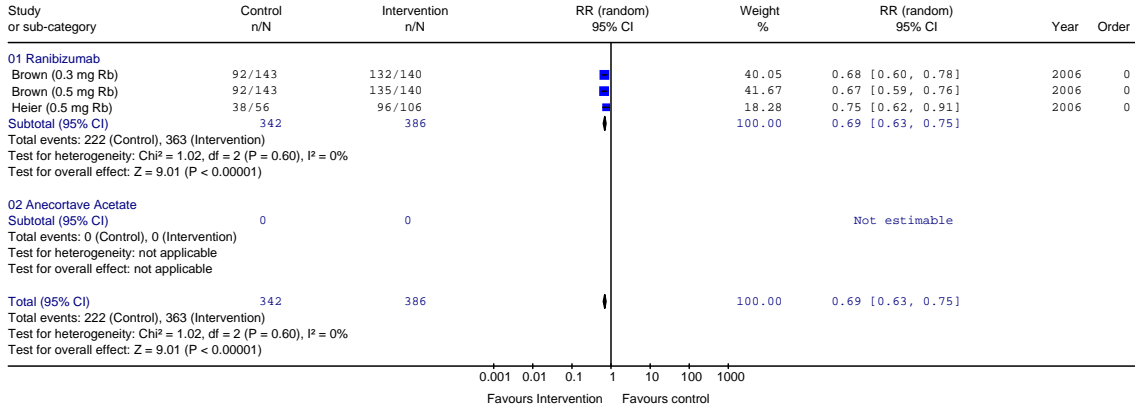
n=sample size, ETDRS=Early Treatment Diabetic Retinopathy Study visual acuity, Rb=Ranibizumab, NA=not available; V-PDT=photodynamic therapy plus verteporfin.

Forest Plots

EFFICACY

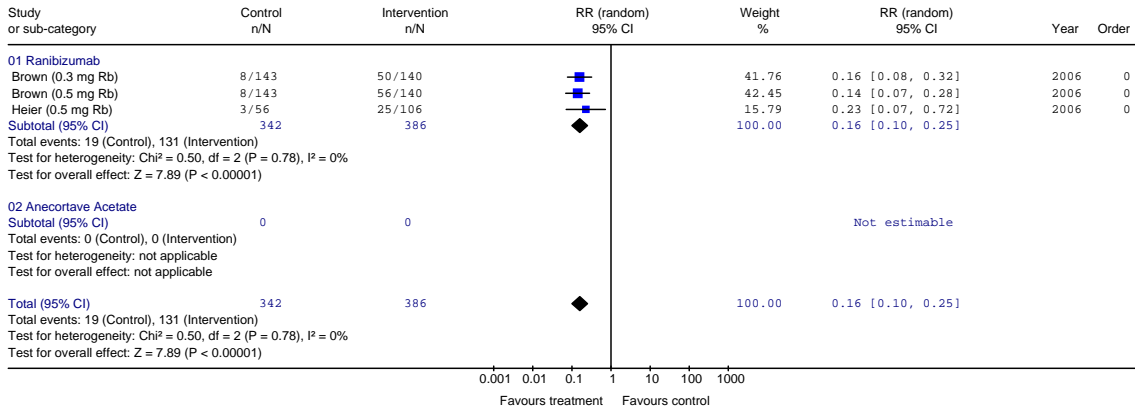
APPENDIX 7: AVOIDING A LOSS OF >15 LETTERS ON THE ETDRS SCALE

Review: AMD - CADTH for HTIS-HTAP program
 Comparison: 17 Avoiding Loss of > 15 Letters on the ETDRS Scale
 Outcome: 01 Avoiding Loss of > 15 Letters on the ETDRS Scale



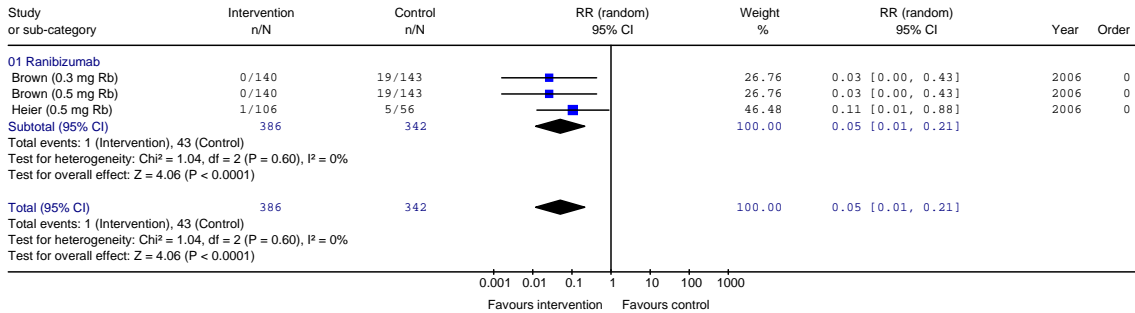
APPENDIX 8: GAIN OF >=15 LETTERS ON THE ETDRS SCALE

Review: AMD - CADTH for HTIS-HTAP program
 Comparison: 18 Gain of >= 15 Letters on the ETDRS Scale
 Outcome: 01 Gain of >= 15 Letters on the ETDRS Scale



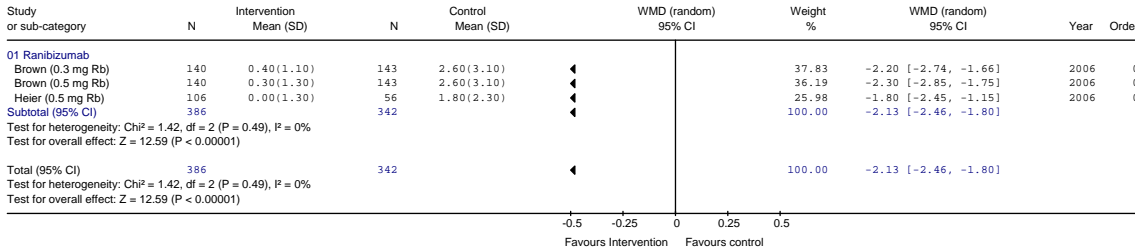
APPENDIX 9: AVOIDING SEVERE VISION LOSS

Review: AMD - CADTH for HTIS-HTAP program
 Comparison: 03 Incurring Severe Vision Loss (>30 letters)
 Outcome: 01 Incurring Severe Vision Loss (> 30 Letters on ETDRS Scale)



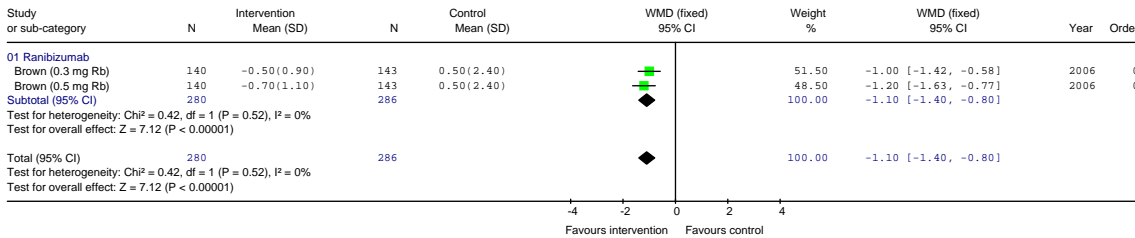
APPENDIX 10: CHANGE IN LESION SIZE (PREDOMINATELY CLASSIC LESIONS)

Review: AMD - CADTH for HTIS-HTAP program
 Comparison: 04 Change in Lesion Size (optic disc units)
 Outcome: 01 Change in Lesion Size



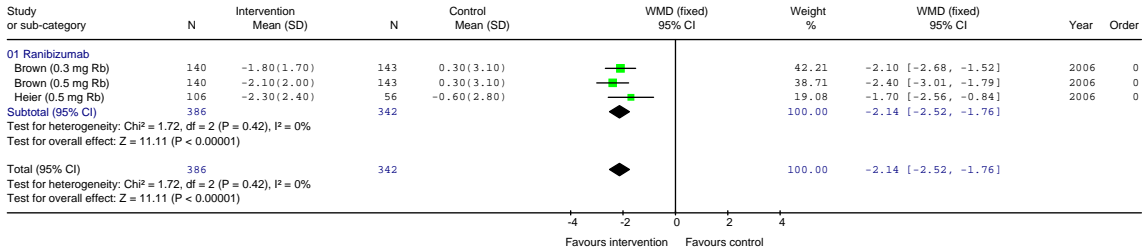
APPENDIX 11: CHANGE IN LESION SIZE (CLASSIC LESIONS)

Review: AMD - CADTH for HTIS-HTAP program
 Comparison: 05 Change in Classic Lesion Size (optic disc units)
 Outcome: 01 Change in Classic Lesion Size



APPENDIX 12: CHANGE IN THE SIZE OF LEAKAGE AREA

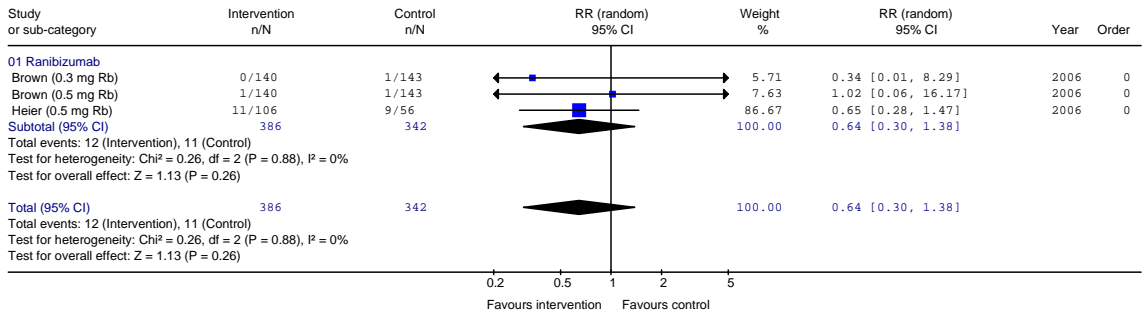
Review: AMD - CADTH for HTIS-HTAP program
 Comparison: 06 Size of Leakage Area (optic disc units)
 Outcome: 01 Size of Leakage Area



HARM: Ocular Adverse Events

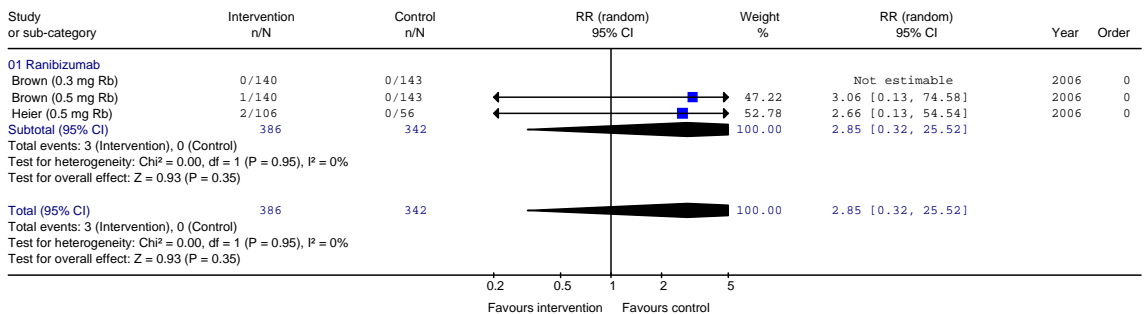
APPENDIX 13: RETINAL DETACHMENT

Review: AMD - CADTH for HTIS-HTAP program
 Comparison: 07 Adverse Ocular Event (Retinal Detachment)
 Outcome: 01 Retinal Detachment



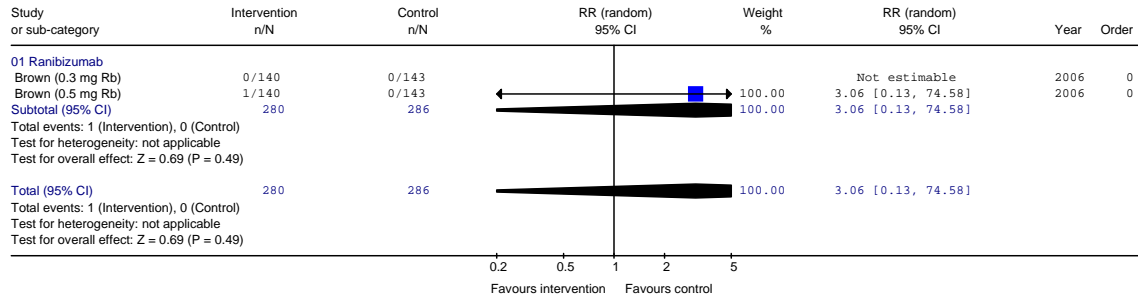
APPENDIX 14: ENDOPHTHALMITIS

Review: AMD - CADTH for HTIS-HTAP program
 Comparison: 08 Adverse Ocular Event (Endophthalmitis)
 Outcome: 01 Endophthalmitis



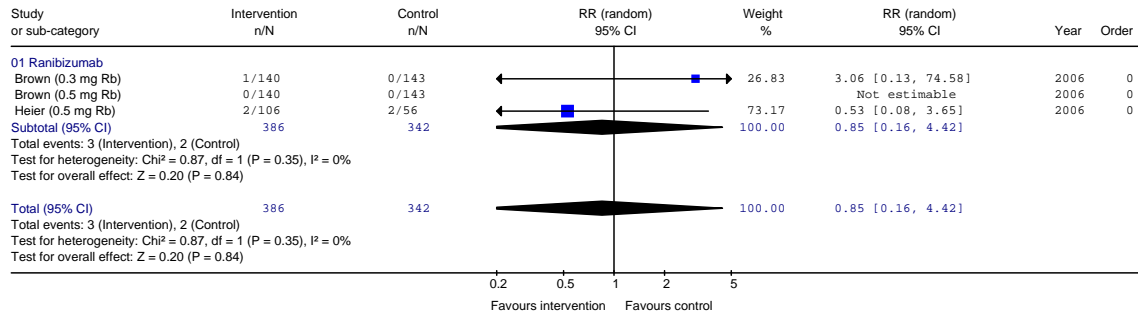
APPENDIX 15: INTRAOCULAR INFLAMMATION

Review: AMD - CADTH for HTIS-HTAP program
 Comparison: 09 Adverse Ocular Event (Intraocular Inflammation)
 Outcome: 01 Intraocular Inflammation



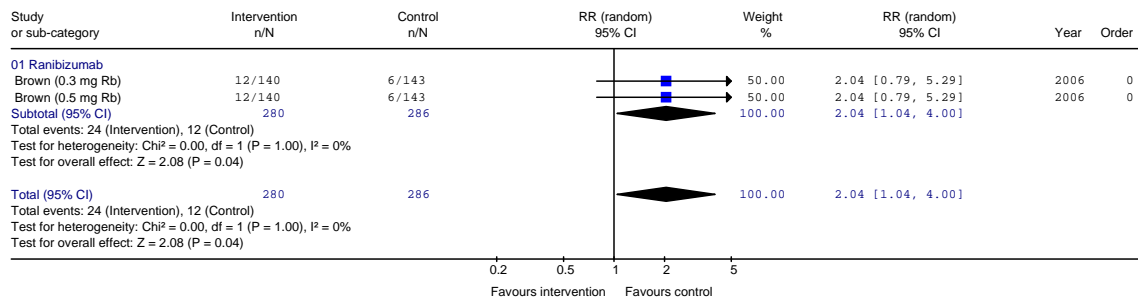
APPENDIX 16: VITREOUS HEMORRHAGE

Review: AMD - CADTH for HTIS-HTAP program
 Comparison: 10 Adverse Ocular Event (Vitreous Hemorrhage)
 Outcome: 01 Vitreous hemorrhage



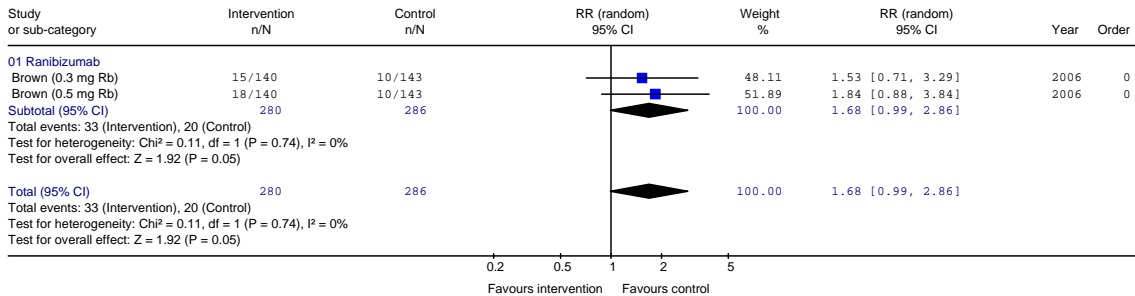
APPENDIX 16A: POST INJECTION IOP >= 30 MM HG

Review: AMD - CADTH for HTIS-HTAP program
 Comparison: 11 Adverse Ocular Event (Post Injection IOP >= 30 mm Hg)
 Outcome: 01 Post Injection IOP >= 30 mm Hg



APPENDIX 16B: CATARACT FORMATION

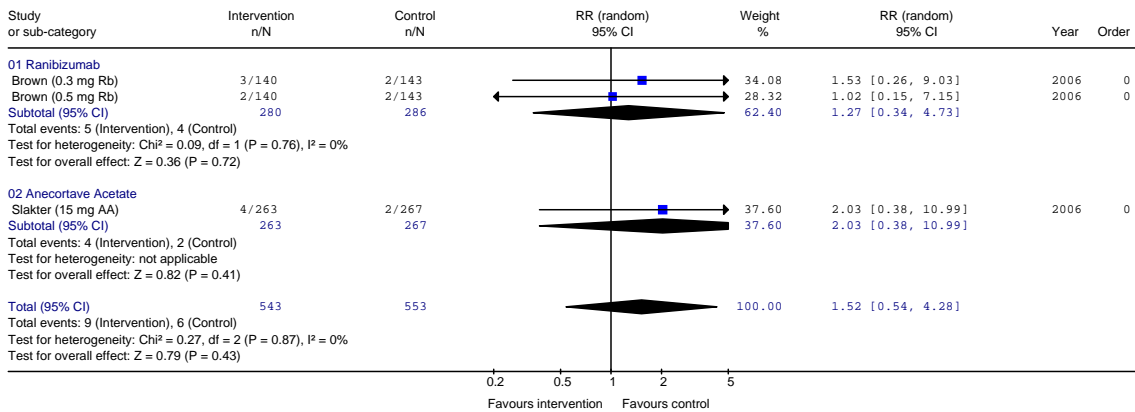
Review: AMD - CADTH for HTIS-HTAP program
 Comparison: 12 Adverse Ocular Event (Cataract Formation)
 Outcome: 01 Cataract Formation



HARM: Systemic Adverse Events

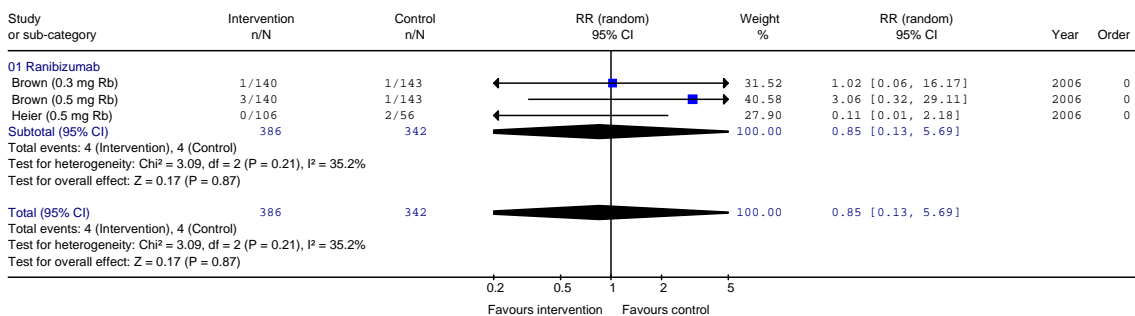
APPENDIX 16C: DEATH

Review: AMD - CADTH for HTIS-HTAP program
 Comparison: 13 Adverse Systemic Events (Death)
 Outcome: 01 Death



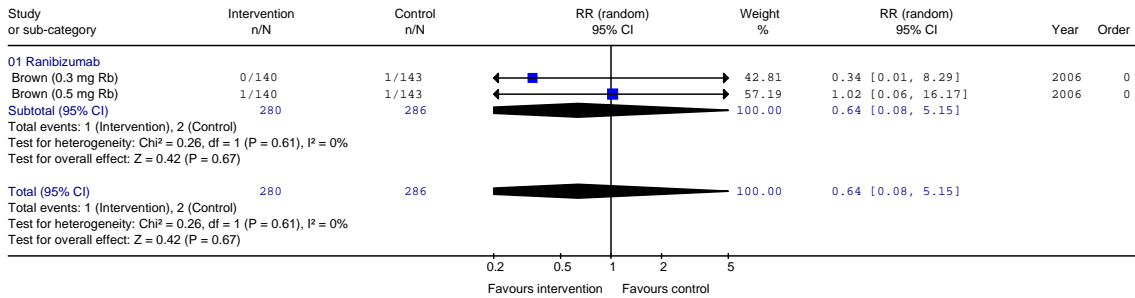
APPENDIX 16D: MYOCARDIAL INFARCTION

Review: AMD - CADTH for HTIS-HTAP program
 Comparison: 14 Adverse Systemic Events (MI)
 Outcome: 01 Myocardial Infarction



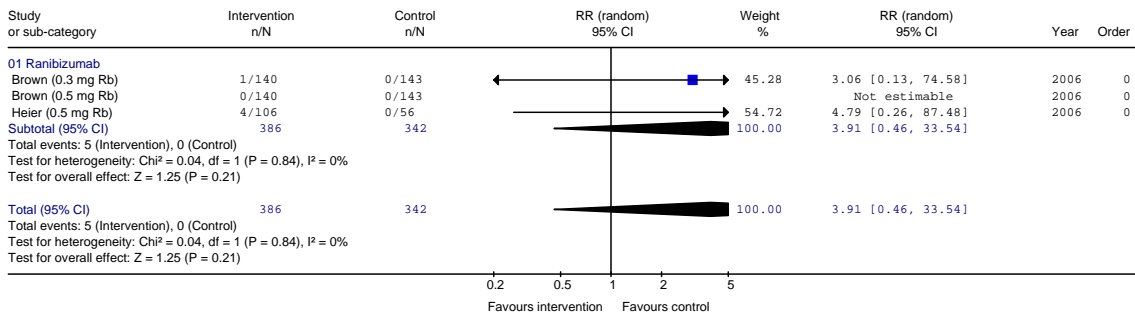
APPENDIX 16E: STROKE

Review: AMD - CADTH for HTIS-HTAP program
 Comparison: 15 Adverse Systemic Events (Stroke)
 Outcome: 01 Stroke



APPENDIX 16F: CEREBRAL INFARCTION

Review: AMD - CADTH for HTIS-HTAP program
 Comparison: 16 Adverse Systemic Events (Cerebral Infarction)
 Outcome: 01 Cerebral Infarction



APPENDIX 17: PLANNED OR ONGOING STUDIES IN AMD

Trial registration	Country	Project title	Start date	Expected completion	Principal investigator	Intervention treatment	Sponsor/ Collaborator
<i>Controlled Clinical Trials</i>							
NCT00376701	Canada	Combination Therapy in Neovascular Age-Related Macular Degeneration (AMD): A Three-Armed, Randomized, Prospective Clinical Trial of Low Fluence Photodynamic Therapy(rPDT) With Adjunctive Avastin and Triamcinolone Acetonide (Kenalog)(Triple Therapy) Versus rPDT With Adjunctive Avastin (Double Therapy) Versus Monotherapy With Avastin.	September 2006	September 2008	T.G. Sheidow, MD	Bevacizumab	<ul style="list-style-type: none"> • Lawson Health Research Institute • QLT Inc • Canadian Retinal Trials Group
NCT00447031	Republic of Korea	Intravitreal Bevacizumab Combined With Intravitreal Triamcinolone Acetonide Injection Versus Intravitreal Bevacizumab for Age Related Macular Degeneration	March 2007	November 2007	Hyoung Jun Koh	Bevacizumab + Triamcinolone acetate	Yonsei University
NCT00504959	Turkey	A Phase IV, Long-Term, Open-Label, Multicenter Extension Study to Evaluate the Safety and Tolerability of Ranibizumab in Patients With Subfoveal Choroidal Neovascularization (CNV) Secondary to Age-Related Macular Degeneration (AMD)	July 2007	NR	Novartis, Study Chair, Board of Hacettepe University	Ranibizumab	Novartis
NCT00517010	USA	Phase 1 Pilot Open Label Prospective Observational Study of Safety and Tolerability of Lucentis Combined With Proton Beam Irradiation in Treating Exudative Age-Related Macular Degeneration	May 2007	May 2009	S. S. Park, MD PhD	Ranibizumab	<ul style="list-style-type: none"> • UC Davis • UC San Francisco • Genentech
NCT00275821	Switzerland	A Randomized, Double-Masked, Active-Controlled, Multi-Center Study Comparing the Efficacy and Safety of Ranibizumab	December 2005	NR	Novartis, Study Chair	Ranibizumab	Novartis

Trial registration	Country	Project title	Start date	Expected completion	Principal investigator	Intervention treatment	Sponsor/ Collaborator
		Administered as Two Dosing Regimens in Patients With Subfoveal Choroidal Neovascularization Secondary to Age-Related Macular Degeneration					
NCT00470678	Republic of Korea Taiwan	An Open-Label, Multicenter Study to Evaluate the Efficacy and Safety of Ranibizumab (0.5 mg) in Patients With Subfoveal Choroidal Neovascularization Secondary to Age-Related Macular Degeneration Over 12 Months	June 2007	NR	Novartis Pharma, Study Chair	Ranibizumab	Novartis
NCT00331864	Switzerland	A Phase IIIb, Open-Label, Multicenter 12-Month Study to Evaluate the Safety, Tolerability and Efficacy of Ranibizumab (0.3 mg) in Patients With Subfoveal Choroidal Neovascularization (CNV) Secondary to Age-Related Macular Degeneration (AMD)	April 2006	NR	Novartis, Study Chair	Ranibizumab	Novartis
NCT00464347	USA	Multi-Center, Randomized, Phase II Clinical Trial to Study the Effects of Preservative-Free Triamcinolone Acetonide and Avastin® in Combination With Photodynamic Therapy in Participants With Neovascular Age Related Macular Degeneration	January 2007	NR	K. G. Csaky, MD, PhD	Avastin + PDT + Preservative-Free Triamcinolone Acetonide	<ul style="list-style-type: none"> • National Eye Institute (NEI) • QLT Inc
NCT00347399	Mexico	Effects of Intravitreal Injection of Bevacizumab in Combination With Verteporfin Photodynamic Therapy	March 2006	June 2007	H. Quiroz-Mercado, MD; J. D. Weizhaus, MD	Bevacizumab	Asociación para Evitar la Ceguera en México
NCT00423189	USA	Lucentis Utilizing Visudyne (LUV Trial)--Reduced Fluence Photodynamic Therapy With	January 2007	NR	D. M Brown, MD	Ranibizumab +	<ul style="list-style-type: none"> • Greater Houston

Trial registration	Country	Project title	Start date	Expected completion	Principal investigator	Intervention treatment	Sponsor/ Collaborator
		Visudyne Combined With Intravitreal Ranibizumab in the Treatment of Age-Related Macular Degeneration				Verteporfin	Retina Research • Novartis
NCT00390208	USA	A Prospective Masked Pilot Study Comparing Group 1 Triple Therapy - PDT Plus IVD and Intravitreal Ranibizumab Versus Group 2 Monotherapy - Intravitreal Ranibizumab Alone.	August 2006;	February 2009	S. K Ray, MD PhD	Verteporfin + Dexamethasone + Ranibizumab	• Bay Area Retina Associates • QLT Inc
NCT00499590	USA	A Phase 3, Randomized, Double-Masked, Parallel-Assignment Study of Intravitreal Bevasiranib Sodium, Administered Every 8 or 12 Weeks as Maintenance Therapy Following Three Injections of Lucentis® Compared With Lucentis® Monotherapy Every 4 Weeks in Patients With Exudative Age-Related Macular Degeneration (AMD).	July 2007	August 2010	D. O'Shaughnessy, PhD	Bevasiranib	Opko Health, Inc.
NCT00492284	USA	A Multicenter, Randomized, Single-Masked Study Comparing Reduced-Fluence Visudyne®-Lucentis® Combination Therapies and Lucentis® Monotherapy in Subjects With CNV Secondary to AMD.	June 2007	January 2010	Oscar Cuzzani, Study Director	Reduced-fluence Verteporfin + Ranibizumab + Dexamethasone	QLT Inc
NCT00455871	USA	Study of Treatment Effects of Combination Therapy of Lucentis Plus Reduced Fluence PDT With Visudyne in Patients With Exudative AMD	April 2007	October 2009	G. K. Shah, MD	Reduced fluence V-PDT + Ranibizumab	Barnes Retina Institute
NCT00470977		Treatment of Exudative and Vasogenic Chorioretinal Diseases Including Variants of AMD and Other CNV Related Maculopathy (Coats' Disease, Idiopathic Perifoveal	May 2007	December 2008	L. A. Yannuzzi, MD	Ranibizumab	Manhattan Eye, Ear & Throat Hospital

Trial registration	Country	Project title	Start date	Expected completion	Principal investigator	Intervention treatment	Sponsor/ Collaborator
		Telangiectasia, Retinal Angiomatous Proliferation, Polypoidal Vasculopathy, Pseudoxanthoma Elasticum, Pathological Myopia, Multi-Focal Choroiditis, Rubeosis Iridis) With Intravitreal Injection of Lucentis (Ranibizumab Injection)					
NCT00327470	North America, Europe, Australia	A 102-Week, Open Label, Multicenter Trial to Investigate the Efficacy of Macugen for the Preservation of Visual Function in Subjects With Neovascular Age-Related Macular Degeneration (AMD) and to Assess the Benefit of Treating Early Choroidal Neovascularization (CNV).	July 2006	NR	Pfizer CT.gov Call Center, Study Director	Pegaptanib Sodium 0.3 mg	Pfizer
NCT00395551	USA	A Single Center Study of the Safety and Efficacy of Multiple Intravitreal Injections of Ranibizumab in Subjects With CNV Secondary to Causes Other Than AMD.	December 2005	NR	J.S. Heier, MD	Ranibizumab	<ul style="list-style-type: none"> • Ophthalmic Consultants of Boston • Genentech
NCT00239928	Japan	Long-Term Study For Pegaptanib Sodium In Patients With Subfoveal Choroidal Neovascularization Secondary To Age-Related Macular Degeneration (Extension Study From A5751010)	September 2005	NR	Pfizer CT.gov Call Center, Study Director	Pegaptanib sodium	Pfizer
NCT00473642	USA	A Prospective Pilot Study of Reduced Fluence Photodynamic Therapy With Visudyne® (Verteporfin) in Combination With Lucentis™ (Ranibizumab) for the Treatment of Age-Related Macular Degeneration	May 2007	December 2008	R. Townsend, MD	Ranibizumab + Verteporfin with 50% fluence photodynamic therapy	Oklahoma State University Center for Health Sciences
NCT00433017	Europe	A 12-Month Randomized, Double-Masked, Controlled, Multicenter, Phase II Study Assessing	February 2007	January 2009	Novartis Pharma,	Verteporfin Ranibizumab	Novartis

Trial registration	Country	Project title	Start date	Expected completion	Principal investigator	Intervention treatment	Sponsor/ Collaborator
		Safety and Efficacy of Verteporfin Photodynamic Therapy Administered in Conjunction With Ranibizumab Versus Ranibizumab Monotherapy in Patients With Subfoveal Choroidal Neovascularization Secondary to Age-Related Macular Degeneration			Study Chair		
NCT00324116	France	A Prospective, Open-Label Multi Center Trial Evaluating The Safety And Efficacy Of 0.3 Mg/Eye Pegaptanib Sodium (Macugen) Intravitreal Injection Given Every 6 Weeks For 54 Weeks In Patients With Small Neovascular Age-Related Macular Degeneration (AMD) Lesions	July 2006	NR	Pfizer CT.gov Call Center, Study Director	Pegaptanib sodium	Pfizer
NCT00354445	USA	A Phase IV, Open Label, Multi-Center, Study of Maintenance Intravitreal Injections of Macugen (Pegaptanib Sodium) Given Every 6 Weeks for 48 Weeks in Subjects With Subfoveal Neovascular Age-Related Macular Degeneration (AMD) Initially Treated With a Modality Resulting in Maculopathy Improvement	June 2006	NR	NR	Pegaptanib sodium	<ul style="list-style-type: none"> • Eyetech Pharmaceuticals • Pfizer
NCT00429962	Switzerland	Randomized, Phase IIIb Study Comparing Safety, Tolerability and Efficacy Between Lucentis® Administered in Conjunction With PDT With Visudyne® and Lucentis® in Patients With Subfoveal CNV Secondary to Age-Related Macular Degeneration	July 2006	January 2008	U. Schneider, MD	Ranibizumab	University Hospital, Basel, Switzerland
NCT00457678	USA	A Multicenter, Randomized, Single-Masked Comparison of Lucentis™ Monotherapy With Triple Therapy of Reduced Fluence Visudyne-Lucentis-Dexamethasone (V-L-D) in Patients With CNV Secondary to AMD as Second Line	NR	NR	J. Slakter, MD	Verteporfin + Bevacizumab + Dexamethasone	Vitreous - Retina-Macula Consultants of New York

Trial registration	Country	Project title	Start date	Expected completion	Principal investigator	Intervention treatment	Sponsor/ Collaborator
		Therapy After Lucentis Monotherapy					
ISRCTN 92166560	UK	A randomised controlled trial (RCT) of alternative treatments to Inhibit VEGF in patients with Age-related choroidal Neovascularisation (IVAN)	July 2007	Early 2012	Prof. U Chakravarthy	Ranibizumab vs. Bevacizumab	NHS Health Technology Assessment Programme
<i>Cohort Study</i>							
N0484128011	UK	Verteporfin photodynamic therapy cohort study for the UK	December 2003	Late 2009	Prof. U Chakravarthy	V-PDT	NHS Health Technology Assessment Programme
<i>Systematic reiview/Meta-analysis/Cost effectiveness reports</i>							
NA	UK	Pegaptanib and ranibizumab for the treatment of age-related macular degeneration	NR	NR	Andrea Sutcliffe	Pegaptanib Ranibizumab	<ul style="list-style-type: none"> • Southampton Health Technology Assessment Centre (SHTAC) • University of Southampton
N0484140572	UK	Is a screening programme for early age-related macular degeneration likely to be cost effective? What are the major areas of uncertainty?	April 2004	March 2008	Dr. JD Karnon	N/A	NHS Health Technology Assessment Programme

Note: a reviewer suggested these ongoing studies: CATT (on ranibizumab and bevacizumab), DENALI, and MONT BLANC.

APPENDIX 18: DATA EXTRACTION SHEET FOR REVIEW OF ECONOMIC LITERATURE

Data Extraction Sheet for Review of Economic Evaluations - Template
Project #460

- 1 Author, e-mail contact, reference manager ID#
- 2 Title, journal, year of publication
- 3 Industry sponsorship
- 4 Study perspective
- 5 Interventions and comparators
- 6 Study design
- 7 Population/indication
- 8 Location
- 9 Outcomes and source
- 10 Currency and currency year
- 11 Estimate of cost effectiveness or relative cost
- 12 Conclusions
- 13 Relevant parameter values and measure of dispersion (if available)
- 14 Narrative summary
- 15 Other information

APPENDIX 19: QUALITY ASSESSMENT OF ECONOMIC STUDIES

Check list item	Brown ⁴⁴	Earnshaw ⁵⁵	Grenier ⁴⁵	Hopley ⁴⁶	Javitt ⁵⁴	Larouche ⁴⁷
Study design						
1 Research question is stated	Yes	Yes	Yes	Yes	Yes	Yes
2 Economic importance of research question is stated	Yes	Yes	Yes	Yes	Yes	Yes
3 Viewpoint(s) of analysis clearly stated and justified	Yes	Yes	Yes	Yes	Yes	No
4 Rationale for choosing alternative programs or interventions compared stated	Yes	Yes	Yes	Yes	Yes	Yes
5 Alternatives being compared clearly described	Yes	Yes	Yes	Yes	Yes	Yes
6 Form of economic evaluation used stated	Yes	Yes	Yes	Yes	Yes	Yes
7 Choice of economic evaluation justified in relation to questions addressed	Yes	Yes	Yes	Yes	Yes	Yes
Data collection					Yes	
8 Source(s) of effectiveness estimates used stated	Yes	Yes	Yes	Yes	Yes	Yes
9 Details of design and results of effectiveness study given (if based on 1 study)	Yes	NA	Yes	Yes	Yes	NA
10 Details of method of synthesis or meta-analysis of estimates given (if based on overview of effectiveness studies)	NA	Yes	Yes	NA	NA	No
11 Primary outcome measure(s) for economic evaluation stated	Yes	Yes	Yes	Yes	Yes	Yes
12 Methods to value health states and other benefits stated	Yes	Yes	Yes	Yes	Yes	Yes
13 Details of subjects from whom valuations obtained given	Yes	No	Yes	Yes	No	Yes
14 Productivity changes (if included) reported separately	NA	NA	NA	NA	NA	NA
15 Relevance of productivity changes to study question discussed	NA	NA	NA	NA	NA	NA
16 Quantities of resources reported separately from unit costs	Yes	Yes	No	Yes	Yes	Yes
17 Methods for estimation of quantities and unit costs described	Yes	Yes	Yes	Yes	Yes	Yes
18 Currency and price data recorded	Yes	Yes	Yes	Yes	Yes	Yes
19 Details of price adjustments for inflation or currency conversion given	No	NA	No	Yes	Yes	No
20 Details of model used given	Yes	Yes	Yes	Yes	Yes	Yes
21 Choice of model used and key parameters on which it is based justified	No	Yes	Yes	Yes	Yes	Yes
Analysis and interpretation of results					Yes	
22 Time horizon of costs and benefits stated	Yes	Yes	Yes	Yes	Yes	Yes
23 Discount rate(s) stated	Yes	Yes	No	Yes	Yes	Yes

24 Choice of rate(s) justified	Yes	No	NA	Yes	No	Yes
25 Explanation given if costs or benefits not discounted	NA	NA	No	NA	NA	NA
26 Statistical test and confidence intervals given for stochastic data	Yes	No	No	Yes	No	Yes
27 Approach to sensitivity analysis given	Yes	Yes	No	Yes	Yes	Yes
28 Choice of variables for sensitivity analysis justified	Yes	Yes	NA	Yes	Yes	Yes
29 Ranges over which variables varied stated	Yes	Yes	NA	Yes	Yes	Yes
30 Relevant alternatives compared	Yes	Yes	Yes	Yes	Yes	Yes
31 Incremental analysis reported	Yes	Yes	Yes	Yes	Yes	Yes
32 Major outcomes presented in disaggregated and aggregated forms	Yes	Yes	Yes	Yes	Yes	Yes
33 Answer to study question given	Yes	Yes	Yes	Yes	Yes	Yes
34 Conclusions follow from data reported	Yes	Yes	No	Yes	Yes	Yes
35 Conclusions accompanied by appropriate caveats	Yes	Yes	No	Yes	Yes	Yes
Sum of “no” and “not clears”	2	3	8	0	3	3
Check list item	Meads ⁴⁸	Raftery ⁵²	Sharma 2001 ⁴⁹	Sharma 2005 ⁵³	Smith ⁵⁰	Wolowacz ⁵¹
Study design						
1 Research question is stated	Yes	Yes	Yes	Yes	Yes	Yes
2 Economic importance of research question is stated	Yes	Yes	Yes	Yes	Yes	Yes
3 Viewpoint(s) of analysis clearly stated and justified	Yes	No	Yes	Yes	Yes	Yes
4 Rationale for choosing alternative programs or interventions compared stated	Yes	Yes	Yes	Yes	Yes	Yes
5 Alternatives being compared clearly described	Yes	Yes	Yes	Yes	Yes	Yes
6 Form of economic evaluation used stated	Yes	Yes	Yes	Yes	Yes	Yes
7 Choice of economic evaluation justified in relation to questions addressed	Yes	Yes	Yes	Yes	Yes	Yes
Data collection						
8 Source(s) of effectiveness estimates used stated	Yes	Yes	Yes	Yes	Yes	Yes
9 Details of design and results of effectiveness study given (if based on 1 study)	Yes	No	Yes	Yes	No	Yes
10 Details of method of synthesis or meta-analysis of estimates given (if based on overview of effectiveness studies)	NA	NA	NA	NA	NA	NA
11 Primary outcome measure(s) for economic evaluation stated	Yes	Yes	Yes	Yes	Yes	Yes
12 Methods to value health states and other benefits stated	Yes	Yes	Yes	Yes	Yes	Yes

13 Details of subjects from whom valuations obtained given	Yes	No	Yes	Yes	Yes	Yes
14 Productivity changes (if included) reported separately	NA	NA	NA	NA	NA	NA
15 Relevance of productivity changes to study question discussed	NA	NA	NA	NA	NA	NA
16 Quantities of resources reported separately from unit costs	Yes	No	No	Yes	No	Yes
17 Methods for estimation of quantities and unit costs described	Yes	Yes	Yes	Yes	Yes	Yes
18 Currency and price data recorded	Yes	Yes	Yes	Yes	Yes	Yes
19 Details of price adjustments for inflation or currency conversion given	No	No	No	No	Yes	Yes
20 Details of model used given	Yes	Yes	Yes	Yes	Yes	Yes
21 Choice of model used and key parameters on which it is based justified	Yes	No	Yes	Yes	Yes	Yes
Analysis and interpretation of results						
22 Time horizon of costs and benefits stated	Yes	Yes	Yes	Yes	Yes	Yes
23 Discount rate(s) stated	NA	Yes	Yes	NA	Yes	Yes
24 Choice of rate(s) justified	NA	No	No	NA	Yes	Yes
25 Explanation given if costs or benefits not discounted	No	NA	NA	NA	NA	NA
26 Statistical test and confidence intervals given for stochastic data	Yes	No	Yes	Yes	Yes	Yes
27 Approach to sensitivity analysis given	Yes	Yes	Yes	No	Yes	Yes
28 Choice of variables for sensitivity analysis justified	Yes	Yes	Yes	No	Yes	Yes
29 Ranges over which variables varied stated	Yes	Yes	Yes	No	Yes	Yes
30 Relevant alternatives compared	Yes	Yes	Yes	No	Yes	Yes
31 Incremental analysis reported	Yes	Yes	Yes	Yes	Yes	Yes
32 Major outcomes presented in disaggregated and aggregated forms	Yes	Yes	Yes	Yes	Yes	Yes
33 Answer to study question given	Yes	Yes	Yes	Yes	Yes	Yes
34 Conclusions follow from data reported	Yes	Yes	Yes	Yes	Yes	Yes
35 Conclusions accompanied by appropriate caveats	Yes	Yes	Yes	Yes	Yes	Yes
Sum of “no” and “not clears”	2	8	3	5	2	0

NA – Not applicable

NC – Not clear

APPENDIX 20: PARAMETERS USED IN THE ECONOMIC EVALUATION

Variable	Value	Source	Range for Sensitivity Analyses
Age Distribution of participants	77±7	ANCHOR ¹⁷ , MARINA ³³	55 to 90
Annual Death Rate	Census Estimate	Arias ⁷⁸	N/A
Annual Discount Rate	5%	CADTH economic guidelines ⁷⁰	0% and 3%
Annual Death Rate for Non-fatal MI	17.7%	JACC ⁷⁹	N/A
Annual. Death Rate for Stroke	6.25%	STROKE ⁸⁰	N/A
Annual Risk of Site Infection with V-PDT	13.4%	TAP ⁶³	N/A
Annual Risk of Retinal Detachment with Pegaptanib	0.67%	VISION ³⁴	N/A
Annual Risk of Endophthalmitis with Pegaptanib	1.3%	VISION ³⁴	N/A
Annual Risk of Traumatic Cataract with Pegaptanib	0.56%	VISION ³⁴	N/A
Annual Risk of Endophthalmitis with Ranibizumab (PC)	1.4%	ANCHOR ¹⁷ , MARINA ³³	N/A
Annual Risk of Ocular Inflammation with Ranibizumab (PC)	17.1%	ANCHOR ¹⁷ , MARINA ³³	N/A
Annual Risk of Non-fatal MI with Ranibizumab (PC)	2.1%	ANCHOR ¹⁷ , MARINA ³³	N/A
Annual Risk of Stroke with	0.7%	ANCHOR ¹⁷ ,	N/A

Variable	Value	Source	Range for Sensitivity Analyses
Ranibizumab (PC)		MARINA ³³	
Annual Risk of Non-ocular hemorrhage with Ranibizumab (PC)	2.1%	ANCHOR ¹⁷ , MARINA ³³	N/A
Weighted Average Annual Risk of Endophthalmitis with Ranibizumab (All lesions)	0.9%	ANCHOR ¹⁷ , MARINA ³³ , Olsen ⁸¹	N/A
Weighted Average Annual Risk of Ocular Inflammation with Ranibizumab (All lesions)	13%	ANCHOR ¹⁷ , MARINA ³³ , Olsen ⁸¹	N/A
Weighted Average Annual Risk of Non-fatal MI with Ranibizumab (All lesions)	1.0%	ANCHOR ¹⁷ , MARINA ³³ , Olsen ⁸¹	N/A
Weighted Average Annual Risk of Stroke with Ranibizumab (All lesions)	1.3%	ANCHOR ¹⁷ , MARINA ³³ , Olsen ⁸¹	N/A
Weighted Average Annual Risk of Non-ocular hemorrhage with Ranibizumab (All lesions)	5.5%	ANCHOR ¹⁷ , MARINA ³³ , Olsen ⁸¹	N/A
Initial Visual Acuity (Letters correct)	53±14	ANCHOR ¹⁷ , MARINA ³³ , TAP ⁶³ , VISION ³⁴	10 to 60
Change in Visual Acuity (Letters lost/gained) Distribution of participants			
V-PDT	-9.97±0.68	See section 5.3.6 “Modeling”	N/A

Variable	Value	Source	Range for Sensitivity Analyses
Pegaptanib	-3.27±0.45	See section 5.3.6 “Modeling”	N/A
Ranibizumab	10.23±0.44	See section 5.3.6 “Modeling”	N/A
Office visits			
1. General Practitioner	\$56.10	Ontario Physician Benefits #A005 ⁸²	N/A
2. Ophthalmologist Consultation	\$66.30	Ontario Physician Benefits #A235 ⁸²	N/A
3. Clinic visit	\$104.95	Ontario Physician Benefits #A236 ⁸²	N/A
Procedure Costs (Not including physicians’ fees)			
4. V-PDT (includes cost of verteporfin)	\$2946.22	OCCP ⁸³	N/A
5. Cryotherapy with buckle/vitreotomy	\$2638.46	OCCP ⁸³	N/A
6. Cataract extraction	\$1036.74	OCCP ⁸³	N/A
7. Intravitreal tap and injection	\$630.57	OCCP ⁸³	N/A
8. Fluorescein angiography	\$150.88	OCCP ⁸³	N/A
9. OCT	\$100	OCCP ⁸³	N/A
10. IOP measurement	\$5	OCCP ⁸³	N/A
Physician fees for procedures			
11. PDT	\$360	Ontario Physician Benefits #G460 ⁸²	N/A

⁸² Ontario Case Costing Project (also called the Ontario Case Costing Initiative)

Variable	Value	Source	Range for Sensitivity Analyses
12. Cryotherapy with buckle/vitrectomy	\$1,715.00	Ontario Physician Benefits E148, E152, E936 E940 ⁸²	N/A
13. Cataract extraction	\$516.35	Ontario Physician Benefits E140, E950 ⁸²	N/A
14. Intavitreal tap and injection	\$181.75	Ontario Physician Benefits E149 ⁸²	N/A
Medication Costs			
15. Macugen (0.3 mg, 90uL one pre-filled syringe)	\$995	PPS Pharma ⁸⁴	N/A
16. Avastin 100 mg (28 doses from one 4ml vial at \$600)	\$21.43	PPS Pharma ⁸⁴	N/A
17. Triamcinolone Kenalog 40mg/ml	\$6.82	Ontario formulary ⁶⁵	N/A
Generic 40mg/ml	\$4.77		
18. Lucentis 5 mg	\$1,575		N/A
19. Maxides 0.1% Oph Oint (3.5g)	\$8.36	Ontario formulary ⁶⁵	N/A
20. Cetamide 0%Oph Oint (3.5g)	\$3.34	Ontario formulary ⁶⁵	N/A
21. Atropine Sulfate 1%Oph Sol (5mL)	\$3.00	Ontario formulary ⁶⁵	N/A
22. Keflex (cephalexin) 500 mg qid (14 day course)	\$13.28	Ontario formulary ⁶⁵	N/A

Variable	Value	Source	Range for Sensitivity Analyses
Annual Cost of Adverse Events			
Cost of Endophthalmitis (.8*(7+14)+.2*(5+12)+5*2+2*19)	\$1,580		N/A
Cost of Traumatic Cataracts (6+13+3*2+2*19)	\$1,769		N/A
Cost of Retinal Detachment (5+12+3*2+2*19+2*20)	\$3,133		N/A
Cost of Ocular Inflammation (6*2+2*19+2*21)	\$420.51		N/A
Cost of Non-ocular Hemorrhage (2*1)	\$112.20		N/A
Cost of Site Infection (22)	\$13.28		N/A
Cost of Stroke			
First Year	\$20,351±175	Hopkins et al ⁶⁸	N/A
Subsequent years	\$4,624±87	Hopkins et al ⁶⁸	N/A
Cost of Non-fatal MI			
First Year	\$10,579±155	Hopkins et al ⁶⁸	N/A
Subsequent years	\$3,483±175	Hopkins et al ⁶⁸	N/A
Annual Treatment Costs			
V-PDT (2*(11+4)+2*10+4*8+8*9)	\$8,025		N/A
Pegaptanib (8*15+8*3+4*8+4*9)	\$9,803		N/A

Variable	Value	Source	Range for Sensitivity Analyses
Ranibizumab (12*18+12*3+4*8+4*9)	\$21,163		\$10,000 to 25,662
Cost of Severe Visual Impairment	\$31,007±15,820	Canterbury Communications ⁶⁷	N/A
Cost of Moderate Visual Impairment	\$8,787±4,483	Canterbury Communications ⁶⁷	N/A
Cost of Mild Visual Impairment	\$2,252±1,149	Canterbury Communications ⁶⁷	N/A
Utility loss due to Stroke	0.68±0.017	Mittmann et al ⁸⁵	N/A
Utility loss due to Non-fatal MI	0.896	Oldridge et al ⁸⁶	N/A
Utility from change in visual acuity	See Equation 1 Section 5.3.8 “Valuing outcomes”	Sharma ⁶⁹	N/A

APPENDIX 21: ETHICAL AND PSYCHOSOCIAL CONSIDERATIONS ASSOCIATED WITH THE PHARMACOLOGICAL MANAGEMENT OF AMD

Author, Country	Study Objective (design, population, intervention, comparator)	Outcome Measures (ethical and psychosocial issues)
Blinder et al. 2003 ²⁰ VIP and TAP Report 1 USA	To determine whether differences in baseline lesion size and visual acuity explain differing results among three RCTs evaluating verteporfin therapy in patients with subfoveal CNV due to AMD.	Ethical: The VIP trial suggests verteporfin isn't beneficial in occult with no classic lesions that are both large and had better visual acuity. In most large lesions presenting with good visual acuity, it may be best to withhold verteporfin therapy unless a recent history of loss is established.
Arnold et al. 2001 ²³ VIP and TAP Report 2 USA	To determine if verteporfin therapy can safely reduce the risk of vision loss compared with placebo in patients with subfoveal CNV due to AMD.	Ethical: Verteporfin therapy may not be beneficial for patients with both larger lesions and good visual acuity. There may be a duty to withhold verteporfin therapy in patients with large lesions presenting with good visual acuity.
Raftery et al. 2007 ⁵² UK	Markov model to compare the clinical and cost-effectiveness of ranibizumab (Leucentis) compared to bevacizumab (Avastin) using published data and assumptions.	Ethical: Ranibizumab (Lucentis) licensed in the USA costs \$2,000 US/injection. Bevacizumab costs \$17-50 US and is licensed for cancer therapy but not AMD. Roche/Genentech owns both drugs but has no intent to license bevacizumab for AMD. While bevacizumab is used widely globally off-label, there is currently no evidence of its efficacy in AMD compared to placebo or ranibizumab. Continued off-label use of bevacizumab raises ethical, legal and policy questions. NICE will issue guidance regarding ranibizumab compared to supportive care and V-PDT late in 2007. A favourable recommendation may make recruitment into a comparative trial of ranibizumab and bevacizumab impossible. Prescribers may be compelled to prescribe ranibizumab as licensed.
AETMIS 2005 ⁴⁷ Canada	Systematic review to assess the efficacy of verteporfin therapy for AMD examining costs	Access and equity: In Quebec, 33 retinologists were able to administer V-PDT to AMD patients but only 15 do so. Each retinologist performed 40-50 treatments/month, 7,400 treatments/year.

Author, Country	Study Objective (design, population, intervention, comparator)	Outcome Measures (ethical and psychosocial issues)
	and organization of care and services.	The number of treatments administered was below the number of AMD patients eligible for PDT. In 2003, one hospital reduced its Visudyne budget by 60% and sent less complex cases to private clinics shifting costs to patients. Patients co-pay to obtain the drug (\$200-839 CAN/year) depending on category insured. Organizational-related problems could prevent patients from being treated within reasonable timeframes. Patients reported problems with accessing angiography due to lack of imaging personnel, nurses and technicians. The lag between when a patient notices a problem and when they are treated may result in loss of vision or less effective treatment.
NHS 2003 ⁴⁸ UK	Systematic review of RCTs and economic evaluations to establish the clinical and cost-effectiveness of V-PDT for neovascular wet AMD.	Access, equity, and psychosocial: There are approximately 150-200 retinologists in the UK. To cover 2800-4650 sessions/year, one would need to perform 14-31 sessions/year. Issues of equity have been identified. First, interventions in older persons have been considered less favourable than those affecting younger individuals because of perceptions that health benefits are less likely to occur. Care should be taken to ensure this perception doesn't preclude the decision on whether the benefits are worth the costs of verteporfin therapy. Secondly, there is evidence that the intervention is already being provided privately and inequitable access exists. Extra resources are required to manage increased referrals, diagnoses, and treatment. The burden of care on individuals, partners and families is great and treatments that reduce this burden, improve quality of life or independence are welcome.