BEVACIZUMAB IN EYE CONDITIONS:

ISSUES RELATED TO QUALITY, USE, EFFICACY AND SAFETY

REPORT BY THE DECISION SUPPORT UNIT

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ABOUT THE DECISION SUPPORT UNIT

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ABBREVIATIONS AND DEFINITIONS

AMD	age-related macular degeneration
APC	Area Prescribing Committee
BCVA	best-corrected visual acuity
BRVO	branch retinal vein occlusion
BUPA	provider of private health insurance
CATT	Comparison of Age-related macular degeneration Treatment Trials
CME	cystoid macular oedema
CNV	choroidal neovascularisation
CRVO	central retinal vein occlusion
CSME	clinically significant macular oedema
DMO	diabetic macular oedema
DRCN	Diabetic Retinopathy Clinical Research Network
ETDRS	Early Treatment Diabetic Retinopathy Study
HbA1c	glycated haemoglobin
IOP	intraocular pressure
IVB	intravitreal bevacizumab
IVP	intravitreal pegaptanib
IVR	intravitreal ranibizumab
IVT	intravitreal triamcinolone
logMAR	logarithm of the minimum angle of resolution
MOBB	Milton Keynes, Oxfordshire, Berkshire East, Berkshire West and Buckinghamshire
NICE	National Institute for Health and Clinical Excellence
NHS	National Health Service
NORCOM	North Derbyshire County PCTs, South Yorkshire and Bassetlaw Commissioning Consortium
NORSCORE	North East Specialised Commissioning Team
NR	not reported
PCT	Primary Care Trust
PDR	proliferative diabetic retinopathy
PDT	photodynamic therapy
PED	pigment epithelium detachment
PIC	punctuate inner choroidopathy
PPP	provider of private health insurance
RCT	randomised controlled trial
RVO	retinal vein occlusion
SHA	Strategic Health Authority
SHIP PCT	Southampton City PCT, Hampshire PCT, Isle of Wight PCT, Portsmouth City PCT.
VEGF	vascular endothelial growth factor

CONTENTS

TABLES

FIGURES

1 INTRODUCTION

1.1 BACKGROUND

Bevacizumab (Avastin, Roche Products Ltd) is licensed as a treatment for cancer. It is a monoclonal antibody which works by inhibiting vascular endothelial growth factor A (VEGF). VEGF is a mediator in the pathogenesis of certain eye conditions, including wet age-related macular degeneration (AMD), diabetic retinopathy and macular oedema secondary to retinal vein occlusions. There is evidence that VEGF inhibitors can improve vision, whereas the main outcome of traditional treatments such as photodynamic therapy for AMD or laser photocoagulation for macular oedema, is to delay deterioration in vision.

There are licensed VEGF inhibitors available in the UK. Ranibizumab (Lucentis, Novartis) is licensed for the treatment of wet AMD, diabetic macular oedema (DMO) and retinal vein occlusion (RVO). Pegaptanib (Macugen) is licensed for the treatment of wet AMD.

However these therapies are much more costly than bevacizumab for use in the eye. Ranibizumab costs £742.17 per injection according to the latest edition of the British National Formulary (ref BNF no 63). Pegaptanib costs £514 per injection.

Whilst bevacizumab does not have a license for ocular use, it is a much less costly alternative. A 4ml vial for its licensed intravenous use costs £242.66. Intravitreal use requires much smaller doses which are produced by breaking open a vial and drawing them up into a fine syringe to deliver small volumes. Many doses for the eye can be produced from a single bevacizumab vial and therefore can be supplied for a much lower cost of approximately £50 to £100. This is one of the reasons that bevacizumab has been used in this manner since 2005.[1-3]

The process of manipulating bevacizumab supplied for use in oncology is not undertaken by the sponsor (Roche) and there have been concerns raised about the risks to patients introduced via this process. The Medicines and Healthcare products Regulatory Agency (MHRA) considers that this manipulation creates an unlicensed medicine.

In this report we provide evidence on four issues relating to the use of bevacizumab in eye conditions. These issues are those considered by NICE to be of value in helping to inform

committee considerations relating to the considerations of bevacizumab as a comparator in Technology Appraisals for RVO. The DSU will answer four questions:

1) What evidence is there relating to the pharmaceutical quality of reformulated bevacizumab as used in eye conditions in general? (section 2)
2) How widespread is Intravitreal Bevacizumab (IVB) used in the UK? (section 3)
3) What is the evidence for efficacy of IVB in adults with RVO and DMO specifically? (section 4). The evidence base around AMD is not included in this review.
4) What evidence is there regarding adverse events for IVB in eye conditions in general? (section 5). Here the evidence from ALL eye conditions is drawn upon.

2 THE PRODUCTION OF BEVACIZUMAB FOR INTRAVITREAL INJECTION

Bevacizumab is supplied in 100mg and 400mg vials for its licensed use as an anti-cancer drug where medication is given intravenously. Intravitreal injections require much smaller doses, typically 1.25mg. Therefore the product must be diluted and aliquoted into individual doses. An individual vial of bevacizumab is opened and drawn up into a fine syringe designed to deliver small volumes. There is some dead space within the syringe and so some of the drug will be wasted. Even so it can be seen that one vial of bevacizumab can provide many doses for use in the eye, and this contributes to the much lower cost.

This process can either be performed by the hospital pharmacist for same day use or it can be manufactured on a larger scale by specialist units. The former approach was typical historically. There is potentially a greater risk of contamination despite the fact that this is performed under strict sterile conditions because doses will be drawn from a vial over several days, requiring repeated puncturing of the rubber seal and greater operator error as one or more pharmacists in each hospital may be involved. The larger scale manufacturing units are more recent and carry out repackaging in bulk under tightly controlled conditions.

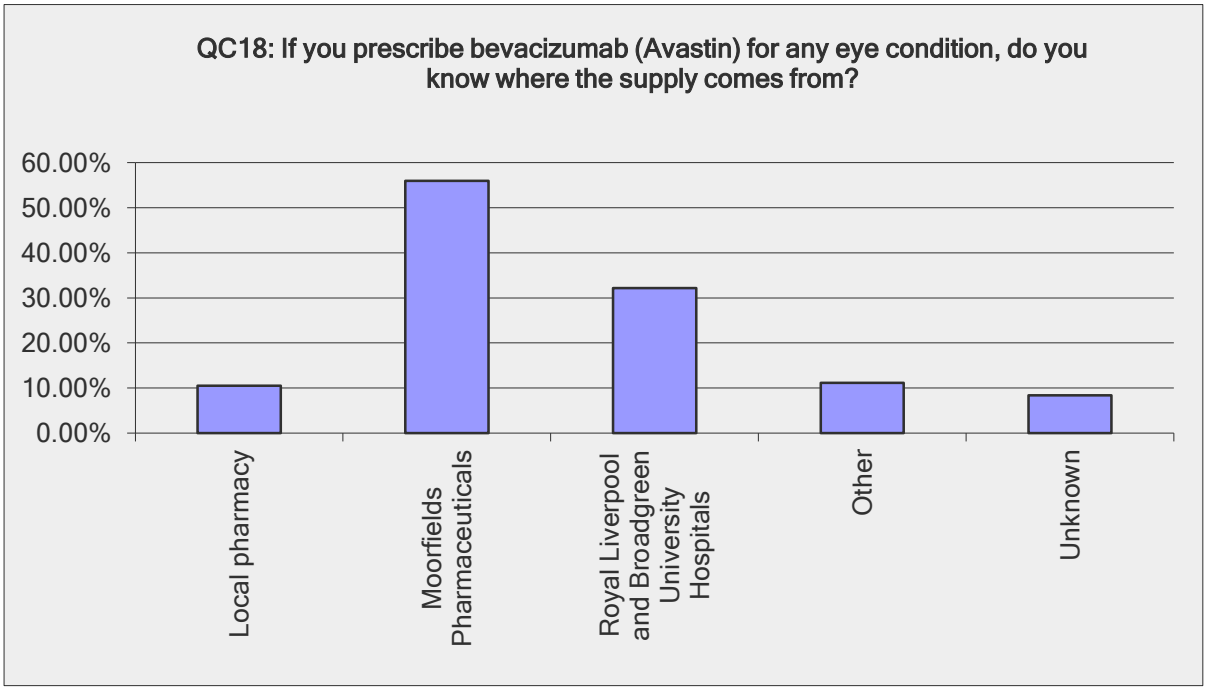
It is the view of the MHRA that ocular use of bevacizumab constitutes an “unlicensed” as opposed to “off-label” use because of the manipulation of the licensed product.[4] In order to supply reformulated bevacizumab, or any other unlicensed medicinal product, sites must hold a “specials” licence issued by the MHRA.[5] Medicines legislation permits the manufacture and supply of unlicensed medicinal products (commonly known as 'specials') subject to

certain conditions. The conditions are that there is a bona fide unsolicited order, the product is formulated in accordance with the requirement of a doctor or dentist registered in the UK, and the product is for use by their individual patients on their direct personal responsibility. A 'special' may not be advertised and may not be supplied if an equivalent licensed product is available which could meet the patient's needs. Essential records must be kept and serious adverse drug reactions reported to the MHRA.

There are two major suppliers of IVB in the UK, though there are other smaller suppliers: Moorfields Pharmaceuticals, which is the manufacturing arm of the Moorfields Eye Hospital NHS Foundation Trust, and Liverpool and Broadgreen University Hospitals pharmacy. Both hold specials licences and began producing these preparations originally to service clinical trials within the NHS.

We undertook a survey of consultant ophthalmologist members of the Royal College of Ophthalmologists (RCO). Whilst the primary aim of this survey was to estimate the extent to which IVB is used in various eye conditions in the UK (and therefore full details of the survey are provided in section 3), we also asked those that prescribe IVB to indicate where the supply comes from. Responses are displayed in Figure 1 below. One hundred and forty three respondents gave a response to this question (excluding 44 N/As). Some respondents indicated multiple sources. 56% indicated that supplies of IVB came from Moorfields Pharmaceuticals. 32% indicated that Liverpool provided their supplies.

Figure 1: Source of supplies for IVB



As part of the IVAN trial, which compares IVB with ranibizumab, Liverpool undertook additional stability testing to provide supplies to the trial. This process can be complex and costly, but is undertaken to establish the safety of extending the shelf-life of the product given the specific circumstances in which it is being manufactured. The stated shelf life of the product supplied by Liverpool is 3 months.

[redacted]

The greatest risk from reformulation of bevacizumab is infection. Infectious endophthalmitis is a medical emergency which can lead to loss of vision or even the eye itself. Despite the requirement for strict aseptic conditions when repackaging bevacizumab, cluster outbreaks of endophthalmitis have arisen with IVB.

The US Food and Drug Administration (FDA) issued a warning concerning repackaged bevacizumab following 12 reported cases of endopthalmitis arising in three clinics using a single source (a compounding pharmacy) where the Avastin was repackaged in August 2011

following a cluster of infections in Miami.[6] The warning stated that "Health care professionals should be aware that repackaging sterile drugs without proper aseptic technique can compromise product sterility, potentially putting the patient at risk for microbial infections. Health care professionals should ensure that drug products are obtained from appropriate, reliable sources and properly administered." The details of the repackaging are not reported. Eleven patients went blind in the affected eye. The most likely cause of this outbreak was contamination during syringe preparation by the compounding pharmacy.[7]

The New York Times reported two additional clusters;[8] one at the Veterans Affairs Hospital in Nashville (4 cases of infection) and another at the Veteran Affairs Hospital in Los Angeles (5 cases). These incidences led to the temporary withdrawal of use of Avastin for AMD in the organisation.

There were 25 reports of signs and symptoms consistent with sterile endophthalmitis or uveitis suspected to be due to bevacizumab supplied by Moorfields in February 2012 which prompted a recall of several batches and a suspension of production as a precaution.[9] Production was restarted at Moorfields on 23 April 2012. No root cause was found. Indeed, one patient received a product not manufactured by Moorfields.

3 THE EXTENT OF USE OF BEVACIZUMAB IN EYE CONDITIONS IN THE UK

The primary aim of this section was to estimate the use of IVB in patients with any eye condition in the UK. Three alternative approaches were employed to make such estimates:

i) A systematic search and review of all publicly available documents from NHS commissioners on the use of bevacizumab in eye conditions
ii) Evidence from the two main manufacturers of bevacizumab on the quantity supplied to both NHS and private practitioners
iii) A survey of hospital based consultant ophthalmologists

The first of these approaches provides indirect evidence relating to use only, since policies on commissioning do not necessarily translate directly into usage at the individual patient level.

3.1 REVIEW OF COMMISSIONING DOCUMENTS

3.1.1 Methods

The aim of the searches was to identify documents relating to bevacizumab use in eye conditions in health establishments in the UK. A mapping process was adopted to identify and retrieve documents that suggested, recommended or supported the use of bevacizumab in the non-private health sectors in England, Scotland and Wales. Searches within specific databases and web-pages of Primary Care Trusts (PCTs) and National Health Service (NHS) sites in England; local health boards in Wales; Health and Social Care Trusts in Northern Ireland and NHS health boards in Scotland were undertaken. In addition, NHS eye hospital websites via NHS Choices were identified and searched. Searching using the Google search engine was also undertaken.

Keyword searching was undertaken in web-pages of healthcare establishments. Searching within these websites was possible by the presence of a search box within the site homepage. Search terms 'bevacizumab' or 'avastin' were used. Articles and papers were considered to contribute data to this evidence base if IVB use was suggested, recommended or supported for the management or treatment of an ophthalmic condition. Retrieved documents were then examined. Relevant data were abstracted. For records related to NHS and PCT web-pages, data extracted included a description of the document (title, type of document, issue date and review date), related condition(s) of interest according to identifiable PCT or clusters of PCTs.

Search results of the web-pages of PCTs and NHS sites in England were searched on 10th – 11th May, 2012; Local health boards in Wales; Health and Social Care Trusts in Northern Ireland and the NHS health boards in Scotland were searched on 28th May 2012. The lists of websites searched are summarised in Appendix 1.

3.1.2 Results

3.1.2.1 Manufacturing and use of bevacizumab in the UK

No relevant results were obtained following searches of the identified web-sites of health board in Wales (n=7); Health and Social Care Trusts in Northern Ireland (n=6) and NHS web-sites (n=14) in Scotland. Seven of the 145 identified NHS and PCT web-sites in England could not be searched due to the absence of a search facility. Of the searchable web-pages,

there were 28 distinct links to information that suggested, recommended or supported the use of bevacizumab in eye conditions. Table 1 summarises information on bevacizumab use in the NHS in England. Three of six eye hospital sites suggest the use of bevacizumab. This information is summarised in Table 2.

Table 1: Information indicating bevacizumab use in the UK (NHS)

PCT	Condition	Document/ summary of information	Source
1. Barnsley PCT	Choroidal neovascular membrane secondary to myopia, inflammatory retinal disease, inherited retinal disease	**NORCOM recommended policy: General policy** *Summary* The document was reviewed and supported by NHS Bassetlaw, NHS Barnsley, NHS Doncaster, and NHS Sheffield. The document indicated a commissioning position to routinely fund intra-vitreal Avastin injection for use in choroidal neovascular membrane secondary to myopia, inflammatory retinal disease, inherited retinal disease and trauma up to a maximum of 4 injections. This policy was effective from 1st April 2010. Date (undefined): 12th March 2010 Review date: January 2012	http://www.barnsley.nhs.uk/Downloads/Policies/Commissioning/Treatment/Policy%20for%20Avastin%20for%20the%20treatment%20of%20non-age%20related%20choroidal%20neovascular%20membrane.pdf
2. Bassetlaw PCT	Choroidal neovascular membrane secondary to myopia, inflammatory retinal disease, inherited retinal disease and trauma	**NORCOM recommended policy: General policy** *Summary* The document was reviewed and supported by NHS Bassetlaw, NHS Barnsley, NHS Doncaster, and NHS Sheffield. The document indicated a commissioning position to routinely fund intra-vitreal Avastin injection for use in choroidal neovascular membrane secondary to myopia, inflammatory retinal disease, inherited retinal disease and trauma up to a maximum of 4 injections. This policy was effective from 1st April 2010. Date of approval : Risk Management July 2010 Review date: January 2012 ◊	http://www.bassetlaw-pct.nhs.uk/images/stories/Policies%20and%20Procedures/ClinicalMg/PCTCM130%20Intra-vitreal%20Avastin%20for%20Non%20AMD.pdf

PCT	Condition	Document/ summary of information	Source
3. Berkshire East PCT 4. Berkshire West PCT	DMO RVO Pre-operative treatment in patients requiring plana vitrectomy due to proliferative diabetic retinopathy	Minutes of sub-committee meetings *Summary* It was noted that the CEC had 'ratified' a number of policies from the Milton Keynes, Oxfordshire, Berkshire East, Berkshire West and Buckinghamshire (MOBB) Priorities Committee.(Minutes of CEC meeting, 14th December 2011, page 51) Two of the policies were related to bevacizumab and are listed below. Policies approved by the the CEC from the Milton Keynes, Oxfordshire, Berkshire East, Berkshire West and Buckinghamshire (MOBB) Priorities Committee included: *Policy 56*: Ranibizumab (Lucentis®), bevacizumab (Avastin®), pegaptanib (Macugen®) and fluocinolone acetonide (Iluvien®) for diabetic macular oedema (An update); *Policy 57*: Dexamethosone implant (Ozurdex®), ranibizumab (Lucentis®) and bevacizumab (Avastin®) for macular oedema caused by retinal vein occlusion (An update) Date of paper - 12th January 2012; Date of meeting 24th January 2012	http://www.berkshirewest.nhs.uk/_store/documents/cb-11-81-sub-committee-minutes.pdf
5. Brighton and Hove City PCT	Neovascular glaucoma	**Bevacizumab as a treatment for neovascular glaucoma** [Policy document] *Summary and recommendations* Intravitreal bevacizumab (IVB) is considered as an option for patients with neovascular glaucoma (rubeotic glaucoma) which may be associated with CRVO or PDR. Issue date February 2011 Review date: February 2014	http://www.brightonhovecitypct.nhs.uk/HealthProfessionals/clinical-areas/EyeDiseases.asp
	Non –AMD choroidal neovascular disease	**Bevacizumab for the treatment of non –AMD choroidal neovascular disease** [Policy document] *Summary and recommendations* IVB can be used for the treatment of non- AMD choroidal neovascularisation, a condition associated with uveitis, myopia and previous trauma. However, unlike AMD-related choroidal neovascularisation, remission of the condition can be achieved following one or two injections of IVB. Issue date February 2011 Review date: February 2014	http://www.brightonhovecitypct.nhs.uk/HealthProfessionals/clinical-areas/EyeDiseases.asp

PCT	Condition	Document/ summary of information	Source
	Pre-operative treatment for vitrectomy surgery in patients with non-remitting DR following conventional laser therapy	**Use of bevacizumab for pre-operative treatment for vitrectomy surgery** [Policy document] *Summary and recommendations:* Bevacizumab can be used to reduce the incidence of intra-operative and post-operative complications such as bleeding. Issue date February 2011 Review date: February 2014	http://www.brightonhovecitypct.nhs.uk/HealthProfessionals/clinical-areas/EyeDiseases.asp
6. Bristol PCT	Choroidal neovascularisation associated with angioid streaks and retinal dystrophies	**Bevacizumab for treatment of choroidal neovascularisation associated with angioid streaks and retinal dystrophies** [Policy document] *Summary and recommendations* -IVB use is guided by pre-specified eligibility criteria. Ranibizumab is considered for 'IVB-treatment' eligible patients who are allergic to IVB. -Prescribing physician must meet requirements for off-label prescribing. -Departmental audit of expected benefits (reduction in laser treatment) and adverse events in treated patients. Issue date: 15th April 2010 Review date: Earliest of either SHA guidance, NICE publication or one year from issue	http://www.bristol.nhs.uk/idoc.ashx?docid=ade55827-20c6-4e6b-8d96-93d1557e5a2e&version=-1
	Neovascular glaucoma due to ischaemic CRVO	**Bevacizumab in the treatment of neovascular glaucoma due to ischaemic central retinal vein occlusion** [Policy document] *Summary and recommendations* - Adjunctive use of IVB in this setting - Usual regime is a single dose of IVB to support pan-retinal photocoagulation therapy. - Prescribing physician must meet requirements for off-label prescribing. - Departmental audit of expected benefits (reduction in laser treatment) and adverse events in treated patients. Issue date: 15th April 2010 Review date: Earliest of SHA guidance, NICE publication or one year from issue.	http://www.bristol.nhs.uk/idoc.ashx?docid=286bc9ed-bb76-4ccc-9415-be3fdf06f49d&version=-1

PCT	Condition	Document/ summary of information	Source
	Non-ischaemic CRVO	**Bevacizumab in the treatment of non-ischaemic central retinal vein occlusion is provided on a restricted basis for patients meeting agreed criteria.** **[**Policy document] *Summary and recommendations:* - IVB use is guided by pre-specified eligibility criteria. - Usual treatment regime will consist of up to 3 doses of IVB. Issue date: 15th April 2010 Review date: Earliest of SHA guidance, NICE publication or one year from issue.	http://www.bristol.nhs.uk/idoc.ashx?docid=528bd80a-c4fb-4389-931a-2dc85e5a54cc&version=-1
7. Buckinghamshire PCT	Diabetic macular oedema [see 4]	Unspecified document: **South Central Priorities Committee (Milton Keynes, Oxfordshire, Berkshire East, Berkshire West and Buckinghamshire PCTs)** Policy recommendation 56: Ranibizumab (Lucentis®), bevacizumab (Avastin®),pegaptanib (Macugen®) and fluocinolone acetonide (Iluvien®) for diabetic macular oedema (An update) *Summary* Evidence supporting the policy of interest was noted to be limited. Therefore, the committee proposed that the policy needed to be considered '*LOW PRIORITY*' Date of issue: November 2011	http://www.buckinghamshire.nhs.uk/wp-content/uploads/2011/10/56-Ranibizumab-bevacizumab-pegaptanib-and-fluocinolone-for-macular-oedema.pdf
	Diabetic retinopathy with complications	**Minutes of meeting (Milton Keynes, Oxfordshire, Berkshire East, Berkshire West and Buckinghamshire (MOBB) Priorities Committee): Date 25th August 2010** *Summary* Funding for the use of bevacizumab pre-operatively in patients that require plana vitrectomy arising as a complication of proliferative diabetic retinopathy	http://www.oxfordshirepct.nhs.uk/professional-resources/priority-setting/minutes/documents/MOBBB_minutes_August_2010.pdf
8. Bury PCT	AMD	**Minutes: NHS Bury Board meeting – 5th August 2010** *Summary* The Board recommended the use of bevacizumab for the standard treatment of AMD (p. 3). It was also proposed that private providers who were keen to use bevacizumab in the AMD patients should be involved.(p. 1) Date of issue: 25th August 2010	http://www.bury.nhs.uk/library/board_papers/2010/ai%204.1%20age-related%20macular%20degeneration%20250810.pdf

PCT	Condition	Document/ summary of information	Source
9. Cornwall and Isles Of Scilly PCT	AMD	**Peninsula Health Technology Commissioning Group - Commissioning decision: bevacizumab for the treatment of neovascular (wet) age related macular degeneration.** [unspecified document type] *Summary* The commissioning group agreed on the use of bevacizumab in the treatment of AMD, as a *'justifiable alternative'* to ranibizumab in patients eligible to treatment according to the criteria specified in the NICE technology appraisal guidance 155. Issue date (date of decision): 22nd June 2011 Review date: Unspecified. However, it was noted that the decision will be reviewed following available data from 'further' comparative randomised studies.	http://www.plymouthpct.nhs.uk/services/Pages/bevacizumabneoamd.aspx
10. County Durham PCT	AMD	**Response to request for information** on the Trust's current policy on the treatment of wet AMD**,** under the provisions of the Freedom of Information Act 2000, received on 6th December 2011[unspecified document type] *Summary* Responses of NHSCD&D were as follows: '*Treatment for wet AMD and use of either Lucentis or Avastin for wet AMD is commissioned by NORSCORE the North East Specialised Commissioning Group on our behalf.*'	http://www.cdd.nhs.uk/cdpct/media/Freedom%20of%20Information/D/Website%20Pending%202011/December%202011/FOI-Response-Wet-Age-Related-Macular-Degeneration-151211.pdf
11. Darlington PCT	[see 10]		
12. Derby City PCT 13. Derbyshire County PCT	Wet AMD	**Document template (v0.6) by Derbyshire County PCT Commissioning Improvement Team: Service specification** *Summary* Within the document, it is noted that 'If and when the dose ranging trial of bevacizumab ('TANDEM)[i] is established this must be actively offered to patients as an option. Patients agreeing to participate will be free to leave the trial and receive ranibizumab if they so wish, at any time.'(p. 3) In another section, it is reported that patients with wet AMD eligible for treatment as per NICE TA 155 recommendations will be offered ranibizumab or bevacizumab as options (p.4). It is not clear whether such patients were participants of the TANDEM trial at the time the document was prepared. Period: 26th November 2008 onwards	http://www.derbycitypct.nhs.uk/UserFiles/Documents/101%20Wet%20AMD%20Service%20Specification.pdf
14. Devon PCT	[see 9]		

[i] The TANDEM Trial: A randomised controlled Trial of high and low dose Avastin® for Neovascular macular Degeneration in the East Midlands.

PCT	Condition	Document/ summary of information	Source
15. Eastern and Coastal Kent PCT	AMD	**Policy Recommendation PR007/03: Anti-vascular Endothelial Growth Factors (Anti-VEGFs) for Age-Related Macular Degeneration (AMD)** *Summary and recommendations* Photo-dynamic therapy is the recommended first-line treatment for patients with *'classic or predominantly classic sub-types of AMD'* in accordance to NICE guidance. Access to pegatanib treatment based on pre-specified criteria. In the section, entitled – key finding and conclusions – it is stated that, *'Lucentis® [ranibizumab] and Macugen® [pegaptanib] are licensed for the treatment of AMD, Avastin® [bevacizumab] is not licensed for use in the treatment of wet AMD, but is used off-label.'*[ii] Issue date: April 2007 Review date : October 2007	http://www.easternandcoastalkent.nhs.uk/EasysiteWeb/getresource.axd?AssetID=9352&type=Full&servicetype=Attachment
16. Great Yarmouth and Waveney PCT	Not specified	**NHS Great Yarmouth and Waveney - Annual Operating Plan 2011-12** [Delivery Plans 2011/12 (Operating Plan 11/12)] *Summary* In relation to Ophthalmology, documented planned action indicated the commencement of Avastin use *'to improve side effects and reduce the use of Lucentis'*. Reported milestones were April 2011 to July 2011. It was unclear what these dates referred to. Date of version: 5th May 2011 Date of review: not stated	http://www.gywpct.nhs.uk/_store/documents/operating_plan_2011_to_2012.pdf
17. Hampshire PCT[iii]	AMD	**Untitled Statement** The SHIP PCT Cluster Board approved a policy for clinicians to offer patients the choice of either Avastin or Lucentis in the treatment of Age-Related Macular Degeneration (AMD). Date: unspecified.	http://www.portsmouth.nhs.uk/Downloads/SHIP%20Cluster/Oct%202011%20-%20Avastin.pdf

[ii] It is unclear whether bevacizumab use is recommended from the information provided.

[iii] A news release on 26th July 2012 (http://www.gponline.com/News/article/1143055/pcts-back-down-lucentis-row/) stated that the SHIP PCT had cancelled the related policy.

PCT	Condition	Document/ summary of information	Source
	Wet AMD	**Policy recommendation 100: Bevacizumab for wet age-related macular degeneration** *Summary and recommendations* The Priorities Committee recommends bevacizumab for all patients with wet AMD, who are eligible to be treated with an anti-VEGF agent. Enhanced audit of clinical outcomes, procedures for IVB procurement and data collection for a local registry were also recommended. Issue date March 2011 Review date: Not stated	http://www.southamptonhealth.nhs.uk/EasysiteWeb/getresource.axd?AssetID=117386&type=Full&servicetype=Attachment
18. Isle Of Wight NHS PCT	[see 17]		
19. North Somerset PCT	Non-ischaemic CRVO	**Bevacizumab in the treatment of non-ischaemic central retinal vein occlusion** [Policy Statement] *Summary* Bevacizumab use in patients is based on specified criteria and policy restrictions. Date of Issue/ approval: 15 April 2010 Review date: Earliest of SHA guidance, NICE publication or one year from issue.	http://www.northsomerset.nhs.uk/Services/funding/Policies/Bevacizumab%20in%20the%20treatment%20of%20non-ischaemic%20central%20retinal%20vein%20occlusion.pdf#search="bevacizumab"
20. Plymouth Teaching PCT	[see 9]		
21. Portsmouth City Teaching PCT	[see 17]		
22. Somerset PCT	AMD	**Minutes of the meeting of the Somerset Primary Care Trust held on Wednesday, 15 December 2010 at Lyngford House, Taunton, Somerset.** *Summary* Minutes of meeting held on 15th December 2010 detailing minutes of previous meetings (on 30th September 2010 and 25th November 2010). This document records the discussion of recommendations of the Prescribing Forum in the off-license use of drugs, including Avastin. It is noted that the Professional Executive committee had supported its use in Age-related macular degeneration.	http://www.somerset.nhs.uk/EasysiteWeb/getresource.axd?AssetID=15205&type=Full&servicetype=Attachment
23. Southampton City PCT	[see 17]		
24. Stockport PCT	AMD	Stockport PCT board, Avastin/Lucentis for AMD [unspecified document] *Summary* Recommendations for the future commissioning of Avastin/ lucentis for AMD Issue date: March 2009	http://www.stockport-pct.nhs.uk/BoardPapers/2009/March/Vicci%20Owen%20Smith/PCT%20BOARD%20-%20Avastin-Lucentis%20-%20March%2009%20item%2013a.doc

PCT	Condition	Document/ summary of information	Source
25. Suffolk PCT	RVO Diabetic Maculopathy DR Neovasucular Glaucoma Choroidal Neovascularisation	T27 Bevacizumab for Retinal Vein Occlusion, Diabetic Maculopathy, Diabetic Retinopathy, Neovasucular Glaucoma or Choroidal Neovascularisation [Form to be completed by attending consultant and endorsed by a designated commissioner of services] *Summary* This document details the criteria for commissioning IVB use within the NHS Suffolk	http://www.suffolk.nhs.uk/LinkClick.aspx?fileticket=nQ9DRPEtZ2g%3d&tabid=321&mid=5912
26. West Sussex PCT	AMD	**Treatments for Age Related Macular Degeneration** [Board meeting document] Appendix 1: Patients information sheet: New treatments for age-related macular degeneration *Summary* It was reported under *'Summary: Treatment for age-related macular degeneration: Policy position of West Sussex Primary Care Trust'* that Avastin, was, at the time, being used in the private sector in the UK and outside of the UK for the treatment of wet AMD. It was also noted that major insurance companies (PPP[a] and BUPA) had accepted IVB usage. The patient information sheet lists Avastin as one of the treatment options, and also provides information about its unlicensed use in this setting. Issue date: 27th March 2008	https://www.google.com/url?q=http://www.westsussex.nhs.uk/domains/westsussex.nhs.uk/local/media//publications/board-papers/27_March_2008/12%2520Age%2520related%2520macular%2520degeneration.doc&sa=U&ei=rxrbT8CsFaHN0QX7uuyCCw&ved=0CAUQFjAA&client=internal-uds-cse&usg=AFQjCNEMV8w6CeFCiLOE-V2qLwqBwUSXOg
	AMD	**Minutes of meeting held on 7th May 2008: Strategic Commissioning Boards** *Summary* Minutes were reported as an accurate version. An accepted proposal regarding the use of Avastin in AMD patients was noted. (p. 2) Date: 9th May 2008	http://www.westsussex.nhs.uk/domains/westsussex.nhs.uk/local/media/publications/board-papers/26_June_2008/09%20Strategic%20commissioning%20board%20minutes%209%20May.pdf
27. Wirral PCT	AMD	**Summary of Wirral Medicines Guide, 6th Edition: Compiled 2007/08** *Summary* This is a joint formulary for primary and secondary care. The retrieved version related to Primary Care management. 'Bevacizumab – hospital only' was recorded under the list of treatment options for various eye conditions. This option was specified for acute macular degeneration.	http://www.wirral.nhs.uk/document_uploads/Disclosure-Sept2009/Formulary0708summarywithamendssept09(2).pdf

PCT	Condition	Document/ summary of information	Source
28. Worcestershire PCT	Neovascular glaucoma Proliferative diabetic retinopathy [PDR]	**Position Statement: Worcestershire NHS: Worcestershire Area Prescribing Committee** *Summary* The document lists choroidal neovascularisation (CNV) in conditions other than wet age-related macular degeneration (AMD)[iv] for which anti-vascular endothelial factor treatment is indicated. In relation to the commissioning of treatment, the report states that restricted use of IVB had been approved for the following: • To facilitate laser coagulation in patients with PDR who had received previous panretinal laser coagulation associated with vitreous haemorrhage • To support *surgical delamination of the fibrovascular membranes* in PDR patients requiring surgery • Adjunct treatment in patients with neovascular glaucoma. Issue date: 10th May 2011 Review date: May 2013 or May 2013 or sooner if national guidance is made available or a new drugs application for an unapproved indication is submitted to the Worcestershire Area Prescribing Committee (APC)	http://www.worcestershire.nhs.uk/file_download.aspx?id=033a8fe4-f0fb-4ad4-95e9-a3c6ad8145af

Abbreviations: AMD-age- related macular degeneration; CNV-choroidal neovascularisation; DMO-diabetic macular oedema; DR-Diabetic retinopathy; RVO-retinal vein occlusion; PDR-proliferative diabetic retinopathy; NICE- National Institute for Health and Clinical Excellence; NHS- National Health Service; PCT- Primary Care Trust

[a]PPP – provider of private health insurance, http://www.axappphealthcare.co.uk/

[b]BUPA- provider of private health insurance, http://www.bupa.co.uk/

[iv] Individual conditions listed in this category include neovascular glaucoma; proliferative diabetic retinopathy; diabetic macular oedema*; macular oedema secondary to retinal vein occlusion; retinopathy of prematurity; multifocal choroidopathy [including punctuate inner choroidopathy (PIC) and multiple evanescent white dot;syndrome]; atypical choroiditides (including histoplasmosis, tuberculous; syphilitic, etc); myopic CNV; CNV in angioid streaks; CNV in choroidal sarcoma; CNV in Gronblad-Strandberg syndrome; CNV in psuedoxanthoma elasticum; CNV in serpiginous choroiditis; CNV in Stargardt's Disease; CNV in vitelliform macular dystrophy. ◊A more recent document could not be accessed.

Table 2: Summary of information related to bevacizumab use in eye hospitals

Hospital	Condition	Documentation	Source(s)
Moorfields Eye Hospital	AMD	New treatments for wet age-related macular degeneration Listed treatment options included Avastin, Macugen and Lucentis	http://www.moorfields.nhs.uk/Eyehealth/Commoneyeconditions/Age-relatedmaculardegeneration/NewtreatmentsforwetAMD http://www.moorfields.nhs.uk/Eyehealth/Commoneyeconditions/Age-relatedmaculardegeneration/Treatment
Manchester Royal Eye Hospital	Subfoveal CNV or juxtafoveal CNV caused by AMD	A representative group of patients included in the Greater Manchester Avastin trial for choroidal neovascularisation (GMAN) trial. The study evaluates two different dosing regimens of Avastin over a period of two years. Funding for the trial is by the Primary Care Trusts of Greater Manchester. Proposed date of completion: December 2012	http://www.cmft.nhs.uk/media-centre/media-archive/new-drug-treatment-could-stop-blindness.aspx lead to GMAN trial http://www.gmantrial.co.uk/background.html
Birmingham Eye Hospitals	Various conditions including AMD, RVO and DR	Avastin is included in list of available treatments at the centre.	http://www.optegra.com/fees/ and http://www.optegra.com/our-hospital/our-technology-and-equipment/ (Birmingham hospital is one of the 5 hospitals working with Optegra //www.optegra.com/our-hospital/birmingham/)

Available evidence is based on 15 policy-related documents, 5 minutes of board meetings or similar discussions and a number of unspecified documents. The most common disease condition considered was AMD. From the existing evidence, it was unclear whether bevacizumab was the first-line of treatment in selected eye conditions in most situations. Typically, PCTs permit the use of IVB as a treatment option alongside other licensed alternatives. However, its role as an adjunctive treatment in pre-operative treatment for vitrectomy surgery in patients with non-remitting diabetic retinopathy (DR) following conventional laser therapy,[10] neovascular glaucoma due to ischaemic central retinal vein occlusion (CRVO)[11] and proliferative diabetic retinopathy (PDR)[12] were reported. Bevacizumab was also recommended *'to improve side effects and reduce the use of Lucentis'* in unspecified settings.[13]

Information on the exact dose of IVB was not stated in any document. Dosing regimens varied between a single dose, one to two doses and up to three doses for neovascular glaucoma due to ischaemic CRVO; non-AMD choroidal neovascular disease and non-ischaemic CRVO respectively.[11] In the related policy documents, patient eligibility criteria were described. The responsibilities of prescribers were also stated. In some cases, information provided in the retrieved documents was unclear. For instance, one PCT noted that it would consider bevacizumab use in AMD patients following the results of the TANDEM trial, a randomised controlled Trial of high and low dose Avastin for Neovascular macular Degeneration in the East Midlands.[14] On the other hand, it mentioned, under another section *'that patients with wet AMD eligible for treatment as per NICE TA 155 recommendations will be offered ranibizumab or bevacizumab as options'*.

In two cases the extensive use of IVB in private practice and internationally was referred to as one of the considerations of funders considering their NHS based policies PCT reports.[15,16]

3.1.2.2 International use of bevacizumab

A study based on 2008 US Medicare claims data found that use of bevacizumab was substantially higher than ranibizumab for patients with AMD. They found that from more than 200,000 beneficiaries, 64.4% received bevacizumab and 35.6% ranibizumab. In 39 out of 50 states the rate of injection was higher with bevacizumab than ranibizumab.[17] Medicare is the national social insurance programme that provides coverage for those aged 65 years and over, as well as some young people with certain disabilities. It is worth noting here that patients typically pay 20% of the drug cost under Medicare coverage.

Other US health insurance companies sanction the use of bevacizumab for eye conditions such as AMD.[18,19]

A survey of Israeli Retinal Specialists obtained an 80% response rate (n=50 respondents) and found that most (56%) offered both bevacizumab and ranibizumab to their patients with AMD.[20] 40% offered bevacizumab as the treatment of choice and just 4% offered ranibizumab as the treatment of choice. These choices were often influenced by the socioeconomic status of the patient, which is relevant because ranibizumab is substantially more expensive than bevacizumab and is not fully covered by Israeli health funds.

An internet survey conducted between November 2005 and April 2006, is reported by Fung *et al*.[21] The International Intravitreal Bevacizumab Survey primarily reported adverse events following the use of bevacizumab for ocular conditions in 70 centres across 12 countries and 4 continents. The survey utilised a web-based questionnaire to collect data on individual centres; data included details of the centre and contributing physicians, number of patients treated and number of administered injections during the course of treatment. The survey reported that 5,228 patients received 7,113 injections during the study period (Nov 2005 to April 2006), with participating centres reporting a mean of 75 patients (median: 40; range: 1-506) and a mean of 102 injections (median: 50; range: 1-691). This translates to an estimated 1.36 injections per patient over a 6 month period. Ranibizumab is usually given once monthly. Further details needed to identify centres or participating countries were not available from the publication. However, it is of note that the authors conclude that "Intravitreal bevacizumab is being used globally for ocular diseases".

3.1.3 Summary

The review of publicly available documentation related to commissioning of services provides some indications of policy directions on the use of bevacizumab in certain regions of the UK. The commonest condition where bevacizumab is used, based on NHS and PCT-related information, is AMD.

Not all PCTs provide publicly available or web-based statements of policy on this matter. Those that do may be out of date and therefore not fully representative of current policy. For example, the Central and East Cheshire PCT site yielded no records related to bevacizumab use, whereas recent news reports make it clear that this PCT cluster does have a policy associated with the unlicensed use

of bevacizumab. (http://www.pharmafield.co.uk/be/post/2012/04/24/Novartis-challenges-PCT-cluster-on-prescribing.aspx).

Identified reports indicate general policy stances in relation to bevacizumab and, in general, consider it as an option alongside the licensed alternatives. However, some commissioners have gone further and state that bevacizumab should be the standard commissioned treatment for some conditions, including AMD despite existing positive NICE guidance relating to ranibizumab. None of these documents directly indicate the number of patients treated with IVB in specific health settings.

3.2 QUANTITY SUPPLIED BY MAIN UK MANUFACTURERS

As reported above, there are two main suppliers of IVB in the UK: Moorfields Pharmaceuticals and Liverpool and Broadgreen Hospitals trust, though supplies may also come from local hospital dispensing units and from other manufacturing units. We made requests to Moorfields and Liverpool for their sales data in order to provide estimates of the extent of UK use. Results are provided in Table 3:

Table 3: Sales of bevacizumab for use in the eye (individual doses)

	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

A very crude approximation of the total supply of IVB can be made based on the response to the survey of use reported in section 2. Here we found that 56% and 32% respectively of clinicians reported that the IVB they prescribe is supplied by Moorfield and Liverpool respectively. Because

respondents can receive supplies from more than one source, responses sum to 118% of the total sample. Therefore, one might estimate that 75% (47% + 27%) of supplies overall are provided by these two manufacturers.

It is impossible to estimate the number of patients treated from these figures since we are unaware of the dosing regimen typically used by clinicians in practice. Two main options considered in the IVAN and CATT trials are for monthly doses or retreatment as required. The CATT study reports that in the first year, the mean number of injections received by those in the "on demand" treatment arm was 7.

Estimates of the populations eligible for treatment using VEGF are difficult to make. There are uncertainties surrounding the precise conditions for which VEGFs are suitable, the prevalence of those populations, the size of those populations eligible for VEGF treatment, the numbers that have previously been treated and stopped therapy, etc. Nevertheless some estimates are required for context.

The manufacturer submission for TA 237 (Ranibizumab for diabetic macular oedema) suggests prevalence figures of between 25,000 and 75,000 in England and Wales. The ERG suggest that prevalence is unknown, that non UK based estimates may be higher, but that their generalisability to the UK may be limited.

The manufacturer submission for TA 229 (Dexamethasone for macular oedema caused by RVO) estimates the annual incident number of patients eligible for treatment at 23,430.
Both the manufacturer submission for technology appraisal of ranibizumab for macular oedema caused by RVO (currently ongoing) and the ERG report highlight the fact that data to estimate the population of patients that may be eligible for treatment with ranibizumab is extremely limited.

In TA 155, Ranibizumab and pegaptanib for age-related macular degeneration, the assessment group cite a study that suggests 4,655 new cases per year eligible for Photodynamic Therapy (PDT) in the UK. Novartis presented estimates of 6,425 eligible patients progressing to treatment per year. Estimates of the eligible population receiving pegaptanib from the manufacturer submission varied by year and according to the assumptions made but were a maximum of [redacted]

3.3 SURVEY OF HOSPITAL BASED CONSULTANTS

We devised a survey which asked clinicians to indicate the extent to which they prescribe IVB, distinguishing AMD, RVO, DMO and other eye conditions and private from NHS practice. The survey was conducted exclusively online during a two week period in the summer of 2012. Participants were invited to complete the survey via an email which was sent to all hospital consultants registered as members of the Royal College of Ophthalmologists (RCO). A single reminder was sent after one week.

1163 invites were sent out and 199 (17%) responses were received.

Responses to the following questions are reported in Table 4:
"Thinking about the last 6 months, in NHS/private patients for whom you consider an anti VEGF drug to be appropriate, do you prescribe bevacizumab (Avastin) in patients diagnosed with AMD/RVO/DMO/other eye conditions:
Always or nearly always / Sometimes/ Hardly ever / Never / NA"

This was asked separately by eye condition and for NHS and private work i.e. 8 different questions. For NHS work only, the following supplementary question was asked, with available options dependent on the answer to the previous question:
"In approximately what proportion of patients with AMD/RVO/DMO/other eye conditions do you prescribe bevacizumab (Avastin)?
under 10% / 10% to 29% / 30% to 49% / 50% to 70% / Over 70%"

We asked respondents to indicate the reasons why they did or did not tend to prescribe IVB, if their practice had changed for AMD patients following the production of positive NICE guidance for ranibizumab in 2008 and where the IVB they prescribe is supplied from. There was also the option for respondents to leave open ended comments at various stages of the survey.

Table 4: Responses to questions on use of IVB by eye condition and by NHS/private practice

		Always or nearly always	Sometimes	Hardly ever	Never	N/A	0%	under 10%	10% to 29%	30% to 49%	50% to 70%	Over 70%
AMD in NHS	n	5	13	14	119	48	119	20	5	1	3	4
	%	3.3%	8.6%	9.3%	78.8%		78.3%	13.2%	3.3%	0.7%	2.0%	2.6%
RVO in NHS	n	30	45	13	63	42	63	30	19	8	20	13
	%	19.9%	29.8%	8.6%	41.7%		41.2%	19.6%	12.4%	5.2%	13.1%	8.5%
DMO in NHS	n	26	43	17	64	39	64	34	16	8	10	18
	%	17.3%	28.7%	11.3%	42.7%		42.7%	22.7%	10.7%	5.3%	6.7%	12.0%
Other eye conditions NHS	n	25	72	17	42	32	42	63	8	4	6	10
	%	16.0%	46.2%	10.9%	26.9%		31.6%	47.4%	6.0%	3.0%	4.5%	7.5%
AMD in private	n	16	27	13	50	82						
	%	15.1%	25.5%	12.3%	47.2%							
RVO in private	n	25	43	9	31	80						
	%	23.1%	39.8%	8.3%	28.7%							
DMO in private	n	25	35	7	36	85						
	%	24.3%	34.0%	6.8%	35.0%							
Other eye conditions private	n	21	33	5	41	87						
	%	21.0%	33.0%	5.0%	41.0%							

We found that for all questions on use there were a large number of respondents that indicated “NA” for all questions. In open ended responses, many indicated that they do not prescribe VEGFs at all but refer patients to retinal specialists. This left ~150 responses to these questions when referring to NHS practice. For private practice the proportion of NAs increased as many of the same do not undertake private work. ~10 responses were obtained for these questions.

For AMD patients in the NHS, most respondents (80%) never prescribe bevacizumab. Only 3% said that they prescribe IVB “always or nearly always”. 5% indicated that they prescribe IVB 50% of the time or more. Responses to this question indicated much lower use than for other eye conditions of for private practice AMD patients. When asked why they do not prescribe IVB for this patient group, the most common reason cited was “NICE guidance” (73% of the 26 that responded). Other common reasons cited were “PCT / funding policy”, “guidance from other bodies”, “fear of litigation” and “concerns around safety”. When asked how their current practice compared to that prior to NICE guidance only 31 responses were obtained. Of those, 55% said they use IVB less now, 10% more now and 26% said they use IVB about the same amount now.

For RVO and DMO, responses were broadly similar regarding NHS practice. Slightly over 40% of respondents never prescribe IVB. Almost 30% of respondents “sometimes” prescribe IVB and 20% “always or nearly always”. Prescribing rates are slighly higher in RVO compared to DMO. 22% of respondents prescribe IVB 50% of the time or more for patients with RVO compared to 19% for DMO.

For other eye conditions respondents were less likely to choose either extreme of “never use” or “always or nearly always”. 46% of respondents indicated that they “sometimes” prescribe IVB.

In all situations, a greater proportion of respondents indicated they were more likely to prescribe IVB in private practice than in NHS practice. 41% of respondents indicated that they prescribe IVB either “always or nearly always” or “sometimes” for patients with AMD in private practice. The figures for RVO, DMO and other eye conditions were 63%, 58% and 54% respectively.

There are clearly some limitations to the survey. The response rate is relatively low given the size of the population that the emailed invitation was mailed to. The RCO used their own membership email records. We have no knowledge of how accurate those might be, nor how many of those clinicians check their emails regularly. The survey was live during late July when many take their holidays.

We do not know if the comparisons of private and NHS practice are robust because these are not the same samples. It may be the case that those that engage in private practice are more likely to also prescribe IVB in NHS practice as well.

3.4 SUMMARY

Three approaches have been described in order to estimate the extent of use of IVB in eye conditions in the UK: a review of commissioning policies, supply data from the two major manufacturers of IVB and a survey of consultant ophthalmologists. In general terms it appears that there is substantial use of IVB across the UK NHS but there is also substantial variation.

Few PCTs advocate the use of IVB exclusively in the documents we identified from publicly available sources, particularly in AMD. The majority of the documents we identified permit the use of IVB but alongside other licensed alternatives.

There are two major manufacturers of IVB in the UK. The quantity of IVB supplied from these centres was almost [redacted] in 2011. How many patients this equates to is unclear as the dosing for different disease areas is unknown and potentially variable. For example, some studies have considered monthly doses of IVB in AMD patients compared to other studies in DMO where a single baseline injection may be used. Estimates of the size of the patient populations treated with these or other therapies is also extremely uncertain.

A survey of hospital based consultants reveals that there is little use of IVB in NHS patients with AMD, mainly as a result of NICE guidance in favour of an alternative therapy. In other disease areas a substantial use of IVB is reported. Use of IVB is even more widespread in private practice, including in patients with AMD.

4 THE EFFICACY OF INTRAVITREAL BEVACIZUMAB FOR THE TREATMENT OF DMO AND RVO

4.1 METHODS

A systematic review of the literature and meta-analysis (where appropriate) was undertaken to evaluate the efficacy of bevacizumab monotherapy in the treatment of diabetic macular oedema (DMO) and retinal vein occlusion (RVO).

A review of the evidence was undertaken in accordance with the general principles recommended in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (http://www.prisma-statement.org/).

4.1.1 Literature searching

a) Electronic databases

Studies were identified by searching the following electronic databases and research registers:

- MEDLINE(R) In-Process & Other Non-Indexed Citations and MEDLINE(R) (Ovid) 1948 to May 2012
- EMBASE (Ovid) 1974 to May 2012
- Cochrane Database of Systematic Reviews (Wiley Interscience) 1996 to May 2012
- Cochrane Central Register of Controlled Trials (Wiley Interscience) 1898 to May 2012
- Health Technology Assessment Database (Wiley Interscience) 1995 to May 2012
- Database of Abstracts of Review of Effects (Wiley Interscience) 1995 to May 2012
- Clinicaltrials.gov (http://www.clinicaltrials.gov/)
- EU Clinical Trials Register (https://www.clinicaltrialsregister.eu)
- *meta*Register of Controlled Trials (www.controlled-trials.com)

Sensitive keyword strategies using free text and, where available, thesaurus terms using Boolean operators and database-specific syntax were developed to search the electronic databases. Synonyms relating to the condition (e.g. RVO or DMO) were combined with synonyms relating to the intervention (e.g. bevacizumab, avastin). A methodological search filter aimed at restricting search results to RCTs was used in the searches of MEDLINE and EMBASE only. No language restrictions were used on any database. Although no date restrictions were applied for the review of IVB in patients with RVO, the clinical effectiveness searches were restricted by date for the review of IVB in patients with DMO. For this review, the current review updated an existing systematic review on IVB for the treatment of DMO[22] (within the scope of the current review). In the review by Fortin *et al.*,[22] the searches examined the period from 1948 to November 2011 (with no language restrictions). The search strategies from the existing systematic review were of good quality and clearly reported. To minimise the risk of missing potentially relevant papers, the clinical effectiveness searches were limited by date from January 2010 to May 2012 in an attempt to cover the period in the last two

years which would overlap with the search period of the existing review. An example of the MEDLINE RVO and DMO search strategy is provided in Appendix 2.

b) Other resources

To identify additional published, unpublished and on-going studies, the reference lists of all relevant studies (including existing systematic reviews) were checked and a citation search of relevant articles (using the Web of Science Citation Index Expanded and Conference Proceedings Citation Index - Science) was undertaken to identify articles that cite the relevant articles. In addition, key experts in the field were contacted.

All identified citations from the electronic searches and other resources were imported into and managed using the Reference Manager bibliographic software, (version 12.0; Thomson Reuters, Philadelphia, PA).

4.1.2 Selection criteria

The inclusion of potentially relevant articles was undertaken using a two-step process. First all titles were examined for inclusion by one reviewer. Any citations that did not meet the inclusion criteria i.e. non-human, unrelated to bevacizumab and or RVO / DMO were excluded. Second, remaining abstracts and full text articles were examined independently. Any disagreements in the selection process were resolved through discussion with a second reviewer and if agreement could not be reached, a third reviewer was consulted. The relevance of each article for the systematic review was assessed according to the following criteria:

a) Study design

All RCTs that were published or unpublished were included. Reviews of primary studies were not included in the analysis, but were retained for discussion and identification of additional studies. Moreover, the following publication types were excluded from the review: animal models; preclinical and biological studies; narrative reviews, editorials, opinions; and non-English language papers.

b) Population

The population comprised adults (defined as ≥ 18 years of age) with DMO or RVO.

c) Interventions

The intervention was the administration of IVB (any dose) monotherapy.

d) Relevant comparators

The relevant comparators for the DMO and RVO reviews were as follows:

- Laser photo-coagulation
- Sham treatment or placebo
- Dexamethasone (RVO review only).

e) Outcomes

The outcomes of interest for the DMO and RVO review were as follows: visual acuity, contrast sensitivity and central macular thickness (DMO review only).

4.1.3 Data abstraction and quality assessment

Data abstraction was performed by one reviewer into a standardised data extraction form. Any uncertainties or queries were resolved by discussion with a second reviewer and if agreement could not be reached, a third reviewer was consulted. Where multiple publications of the same study were identified, data were extracted and reported as a single study. Moreover, for the DMO review all relevant data was extracted from the Fortin *et al*. review[22] in the first instance, and cross checked for accuracy with the original papers. Where necessary, additional data was extracted from the original papers or in cases where information was missing from the articles, authors of the respective studies were contacted to provide further details.

The following information was extracted for all studies when reported: study characteristics (e.g. author, year of publication, country, follow-up, funding), participant details (e.g. inclusion and exclusion criteria), intervention and comparator details (e.g. description and dose) and outcomes.

The methodological quality of each included study was assessed by one reviewer. Any uncertainties or queries were resolved by discussion with a second reviewer and if agreement could not be reached, a third reviewer was consulted. The study quality characteristics were assessed according to the Cochrane Collaboration Risk of Bias Tool (namely sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and 'other issues').[23]

4.1.4 Data analysis

Data were tabulated and discussed in a narrative review. Where appropriate, meta-analyses were employed to estimate a summary measure of effect on relevant outcomes using the Cochrane Review Manager software RevMan 5.0 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). The relative risk and/ or risk difference were calculated for dichotomous outcomes. Where continuous scales of measurement were used, the mean difference was used. A standard I-squared statistic for heterogeneity was used to test for heterogeneity of treatment effect between trials and a threshold of 50% was considered significant. The fixed effects model was applied to obtain summary statistics of pooled trials unless significant between study heterogeneity was present, in which case a random effects method was used.

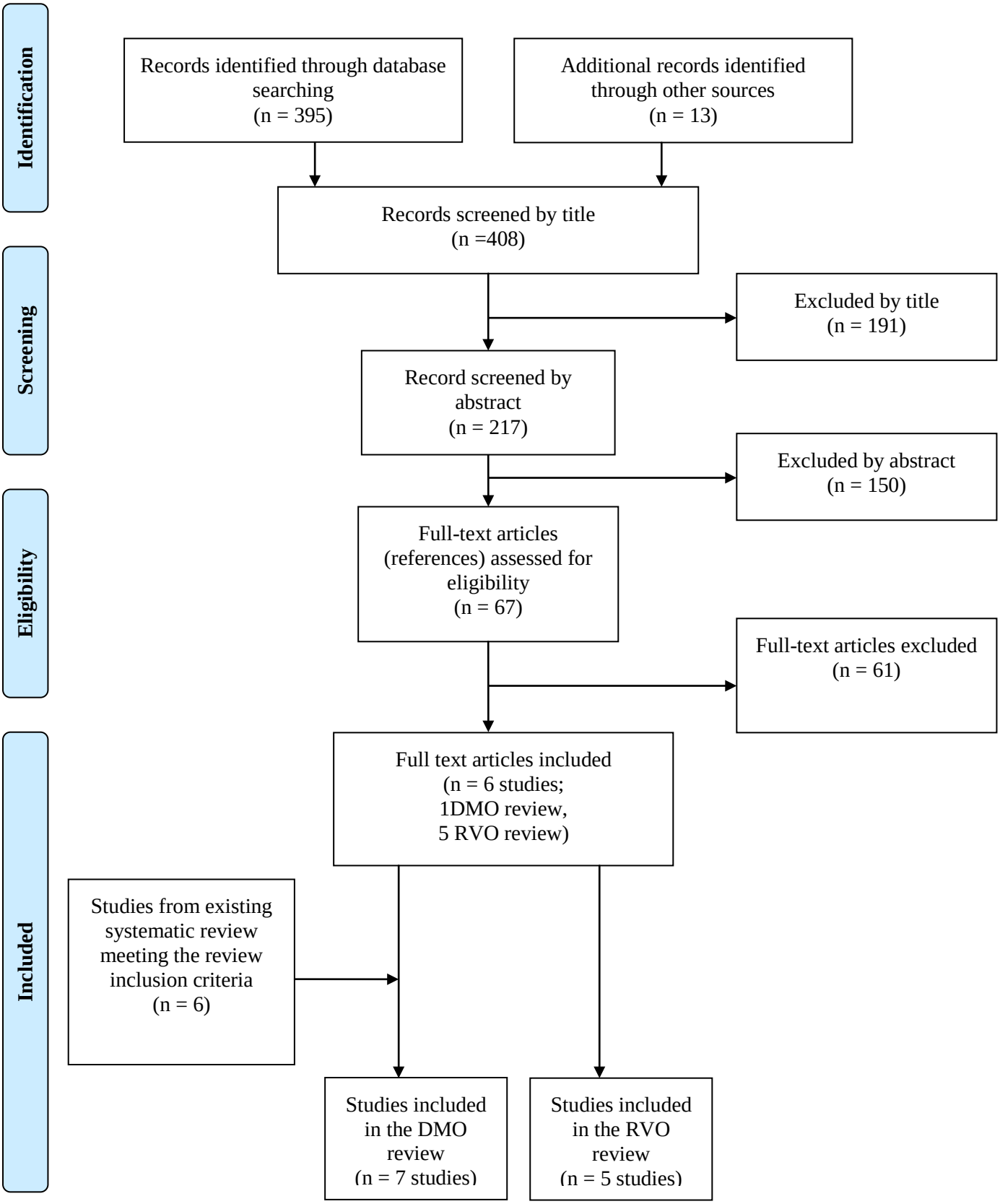
4.2 RESULTS

4.2.1 Quantity and quality of research available

4.2.1.1 Number of studies identified/included

The literature searches identified 408 citations. For the DMO review, one RCT[24] met the inclusion criteria and was added to the six trials[25-30] from the previous systematic review.[22] For the RVO review, five RCTs[31-35] met the inclusion criteria. A flow chart describing the process of identifying relevant literature can be found in Figure 2. A summary of excluded full text papers with reasons is presented in Appendix 3.

Figure 2: Study flow chart (adapted): Efficacy review[36]



4.2.1.2 Number and type of studies excluded

A total of 62 full text articles were excluded as they did not meet all the pre-specified inclusion criteria. The majority of the articles were excluded primarily on the basis of inappropriate study design (not RCTs), incorrect intervention (not IVB for the treatment of DMO or RVO), incorrect comparator or unsuitable publication type (reviews, commentaries or editorials). A full list of excluded studies with reasons for exclusion is presented in Appendix 3.

4.2.2 Assessment of effectiveness

4.2.2.1 Description of included studies (design and patient characteristics)

- **DMO review**

Seven RCTs contributed data to the review of efficacy in DMO patients. One study[25] compared bevacizumab with sham injection. Six studies compared bevacizumab to laser photocoagulation.[24,26-30] Studies were conducted in Iran, USA, UK and Egypt, and included patients diagnosed with DMO. Two studies[25,26] enrolled patients with DMO refractory to laser treatment. Two studies[29,30] enrolled treatment-naive patients. Solaiman[22] randomised the smallest number of eyes (n=62), whilst Soheilian[21] was the largest study with (n=150) eyes. Michaelides[18] randomised (n=80) eyes, Mansourian[16] (n=103) eyes, DRCRN[27] (n=109) eyes, Ahmadieh[25] (n=115) eyes and Faghihi[28] randomised (n=130) eyes. The frequency of injections (where reported) varied between the studies. In the Ahmadieh[25] study 1.25 mg of bevacizumab was given at baseline and weeks 6, 12 in comparison to sham injection. In the studies using laser therapy as the control group, Faghihi[28] reported using 1.25 mg of bevacizumab but repeat injections were not stated. Mansourian[24] reported using 1.25 mg of bevacizumab but did not report if repeat injections were used. Michaelides[26] gave 1.25mg of bevacizumab at baseline, and at 6 and 12 weeks, and subsequent injections were administered until a stable central macular thickness was attained, but the number of patients requiring further injections was not reported. Solaiman[30] gave 1.25mg of bevacizumab once at baseline. Soheilian[29] gave 1.25 mg at baseline and retreatment given based on persistence of clinically significant macular oedema, although the number of patients given additional IVB was not reported. In the DRCRN[27] study participants in group 1 were given 1.25 mg of bevacizumab at baseline and week 6; group 2 received 2.5 mg at baseline and week 6 and in group 3, 1.25 mg of bevacizumab was given at baseline. Further details of the design and patients characteristics are presented in Appendix 4.

- **RVO review**

Five RCTs were identified that examined the effectiveness of IVB on BCVA in patients with RVO. Two were reported in journal articles,[31,34] whereas the remaining three were only available as conference abstracts[32,33,35] so limited information is available for these three studies. Three RCTs examined the impact of IVB among patients with central retinal vein occlusion (CRVO)[31-33] and two others examined patient populations with branch retinal vein occlusion (BRVO)[34,35] (Appendix 5, table A8). Three studies compared 1.25 mg doses of IVB with sham injections that were six weeks apart, however two studies examined the effectiveness of two IVB/sham injections (at baseline and week 6), measuring outcomes at 6 and 12 weeks,[34,35] whereas in the other study four IVB/sham injections were administered (at baseline and weeks 6, 12 and 18), with outcomes measured at 6, 12, 18 and 24 weeks.[31] In two studies reported in abstracts the IVB was compared with IVB/triamcinolone combined therapy (not examined in this review) and sham injections, however concentrations of IVB administered were not reported.[32,33] One of these abstracts also did not report the number of injections administered,[32] however in the other IVB was administered three times, six weeks apart. Studies sizes were similar with Epstein[31] randomising 60 eyes, Habibabadi[32] randomised 63 patients, and Moradian[27] randomised 70 patients.

The method used to assess BCVA differed across trials. One trial assessed change in BCVA by the number of ETDRS letters,[31] whereas another measured change in BCVA using a Snellen chart transformed to logMAR.[34] The three trials reported in abstracts did not provide any details on the measurement of BCVA.[32,33,35]

One trial[34] had slightly older participants and a lower proportion of females than another trial,[31] with no information on participants being specified in the three trials reported in abstracts only (Appendix 5, table A9). Baseline BCVA could not easily be compared between trials as the only two trials reporting this variable used different measures of BVCA. Both trials for which baseline participant characteristics were given reported no difference in baseline study characteristics;[31,34] it was not possible to ascertain similarity of groups at baseline in the studies reported in abstracts only.[32,33,35]

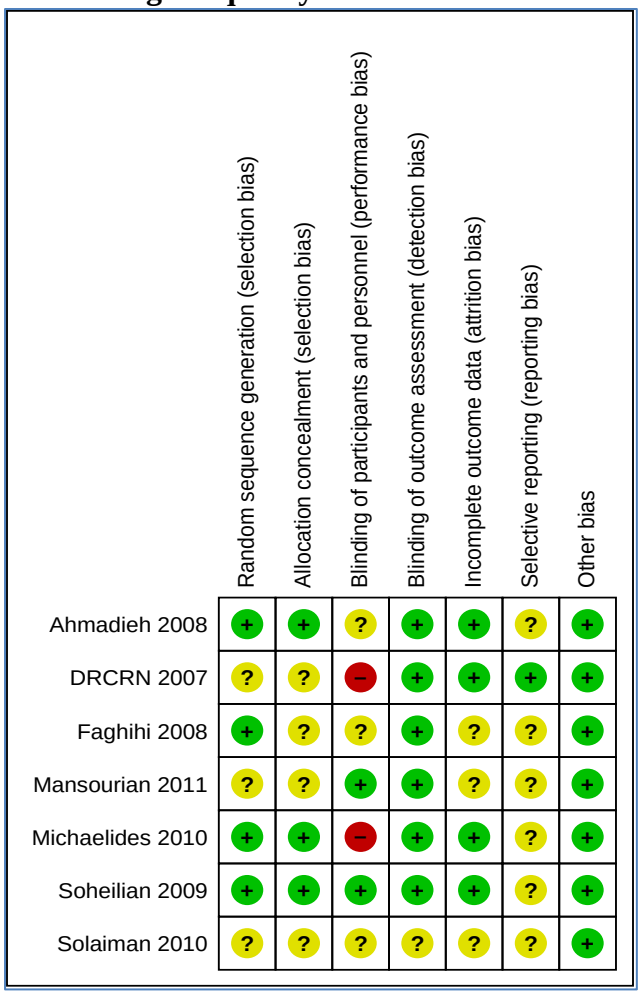
4.2.2.2 Quality assessment of RCTs

- **DMO review**

Only four studies reported how randomisation was performed.[25,26,28,29] Three studies[25,26,29] reported methods used to conceal allocation to treatment. Blinding of participants and personnel was

attempted by two studies[24,29] whilst three studies[25,28,30] did not report if blinding was attempted, and in two studies blinding was not undertaken.[26,27] Blinding of outcome assessors was reported in six studies.[24-29] Study attrition was only reported in four studies.[25-27,29] It was unclear in six studies if outcomes were selectively reported, one study[27] stated outcomes measures *a priori*. A summary of the methodological quality of each included study is presented in Figure 3.

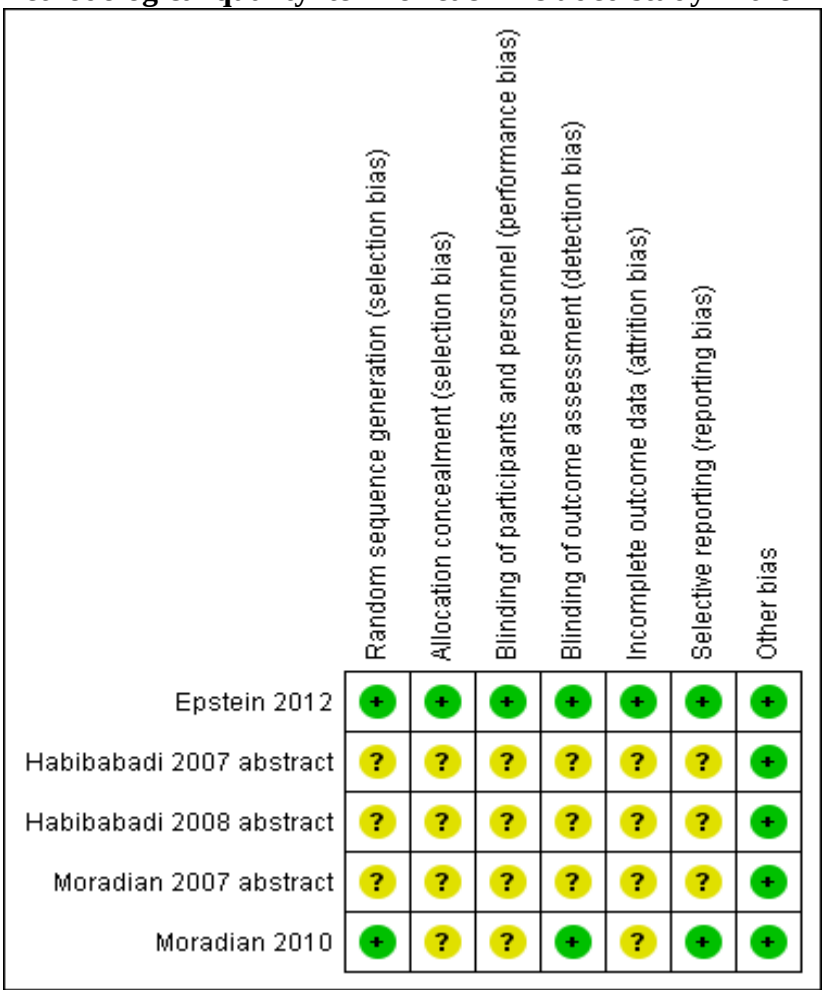
Figure 3: Methodological quality summary: Review authors judgments about each methodological quality item for each included study in the DMO review



- **RVO review**

The overall methodological quality of the five included studies is summarised in Figure 4. One of the included RCTs was considered to be of good quality [34] and another was of moderate quality.[31] The quality of three RCTs was largely unclear,[32,33,35] due to only an abstract being available.

Figure 4: Methodological quality summary: Review authors judgments about each methodological quality item for each included study in the RVO review



4.2.2.3 Effects of interventions

- **DMO review**

Results were synthesised by meta-analyses for the DMO efficacy data. Comparators were laser therapy and sham injections. The following outcomes were considered: improvement in BCVA (ETRDS of 15 letters or 3 lines) at 6 weeks, 12 weeks to 16 weeks and 36-52 weeks; BCVA (ETRDS 15 letters) at 12 weeks and 12 months; mean difference in BCVA logMAR by 4 to 6 weeks, 12 to 16 weeks, at 24 weeks, at 48 weeks and up to 2 years; mean change in BCVA (ETDRS

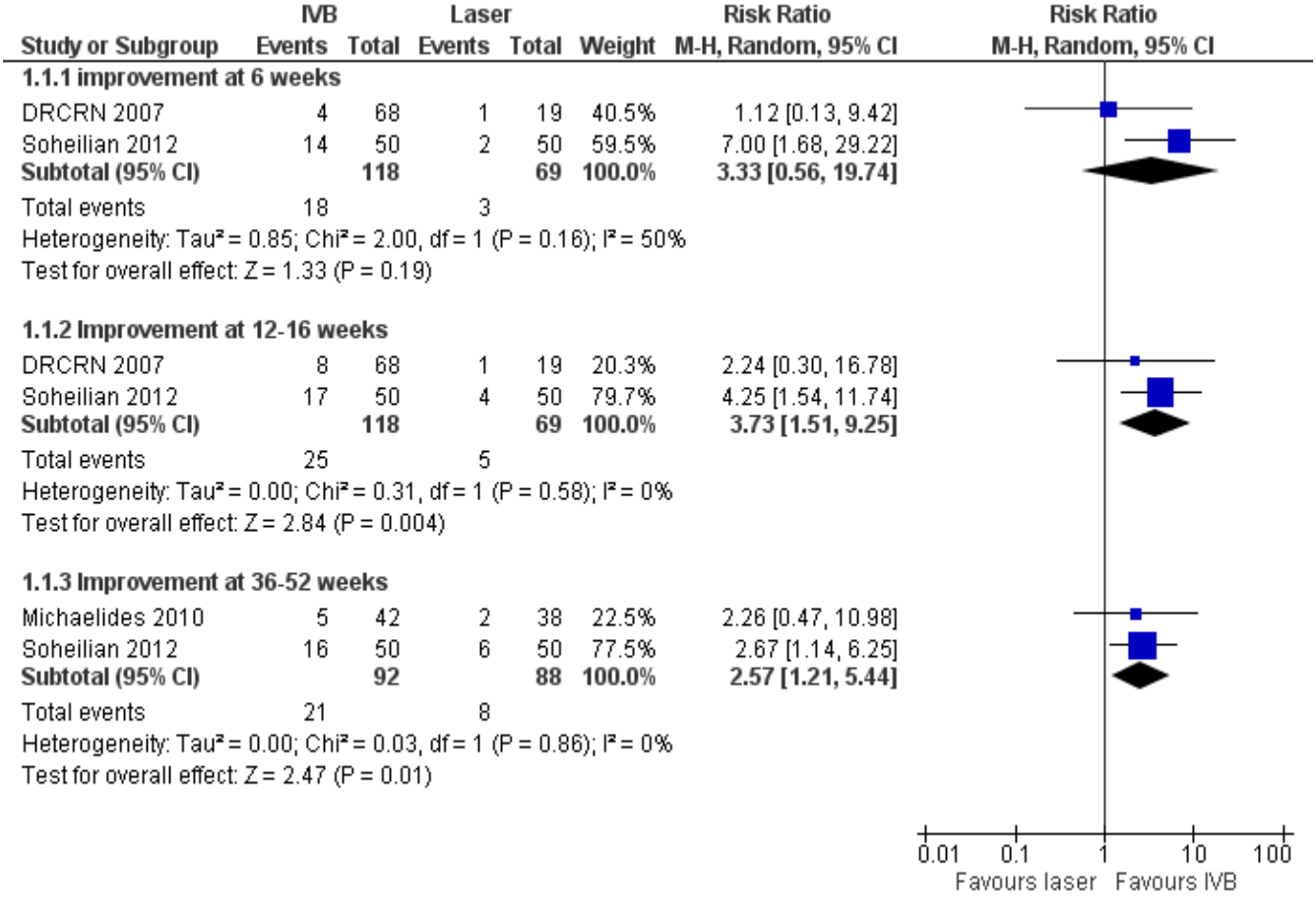
logMAR) score; deterioration of BCVA (ETRDS of 15 letters or 3 lines) at 6 weeks, at 12 weeks to 16 weeks and at 36-54 weeks and mean change in central macular thickness (CMT) scores at 6, 12, 18 and 24 weeks.

a) Bevacizumab versus laser therapy

i) Outcome: BCVA ETDRS 15-Letter (3 lines)

Figure 5 summarises the BCVA ETDRS 15-Letter (3 lines) data of IVB compared with laser therapy. By six weeks (using fixed effects model) improvement on BCVA 15-letters significantly favoured the IVB group (Graph not shown, 2 RCTs, n=187, RR 4.42 CI 1.45 to 13.46) compared with laser therapy, but data were heterogeneous (I^2 =50%). Due to significant heterogeneity, converting to a random effects meta-analysis rendered the data non-significant (2 RCTs, n=187, RR 3.33 CI 0.56 to 19.74). Significant improvement at 12-16 weeks occurred in the IVB group (2 RCTs, n=187, RR 3.73 CI 1.51 to 9.25) compared with laser therapy. Longer term BCVA data from 36 to 52 weeks significantly favoured IVB (2 RCTs, n=180, RR 2.57 CI 1.21 to 5.44) compared with laser therapy.

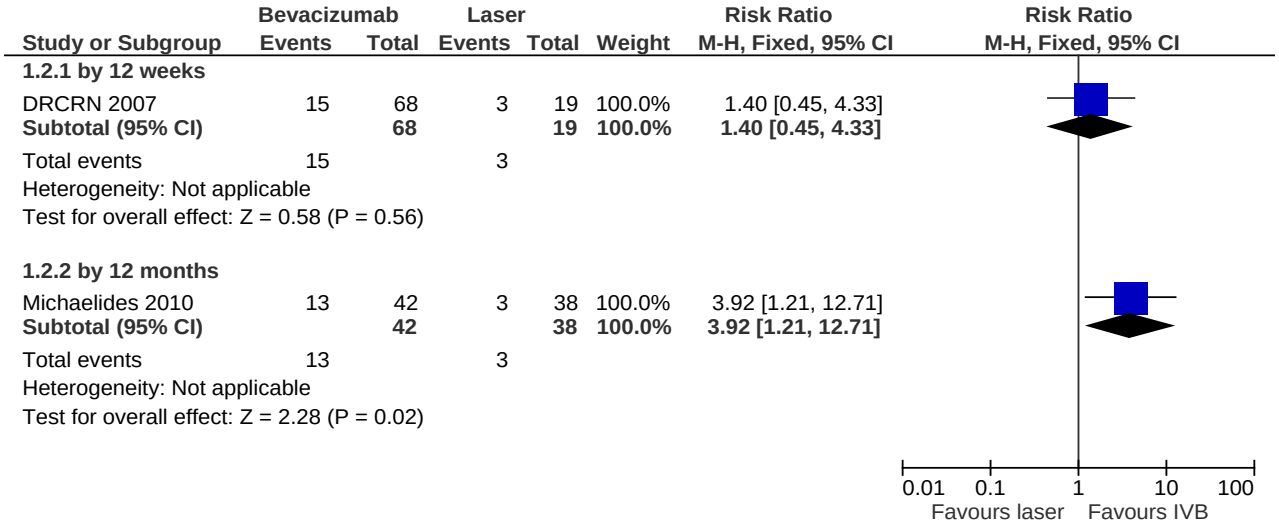
Figure 5: Improvement in BCVA ETDRS 15- letter (3 lines)



ii) Outcome: BCVA ETDRS ≥10 Letters

Figure 6 summarises the BCVA ETDRS data of IVB compared with laser therapy. At 12 weeks, no significant difference (1 RCT, n=87, RR 1.40 CI 0.45 to 4.33) was found. Results at 12 months revealed significantly greater improvement in BCVA in IVB group (1 RCT, n=80, RR 3.92 CI 1.21 to 12.71) compared with laser therapy.

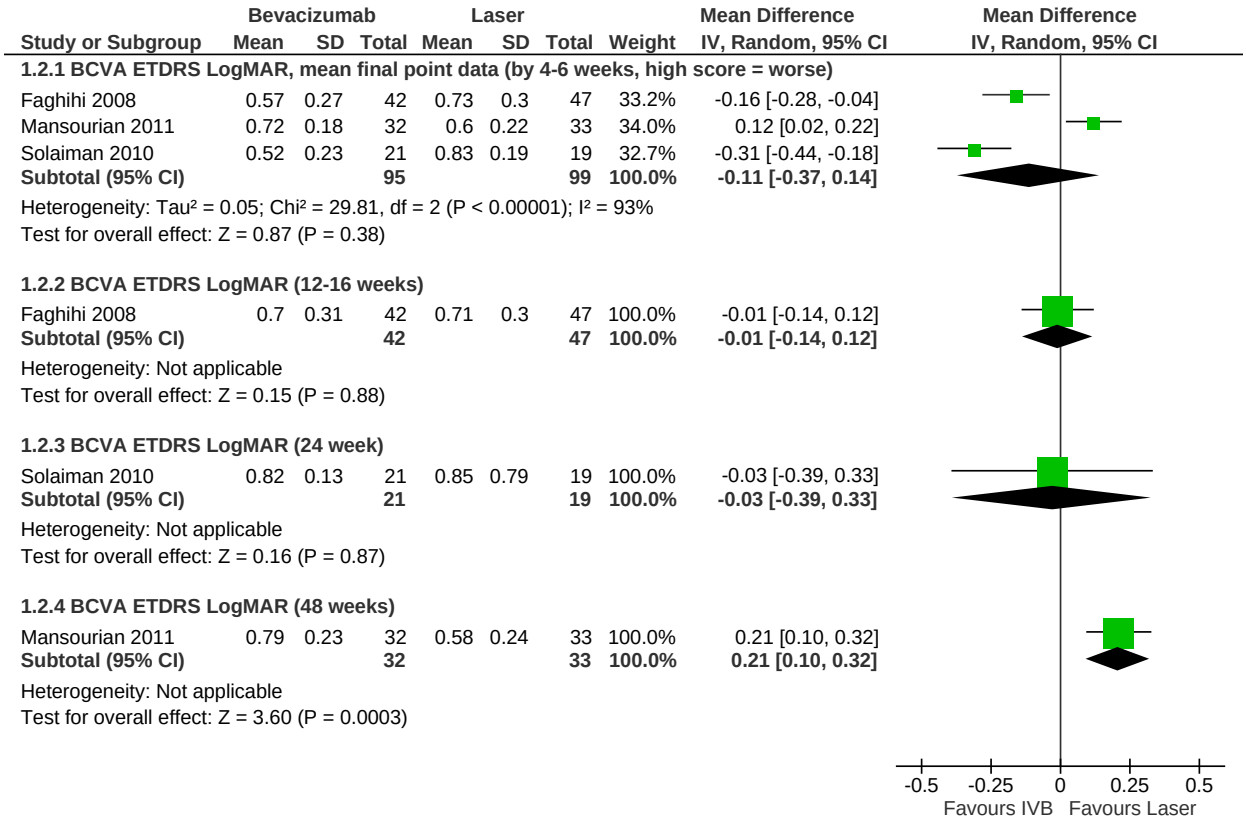
Figure 6: Improvement in BCVA ETDRS ≥10 letters



iii) Outcome: Mean difference in BCVA logMAR for Bevacizumab versus Laser (high score=worse)

Figure 7 summarises the BCVA ETDRS logMAR data of IVB compared with laser therapy. At 4 to 6 weeks, the IVB group had significantly lower mean BCVA scores compared with laser therapy (Graph not shown, 3 RCTs, n=194, RR -0.07 CI -0.14 to -0.01), although data were heterogeneous (I^2=93%) and therefore a random effects model was adopted which rendered 4-6 week data non-significant (RR -0.11 CI-0.37 to 0.14). Soheilian[29] also reported results at six weeks but data are skewed (not normally distributed) and were not added to the meta-analysis. At 12 to16 weeks data were equivocal between IVB and laser therapy (1 RCT, n=89, RR -0.01 CI -0.14 to 0.12). Three studies[24,29,30] reported BCVA logMAR scores but the data were skewed and were not added to the meta-analysis. At 24 weeks data were equivocal between IVB and laser therapy (1 RCT, n=40, RR -0.03 CI -0.39 to 0.33). One study[24] reported results at 24 weeks but the data were skewed and not added to the meta-analysis. At 48 weeks, significantly greater improvement in BVCA occurred in the laser group (1 RCT, n=65, RR 0.21, CI 0.10 to 0.32) compared with the IVB group (Figure 7). One study[29] reported one and two year outcome data for BCVA but data are skewed and not added to the meta-analysis.

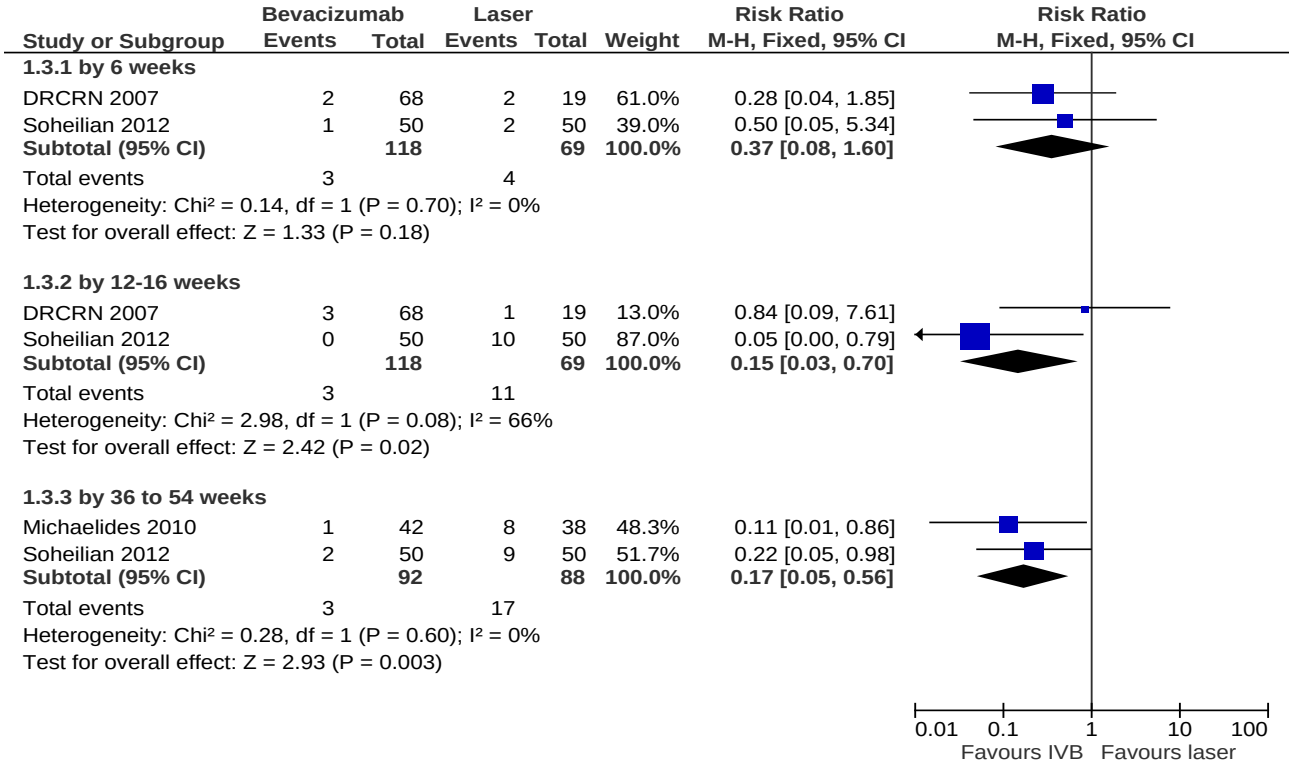
Figure 7: Mean difference in BCVA ETDRS LogMAR score



iv) Deterioration or any deterioration (BCVA ETDRS 15 letter - 3 lines)

Figure 8 summarises the deterioration in BCVA of patients treated with IVB compared with laser therapy. Two studies reported data at 6 weeks and no significant difference in deterioration of BCVA 15-letters was found between IVB and laser therapy (n=187, RR 0.37 CI 0.08, 1.60). By 12-16 weeks, significantly fewer participants in the IVB group had visual acuity deterioration compared with laser therapy (2 RCTs, n=187, RR 0.15 CI 0.03 to 0.70). However, data were heterogeneous (I^2=66%). Random effects analysis rendered this outcome non-significant (Graph not shown, RR 0.22 CI 0.01 to 4.84). Longer term follow up data (36 to 54 weeks) significantly favoured IVB (2 RCTs, n=180, RR 0.17 CI 0.05 to 0.56) compared with laser therapy.

Figure 8: Deterioration or any deterioration (BCVA ETDRS 15 -letter - 3 lines) (High score = worse)

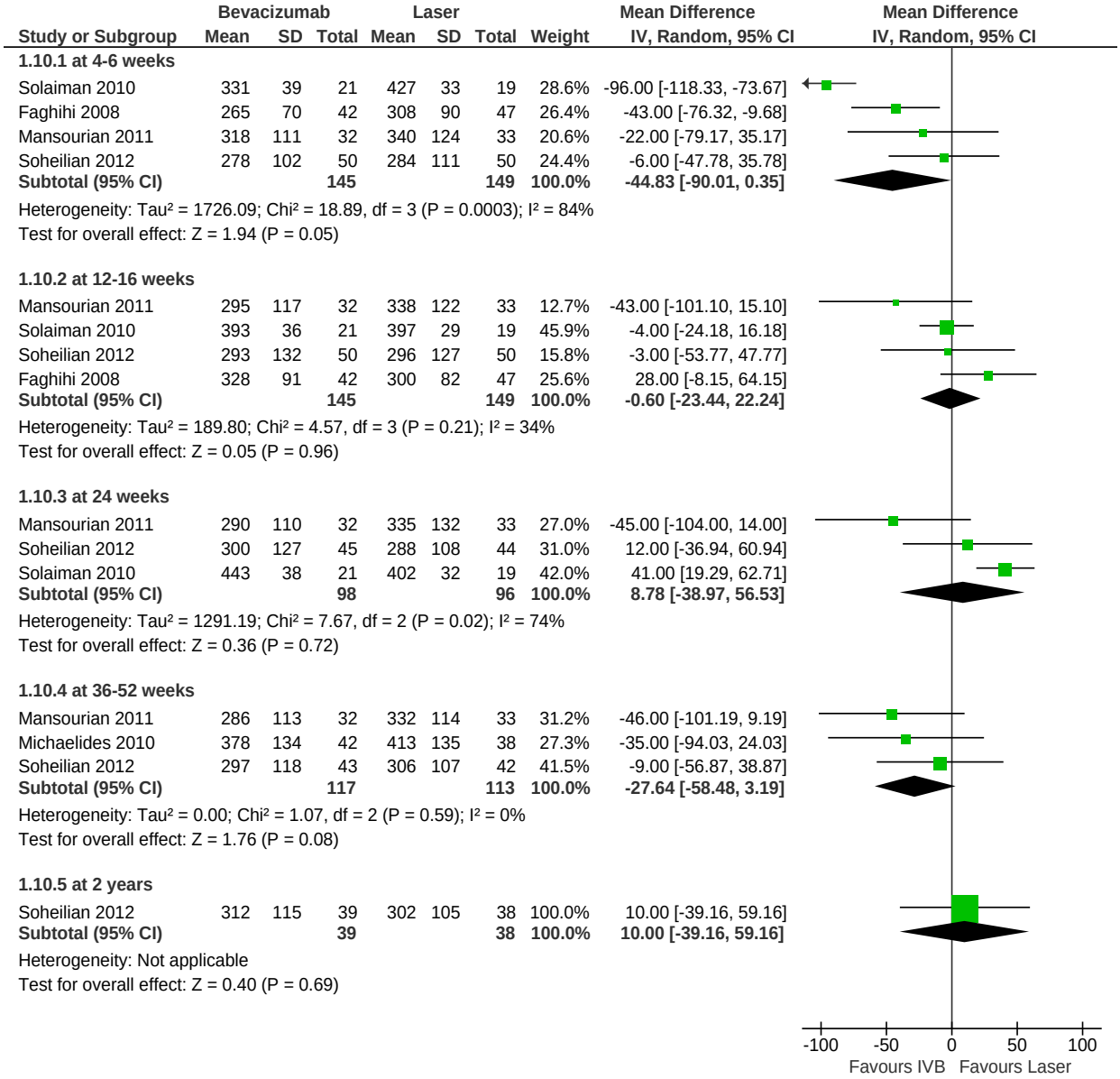


v) Mean difference in Central Macular Thickness score

Figure 9 summarises the CMT mean scores of IVB compared with laser therapy. Fixed effects analysis of CMT mean scores at 4 to 6 weeks significantly favoured IVB (Graph not shown, 4 RCTs, n=294, RR -63.79 CI -80.05 to -47.54) compared with laser therapy but data were heterogeneous (I^2 =84%). Using a random effects model, the data remained significant (p=0.05) however, the confidence intervals were wider (RR -44.83 CI -90.01 to 0.35). At 12 to 16 weeks the CMT mean

scores were equivocal between IVB and the laser therapy groups (4 RCTs, n=294, RR -0.60 CI -23.44 to 22.24). At 24 weeks, no significant differences were found in CMT mean scores (3 RCTs, n=194, RR 8.78 CI -38.97 to 56.53) between IVB and laser therapy. Longer term data at 36 to 52 weeks found no significant difference in CMT mean scores between IVB and laser therapy (3 RCTs, n=230, RR -27.64 CI -58.48, 3.19). No significant differences were found in CMT mean scores at two year follow up between IVB and laser therapy (1 RCT, n=77, RR 10.00 CI -39.16 to 59.16).

Figure 9: Mean difference in CMT scores (High score = worse)

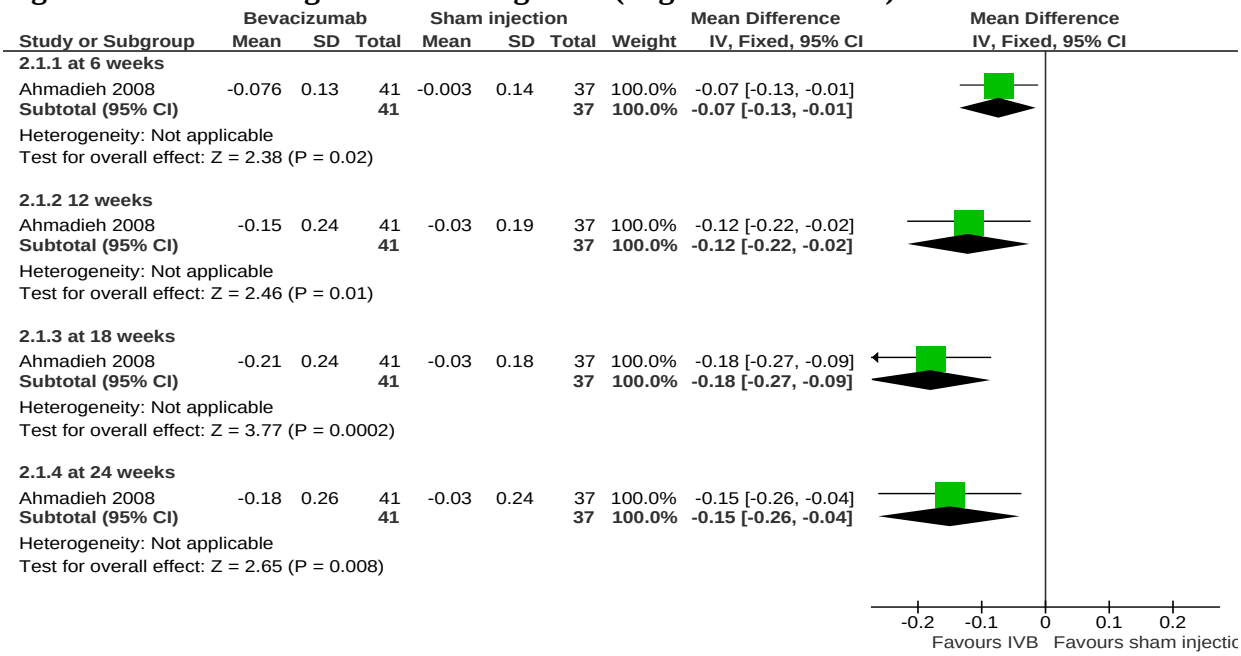


b) Bevacizumab versus sham injection

i) Outcome: Mean change in BCVA LogMAR

One study[25] (n=78) reported data for IVB versus sham injection. At 6 weeks significantly greater improvement occurred in the IVB group (RR -0.07 CI -0.13 to 0.01) compared with sham injection for BCVA. Results at 12 weeks (RR -0.12 CI -0.22 to -0.02), 18 weeks (RR -0.18 CI -0.27 to 0.09) and 24 weeks follow up also significantly favoured IVB (RR -0.15 CI -0.26 to 0.04) compared with sham injection (Figure 10).

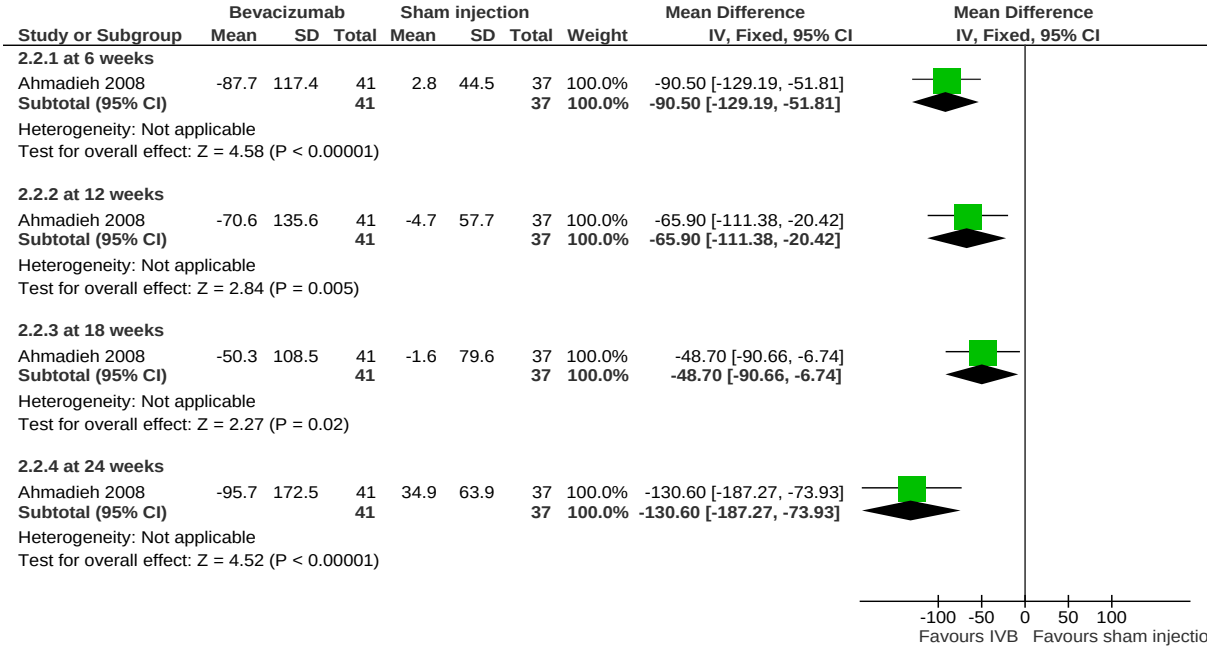
Figure 10: Mean change in BCVA LogMAR (High score = worse)



ii) Mean change in CMT scores

One study[25] (n=78) reported data for IVB versus sham injection (Figure 11). At 6 weeks, significantly greater improvement occurred in the IVB group (RR -90.50 CI-129.19 to -51.81) compared with the sham injection group. Follow up data at 12 weeks (RR-65.90 CI -111.38 to -20.42), 18 weeks (RR -48.70 CI -90.66, -6.74) and 24 weeks (RR -130.60 CI -187.27, -73.93) also significantly favoured the IVB group.

Figure 11: Mean change in CMT scores (High score = worse)



- **RVO review**

Due to heterogeneity in the type of RVO (central and branch) and method of assessing BCVA, a meta-analysis was considered inappropriate. All trials[31-35] reported significant mean improvements in BCVA in the IVB group over time (p values ranged from 0.047 to p<0.0001). Of the two trials that presented results for the sham group, one reported a mean improvement in BCVA over the 12-week study duration,[34] whereas the other reported a mean worsening in BCVA over the 24-week study duration.[31] Further details are provided in Appendix 6.

Only two of the five trials[31,34] reported differences between groups at the follow-up measurement points. In one trial of patients with BRVO,[34] where interventions were administered twice, 6 weeks apart, the two groups were statistically different at 6 weeks (p=0.05), however by 12 weeks the difference was no longer significant (p=0.064). In another trial of patients with CRVO,[31] where interventions were administered four times, 6 weeks apart, there was a significant difference between groups in weeks 12, 18 and 24 (p<0.01), but not at week 6. Taken together, these findings suggest that administering four 1.25 mg IVB injections at 6-weekly intervals can be more effective for longer-term improvement in BCVA than administering two 1.25 mg IVB injections at 6-weekly intervals, although this must be interpreted with caution given the small number of studies and the differences in participant age, gender distribution and type of RVO.

4.2.3 Discussion

- **DMO review**

Efficacy measures for visual acuity (BCVA ETDRS 15-letter -3 lines) favoured bevacizumab (6 week and 12-16 week outcomes) compared with laser therapy, although the effect size diminished as follow up times increased. Visual acuity (BCVA ETDRS 10-letters) indicated no benefit for IVB at 12 weeks; however longer term data at 12 months from a single study favoured IVB. The effect of bevacizumab on BCVA LogMAR scores was significantly different compared with laser therapy at 6 weeks although data were heterogeneous, but 12 and 24 week data were equivocal. Longer term follow up data at 48 weeks significantly favoured laser therapy, but this was based on one small study (n=65). Deterioration in BCVA (15-letter – 3 lines) for short term data at 6 weeks was not significantly different; data reported up to 16 weeks favoured bevacizumab but was heterogeneous; longer term data up to 54 weeks favoured bevacizumab, which suggests that benefits are only achieved during longer term treatment. The number of injection that patients received varied between the studies or was not clearly reported and it is not clear what impact this has on efficacy.

No consistent treatment direction emerged for mean scores in central macular thickness; initially CMT scores favoured bevacizumab (4-6 week data) but data were heterogeneous, and at 12-16 weeks data were equivocal. Data reported at 24 weeks was also heterogeneous and was not significantly different. Longer term data at one year indicated a trend favouring IVB but data were non-significant, whilst two year data from a single study indicated no significant difference between IVB and laser therapy.

Only one study compared bevacizumab with sham injection. Outcome measures of change scores in visual acuity up to 24 weeks favoured bevacizumab, although the data are limited by the small sample size used (n=78). Mean change scores in central macular thickness across 6, 12, 18 and 24 weeks favoured bevacizumab compared with sham injection.

- **RVO review**

Overall, IVB appeared to confer some improvement in BCVA among patients with branch and central RVO, although three of the five trials[32,33,35] were only reported in abstract form and detailed data were not available. From the two trials[31,34] that reported differences between BCVA and control (sham injection) groups, it seems that administering four 1.25 mg IVB injections at 6-weekly intervals[31] can be more effective for longer-term improvement in BCVA than administering two 1.25

mg IVB injections at 6-weekly intervals.[34] Caution is warranted in interpreting this finding however, due to the small number of studies, relatively small sample sizes and the differences in participant age, gender distribution and type of RVO. The relatively short-term follow-up durations of the studies reviewed should also be borne in mind; the maximum follow-up duration was 24 weeks.

4.2.4 Comparison of findings with existing literature

In the DMO studies, improvement at 12-16 weeks was seen in BCVA ETDRS 15-letter scores, although the treatment effect of bevacizumab was reduced in longer term follow-up data at 3-52 weeks. This is consistent with reports indicating that bevacizumab is most effective from 6-12 weeks after the initial injection.[30]

Compared with sham injection, the treatment effects of bevacizumab were more consistent and indicated significantly greater improvement in BCVA and CMT scores, although this is based on a single study (n=78) with a follow up time of 24 weeks. In the RVO studies, detailed data were not available for three of the studies, which were only reported in abstract form and also did not report group differences at follow-up. It seems that on-going IVB injections may be more effective at increasing BCVA than only two injections; however, this conclusion is based on the findings of two trials with relatively small sample sizes and relatively short-term follow-up (the longest was 24 weeks) that differed in terms of participants' age, gender distribution and type of RVO.

4.2.5 Conclusions

From the available evidence, results for visual acuity from dichotomous data generally favoured bevacizumab compared with laser therapy, but data were often heterogeneous and between group differences were often related to longer follow up times. However, BCVA LogMAR scores indicate that only longer term treatment is advantageous over laser therapy, whilst changes in CMT did not indicate that IVB confers a sustained advantage over laser therapy. Compared with sham injection bevacizumab was superior for the outcomes of BCVA logMAR, and mean change in CMT but these findings are based on a single small study. For patients with RVO, bevacizumab appears to provide some improvement in BCVA but more studies are needed before valid conclusions are reached.

5 EVIDENCE REGARDING THE SAFETY OF IVB FOR THE TREATMENT OF EYE CONDITIONS IN GENERAL

5.1 METHODS

A systematic review of the literature and meta-analysis (where appropriate) was undertaken to evaluate the safety of IVB monotherapy for the treatment of all eye conditions.

A review of the evidence was undertaken in accordance with the general principles recommended in the PRISMA statement (http://www.prisma-statement.org/).

5.1.1 Literature searching

a) Electronic databases

Studies were identified by searching the following electronic databases.

- MEDLINE(R) In-Process & Other Non-Indexed Citations and MEDLINE(R) (Ovid) 1948 to May 2012
- EMBASE (Ovid) 1974 to May 2012
- Cochrane Database of Systematic Reviews (Wiley Interscience) 1996 to May 2012
- Cochrane Central Register of Controlled Trials (Wiley Interscience) 1898 to May 2012
- Health Technology Assessment Database (Wiley Interscience) 1995 to May 2012
- Database of Abstracts of Review of Effects (Wiley Interscience) 1995 to May 2012
- TOXLINE (US NIH) 1965 to May 2012

Sensitive search strategies using free text and thesaurus terms were developed to search the electronic databases. Synonyms relating to the intervention (e.g. bevacizumab, avastin) were combined with adverse events floating subheadings or specific adverse events terms (e.g. a list of adverse events such as endophthalmitis, retinal detachment and stroke listed in an International IVB safety survey published by Fung *et al.*[21]) Adverse events statements were combined with the Boolean operator 'NOT' with chemotherapy terms so that records retrieved would be related bevacizumab for eye conditions rather than chemotherapy treatment. The current review updated (and adapted) the search strategy reported in an existing systematic review on adverse events of intravitreal anti-VEGF[37] (within the scope of the current review). In the review by van der Reis *et al.*,[37] the searches examined the period from 1948 to 2009. The adverse event searches were limited by date from January 2009 to May 2012. The search methodology used by van der Reis *et al.*[38] was considered by the review team to be of good quality however fewer adverse event terms were used and some terms

were considered too broad such as “cause” and “response” and a study design filter for experimental and functional study design for electrophysiology or in vitro or cytology studies was applied. The review team adapted van der Reis *et al*’s search strategy by including more adverse events terms and removing the broader terms. In addition, it was not considered necessary to apply an experimental and functional study design filter. No language restrictions were used on any database. An example of the MEDLINE search strategy is provided in Appendix 7.

b) Other resources

To identify additional published, unpublished and on-going studies, the reference lists of all relevant studies (including existing systematic reviews) were checked and a citation search of relevant articles (using the Web of Science Citation Index Expanded and Conference Proceedings Citation Index - Science) was undertaken to identify articles that cite the relevant articles. In addition, key experts in the field were contacted.

All identified citations from the electronic searches and other resources were imported into and managed using the Reference Manager bibliographic software, (version 12.0; Thomson Reuters, Philadelphia, PA).

5.1.2 Selection criteria

The inclusion of potentially relevant articles was undertaken using a two-step process. First all titles were examined for inclusion by one reviewer. Any citations that clearly did not meet the inclusion criteria i.e. non-human, unrelated to bevacizumab were excluded. Second, all abstracts and full text articles were examined independently by a minimum of two reviewers. Any disagreements in the selection process were resolved through discussion. The relevance of each article for the systematic review was assessed according to the following criteria:

a) Study design

All published or unpublished RCTs, controlled trials or observational studies including ≥10 participants reporting adverse events data following IVB administration were included. Reviews of primary studies were not included in the analysis, but were retained for discussion and identification of additional studies. Moreover, the following publication types were excluded from the review: animal models; preclinical and biological studies; narrative reviews, editorials, opinions; non-English language papers, case reports, and case series with less than 10 participants.

b) Population

The population comprised adults (defined as ≥ 18 years of age) with any eye condition. However, patients with eye conditions who had received prior surgery (vitrectomy) or other non-surgical treatments/ procedures (e.g. photodynamic therapy, corticosteroids, other anti-VEGF therapies, laser photocoagulation and radiation delivered to the eye) were excluded.

c) Interventions

The intervention was the administration of IVB (any dose) monotherapy as the primary treatment of an eye condition. The following were excluded: administration of bevacizumab other than via the intravitreal route (e.g. intracameral, subconjunctival, systemic, nasal etc.), IVB as a combination therapy and IVB used as an adjunctive treatment or peri-operative/pre-operative/post-operative treatment.

d) Relevant comparators

Comparators were limited to monotherapies for RCTs.

e) Outcomes

The outcomes of interest for the safety review divided into ocular (eye) and systemic adverse effects as presented in Figure 12. Data on safety was limited to important and serious adverse events. A serious adverse event is defined by the Food and Drugs Agency (http://www.fda.gov/safety/medwatch/howtoreport/ucm053087.htm) as 'any undesirable experience associated with the use of a medical product in a patient' with an outcome results in death, hospitalisation (initial or prolonged), congenital birth defects, disability or permanent damage, life-threatening medical events that require medical or surgical intervention to prevent impairment or damage. Studies that evaluated but reported that no adverse events (specified and unspecified as per review) were observed were considered eligible for inclusion. Estimates of the incidence of adverse events were calculated by dividing the number of events by the number of patients that received IVB (event rate per patient) or the number of eyes treated (event rate per treated eye).

Figure 12: Safety review outcomes

Systemic adverse events	Ocular adverse events
• Death • Hospitalisation • Non ocular haemorrhage (gastrointestinal, pulmonary, other non-ocular bleeds) • Arterial thromboembolism • Hypertension • Myocardial infarction • Cerebrovascular accident (stroke) • Transient ischaemic attack	• Infectious endophthalmitis (infection of the eye) • Retinal detachment • Retinal (pigment epithelium) tear • Anterior chamber reaction (includes acute intraocular inflammation; uveitis (inflammation of the anterior chamber) and hypopyon) • Ocular haemorrhage • Lens damage/injury (including cataract, clouding of the lens) • Ocular hypertension (raised intraocular pressure >21 mmHg) • Visual loss

5.1.3 Data abstraction and quality assessment

Data abstraction was performed by one reviewer into a standardised data extraction form. Any uncertainties or queries were resolved by discussion with a second reviewer and if agreement could not be reached, a third reviewer was consulted. Where multiple publications of the same study were identified, data were extracted and reported as a single study. Moreover, all relevant studies from the van der Reis *et al*.[39] review were examined and data extracted.

The following information was extracted for all studies when reported: study characteristics (e.g. author, year of publication, follow-up, funding), participant details (e.g. number of patients, eye condition, mean age, and baseline comparability), intervention and comparator details (e.g. description including method of preparation, dose including frequency, number of injections) and outcomes.

The methodological quality of each included RCT study was assessed by one reviewer (no quality assessment was undertaken for observational studies). Any uncertainties or queries were resolved by discussion with a second reviewer and if agreement could not be reached, a third reviewer was consulted. The study quality characteristics were assessed according to a Cochrane Collaboration Risk of Bias Tool for RCTs (namely sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and 'other issues').[23] This was modified to include additional items to assess the quality of adverse effects data (namely follow-up time

sufficient to assess safety [to assess long-term harm such as fatal or non-fatal systemic complications, follow-up time less than 6 months were considered insufficient to assess these complications], definition of reported adverse event, definition of method used to collect adverse event data, transparency of patient flow and validity of safety data.)

5.1.4 Data analysis

Data were entered and where appropriate, meta-analysed to estimate a summary measure of effect on relevant outcomes using the Cochrane Review Manager software RevMan 5.1 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). The relative risk was calculated for dichotomous outcomes. The fixed effects model (Mantel-Haenszel method) was applied to obtain summary statistics of pooled trials of rare events as it has been shown to be the more appropriate and less biased approach compared to a random effects model (inverse variance method).[40]

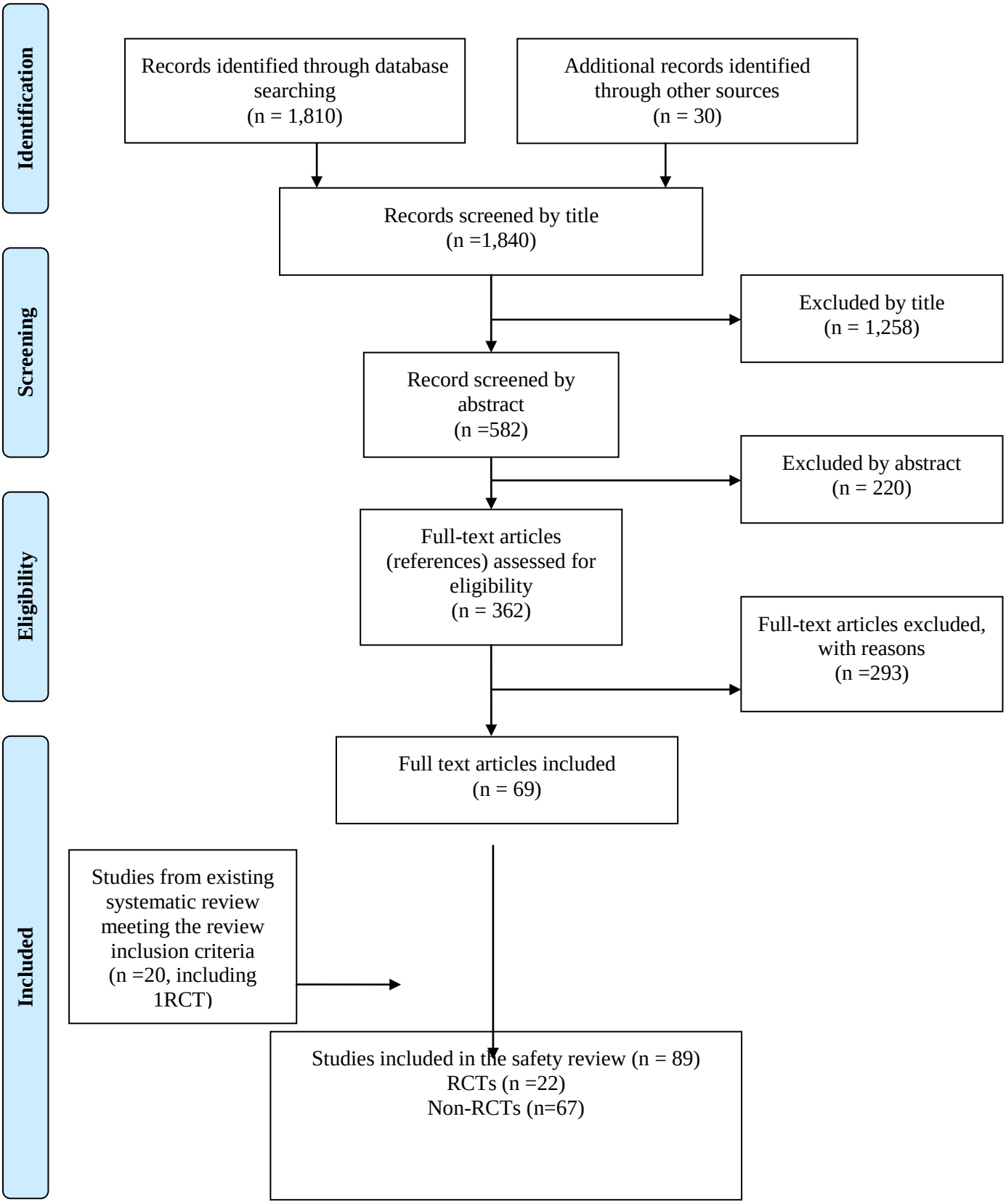
5.2 RESULTS

5.2.1 Quantity and quality of research available

5.2.1.1 Number of studies identified/included

The literature searches identified 1,831 citations. Of these, 69 full text articles met the inclusion criteria (n= 21 RCTs, n= 48 non-randomised studies) and were added to the 20 studies from the previous systematic review (n= 1 RCT, n= 19 non-randomised studies).[41] A flow chart describing the process of identifying relevant literature can be found in Figure 13.

Figure 13: Study flow chart (adapted): Safety review[36]



5.2.1.2 Number and type of studies excluded

A total of 284 full text articles were excluded as they did not meet all the pre-specified inclusion criteria. The majority of the articles were excluded primarily on the basis of inappropriate study design, unsuitable publication type (reviews, commentaries or editorials) or due to lack of usable data. A full list of excluded studies with reasons for exclusion is presented in Appendix 11.

5.2.1.3 Description of included studies

- **RCTs**

A total of 22 RCTs were included[25,26,42 27-29,31,34,43-56] evaluating the safety of bevacizumab compared with laser therapy (n=9), sham injection (n=5), IVT (n=5), IVR (n=4), pegaptanib (n=2) and observational control (n=1).

Seven studies included participants with AMD, eight studies with DMO, four studies with RVO, one study with patients with pathologic myopia, one study with vitreous haemorrhage secondary to Eale's disease, and one study included patients with neovascular glaucoma. For details on participants, intervention and outcomes see Appendix 8.

- **Observational studies**

Sixty-seven non-RCT studies were included in the safety review of IVB. Sample sizes ranged from 11 patients[57] to 27,962 patients.[58] Reported ages ranged from 33 years (median)[59] to 82 years (mean).[60,61] A majority of studies provided adverse events data for a single condition (e.g. age-related macular degeneration), while fewer studies evaluated clusters of patients with more than 3 eye conditions. A summary of study characteristics of observational studies is provided in Appendix 9.

Administration of 1.25 mg/0.05ml was the most commonly reported dosage of IVB. Other dosages were 1mg,[57,62-65] 1.5 mg[66,67] and 2.5mg.[68-72] Frequency of dosing and follow-up schedules varied across studies. The mean number of injections per patient or eye ranged from 1[59,63,73-77] to 7.[78] One study reported a total of 10,958 injection.[79] Information on the source of IVB preparation was reported in less than a fifth (19%; n=13/67) of included studies.[60,63,64,66,69,80-87] IVB injections were mainly provided by a local dispensing service such as the hospital's pharmacy. In one study study,[75] bevacizumab was provided by Alcaine; Alcon-Couvreur, Puurs, Belgium, a manufacturer of

ophthalmic surgical products[e]. Funding from a non-pharmaceutical institution (e.g. academic source) was declared in 18 reports.[71,88 58,69,89,90 62,65,91-100] However, one study[86] was partly funded by a pharmaceutical organisation.

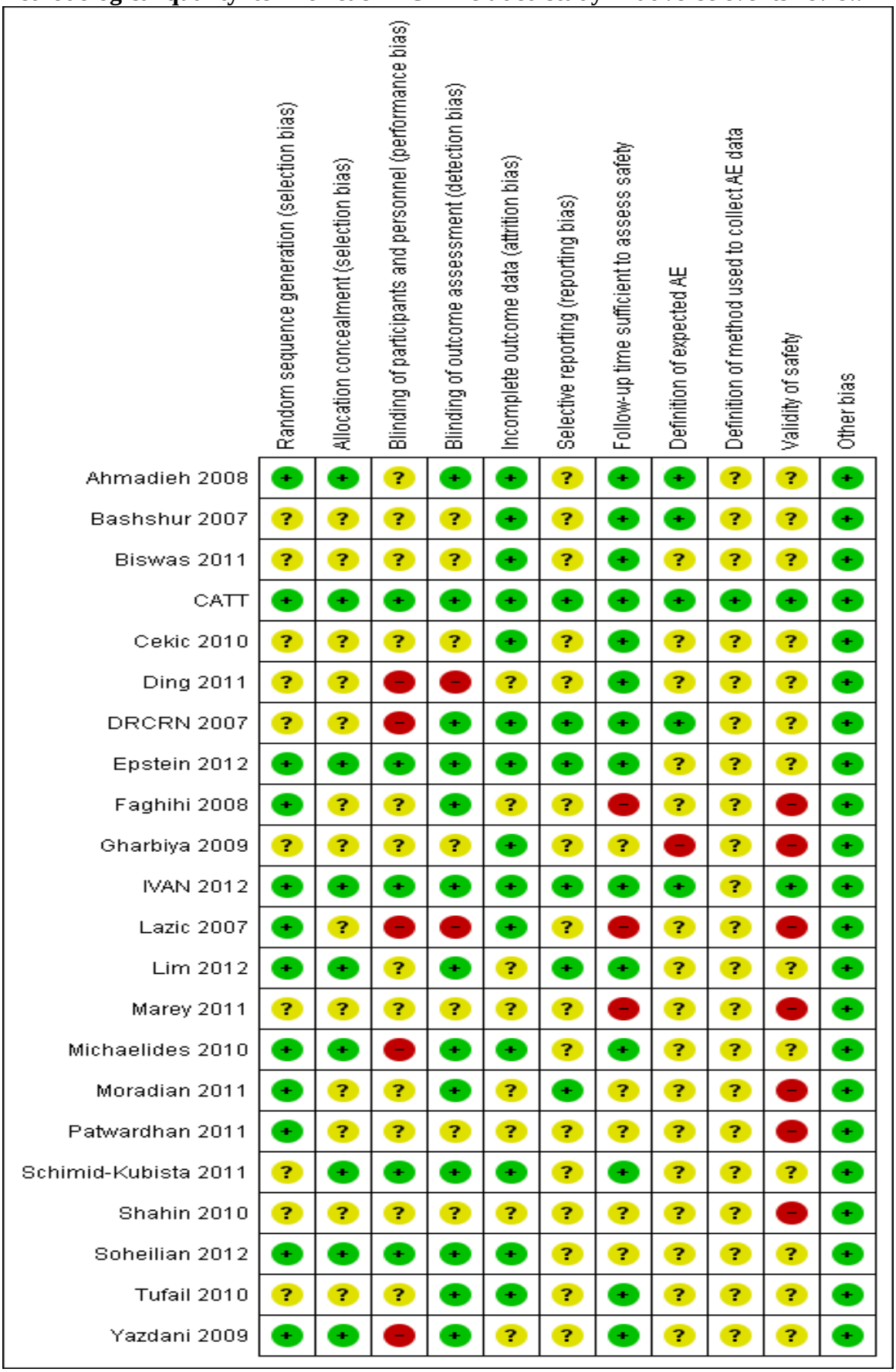
5.2.1.4 Quality characteristics

- **RCTs**

Twelve studies reported how randomisation was performed.[25,26,28,29,31,34,45,48-50,52,56] It is unclear if randomisation was adequately performed in the remaining 10 studies, although no imbalances were identified in baseline measures. Ten studies reported methods used to conceal allocation to treatment.[25,26,29,31,34,45,48,50,53,56] It is unclear if allocation concealment was performed in the remaining 12 studies. Blinding of participants and personnel was attempted by five studies.[29,31,45,48,53] Blinding of outcome assessors was reported in twelve studies.[25,26,28,29,31,34,45,48,50,53,55,56] Study attrition was reported in fourteen studies.[25-27,29,31,42-45,47-49,53,55] It was unclear in 17 studies if outcomes were selectively reported, five studies reported outcomes measures a priori. [27,31,45,48,50] The validity of the safety data was assessed according to sufficient length of follow up to detect adverse events, definitions of expected adverse events and methods used to collect data. Only two studies[45,48] met the criteria for valid safety data. A summary of the methodological quality of each included study is presented in Figure 14.

[e] http://www.alcon.com/en/alcon-locations/belgium.aspx

Figure 14: Methodological quality summary: Review authors judgments about each methodological quality item for each RCT included study in adverse events review



- **Observational studies**

A formal quality assessment was not undertaken for included observational studies. It was anticipated that a variety of study designs would be identified. While checklists exist for evaluating the methodological quality of a range of non-randomised studies, there is no agreement on how to incorporate a single tool to appraise different study types in a review.[101,102] For this review, criteria assessed included study design (e.g. prospective or retrospective), length of follow-up and baseline comparability when appropriate. Where data was available, information on the IVB administration and preparation was also considered.

Of the identified observational studies, approximately 65% (n=44/67) were retrospective in design. Baseline characteristics of study populations were comparable in 2 non-randomised studies[69,75] and 3 case-control studies.[74,78,103] Comparability at baseline was generally absent or not relevant in the remaining studies which were predominantly reports of case series. The length of follow-up periods was at least up to 6 months in 18 studies.

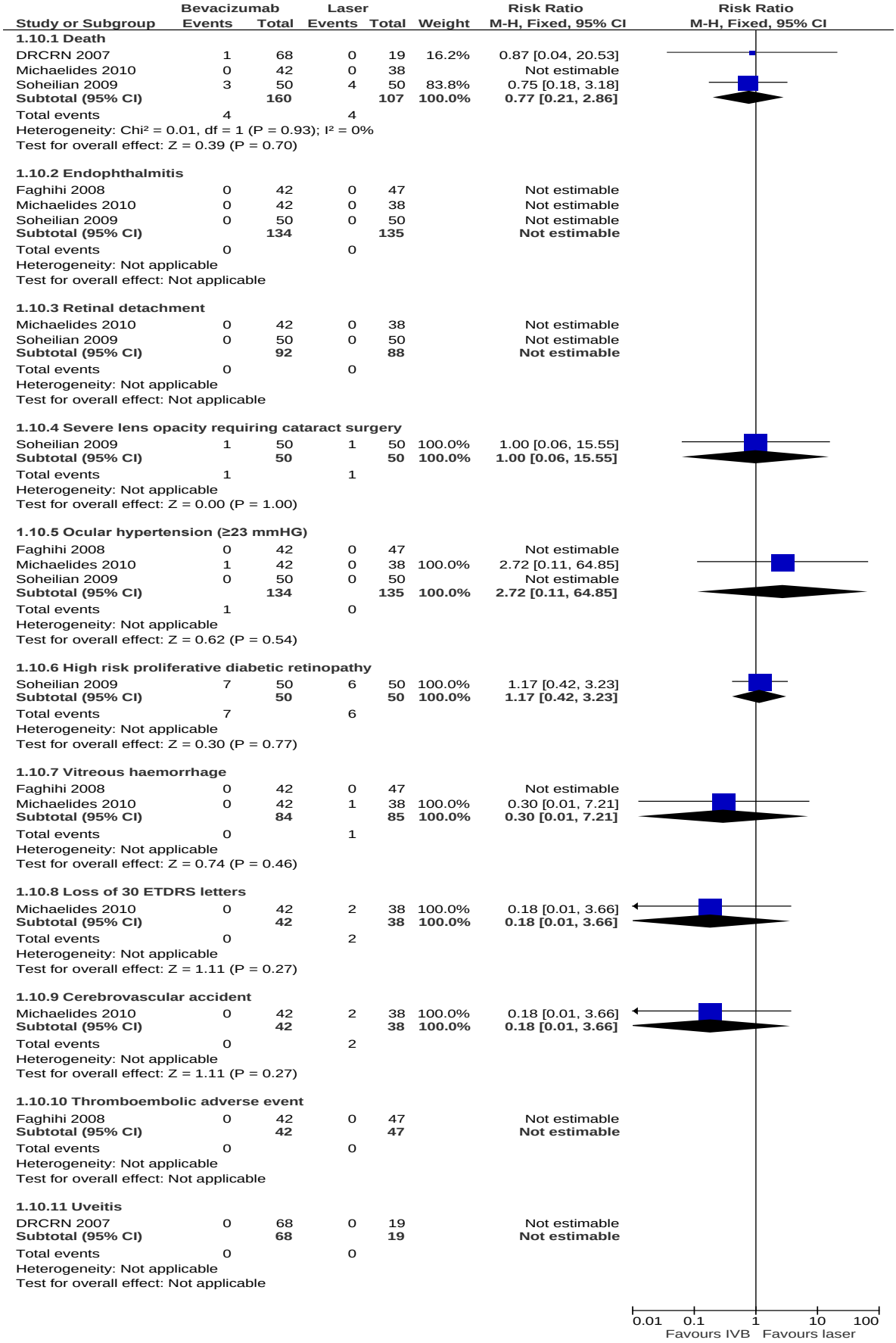
5.2.2 Assessment of adverse events

- **Randomised controlled trials**

i) IVB versus laser therapy for DMO

Reports of adverse events were low and were not significantly different between IVB and laser therapy. Other ocular and systemic safety measures had zero events in both treatment groups. (Figure 15).

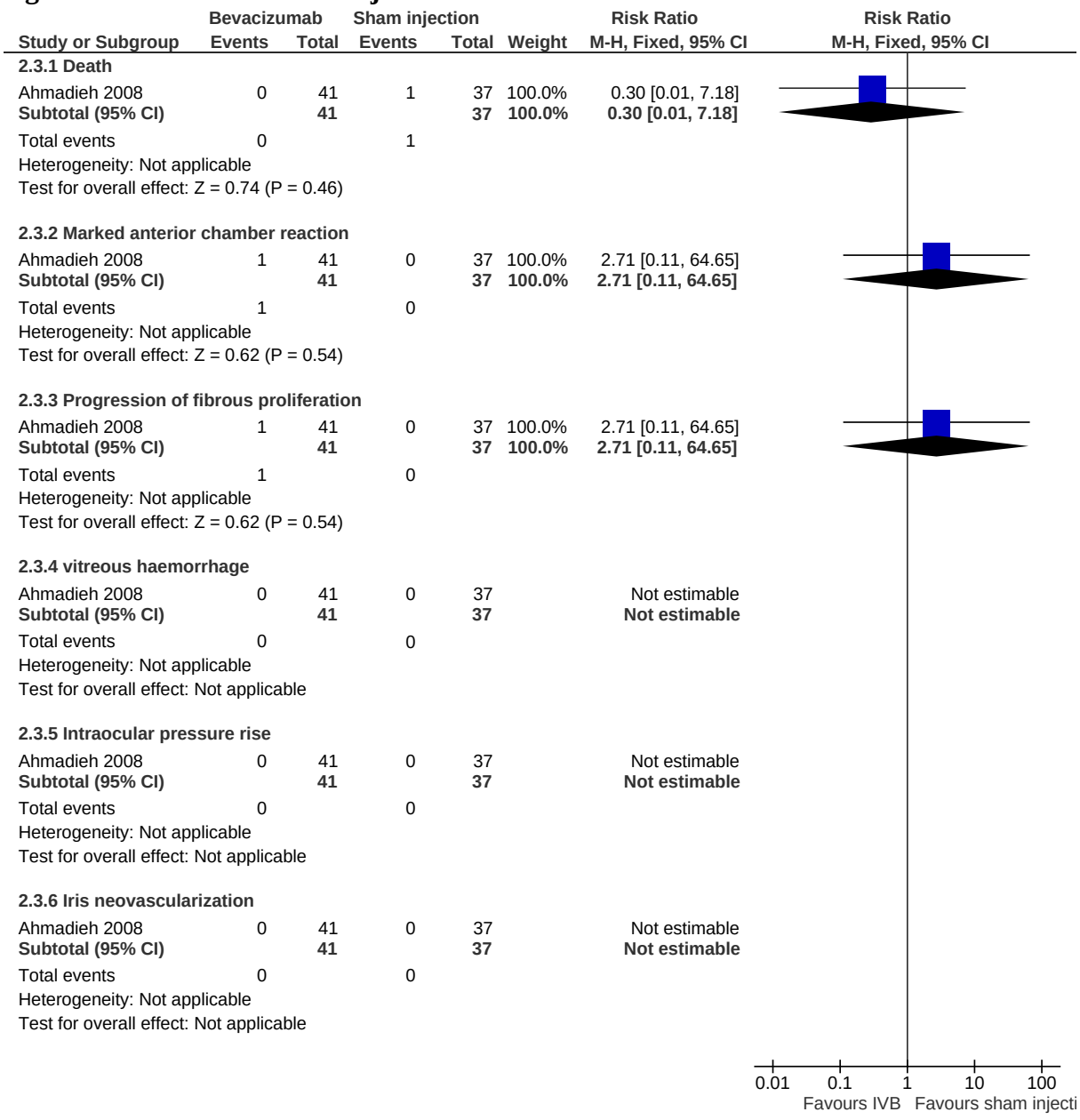
Figure 15: IVB versus laser for DMO



ii) IVB versus sham injection for DMO

Similarly, adverse events were low in the IVB and sham injection groups with no significant differences found between groups. Other ocular safety measures had zero events in both treatment groups (Figure 16).

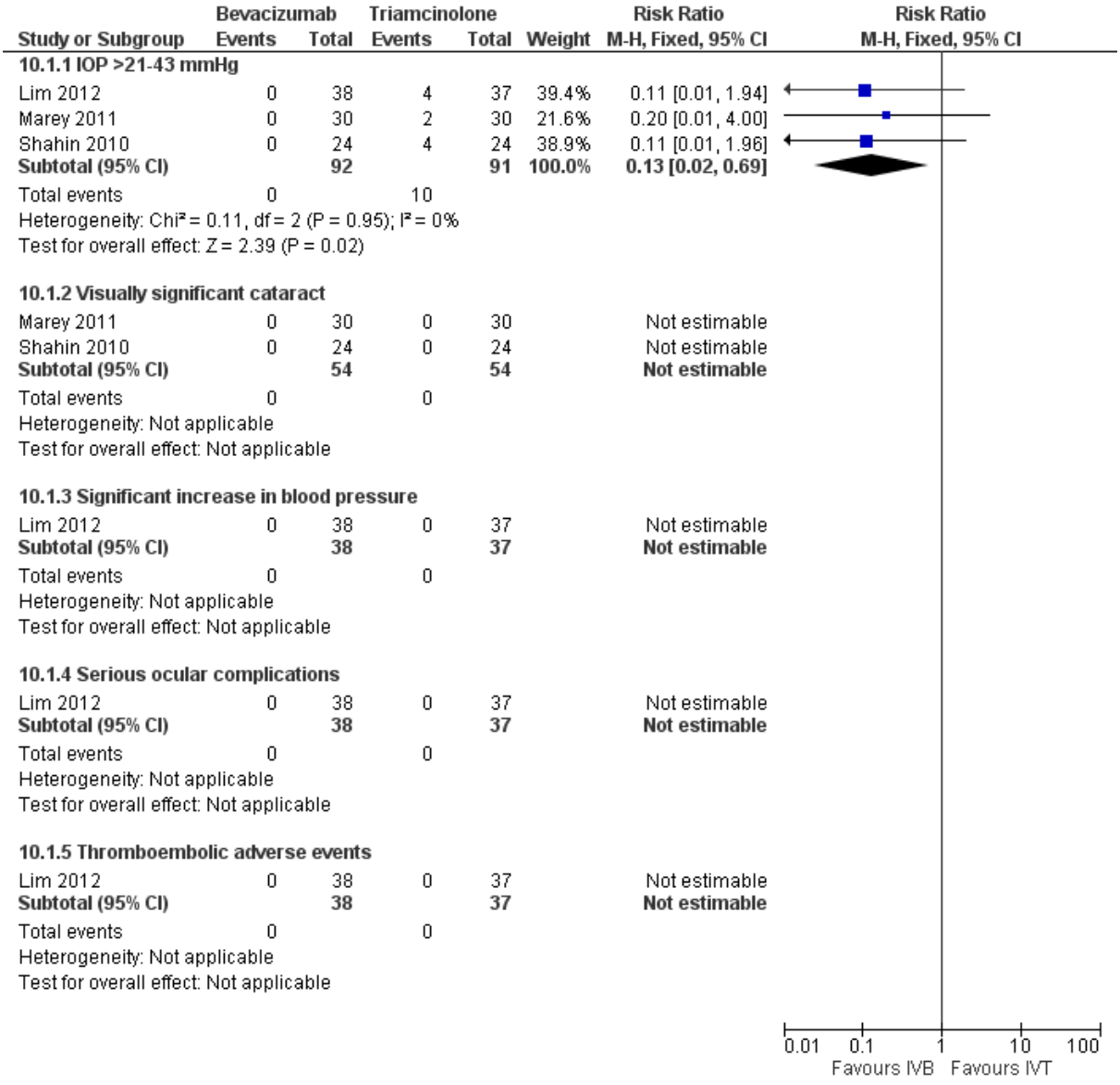
Figure 16: IVB versus sham injection for DMO



iii) IVB versus IVT in DMO

Rates of raised IOP>21mmHg were significantly higher in the IVT group (3 RCTs, n=183, RR 0.13 CI 0.02 to 0.69) compared with IVB. Other ocular and systemic safety measures had zero events in both treatment groups (Figure 17).

Figure 17: IVB versus IVT in DMO

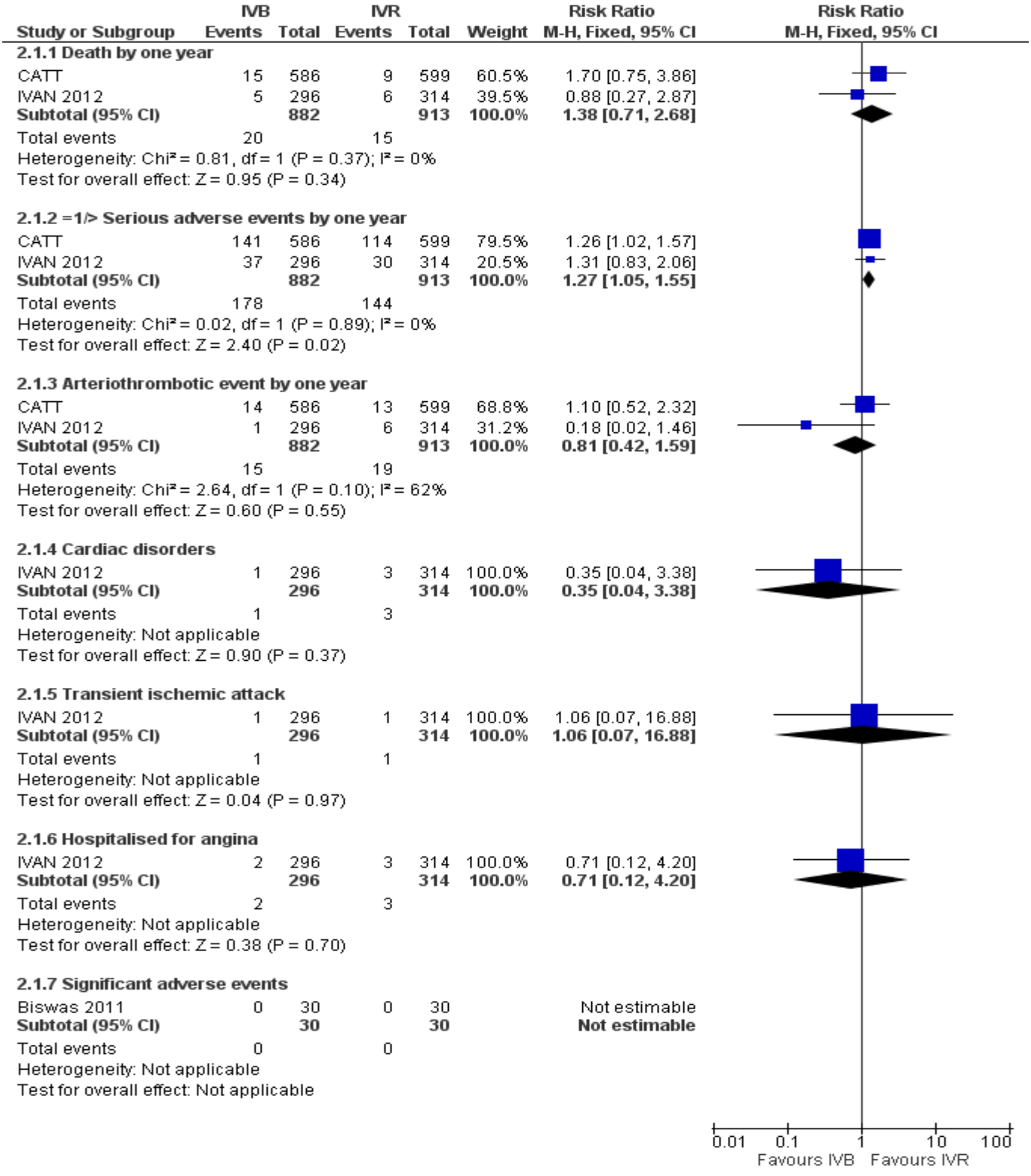


iv) IVB versus IVR for AMD (one year data)

Death at one year was not significantly different (2 RCT, n=1795 RR 1.38 CI 0.71 to 2.68) between IVB and IVR. Any serious systemic adverse event was significantly lower in the IVR group (2 RCT n=322, RR 1.27 CI 1.05 to 1.55) compared with IVB. Arteriothrombotic events were not significantly different between IVB and IVR (2 RCT, n=1795, RR 0.81 CI 0.42 to 1.59) at one year.

In the IVAN study, cardiac disorders, transient ischaemic attack, and hospitalisation for angina were not significantly different between IVB and IVR. One study by Biswas (2011)[44] reported no events for significant adverse events (Figure 18).

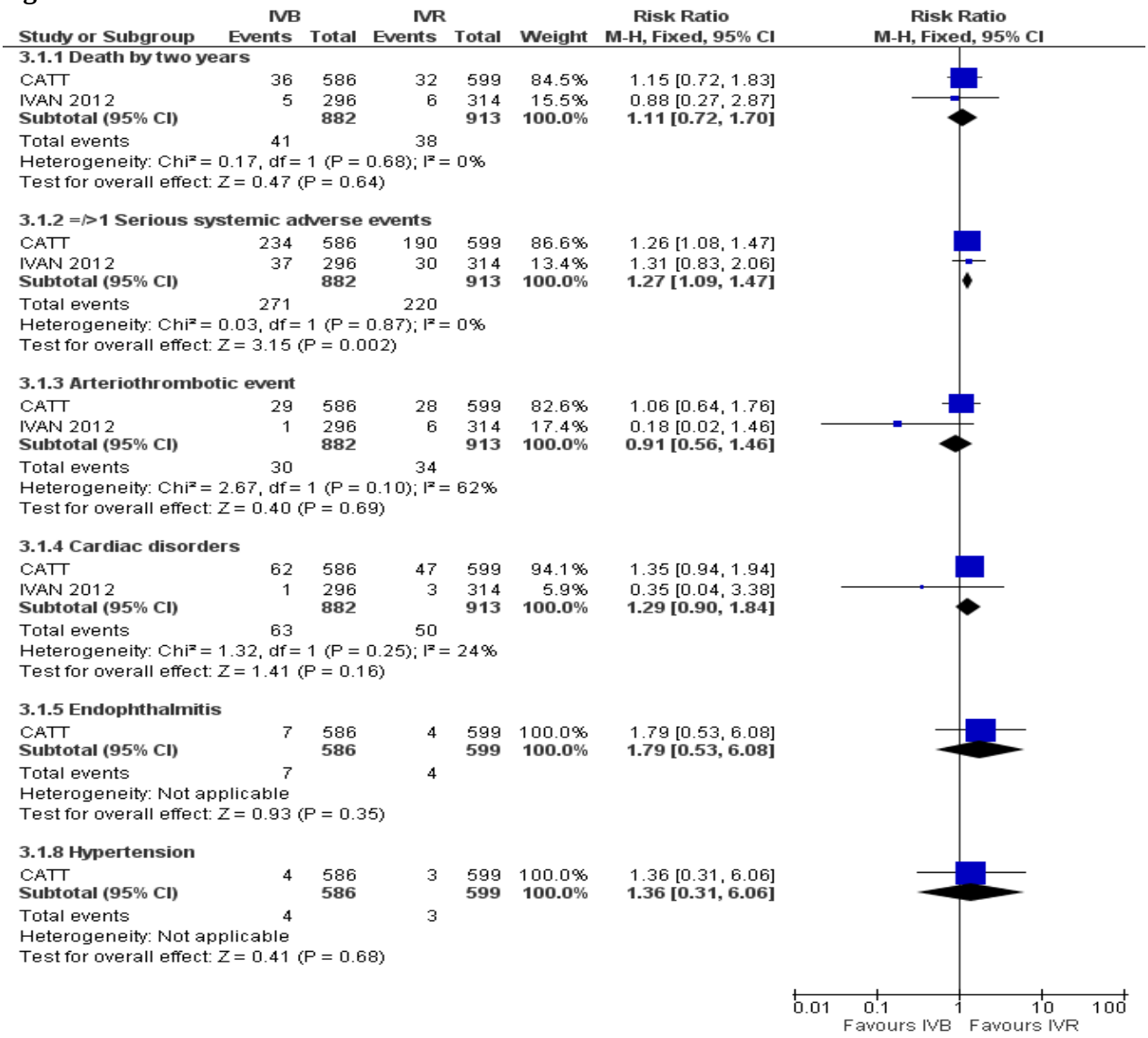
Figure 18: IVB versus IVR for AMD



iv) IVB versus IVR for AMD

The CATT[45] (2 year data) and IVAN[48] (1 year preliminary data) were pooled to provide long term data analyses. There was no significant difference in death between IVB and IVR. Any serious systemic adverse event remained significantly lower in the IVR group (n=1795, RR 1.27 CI 1.09 to 1.47) compared with IVB. Other adverse events including arteriothrombotic events, cardiac disorders endophthalmitis, and hypertension, were not significantly different between IVB and IVR treatment groups (Figure 19).

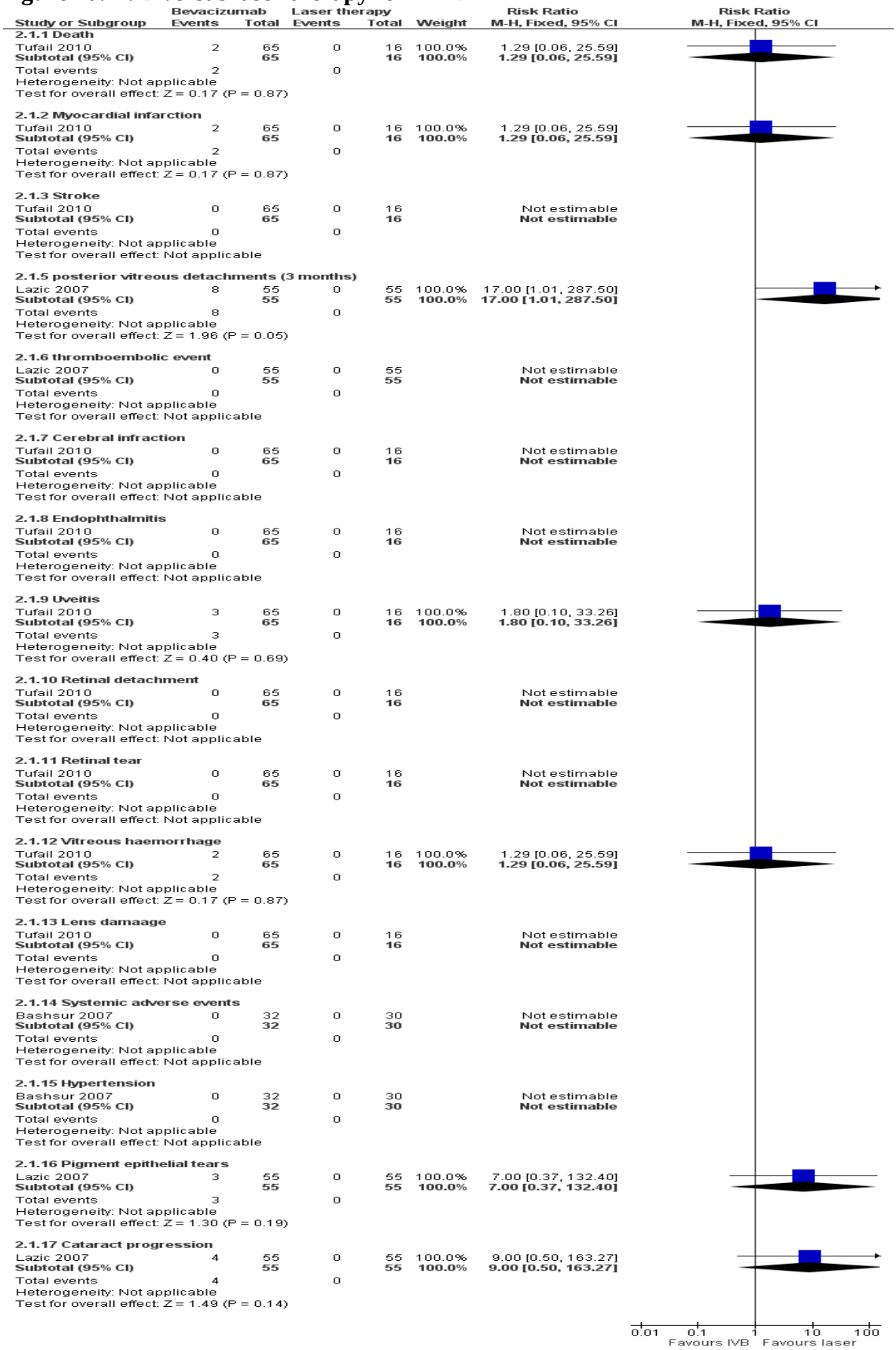
Figure 19: IVB versus IVR for AMD



v) IVB versus laser therapy for AMD

Three studies reported adverse event data for IVB and laser therapy in patients with AMD. One short term study at 3 months[49] found that posterior vitreous detachment was significantly higher in the IVB group compared with laser therapy, although confidence intervals are wide (n=110, RR 17.00 CI 1.01 to 287.50). Death, myocardial infarction, uveitis, vitreous haemorrhage, pigment epithelial tears and cataract progression were low and indicated no significant differences between IVB and IVR. Other ocular and systemic safety measures had zero events in both treatment groups (Figure 20).

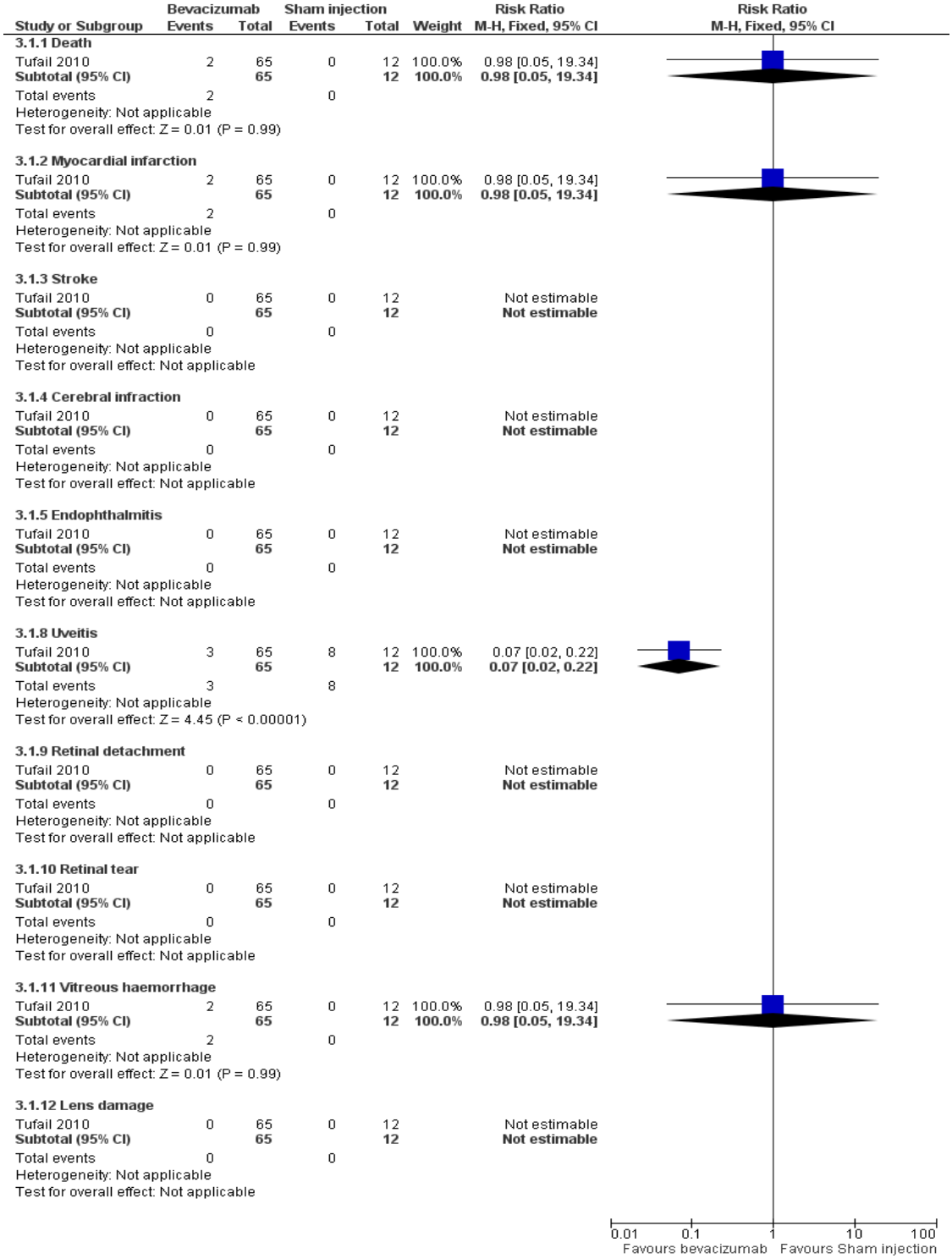
Figure 20: IVB versus laser therapy for AMD



vi) IVB versus sham injection for AMD

No significant differences were found for death, myocardial infarction or vitreous haemorrhage. Uveitis was significantly lower in the IVB group (1 RCT, n=77, RR 0.07 CI 0.02 to 0.22). Other ocular and systemic adverse events were unremarkable with no event rates in either treatment group. (Figure 21).

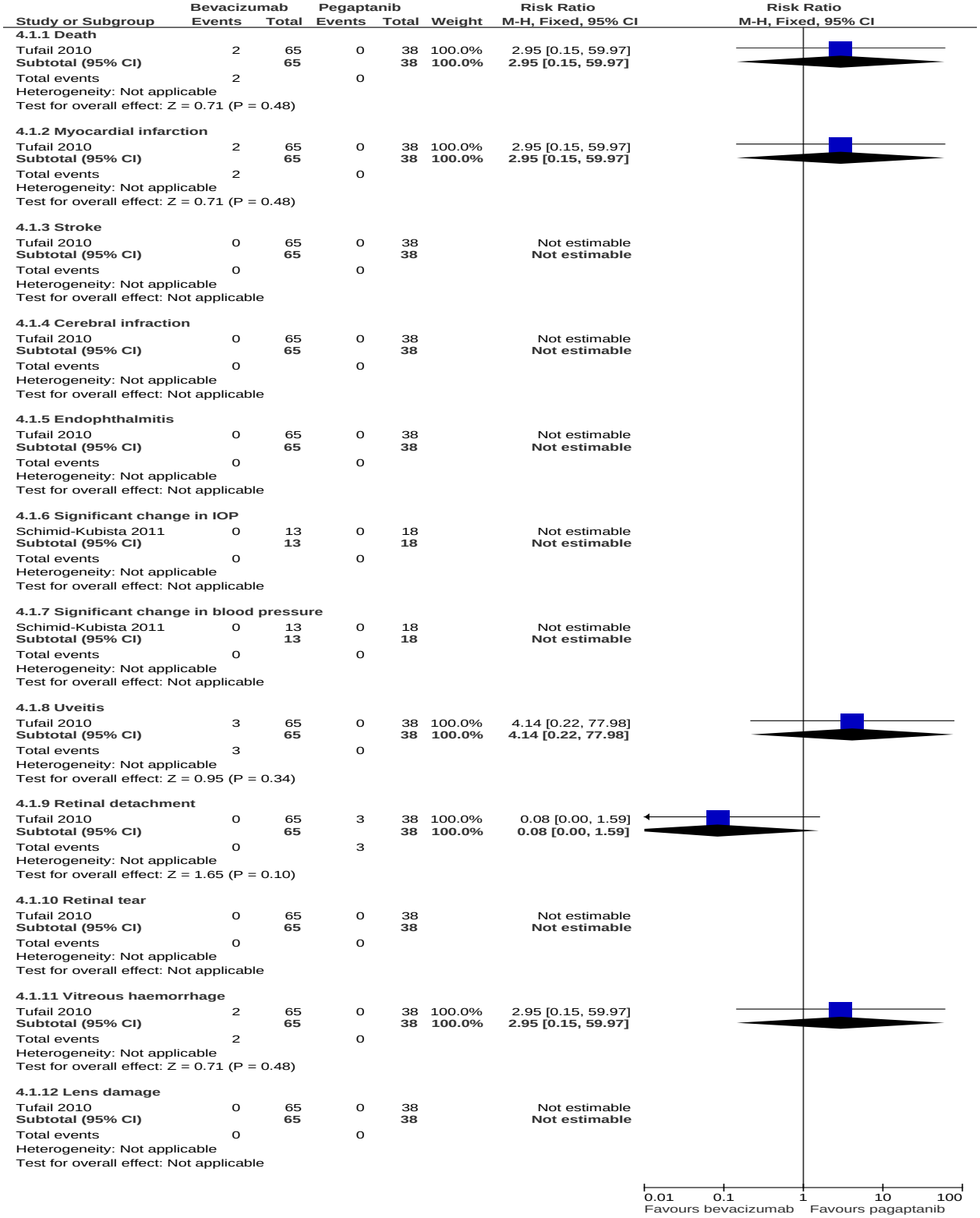
Figure 21: IVB versus sham injection for AMD



vii) IVB versus pegaptanib for AMD

No significant differences were found for death, myocardial infarction, uveitis, retinal detachment, or vitreous haemorrhage. Other ocular and systemic adverse events were unremarkable with no event rates in either treatment group (Figure 22).

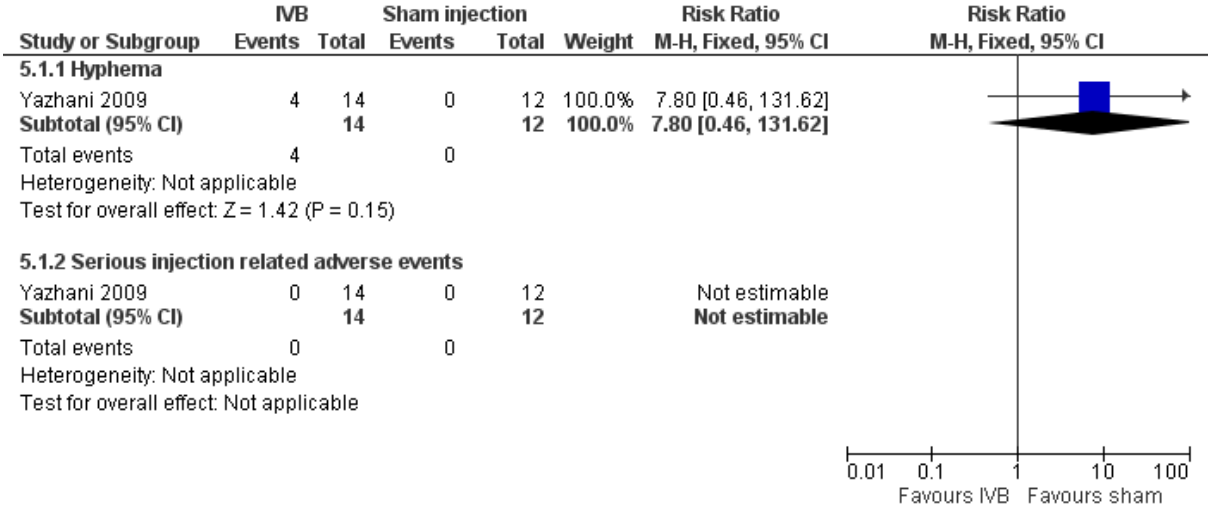
Figure 22: IVB versus pegaptanib for AMD



viii) IVB versus sham injection for neovascular glaucoma

No significant differences were found between IVB and sham injection for the outcome of hyphema. No serious injection related adverse events occurred (Figure 23).

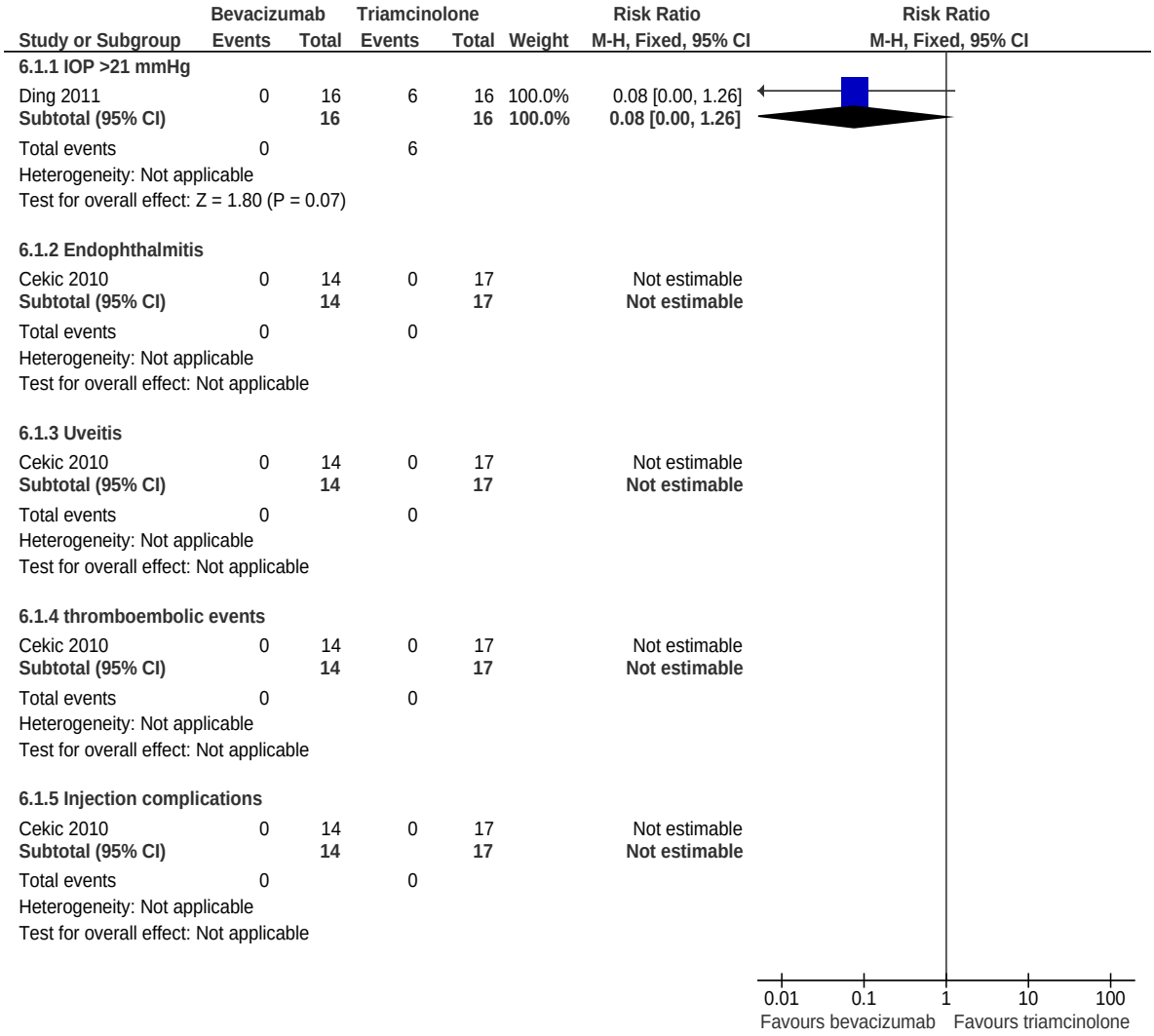
Figure 23: IVB versus sham injection for neovascular glaucoma



iv) IVB versus IVT for RVO

In a single study (n=32), rates of IOP>21mmHg were not significantly different between IVB and IVT although the data suggest a trend towards higher rates of raised IOP in the IVT group. Other ocular and systemic adverse events were unremarkable with no event rates in either treatment group (Figure 24).

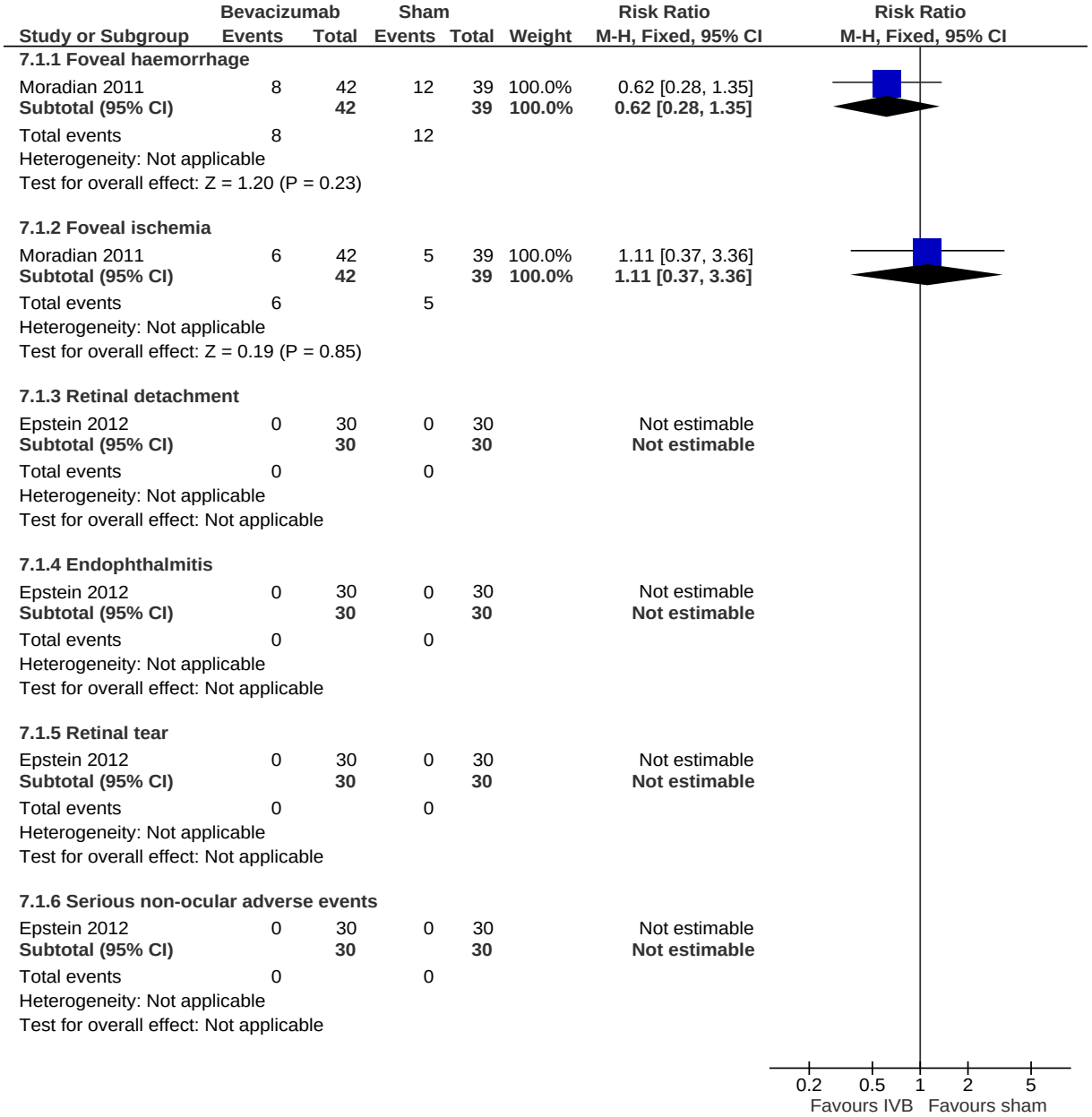
Figure 24: Adverse event IVB versus IVT for RVO



x) IVB versus sham injection for RVO

No significant differences in rates of foveal haemorrhage, or ischemia were found between IVB and sham injection. Other ocular and serious non-ocular adverse events were unremarkable with no event rates in either treatment group (Figure 25).

Figure 25: IVB versus sham injection for RVO



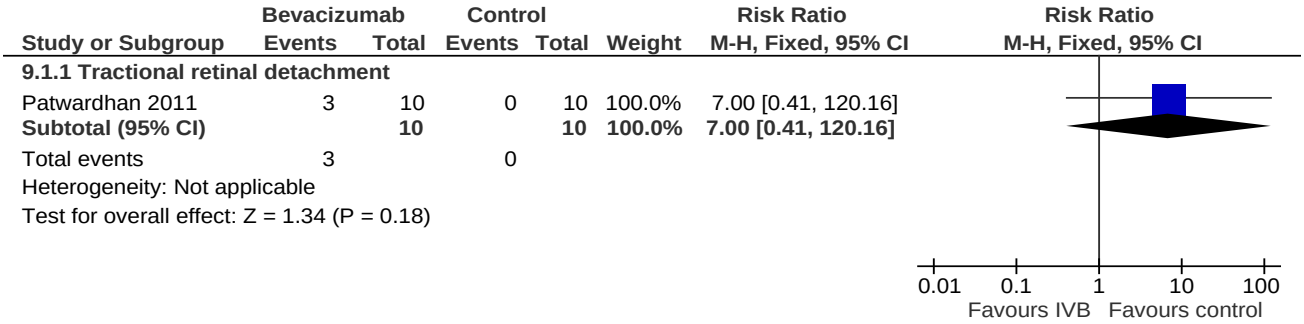
xi) IVB versus IVR in choroidal neovascularization in pathological myopia

A single study[47] (n=32) reported no incidences of systemic or ocular adverse events between IVB and IVR during 6 months follow up.

xii) IVB versus observational control in Eale's *disease*

In a single study (n=20) no significant differences were found in rates of tractional retinal detachment (Figure 26) between IVB and observational control group.

Figure 26: IVB versus observational control in Eales disease



5.2.2.1 Observational studies

A summary of adverse events is presented in Appendix 10. Available evidence suggests fewer systemic events compared to ocular adverse events. A number of studies did not provide detailed information on the type of adverse events assessed. Of the 67 included observational studies, 84% (n=56/67) of studies did not report or observe systemic adverse events following IVB treatment. Twenty-eight studies (41%) did not report or observe ocular adverse events of interest. Reported adverse events were generally low; however, in a few studies high incidence rates for hypertension,[77] anterior chamber inflammation,[104] retinal detachment,[59] ocular haemorrhage,[105,106] visual loss[107,108] and increased intraocular pressure (ocular hypertension)[109-111] were reported.

- **Systemic adverse events**

Systemic adverse events reported included death (0.43%-1.83%)[60,90,106,112] hospitalisation;[86] arterial thromboembolism (1.35%);[86] hypertension; (0.3% to 15%)[62,77,92,106] myocardial infarction (0.09% to 1.27%);[58,69,86,106] cerebrovascular accident (0.14% to 0.5%);[58,62,89,106,112] and transient ischaemic attack (0.45% to 1.03%).[86,90]

Evidence on systemic events was not conclusive. One large study involving an analysis of 146, 942 Medicare payees between 2005 and 2006 reported a significantly lower risk of all-cause mortality

and stroke in patients who received IVR compared to patients treated with IVB.[58] However, a secondary analysis limited to only newly-treated patients on IVR or IVB showed no significant difference between treatment groups. Patients included this study were those who had received first-line treatment for AMD. Data were censored at the time that a patient's treatment was switched from initially assigned intervention to another. Between July and December of the study year (2006), study population was limited to treatment-naïve patients who received bevacizumab or ranibizumab. With the exception of the presence of diabetes mellitus, baseline characteristics between IVR and IVB patients were similar (28% versus 25%, p<0.001). The authors concluded that '*the risks of mortality, myocardial infarction and stroke were not different between groups'*. However, as the sample size of patients for the secondary analysis (IVB: IVR) was smaller compared to the primary analysis, it is important to interpret the results with caution. However, Sharma[86] reported an increased risk of arterial thromboembolic events (odds ratio [IVB:IVR]=1.71;95%CI 0.44-41). In this study, arterial thromboembolic events included emergency room visits for patients with transient ischaemic attacks, myocardial infarction and pulmonary embolism.

- **Ocular adverse events**

At least 1 ocular event was reported in all included studies. The least commonly reported adverse events were related to lens damage (0.4%)[106] and retinal detachment (1.2%).[72] Visual loss was the most commonly reported ocular event.[69,73,74,108,111,113-115] However, the definition of visual loss was often unclear and occasionally associated with adverse events such as anterior chamber inflammation, severe intraocular inflammation or retinal detachment. As a result, the relationship between visual loss and IVB requires cautious interpretation. .

Infectious endophthalmitis was reported in 10 studies (range 0.02% to 0.9%). Three of the 13 studies[60,63,64,66,69,80-87] in which locally prepared IVB was administered mentioned reports of infectious endophthalmitis. Reported rates were 0.02% (n=3/12,585 injections),[83] 0.16% (n=1/625),[66]and 0.8% (n=1/112).[80] A rate of 0.9% (n=1/109) was reported in a study with IVB supplied by a compounding pharmacy.[60] Positive cultures of micro-organisms were reported in two studies.[60,106]

5.3 DISCUSSION

5.3.1 Randomised controlled trials

Overall, adverse event rates were low in all bevacizumab and comparators groups, and most outcomes were not significantly different. Raised intraocular pressure (>21mmHg) was significantly higher in the triamcinolone group compared with bevacizumab. Uveitis in one study was significantly higher in the bevacizumab group compared with those receiving sham injection but other studies recording uveitis did not support this finding. Tufail *et al*.[55] reported that there was no increased risk of adverse events in patients treated with IVR or IVB compared with those receiving sham treatment. However, a higher risk of adverse events was reported in head-to-head comparisons of IVR and IVB by investigators of the Comparison of Age-related Macular Degeneration Treatments Trials.[45,116] However, there are concerns that adverse events assessed were not those that are usually related to the action of anti-VEGF therapy.[117] It is also important to note that IVB patients in this study receiving more treatments had a better safety profile compared to participants with fewer injections.

Serious systemic adverse events ≥1, from the IVAN[48] and CATT[45] studies (1-year data and 1 & 2-year data combined) indicated significantly higher rates in the bevacizumab treatment group, although the IVAN result was not significant, but when added into the meta-analysis with the CATT study, the overall finding was significant. Authors of CATT also examined the baseline characteristics and adjusted for any small group differences but this did not change the outcome. Further analyses were undertaken by authors of IVAN on the difference between different regimens (continuous/discontinuous) for death, arteriothrombotic events and any serious systemic adverse event using pooled estimates of IVAN and CATT data, but no significant differences were found. Event rates were proportionally higher in the CATT study which may have been due to differences in definitions used to report serious adverse events. The CATT study defined serious adverse events as arteriothrombotic events, systemic haemorrhage, congestive heart failure, venous thrombotic events, hypertension, and vascular death. The IVAN study defined serious systemic adverse events as including any non-ocular serious adverse event. Also, The CATT study included slightly older participants and reported data at two years follow up, whereas the IVAN study reported preliminary data at one year. It is possible that the CATT and IVAN study did not have had sufficient statistical power to detect differences in adverse events.[58] However, future studies and the anticipated two year follow-up data from the IVAN study will help to clarify if there is a real difference in systemic adverse event rates, or whether this is a chance statistical finding.

Many of the studies reported zero event rates for the safety outcomes. It is common practice to exclude all zero-total-event trials from meta-analyses because they provide no information about the magnitude of the odds or risk ratios and do not contribute to producing a combined treatment effect greater or less than nil.[40,118,119] However, these trials may provide relevant information by showing that event rates for both the intervention and control groups are low and relatively equal.[120-122] Including such trials can sometimes decrease the effect size estimate and narrow confidence intervals. Diamond *et al*.[123] suggest that excluding trials with zero events in the index meta-analysis probably exaggerated risk estimates and that including these trials by applying continuity adjustments in this instance temper the exaggerated estimates. Moreover, seven studies reported outcomes at less than 6 month which limits the chance to detect adverse events, especially systemic adverse effects. Only two studies[45,48] were adequately conducted to meet the quality assessment criteria.

5.3.2 Observational studies

The review of observational data showed that ocular adverse events were more common than systemic events. The reporting of safety, generally, could not be linked with source of funding as reported in the review conducted by Schmucker.[124] Reported ocular rates were also comparatively higher than incidence rates for systemic adverse events. Rates differed from those reported in the van der Reis[125] review which included case reports and calculated cumulative incidence rates across different study types. This can be explained further by the differences in review methods (e.g. eligibility, grouping of adverse events and synthesis of results).

A number of population-based studies have been conducted to assess the safety of IVB with inconsistent findings. While a number of included studies did not report or observe serious adverse events, reported incidence rates were high in a few studies. These rates were commonly associated with anterior chamber reaction[86,104,112] raised intraocular pressure[109] and ocular haemorrhage.[81,105] Despite the incidence of increased IVB-related adverse events in these studies, there are concerns associated with small sample sizes and potential confounding.

Data from a few larger studies provided information on how likely confounding factors were handled in the assessment of adverse events. For example, Curtis *et al*[58] undertook a primary analysis of their results and reported an increased risk of stroke in individuals treated with IVB compared to those receiving IVR. However, a further analysis, adjusting for the potential confounding of

socioeconomic status resulted in no difference in adverse event risk between the two treatment groups. On the other hand, results of an unpublished study of Medicare patients[112] found an increased risk of stroke and death in IVB patients. The available abstract, however, did not provide sufficient information to an in-depth analysis of the results of this study.

A recently published population-based, nested case-control study reported by Campbell *et al.*[117] (n=91,378) compared adverse events due to IVR and IVB. The authors reported that there was no relationship between the risk of systemic events such as myocardial infarction, venous thromboembolism, stroke or congestive heart failure and the administration of IVR or IVB. While, the risk of systemic adverse events was similar for the two treatment groups, there was an increased risk of acute myocardial infarction for a subgroup of diabetic patients that received IVB. For patients who were exclusive users of IVB or IVR, reported adjusted odds ratios (IVB versus IVR) were 1.23 (0.85 to 1.77) for acute myocardial infarction, 1.03 (0.67 to 1.60) for ischaemic stroke, 0.92 (0.51 to 1.69) for venous thromboembolism and 1.35 (0.93 to 1.95) for congestive heart failure. It must be noted that this finding was based on a single analysis of one outcome in a specific subgroup of the study population. Furthermore, exclusive users of IVB or IVR referred to patients who received treatment in a practice that administered a minimum of 20 injections, of which 95% or more were single drug treatments.

5.3.2.1 Relationship between adverse events and IVB preparation

The relationship between IVB preparation and infectious endophthalmitis could not be established in this review. This was due to the varied quality and extent of reporting in the included papers which limited detailed analyses of the link between IVB preparation and rates of infectious endophthalmitis. Information on IVB preparation was reported in only 19% of included studies. A single study[106] reported that seven cases of bacterial endophthalmitis were associated with positive cultures of coagulase negative staphylococci, *Staphylococcus aureus* and *Streptococcus pneumoniae*. Of these, 6 patients had received IVB injections stored in single-use syringes. No further information was provided on length or temperature of storage conditions. However, the study authors reported that bevacizumab was refrigerated in two ways; preparations were stored as a single vial of 100ml/4mg to be re-utilised as needed or as '*aliquoted*' sterile single-use syringes. It was not certain whether IVB injections were prepared locally or by a compounding pharmacy. However in another study, Fong 2008[60] (n=109), one case of *Staphylococcus epidermidis* endopthalmitis was reported following the third IVB injection in a treated patient. In this study, a compounding pharmacy supplied 1.25mg/0.05ml of bevacizumab prepared under aseptic conditions in 1.0ml single-use

syringes. The lack of additional information made it difficult to assess factors that could have resulted in endopthalmitis in this patient.

According to the Royal College of Ophthalmologists: Information from the Professional Standards Committee,[126] 'most cases of postoperative endophthalmitis are caused by patients' own bacterial flora. Standard procedures should therefore aim to limit the risk from this source e.g. by isolating the lid margins with a non-permeable drape, and by using preoperative 5% povidone iodine in the conjunctival sac. Alternatively, the source of infection may be exogenous: for example cases may result from contaminated instruments, intraocular solutions or implants either due to manufacturing problems, faulty sterilization, poor operating technique or theatre environment. Such cases may include fungal endophthalmitis.'

Presently, case reports related to contaminated batches of IVB have been the primary source for data on the link between adverse events and intravitreal preparations. A published review of patient safety information held by the National Patient Safety Agency in England and Wales[127] reported an increased risk of serious adverse events including endophthalmitis following IVB treatment. The authors acknowledged that identifying the source of infection (that is contaminated injection procedure or infected anti-VEGF) could be complex. On the contrary, Jonas[67] reporting on adverse events rates in a study population which included patients who had received IVB and IVT, indicated that event rates were statistically independent of drug injected (P=0.45); operating surgeon (P=0.18) and patient's age (P=0.87).

5.3.3 Limitations of evidence

Considering RCTs, many of the studies randomised small numbers of participants and these may have been underpowered to detect differences in adverse events.[124,128] Generalisability of findings may also be limited due to differences between study participants and patients seen in routine practice. Furthermore, there are concerns related to ascertainment of exposure particularly in observational studies.[117] Current evidence from observational data appears to be limited with respect to definition, evaluation and reporting of safety outcomes as well as length of follow-up. The quality of reporting of studies made it impossible to evaluate the impact of both known and unknown confounding factors (e.g. the use of prophylactic anti-biotic eye drops) on the incidence of adverse events. Consequently, it is uncertain whether the high incidence of events such as visual loss occurred as a result of treatment or progression of the patient's condition. In general, there seems to be insufficient data to explore the relationship between the incidence of adverse events and other

variables such as injection techniques, pre-existing risk factors (e.g. immunosuppression, cross-contamination) and quality of IVB.

It is also important to highlight limitations related to undertaking the review. The influence of excluding non-English publications in this review is unclear. Additionally, adopting a narrow focus in the definition of adverse events implies that data on less serious or rare events were not presented in this review.

5.4 CONCLUSIONS

Overall, the review demonstrated that rates of adverse events following IVB were low when compared to other intravitreal treatments, sham injection and laser therapy. Most outcomes were not significantly different between groups. Higher risks of adverse events have been reported in head-to-head studies of IVB versus ranibizumab.[45,116] However, this trend tends to disappear when possible confounders such as socio-economic status (related to cost and access to treatment) are controlled in the analysis of study results.[58] The most robust data set for safety are from the IVAN[48] and CATT[45] trials which were large trials that reported longer term data. Serious systemic adverse events were significantly higher in the bevacizumab group.

The available evidence related to IVB-related adverse events from observational data was limited as have been reported elsewhere.[124,129] Included studies are often associated with methodological weaknesses that limited the validity of the reported findings. In this review, the relationship between locally produced IVB preparations and infectious endophthalmitis could not be established. In general, the likelihood of confounding is a threat to the validity of findings.[130]

6 CONCLUSIONS AND IMPLICATIONS FOR DECISION-MAKING

NICE requested the DSU to consider four questions of potential relevance to the consideration of IVB as a comparator in appraisals of licensed therapies for DMO and RVO.

1) What evidence is there relating to the pharmaceutical quality of reformulated bevacizumab as used in eye conditions in general? (section 2)
2) How widespread is Intravitreal Bevacizumab (IVB) use in the UK? (section 3)
3) What is the evidence for efficacy of IVB in adults with RVO and DMO specifically? (section 4).

4) What evidence is there regarding adverse events for IVB in eye conditions in general? (section 5).

This report provides evidence on each of those questions in turn.

6.1 THE MANUFACTURING PROCESS

Licensed bevacizumab is supplied for intravenous use in cancer patients. For intravitreal injection, much smaller quantities are required. Reformulating bevacizumab for use in the eye is considered by the MHRA to result in an unlicensed product. As such, manufacturers must hold a "specials" license from the MHRA which requires the adherence to a range of conditions and associated inspections. Both of the major manufacturers in the UK, Liverpool and Moorfields hold such licenses. There have been cluster outbreaks of infection reported internationally, including a suspected case involving Moorfields. However, some argue that the risks of infection are greater when local pharmacists perform this compounding and this should therefore be avoided. According to our survey of consultant ophthalmologists, a small but significant proportion of supplies are currently produced by local pharmacies.

6.2 EXTENT OF USE IN THE NHS

We found evidence from publicly available documents that only a small number of commissioners are actively promoting the use of IVB over other licensed alternatives in patients with AMD. IVB is more typically reported as a treatment option in those situations where it is referred to at all in this patient group. Greater variation is evident in other eye conditions.

Sales figures from the two main suppliers indicate that they together supplied nearly [redacted] of IVB in 2011. It is difficult to estimate the proportion of all eligible patient populations that this represents but is clearly a non-trivial quantity.

A survey of consultant ophthalmologist members of the RCO reinforced the view that, following NICE guidance in favour of the use of ranibizumab in patients with AMD, few clinicians use IVB in this patient group. In other conditions where no such guidance exists, such as DMO and RVO, there is significant use of IVB. IVB use is more widespread in private practice, mirroring the findings of international studies in settings where patient copayments are commonplace.

The NICE 2008 Method Guide states that comparators should include "routine and best practice in the NHS" (Section 2.2.4). Further relevant guidance is given in the following two paragraphs:

"There will often be more than one relevant comparator technology because routine practice may vary across the NHS and because best alternative care may differ from routine NHS practice. For example, this may occur when new technologies are used inconsistently across the NHS."

And

"Relevant comparator technologies may also include those that do not have a marketing authorisation (or CE mark for medical devices) for the indication defined in the scope but that are used routinely for the indication in the NHS."

It would seem that based on the evidence we have identified, the use of unlicensed IVB is variable across the NHS as a whole. However, IVB is widely used by a substantial number of clinicians and hospitals in the NHS for DMO, RVO and eye conditions other than AMD. AMD use has diminished as a result of NICE guidance in favour of a licensed alternative.

6.3 EVIDENCE OF EFFICACY IN DMO AND RVO

Seven RCTs were included in the review of efficacy in DMO patients. One study compared IVB with sham injection. Six studies compared IVB to laser photocoagulation. Compared to sham injection the results favour IVB in terms of change in visual acuity and change in central macular thickness. Meta analysis of studies comparing IVB to laser therapy provide broadly favourable results for IVB but some outcomes are only superior at longer term follow up of one year. For example, results favour IVB for deterioration or any deterioration (BCVA ETDRS 15-letter -3 lines) from 26 to 54 weeks (2 RCTs, n=180, RR 0.17 CI 0.05 to 0.56). The effect of IVB on BCVA LogMAR scores was significantly different compared with laser therapy at 6 weeks although data were heterogeneous, whilst 12 and 24 week data were equivocal. Longer term follow up data at 48 weeks significantly favoured laser therapy, though this was based on one small study (n=65). No significant differences for mean scores in central macular thickness were detected beyond 4-6 weeks.

Data were limited for RVO. We included five trials comparing IVB with sham injection but three were available only in abstract form and only two provided data on the differences between the two treatment options. Analysis is also hampered by the relatively short follow up in these studies (the maximum was 24 weeks) and the different types of RVO patients (central and branch). In one trial of patients with BRVO where interventions were administered twice, 6 weeks apart, the two groups were statistically different at 6 weeks (p=0.05), however by 12 weeks the difference was no longer

significant (p=0.064). In another trial of patients with CRVO,23 where interventions were administered four times, 6 weeks apart, there was a significant difference between groups in weeks 12, 18 and 24 (p<0.01), but not at week 6.

6.4 REVIEW OF EVIDENCE OF ADVERSE EVENTS

89 studies were included in a systematic review of adverse events, 22 of which were RCTs. Trials compared IVB with a number of different therapies and eye conditions, though most were in AMD, DMO and RVO. In these studies, adverse event rates were low overall in all bevacizumab and comparators groups, and most outcomes were not significantly different. Of particular note is the fact that in head to head comparisons of IVR and IVB (CATT and IVAN trials), when results are meta-analysed, there is a statistically significantly higher rate of 1 or more serious systematic adverse event (RR 1.27, 95% CI 1.09 to 1.47) in the IVB group. Some potential caveats to this finding are relevant. The IVAN study alone did not show a statistically significant difference. Event rates were higher in the CATT study overall which may be due to different definitions of serious adverse events. It is also important to note that these SAEs were more common in those patients randomized to receive discontinuous rather than continuous treatment, that is, those with lower exposure to the drug experienced higher adverse event rates. Also in the CATT study there were some imbalances between randomised patients that may be relevant. More patients randomized to IVB had had a previous transient ischaemic attack (TIA) compared to those in the IVR arms (44 vs 24). Similarly, more IVB patients had a history of myocardial infarction (MI) – 76 vs 64.[116] These patients may be more likely to be on therapies such as anticoagulants that may contribute to the observed higher incidence of GI haemorrhage.

Despite these caveats we consider these trial designs to offer the most robust assessment of adverse events. Further investigation and follow up from these and other trials will be of value.

Overall, the evidence on safety of IVB from observational studies was inconclusive. The majority of studies were retrospective in design with small study samples or inadequate follow-up periods (less than 6 months). With respect to larger studies, observational data from Curtis et al[58] suggest no difference in the risk of adverse events between IVB and IVR once socioeconomic confounders are accounted for. On the other hand, results of an unpublished study of Medicare patients funded by Genentech[112] found an increased risk of stroke and death in IVB patients. The available abstract, however, did not provide sufficient information to an in-depth analysis of the results of this study. A

recently published population-based, nested case-control study reported by Campbell et al.[117] (n=91,378) compared adverse events due to IVR and IVB. The authors reported that there was no relationship between the risk of systemic events such as myocardial infarction, venous thromboembolism, stroke or congestive heart failure and the administration of IVR or IVB. While, the risk of systemic adverse events was similar for the two treatment groups, there was an increased risk of acute myocardial infarction for a subgroup of diabetic patients that received IVB.

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8 APPENDICES

APPENDIX 1: SEARCH RESULTS OF NHS AND PCT WEB-PAGES

Table A 1: Search results of Primary Care Trust and NHS site searches in England
Source: http://www.nhs.uk/ServiceDirectories/Pages/PrimaryCareTrustListing.aspx

PCT		Results?*
1.	Ashton, Leigh and Wigan PCT	No
2.	Barking and Dagenham PCT	No
3.	Barnet PCT	No
4.	Barnsley PCT	Yes
5.	Bassetlaw PCT	Yes
6.	Bath and North East Somerset PCT	No
7.	Bedfordshire PCT	Unclear
8. 9.	Berkshire East PCT Berkshire West PCT	Yes
10.	Birmingham East and North PCT	No
11.	Blackpool PCT	No
12.	Bolton PCT	Unclear
13.	Bournemouth and Poole Teaching PCT	No
14.	Bradford and Airedale Teaching PCT	No
15.	Brent Teaching PCT	No
16.	Brighton and Hove City PCT	Yes
17.	Bristol PCT	Yes
18.	Bromley PCT	Not available
19.	Buckinghamshire PCT	Yes
20.	Bury PCT	Yes
21.	Calderdale PCT	Unclear
22.	Cambridgeshire PCT	No
23.	Camden PCT	No
24.	Central and Eastern Cheshire PCT	No
25.	Central Lancashire PCT	No
26.	City and Hackney Teaching PCT	No
27.	Cornwall and Isles Of Scilly PCT	Yes
28.	County Durham PCT	Yes
29.	Coventry Teaching PCT	No
30.	Croydon PCT	No
31.	Cumbria Teaching PCT	No
32.	Darlington PCT (see County Durham)	Yes
33. 34.	Derby City PCT Derbyshire County PCT	Yes
35.	Devon PCT (See Cornwall)	Yes
36.	Doncaster PCT	No

37.	Dorset PCT	No
38.	Dudley PCT	No
39.	East Lancashire Teaching PCT	No
40.	East Riding Of Yorkshire PCT	No
41.	East Sussex Downs and Weald PCT	No
42.	Eastern and Coastal Kent PCT	Yes
43.	Enfield PCT	Not available
44.	Gateshead PCT	Unclear
45.	Gloucestershire PCT	No
46.	Great Yarmouth and Waveney PCT	Yes
47.	Greenwich Teaching PCT	Not available
48.	Halton and St Helens PCT	No
49.	Hammersmith and Fulham PCT	No
50.	Hampshire PCT	Yes
51.	Haringey Teaching PCT	Not available
52.	Harrow PCT	No
53.	Hartlepool PCT	No
54.	Hastings and Rother PCT	No
55.	Havering PCT	No
56.	Heart Of Birmingham Teaching PCT	No
57.	Herefordshire PCT	No
58.	Hertfordshire PCT	No
59.	Heywood, Middleton and Rochdale PCT	No
60.	Hillingdon PCT	No
61.	Hounslow PCT	No
62.	Hull Teaching PCT	No
63.	Isle Of Wight NHS PCT (see Hampshire)	Yes
64.	Islington PCT	No
65.	Kensington and Chelsea PCT	No
66.	Kingston PCT	No
67.	Kirklees PCT	Unclear
68.	Knowsley PCT	No
69.	Lambeth PCT	Not available
70.	Leeds PCT	No
71.	Leicester City PCT	No
72.	Leicestershire County and Rutland PCT	Unclear
73.	Lewisham PCT	Not available
74.	Lincolnshire Teaching PCT	No
75.	Liverpool PCT	No
76.	Luton PCT	No
77.	Manchester PCT	No
78.	Medway PCT	No
79.	Mid Essex PCT	No
80.	Middlesbrough PCT	No
81.	Milton Keynes PCT	No
82.	Newcastle PCT	No

83.	Newham PCT	No
84.	Norfolk PCT	No
85.	North East Essex PCT	No
86.	North Lancashire Teaching PCT	No
87.	North Lincolnshire PCT	Unclear
88.	North Somerset PCT	Yes
89.	North Staffordshire PCT	No
90.	North Tyneside PCT	No
91.	North Yorkshire and York PCT	Unclear
92.	Northamptonshire Teaching PCT	No
93.	Nottingham City PCT	No
94.	Nottinghamshire County Teaching PCT	No
95.	Oldham PCT	No
96.	Oxfordshire PCT	No
97.	Peterborough PCT	No
98.	Plymouth Teaching PCT (Also see Cornwall)	Yes
99.	Portsmouth City Teaching PCT (Also see Hampshire)	Yes
100.	Redbridge PCT	No
101.	Redcar and Cleveland PCT	No
102.	Richmond and Twickenham PCT	No
103.	Rotherham PCT	No
104.	Salford PCT	No
105.	Sandwell PCT	No
106.	Sefton PCT	No
107.	Sheffield PCT	Unclear
108.	Shropshire County PCT	No
109.	Solihull PCT	No
110.	Somerset PCT	Yes
111.	South Birmingham PCT	No
112.	South East Essex PCT	No
113.	South Gloucestershire PCT	No
114.	South Staffordshire PCT	No
115.	South Tyneside PCT (See Gateshead)	Unclear
116.	South West Essex PCT	No
117.	Southampton City PCT (See also Hampshire)	Yes
118.	Southwark PCT	No
119.	Stockport PCT	Yes
120.	Stockton-on-Tees Teaching PCT	No
121.	Stoke On Trent PCT	No
122.	Suffolk PCT	Yes
123.	Sunderland Teaching PCT (See Gateshead)	Unclear
124.	Surrey PCT	No
125.	Sutton and Merton PCT	No
126.	Swindon PCT	Unclear
127.	Tameside and Glossop PCT	No
128.	Telford and Wrekin PCT	No

129. Tower Hamlets PCT	No
130. Trafford PCT	Unclear
131. Wakefield District PCT	No
132. Walsall Teaching PCT	No
133. Waltham Forest PCT	No
134. Wandsworth PCT	No
135. Warrington PCT	No
136. Warwickshire PCT	No
137. West Essex PCT	No
138. West Kent PCT	No
139. West Sussex PCT	Yes
140. Western Cheshire PCT	No
141. Westminster PCT	No
142. Wiltshire PCT	Unclear
143. Wirral PCT	Yes
144. Wolverhampton City PCT	Not available
145. Worcestershire PCT	Yes

*Yes = results on search "bevacizumab" or "avastin" are available - recommendation/policy document
No = no relevant results/results on "bevacizumab" or "avastin" for eye conditions in PCT website searches
Unclear = results on "bevacizumab" or "avastin" is available. Document is a letter, provisional statement or discussion document on use of bevacizumab.
Not available = No search box in PCT website to search for "bevacizumab" or "avastin"

Table A 2: Search results of Local Health Board sites in Wales

Source: http://www.nhsdirect.wales.nhs.uk/localservices/localhealthboards/

Health board	**Results?***
1. Abertawe Bro Morgannwg University Health Board	No†
2. Aneurin Bevan Health Board	No†
3. Betsi Cadwaladr University Health Board	No†
4. Cardiff & Vale University Health Board	No†
5. Cwm Taf Health Board	No
6. Hywel Dda Health Board	No†
7. Powys Teaching Health Board	No†

*Yes = results on search "bevacizumab" or "avastin" are available - recommendation/policy document
No = no relevant results/results on "bevacizumab" or "avastin" for eye conditions in health board website search
No search = No search box in PCT website to search for "bevacizumab" or "avastin"
†Concerns bevacizumab for the treatment of advanced renal cancer.

Table A 3: Search results of Health and Social Care Trusts in Northern Ireland
Source: http://www.dhsspsni.gov.uk/index/hss.htm

Health and Social Care Trust	Results?*
www.belfasttrust.hscni.net	No
www.southerntrust.hscni.net	No
www.setrust.hscni.net	No
www.westerntrust.hscni.net	No
www.northerntrust.hscni.net	No
www.niamb.co.uk	No

*Yes = results on search "bevacizumab" or "avastin" are available, could be recommendation/policy document
No = no relevant results/results on "bevacizumab" or "avastin" for eye conditions in PCT website searches

Table A 4: Search results of NHS health board sites in Scotland
Source: http://www.nhsinform.co.uk/nhs-in-your-area.aspx

NHS Health board	Results?*
1. NHS Ayrshire and Arran	No
2. NHS Borders	No
3. NHS Dumfries and Galloway	No
4. NHS Fife	No†
5. NHS Forth Valley	No
6. NHS Grampian	No
7. NHS Greater Glasgow and Clyde	No¤
8. NHS Highland	No§
9. NHS Lanarkshire	No
10. NHS Lothian	No
11. NHS Orkney	No
12. NHS Shetland	Not available
13. NHS Tayside	No
14. NHS Western Isles	No

*Yes = results on search "bevacizumab" or "avastin" are available - recommendation/policy document
No = no relevant results/results on "bevacizumab" or "avastin" for eye conditions in health board website search
Not available = No search box in PCT website to search for "bevacizumab" or "avastin"
†Concerns bevacizumab for the treatment of advanced ovarian cancer.
¤Concerns bevacizumab in health bulletins.
§Relates to discussions around the use of Lucentis or Avastin

Table A 5: Search results of Eye Hospital sites
Source: http://www.nhs.uk/Pages/HomePage.aspx
Searched for 'bevacizumab' or 'avastin' in each hospital website

Eye hospital	**Results?***
Bristol Eye Hospital	No
Manchester Royal Eye Hospital	Yes
Moorfields Eye Hospital (City Road)	Yes
Optegra Birmingham Eye Hospital	Yes
Sussex Eye Hospital	No
Western Eye Hospital	No
Yorkshire Eye Hospital†	Not available

*Yes = results on search "bevacizumab" or "avastin" are available, could be recommendation/policy document
No = no relevant results/results on "bevacizumab" or "avastin" for eye conditions in hospital website search
†Yorkshire Eye Hospital is now called the Optegra Yorkshire Eye Hospital.

APPENDIX 2: MEDLINE SEARCH STRATEGY – EFFICACY REVIEW

Review: DMO

Search date: 21st May 2012

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

1. bevacizumab.mp.
2. avastin.mp.
3. 1 or 2
4. diabet$.mp.
5. diabetic retinopathy/
6. (diabet$ adj2 retinopath$).mp.
7. macular edema/
8. ((central or diabetes or diabetic or fovea or macula or macular or retina or retinal) adj2 (edema? or oedema?)).mp.
9. (dme or dmo).mp.
10. (irvine-gass adj2 syndrome).mp.
11. or/4-10
12. 3 and 11
13. Randomized controlled trials as Topic/
14. Randomized controlled trial/
15. Random allocation/
16. randomized controlled trial.pt.
17. Double blind method/
18. Single blind method/
19. Clinical trial/
20. exp Clinical Trials as Topic/
21. controlled clinical trial.pt.
22. or/13-21
23. (clinic$ adj25 trial$).ti,ab.
24. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$ or mask$)).tw.
25. Placebos/
26. Placebo$.tw.
27. (allocated adj2 random).tw.
28. or/23-27
29. 22 or 28
30. Case report.tw.
31. Letter/
32. Historical article/
33. 30 or 31 or 32
34. exp Animals/
35. Humans/
36. 34 not (34 and 35)
37. 33 or 36
38. 29 not 37
39. 12 and 38
40. limit 39 to yr="2010 -Current"

Review: RVO

Search date: 21st May 2012

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

1. bevacizumab.mp.
2. avastin.mp.
3. 1 or 2
4. Retinal Vein Occlusion/
5. Retina vein/
6. ((retina or retinal or branch or central) adj3 vein occlusion).mp.
7. ((vein$ or occlu$ or obstruct$ or clos$ or stricture$ or steno$ or block$ or embolism$) adj3 retina$).mp.
8. (RVO or CRVO or CVO or BRVO).mp.
9. or/4-8
10. 3 and 9
11. Randomized controlled trials as Topic/
12. Randomized controlled trial/
13. Random allocation/
14. randomized controlled trial.pt.
15. Double blind method/
16. Single blind method/
17. Clinical trial/
18. exp Clinical Trials as Topic/
19. controlled clinical trial.pt.
20. or/11-19
21. (clinic$ adj25 trial$).ti,ab.
22. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$ or mask$)).tw.
23. Placebos/
24. Placebo$.tw.
25. (allocated adj2 random).tw.
26. or/21-25
27. 20 or 26
28. Case report.tw.
29. Letter/
30. Historical article/
31. 28 or 29 or 30
32. exp Animals/
33. Humans/
34. 32 not (32 and 33)
35. 31 or 34
36. 27 not 35
37. 10 and 36

APPENDIX 3

Table A 6: Efficacy review - table of excluded studies with reasons

	Author, year	Reason for exclusion
1.	Abu-Yaghi[131]	Not RCT, not DMO (patients with diabetic retinopathy)
2.	Ah-Chan 2006[132]	Not RCT (review, not systematic)
3.	Ahn 2011[133]	Not DMO
4.	Algvere 2011[134]	No control group
5.	Algvere 2008[135]	Not RCT
6.	Badala 2008[136]	Not RCT (review, not systematic)
7.	Bressler[137]	Full text report unobtainable
8.	Bright 2008[138]	Not IVB
9.	Campochiaro 2010[139]	Not IVB
10.	CATT Research Group 2011[116]	Not RVO (patients with AMD)
11.	Cekic 2010[42]	No relevant comparator
12.	Cho 2010[140]	Case series
13.	Ciulla 2009[141]	Not RCT (review, not systematic)
14.	Di Lauro 2010[142]	Not DMO (patients with severe proliferative diabetic retinopathy)
15.	Ding 2011[46]	No relevant comparator
16.	Farahvash 2011[143]	Not DMO
17.	Fard 2011[144]	No relevant comparator
18.	Feltgen 2010[145]	Not RCT, not English
19.	Ferrara 2010[146]	Not RCT (review, not systematic)
20.	Figueroa[147]	No control group
21.	Forte 2012[148]	Not RCT
22.	Fulda 2010[149]	Full text report unobtainable
23.	Garber 2010[150]	Not RCT
24.	Gulati 2011[151]	Not RCT (review, not systematic)
25.	Han 2012[152]	Not DMO
26.	Hara 2010[153]	Not English language
27.	Hernandez-Da-Mota 2010[154]	No relevant comparator
28.	Isaac 2012[155]	No relevant comparator
29.	Iu 2007[156]	Not RCT (review, not systematic)
30.	Jaissle 2006[157]	Not RCT, not English
31.	Jeganathan 2009[158]	Not RCT (review, not systematic)
32.	Kakkassery 2010[159]	Not English language
33.	Karim 2010[160]	Not RCT (review, not systematic)
34.	Kazazi-Hyseni 2010[161]	Not RCT
35.	Lim (2012)[50]	No relevant comparator
36.	Lynch 2007[162]	Not RCT (review, no additional studies to include)
37.	Marey (2011)[51]	No relevant comparator
38.	Mete 2010[163]	Not RCT
39.	Micieli 2010[164]	Not RCT
40.	Montero[165]	Full text report unobtainable
41.	Moradian 2011[34]	Not DMO
42.	Nghiem-Buffet 2009[166]	Not RCT, not English

43.	Nicholson 2010[167]	Not RCT (review, not systematic)
44.	Ockrim 2010[168]	Not RCT
45.	Paccola (2008)[169]	No relevant comparator
46.	Prager 2009[170]	Not RCT
47.	Russo 2009 [171]	Not RCT
48.	Shahin &El-Lakkany (2010)[54]	No relevant comparator
49.	Sivkova 2010[172]	No control group
50.	Soheilian 2010[173]	Not DMO
51.	Stewart 2012[174]	Not RCT (review, not systematic)
52.	Subramanian 2010[175]	Not DMO (patients with AMD)
53.	Synek 2010[176]	No relevant comparator
54.	Synek 2011[177]	No relevant comparator
55.	Wang 2011[178]	No relevant comparator
56.	Wolf-Schnurrb 2011[179]	Not RCT
57.	Wykoff 2011[180]	Full text report unobtainable
58.	Yilmaz 2011[181]	Not RCT systematic review
59.	Zechmeister-Koss 2012[182]	Not RCT systematic review
60.	Zhang 2011[183]	Not RCT
61.	Zhao 2011[184]	Not RCT (systematic review of diabetic retinopathy)

APPENDIX 4

Table A 7: Design and patient characteristics of included studies: DMO review of efficacy

Author, year, country, No. of eyes (patients), IVB Preparation	Inclusion criteria /exclusion criteria	Baseline data, Sponsor	Interventions	Comparators	Outcomes
Ahmadieh 2008[25] Iran N = 115 (101) (IVB prepared by F Hoffmann La Roche Ltd Basel, Switzerland)	Patients with significant macular oedema, refractory to previous laser treatment were included. Visual acuity ≥20/40, history of cataract surgery within the past 6 months, prior intraocular injection or vitrectomy, glaucoma or ocular hypertension, proliferative diabetic retinopathy were excluded.	Total mean age = 59 years. Authors have no financial conflicts of interested.	**Bevacizumab** 1.25 mg at baseline and weeks 6, 12 (n=41 eyes)	**Sham injection** (n=37 eyes)	Change in CMT; Change in BCVA logMAR; Safety assessments
DRCRN 2007[27] USA N = 109 (109) (No IVB preparation details)	Type 1 or 2 Diabetes; ETDRS VA letter score ≥ 24 (20/320 or better) and ≤78 (2/32 or worse); central macular thickness ≥ 275 μm; no previous treatment for DMO within last 3 months	Median age 65 Authors have financial interests with Genentech (Avastin)	**1: Bevacizumab:** (1.25 mg) at baseline and week 6 (n = 22 eyes) **2: Bevacizumab:** (2.5 mg) at baseline, week 6 (n = 24 eyes) **3: Bevacizumab:** (1.25 mg) baseline, sham at week 6 (n = 22 eyes) (Total N=68 eyes)	**Laser** at baseline (n =19)	Central macular thickness and BCVA ETDRS; safety assessments
Faghihi 2008[28] Iran N = 130 (110) (No IVB preparation details)	Type 2 diabetes with DMO; BCVA ≤ 20/40; CMT ≥ 250 μm; patients with history of treatment for diabetic retinopathy were excluded.	IVB mean age =59 years Laser mean age=56 years Financial conflicts of interest not reported	**Bevacizumab:** 1.25 mg (no further details) (n = 42 eyes)	**Laser** (n = 47 eyes)	BCVA improvement Central macular thickness reduction

Author, year, country, No. of eyes (patients), IVB Preparation	Inclusion criteria /exclusion criteria	Baseline data, Sponsor	Interventions	Comparators	Outcomes
Mansourian 2011[24] Iran N= 103 (150) (No IVB preparation details)	Patients with previous panretinal or focal laser photocoagulation, prior intraocular surgery or injection, history of glaucoma or ocular hypertension, VA of 20/40 or better or worse than 20/300, presence of iris neovascularization, high-risk proliferative diabetic retinopathy, and significant media opacity were excluded	No baseline details Financial conflicts of interest not reported	**Bevacizumab:** 1.25 mg (no further details) (n=32)	**Laser** (n=33)	Change in central macular thickness; change in BCVA logMAR
Michaelides 2010[26] UK N = 80 (80) (IVB prepared by Moorfields, London)	Type 1 or 2 diabetes; BCVA between 35 and 69 letters on ETDRS at 4 m; patients with any ocular condition that may affect macular oedema or alter VA during the course of the study were excluded.	IVB mean age: 64 years. Laser mean age:63 years. Authors have no financial conflicts of interested.	**Bevacizumab:** 1.25 mg at baseline, and at 6 and 12 weeks. Subsequent injections administered until a stable central macular thickness attained: minimum of 3 and maximum of 9 over 12 months (n = 42 eyes)	**Laser:** at baseline and retreatment at 4-month review, if required (weeks 16, 32, and 48) (n = 38 eyes)	Mean ETDRS BCVA; mean central macular thickness; % gaining ≥10 ETDRS letters; % who lost < 10 ETDRS letters; safety assessments
Solaiman 2010[30] Egypt N = 62 (48) (No IVB preparation details)	Diffuse diabetic macular oedema; central macular thickness ≥ 350 µm No history of intravitreal injection, surgical intervention, or retinal laser	Mean age 57 years. Authors have no financial conflicts of interested.	**Bevacizumab:** 1.25 mg (n = 21 eyes)	**Laser** once at baseline (n = 19 eyes)	Changes in central macular thickness; changes in BCVA;
Soheilian 2012[29] Iran N = 150 (129) (IVB prepared by F Hoffmann La Roche Ltd Basel, Switzerland)	Patients with DMO based on ETDRS with no previous laser treatment, or intraocular surgery.	IVB mean age: 60 years. Laser: mean age 61 years. Authors have no financial conflicts of interested.	**Bevacizumab:** 1.25 mg at baseline (n= 50 eyes) Retreatment based on persistence of clinically significant macular oedema according to ETDRS criteria	**Laser** (n = 50 eyes)	Change in BCVA (logMAR; central macular thickness changes; safety assessments

APPENDIX 5

Table A 8: Design and patient characteristics of included studies: RVO review of efficacy - Study characteristics

Author, year, country, number of eyes (patients), IVB preparation	Inclusion criteria /exclusion criteria	Sponsor / Disclosures	Interventions [treatment protocol]	Comparators	Outcomes
Epstein 2012[31] Sweden N = 60 (60) (IVB prepared at the hospital pharmacy under sterile conditions)	**Inclusion:** CRVO with a duration of ≤ 6 months BCVA between 15–65 ETDRS letters (Snellen equivalent approx 20/50 to 20/500) Mean central subfield thickness ≥ 300μm as measured by OCT (Cirrus OCT) **Exclusion:** CRVO with neovascularisation Any previous treatment for CRVO Intraocular surgery during the previous 3 months Vascular retinopathy of other causes Glaucoma with advanced visual field defect or uncontrolled ocular hypertension >25mmHg despite full therapy Myocardial infarction or stroke during the last 12 months	Authors have financial interests with Alcon, Allergan, Bayer and Novartis.	**Group 1:** Bevacizumab (1.25mg/0.05ml) at baseline and at weeks 6, 12 and 18 (n = 30 eyes) **Group 2:** Sham at baseline and at weeks 6, 12 and 18 (n = 30 eyes)	Group 2: sham	Change in BCVA (number of ETDRS letters)
Habibabadi 2007[32] (abstract) Not stated N = 94 (No IVB preparation details)	**Inclusion:** Patients with CRVO	Financial conflicts of interest not reported.	**Group 1:** Bevacizumab (concentration and number of injections not reported) **Group 2:** Bevacizumab combined with triamcinolone (concentration and number of injections not reported) **Group 3:** Sham (number of injections not reported)	Group 3: sham *Note group 2 excluded as bevacizumab augmented with intravitreal triamcinolone*	BCVA (no further details)

Author, year, country, number of eyes (patients), IVB preparation	Inclusion criteria /exclusion criteria	Sponsor / Disclosures	Interventions [treatment protocol]	Comparators	Outcomes
Habibabadi 2008[33] (abstract) Not stated N = 63 patients (No IVB preparation details)	**Inclusion:** Patients with CRVO	Financial conflicts of interest not reported.	**Group 1:** Bevacizumab (concentration not reported) at baseline, 6 and 12 weeks **Group 2:** Bevacizumab combined with triamcinolone (concentration not reported) at baseline, then just bevacizumab at 6 and 12 weeks **Group 3:** Sham (number of injections not reported)	Group 3: sham *Note group 2 excluded as bevacizumab augmented with intravitreal triamcinolone*	BCVA (no further details)
Moradian 2007[35] (abstract) Not reported N = 70 (No IVB preparation details)	**Inclusion:** acute BRVO	Financial conflicts of interest not reported.	**Group 1:** Bevacizumab (1.25mg/0.05ml) at baseline and 6 weeks (n = 34) **Group 2:** Sham at baseline and 6 weeks (n = 36)	Group 2: sham	BCVA (no further details)
Moradian 2011[34] Iran N = 81 (81) (No IVB preparation details)	**Inclusion:** acute BRVO and a best-corrected visual acuity (BCVA) equal to or less than 20/50 **Exclusion:** One-eyed patients Surgical candidate eyes Intraocular surgery in the past 6 months Macular thickening less than 250 μm by optical coherence tomography (OCT) BCVA≥20/40 Ocular media haziness that precluded evaluation by OCT and funduscopy Any new vessel formation Accompanying arterial obstruction Signs of chronicity (vascular shunts) Other macular diseases that affect central vision Pregnancy Patient incompliance Uncontrolled hypertension or any recent history of myocardial infarction or cerebral vascular accident within the past 6 months	Authors have no financial conflicts of interest.	**Group 1:** Bevacizumab (1.25mg/0.05ml) at baseline and 6 weeks (n = 42) **Group 2:** Sham at baseline and 6 weeks (n = 39)	Group 2: sham	BCVA measured with a Snellen chart then transformed to logMAR; adverse events (complications)

Table A 9: Design and patient characteristics of included studies: RVO review of efficacy - Patient characteristics at baseline

Author, year	Group	Mean age (SD)	Female n (%)	Condition	Previous treatment [for RVO]	Mean BCVA, EDTRS (letters±SD)	Mean BCVA (logMAR±SD)
Epstein 2012[31]	IVB	70.6±12.6	11 (37%)	CRVO	Not reported	44.4±15.3	Not reported
	Sham	70.4±10.4	13 (43%)	CRVO		43.9±16.0	
Habibabadi 2007[32] (abstract)	IVB	Not reported	Not reported	CRVO	Not reported	Not reported	Not reported
	Sham						
Habibabadi 2008[33] (abstract)	IVB	Not reported	Not reported	CRVO	Not reported	Not reported	Not reported
	Sham						
Moradian 2007[35] (abstract)		Not reported	Not reported	BRVO	Not reported	Not reported	Not reported
Moradian 2011[34]	IVB	58.1 (7.9)	47 (58%)	BRVO	Not reported	Not reported	0.74±0.38
	Sham	57.2 (11.4)					0.80±0.38

Abbreviations: IVB: intravitreal bevacizumab; RVO – retinal vein occlusion; CRVO – central retinal vein occlusion; BRVO – branch retinal vein occlusion

APPENDIX 6

Table A 10: Summary of efficacy outcomes for the RVO review - Bevacizumab monotherapy versus sham injection

Author, year	Group	Assessment time-point (weeks)	Mean change in BCVA (±SD)	Percentage of eyes (patients) with improvement in BCVA, ≥ 15 letters (3 lines), EDTRS	Percentage of eyes (patients) achieving improvement in BCVA of 10 -15 letters, EDTRS	Percentage of eyes (patients) with stable BCVA	Percentage of eyes (patients) with worsening BCVA
Epstein 2012[31]	IVB	6 weeks	7.5 letters	NR	NR	NR	NR
		12 weeks	11.4 letters	NR	NR	NR	NR
		18 weeks	13.9 letters	NR	NR	NR	NR
		24 weeks	14.1 letters	60.0% (60.0%)	NR	NR	6.7% (6.7%)
	Sham	6 weeks	-0.3 letters	NR	NR	NR	NR
		12 weeks	-3.9 letters	NR	NR	NR	NR
		18 weeks	-3.2 letters	NR	NR	NR	NR
		24 weeks	-2.0 letters	20.0% (20.0%)	NR	NR	23.3% (6.7%)
Habibabadi 2007[32] (abstract)	IVB	6 weeks	NR	NR	NR	NR	NR
	Sham	6 weeks	NR	NR	NR	NR	NR
Habibabadi 2008[33] (abstract)	IVB	18 weeks	NR	NR	NR	NR	NR
	Sham	18 weeks	NR	NR	NR	NR	NR
Moradian 2007[35] (abstract)	IVB	6 weeks	NR	NR	NR	NR	NR
		12 weeks	NR	NR	NR	NR	NR
	Sham	6 weeks	NR	NR	NR	NR	NR
		12 weeks	NR	NR	NR	NR	NR
Moradian 2011[34]	IVB	6 weeks	0.19±0.24 logMAR	NR	NR	NR	NR
		12 weeks	0.31±0.30 logMAR	NR	NR	NR	NR
	Sham	6 weeks	0.08±0.25 logMAR	NR	NR	NR	NR
		12 weeks	0.15±0.03 logMAR	NR	NR	NR	NR

Abbreviations: EDTRS - Early Treatment Diabetic Study; SD – standard deviation; BCVA- visual acuity; NR – not reported

APPENDIX 7: MEDLINE SEARCH STRATEGY – SAFETY REVIEW

Review: Safety

Search date: 24 May 2012

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

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1. bevacizumab.mp.
2. avastin.mp.
3. 1 or 2
4. ae.fs.
5. to.fs.
6. po.fs.
7. or/4-6
8. 3 and 7
9. (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$).ti,ab.
10. 8 not 9
11. ((side or adverse or undesirable) adj2 (event$ or effect$ or reaction$ or outcome$)).ab,ti.
12. adrs.ab,ti.
13. (safe or safety).ab,ti.
14. (treatment adj emergent).ab,ti.
15. tolerability.ab,ti.
16. toxicity.ab,ti.
17. or/11-16
18. 3 and 17
19. (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$).ti,ab.
20. 18 not 19
21. exp Endophthalmitis/ci
22. endophthalmiti$.ab,ti.
23. (intraocular adj2 (pressure$ or tension$)).ab,ti.
24. hypotony.ab,ti.
25. exp Cataract/ci
26. cataract$.ab,ti.
27. Retinal Detachment/ci
28. (retina$ adj2 detach$).ab,ti.
29. exp Retinal Artery Occlusion/ci [Chemically Induced]
30. retina$ artery occlu$.ab,ti.
31. crao.ab,ti.
32. vitreoretinal fibros$.ab,ti.
33. discomfort.ab,ti.
34. pain.ab,ti.
35. corneal abrasion.ab,ti.
36. lens injur$.ab,ti.
37. Uveitis/ci [Chemically Induced]
38. uveitis.ab,ti.
39. infection$.ab,ti.
40. itch$.ab,ti.

41. (vision adj2 (loss or reduced or subnormal or diminished or abnormal)).ab,ti.
42. (subconjunctival adj (haemorrhag$ or hemorrhag$)).ab,ti.
43. ((subretinal or retina$) adj (haemorrhag$ or hemorrhag$)).ab,ti.
44. (retina$ adj3 tear$).ab,ti.
45. rpe tears.ab,ti.
46. blood pressure.ab,ti.
47. Venous Thrombosis/ci [Chemically Induced]
48. Ischemic Attack, Transient/ci [Chemically Induced]
49. Stroke/ci [Chemically Induced]
50. Myocardial Infarction/ci [Chemically Induced]
51. Death/
52. or/21-51
53. 3 and 52
54. (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$).ti,ab.
55. 53 not 54
56. 10 or 20
57. 55 or 56
58. limit 57 to yr="2009 -Current"

APPENDIX 8

Table A 11: Study characteristics of RCTs included in safety review

Author, year, country, number of eyes (patients) Sponsor	Inclusion criteria /exclusion criteria	Baseline details	Interventions [treatment protocol], IVB preparation	Comparators	Outcomes
Ahmadieh (2008)[25] Iran N = 115 (101) (IVB prepared by F Hoffmann La Roche Ltd Basel, Switzerland)	Patients with significant macular oedema, refractory to previous laser treatment were included. Visual acuity ≥20/40, history of cataract surgery within the past 6 months, prior intraocular injection or vitrectomy, glaucoma or ocular hypertension, proliferative diabetic retinopathy were excluded.	Total mean age = 59 years. Authors have no financial conflicts of interested.	**Bevacizumab** 1.25 mg at baseline and weeks 6, 12 (n=41 eyes)	**Sham injection** (n=37 eyes)	Death Marked anterior chamber reaction Progression of fibrous proliferation Outcomes at 24 weeks
Bashshur 2007[69] Lebanon No. eyes NR 62 subjects. Authors report no conflicts of interest	Neovascular AMD. BCVA 20/50 and 20/200. Submacular hemorrhage not involving the fovea. prior treatment for CNV associated AMD excluded.	IVB mean age 75 years; Laser mean age 74 years	**Bevacizumab:** 2.5mg, mean 2.4 injections (n=32) IVB prepared in hospital pharmacy	**Laser therapy:** mean 2.3 sessions (n=30)	Systemic adverse events Hypertension Outcomes at 6 months
Biswas 2011[44] India 60 eyes in 60 patients. Conflicts of interest not reported	CNV associated AMD, age >50 years, BCVA between 25-70 ETDRS letters, treatment naive CNV. Co-existing ocular pathologies, history of CVA, MI were excluded.	No details	**Bevacizumab:** 1.25mg (n=30), 3 monthly injections (mean 4.3). Methods of IVB preparation not reported	**Ranibizumab:** 0.5mg (n=30), 3 monthly injections (mean 5.6).	Significant adverse events Outcome at 18 months
CATT 2012[45] USA (n=1107) One author received financial support from Genentech	Eligible eyes had active choroidal neovascularization secondary to AMD, no previous treatment, visual acuity between 20/25 and 20/320, and neovascularization, fluid, or haemorrhage under the fovea.	IVB mean age 80 years; IVR mean age 79 years.	**Bevacizumab:** 1.25mg, (monthly or as needed)	**Ranibizumab:** 0.5mg (monthly or as needed)	Death Endophthalmitis, Hypertension Adverse events associated with anti-VEGF treatment Arteriothrombotic adverse events Outcomes at 2 years
Cekic 2010[42] Turkey 52 eyes in 52 subjects Conflicts of interest not reported	Patients with macular oedema due to branch retinal vein occlusion. Included if visual acuity 20/40 or worse, and CMT of 250 or greater.	IVB mean age 60 years; IVT mean age 66 years; duration of BRVO IVB=5.6 months; IVT 4.7 months	**Bevacizumab:**1.25 mg mean 1.6 injections (n=14) Methods of IVB preparation not reported	**Triamcinolone:** 4mg, mean1.4 injections (n=17)	Endophthalmitis, uveitis, thromboembolic events Outcomes at 6 months

Author, year, country, number of eyes (patients) Sponsor	Inclusion criteria /exclusion criteria	Baseline details	Interventions [treatment protocol], IVB preparation	Comparators	Outcomes
Ding 2011[46] China 32 eyes in 31 subjects. No financial conflicts of interest	Patients with macular oedema secondary to RVO, older than 18 years, BCVA worse than 20/40 (logarithm of the minimal angle of resolution [logMAR] =0.3), clinically detectable ME involving fovea with a thickness of >250µm; no history of previous treatments. Exclusion criteria intraocular pressure (IOP) >21mmHg, previous intraocular surgery within the past 2 years or grid photocoagulation for MO.,	IVB mean age 53 years; duration 12 weeks. IVT mean age 55 years; duration18 weeks.	**Bevacizumab:**1.25 mg (n=16) Methods of IVB preparation not reported	**Triamcinolone:** 4mg (n=16)	IOP>21mmHg Outcomes at 9 months
DRCRN (2007)[27] USA N = 109 (109) (No IVB preparation details)	Type 1 or 2 Diabetes; ETDRS VA letter score ≥ 24 (20/320 or better) and ≤78 (2/32 or worse); central macular thickness ≥ 275 µm; no previous treatment for DMO within last 3 months	Median age 65 Authors have financial interests with Genentech (Avastin)	**1: Bevacizumab:** (1.25 mg) at baseline and week 6 (n = 22 eyes) **2: Bevacizumab:** (2.5 mg) at baseline, week 6 (n = 24 eyes) **3: Bevacizumab:** (1.25 mg) baseline, sham at week 6 (n = 22 eyes) (Total N=68 eyes)	**Laser** at baseline (n =19)	Death Uveitis Outcomes at 12 weeks Safety over a 70 week period
Epstein (2012)[31] Sweden 60 eyes in 60 subjects. Author consultant for Novartis	Inclusion: CRVO with a duration of ≤ 6 months BCVA between 15–65 ETDRS letters (Snellen equivalent approx 20/50 to 20/500); Mean central subfield thickness ≥ 300µm. Exclusion: CRVO with neovascularisation Any previous treatment for CRVO Intraocular surgery during the previous 3 months Vascular retinopathy of other causes Glaucoma with advanced visual field defect or uncontrolled ocular hypertension >25mmHg despite full therapy Myocardial infarction or stroke during the last 12 months	No significant differences in baseline characteristics between groups.	**Bevacizumab:** (1.25mg/0.05ml) at baseline and at weeks 6, 12 and 18 (n= 30) IVB prepared in hospital pharmacy by dividing a vial of bevacizumab (Avastin) into small vials for each patient	**Sham injection:** at baseline and at weeks 6, 12 and 18 (n= 30)	Endophthalmitis Retinal tear Retinal detachment No serious non-ocular adverse events Outcomes at 6 months

Author, year, country, number of eyes (patients) Sponsor	Inclusion criteria /exclusion criteria	Baseline details	Interventions [treatment protocol], IVB preparation	Comparators	Outcomes
Faghihi (2008)[28] Iran N = 130 (110) Financial conflicts of interest not reported	Type 2 diabetes with DMO; BCVA ≤ 20/40; CMT ≥ 250 μm; patients with history of treatment for diabetic retinopathy were excluded.	IVB mean age =59 years Laser mean age=56	**Bevacizumab:** 1.25 mg (no further details) (n = 42 eyes) No IVB preparation details	**Laser** (n = 47 eyes)	Safety assessment Vitreous haemorrhage Ocular hypertension (≥23 mmHg) Outcome 16 weeks
Gharbiya 2010[47] Italy 32 eyes in 32 subjects, one author received unrelated Novartis fellowship; no conflicts stated by other authors	Pathologic myopia, defined as axial length more than 26.5 mm;subfoveal or juxtafoveal choroidal neovascularisation.	IVB mean age 59. yrs IVT mean age 60 yrs; Foveal center thickness IVB 237; IVT 251; no significant differences in baseline characteristics between groups.	**Bevacizumab:** 1.25 mg, as needed, after the first Injection. Methods of IVB preparation not reported	**Ranibizumab:** 0.5 mg as needed, after the first injection.	Systemic adverse events Endophthalmitis, Retinal detachment Vitreous haemorrhage Hypertension IOP Outcomes at 6 months
IVAN 2012[48] UK 610 Author(s) have conflicts of interest with Novartis	Adults ≥50 years old with previously untreated neovascular AMD in the study eye and best corrected visual acuity ≥25 letters on the Early Treatment Diabetic Retinopathy Study chart were eligible.	IVB mean age 77 years; IVR mean age 77 years. Baseline characteristics similar across groups	**Bevacizumab:** 1.25mg (continuous and discontinuous treatment) Commercially obtained IVB. Bevacizumab was repackaged in prefilled syringes in an aseptic facility	**Ranibizumab:** 0.5mg (continuous and discontinuous treatment)	Serious adverse events Death Arteriothrombotic events Transient ischaemic attack Hospitalized for angina Outcomes at 1 year
Lazic 2007[49] Croatia 165 eyes in 165 subjects. Authors have no commercial or proprietary interest regarding the products	Minimally classic or occult CNV due to AMD in 1 or both eyes were enrolled. Excluded the subjects with cataract or media opacities that could significantly interfere with optic coherence tomography imaging & image analysis (inadequate signal strength & quality).	Baseline characteristics (age, gender, size of the lesion, status of the fellow eye, and CNV type) showed no relevant differences between the 3 groups	**Bevacizumab:** 1.25 mg (N=55) Methods of IVB preparation not reported	**1. Laser therapy:** according to recommended standard procedures (N=55) **2. Combination treatment** (N=55)	Pigment epithelial tears Posterior vitreous detachment Thromboembolic events Cataract progression Outcomes at 3 months.

Author, year, country, number of eyes (patients) Sponsor	Inclusion criteria /exclusion criteria	Baseline details	Interventions [treatment protocol], IVB preparation	Comparators	Outcomes
Lim 2012[50] Korea 120 eyes in 110 subjects, Authors have no commercial conflicts of interest	Diabetic macular oedema (ETDRS) criteria, macular oedema with central macular thickness of at least 300µm by optical coherence tomography (OCT). Exclusion criteria : unstable medical status, including glycaemic control and blood pressure, any previous treatment for diabetic macular oedema, including intravitreal, sub-Tenon injection or macular photocoagulation, history of vitreoretinal surgery, uncontrolled glaucoma, proliferative diabetic retinopathy with active neovascularization, previous panretinal photocoagulation.	IVB mean age 61 years IVT mean age 59 years	**Bevacizumab:** 1.25mg (n=36)	**1. Triamcinolone:** 2mg, (n=38) 2. IVB + IVT (n=37)	Hypertension Thromboembolic AE Serious ocular complications IOP Outcomes at 1 year.
Marey 2011[51] Egypt 90 eyes in 90 subjects Authors have no commercial conflicts of interest	Clinically significant DMO based on (ETDRS) Exclusion criteria were: previous laser treatment, previous intraocular injection, previous intraocular surgery, history of glaucoma or ocular hypertension, and significant media opacity.	Mean age in IVB 57 years. Mean age in IVT 57 years.	**Bevacizumab:** 1.25mg (n=30) Methods of IVB preparation not reported	**1. Triamcinolone:** 4mg, (n=30) 2. IVB + IVT (n=30)	IOP>22mmH Cataracts Outcomes at 12 weeks
Michaelides 2010[26] UK N = 80 (80) Authors have no financial conflicts of interested.	Type 1 or 2 diabetes; BCVA between 35 and 69 letters on ETDRS at 4 m; patients with any ocular condition that may affect macular oedema or alter VA during the course of the study were excluded.	IVB mean age: 64 years. Laser mean age:63 years. (IVB prepared by Moorfields, London)	**Bevacizumab:** 1.25 mg at baseline, and at 6 and 12 weeks. Subsequent injections administered until a stable central macular thickness attained: minimum of 3 and maximum of 9 over 12 months (n = 42 eyes)	**Laser:** at baseline and retreatment at 4-month review, if required (weeks 16, 32, and 48) (n = 38 eyes)	Death Ocular hypertension Loss of 30 ETDRS letters Vitreous haemorrhage Cerebrovascular accident Outcomes at 12 months

Author, year, country, number of eyes (patients) Sponsor	Inclusion criteria /exclusion criteria	Baseline details	Interventions [treatment protocol], IVB preparation	Comparators	Outcomes
Moradian 2011[34] Iran N = 81 (81)	Inclusion: acute BRVO and a best-corrected visual acuity (BCVA) equal to or less than 20/50 Exclusion: One-eyed patients Surgical candidate eyes Intraocular surgery in the past 6 months Macular thickening less than 250 µm by optical coherence tomography (OCT) BCVA≥20/40 Ocular media haziness that precluded evaluation by OCT and funduscopy Any new vessel formation Accompanying arterial obstruction Signs of chronicity (vascular shunts) Other macular diseases that affect central vision Pregnancy Patient incompliance Uncontrolled hypertension or any recent history of myocardial infarction or cerebral vascular accident within the past 6 months	No significant differences in baseline characteristics between groups	**Bevacizumab:** (1.25mg/0.05ml) at baseline and 6 weeks (n = 42) Methods of IVB preparation not reported	**Sham injection:** at baseline and 6 weeks (n = 39)	Foveal haemorrhage Foveal ischemia Outcomes at 12 weeks
Patwardhan 2011[52] India 20 eyes of 20 subjects. Authors have no commercial or proprietary interest	Vitreous haemorrhage of 0-3 months duration (grade 3 or 4), secondary to Earls disease. Patients with retinal detachment at presentation, history on any intervention , undergone proior surgery or laser photocoagulation were excluded.	IVB mean age 26 years. Control mean age 25 years.	**Bevacizumab:** 1.25 mg every four weeks. Methods of IVB preparation not reported	**Control no treatment:**	Retinal detachment Outcomes at 12 weeks
Schimid-Kubista 2011[53] Austria 48 eyes in 48 subjects. Authors have no commercial or proprietary interest regarding the products	Neovascular age related macular degeneration.excluded if any prior treatment for CNV.	IVB median age 77 years. Pegaptanib median age 79 years.	**Bevacizumab:** 1.0 mg x3 injections (n=13) Methods of IVB preparation not reported	**Pegaptanib:** 0.3 mg x3 injections (n=18) 2. Combination treatment: (n=17)	No significant IOP increase No significant BP increase Outcomes at 6 months

Author, year, country, number of eyes (patients) Sponsor	Inclusion criteria /exclusion criteria	Baseline details	Interventions [treatment protocol], IVB preparation	Comparators	Outcomes
Shahin 2010[54] Egypt 48 eyes, in 32 subjects. Conflicts of interest not reported	Diffuse diabetic macular oedema, without previous laser therapy	No details	**Bevacizumab:** single 1.25mg (n=24) Methods of IVB preparation not reported	**Triamcinolone:** single 4mg injection (n=24)	IOP (≥23-43 mmHG) Visually significant cataract Outcomes at 3 months
Soheilian 2012[29] Iran N = 150 (129) (IVB prepared by F Hoffmann La Roche Ltd Basel, Switzerland) Authors have no financial conflicts of interested.	Patients with DMO based on ETDRS with no previous laser treatment, or intraocular surgery.	IVB mean age: 60 years. Laser: mean age 61 years.	**Bevacizumab:** 1.25 mg at baseline (n= 50 eyes)	**Laser** (n = 50 eyes)	Death Lens opacities Ocular hypertension High risk proliferative diabetic retinopathy Outcomes at 2 years
Tufail 2010[55] UK No. eyes NR (n=131) Author(s) involvement with Novartis advisory boards	Age related macular degeneration; aged at least 50, have a lesion in the study eye with a total size of less than 12 optic disc areas for minimally classic or occult lesions; have BCVA of 6/12 to approximately 6/96 (Snellen equivalent), assessed with the use of charts from (ETDRS) (70 to 25 ETDRS 1 m equivalent letter scores.	IVB mean age 79 years. Groups (1,2,3) mean age 81years. baseline measures similar in all groups.	**Bevacizumab:** 1.25 mg, three loading injections at six week intervals followed by further treatment if required at six week intervals (mean injections 7.1 range 3-9) (n=65). Methods of IVB preparation not reported	**1. Laser t**herapy: (n=38) **2. Pegaptanib:** 0.3mg, mean injections 8.9 (n=16) **3. Sham injection:** (n=12)	Endophthalmitis Uveitis Retinal detachment Retinal tear Vitreous haemorrhage Lens damage Myocardial infarction Stroke Cerebral infarction Death Outcomes at one year
Yazdani 2009[56] Iran 26 eyes in 26 subjects. Authors report no conflicts of interest	Neovascular glaucoma; excluded monocular subjects, BCVA better than 20/200, presence of infectious ocular disease	IVB mean age 57, Sham mean age 62.	**Bevacizumab:** 2.5mg, 3 injections at monthly intervals (n=14). Methods of IVB preparation not reported	**Sham injection:** (n=12)	Hyphema Injection related adverse events Outcomes at 6 months

APPENDIX 9

Table A 12: Study characteristics of observational studies included in safety review

Study reference	Study type	Condition included patients [mean age in years]	Number of patients (number of eyes)	Baseline comparability (yes/no/ unknown/not applicable)	Dosage (mg) including frequency of dosing	Number of injections/ patients (mean)	Follow-up	Information on preparation of bevacizumab	Funding	Notes
Abraham-Marin 2007[104]	Case series, (prospective)	CNV due to AMD [76]	39 (39)	NA	2.5mg	1	4 weeks	NR	NR	
Arevalo 2008[71]	Case series, (retrospective)	CNV due to AMD [73.7]	63 (63)	Unknown	1.25mg (59%); 2.5mg (41%)	3.5	12 months (minimum)	NR	Arevalo-Coutinho Foundation for Research in Ophthalmology, Venezuela	
Artunay 2009[113]	Case series, (retrospective)	Various[f] [NR]	NR (1822)	NA	1.25 mg once or repeated	NR	1-7 days, 4 weeks, 8 weeks	NR	NR	
Azad 2008[105]	Non-randomised trial (prospective)	subfoveal CNV due to AMD [63]	40 (40)	NA	1.25mg	2.4	6 months	NR	NR	
Bakri 2009[88]	Case series, (retrospective)	Various[g] [NR]	35 (70)	NA	1.25 mg	5.9	39 days	NR	The Research To Prevent Blindness, New York	
Bashshur 2009[69]	Nonrandomised trial, open-label, prospective (extension study)	CNV due to AMD [72.2]	51 (51)	NA	2.5 mg	2.5 (3.4 during first 12 months, decreased to 1.5 during second year)	24 months	local dispensing service	American University of Beirut Medical Center	
Carneiro 2010[89]	Cohort, (prospective)	Subfoveal or juxtafoveal CNV secondary to AMD [76.9]	(80)	NR	1.25 mg	4	6 months, 12 months	NR	Sociedade Portuguesa de Oftalmologia, Hospitalde Sao Joao,	

[f] Azad 2008[105] studied patients with the following conditions: AMD,CNV due to myopic degeneration idiopathic and other secondary causes ,cystoid or diffuse MO from CRVO, BRVO, diabetes, uveitis and retinitis pigmentosa proliferative retinopathies

[g] Population included patients CNV due to AMD;DMO;DR;MO due to RVO or autoimmune retinopathy

Study reference	Study type	Condition included patients [mean age in years]	Number of patients (number of eyes)	Baseline comparability (yes/no/ unknown/not applicable)	Dosage (mg) including frequency of dosing	Number of injections/ patients (mean)	Follow-up	Information on preparation of bevacizumab	Funding	Notes
Carneiro 2011[90]	cohort (retrospective) : IVB vs. IVR	AMD [77.8]	97 (IVB group)	Yes [IVB:IVR]	1.25 mg;	7.8	2.3 years	NR	Sociedade Portuguesa de Oftalmologia, Hospitalde Sao Joao, Swiss National Foundation and Walter & Gertrud Sienenthaler Foundation	Increased rate of ATEs in IVB group compared to IVT (secondary analyses
Chen 2010[185]	Non-randomised cohort (retrospective)	MO due to BRVO [60.7]	24 (25)	Yes [IVB:IVT:control; n=83]	2.5 mg single injection then as needed	NR	10 months (mean)	NR	NR	Patients received IOP-lowering treatment during follow-up period if IOP ≥ 21mmHg. Anterior paracentesis was performed before IVB to reduce ocular pressure. Author's conclusion: IVB better than IVT
Cleary 2008[80]	Case series (retrospective)	Neovascular AMD [75]	111(112)	NA	1.25 mg, once then as needed	NR	4.9 (range 1-12)	Local dispensing service	None	
Costa 2006[81]	Non-randomised dose escalation study (prospective)	CNV caused by AMD [74.6]	45(45) mg]	Yes [1.0 mg:1.5 mg:2.0 mg]	1.0 mg, 1.5 mg and 2.0 mg	NR	3	Local dispensing service (Brazil)	Public funding (Foundation for Research Support of the State of São Paulo)	Reported as a dose escalation study but difficult to tell how many doses each participant was given and how far apart
Costagliola 2009[82]	Case series (retrospective)	CNV (subfoveal) due to AMD [73.2]	68(68)	NA	1.25; then monthly as per needed	3.87 (first 6 months); 1.09(for remaining 6 months)	12	Local dispensing service (Italy)	NR	Exclusion criteria included previous history of thromboembolic events; uncontrolled hypertension, BP >150/90mmHg. Topical antibiotics prescribed for 3 days, after injection.

Study reference	Study type	Condition included patients [mean age in years]	Number of patients (number of eyes)	Baseline comparability (yes/no/ unknown/not applicable)	Dosage (mg) including frequency of dosing	Number of injections/ patients (mean)	Follow-up	Information on preparation of bevacizumab	Funding	Notes
Curtis 2010 [58]	Cohort (retrospective)	AMD [median 81.0]	27,962 (IVB only; n= 146,942)	Yes [IVB: PDT: IVP: IVR]	NR	NR	12 months	NR	Research agreement between OSI Eyetech and Duke University	Patient data were censored when at the time when a treatment which was different from initially assigned intervention was received. Between July and December 2006, study population was limited to treatment-naïve patients who received bevacizumab or ranibizumab.
Falkenstein 2007[110]	Case series (prospective)	AMD [79.4]	70(NR)	NA	1.25mg assumed (0.05ml)	1.74 (calculated from 122 injections for 70 patients)	3,10 and 15 minutes	NR	NR	
Fintak 2008[83]	cohort (retrospective)	Various, mostly AMD [NR]	12,585 (IVB injections)	NR	1.25 mg	NR	5 days	Local dispensing service (USA)	NR	Number of injections not reported
Fong 2008[60]	Case series (retrospective)	AMD [82]	109(109)	NA	1.25 mg, three consecutive monthly injections then as needed	NR	9.4 months (range 6-12)	Compounding pharmacy (UK)	NR	
Frenkel 2010[109]	cohort (retrospective)	AMD [80]	47[h]	Unknown [IVB: ranibizumab: pegaptanib]	1.25mg	1	20 minutes	NR	NR	First injection only selected for the study
Fukami 2011[108] (abstract)	case series (retrospective)	NR [NR]	12(12)	NA	NR	NR	2 days	NR	NR	
Gamulescu 2010[186]	cohort (retrospective) [i]	AMD [77.5]	30(NR)	NR	1.25mg every 4 weeks 3 initial injections	NR	2-4 months after last injection	NR	NR	

[h] Forty-seven patients out of a study population of 71 received bevacizumab. NOTE: Some patients received all 3 anti-VEGF medications while others received just one treatment type. However, authors reported that only the first anti-VEGF injection was considered in the study.
[i] Gamulescu 2010[186] included a control group that received ranibizumab.

Study reference	Study type	Condition included patients [mean age in years]	Number of patients (number of eyes)	Baseline comparability (yes/no/ unknown/not applicable)	Dosage (mg) including frequency of dosing	Number of injections/ patients (mean)	Follow-up	Information on preparation of bevacizumab	Funding	Notes
Gomi 2008[57]	case series (Retrospective)	Polypoidal choroidal vasculopathy [65.4]	11 (11)	NA	1 mg [j] Once or as needed	NR	9.4 months (± 4.4)	NR	NR	
Good 2011[78]	cohort (retrospective) [k]	AMD [76.6]	NR (101)[l]	yes	1.25 mg	7.0	86.6 days mean	NR	NR	
Goverdhan 2008[73]	case series (retrospective)	CNV due to AMD [79.5]	53 (53)	NA	1.25 mg Repeat injections offered if CNV persisted or fresh haemorrhage or subretinal fluid observed.	1.36	Day 1 and after 2 week visits then at 4-week intervals. Minimum-6 months (range 4 to 12 months)	NR	NR	
Gower 2011[112] (abstract)	cohort (retrospective)	Neovascular AMD [NR]	NR (NR)	NR [IVB:IVR]	NR	NR	NR	NR	NR	Hazard ratios adjusted for baseline comorbidities, demographics and socio-economic status
Hernandez-Rojas 2007[68]	case series (prospective)	CNV in pathologic myopia [53.86]	13 (13) [at follow-up – one patients lost to follow-up]	NA	2.5 mg/0.1 ml once or as needed	NR	3 months	NR	NR	
Higashide 2012[114]	Case series (retrospective)	Neovascular glaucoma [63.5]	70 (84)	NA	1.25 mg	1.4	3 months	NR	NR	

[j] Re-injection in 5 eyes, 1 or 2 months after first injection at physician discretion
[k] Good 2011[78] included a control group that received ranibizumab.
[l] 101 eyes received bevacizumab only, 96 eyes received ranibizumab only, 18 eyes received bevacizumab and ranibizumab

Study reference	Study type	Condition included patients [mean age in years]	Number of patients (number of eyes)	Baseline comparability (yes/no/ unknown/not applicable)	Dosage (mg) including frequency of dosing	Number of injections/ patients (mean)	Follow-up	Information on preparation of bevacizumab	Funding	Notes
Hollands 2007[187]	Case series (prospective)	Neovascular AMD (84.6%); DMO (6.7%); Other including ocular histoplasmosis (8.7%) [76]	104	NA	1.25 mg	NR	30 minutes	NR	NR	
Ikuno 2009[65]	Case series (retrospective)	CNV due to myopia [58.4]	63 (63)	NA	1 mg	2.4	12 months	NR	The Ministry of Education, Culture, Sports Science and Technology of Japan; Health and Labor Sciences Research of Japan	Re-injection considered after 2 to 3 months if fluorescein leakage in angiograam or subretinal fluid persisted
Inman 2011[85]	Case series (retrospective)	NR	608 (sample included patients that received IVB, IVP and IVR)	NA	NR	Unclear (1841 injections of IVB, 428 IVP and 2421 IVR)	4.4 years	Local dispensing service	NR	This study reported incidence of infectious endophthalmitis associated with 2% topical lidocaine gel anaesthesia. No information on conditions being treated or patient demographics.
Jaissle 2009[95]	Case series (prospective)	MO due to BRVO [Median age: 68 years]	23 (23)	NA	1.25 mg (Re-injection considered if macular oedema persisted in foveal area and visual acuity 20/32 or worse)	NR	1 year. (examined every 6 weeks)	NR	German Opthalmological Society	During the 1-year follow-up, an average of 2.4 re-injections (range, 0–5) were administered, with a mean of 1.6 re-injections within the first 6 months (weeks 6 to 24) and a further 0.8 re-injections over the latter 6 months (weeks 30 to 48).

Study reference	Study type	Condition included patients [mean age in years]	Number of patients (number of eyes)	Baseline comparability (yes/no/ unknown/not applicable)	Dosage (mg) including frequency of dosing	Number of injections/ patients (mean)	Follow-up	Information on preparation of bevacizumab	Funding	Notes
Johnson 2010[96]	Case series (retrospective)	Various[m] [76.5]	173 (193)	NA	NR	3.98	Median follow-up; 40 days (range 19 to 170 days)	NR.	Queen's University, Canada	
Jonas, 2007[66]	Case series (retrospective)	AMD	625 (684)	NA	1.5mg	1.95	≥4 weeks	Local dispensing service	NR	534 re-injections
Jonas 2008[67]	Case series (retrospective, consecutive)	Various	NR (3818 IVB injections)	NA	1.5mg	NR	≥3 months	NR	None	
Julian 2011[188]	Case series (retrospective)	CNV due to uveitis[41.9 (median)	15 (15)	NA	1.25 mg (Retreatment based on signs of active neovascularisation)	4.25	17.6 (median)	NR	NR	In all cases, optimum control of intraocular inflammation was achieved by the time IVB was initiated
Kim 2009[74]	Before-after study of IVB group and triamcinolone acetonide group (retrospective)	MO due to BRVO [56.86]	50 (50) (22 received IVB and 28 received triamcinolone acetonide)	NA	1.25 mg single dose	NR	24 weeks	NR	NR	NR
Kim 2011[91]	Case series (retrospective)	DMO	48[65]	Yes [3 morphological forms of DMO]	1.25mg	NR	≥12 months	NR	Grant from Kyung Hee University	
Kim 2011[75]	Non-randomised controlled study (prospective, consecutive)	AMD, RVO, DMO [64.8]	60(60)	Yes	1.25 mg	1	NR	NR	NR	

[m]Population included patients AMD, diabetes, retinal vein occlusion and other eye conditions

Study reference	Study type	Condition included patients [mean age in years]	Number of patients (number of eyes)	Baseline comparability (yes/no/ unknown/not applicable)	Dosage (mg) including frequency of dosing	Number of injections/ patients (mean)	Follow-up	Information on preparation of bevacizumab	Funding	Notes
Kiss 2006[63]	case – control (retrospective) [n]	AMD	61	Yes	1 mg	1	7 days	Local dispensing service	NR	
Krebs 2009[92]	Case series (prospective)	AMD [NR]	44(44)	unknown	1.25 mg 3 monthly injections based on OCT and FA findings;	2.6	1 week, 1 month and 3 months	NR	L. Boltzmann Institute	
Kriechbaum 2008[64]	Case series (prospective)	MO due to BRVO or CRVO [66]	28(29)	unknown	1mg at 4-week intervals 3 intravitreal injections	5.3	1, 7 and 28 months	Local dispensing service	NR	
Krishnan 2009[111]	Case control (retrospective) [o]	CNV due to AMD [80.5]	14	No	1.25mg	NR	2 and 4 weeks	NR	NR	
Kumar 2012[59]	Case series (retrospective)	Eales' disease [median 33]	14(14)	unknown	1.25mg	1	3 months	NR	NR	
Lazic 2007[189]	Case series (prospective)	CNV secondary to AMD	102(102)	NA	1.25 mg, once then as needed	NR	≥1.5 months	NR	None	Follow-up was 6-weekly and ongoing
Lima 2009[93]	Retrospective cohort study	Various, mostly AMD	326 (IVB injections)	NR	NR	NR	NR	NR	Macula Foundation Inc.	Same-day bilateral injections
Lommatzsch 2009[61]	Case series (retrospective)	AMD [77.7]	86	NR	1.25mg at 6 week intervals	NR	42.4 weeks	NR	NR	
Lorenz 2010[84]	Case series (retrospective)	Various[p]	144 (145)	yes	1.25mg	1.63	14	local dispensing service	None	

[n] Kiss 2006[63] included a control group that received triamcinolone acetonide.
[o] Krishnan 2009[111] included a control group that received ranibizumab.
[p]Population included patients with AMD, BRVO, CRVO and myopic choroidal neovascularisation.

Study reference	Study type	Condition included patients [mean age in years]	Number of patients (number of eyes)	Baseline comparability (yes/no/ unknown/not applicable)	Dosage (mg) including frequency of dosing	Number of injections/ patients (mean)	Follow-up	Information on preparation of bevacizumab	Funding	Notes
Mason 2008[94]	Case series (retrospective)	Various[q]	NR	NR	1.25mg	NR	NR	NR	University research grant, New York.	
Manayath 2009[190]	case series (prospective)	CMO due to CRVO 15 [64]	15	no	1.25mg	2.2	6-18 months	NR	NR	
Rasier 2009[77]	Quasi-experimental [r]	AMD [67.2]	82	unknown	1.25mg	1	6 weeks	NR	NR	
Russo 2009[171]	Non-randomised controlled trial	MO due to BRVO	15(15)	Yes [IVB:LGP]	1.25 mg, once or repeated as necessary	NR	12 months	NR	NR	No. of eyes/patients refers to IVB group
Saeed 2011[191]	Cohort (prospective)	Retinal vascular occlusions and other causes of CMO [68.6]	18	NA	1.25mg	NR	NR	NR	NR	Authors reported that nti-VEGF related reflux was not associated with a sub-therapeutic effect
Shah 2011[79]	Cohort (retrospective)	Various	10,958 (IVB injections)	NR	NR	NR	6 days	NR	NR	
Sharma 2012[86]	Cohort (retrospective)	AMD (122), DMO (25), RVO (19) [IVB-76.9]	173 (693 IVB injections)	No (difference in age and VA) [IVB:IVR]	1mg	unclear	NR	Local dispensing service	Part-funded by Novartis (and part-funded by Canadian Institutes for Health Research)	IVR patients were on average 1.8 years older than IVB patients (78.7 versus 76.9, p 0.01) and had slightly worse baseline vision (6/76 versus 6/64, p 0.013). 195 out of the 351 patients that received IVR, had been treated previously with IVB (mean, 4.3 injections per patient). Prior treatment in IVB group unclear.

[q] Population included patients with neovascular age-related macular degeneration; branch retinal vein occlusion, central retinal vein occlusion; cystoid macular oedema; proliferative diabetic retinopathy; diabetic macular oedema.

[r] Rasier 2009[77] studied between-group comparison of hypertensive / nonhypertensive patients.

Study reference	Study type	Condition included patients [mean age in years]	Number of patients (number of eyes)	Baseline comparability (yes/no/ unknown/not applicable)	Dosage (mg) including frequency of dosing	Number of injections/ patients (mean)	Follow-up	Information on preparation of bevacizumab	Funding	Notes
Shienbaum 2012[192]	Case series(retrospective)	AMD	73 (74)	Yes [IVB:IVR]	NR. [Monthly treatment until no intraretinal or subretinal fluid on optical coherence tomography. Treatment intervals determined by signs of exudation	NR	1.41 years	NR	No	
Shima 2008[62]	Case series (retrospective)	Various[s]	707 (1300 injections)	NR	1mg Once or repeated injections	NR	≥2 months	NR	Health Sciences Research Grant, Ministry of Health, Labour and Welfare, Japan	
Shimada 2011[98]	Case series (retrospective)	Myopic CNV [58.4]	74(74)	NA	1.25mg At baseline, week 1, then monthly (unspecified length of time)	NR	12 months (SD-4.3)	NR	Grants 19390441 and 19659445 from the Japan Society for the Promotion of Science, Tokyo, Japan	
Sivkova 2010[172]	case series (prospective)	CME due to DR, BRVO and CRVO [DR - 59.7; RVO - 68]	96(107)	Unclear [DR:RVO]	1.25mg 3 consecutive injections at 1-montly intervals	NR	4 months	NR	NR	No significant difference in adverse events between groups
Sohn 2011[99]	Case control (prospective) [t]	DMO [54.45]	11	NA	1.25mg	NR	1.3 months	NR	Gachon Univeristy, Incheon Korea	

[s] Conditions included AMD, DR, CNV, BRVO, CRVO and other pathologies (unspecified).
[t] Control group received triamcinolone acetonide

Study reference	Study type	Condition included patients [mean age in years]	Number of patients (number of eyes)	Baseline comparability (yes/no/ unknown/not applicable)	Dosage (mg) including frequency of dosing	Number of injections/ patients (mean)	Follow-up	Information on preparation of bevacizumab	Funding	Notes
Song 2011[100]	Case control (retrospective) [u]	DMO [57.1]	35 (58)	Yes [IVB:IVT]	1.25mg	NR	8 weeks	NR	Institute for Medicine research grant of Kosin University College of Medicine	
Sonmez 2011[193]	Case series (prospective)	subfoveal CME due to AMD [69.4(6.85)]	24 (24)	NA	1.25mg Week 0,6 and 12, then every 12 weeks until week 48	5	NR	NR	NR	Of 27 patients, 3 were lost to follow-up/protocol violation)
Spandau 2006[115] (abstract)	case series (retrospective, consecutive)	AMD	63	NA	1.5mg	NR	≥2 months	NR	NR	
Torres-Soriano 2012[194]	Case series (prospective)	CNV PDR, RVO (31) [NR]	31	NA	2.5mg, frequency not reported	1.3	1 month	NR	NR	
Valmaggia 2009[87]	Case series (retrospective)	CNV due to ARMD [75.5]	(324)	NA	1.25 mg; then every 6 weeks. Frequency not reported	3.3	NR	Local pharmacy	NR	
Weinberger 2007[97]	Case series (retrospective)	PED in exudative AMD [76]	31 (31)	NA	1.25 mg once	NR	1-7 months	NR	Academic institution	
Wickremasinghe 2008[195]	Case series (retrospective)	Neovascular AMD	1,278 IVB injections	NA	1.25 mg	NR	1 week	NR	NR	
Wu 2008[106]	interventional case series (prospective)	Various (including RVO, DMO)	1,173 (1,310)	NA	1.25 mg (16%), 2.5 mg (89%)	3.7 (3.3 per eye)	12-15 (13.6)	NR	No	
Yoon 2012[196]	Case series (retrospective)	Myopic CNV [49]	26	NA	1.25mg	2.2	12 months	NR	NR	Of the 40 patients included in the study, 14 received IVR

[u] Control group received triamcinolone acetonide

Study reference	Study type	Condition included patients [mean age in years]	Number of patients (number of eyes)	Baseline comparability (yes/no/ unknown/not applicable)	Dosage (mg) including frequency of dosing	Number of injections/ patients (mean)	Follow-up	Information on preparation of bevacizumab	Funding	Notes
Zhang 2012[197]	non-randomised interventional case series (prospective)	Subfoveal idiopathic CNV [32]	40	NA	1.25m.g	2	12 months	NR	NR	

Abbreviations: AMD-age-related macular degeneration, BRVO-branch retinal vein occlusion, CRVO-central retinal vein occlusion, CME-cystoid macular oedema, CNV-choroidal neovascularization, DMO-diabetic macular oedema, DR-diabetic retinopathy, DRT-diffuse retinal thickening, IVB-intravitreal bevacizumab, IVP-intravitreal pegaptinib, IVR-intravitreal ranibizumab, MO- macular oedema, NA-not applicable, NR –not reported, RVO-retinal vein occlusion, PED-pigment epithelium detachment, SRD-serous retinal detachment

APPENDIX 10: ADVERSE EVENT RATES FROM OBSERVATIONAL STUDIES

Table A 13: Systematic adverse events in included observational studies

Study reference	Death (%) [n/N]	Hospitalisation(%) [n/N]	Non-ocular haemorrhage(%) [n/N]	Arterial thromboembolism(%) [n/N]	Hypertension(%) [n/N]	Myocardial infarction(%) [n/N]	Cerebrovascular accident(%) [n/N]	Transient ischaemic attack(%) [n/N]	Notes
Abraham-Marin 2007[104]	NR	NR	NR	NR	NR	NR	NR	NR	
Arevalo 2008[71]	NR	NR	NR	0	NR	0	0	0	
Artunay 2009[113]	NR	NR	NR	NR	NR	NR	NR	NR	
Azad 2008[105]	NR	NR	NR	NR	NR	NR	NR	NR	
Bakri 2009[88]	NR	NR	NR	0	NR	0	0	NR	
Bashshur 2009[69]	NR	NR	NR	NR	NR	1.27[1/79]	NR	NR	One patient required coronary pass surgery for unstable angina. It was reported that the association between treatment and event could not be established.
Carneiro 2010[89]	NR	NR	NR	NR	NR	NR	2.5 (2/80) (patients subjected to repeat injections)	NR	Authors reported that the two cases of cerebrovascular accident occurred in women over 70 years of age who had other risk factors. The event occurred 3 weeks after IVB when systemic concentrations of bevacizumab are considered to be lower.

Study reference	Death (%) [n/N]	Hospitalisation(%) [n/N]	Non-ocular haemorrhage(%) [n/N]	Arterial thromboembolism(%) [n/N]	Hypertension(%) [n/N]	Myocardial infarction(%) [n/N]	Cerebrovascular accident(%) [n/N]	Transient ischaemic attack(%) [n/N]	Notes
Carneiro 2011[90]	1.03[1/97]	NR	NR	1.03[1/97]	NR	See note	6.19[6/97]	1.03[1/97]	Arterial thromboembolic events-12.4% [12/97] included peripheral thromboembolic events (n=1), sudden death (n=1), TIA (n=1), MI (n=2), unstable angina (n=1)], and stroke (n=6 of which 2 were lethal). Authors reported that IVB increased the risk of arterial thromboembolic events (ATE) when compared with ranibizumab (i.e. 3 events: stroke, n=2; and MI, n=1). However, in an elderly population with multiple cardiovascular risk factors, new ATEs may not be attributed exclusively to IVB administration
Chen 2011[185]	NR	NR	NR	NR	NR	NR	NR	NR	

Study reference	Death (%) [n/N]	Hospitalisation(%) [n/N]	Non-ocular haemorrhage(%) [n/N]	Arterial thromboembolism(%) [n/N]	Hypertension(%) [n/N]	Myocardial infarction(%) [n/N]	Cerebrovascular accident(%) [n/N]	Transient ischaemic attack(%) [n/N]	Notes
Cleary 2008[80]	NR	NR	NR	NR	0	NR	NR	NR	No systemic adverse events such as thrombosis or hypertension
Costa 2006[81]	NR	NR	NR	NR	0	NR	NR	NR	No systemic or serious adverse events were observed.
Costagliola 2009[82]	NR	NR	NR	0	NR	NR	NR	NR	
Curtis 2010[58]	3.8 [1058/27,962]	NR	NR	NR	NR	8.2 [2,286/27,962]	8.7 [2,422/27,962]	NR	
Falkenstein 2007[110]	NR	NR	NR	NR	NR	NR	NR	NR	
Fintak 2008[83]	NR	NR	NR	NR	NR	NR	NR	NR	
Fong 2008[60]	1.83 [2/109]	NR	NR	NR	NR	NR	NR	NR	One death due to MI 6 weeks after 3rd IVB injection (history of hypertension), other was due to upper respiratory tract infection, 2 months after 3rd IVB injection (no medical history)
Frenkel 2010[109]	NR	NR	NR	NR	NR	NR	NR	NR	
Fukami 2011[108]	NR	NR	NR	NR	NR	NR	NR	NR	
Gamulescu 2010[186]	NR	NR	NR	NR	NR	NR	NR	NR	
Gomi 2008[57]	NR	NR	NR	NR	NR	NR	NR	NR	
Good 2011[78]	NR	NR	NR	NR	NR	NR	NR	NR	
Goverdhan 2008[73]	NR	NR	NR	NR	NR	NR	NR	NR	No systemic AEs reported.

Study reference	Death (%) [n/N]	Hospitalisation(%) [n/N]	Non-ocular haemorrhage(%) [n/N]	Arterial thromboembolism(%) [n/N]	Hypertension(%) [n/N]	Myocardial infarction(%) [n/N]	Cerebrovascular accident(%) [n/N]	Transient ischaemic attack(%) [n/N]	Notes
Gower 2011[112] (abstract)	11% higher than for IVR (HR: 1.11; 99% CI 1.01-1.23)	NR	NR	NR	NR	NR	57% higher risk than for IVR(HR: 1.57; 99% CI 1.04-2.37)	NR	Hazard ratios adjusted for baseline comorbidities, demographics and socio-economic status. Haemorrhagic cerebrovascular accident rates reported – no difference for ischemic events.
Hernandez-Rojas 2007[68]	NR	NR	NR	NR	NR	NR	NR	NR	
Higashide 2012[114]	NR	NR	NR	NR	NR	0	0	NR	Authors reported that no cases experienced systemic side effects including myocardial infarction and cerebrovascular accidents within 3 months after bevacizumab injection.
Hollands 2007[187]	NR	NR	NR	NR	NR	NR	NR	NR	
Ikuno 2009[65]	NR	NR	NR	NR	NR	NR	NR	NR	
Inman 2011[85]	NR	NR	NR	NR	NR	NR	NR	NR	This study reported incidence of infectious endophthalmitis associated with anaesthetic procedure.

Study reference	Death (%) [n/N]	Hospitalisation(%) [n/N]	Non-ocular haemorrhage(%) [n/N]	Arterial thromboembolism(%) [n/N]	Hypertension(%) [n/N]	Myocardial infarction(%) [n/N]	Cerebrovascular accident(%) [n/N]	Transient ischaemic attack(%) [n/N]	Notes
Jaissle 2009[95]	NR	NR	NR	NR	NR	NR	NR	NR	Authors reported that no obvious bevacizumab-related ocular or systemic adverse events were apparent.
Johnson 2010[96]	NR	NR	NR	NR	NR	NR	NR	NR	
Jonas, 2007[66]	NR	NR	NR	NR	NR	NR	NR	NR	
Jonas 2008[67]	NR	NR	NR	NR	NR	NR	NR	NR	
Julian 2011[188]	NR	NR	NR	NR	NR	NR	NR	NR	Authors reported that there were no adverse events related to IVB nor to the injection procedure.
Kim 2009[74]	NR	NR	NR	NR	NR	NR	NR	NR	Authors reported that 'no general complications' were observed.
Kim 2011[91]	NR	NR	NR	NR	NR	NR	NR	NR	Authors reported that 'no other systemic complications such as cardiovascular events or cerebral accidents were encountered..'
Kim 2011[75]	NR	NR	NR	NR	NR	NR	NR	NR	
Kiss 2006[63]	NR	NR	NR	NR	NR	NR	NR	NR	
Krebs 2009[92]	NR	NR	NR	NR	4.5[2/44] (Patients were on anti-hypertensives at baseline)	0	0	0	Authors reported that no serious systemic or drug-related adverse events were observed during the follow-up period.

Study reference	Death (%) [n/N]	Hospitalisation(%) [n/N]	Non-ocular haemorrhage(%) [n/N]	Arterial thromboembolism(%) [n/N]	Hypertension(%) [n/N]	Myocardial infarction(%) [n/N]	Cerebrovascular accident(%) [n/N]	Transient ischaemic attack(%) [n/N]	Notes
Kriechbaum 2008[64]	NR	NR	NR	NR	NR	NR	NR	NR	
Krishnan 2009[111]	NR	NR	NR	NR	NR	NR	NR	NR	
Kumar 2012[59]	NR	NR	NR	NR	NR	NR	NR	NR	
Lazic 2007[189]	NR	NR	NR	NR	NR	NR	NR	NR	No inflammation, infection, thrombo-embolic events or ocular toxicity were reported.
Lima 2009[93]	NR	NR	NR	NR	NR	NR	NR	NR	
Lommatzsch 2009[61]	NR	NR	NR	NR	NR	NR	NR	NR	
Lorenz 2010[84]	NR	NR	NR	NR	NR	NR	NR	NR	
Mason 2008 [94]	NR	NR	NR	NR	NR	NR	NR	NR	
Manayath 2009[190]	NR	NR	NR	NR	NR	NR	NR	NR	
Rasier 2009[77]	NR	NR	NR	NR	15.58[13/82]	NR	NR	NR	
Russo 2009[171]	NR	NR	NR	NR	NR	NR	NR	NR	No obvious systemic adverse events were observed.
Saeed 2011[191]	NR	NR	NR	NR	NR	NR	NR	NR	
Shah 2011[79]	NR	NR	NR	NR	NR	NR	NR	NR	

Study reference	Death (%) [n/N]	Hospitalisation(%) [n/N]	Non-ocular haemorrhage(%) [n/N]	Arterial thromboembolism(%) [n/N]	Hypertension(%) [n/N]	Myocardial infarction(%) [n/N]	Cerebrovascular accident(%) [n/N]	Transient ischaemic attack(%) [n/N]	Notes
Sharma 2012[86]	NR	See note	NR	1.35 [3/222] (see note)	NR	0.09[2/222]		0.45[1/222]	Rates are presented per number of injections.[xxii] Arterial thromboembolism was defined as an emergency room visit within 1 month of injection in which the patient was diagnosed with a myocardial infarction, ischemic stroke, transient ischemic attack, or pulmonary embolism.
Shienbaum 2012 [192]	NR	NR	NR	NR	NR	NR	NR	NR	Authors reported that no adverse ocular or systemic events were observed.
Shienbaum 2012[192]	NR	NR	0	0	0	0	0	0	Authors reported that no adverse ocular or systemic events were observed.

[xxii] Incidence of systemic adverse events was reported for patients with addresses within the greater Kingston region (n=222/693 injections)

Study reference	Death (%) [n/N]	Hospitalisation(%) [n/N]	Non-ocular haemorrhage(%) [n/N]	Arterial thromboembolism(%) [n/N]	Hypertension(%) [n/N]	Myocardial infarction(%) [n/N]	Cerebrovascular accident(%) [n/N]	Transient ischaemic attack(%) [n/N]	Notes
Shima 2008[62]	NR	NR	NR	NR	0.0.28[2/707]	NR	0.14[1/707]	NR	Other reported complications : facial skin redness (n = 1) - 0.14%; itchy diffuse rash (n = 1- 0.14%; and menstrual irregularities (n = 3) - 0.42%.
Shimada 2011[98]	NR	NR	NR	NR	NR	NR	NR	NR	
Sivkova 2010[172]	NR	NR	NR	0	NR	NR	NR	NR	
Sohn 2011[99]	NR	NR	NR	NR	NR	NR	NR	NR	
Song 2011[100]	NR	NR	NR	NR	NR	NR	NR	NR	
Sonmez 2011[193]	NR	NR	NR	0	NR	NR	NR	NR	Authors reported that 'no serious ocular or nonocular adverse events were noted'.
Spandau 2006[115]	NR	NR	NR	NR	NR	NR	NR	NR	
Torres-Soriano 2012[194]	NR	NR	NR	NR	NR	NR	NR	NR	
Valmaggia 2009[87]	NR	NR	NR	NR	NR	NR	NR	NR	
Weinberger 2007[97]	NR	NR	NR	NR	NR	NR	NR	NR	
Wickremasinghe 2008[195]	NR	NR	NR	NR	NR	NR	NR	NR	
Wu 2008[106]	0.43[5/1,173]	NR	NR	NR	0.66 [7/1,173]	0.43[5/1,173]	0.51[6/1,173]	NR	
Yoon 2012[196]	NR	NR	NR	NR	NR	NR	NR	NR	
Zhang 2012[197]	NR	NR	NR	0	0	NR	NR	NR	

Abbreviations: n-number, NR-not reported, IVB-intravitreal bevacizumab

Table A 14: Ocular adverse events in included observational studies

Study reference	Infectious endophthalmitis(%) [n/N]	Retinal detachment(%) [n/N]	Retinal tear(%) [n/N]	Anterior chamber reaction(%) [n/N]	Ocular haemorrhage(%) [n/N]	Lens damage(%) [n/N]	Ocular Hypertension(%) [n/N]	Visual loss(%) [n/N]	Notes
Abraham-Marin 2007[104]	NR	NR	NR	20.50[8/39]	7.69[3/39]	NR	NR	NR	None of the patients with intraocular inflammation required treatment and inflammatory cells spontaneously resolved.
Artunay 2009[113]	0.16[3/1822]	0	NR	0.16[3/1822]	NR	NR	NR	0.16[3/1822] (blurry vision)	Adverse events reported for 1822 eyes
Azad 2008[105]	NR	NR	NR	NR	25.00[10/40]	NR	0	NR	
Bakri 2009[88]	NR	NR	NR	NR	NR	NR	NR	NR	1 patient with hypopyon was pre-treated.
Bashshur 2009[69]	NR	NR	NR	NR	NR	NR	NR	NR	No ocular side effects were reported
Carneiro 2010[89]	NR	NR	2.5 [2/80]	NR	1.25 [1/80]	NR	NR	7.5[6/80]	Incidence of subretinal macular haemorrhage reported. Vision loss was attributed to subretinal fibrosis n=2) and atrophy of the retinal pigment epithelium (n=4)
Carneiro 2011[90]	NR	NR	NR	NR	NR	NR	NR	NR	
Cavalcante 2010[198]	0.01 [1/7315] Per injection	NR	NR	NR	NR	NR	NR	NR	
Chan 2007[70]	NR	NR	2.07[22/1064]	NR	NR	NR	NR	NR	
Chen 2011[185]	0	0	NR	0	0	0	0	NR	
Cleary 2008[80]	0.89 [1/112]	NR	2.68 [3/112]	NR	2.68 [3/112]	NR	NR	NR	Submacular haemorrhage considered.
Costa 2006[81] – 1.0 mg	0	NR	NR	0	33.33 [5/15]	NR	NR	NR	Subconjunctival haemorrhage considered. No uveitis observed.
Costa 2006[81] – 1.5 mg	0	NR	NR	0	53.33 [8/15]	NR	NR	NR	Subconjunctival haemorrhage considered. No uveitis observed.
Costa 2006[81] – 2.0 mg	0	NR	NR	0	26.67 [4/15]	NR	NR	NR	Subconjunctival haemorrhage considered. No uveitis observed.

Study reference	Infectious endophthalmitis(%) [n/N]	Retinal detachment(%) [n/N]	Retinal tear(%) [n/N]	Anterior chamber reaction(%) [n/N]	Ocular haemorrhage(%) [n/N]	Lens damage(%) [n/N]	Ocular Hypertension(%) [n/N]	Visual loss(%) [n/N]	Notes
Costagliola 2009[82]	0	NR	0	0	NR	NR	NR	NR	
Curtis 2010[58]	NR	NR	NR	NR	NR	NR	NR	NR	
Falkenstein 2007[110]	NR	NR	NR	NR	NR	NR	14.00[10/70]	NR	IOP >30 mm Hg at 10 minutes
Fintak 2008[83]	0.02 [3/12585] Per injection	NR	NR	NR	NR	NR	NR	NR	
Fong 2008[60]	0.92 [1/109]	NR	NR	NR	NR	NR	NR	NR	Culture positive Staphylococcus epidermidis endophthalmitis
Frenkel 2010[109]	NR	NR	NR	NR	NR	NR	20.00 [15/75]	NR	IOP > 40mmHg spike (0-2 min)
Fukami 2011[108]	NR	NR	NR	50.00[6/12]	NR	NR	NR	50.00[6/12]	Authors described anterior chamber reaction as sterile endophthalmitis and also referred to blurred vision after IVB treatment.
Funk 2009[199]	NR	NR	NR	NR	NR	NR	NR	NR	
Gamulescu 2010[186]	0	NR	NR	0	NR	NR	NR	NR	
Gomi 2008[57]	NR	NR	0	NR	0	NR	NR	NR	
Good 2011[78]	NR	NR	NR	NR	NR	NR	9.90 [10/101]	NR	IOP ≥22 mm Hg
Goverdhan 2008[73]	NR	NR	NR	NR	7.55[4/53]	NR	NR	1.89[1/53]	Submacular haemorrhage. Visual loss of 6 lines or 30 ETDRS letters
Gower 2011[112] (abstract)	NR	NR	NR	80% higher risk than for ranibizumab (HR: 1.8; 99% CI: 1.2-2.8)	NR	NR	19% lower risk than for ranibizumab (HR: 0.81; 99% CI: 0.71-0.93)	NR	Hazard ratios adjusted for baseline comorbidities, demographics and socio-economic status. Ocular inflammation for ACR.
Hernandez-Rojas 2007[68]	NR	NR	NR	NR	NR	NR	NR	NR	

Study reference	Infectious endophthalmitis(%) [n/N]	Retinal detachment(%) [n/N]	Retinal tear(%) [n/N]	Anterior chamber reaction(%) [n/N]	Ocular haemorrhage(%) [n/N]	Lens damage(%) [n/N]	Ocular Hypertension(%) [n/N]	Visual loss(%) [n/N]	Notes
Higashide 2012[114]	0	0	NR	0	0	0	NR	2.38[2/84]	Authors reported that no cases had marked inflammation, lens injuries, marked vitreous haemorrhage, retinal detachment, or endophthalmitis
Hollands 2007[187]	NR	NR	NR	NR	NR	NR	2.88[3/104]	NR	Authors reported that IVB injection is safe with respect to short-term IOP changes, as almost all patients (97.1%) IOP returned to a safe range (<25 mm Hg) within 30 minutes. Elevated IOP at 30 minutes after injection does occur, rarely, thus clinicians should consider checking IOP after injection as a precaution. Transient extreme IOP elevations occur in a significant percentage of patients, but the consequences of these events are unknown.
Ikuno 2009[65]	NR	See notes	NR	NR	NR	NR	NR	NR	Authors reported that two eyes developed chemosis at the injection site one day after IVB that resolved with a topical steroid treatment in one week. One eye developed a retinal detachment two months after IVB; however, the relationship between IVB and the detachment was questionable.

Study reference	Infectious endophthalmitis(%) [n/N]	Retinal detachment(%) [n/N]	Retinal tear(%) [n/N]	Anterior chamber reaction(%) [n/N]	Ocular haemorrhage(%) [n/N]	Lens damage(%) [n/N]	Ocular Hypertension(%) [n/N]	Visual loss(%) [n/N]	Notes
Inman 2011[85]	0	NR	NR	NR	NR	NR	NR	NR	
Jaissle 2009[95]	0	NR	0	NR	NR	NR	NR	NR	Authors reported that no cases of endophthalmitis, retinal detachment or any other severe procedure-related complications were observed in a total of 78 injections.
Johnson 2010[96]	NR	NR	NR	5.20[9/173] (1.3% of total injections, 9/689)	NR	NR	NR	NR	Authors reported that IVB is associated with a low but significant risk of acute intraocular inflammation and may result in significant visual loss.
Jonas, 2007[66]	0.0016 [1/625] (1 per 1000 injections)	NR	NR	NR	NR	NR	NR	NR	Authors reported that the rate of infectious endophthalmitis after an IVB injection of 1.5mg may be approximately 1:1000.
Jonas 2008[67]	0.05[2/3818]	0.03[1/3818]	NR	NR	NR	0.05[2/3,818]	NR	NR	Two patients in the IVB group developed progressive cataract following treatment.
Julian 2011[188]	NR	NR	NR	NR	NR	NR	NR	NR	Authors reported that there were no adverse events related to IVB nor to the injection procedure.
Kim 2009[74]	0	0	NR	NR	0	0	0	9.09[2/22]	
Kim 2011[91]	0	0	0	NR	NR	NR	0	NR	
Kim 2011[75]	0	0	0	0	NR	NR	0	NR	

Study reference	Infectious endophthalmitis(%) [n/N]	Retinal detachment(%) [n/N]	Retinal tear(%) [n/N]	Anterior chamber reaction(%) [n/N]	Ocular haemorrhage(%) [n/N]	Lens damage(%) [n/N]	Ocular Hypertension(%) [n/N]	Visual loss(%) [n/N]	Notes
Kiss 2006[63]	NR	NR	NR	6.52[3/46]	NR	NR	NR	NR	Authors reported that no inflammatory response was detected clinically and by laser flare meter after IVB administration. It was suggested that the slight reduction in anterior chamber flare could be due to known anti-inflammatory effect of anti-VEGF.
Krebs 2009[92]	0	0	NR	0	NR	0	6.8[3/44 eyes]	NR	
Kriechbaum 2008[64]	0	0	NR	0	NR	NR	NR	NR	Authors stated that none of the patients experienced severe local adverse events.
Krishnan 2009[111]	NR	NR	NR	NR	28.57[4/14]	NR	NR	7.14[1/14]	Association between visual loss and IVB administration was unclear.
Kumar 2012[59]	NR	28.57[4/14]	NR	NR	NR	NR	0	NR	
Lazic 2007[189]	NR	NR	1.96 [2/102]	NR	NR	NR	NR	NR	Reported as pigment epithelium rip
Lima 2009[93]	NR	NR	NR	0.31 [1/326] Per injection	NR	NR	NR	NR	
Lommatzsch 2009[61]	0	NR	15.12[13/86]	NR	NR	NR	NR	NR	
Lorenz 2010[84]	NR	NR	NR	NR	NR	NR	NR	NR	
Mason 2008 [94]	0.02[1/5233]	NR	NR	NR	NR	NR	NR	NR	
Manayath 2009[190]	0	0	NR	NR	NR	NR	NR	NR	
Rasier 2009[77]	NR	NR	NR	NR	7.31[6/82]	NR	NR	NR	
Russo 2009[171]	NR	NR	NR	NR	NR	NR	NR	NR	Nine patients had minor local AEs listed as conjunctival hyperaemia and subconjunctival haemorrhage, but no numbers given for each one
Saeed 2011[191]	NR	0	NR	NR	NR	NR	NR	NR	

Study reference	Infectious endophthalmitis(%) [n/N]	Retinal detachment(%) [n/N]	Retinal tear(%) [n/N]	Anterior chamber reaction(%) [n/N]	Ocular haemorrhage(%) [n/N]	Lens damage(%) [n/N]	Ocular Hypertension(%) [n/N]	Visual loss(%) [n/N]	Notes
Shah 2011[79]	0.11 [12/10958] Per injection	NR	NR	NR	NR	NR	NR	NR	
Sharma 2012[86]	0	0	NR	1.30[9/693]	NR	NR	NR	NR	Adverse event rates reported per injection.[xxiii]
Shienbaum 2012 [192]	NR	NR	NR	NR	NR	NR	NR	NR	Safety study- Reported no adverse ocular or systemic events observed.
Shima 2008[62]	NR	NR	0.14[1/707]	NR	NR	0.14[1/707]	NR	0.14[1/707]	Ocular complications also included corneal abrasion (n = 2) - 0.28%; chemosis (n = 2) - 0.28%; ocular inflammation (n = 2) - 0.28%. Acute visual loss occurred in a patient with PDR
Shimada 2011[98]	NR	NR	NR	NR	NR	NR	NR	NR	
Sivkova 2010[172]	0	0	0	0	0	0	0.79[1/127]	0	
Sohn 2011[99]	0	0	NR	NR	NR	NR	NR	NR	
Song 2011[100]	NR	NR	NR	NR	NR	NR	0	NR	
Sonmez 2011[193]	0	NR	4.17 [1/24;eye]	0	9.2% [11/24; injections]	NR	NR	NR	Authors reported that no serious 'drug-related' ocular adverse events occurred. Ocular bleeding referred to subconjunctival haemorrhage at the injection site.
Spandau 2006[115]	NR	NR	6.35[4/63]	NR	NR	NR	NR	1.59[1/63]	One of the four patients with retinal tear developed visual loss. Patients included in this study had underlying pigment epithelium detachment.

[xxiii] This rate is based on the total number of IVB injections evaluated (n=693).

Study reference	Infectious endophthalmitis(%) [n/N]	Retinal detachment(%) [n/N]	Retinal tear(%) [n/N]	Anterior chamber reaction(%) [n/N]	Ocular haemorrhage(%) [n/N]	Lens damage(%) [n/N]	Ocular Hypertension(%) [n/N]	Visual loss(%) [n/N]	Notes
Torres-Soriano 2012[194]	NR	NR	NR	NR	NR	NR	NR	NR	
Weinberger 2007[97]	NR	NR	2.24[178]	NR	NR	NR	NR	NR	17.4%(n=31/178) patients treated with IVB had initial PED at presentation.
Valmaggia 2009[87]	0	0		0	0	0	0	NR	Vitreous haemorrhage assessed
Wickremasinghe 2008[195]	NR	NR	NR	1.49 [19/1278] Per injection	NR	NR	NR	NR	
Wu 2008[106]	0.60[7/1173]	0.68[8/1173]	NR	0.43[5/1173]	71.52[839/1,173]	NR	NR	(see note)	The cultures of patients with bacterial endopthalmitis yielded 5 cases of coagulase negative staphylococci and one case each of Staphylococcus aureus and Streptococcus pneumoniae. It is uncertain whether reported visual loss 0.51[6/1,173] was an efficacy outcome or safety outcome. Note: Visual loss was not listed under ocular complications (see Table 4 of published paper).
Yoon 2012[196]	0	0	NR	NR	NR	NR	NR	NR	
Zhang 2012[197]	0	0	NR	0	NR	NR	NR	NR	

Abbreviations: AE-adverse event, n-number, ETDRS-Early treatment diabetic retinopathy study, NR-not reported, PDR-proliferative diabetic retinopathy, PED-pigment epithelium detachment

APPENDIX 11

Table A 15: Safety review - table of excluded studies with reasons

Eligibility critera	Study references	Total number
Population not relevant	Aggio 2007[200] Ahmadieh 2011[201] Aisenbrey 2007[202] Algvere 2008[203] Arevalo 2009[72] Arias 2007[107] Arias 2008[204] Arias 2008[103] Avery 2006[205] Bae 2011[206] Bashshur 2006[207] Beutel 2010[208] Bonin-Filho 2009[209] Brouzas 2009[210] Cervantes-Castandea 2009[211] Chan 2009[212] Chau 2009[213] Chen 2011[214] Cheng 2011[215] Chiang 2012[216] Cavalcante 2010[198] Davis 2010[217] Ehlers 2011[218] Ehrlich 2008[219] Fang 2008[220] Finger 2008[221] Finger 2012[222] Forte 2011[223] Funk 2010[224] Garg 2008[225] Gelisken 2009[226] Ghanem 2009[227] Gharbiya 2009[228] Ghazi 2010[229] Gregori 2008[230] Hasanreisoglu 2009[231] Honda 2008[232] Hou 2009[233] Hung 2010[234] Jiang 2009[235] Jonas 2011[236] Kim 2011[237] Kook 2008[238] Kotecha 2011[76] Kramer 2010[239] Kumar 2007[240] Kuo 2011[241] Lupinacci 2008[242] Moradian 2008[243] Nielsen 2012[244] Nuti 2011[245] Roh 2009[246] Roh 2010[247] Ronan 2007[248] Roth 2009[249] Ruiz-Moreno 2010[250] Schadlu 2008[251] Seo 2009[252] Shetty 2008[253] Shimura 2008[254]	79

Eligibility critera	Study references	Total number
	Skaat 2011[255] Soheilian 2010[173] Soliman 2008[256] Song 2009[257] Spielberg 2009[258] Stahl 2009[259] Stergiou 2011[260] Subramanian 2010[175] Synek 2011[177] Tao 2010[261] Tran 2008[262] Tseng 2012[263] Wang 2011[178] Warid Al-Laftah 2010[264] Weiss 2009[265] Wu 2012[266] Yamaike 2009[267] Yeung 2010[268] Zhang 2011[183]	
Intervention not relevant	Alkawas 2010[269] Arevalo 2011[270] Arias 2010[271] Cleary 2011[272] Curtis 2010[58] Dayani 2007[273] Frenkel 2007[274] Furino 2009[275] Hariprasad 2006[276] Hernandez da Mota 2010[154] Kopecna 2011[277] Koss 2010[278] Moraczewski 2008[279] Myung 2010[280] Suzuki 2010[281] Takahashi 2010[282] Tao 2010[283] Treumer 2010[284] Udaondo 2011[285] Vasudev 2009[286] Voykov 2010[287] Wakabayashi 2008[288] Wong 2008[289] Wu 2009[290] Yamashiro 2010[291] Yoon 2010[292]	26
Study type not relevant	Abbate 2011[293] Abdallah 2009[294] Al-Qureshi 2012[295] Avastin and Lucentis are equally effective…[296] Battaglia 2009[297] Beaumont 2011[298] Blair 2012[299] Campochiaro 2012[300] Chang 2007[301] Cheung 2012[302] Chung 2010[303] First reports of serious adverse reactions 2009[304] First reports of serious adverse reactions 2009[305] First reports of serious adverse reactions 2010[306] Food and Drug Administration 2009[307] Fung 2006[21] Gunther 2009[308] Kernt 2007[309] Martin 2011[310] Martinez-Ferez 2011[311] Schouten 2009[312]	34

Eligibility critera	Study references	Total number
	Schultz 2011[313] Schwartz 2009[314] Schwartz 2009[315] Seet 2012[316] Soiberman 2010[317] Spitzer 2008[318] Summary of recent evidence… 2011[319] Utman 2008[320] Veritti 2012[321] Waisbourd 2011[322] WHO 2011[323] Wu 2009[324] Ziemssen 2009[325]	
Case reports/case series/case control studies <10 patients	Aggio 2007[326] Alkuraya 2008[327] Amselem 2009[328] Anto 2012[329] Arriola-Villalobos 2008[330] Artunay 2010[331] Bae 2010[332] Bakri 2006[333] Bakri 2008[88] Baskin 2011[334] Brouzas 2009[335] Byeon 2009[336] Chen 2009[337] Chieh 2007[338] Chilov 2007[339] Forooghian 2008[340] Freund 2006[341] Gamulescu 2007[342] Gelisken 2006[343] Gibran 2007[344] Guthoff 2010[345] Hannan 2007[346] Jalil 2007[347] Jonas 2009[348] Kawashima 2008[349] Kim 2008[350] Kopel 2008[351] Maier 2009[352] Mathews 2007[353] Mennel 2007[354] Meyer 2006[355] Meyer 2007[356] Mitamura 2008[357] Montero 2008[358] Neri 2008[359] Nicolo 2006[360] Peng 2009[361] Piermici 2006[362] Rodrigues 2007[363] Rosenfeld 2005[1] Sayanagi 2009[364] Shah 2011[365] Shah 2011[366] Shaikh 2007[367] Shan 2006[368] Shimura 2010[369] Shoeibi 2011[370] Song 2010[371] Subramanyam 2007[372] Tarantola 2010[373] Teixeira 2010[374] Tranos 2007[375] Wiegand 2009[376]	56

Eligibility critera	Study references	Total number
	Wu 2009[377] Yenerel 2008[378] Yoon 2009[379]	
Foreign language	Angulo Bocco 2008[380] Baeteman 2009[381] Bidot 2011[382] Demircelik 2009[383] Dithmar 2009[384] Dolezalova 2010[385] Fukami 2011[108] Guthoff 2011[386] Guthoff 2011[387] Hasler 2008[388] Hoh 2008[389] Hong 2010[390] Horn 2008[391] Jamrozy-Witkowska 2011[392] Malgorzata 2010[393] Meng 2009[394] Meyer 2007[395] Meyer 2008[396] Meyer 2008[397] Schaal 2009[398] Schaal 2009[399] Schaal 2009[400] Schiano 2009[401] Sekeryapan 2011[402] Sun 2010[403] The Lucentis Avastin story 2009[404] Vidinova 2009[405] Yu 2010[406] Zhou 2010[407] Zwaan 2009[408]	30