# APPENDIX A: SEARCH STRATEGY

**MEDLINE** (PubMed) searched 5/8/2013

| Search | Query |
|---|---|
| #9 | Search (#8) AND #7 |
| #8 | Search ((((((femtosecond) OR alcon lensx) OR optimedica catalys) OR lensar) OR victus) OR intralase) OR ifs laser systems OR "all-laser Lasik" |
| #7 | Search (#6) OR #5 |
| #6 | Search cataract |
| #5 | Search "Cataract"[51] OR "Cataract Extraction"[51] |

76 unique cites added to EndNote Library

**Cochrane Central Register of Controlled Trials and Database of Sytematic Reviews** (OVID), searched 5/8/2013

| # | Searches |
|---|---|
| 1 | exp Cataract Extraction/ or exp Cataract/ or cataract.mp. |
| 2 | femtosecond.mp. |
| 3 | alcon lensx.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] |
| 4 | optimedica catalys.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] |
| 5 | lensar.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] |
| 6 | victus.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] |
| 7 | intralase.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] |
| 8 | ifs laser systems.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] |
| 9 | All-laser lasik.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] |
| 10 | 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 |
| 11 | 1 and 10 |

3 unique cites added to EndNote Library

**Additional databases, societies and journals,** searched 4/17/2013 to 7/9/2013:

1. ASCRS: American Society of Cataract and Refractive Surgery http://www.ascrs.org/ [See also abstracts that were locked out at end of document]
2. Journal of Cataract & Refractive Surgery http://www.jcrsjournal.org/
3. American Academy of Ophthalmology http://www.aao.org/

4. International Society of Refractive Surgery http://www.aao.org/isrs/
5. American Academy of Opthalmic Executives http://www.aao.org/aaoe/
6. The Foundation of the American Academy of Ophthalmology http://www.faao.org/
7. The Royal College of Ophthalmologists http://www.rcophth.ac.uk/
8. The Association for Research in Vision and Ophthalmology http://www.arvo.org/
9. The Journal of Cataract and Refractive Surgery http://www.jcrsjournal.org/
10. Ophthalmology, the official journal of the American Academy of Ophthalmology – http://www.aaojournal.org/
11. COS Conference Papers Index
12. Proceedings First (OCLC)
13. http://clinicaltrials.gov/
14. http://www.fda.gov/

# APPENDIX B: INCLUSION/EXCLUSION CRITERIA

| Code | Definition | Exclusion criteria/notes | KQ1 – Benefits | KQ2 –Adverse effects | KQ3 – Learning curve |
|---|---|---|---|---|---|
| I-1<br>I-2<br>I-3<br>I-SR | Include; addresses KQ1, KQ2, or KQ3<br>SR = systematic review | | KQ1: What are the benefits of FLACS compared with conventional cataract surgery? | KQ2a: What are the unique risks associated with FLACS?<br>KQ2b: What are the risks of FLACS compared to conventional cataract surgery? | KQ3: What are the intra-operative and post-operative risks of FLACS with regard to the experience f the surgeon? |
| X1 | Non-English language | | | | |
| X2 | Does not pertain to femtosecond laser technology | | | | |
| X3 | Intervention not in scope | Exclude studies of lasers used for procedures other than cataract surgery | Included interventions: femtosecond lasers used for cataract surgery applications | Same interventions as KQ1 | Same interventions as KQ1 |
| X4 | Study population not in scope | Note: FLACS is contraindicated in the following populations: advanced glaucoma; high anxiety; tremors; dementia; facial or ocular anatomy that precludes docking | Included population: adults undergoing cataract surgery | Same population as KQ1. | Same population as KQ1 |
| X5 | No primary data or study design not in scope, according to each KQ. | Exclude non-systematic or narrative reviews, editorials and opinions.<br>Add code B (e.g. X5-B) to consider using the article in Discussion, or possibly describe the study data as a lower level of evidence. | Include controlled study designs:<br>• Randomized controlled trials (RCTs)<br>• Non-randomized controlled clinical trials<br>• Controlled before/after studies | Included study designs for harms:<br>• Controlled studies<br>• Quasi-experimental studies<br>• Cohort studies<br>• Case-control studies<br><br>Excluded study designs:<br>• Case reports<br>• Case series | • Same study designs listed for KQ2<br>• Cost-evaluation studies |
| X6 | Outcomes that are not in scope | | Short-term patient outcomes:<br>• Visual acuity: post-operative day 1<br><br>Long-term patient outcomes:<br>• Visual acuity: after post-operative day 1 (typically recorded after 1 week, 1 month, or 90 days)<br>• Quality of life (QOL) measures | Intra-operative complications:<br>• Capsular blockage syndrome<br>• Dislocated nucleus<br>• Capsular tear<br>Post-operative complications:<br>• Infection<br>• Retinal swelling/cystoid edema (CME)<br>• Intraocular (IOL) decentration<br>• Corneal edema<br>Other reported harms | • Cost<br>• All other specified outcomes |
| X7 | Other reason: specify | Add comments or keywords as needed. | | | |
| X99 | Full text not accessible | | | | |
| B | Background | Add to any of the above X codes (e.g., X5–B) if the article contains information that may be useful for the introduction, discussion, limitations, future research, or other contextual purposes.<br>Add comments or keywords as needed. | | | |

# APPENDIX C: ELIGIBILITY CHARACTERISTICS OF STUDIES (PICOTS TABLE)

| | KQ1: Benefits<br>What is the evidence that FLACS is associated with better outcomes than conventional cataract surgery? | KQ2: Adverse effects<br>KQ2a: What are the adverse effects that have been reported for FLACS?<br>KQ2b: What is the evidence that FLACS is associated with a lower risk of adverse effects than conventional cataract surgery? | KQ3: Learning curve<br>What is the evidence that the experience of the surgeon is associated with adverse effects of FLACS? |
|---|---|---|---|
| Population | Adults undergoing cataract surgery.<br>Considerations: femtosecond laser surgery is relatively contraindicated in patients with: advanced glaucoma, high anxiety, tremors, dementia, facial or ocular anatomy that precludes adequate LASER docking (i.e. small palpebral fissures, prominent brows) and previous refractive surgery or corneal opacities. | | |
| Intervention | Femtosecond laser technology is used in cataract surgery to assist or replace aspects of conventional cataract surgery, including corneal incisions, capsulotomy and lens fragmentation.<br>Lasers at or near the point of commercial release include: Alcon LenSx (Alcon Laboratories, Fort Worth, TX, USA), OptiMedica Catalys (OptiMedica Corp, Santa Clara, CA, USA), LensAR (LensAR Inc, Winter Park, FL, USA), VICTUS (Bausch + Lomb, Aliso Viejo, CA, USA; and Technolas Perfect Vision GmbH, Munich, Germany), IntraLase FS and iFS Laser Systems (Abbott Medical Optics, Abbott Park, IL, USA).<br>This review is inclusive of studies of any femtosecond laser used for cataract surgery applications regardless of FDA status. | | |
| Comparator | Conventional cataract surgery, defined as small-incision phacoemulsification with planned posterior-chamber intraocular lenses (IOL). | | |
| Included study designs | Controlled studies including randomized controlled trials, non-randomized controlled clinical trials, controlled before/after studies and observational studies | Controlled studies, observational studies, case-control studies, case reports, case series. | Controlled studies; observational study designs including economic evaluation studies). |
| Excluded study designs | Case reports, case series and studies that do not report primary data such as editorials and non-systematic reviews. | Studies that do not report primary data such as editorials and non-systematic reviews. | Studies that do not report primary data such as editorials and non-systematic reviews. |
| Outcomes of interest | Short-term patient outcomes<br>• Visual acuity: post-operative day 1<br>Long-term patient outcomes<br>• Visual acuity: after post-operative day 1 (typically recorded post-operative 1 week, 1 month, or 90 days)<br>• Quality of Life (QOL) measures | Surgical Complications<br>• Intra-operative<br>  • Capsular blockage syndrome<br>  • Dislocated nucleus<br>  • Capsular tear<br>  • Docking failure or loss of docking<br>• Post-operative<br>  • Infection<br>  • Retinal swelling/Cystoid Macular Edema (CME)<br>  • Intraocular (IOL) decentration<br>  • Corneal edema | • Cost<br>• All other surgical complications listed<br>• Other adverse effects reported |
| Timing | Our operational definition to be used for timing of patient outcomes is as follows:<br>• Short-term—patient outcomes on post-operative day 1<br>• Long term—patient outcomes > after post-operative day 1 (no upper limit)<br>Considerations: Standards for reporting timing of post-operative outcomes often have variable time-horizons. For example, potential harms such as CME or IOL decentration, may be reported from as early as post-operative day one or after months to years in some studies. | | |
| Setting | Any | | |

# APPENDIX D: ASSESSMENT OF METHODOLOGIC QUALITY IN STUDIES OF FEMTOSECOND LASER ASSISTED CATARACT SURGERY

## The Newcastle-Ottowa tool for observational studies

| Author, year; study setting | Non-biased selection | High overall loss to follow-up or differential loss to follow-up | Adequate duration of follow-up | Outcomes pre-specified and defined | Ascertainment techniques adequately described | Non-biased and adequate ascertainment methods | Statistical analysis of potential confounders |
|---|---|---|---|---|---|---|---|
| Conrad-Hengerer, 2012[21] University of Bochum, Germany | Unclear "A standardized lens-softening pattern… was used in 1 study group and a 500 mm grid size in the other study group after randomization" | No | NA | Yes | Yes | Yes | No "Descriptive statistical analysis was performed using SPSS. The ttest was used to compare the sample means. Boxplots were used for analysis." |
| Schultz, 2013[22] University of Bochum, Germany | No "Patients scheduled for elective femtosecond laser–assisted cataract surgery" | NA. Primary outcome was intraoperative. | NA | Yes | Yes | Yes | Unclear |
| Mihaltz, 2011[17] Semmelweis University Budapest, Hungary | Unclear "Femtosecond capsulotomies were performed in 48 eyes of 43 patients … Continuous curvilinear capsulorrhexis by forceps was performed on 51 eyes of 38 patients, which served as a control group" | No | Yes | Yes | Yes | Yes | No "Statistical analysis was performed by comparing two samples at a time using the Student t test for analysis of mean visual and refractive values and intraocular optical quality parameters in both study groups" |
| Nagy, 2012[20] Semmelweis University Budapest, Hungary | No "The study group comprised 12 eyes of 12 patients. The control group comprised 13 eyes of 13 patients." | No | Yes | Yes | Yes | Yes | Yes |
| Nagy, 2011[26] Semmelweis University Budapest, Hungary | Yes "Using computer randomization, patients and their right/left eyes were randomly selected for femtosecond and manual surgery." | No | Yes | Yes | Yes | Yes | Unclear |
| Kranitz, 2012[15] Semmelweis University Budapest, Hungary | Yes "Randomization was done using computer-generated tables" | No | Yes | Yes | Yes | Yes | Unclear |

| Author, year; study setting | Non-biased selection | High overall loss to follow-up or differential loss to follow-up | Adequate duration of follow-up | Outcomes pre-specified and defined | Ascertainment techniques adequately described | Non-biased and adequate ascertainment methods | Statistical analysis of potential confounders |
|---|---|---|---|---|---|---|---|
| Takacs, 2012[18] Semmelweis University Budapest, Hungary | Yes "Patients were randomly assigned (using computer randomization) to either group by the surgeon" | No | Yes | Yes | Yes | Yes | Unclear |
| Filkorn, 2012[14] Semmelweis University Budapest, Hungary | Yes "Patients were randomly assigned to each group using a computer randomization chart." | No | Yes | Yes | Yes | Yes | Unclear |
| Kranitz, 2011[6] Semmelweis University Budapest, Hungary | No ""Femtosecond capsulotomies were carried out in 20 eyes of 20 patients and manual CCC was performed in 20 eyes of 20 patients undergoing cataract sugery with IOL implantation." | No | Yes | Yes | Yes | Yes | Unclear. GEE models used to correct for correlated measures for patients having both eyes operated. |
| Ecsedy, 2011[19] Semmelweis University Budapest, Hungary | No "…femtosecond laser-assisted phacoemulsification with the LenSx laser system was carried out in 20 eyes from 20 patients with cataract. Traditional phacoemulsification was performed on 20 eyes from 20 additional patients with cataract." | No | Yes | Yes | Yes | Yes | Unclear |
| Abell, 2012[4] Launceton Eye Hospital, Tasmania, Australia | No "Patients who underwent conventional cataract surgery (i.e. did not have femtosecond laser) were classified as the control group" | No | Yes | Yes | Yes | Yes | Unclear |
| Abell, 2013[16] Tasmanian Eye Institute, Launceton, Tasmania, Australia | No "Cases (n=150) included patients who elected to undergo femtosecond laser pretreatment " | No | Yes | Yes | Yes | Yes | Unclear |
| Kerr, 2013[25] Tasmanian Eye Institute, Launceton, Tasmania, Australia | No "Consecutive patients having femtosecond laser pretreatment to cataract extraction were recruited" | No | Yes | Yes | Yes | Yes | Unclear |

| Author, year; study setting | Non-biased selection | High overall loss to follow-up or differential loss to follow-up | Adequate duration of follow-up | Outcomes pre-specified and defined | Ascertainment techniques adequately described | Non-biased and adequate ascertainment methods | Statistical analysis of potential confounders |
|---|---|---|---|---|---|---|---|
| Bali, 2012[23]<br>Vision Eye Institute, Chatswood, Australia | No<br>"…study included the initial 200 consecutive femtosecond laser cataract surgeries, refractive lens exchange surgeries, or both performed at the Vision Eye Institute " | No | Yes | Yes | Yes | Yes | No |
| Roberts, 2013[24]<br>Vision Eye Institute, Chatswood, Australia | No<br>"…prospective, multicenter, nonrandomized, postmarket evaluation undertaken after local regulatory approval was obtained for clinical use of the LenSx system" | NA. Primary outcome was intraoperative. | NA | Yes | Yes | Yes | Unclear |

Abbreviations: NA = not applicable.

## The Cochrane Collaboration's tool for assessing risk of bias

| Author, year; study setting | Sequence generation | Allocation concealment | Blinding of participants, personnel and outcome assessors | Incomplete outcome data | Selective outcome reporting | Risk of bias* |
|---|---|---|---|---|---|---|
| Nagy, 2011[26]<br><br>Semmelweis University Budapest, Hungary | Low: "Using computer randomization, patients and their right/left eyes were randomly selected for femtosecond and manual surgery." | Unclear: No information provided | Unclear: No information provided, but one of the authors completed all surgeries, suggesting a lack of personnel blinding. | Low: Report no attrition and exclusions appear to all be pre-randomization. | Unclear: Reported on key outcomes but unclear if other outcomes were assessed but not reported. | Unclear |
| Kranitz, 2012[15]<br><br>Semmelweis University Budapest, Hungary | Low: "Randomization was done using computer-generated tables" | Unclear: No information provided | Unclear: No information provided, but one of the authors completed all surgeries, suggesting a lack of personnel blinding. | Low: Report no attrition and exclusions appear to all be pre-randomization. | Unclear: Reported on key outcomes but unclear if other outcomes were assessed but not reported. | Unclear |
| Takacs, 2012[18]<br><br>Semmelweis<br><br>University Budapest, Hungary | Low: "Patients were randomly assigned (using computer randomization) to either group by the surgeon" | Unclear: No information provided | Unclear: No information provided, but one of the authors completed all surgeries, suggesting a lack of personnel blinding. | Low: Report no attrition and exclusions appear to all be pre-randomization. | Unclear: Reported on key outcomes but unclear if other outcomes were assessed but not reported. | Unclear |
| Filkorn, 2012[14]<br><br>Semmelweis University Budapest, Hungary | Low: "Patients were randomly assigned to each group using a computer randomization chart" | Unclear: No information provided | Unclear: No information provided, but one of the authors completed all surgeries, suggesting a lack of personnel blinding. | Low: Report no attrition and exclusions appear to all be pre-randomization. | Unclear: Reported on key outcomes but unclear if other outcomes were assessed but not reported. | Unclear |

*Risk of bias: Low = Plausible bias unlikely to seriously alter the results;
Unclear = Plausible bias that raises some doubt about the results;
High = Plausible bias that seriously weakens confidence in the results.

# APPENDIX E: PEER REVIEW COMMENTS AND RESPONSES

| | Reviewer | Comment | Response |
|---|---|---|---|
| | Question 1: Are the objectives, scope and methods for this review clearly described? | | |
| | 1 | Yes. I think the objectives were well spelled out. We did not ask specifically for any cost/benefit analysis so was done nicely. | Noted, thank you. |
| | 3 | Yes. (No comment) | Noted. |
| | 4 | Yes. (No comment) | Noted. |
| | 5 | Yes. The objectives could be more clearly stated as the purpose of this work is to systematically review and critically appraise the available evidence of FSL assisted cataract surgery vs conventional surgery. | We thank the reviewer for the comment. The reviewer is correct that one aspect of the review is to appraise available evidence of FSL compared to conventional cataract surgery. However, the harms and learning curve assessment questions were not limited to comparative studies. We have clarified the objectives of the report in the background and methods sections. |
| | 2. Is there any indication of bias in our synthesis of the evidence? | | |
| | 1 | No. I did not see any, but the papers reviewed certainly had bias as you pointed out. | Noted, thank you. |
| | 3 | No. (No comment) | Noted. |
| | 4 | No. (No comment) | Noted. |
| | 5 | No. (No comment) | Noted. |
| | 3. Are there any published or unpublished studies that we may have overlooked? | | |
| | 1 | No. None that I am aware of. | Noted. |
| | 3 | No. (No comment) | Noted. |
| | 4 | No. Given the technology is fairly new as far as FDA approval, high level evidence literature is limited. | Noted. |
| | 5 | Yes. Methods: The recommended databases to search (as a minimum) by the Cochrane Collaboration is EMBASE, MEDLINE, and CENTRAL. I suggest reviewing EMBASE and CENTRAL in addition to all the other sources searched. | We have clarified the databases searched in Figure 2 (literature flow) of the report. Our search of the Cochrane library included the CENTRAL register of controlled trials. Unfortunately, our library does not subscribe to EMBASE so we do not have access to that database. However, we are reasonably confident that we have captured the relevant literature for the topic, given that we have searched the grey literature and recent conference proceedings in this quickly evolving field. |

| | Reviewer | Comment | Response |
|---|---|---|---|
| | 4. Please write additional suggestions or comments below. If applicable, please indicate the page and line numbers from the draft report. | | |
| | 1 | Were any of the papers quoted funded directly by manufacturers? It seems like even in the papers quoted you had methodological questions, for instance were patients used in multiple reports and that most of the "better" papers were all done by one surgeon, so the question of learning curve remains? | We examined the acknowledgements listed for each of the papers and could only report on the consulting fees and honoraria received by study authors. In addition, there were very few papers examining the issue of learning curve. As a result, the evidence available to answer key question 3 is very sparse. |
| | 2. | I appreciate the amount of effort the coordinators have made for this systematic review. I have the following comments. A limitation of meta-analysis restricted to methodologically sound comparison studies is failure to capture relatively infrequent but important adverse outcomes that begin to be reported as individual or small series reports several years after institution of a new technology. This pattern was seen in corneal refractive surgery after institution of LASIK (laser in situ keratomileusis). Case reports of ischemic optic neuropathy (anterior or posterior) with partial loss of vision were linked to the high intraocular pressures from the metal suction rings used for the standard microkeratome procedure (references 1-3). A similar case of optic neuropathy has been reported with a femtosecond laser using a low-pressure suction ring (reference 4). As a LASIK surgeon, I am aware of other unreported cases. As you note in your review, all docking devices currently used in femtosecond platforms lead to an increase in intraocular pressure, which puts the microcirculation of the optic nerve at risk, especially in patients with microvascular disease from diabetes or hypertension. This effect may be especially important in the VHA population. Ischemic optic neuropathy has also been reported after uncomplicated conventional phacoemulsification (References 5-7).<br>References.<br>1. Lee AG, et al. Optic neuropathy associated with laser in situ keratomileusis. J Cataract Refract Surg 2000;11:1581-4.<br>2. Bushley DM, et al. Visual field defect associated with laser in situ keratomileusis. Am J Ophthalmol 2000;129:668-71.<br>3. Cameron BD, et al. Laser in situ keratomileusis-induced optic neuropathy. Ophthalmology 2001;108:660-5.<br>4. Maden A, et al. Nonarteritic ischemic optic neuropathy after LASIK with femtosecond laser flap creation. J Neuro-Ophthalmol 2008;28:242-3.<br>5. Lee H, et al. A case of decreased visual field after uneventful cataract surgery; nonarteritic anterior ischemic optic neuropathy. Korean J Ophthalmol 2010;24:57-61.<br>6. Luscavage LE, et al. Posterior ischemic optic neuropathy after uncomplicated cataract extraction. Am J Ophthalmol 2001;132:408-9.<br>7. McCulley TJ, et al. Incidence of nonarteritic anterior ischemic optic neuropathy associated with cataract extraction. Ophthalmology 2001;108:1275-8. | We thank the reviewer for the insightful comments. In an attempt to identify all of the adverse events associated with FLACS, we included various study designs, even those of case reports. As the reviewer points out, these low prevalence events are not appropriate for meta-analysis. As noted in our review, all of the FSL platforms have been associated with some elevation of IOP during the procedure. This has not been noted to be as severe as the amaurosis-inducing levels common with LASIK procedures, which generate high IOPs with the use of microkeratomes. Our report does reflect the concern with even mild elevations of IOP being potentially harmful to glaucoma patients and may therefore exclude Veterans with this common comorbidity from being candidates for FLACS. |

| | Reviewer | Comment | Response |
|---|---|---|---|
| | 2. | You mention disposable costs for FLACS of $150-300. What are the disposable costs for conventional phaco? | Our review has been amended to reflect this cost issue. The disposable costs of FLACS and conventional phacoemulsification surgery are comparable (both involve irrigation/ aspiration and phacoemulsification procedures). The additional incremental cost of FLACS is the $150-300 per patient charge for the sterile, single-use patient interface device. |
| | 3 | The draft report addresses on point the request for information. | Noted. |
| | 4 | The review covers as one of its key questions "What is the evidence that the experience of the surgeon is associated with adverse effects of FLACS?" a couple studies showed less adverse events with more experience with FLACS. It would be nice to compare the surgical learning curve of FLACS vs Conventional cataract. There is some early literature in presentation and poster on this…not sure publications exists. This will be key for the VA given it is very involved in resident cataract surgery teaching.<br>Prickett, 2013[40]<br>Initial Resident Experience Performing Cataract Surgery with and without Femtosecond Laser<br>(Conference proceeding)<br>ARVO Poster Session, 2013 | Thank you for the comment. However, the comparative learning curve of FLACS versus conventional surgery is outside of the scope of the review. This will be important in future questions of learning curve comparing surgical procedures (conventional compared to FLACS) |
| | 5 | Although meta-analyses of observational studies are not as frequent as for RCTs, there are guidelines (MOOSE) that are accepted to estimate summary effects based on observational studies. Nonetheless, if the authors consider that the quality of the observational studies (e.g., bias) preclude a meta-analysis, then is ok not to do it. | We thank the reviewer for the comment, and agree that the concerns with the included observational studies preclude meta-analyses of additional outcomes. |
| | Optional Dissemination and Implementation Questions | | |
| | 5. Are there any VA clinical performance measures, programs, quality improvement measures, patient care services, or conferences that will be directly affected by this report? If so, please provide detail. | | |
| | 1 | None that I am aware of. I have heard of several more machines being requested and some purchased across the VA system. | Noted. |
| | 3 | The report supports the FDA approval of this technology | Noted. |
| | 4 | No. (No comment) | Noted. |
| | 6. Please provide any recommendations on how this report can be revised to more directly address or assist implementation needs. | | |
| | 1 | None. The way I interpreted your results was that there was weak to moderate support of some advantages to this technology but the same for the adverse effects. Even this information is generated from reports that have either stated or possible conflict of interest. While not in your prevue, I am hoping this report can be submitted with any application for technology across the VISN. | Noted, thank you for your comment. |
| | 3 | No recommendation | Noted. |
| | 4 | No. (No comment) | |

| | Reviewer | Comment | Response |
|---|---|---|---|
| | 5 | In methodology there are some issues that should be addresed:<br>DATA ANALYSIS:<br>How heterogeneity was assessed and examined (stratification, regression)?, how bias was evaluated ? , which effect measure was used for meta-analysis and which weighting method (random, fixed models)?<br>Also, it should be stated that STATA was used for statistical analysis. | We have provided more information in the methodological details of the meta-analyses. All analyses were conducted in StataIC 11, and we assessed the presence of statistical heterogeneity among the studies by using standard chi-square tests, and the magnitude of heterogeneity by using the $I^2$ statistic. We explored models using both mean and ratio of means (SoM) based on a random effects model (combining means used the DL method and combining SoM used the PL method) – however, we do not report the combined estimates due to too much heterogeneity and rely on the forest plots as a visual aid for readers. |