APPENDIX A. SEARCH STRATEGIES

DATABASE SEARCHED & TIME PERIOD COVERED:
PubMed – 2006/1/1 to 2017/4/30

LANGUAGE:
English

SEARCH STRATEGY:
lenses, intraocular OR lens implantation, intraocular OR accommodation, ocular OR accommodative lens* OR accommodating lens* OR multifocal lens* OR multifocal intraocular lens*
AND
cataract extraction OR cataract*[tiab]
AND
systematic[sb]
Limited to English and 2006-2017

APPENDIX B. PEER REVIEW COMMENTS/AUTHOR RESPONSES

Comment	Response
Conclusions too favorable given all problems with studies on multifocal IOLs.	We have somewhat reduced the favorability.
Page 20 line 48 “independence” is spelled wrong Page 20 line 53 should be "than" not "that" page 29 Line 17 Summary # 1. I don't think you can say the risk of surgery with multifocals is no greater as the undesirable visual issues post-operative-(glare, halos, decreased contrast) are uncorrectable and there is likely an increased risk of need for lens exchange which is a risky procedure. Do the authors mean the intraoperative risk is no greater? Page 32 lines 40-44: As far as the statement "there is no data to support complications or effectiveness of cataract surgery varies by population characteristics". This statement is likely not true. We do know certain characteristics and ocular co-morbidities increase the risk of undesirable visual outcomes (glare, halos, decreased contrast) with multifocals. This would then logically increase the risk of lens exchange and unfavorable visual outcomes. We would need to know what the prevalence of these characteristics such as dry eye and macular changes are in the VA population getting cataract surgery compared to the general population getting cataract surgery. Page 32 line 53-57 Conclusions: I would add the need for additional patient face-to-face or "chair" time and therefore resources and the higher need for lens exchange	Thank you for pointing this out, this has been corrected. Thank you for pointing this out, this has been corrected. The reviewer is correct, we meant interoperative risks. We have made this change. We changed this statement to saying the applicability is uncertain. We made this addition.
This is well written summary of the literature. Unfortunately much of the literature was excluded to answer if multifocal lenses are more effective than monofocal lenses after implantation. I feel the authors made valid conclusions with the limited articles that met criteria for review.	Thank you for your comment.
My primary concern: there should be more of an emphasis in the poor quality of the studies (see page 13—e.g., only two were registered prospectively!), in the Discussion and Conclusions (pages 5-6). In this context, for example, “moderate evidence supports….” is overly optimistic. I really	We have somewhat reduced our conclusions, in terms of applicability and potential for harms, but believe the assessment of quality of evidence as “moderate” for the conclusion that multifocal IOL, produce better uncorrected near vision and spectacle independence is justified. The

think more rigorous studies need to be done to support these IOLs (though this question is probably irrelevant given the significant financial incentives to use them outside the VA) and they should be in US populations (none of the studies in the ESP were done in the US, which I found very surprising and very disheartening). My opinion: much more caution needs to be emphasized in the report!	methodologic limitations of the RCTs are already accounted for in the downgrade of the quality of evidence from high to moderate.
Another concern: the ESP states that the findings are generalizable to the VA population (top of page 6). Given that none of the studies were done in US populations and that VA patients undergoing cataract surgery have much higher burden of illness that their non-VA counterparts in the US, I find this conclusion problematic. We simply do not know.	This change was already made.
This was a very sound study that examined the outcomes of multifocal and accommodating IOL implantation relative to monofocal IOL implantation in cataract surgery. The methods of paper selection and the key investigational questions were clearly laid out. The statistical methods that were employed were appropriate. Given the data presented, I agree with the conclusions that were drawn with respect to the key questions.	Thank you for your comment.
The results of the stringent screening process for the included papers highlights the deficiencies in the current literature and the challenges that present themselves when trying to design studies that answer the questions of interest.	Thank you for your comment.
A weakness of the study (which is beyond the authors' control) is the selection of IOLs that were available for examination in published randomized clinical trials. A few of the IOLs are not available in the US (Acri LISA, TwinSet) or are outdated technology not in current use (Array, ReZoom). Of the remaining IOLs (ReSTOR SN6AD3, Tenis ZM900/9001, Tecnis ZMB00), their use is being significantly replace by "lower-add" MFIOLs or extended depth-of-focus IOLs. The newer IOLs may have improved side effect profiles, but unfortunately the available literature is not of sufficient quality for a similar evaluation of their performance. Maybe mention could be made of these issues in the discussion and/or conclusion, if the authors feel it is appropriate.	We have added this information to the conclusion.
In today's environment, I would be careful with the statement that corneal topography is not needed for "standard" cataract surgery. I believe the consensus that corneal topography is or should be an essential component of any cataract surgery has spread or is spreading beyond subspecialty	We made the change.

societies, such as the ASCRS. I do agree that retinal OCT is an additional test that is required prior to multifocal implantation.	
Some mention was made concerning astigmatism levels in these patients. If possible, it would be helpful to provide more detail on the levels of post-operative astigmatism in these patients (since, as mentioned, MFIOLs perform best with low levels of residual astigmatism/refractive error). Similarly, if available and statistically valid, a more formal comparison of distance-corrected near visual acuity would also be informative.	We made this addition.
Again, this is a well done study that begins to answer the questions on MFIOL performance relative to monofocal IOLs, although it is very limited by the quality of the available literature. I do believe that a randomized trial in the VA population would be helpful and that the use of these IOLs must be done with a very thorough preoperative work-up, extensive discussion with patients, and an overall conservative philosophy.	Thank you for your comment.

APPENDIX C. EVIDENCE TABLES

Author Year Country	Design (Single or Multi-Center) Prospectively registered	Intervention	Comparison	Sample Size (Patients) Mean Age % Female	Duration of Follow-up	Outcomes
Marchini, 2007[11] Italy	RCT Multi-site Not reported as registered	1) 1CU (accommodative) 2) Crystalens AT-45	Conventional monofocal IOL	38 Mean age = NR %Female = NR	12 months	VA - BCDVA o 1CU (0.02) o AT-45 (0.04) o ACR6D (0.04) - UCNVA – just states not sig different (no actual data) - Best-corrected near-distance VA – "excellent and comparable between 3 groups" Other - Change in ACD (mm) o 1CU (0.09) o AT-45 (0.17) o ACR6D (-0.03) o P = 0.002 - Change in SPCA (mm) o 1CU (2.78) o AT-45 (2.08) o ACR6D (1.78) o P = 0.816 - NDRA (diopters) o 1CU (1.29) o AT-45 (1.50) o ACR6D (2.15) o P = 0.002 - AA (diopters) o 1CU (1.40) o AT-45 (0.96) o ACR6D (1.23) o P = 0.102 - Distance corrected NVA (Jaeger) o 1CU (7) o AT-45 (10)

						o ACR6D (13) o P = 0.001
Zeng, 2007[12] China	RCT Single-site Not reported as registered	Array SA40N	1) AcrySof SA60AT 2) Tecnis Aspherical	124 Mean age = 65.4 %Female = NR	3 months	VA - BCVA o Z9001 (0.00) o SA40N (0.01) o SA60AT (0.01) o P = 0.303 Corneal aberrations - No sig difference btw IOL groups - Spherical aberration o Z9001 (0.24) o SA40N (0.21) o SA60AT (0.26) o P = 0.81 - Coma o Z9001 (0.35) o SA40N (0.33) o SA60AT (0.32) o P = 0.54 - RMS o Z9001 (1.54) o SA40N (1.58) o SA60AT (1.62) o P = 0.37 Higher-order aberrations - SA40N > SA60AT > Z9001 - C12 o Z9001 (0.05) o SA40N (0.40) o SA60AT (0.20) o P = 0.000 - RMS4 o Z9001 (0.26) o SA40N (0.45) o SA60AT (0.32) o P = 0.000 - RMSH o Z9001 (0.45) o SA40N (1.02) o SA60AT (0.69) o P = 0.000 Contrast sensitivity

						- Measure with and without glare at 4 spatial frequencies - Z9001 > SA60AT > SA40N (P<0.01) - Examples: - Glare Cpd 6 o Z9001 (1.87) o SA40N (1.69) o SA60AT (1.71) o P = 0.004 - Without glare CPD6 o Z9001 (1.97) o SA40N (1.68) o SA60AT (1.72) o P = 0.000
Cillino, 2008[16] Italy	RCT Single site Not reported as registered	1) Rezoom NXG1 2) Tecnis ZM900 3) Array SA40N	AR40 (US monofocal)	68 Mean age = 62.3 % Female = 53.2	12 months	1) Complete spectacle independence Tecnis ZM900 87.5%+ Rezoom NXG1 53.5%+ Array SA40N 43.7%* AR40 20%* (+ p < 0.05; * p = 0.53) 2) VF7 Mean score Tecnis ZM900 99.1 Rezoom NXG1 94.6 Array SA40N 93.8 AR40 87.1 (p = 0.002) Difficulty reading small print - Tecnis ZM900 – 98.9 - Rezoom NXG1 – 78.1 - Array SA40N – 73.3 - AR40 – 56.7 - P < 0.0005 Fine handwork - Tecnis ZM900 – 94.6 - Rezoom NXG1 – 92.2 - Array SA40N – 96.7 - AR40 – 56.7 - P < 0.0005 3) VA (mean Snellen in decimal form)

						Uncorrected distance VA - Tecnis ZM900 – 0.69 - Rezoom NXG1 – 0.86 - Array SA40N – 0.87 - AR40 – 0.79 - P = 0.134 Best corrected distance VA - Tecnis ZM900 – 0.99 - Rezoom NXG1 – 0.98 - Array SA40N – 0.97 - AR40 – 1.00 - P = 0.958 Uncorrected near VA - Tecnis ZM900 – 0.72 - Rezoom NXG1 – 0.61 - Array SA40N – 0.63 - AR40 – 0.42 - P < 0.0005 Best corrected near VA - Tecnis ZM900 – 0.84 - Rezoom NXG1 – 0.81 - Array SA40N – 0.87 - AR40 – 0.80 - P = 0.501 Best corrected distance near VA - Tecnis ZM900 – 0.78 - Rezoom NXG1 – 0.56 - Array SA40N – 0.63 - AR40 – 0.39 - P < 0.0005 Uncorrected intermediate VA - Tecnis ZM900 – 0.69 - Rezoom NXG1 – 0.75 - Array SA40N – 0.67 - AR40 – 0.61 - P = 0.001 Best corrected intermediate VA

						- Tecnis ZM900 – 0.90 - Rezoom NXG1 – 0.75 - Array SA40N – 0.83 - AR40 – 0.77 - P = 0.316 4) Contrast sensitivity curve - ZM900 and AR40 better than Rezoom and Array (P = 0.038) 5) Glare (# cases) - Tecnis ZM900 – 1 - Rezoom NXG1 – 5 - Array SA40N – 1 - AR40 – 1 - P > 0.05 6) Halo (# cases) - Tecnis ZM900 – 2 - Rezoom NXG1 – 9 - Array SA40N – 7 - AR40 – 0 o ZM900 v Rezoom = 0.017 o Rezoom v Mono = 0.0007 o Array v Mono = 0.007 7) Overall patient satisfaction - Tecnis ZM900 – 4.7 - Rezoom NXG1 – 4.5 - Array SA40N – 4.4 - AR40 – 4.6 - P = 0.071
Palmer, 2008[19] Spain	RCT Single site Not reported as registered	1) Tecnis MFIOL ZM900 2) ReZoom (zonal refractive) 3) Twin Set (asymmetric diffractive)	Tecnis Z9000 (monofocal)	114 patients Mean age = 73.7 % Female = 62.5	3 months	Spectacle independence Tecnis Z9000 4% Twinset 87.5% Tecnis ZM900 77% Rezoom 44% Visual Acuity Binocular distance UCVA Tecnis Z9000 0.13 Twinset 0.18 Tecnis ZM900 0.14 ReZoom 0.16

						Binocular CDVA Tecnis Z9000 0.05 Twinset 0.08 Tecnis ZM900 0.07 ReZoom 0.11 Binocular CNVA Tecnis Z9000 0.04 Twinset 0.01 Tecnis ZM900 0.01 ReZoom 0.03 Photopsia Tecnis Z9000 81% Twinset 47% Tecnis ZM900 48% ReZoom 53%
Zhao, 2010[15] China	RCT Single site Not reported as registered	ReSTOR SA60D3	Acrysof SA60AT	161 patients Mean age = 66 % Female = 47.2	6 months	Spectacle independence ReSTOR 66.6% Monofocal 23.5% (p < 0.05) VF 7 Post-operative score ReSTOR 97.3 Monofocal 89.8 (p < 0.05) Patient satisfaction score (1 to 5) ReSTOR 4.7 Monofocal 4.3 (p = not significant) Halos ReSTOR 43.1% Monofocal 20.2% (p < 0.01) Contrast sensitivity: not significant

Alio, 2011[17] Spain	RCT Single site Not reported as registered	1) AcrySof ReSTOR SN6AD3 2) Acri.LISA 366D (Non-US, diffractive MF)	Acri.Smart 48S (Non-US, monofocal)	53 Mean age = 63 % Female = NR	3 months	VA - UDVA (logmar) o Acri.Smart (0.03) o ReSTOR (0.05) o Acri.LISA (0.05) o Monofocal better (P = 0.01) - CDVA o Acri.Smart (0.02) o ReSTOR (0.02) o Acri.LISA (0.00) o No difference (P = 0.24) - UNVA o Acri.Smart (0.47) o ReSTOR (0.28) o Acri.LISA (0.19) o Multifocal better (P <0.01)
Alio 2011[10] Spain	RCT Multi-site Not reported as registered	1) AcrySof ReSTOR SN6AD3 2) Acri.LISA 366D (Non-US, diffractive MF) 3) ReZoom	Acri.Smart 48S (Non-US, monofocal)	152 Mean age = 71 %Female = NR	6 months	VA - UDVA (logmar) o Acri.Smart (0.09) o ReSTOR (0.15) o Acri.LISA (0.12) o Rezoom (0.12) o Monofocal better (P = 0.02) - CDVA o Acri.Smart (0.04) o ReSTOR (0.06) o Acri.LISA (0.06) o Rezoom (0.06) o No difference (P = 0.25) - Reading acuity o Only graphical data o ReSTOR and Acri.LISA better than monofocal (P<0.01) - Smallest print size o ReSTOR and Acri.LISA better than monofocal and Rezoom (P<0.01) - Reading speed and distance Difficult to interpret ? relevant

Ji, 2012[13] China	RCT Single site Not reported as registered	Acrysof ReSTOR (? Model #)	Acrysof Natural (Monofocal, ? Model #)	51 (64 eyes) Mean age = 63.1 % Female = 56.9	3 months	1) VA Best corrected distance VA Acrysof ReSTOR 0.71 Acrysof Natural 0.75 No significant difference (p = 0.77) Uncorrected near VA Acrysof ReSTOR 0.58 Acrysof Natural 0.21 (p = 0.008) 2) Contrast sensitivity Measured mesopic/photopic at 6 spatial frequencies -Multifocal scored lower than monofocal under all conditions all P<0.05 Example: Mesopic, 2.5 spatial freq - ReSTOR 33.46 - Natural 41.67 - P = 0.03 Photopic, 2.5 spatial freq - ReSTOR 15.57 - Natural 22.83 - P = 0.02 3) Wavefront analysis RMS 4mm pupil - ReSTOR 0.21 - Natural 0.50 - P = 0.00 6mm pupil - ReSTOR 0.41 - Natural 0.96 - P = 0.02 Not sure if these are useful
Peng, 2012[14] China	RCT Single site Not reported as registered	ReSTOR Sn6AD1	Alcon SN60WF	102 patients Mean age = 66 % Female = 52.4	6 months	Spectacle independence ReSTOR 74% Monofocal 28.9% Visual acuity Uncorrected distance – VA ReSTOR .03

						Monofocal .08 Uncorrected near VA ReSTOR .07 Monofocal .64 Visual Disturbance ReSTOR > Monofocal for glare, night driving, halos Example: problems with night vision 1.2 vs 0.6 on 0 to 7 impact rating scare Monofocal IOL > ReSTOR got blurry near vision Patient satisfaction ReSTOR 8.14 Monofocal 6.23 (P < 0.001) Contrast: MTF 3.0mm ReSTOR worse at 5 – 10 cpd MTF 5.00 – no difference
Rasp, 2012[20] Austria	RCT Single site	1) Acrysof ReSTOR SN6AD3 2) AT.LISA 366D (Non-US, diffractive MF) 3) Rezoom NXG1 4)Tecnis ZMA00	Acri.Smart 48S (Non-US, monofocal)	143 Mean age = 75.9 % female = NR	12 months	1) VA - Uncorrected distance VA (logMAR) - Acri-Smart (0.08) - Acri.LISA (0.16) - ReSTOR (0.17) - Rezoom (0.11) - ZMA00 (0.10) - No significant difference reported Corrected distance VA (logMAR) - Acri-Smart (0.03) - Acri.LISA (0.05) - ReSTOR (0.11) - Rezoom (0.07) - ZMA00 (0.05) - No significant difference reported 2) Reading performance - Uncorrected reading acuity (logRAD) - Acri-Smart (0.47) - Acri.LISA (0.23) - ReSTOR (0.28) - Rezoom (0.40) - ZMA00 (0.27) - All multifocals better than

						monofocal (P < 0.001) - Reading speed - Uncorrected (WPM) - Acri-Smart (148) - Acri.LISA (178) - ReSTOR (147) - Rezoom (152) - ZMA00 (139) - P values: - Acrismart vs AcriLISA(0.001) - ReSTOR vs AcriLISA (0.003) - Rezoom vs AcriLISA (0.016) - Tecnis vs AcriLISA (0.00) - Corrected - No significant difference (P>0.21) - Reading distance (cm) - Uncorrected - Acri.LISA (31.6), ReSTOR (31.8), and ZMA00 (32.1) better than Acri.Smart (38.9) and Rezoom (37.1) P values: - Significant difference between AcriSmart vs AcriLISA/ReSTOR/ZMA00 (P=0.00) - Significant difference between Rezoom vs AcriLISA/ReSTOR/ZMA00 (P = 0.04) - Corrected - Acri.LISA (31.3), ReSTOR (31.4), and ZMA00 (30.8) better than Acri.Smart (36.7) and Rezoom (35.5) P value: Significant difference between AcriSmart vs AcriLISA/ReSTOR/ZMA00 (P = 0.006) - Smallest print size (mm) - Acri.LISA (0.74) ReSTOR (0.87) and ZMA00 (0.87) better than Acri.Smart (1.76) and Rezoom (1.38) (P = 0.26)

Wilkins, 2013[9] England	RCT Multi-site Registered on controlled-trials.com, ISRCTN37400841	Tecnis ZM900	Akreos AO with monovision	212 patients Mean age = 67.8 % Female = 56.6	4 months	Spectacle independence (do you wear glasses?) Tecnis Monovision Always 2.1% 3.2% Sometimes 36.6% 71% Never 71.3% 25.8% VF -11R (pre to post) TecnisZM900 Pre 2.7 Post 3.4 Monovision Pre 2.66 Post 3.25 (p = not significant) Visual acuity Binocular UDVA (p = 0.377) Monovision 0.06 MFIOL 0.08 Binocular UIVA (p = 0.000) Monovision 0.15 MFIOL 0.22 Binocular UNVA (p=0.037) Monovision 0.01 MFIOL -0.03 Contrast TecnisZM900 1.39 Monovision 1.45 (P=0.009) Glare/Dazzle Monovision MFIOL None 44 21 Barely 37 36 Annoying 16 36 Debilitating 2 6
Labiris, 2015[18] Greece	RCT Single site Registered on clinicaltrials.gov, NCT81998698	Isert PY60MV (Non-US, refractive MF)	Mini-monovision with Alcon SN60WF	75 Mean age = 60.4 % female = NR	6 months	Spectacle independence Intervention: 65.7% Comparison: 31.4% VF-14 score Intervention: 90.1

						Comparison: 91.6 (p=0.11) VF-14 near vision Intervention: 91.4 Comparison: 89.0 (p=0.09) VF-14 distance vision Intervention: 89.1 Comparison: 92.9 (p=.08) VA: UDVA Intervention: 0.92 Comparison: 0.95 (p = 0.15) UNVA Intervention: 1.21 Comparison: 1.87 (p = 0.47) Other visual tests: Contrast sensitivity Intervention: 1.40 Comparison: 1.39 (p = 0.41) Glare (4-point scale) Intervention: 0.21 Comparison: 0.06 (p = 0.08) Shadows Intervention: 0.57 Comparison: 0.21 (p = 0.02) Stereopsis Intervention: 75 Comparison: 71 (p = 0.12)

APPENDIX D. CITATIONS FOR EXCLUDED STUDIES

Lens not of interest (n=30)

1. Alio JL, Plaza-Puche AB, Pinero DP. Rotationally asymmetric multifocal IOL implantation with and without capsular tension ring: refractive and visual outcomes and intraocular optical performance. *Journal of refractive surgery (Thorofare, NJ : 1995).* 2012;28(4):253-258.

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13. Javitt JC, Steinert RF. Cataract extraction with multifocal intraocular lens implantation: a multinational clinical trial evaluating clinical, functional, and quality-of-life outcomes. *Ophthalmology.* 2000;107(11):2040-2048.

14. Joshi RS. Diffractive multifocal intraocular lens compared to pseudo-accommodative intraocular lens implant for unilateral cataracts in pre-presbyopic patients. *Middle East African journal of ophthalmology.* 2013;20(3):207-211.

15. Jusufovic V, Sarajlic D, Zvornicanin J, Musanovic Z, Halilbasic M. Comparison of the binocular vision quality after implantation of monofocal and multifocal intraocular lenses. *Acta Medica Saliniana.* 2011;40(2):63-68. http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/693/CN-00897693/frame.html.

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No monofocal comparison (n=21)

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APPENDIX E. RESULTS OF POOLED ANALYSES COMPARING MULTIFOCAL IOLS WITH MONOVISION

Figure 1. Multifocal IOLs Compared to Monovision Uncorrected Distance

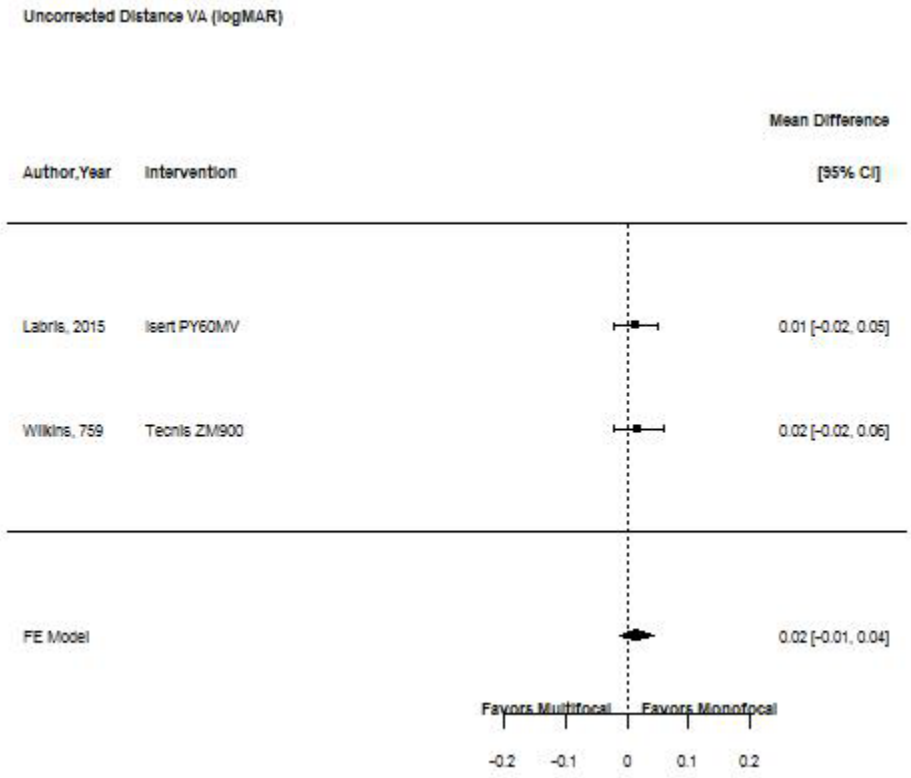

Figure 2. Multifocal IOLs Compared to Monovision Uncorrected Near

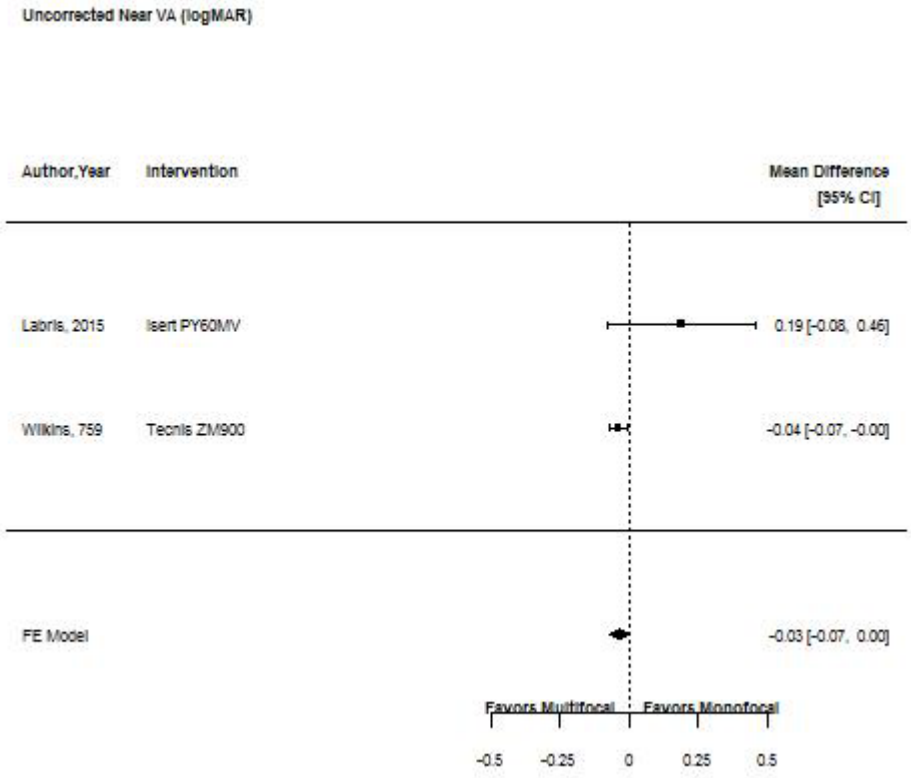

Figure 3. Multifocal IOLs Compared to Monovision Quality of Life

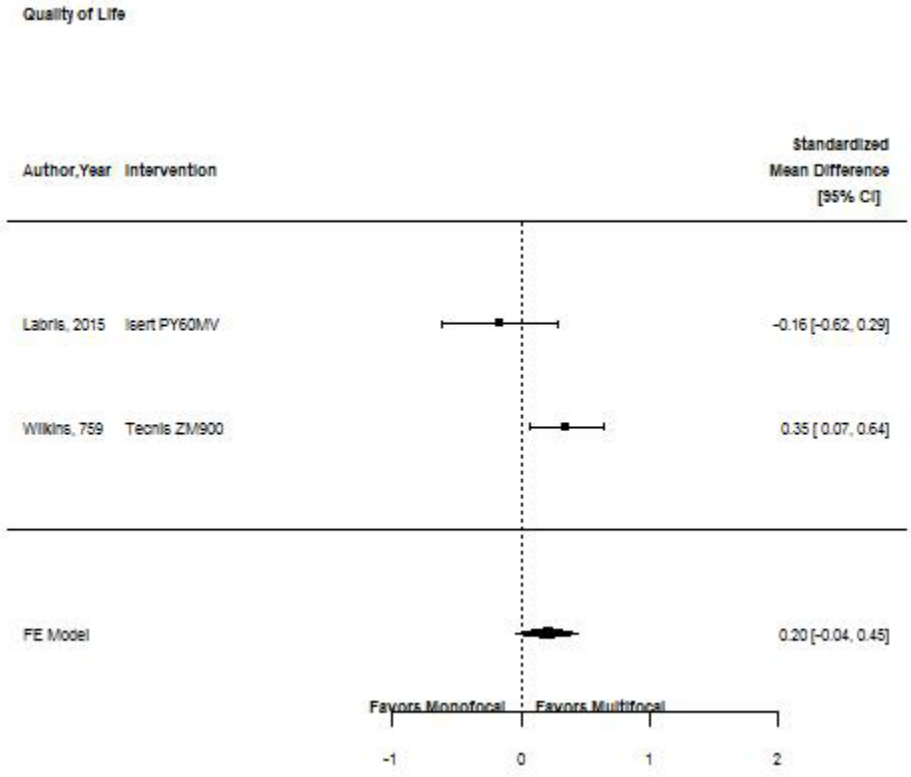

Figure 4. Multifocal IOLs Compared to Monovision Spectacle Independence