

Supplementary materials

Table S1-The 91 studies included in the meta-analysis.

| Study PMID | Year | Study type (1=retrospective 2=prospective) | Study phase (1,2,3,4, real world) | Study size | Drug |
|------------|------|--|--------------------------------------|------------|------|
| 21639808 | 2011 | 2 | 3 | 337 | V |
| 22735384 | 2012 | 2 | 3 | 187 | D |
| 23020132 | 2012 | 2 | 1-2 | 54 | D |
| | 2012 | 2 | 1-2 | 54 | DT |
| | 2012 | 2 | 1-2 | 54 | DT |
| 22663011 | 2012 | 2 | 3 | 214 | T |
| 22356324 | 2012 | 2 | 2 | 132 | V |
| 23051966 | 2012 | 2 | 2 | 89 | D |
| | 2012 | 2 | 2 | 83 | D |
| 22805291 | 2012 | 2 | 1 | 70 | T |
| 22805292 | 2012 | 2 | 1 | 26 | T |
| 23248257 | 2013 | 2 | 2 | 97 | T |
| 23414587 | 2013 | 2 | 2 | 30 | B |
| | 2013 | 2 | 2 | 41 | B |
| 23918947 | 2013 | 2 | 2 | 92 | D |
| 24445759 | 2014 | 2 | 4 | 371 | V |
| 24241686 | 2014 | 1 | real world | 50 | V |
| 25037139 | 2014 | 2 | 1-2 | 66 | VC |
| | 2014 | 2 | 1-2 | 63 | VC |
| 25287827 | 2014 | 2 | 1-2 | 26 | DT |
| | 2014 | 2 | 1-2 | 45 | DT |
| 24582505 | 2014 | 2 | 2 | 3222 | V |
| 24508103 | 2014 | 2 | 3 | 335 | V |
| 24295639 | 2014 | 2 | 3 | 24 | V |
| 25265492 | 2014 | 2 | 3 | 211 | DT |
| | 2014 | 2 | 3 | 212 | D |
| 25265494 | 2014 | 2 | 3 | 247 | VC |
| | 2014 | 2 | 3 | 248 | V |
| 25399551 | 2015 | 2 | 3 | 352 | V |
| | 2015 | 2 | 3 | 352 | DT |
| 26037941 | 2015 | 2 | 3 | 211 | DT |
| | 2015 | 2 | 3 | 212 | D |
| 26352686 | 2015 | 2 | 2 | 28 | V |
| | 2015 | 2 | 2 | 26 | V |
| 26460303 | 2015 | 2 | 2 | 21 | V |
| 25722381 | 2015 | 2 | 2 | 86 | T |
| 25956405 | 2015 | 1 | - | 27 | V |

| 26287849 | 2015 | 2 | 2 | 20 | V |
|------------|------|--|--------------------------------------|------------|------|
| 26392102 | 2015 | 2 | 2 | 43 | DT |
| Study PMID | Year | Study type (1=retrospective 2=prospective) | Study phase (1,2,3,4, real world) | Study size | Drug |
| 24661317 | 2015 | 2 | real world | 19 | V |
| 25952781 | 2015 | 2 | real world | 385 | V |
| 26557775 | 2015 | 2 | real world | 75 | V |
| 27080216 | 2016 | 2 | 2 | 84 | D |
| 27283860 | 2016 | 2 | 2 | 57 | DT |
| 27460442 | 2016 | 2 | 2 | 26 | V |
| | 2016 | 2 | 2 | 25 | V |
| 26208946 | 2016 | 2 | real world | 59 | V |
| 26981153 | 2016 | 2 | real world | 40 | D |
| 26983408 | 2016 | 2 | 3 | 301 | V |
| 27071922 | 2016 | 2 | 1 | 21 | B |
| 27470608 | 2016 | 1 | - | 48 | DT |
| 27480103 | 2016 | 2 | 3 | 247 | VC |
| | 2016 | 2 | 3 | 248 | V |
| 28151720 | 2017 | 2 | 2 | 20 | T |
| 27993793 | 2017 | 2 | 2 | 146 | V |
| 28268064 | 2017 | 2 | 2 | 25 | DT |
| 28592387 | 2017 | 2 | 2 | 76 | DT |
| | 2017 | 2 | 2 | 16 | DT |
| | 2017 | 2 | 2 | 16 | DT |
| | 2017 | 2 | 2 | 16 | DT |
| | 2017 | 2 | 2 | 17 | DT |
| 28919011 | 2017 | 2 | 2 | 36 | DT |
| 29121415 | 2017 | 2 | 2 | 20 | T |
| 28444112 | 2017 | 2 | 3 | 246 | V |
| | 2017 | 2 | 3 | 247 | VC |
| 28475671 | 2017 | 2 | 3 | 209 | DT |
| | 2017 | 2 | 3 | 211 | D |
| 28284557 | 2017 | 2 | 3 | 269 | B |
| 28891408 | 2017 | 2 | 3 | 438 | DT |
| 28152546 | 2017 | 2 | 1 | 44 | B |
| 28501764 | 2017 | 2 | 4 | 3219 | V |
| 28567600 | 2017 | 1 | - | 30 | D |
| 28611198 | 2017 | 2 | 1 | 35 | E |
| 28963614 | 2017 | 1 | - | 43 | V |
| 29285228 | 2017 | 2 | 3 | 21 | D |
| 29076950 | 2017 | 2 | 2 | 31 | V |
| 29384960 | 2017 | 1 | - | 48 | D |
| | 2017 | 1 | - | 87 | DT |

| Study PMID | Year | Study type (1=retrospective 2=prospective) | Study phase (1,2,3,4, real world) | Study size | Drug |
|------------|------|--|--------------------------------------|------------|------|
| 29477665 | 2018 | 2 | 3 | 247 | V |
| | 2018 | 2 | 3 | 192 | EB |
| 29573941 | 2018 | 2 | 3 | 194 | E |
| | 2018 | 2 | 3 | 191 | V |
| | 2018 | 2 | 3 | 192 | EB |
| 30219628 | 2018 | 2 | 3 | 194 | E |
| | 2018 | 2 | 3 | 191 | V |
| 30343620 | 2018 | 2 | 3 | 438 | DT |
| 29724167 | 2018 | 2 | 1 | 46 | V |
| 29785570 | 2018 | 2 | 1 | 28 | B |
| 30081673 | 2018 | 1 | - | 76 | DT |
| 29438093 | 2018 | 2 | 2 | 93 | DT |
| 29188284 | 2018 | 2 | 2 | 26 | V |
| 30351999 | 2018 | 2 | 2 | 24 | V |
| 30690294 | 2019 | 2 | 3 | 214 | T |
| | 2019 | 2 | 3 | 192 | EB |
| 31437754 | 2019 | 2 | 3 | 192 | E |
| | 2019 | 2 | 3 | 186 | V |
| 30580112 | 2019 | 2 | real world | 3219 | V |
| | 2019 | 2 | 1 | 63 | VC |
| 31732523 | 2019 | 2 | 1 | 66 | VC |
| | 2019 | 2 | real world | 139 | D |
| 30386910 | 2019 | 2 | real world | 698 | V |
| 31876308 | 2019 | 2 | real world | 50 | DT |
| 31171444 | 2019 | 2 | 2 | 35 | DT |
| 32914022 | 2019 | 2 | 2 | 62 | V |
| | 2020 | 2 | 3 | 192 | EB |
| 31901705 | 2020 | 2 | 3 | 192 | E |
| | 2020 | 2 | 3 | 186 | V |
| 32822286 | 2020 | 2 | 3 | 201 | B |
| 32234665 | 2020 | 2 | 2 | 24 | T |
| 32534242 | 2020 | 2 | 2 | 77 | DT |
| 32818466 | 2020 | 2 | 2 | 43 | DT |
| | 2020 | 2 | 2 | 104 | DT |
| 33020646 | 2020 | 2 | 2 | 101 | DT |
| 33361337 | 2020 | 2 | 2 | 60 | DT |
| 32699976 | 2020 | 2 | real world | 112 | DT |
| 31895752 | 2020 | 1 | - | 271 | DT |
| 32534646 | 2020 | 2 | 3 | 281 | VC |
| 32758030 | 2020 | 2 | 3 | 35 | DT |

| Study PMID | Year | Study type (1= retrospective 2=prospective) | Study phase (1,2,3,4, real world) | Study size | Drug |
|-------------------|-------------|--|--|-------------------|-------------|
| 32875931 | 2020 | 1 | - | 62 | V |
| 34158360 | 2021 | 2 | 3 | 248 | V |
| | 2021 | 2 | 3 | 247 | VC |
| 34455067 | 2021 | 2 | 2 | 93 | DT |
| 33637626 | 2021 | 2 | 2 | 50 | B |

Table S2-Evaluation of the bias risk according to Risk Of Bias In Non-randomized Studies of Interventions guidelines (ROBINS I). (Sterne JAC, Higgins JPT, Elbers RG, Reeves BC and the development group for ROBINS-I. *“Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I): detailed guidance”*. Updated 12 October 2016. <http://www.riskofbias.info>)

| BIAS DUE TO CONFOUNDING | | | | | | | | | | |
|--------------------------------|-------------|------------|------------|------------|------------|------------|------------|------------|------------|-------------------|
| Study PMID | Year | 1.1 | 1.2 | 1.3 | 1.4 | 1.5 | 1.6 | 1.7 | 1.8 | Bias level |
| 21639808 | 2011 | N | NA | NA | NA | NA | NA | NA | NA | Low |
| 22356324 | 2012 | N | NA | NA | NA | NA | NA | NA | NA | Low |
| 22663011 | 2012 | N | NA | NA | NA | NA | NA | NA | NA | Low |
| 22735384 | 2012 | N | NA | NA | NA | NA | NA | NA | NA | Low |
| 23051966 | 2012 | N | NA | NA | NA | NA | NA | NA | NA | Low |
| 22805291 | 2012 | N | NA | NA | NA | NA | NA | NA | NA | Low |
| 23020132 | 2012 | N | NA | NA | NA | NA | NA | NA | NA | Low |
| 22805292 | 2012 | N | NA | NA | NA | NA | NA | NA | NA | Low |
| 23248257 | 2013 | PN | NA | NA | NA | NA | NA | NA | NA | Low |
| 23406731 | 2013 | PN | NA | NA | NA | NA | NA | NA | NA | Low |
| 23414587 | 2013 | PN | NA | NA | NA | NA | NA | NA | NA | Low |
| 23918947 | 2013 | PN | NA | NA | NA | NA | NA | NA | NA | Low |
| 24295639 | 2014 | N | NA | NA | NA | NA | NA | NA | NA | Low |
| 24445759 | 2014 | N | NA | NA | NA | NA | NA | NA | NA | Low |
| 24508103 | 2014 | N | NA | NA | NA | NA | NA | NA | NA | Low |
| 24241686 | 2014 | PN | NA | NA | NA | NA | NA | NA | NA | Low |
| 24582505 | 2014 | PN | NA | NA | NA | NA | NA | NA | NA | Low |
| 25037139 | 2014 | N | NA | NA | NA | NA | NA | NA | NA | Low |
| 25265492 | 2014 | N | NA | NA | NA | NA | NA | NA | NA | Low |
| 25265494 | 2014 | N | NA | NA | NA | NA | NA | NA | NA | Low |
| 25287827 | 2014 | N | NA | NA | NA | NA | NA | NA | NA | Low |
| 25399551 | 2015 | N | NA | NA | NA | NA | NA | NA | NA | Low |
| 24661317 | 2015 | PN | NA | NA | NA | NA | NA | NA | NA | Low |
| 25952781 | 2015 | PN | NA | NA | NA | NA | NA | NA | NA | Low |
| 26557775 | 2015 | PN | NA | NA | NA | NA | NA | NA | NA | Low |
| 25722381 | 2015 | PN | NA | NA | NA | NA | NA | NA | NA | Low |
| 25956405 | 2015 | N | NA | NA | NA | NA | NA | NA | NA | Low |
| 26037941 | 2015 | N | NA | NA | NA | NA | NA | NA | NA | Low |
| 26287849 | 2015 | PN | NA | NA | NA | NA | NA | NA | NA | Low |
| 26352686 | 2015 | N | NA | NA | NA | NA | NA | NA | NA | Low |
| 26392102 | 2015 | N | NA | NA | NA | NA | NA | NA | NA | Low |
| 26109403 | 2015 | PN | NA | NA | NA | NA | NA | NA | NA | Low |
| 26460303 | 2015 | PN | NA | NA | NA | NA | NA | NA | NA | Low |
| 26208946 | 2016 | PN | NA | NA | NA | NA | NA | NA | NA | Low |
| 26981153 | 2016 | PN | NA | NA | NA | NA | NA | NA | NA | Low |
| 26983408 | 2016 | PN | NA | NA | NA | NA | NA | NA | NA | Low |
| Study PMID | Year | 1.1 | 1.2 | 1.3 | 1.4 | 1.5 | 1.6 | 1.7 | 1.8 | Bias level |

| | | | | | | | | | | |
|-------------------|-------------|------------|------------|------------|------------|------------|------------|------------|------------|-------------------|
| 27080216 | 2016 | PN | NA | NA | NA | NA | NA | NA | NA | Low |
| 27071922 | 2016 | N | NA | NA | NA | NA | NA | NA | NA | Low |
| 27283860 | 2016 | PN | NA | NA | NA | NA | NA | NA | NA | Low |
| 27460442 | 2016 | PN | NA | NA | NA | NA | NA | NA | NA | Low |
| 27470608 | 2016 | PN | NA | NA | NA | NA | NA | NA | NA | Low |
| 27480103 | 2016 | N | NA | NA | NA | NA | NA | NA | NA | Low |
| 28151720 | 2017 | PN | NA | NA | NA | NA | NA | NA | NA | Low |
| 28152546 | 2017 | N | NA | NA | NA | NA | NA | NA | NA | Low |
| 27993793 | 2017 | PN | NA | NA | NA | NA | NA | NA | NA | Low |
| 28284557 | 2017 | N | NA | NA | NA | NA | NA | NA | NA | Low |
| 28444112 | 2017 | N | NA | NA | NA | NA | NA | NA | NA | Low |
| 28268064 | 2017 | PN | NA | NA | NA | NA | NA | NA | NA | Low |
| 28501764 | 2017 | PN | NA | NA | NA | NA | NA | NA | NA | Low |
| 28592387 | 2017 | PN | NA | NA | NA | NA | NA | NA | NA | Low |
| 28567600 | 2017 | PN | NA | NA | NA | NA | NA | NA | NA | Low |
| 28611198 | 2017 | N | NA | NA | NA | NA | NA | NA | NA | Low |
| 28475671 | 2017 | PN | NA | NA | NA | NA | NA | NA | NA | Low |
| 28891408 | 2017 | N | NA | NA | NA | NA | NA | NA | NA | Low |
| 28919011 | 2017 | PN | NA | NA | NA | NA | NA | NA | NA | Low |
| 28963614 | 2017 | PN | NA | NA | NA | NA | NA | NA | NA | Low |
| 29285228 | 2017 | PN | NA | NA | NA | NA | NA | NA | NA | Low |
| 29076950 | 2017 | PN | NA | NA | NA | NA | NA | NA | NA | Low |
| 29384960 | 2017 | PN | NA | NA | NA | NA | NA | NA | NA | Low |
| 29121415 | 2017 | PN | NA | NA | NA | NA | NA | NA | NA | Low |
| 29477665 | 2018 | N | NA | NA | NA | NA | NA | NA | NA | Low |
| 29188284 | 2018 | PN | NA | NA | NA | NA | NA | NA | NA | Low |
| 29573941 | 2018 | N | NA | NA | NA | NA | NA | NA | NA | Low |
| 29724167 | 2018 | N | NA | NA | NA | NA | NA | NA | NA | Low |
| 29785570 | 2018 | N | NA | NA | NA | NA | NA | NA | NA | Low |
| 30219628 | 2018 | N | NA | NA | NA | NA | NA | NA | NA | Low |
| 30081673 | 2018 | PN | NA | NA | NA | NA | NA | NA | NA | Low |
| 29438093 | 2018 | PN | NA | NA | NA | NA | NA | NA | NA | Low |
| 30343620 | 2018 | N | NA | NA | NA | NA | NA | NA | NA | Low |
| 30351999 | 2018 | N | NA | NA | NA | NA | NA | NA | NA | Low |
| 30468696 | 2019 | PN | NA | NA | NA | NA | NA | NA | NA | Low |
| 30580112 | 2019 | PN | NA | NA | NA | NA | NA | NA | NA | Low |
| 30690294 | 2019 | N | NA | NA | NA | NA | NA | NA | NA | Low |
| 31171444 | 2019 | PN | NA | NA | NA | NA | NA | NA | NA | Low |
| 32914022 | 2019 | PN | NA | NA | NA | NA | NA | NA | NA | Low |
| 31437754 | 2019 | N | NA | NA | NA | NA | NA | NA | NA | Low |
| 31732523 | 2019 | N | NA | NA | NA | NA | NA | NA | NA | Low |
| 30386910 | 2019 | N | NA | NA | NA | NA | NA | NA | NA | Low |
| Study PMID | Year | 1.1 | 1.2 | 1.3 | 1.4 | 1.5 | 1.6 | 1.7 | 1.8 | Bias level |

| | | | | | | | | | | |
|----------|------|----|----|----|----|----|----|----|----|-----|
| 31876308 | 2019 | PN | NA | NA | NA | NA | NA | NA | NA | Low |
| 31901705 | 2020 | N | NA | NA | NA | NA | NA | NA | NA | Low |
| 32234665 | 2020 | PN | NA | NA | NA | NA | NA | NA | NA | Low |
| 31895752 | 2020 | PN | NA | NA | NA | NA | NA | NA | NA | Low |
| 32534242 | 2020 | PN | NA | NA | NA | NA | NA | NA | NA | Low |
| 32534646 | 2020 | PN | NA | NA | NA | NA | NA | NA | NA | Low |
| 32818466 | 2020 | PN | NA | NA | NA | NA | NA | NA | NA | Low |
| 32822286 | 2020 | N | NA | NA | NA | NA | NA | NA | NA | Low |
| 33020646 | 2020 | PN | NA | NA | NA | NA | NA | NA | NA | Low |
| 32758030 | 2020 | PN | NA | NA | NA | NA | NA | NA | NA | Low |
| 32875931 | 2020 | PN | NA | NA | NA | NA | NA | NA | NA | Low |
| 32699976 | 2020 | PN | NA | NA | NA | NA | NA | NA | NA | Low |
| 33361337 | 2020 | PN | NA | NA | NA | NA | NA | NA | NA | Low |
| 33637626 | 2021 | N | NA | NA | NA | NA | NA | NA | NA | Low |
| 34455067 | 2021 | PN | NA | NA | NA | NA | NA | NA | NA | Low |
| 34243078 | 2021 | N | NA | NA | NA | NA | NA | NA | NA | Low |
| 34158360 | 2021 | N | NA | NA | NA | NA | NA | NA | NA | Low |

BIAS IN SELECTION OF PARTICIPANTS INTO THE STUDY

| Study PMID | Year | 2.1 | 2.2 | 2.3 | 2.4 | 2.5 | Bias level |
|-------------------|-------------|------------|------------|------------|------------|------------|-------------------|
| 21639808 | 2011 | N | NA | NA | Y | NA | Low |
| 22356324 | 2012 | N | NA | NA | PY | NA | Low |
| 22663011 | 2012 | N | NA | NA | PY | NA | Low |
| 22735384 | 2012 | N | NA | NA | Y | NA | Low |
| 23051966 | 2012 | N | NA | NA | Y | NA | Low |
| 22805291 | 2012 | PN | NA | NA | PY | NA | Low |
| 23020132 | 2012 | N | NA | NA | Y | NA | Low |
| 22805292 | 2012 | PN | NA | NA | PY | NA | Low |
| 23248257 | 2013 | N | NA | NA | Y | NA | Low |
| 23406731 | 2013 | N | NA | NA | Y | NA | Low |
| 23414587 | 2013 | PN | NA | NA | PY | NA | Low |
| 23918947 | 2013 | PN | NA | NA | PY | NA | Low |
| 24295639 | 2014 | N | NA | NA | Y | NA | Low |
| 24445759 | 2014 | N | NA | NA | PY | NA | Low |
| 24508103 | 2014 | N | NA | NA | Y | NA | Low |
| 24241686 | 2014 | N | NA | NA | Y | NA | Low |
| 24582505 | 2014 | N | NA | NA | PY | NA | Low |
| 25037139 | 2014 | PN | NA | NA | PY | NA | Low |
| 25265492 | 2014 | N | NA | NA | Y | NA | Low |
| 25265494 | 2014 | N | NA | NA | Y | NA | Low |
| 25287827 | 2014 | N | NA | NA | Y | NA | Low |
| 25399551 | 2015 | N | NA | NA | Y | NA | Low |
| 24661317 | 2015 | N | NA | NA | Y | NA | Low |
| 25952781 | 2015 | N | NA | NA | Y | NA | Low |
| 26557775 | 2015 | N | NA | NA | Y | NA | Low |
| 25722381 | 2015 | PN | NA | NA | PY | NA | Low |
| 25956405 | 2015 | N | NA | NA | Y | NA | Low |
| 26037941 | 2015 | N | NA | NA | PY | NA | Low |
| 26287849 | 2015 | N | NA | NA | Y | NA | Low |
| 26352686 | 2015 | PN | NA | NA | PY | NA | Low |
| 26392102 | 2015 | N | NA | NA | PY | NA | Low |
| 26109403 | 2015 | PN | NA | NA | Y | NA | Low |
| 26460303 | 2015 | PN | NA | NA | PY | NA | Low |
| 26208946 | 2016 | N | NA | NA | PY | NA | Low |
| 26981153 | 2016 | N | NA | NA | Y | NA | Low |
| 26983408 | 2016 | PN | NA | NA | PY | NA | Low |
| 27080216 | 2016 | PN | NA | NA | PY | NA | Low |
| 27071922 | 2016 | PN | NA | NA | PY | NA | Low |
| 27283860 | 2016 | PN | NA | NA | PY | NA | Low |
| 27460442 | 2016 | PN | NA | NA | PY | NA | Low |

| | | | | | | | |
|-------------------|-------------|------------|------------|------------|------------|------------|-------------------|
| 27470608 | 2016 | N | NA | NA | Y | NA | Low |
| 27480103 | 2016 | N | NA | NA | Y | NA | Low |
| 28151720 | 2017 | PN | NA | NA | PY | NA | Low |
| 28152546 | 2017 | PN | NA | NA | PY | NA | Low |
| 27993793 | 2017 | PN | NA | NA | PY | NA | Low |
| 28284557 | 2017 | N | NA | NA | Y | NA | Low |
| 28444112 | 2017 | N | NA | NA | Y | NA | Low |
| 28268064 | 2017 | PN | NA | NA | PY | NA | Low |
| 28501764 | 2017 | N | NA | NA | Y | NA | Low |
| 28592387 | 2017 | PN | NA | NA | PY | NA | Low |
| 28567600 | 2017 | N | NA | NA | Y | NA | Low |
| 28611198 | 2017 | PN | NA | NA | PY | NA | Low |
| 28475671 | 2017 | N | NA | NA | Y | NA | Low |
| 28891408 | 2017 | N | NA | NA | PY | NA | Low |
| 28919011 | 2017 | PN | NA | NA | PY | NA | Low |
| 28963614 | 2017 | N | NA | NA | Y | NA | Low |
| 29285228 | 2017 | PN | NA | NA | PY | NA | Low |
| 29076950 | 2017 | PN | NA | NA | PY | NA | Low |
| 29384960 | 2017 | N | NA | NA | Y | NA | Low |
| 29121415 | 2017 | PN | NA | NA | PY | NA | Low |
| 29477665 | 2018 | N | NA | NA | Y | NA | Low |
| 29188284 | 2018 | PN | NA | NA | PY | NA | Low |
| 29573941 | 2018 | N | NA | NA | Y | NA | Low |
| 29724167 | 2018 | PN | NA | NA | PY | NA | Low |
| 29785570 | 2018 | PN | NA | NA | PY | NA | Low |
| 30219628 | 2018 | N | NA | NA | Y | NA | Low |
| 30081673 | 2018 | N | NA | NA | Y | NA | Low |
| 29438093 | 2018 | PN | NA | NA | PY | NA | Low |
| 30343620 | 2018 | N | NA | NA | Y | NA | Low |
| 30351999 | 2018 | PN | NA | NA | PY | NA | Low |
| 30468696 | 2019 | N | NA | NA | Y | NA | Low |
| 30580112 | 2019 | N | NA | NA | PY | NA | Low |
| 30690294 | 2019 | N | NA | NA | Y | NA | Low |
| 31171444 | 2019 | PN | NA | NA | PY | NA | Low |
| 32914022 | 2019 | PN | NA | NA | PY | NA | Low |
| 31437754 | 2019 | N | NA | NA | Y | NA | Low |
| 31732523 | 2019 | PN | NA | NA | PY | NA | Low |
| 30386910 | 2019 | N | NA | NA | PY | NA | Low |
| 31876308 | 2019 | N | NA | NA | Y | NA | Low |
| 31901705 | 2020 | N | NA | NA | Y | NA | Low |
| 32234665 | 2020 | PN | NA | NA | PY | NA | Low |
| 31895752 | 2020 | PN | NA | NA | PY | NA | Low |
| Study PMID | Year | 2.1 | 2.2 | 2.3 | 2.4 | 2.5 | Bias level |

| | | | | | | | |
|----------|------|----|----|----|----|----|-----|
| 32534242 | 2020 | PN | NA | NA | PY | NA | Low |
| 32534646 | 2020 | PN | NA | NA | PY | NA | Low |
| 32818466 | 2020 | PN | NA | NA | PY | NA | Low |
| 32822286 | 2020 | N | NA | NA | Y | NA | Low |
| 33020646 | 2020 | PN | NA | NA | PY | NA | Low |
| 32758030 | 2020 | PN | NA | NA | PY | NA | Low |
| 32875931 | 2020 | PN | NA | NA | PY | NA | Low |
| 32699976 | 2020 | N | NA | NA | Y | NA | Low |
| 33361337 | 2020 | PN | NA | NA | PY | NA | Low |
| 33637626 | 2021 | PN | NA | NA | PY | NA | Low |
| 34455067 | 2021 | PN | NA | NA | PY | NA | Low |
| 34243078 | 2021 | N | NA | NA | Y | NA | Low |
| 34158360 | 2021 | N | NA | NA | Y | NA | Low |

BIAS IN CLASSIFICATIONS OF INTERVENTIONS

| Study PMID | Year | 3.1 | 3.2 | 3.3 | Bias level |
|-------------------|-------------|------------|------------|------------|-------------------|
| 21639808 | 2011 | Y | Y | N | Low |
| 22356324 | 2012 | NI | NI | PN | Low |
| 22663011 | 2012 | Y | Y | N | Low |
| 22735384 | 2012 | Y | Y | N | Low |
| 23051966 | 2012 | Y | Y | N | Low |
| 22805291 | 2012 | Y | Y | PN | Low |
| 23020132 | 2012 | Y | Y | N | Low |
| 22805292 | 2012 | PY | Y | PN | Low |
| 23248257 | 2013 | Y | Y | N | Low |
| 23406731 | 2013 | Y | Y | N | Low |
| 23414587 | 2013 | PY | PY | PN | Low |
| 23918947 | 2013 | PY | PY | PN | Low |
| 24295639 | 2014 | Y | Y | N | Low |
| 24445759 | 2014 | NI | NI | PN | Low |
| 24508103 | 2014 | Y | Y | N | Low |
| 24241686 | 2014 | Y | Y | PN | Low |
| 24582505 | 2014 | Y | Y | PN | Low |
| 25037139 | 2014 | Y | Y | PN | Low |
| 25265492 | 2014 | Y | Y | N | Low |
| 25265494 | 2014 | Y | Y | N | Low |
| 25287827 | 2014 | Y | Y | PN | Low |
| 25399551 | 2015 | Y | Y | N | Low |
| 24661317 | 2015 | NI | NI | PN | Low |
| 25952781 | 2015 | Y | Y | PN | Low |
| 26557775 | 2015 | NI | NI | PN | Low |
| 25722381 | 2015 | Y | Y | PN | Low |
| 25956405 | 2015 | Y | Y | PN | Low |
| 26037941 | 2015 | Y | Y | N | Low |
| 26287849 | 2015 | NI | NI | PN | Low |
| 26352686 | 2015 | PY | PY | PN | Low |
| 26392102 | 2015 | PY | PY | PN | Low |
| 26109403 | 2015 | Y | PY | PN | Low |
| 26460303 | 2015 | PY | PY | PN | Low |
| 26208946 | 2016 | PY | Y | PN | Low |
| 26981153 | 2016 | PY | Y | PN | Low |
| 26983408 | 2016 | PY | PY | PN | Low |
| 27080216 | 2016 | PY | PY | PN | Low |
| 27071922 | 2016 | PY | PY | PN | Low |
| 27283860 | 2016 | PY | PY | PN | Low |

| | | | | | |
|-------------------|-------------|------------|------------|------------|-------------------|
| 27460442 | 2016 | PY | PY | PN | Low |
| 27470608 | 2016 | Y | Y | PN | Low |
| 27480103 | 2016 | Y | Y | N | Low |
| 28151720 | 2017 | NI | PY | PN | Low |
| 28152546 | 2017 | Y | Y | PN | Low |
| 27993793 | 2017 | PY | PY | PN | Low |
| 28284557 | 2017 | Y | Y | N | Low |
| 28444112 | 2017 | Y | Y | N | Low |
| 28268064 | 2017 | PY | PY | PN | Low |
| 28501764 | 2017 | Y | Y | N | Low |
| 28592387 | 2017 | PY | PY | PN | Low |
| 28567600 | 2017 | Y | Y | PN | Low |
| 28611198 | 2017 | Y | Y | PN | Low |
| 28475671 | 2017 | Y | Y | PN | Low |
| 28891408 | 2017 | NI | Y | N | Low |
| 28919011 | 2017 | PY | PY | PN | Low |
| 28963614 | 2017 | Y | Y | PN | Low |
| 29285228 | 2017 | PY | PY | PN | Low |
| 29076950 | 2017 | PY | PY | PN | Low |
| 29384960 | 2017 | Y | Y | PN | Low |
| 29121415 | 2017 | PY | PY | PN | Low |
| 29477665 | 2018 | Y | Y | N | Low |
| 29188284 | 2018 | PY | PY | PN | Low |
| 29573941 | 2018 | Y | PY | N | Low |
| 29724167 | 2018 | Y | Y | PN | Low |
| 29785570 | 2018 | PY | Y | PN | Low |
| 30219628 | 2018 | Y | Y | N | Low |
| 30081673 | 2018 | Y | PY | N | Low |
| 29438093 | 2018 | PY | Y | PN | Low |
| 30343620 | 2018 | Y | PY | N | Low |
| 30351999 | 2018 | PY | PY | PN | Low |
| 30468696 | 2019 | Y | Y | N | Low |
| 30580112 | 2019 | Y | Y | PN | Low |
| 30690294 | 2019 | Y | Y | N | Low |
| 31171444 | 2019 | PY | PY | PN | Low |
| 32914022 | 2019 | PY | PY | PN | Low |
| 31437754 | 2019 | Y | Y | N | Low |
| 31732523 | 2019 | Y | Y | PN | Low |
| 30386910 | 2019 | Y | Y | PN | Low |
| 31876308 | 2019 | Y | Y | PN | Low |
| 31901705 | 2020 | Y | Y | N | Low |
| Study PMID | Year | 3.1 | 3.2 | 3.3 | Bias level |
| 32234665 | 2020 | PY | PY | PN | Low |

| | | | | | |
|----------|------|----|----|----|-----|
| 31895752 | 2020 | PY | PY | PN | Low |
| 32534242 | 2020 | PY | PY | PN | Low |
| 32534646 | 2020 | PY | PY | PN | Low |
| 32818466 | 2020 | PY | PY | PN | Low |
| 32822286 | 2020 | Y | Y | N | Low |
| 33020646 | 2020 | PY | PY | PN | Low |
| 32758030 | 2020 | PY | PY | PN | Low |
| 32875931 | 2020 | PY | PY | PN | Low |
| 32699976 | 2020 | Y | Y | N | Low |
| 33361337 | 2020 | PY | PY | PN | Low |
| 33637626 | 2021 | PY | PY | PN | Low |
| 34455067 | 2021 | PY | PY | PN | Low |
| 34243078 | 2021 | Y | Y | N | Low |
| 34158360 | 2021 | Y | Y | N | Low |

BIAS DUE TO DEVIATIONS FROM INTENDED INTERVENTIONS

| Study PMID | Year | 4.1 | 4.2 | 4.3 | 4.4 | 4.5 | 4.6 | Bias level |
|-------------------|-------------|------------|------------|------------|------------|------------|------------|-------------------|
| 21639808 | 2011 | N | NA | NI | NI | NI | NA | Low |
| 22356324 | 2012 | N | NA | NI | NI | NI | NA | Low |
| 22663011 | 2012 | N | NA | NI | NI | NI | NA | Low |
| 22735384 | 2012 | N | NA | NI | NI | NI | NA | Low |
| 23051966 | 2012 | N | NA | NA | NA | NA | NA | Low |
| 22805291 | 2012 | NI | NI | NI | PY | Y | NA | Low |
| 23020132 | 2012 | N | NA | NI | NI | NI | NA | Low |
| 22805292 | 2012 | NI | NI | NI | PY | Y | NA | Low |
| 23248257 | 2013 | PN | NA | NI | NI | NI | NA | Low |
| 23406731 | 2013 | NI | NA | NI | Y | Y | NA | Low |
| 23414587 | 2013 | PN | NA | NI | NI | NI | NA | Low |
| 23918947 | 2013 | PN | NA | NI | NI | NI | NA | Low |
| 24295639 | 2014 | N | NA | NI | NI | NI | NA | Low |
| 24445759 | 2014 | N | NA | NI | NI | NI | NA | Low |
| 24508103 | 2014 | N | NA | NI | NI | NI | NA | Low |
| 24241686 | 2014 | NI | NA | NI | PY | PY | NA | Low |
| 24582505 | 2014 | NI | NA | NI | NI | Y | NA | Low |
| 25037139 | 2014 | NI | NI | NI | PY | Y | NA | Low |
| 25265492 | 2014 | N | NA | NI | NI | NI | NA | Low |
| 25265494 | 2014 | N | NA | NI | NI | NI | NA | Low |
| 25287827 | 2014 | N | NA | PY | PY | PY | NA | Low |
| 25399551 | 2015 | N | NA | NI | NI | NI | NA | Low |
| 24661317 | 2015 | NI | NA | NI | PY | PY | NA | Low |
| 25952781 | 2015 | N | NA | NI | NI | NI | NA | Low |
| 26557775 | 2015 | NI | NA | NI | PY | PY | NA | Low |
| 25722381 | 2015 | PN | NA | NI | NI | NI | NI | Low |
| 25956405 | 2015 | NI | NA | NI | PY | PY | NA | Low |
| 26037941 | 2015 | N | NA | NI | NI | NI | NA | Low |
| 26287849 | 2015 | NI | NA | NI | PY | PY | NA | Low |
| 26352686 | 2015 | PN | NA | NI | NI | NI | NA | Low |
| 26392102 | 2015 | N | NA | PY | PY | PY | NA | Low |
| 26109403 | 2015 | NI | NA | NI | PY | PY | NA | Low |
| 26460303 | 2015 | PN | NA | NI | NI | NI | NA | Low |
| 26208946 | 2016 | N | NA | NI | NI | NI | NA | Low |
| 26981153 | 2016 | NI | NA | NI | PY | PY | NA | Low |
| 26983408 | 2016 | PN | NA | PY | PY | PY | NA | Low |
| 27080216 | 2016 | PN | NA | NI | NI | NI | NA | Low |
| 27071922 | 2016 | NI | NI | NI | PY | PY | NA | Low |
| 27283860 | 2016 | PN | NA | NI | NI | NI | NA | Low |
| 27460442 | 2016 | PN | NA | NI | NI | NI | NA | Low |

| Study PMID | Year | 4.1 | 4.2 | 4.3 | 4.4 | 4.5 | 4.6 | Bias level |
|-------------------|-------------|------------|------------|------------|------------|------------|------------|-------------------|
| 27470608 | 2016 | NI | NA | NI | PY | PY | NA | Low |
| 27480103 | 2016 | N | NA | NI | NI | NI | NA | Low |
| 28151720 | 2017 | PN | NA | NI | NI | NI | NA | Low |
| 28152546 | 2017 | NI | NI | NI | PY | Y | NA | Low |
| 27993793 | 2017 | PN | NA | NI | NI | NI | NA | Low |
| 28284557 | 2017 | N | NA | NI | NI | NI | NA | Low |
| 28444112 | 2017 | N | NA | NI | NI | NI | NA | Low |
| 28268064 | 2017 | PN | NA | NI | NI | NI | NA | Low |
| 28501764 | 2017 | NI | NA | NI | Y | Y | NA | Low |
| 28592387 | 2017 | PN | NA | NI | NI | NI | NA | Low |
| 28567600 | 2017 | NI | NA | NI | PY | PY | NA | Low |
| 28611198 | 2017 | NI | NI | NI | PY | Y | NA | Low |
| 28475671 | 2017 | NI | NA | NI | PY | PY | NA | Low |
| 28891408 | 2017 | N | NA | NI | NI | NI | NA | Low |
| 28919011 | 2017 | PN | NA | NI | NI | NI | NA | Low |
| 28963614 | 2017 | NI | NA | NI | PY | PY | NA | Low |
| 29285228 | 2017 | PN | NA | PY | PY | PY | NA | Low |
| 29076950 | 2017 | PN | NA | NI | NI | NI | NA | Low |
| 29384960 | 2017 | NI | NA | NI | PY | PY | NA | Low |
| 29121415 | 2017 | PN | NA | NI | NI | NI | NA | Low |
| 29477665 | 2018 | N | NA | NI | NI | NI | NA | Low |
| 29188284 | 2018 | PN | NA | NI | NI | NI | NA | Low |
| 29573941 | 2018 | N | NA | NI | NI | NI | NA | Low |
| 29724167 | 2018 | NI | NI | NI | PY | Y | NA | Low |
| 29785570 | 2018 | NI | NI | NI | PY | Y | NA | Low |
| 30219628 | 2018 | N | NA | NI | NI | NI | NA | Low |
| 30081673 | 2018 | NI | NA | NI | Y | Y | NA | Low |
| 29438093 | 2018 | NI | NA | NI | PY | Y | NA | Low |
| 30343620 | 2018 | N | NA | NI | NI | NI | NA | Low |
| 30351999 | 2018 | PN | NA | NI | NI | NI | NA | Low |
| 30468696 | 2019 | NI | NA | NI | Y | Y | NA | Low |
| 30580112 | 2019 | NI | NA | NI | NI | Y | NA | Low |
| 30690294 | 2019 | N | NA | NI | NI | NI | NA | Low |
| 31171444 | 2019 | PN | NA | NI | NI | NI | NA | Low |
| 32914022 | 2019 | PN | NA | NI | NI | NI | NA | Low |
| 31437754 | 2019 | NI | NA | NI | Y | Y | NA | Low |
| 31732523 | 2019 | NI | NI | NI | PY | Y | NA | Low |
| 30386910 | 2019 | NI | NA | NI | PY | PY | NA | Low |
| 31876308 | 2019 | NI | NA | NI | PY | PY | NA | Low |
| 31901705 | 2020 | N | NA | NI | NI | NI | NA | Low |
| 32234665 | 2020 | PN | NA | NI | NI | NI | NA | Low |
| 31895752 | 2020 | PN | NA | NI | NI | NI | NA | Low |

| Study PMID | Year | 4.1 | 4.2 | 4.3 | 4.4 | 4.5 | 4.6 | Bias level |
|-------------------|-------------|------------|------------|------------|------------|------------|------------|-------------------|
| 32534242 | 2020 | PN | NA | NI | NI | NI | NA | Low |
| 32534646 | 2020 | PN | NA | NI | NI | NI | NA | Low |
| 32818466 | 2020 | PN | NA | NI | NI | NI | NA | Low |
| 32822286 | 2020 | N | NA | NI | NI | NI | NA | Low |
| 33020646 | 2020 | PN | NA | NI | NI | NI | NA | Low |
| 32758030 | 2020 | PN | NA | NI | NI | NI | NA | Low |
| 32875931 | 2020 | PN | NA | NI | NI | NI | NA | Low |
| 32699976 | 2020 | NI | NA | NI | Y | Y | NA | Low |
| 33361337 | 2020 | PN | NA | NI | NI | NI | NA | Low |
| 33637626 | 2021 | PN | NA | NI | NI | NI | NA | Low |
| 34455067 | 2021 | PN | NA | NI | NI | NI | NA | Low |
| 34243078 | 2021 | N | NA | NI | NI | NI | NA | Low |
| 34158360 | 2021 | N | NA | NI | NI | NI | NA | Low |

BIAS DUE TO MISSING DATA

| Study PMID | Year | 5.1 | 5.2 | 5.3 | 5.4 | 5.5 | Bias level |
|-------------------|-------------|------------|------------|------------|------------|------------|-------------------|
| 21639808 | 2011 | PY | PN | PN | NA | NA | Low |
| 22356324 | 2012 | PY | PN | Y | NA | Y | Low |
| 22663011 | 2012 | Y | N | N | NA | NA | Low |
| 22735384 | 2012 | Y | N | N | NA | NA | Low |
| 23051966 | 2012 | Y | N | N | NA | NA | Low |
| 22805291 | 2012 | Y | PN | PN | NA | NA | Low |
| 23020132 | 2012 | Y | N | N | NA | NA | Low |
| 22805292 | 2012 | Y | PN | PN | NA | NA | Low |
| 23248257 | 2013 | Y | PN | PN | NA | NA | Low |
| 23406731 | 2013 | NI | NI | NI | NA | NA | Low |
| 23414587 | 2013 | PY | PN | PN | NA | NA | Low |
| 23918947 | 2013 | PY | PN | PN | NA | NA | Low |
| 24295639 | 2014 | Y | N | N | NA | NA | Low |
| 24445759 | 2014 | PY | PN | Y | NA | Y | Low |
| 24508103 | 2014 | Y | N | N | NA | NA | Low |
| 24241686 | 2014 | Y | PN | PN | NA | NA | Low |
| 24582505 | 2014 | PY | PN | PN | NA | NA | Low |
| 25037139 | 2014 | Y | PN | PN | NA | NA | Low |
| 25265492 | 2014 | Y | N | N | NA | NA | Low |
| 25265494 | 2014 | Y | N | N | NA | NA | Low |
| 25287827 | 2014 | Y | PN | PN | NA | NA | Low |
| 25399551 | 2015 | Y | N | N | NA | NA | Low |
| 24661317 | 2015 | PY | PN | PN | NA | NA | Low |
| 25952781 | 2015 | PY | PN | PN | NA | NA | Low |
| 26557775 | 2015 | PY | PN | PN | NA | NA | Low |
| 25722381 | 2015 | PY | PY | NI | Y | PN | Low |
| 25956405 | 2015 | Y | PN | PN | NA | NA | Low |
| 26037941 | 2015 | PY | PN | PN | NA | NA | Low |
| 26287849 | 2015 | PY | PN | NI | NA | NA | Low |
| 26352686 | 2015 | PY | PN | PN | NA | NA | Low |
| 26392102 | 2015 | Y | PN | NI | NA | NA | Low |
| 26109403 | 2015 | PY | N | PN | NA | NA | Low |
| 26460303 | 2015 | PY | PN | PN | NA | NA | Low |
| 26208946 | 2016 | N | PN | N | NI | PY | Low |
| 26981153 | 2016 | Y | N | PN | NA | NA | Low |
| 26983408 | 2016 | PY | PN | PN | NA | NA | Low |
| 27080216 | 2016 | PY | PN | PN | NA | NA | Low |
| 27071922 | 2016 | Y | N | N | NA | NA | Low |
| 27283860 | 2016 | PY | PN | PN | NA | NA | Low |
| 27460442 | 2016 | PY | PN | PN | NA | NA | Low |
| 27470608 | 2016 | Y | PN | PN | NA | NA | Low |

| Study PMID | Year | 5.1 | 5.2 | 5.3 | 5.4 | 5.5 | Bias level |
|-------------------|-------------|------------|------------|------------|------------|------------|-------------------|
| 27480103 | 2016 | Y | N | N | NA | NA | Low |
| 28151720 | 2017 | PY | PN | PN | NA | NA | Low |
| 28152546 | 2017 | Y | PN | PN | NA | NA | Low |
| 27993793 | 2017 | PY | PN | PN | NA | NA | Low |
| 28284557 | 2017 | PY | PN | PN | NA | NA | Low |
| 28444112 | 2017 | PY | PN | PN | NA | NA | Low |
| 28268064 | 2017 | PY | PN | PN | NA | NA | Low |
| 28501764 | 2017 | NI | NI | NI | NA | NA | Low |
| 28592387 | 2017 | PY | PN | PN | NA | NA | Low |
| 28567600 | 2017 | Y | PN | PN | NA | NA | Low |
| 28611198 | 2017 | Y | PN | PN | NA | NA | Low |
| 28475671 | 2017 | Y | PN | PN | NA | NA | Low |
| 28891408 | 2017 | PY | PN | PN | NA | NA | Low |
| 28919011 | 2017 | PY | PN | PN | NA | NA | Low |
| 28963614 | 2017 | Y | PN | PN | NA | NA | Low |
| 29285228 | 2017 | PY | PN | PN | NA | NA | Low |
| 29076950 | 2017 | PY | PN | PN | NA | NA | Low |
| 29384960 | 2017 | Y | PN | PN | NA | NA | Low |
| 29121415 | 2017 | PY | PN | PN | NA | NA | Low |
| 29477665 | 2018 | Y | N | N | NA | NA | Low |
| 29188284 | 2018 | PY | PN | PN | NA | NA | Low |
| 29573941 | 2018 | Y | N | N | NA | NA | Low |
| 29724167 | 2018 | Y | PN | PN | NA | NA | Low |
| 29785570 | 2018 | Y | PN | PN | NA | NA | Low |
| 30219628 | 2018 | Y | N | N | NA | NA | Low |
| 30081673 | 2018 | NI | NI | NI | NA | NA | Low |
| 29438093 | 2018 | Y | PN | PN | NA | NA | Low |
| 30343620 | 2018 | Y | N | N | NA | NA | Low |
| 30351999 | 2018 | PY | PN | PN | NA | NA | Low |
| 30468696 | 2019 | NI | NI | NI | NA | NA | Low |
| 30580112 | 2019 | PY | PN | PN | NA | NA | Low |
| 30690294 | 2019 | Y | N | N | NA | NA | Low |
| 31171444 | 2019 | PY | PN | PN | NA | NA | Low |
| 32914022 | 2019 | PY | PN | PN | NA | NA | Low |
| 31437754 | 2019 | NI | NI | NI | NA | NA | Low |
| 31732523 | 2019 | Y | PN | PN | NA | NA | Low |
| 30386910 | 2019 | Y | PN | PN | NA | NA | Low |
| 31876308 | 2019 | Y | PN | PN | NA | NA | Low |
| 31901705 | 2020 | Y | N | N | NA | NA | Low |
| 32234665 | 2020 | PY | PN | PN | NA | NA | Low |
| 31895752 | 2020 | PY | PN | PN | NA | NA | Low |
| 32534242 | 2020 | PY | PN | PN | NA | NA | Low |

| Study PMID | Year | 5.1 | 5.2 | 5.3 | 5.4 | 5.5 | Bias level |
|-------------------|-------------|------------|------------|------------|------------|------------|-------------------|
| 32534646 | 2020 | PY | PN | PN | NA | NA | Low |
| 32818466 | 2020 | PY | PN | PN | NA | NA | Low |
| 32822286 | 2020 | Y | N | N | NA | NA | Low |
| 33020646 | 2020 | PY | PN | PN | NA | NA | Low |
| 32758030 | 2020 | PY | PN | PN | NA | NA | Low |
| 32875931 | 2020 | NI | NI | NI | NA | NA | Low |
| 32699976 | 2020 | NI | NI | NI | NA | NA | Low |
| 33361337 | 2020 | PY | PN | PN | NA | NA | Low |
| 33637626 | 2021 | PY | PN | PN | NA | NA | Low |
| 34455067 | 2021 | PY | PN | PN | NA | NA | Low |
| 34243078 | 2021 | PY | PN | PN | NA | NA | Low |
| 34158360 | 2021 | Y | N | N | NA | NA | Low |

BIAS IN MEASUREMENT OF OUTCOMES

| Study PMID | Year | 6.1 | 6.2 | 6.3 | 6.4 | Bias level |
|-------------------|-------------|------------|------------|------------|------------|-------------------|
| 21639808 | 2011 | PN | NI | PY | PN | Low |
| 22356324 | 2012 | PN | Y | NI | N | Low |
| 22663011 | 2012 | PN | PN | NI | N | Low |
| 22735384 | 2012 | PN | PN | NI | N | Low |
| 23051966 | 2012 | PN | PN | NI | N | Low |
| 22805291 | 2012 | NI | NI | NI | NI | Low |
| 23020132 | 2012 | PN | Y | PY | PN | Low |
| 22805292 | 2012 | NI | NI | NI | NI | Low |
| 23248257 | 2013 | PN | N | Y | N | Low |
| 23406731 | 2013 | PY | Y | Y | PN | Low |
| 23414587 | 2013 | PN | PY | NI | N | Low |
| 23918947 | 2013 | PN | PY | NI | N | Low |
| 24295639 | 2014 | PN | NI | NI | N | Low |
| 24445759 | 2014 | PN | Y | NI | N | Low |
| 24508103 | 2014 | PN | NI | NI | N | Low |
| 24241686 | 2014 | PN | NI | NI | NI | Low |
| 24582505 | 2014 | NI | NI | NI | NI | Low |
| 25037139 | 2014 | NI | NI | NI | NI | Low |
| 25265492 | 2014 | PN | Y | PY | PN | Low |
| 25265494 | 2014 | PN | Y | PY | PN | Low |
| 25287827 | 2014 | PN | PY | PY | PN | Low |
| 25399551 | 2015 | PN | Y | PY | PN | Low |
| 24661317 | 2015 | N | NI | NI | NI | Low |
| 25952781 | 2015 | PN | NI | NI | NI | Low |
| 26557775 | 2015 | PN | NI | NI | NI | Low |
| 25722381 | 2015 | PN | PY | PY | PN | Low |
| 25956405 | 2015 | PN | NI | NI | NI | Low |
| 26037941 | 2015 | N | N | PY | PN | Low |
| 26287849 | 2015 | PN | NI | NI | NI | Low |
| 26352686 | 2015 | PN | PY | NI | N | Low |
| 26392102 | 2015 | PN | PY | PY | PN | Low |
| 26109403 | 2015 | PN | NI | NI | NI | Low |
| 26460303 | 2015 | PN | PY | NI | N | Low |
| 26208946 | 2016 | PY | Y | NI | PN | Low |
| 26981153 | 2016 | PN | NI | NI | NI | Low |
| 26983408 | 2016 | PN | PY | PY | PN | Low |
| 27080216 | 2016 | PN | PY | NI | N | Low |
| 27071922 | 2016 | NI | NI | NI | NI | Low |
| 27283860 | 2016 | PN | PY | NI | N | Low |
| 27460442 | 2016 | PN | PY | NI | N | Low |
| 27470608 | 2016 | PN | NI | NI | NI | Low |

| Study PMID | Year | 6.1 | 6.2 | 6.3 | 6.4 | Bias level |
|-------------------|-------------|------------|------------|------------|------------|-------------------|
| 27480103 | 2016 | PN | Y | PY | PN | Low |
| 28151720 | 2017 | PN | PY | PY | PN | Low |
| 28152546 | 2017 | NI | NI | NI | NI | Low |
| 27993793 | 2017 | PN | PY | NI | N | Low |
| 28284557 | 2017 | PN | NI | PY | PN | Low |
| 28444112 | 2017 | PN | NI | PY | PN | Low |
| 28268064 | 2017 | PN | PY | NI | N | Low |
| 28501764 | 2017 | PY | Y | Y | PN | Low |
| 28592387 | 2017 | PN | PY | NI | N | Low |
| 28567600 | 2017 | PN | NI | NI | NI | Low |
| 28611198 | 2017 | NI | NI | NI | NI | Low |
| 28475671 | 2017 | PN | NI | NI | NI | Low |
| 28891408 | 2017 | N | N | PY | PN | Low |
| 28919011 | 2017 | PN | PY | NI | N | Low |
| 28963614 | 2017 | PN | NI | NI | NI | Low |
| 29285228 | 2017 | PN | PY | NI | N | Low |
| 29076950 | 2017 | PN | PY | NI | N | Low |
| 29384960 | 2017 | PN | NI | NI | NI | Low |
| 29121415 | 2017 | PN | PY | NI | N | Low |
| 29477665 | 2018 | PN | NI | NI | N | Low |
| 29188284 | 2018 | PN | PY | NI | N | Low |
| 29573941 | 2018 | PN | Y | PY | PN | Low |
| 29724167 | 2018 | NI | NI | NI | NI | Low |
| 29785570 | 2018 | NI | NI | NI | NI | Low |
| 30219628 | 2018 | PN | Y | PY | PN | Low |
| 30081673 | 2018 | PY | Y | Y | PN | Low |
| 29438093 | 2018 | PN | NI | NI | NI | Low |
| 30343620 | 2018 | PN | Y | PY | PN | Low |
| 30351999 | 2018 | PN | PY | NI | N | Low |
| 30468696 | 2019 | PY | Y | Y | PN | Low |
| 30580112 | 2019 | NI | NI | NI | NI | Low |
| 30690294 | 2019 | PN | Y | PY | PN | Low |
| 31171444 | 2019 | PN | PY | NI | N | Low |
| 32914022 | 2019 | PN | PY | NI | N | Low |
| 31437754 | 2019 | PY | Y | Y | PN | Low |
| 31732523 | 2019 | NI | NI | NI | NI | Low |
| 30386910 | 2019 | PN | NI | NI | NI | Low |
| 31876308 | 2019 | PN | NI | NI | NI | Low |
| 31901705 | 2020 | PN | Y | PY | PN | Low |
| 32234665 | 2020 | PN | PY | NI | N | Low |
| 31895752 | 2020 | PN | PY | NI | N | Low |
| 32534242 | 2020 | PN | PY | NI | N | Low |

| Study PMID | Year | 6.1 | 6.2 | 6.3 | 6.4 | Bias level |
|-------------------|-------------|------------|------------|------------|------------|-------------------|
| 32534646 | 2020 | PN | NI | NI | N | Low |
| 32818466 | 2020 | PN | PY | NI | N | Low |
| 32822286 | 2020 | PN | NI | NI | N | Low |
| 33020646 | 2020 | PN | PY | NI | N | Low |
| 32758030 | 2020 | PN | PY | NI | N | Low |
| 32875931 | 2020 | PN | PY | NI | N | Low |
| 32699976 | 2020 | PY | Y | Y | PN | Low |
| 33361337 | 2020 | PN | PY | NI | N | Low |
| 33637626 | 2021 | PN | PY | NI | N | Low |
| 34455067 | 2021 | PN | PY | NI | N | Low |
| 34243078 | 2021 | PN | NI | PY | PN | Low |
| 34158360 | 2021 | PN | Y | PY | PN | Low |

BIAS IN SELECTION OF THE REPORTED RESULT

| Study PMID | Year | 7.1 | 7.2 | 7.3 | Bias level |
|-------------------|-------------|------------|------------|------------|-------------------|
| 21639808 | 2011 | N | N | N | Low |
| 22356324 | 2012 | N | N | N | Low |
| 22663011 | 2012 | N | N | N | Low |
| 22735384 | 2012 | N | N | N | Low |
| 23051966 | 2012 | N | N | N | Low |
| 22805291 | 2012 | N | N | N | Low |
| 23020132 | 2012 | N | N | N | Low |
| 22805292 | 2012 | N | N | N | Low |
| 23248257 | 2013 | N | N | N | Low |
| 23406731 | 2013 | N | NI | N | Low |
| 23414587 | 2013 | N | N | N | Low |
| 23918947 | 2013 | N | N | N | Low |
| 24295639 | 2014 | N | N | N | Low |
| 24445759 | 2014 | N | N | N | Low |
| 24508103 | 2014 | N | N | N | Low |
| 24241686 | 2014 | NI | N | PY | Low |
| 24582505 | 2014 | PN | PN | PN | Low |
| 25037139 | 2014 | N | N | N | Low |
| 25265492 | 2014 | N | N | N | Low |
| 25265494 | 2014 | N | N | N | Low |
| 25287827 | 2014 | N | N | N | Low |
| 25399551 | 2015 | N | N | N | Low |
| 24661317 | 2015 | NI | N | PY | Low |
| 25952781 | 2015 | N | PN | N | Low |
| 26557775 | 2015 | NI | N | PY | Low |
| 25722381 | 2015 | N | PN | PN | Low |
| 25956405 | 2015 | NI | N | PY | Low |
| 26037941 | 2015 | N | N | N | Low |
| 26287849 | 2015 | NI | N | PY | Low |
| 26352686 | 2015 | N | N | N | Low |
| 26392102 | 2015 | N | N | N | Low |
| 26109403 | 2015 | NI | N | PY | Low |
| 26460303 | 2015 | N | N | N | Low |
| 26208946 | 2016 | Y | PN | N | Low |
| 26981153 | 2016 | NI | N | PY | Low |
| 26983408 | 2016 | N | N | N | Low |
| 27080216 | 2016 | PN | N | N | Low |
| 27071922 | 2016 | PN | PN | PN | Low |
| 27283860 | 2016 | N | PN | N | Low |
| 27460442 | 2016 | PN | N | N | Low |

| Study PMID | Year | 7.1 | 7.2 | 7.3 | Bias level |
|-------------------|-------------|------------|------------|------------|-------------------|
| 27470608 | 2016 | NI | N | PY | Low |
| 27480103 | 2016 | N | N | N | Low |
| 28151720 | 2017 | PN | PN | N | Low |
| 28152546 | 2017 | PN | N | N | Low |
| 27993793 | 2017 | PN | PN | PN | Low |
| 28284557 | 2017 | N | N | PN | Low |
| 28444112 | 2017 | N | N | N | Low |
| 28268064 | 2017 | PN | N | N | Low |
| 28501764 | 2017 | N | NI | N | Low |
| 28592387 | 2017 | PN | N | N | Low |
| 28567600 | 2017 | NI | N | PY | Low |
| 28611198 | 2017 | N | N | N | Low |
| 28475671 | 2017 | NI | N | PY | Low |
| 28891408 | 2017 | N | N | N | Low |
| 28919011 | 2017 | PN | N | N | Low |
| 28963614 | 2017 | NI | N | PY | Low |
| 29285228 | 2017 | PN | PN | N | Low |
| 29076950 | 2017 | PN | PN | N | Low |
| 29384960 | 2017 | NI | N | PY | Low |
| 29121415 | 2017 | PN | N | PN | Low |
| 29477665 | 2018 | N | N | N | Low |
| 29188284 | 2018 | PN | PN | N | Low |
| 29573941 | 2018 | N | PN | N | Low |
| 29724167 | 2018 | N | N | N | Low |
| 29785570 | 2018 | PN | N | N | Low |
| 30219628 | 2018 | N | N | N | Low |
| 30081673 | 2018 | N | NI | N | Low |
| 29438093 | 2018 | NI | N | PY | Low |
| 30343620 | 2018 | N | PN | N | Low |
| 30351999 | 2018 | PN | N | PN | Low |
| 30468696 | 2019 | N | NI | N | Low |
| 30580112 | 2019 | PN | PN | PN | Low |
| 30690294 | 2019 | PN | N | N | Low |
| 31171444 | 2019 | PN | N | PN | Low |
| 32914022 | 2019 | PN | N | PN | Low |
| 31437754 | 2019 | N | NI | N | Low |
| 31732523 | 2019 | N | N | N | Low |
| 30386910 | 2019 | NI | PN | PY | Low |
| 31876308 | 2019 | NI | N | PY | Low |
| 31901705 | 2020 | N | N | N | Low |
| 32234665 | 2020 | PN | N | N | Low |
| 31895752 | 2020 | PN | PN | PN | Low |

| Study PMID | Year | 7.1 | 7.2 | 7.3 | Bias level |
|-------------------|-------------|------------|------------|------------|-------------------|
| 32534242 | 2020 | PN | N | N | Low |
| 32534646 | 2020 | PN | N | N | Low |
| 32818466 | 2020 | PN | N | N | Low |
| 32822286 | 2020 | N | N | N | Low |
| 33020646 | 2020 | PN | PN | N | Low |
| 32758030 | 2020 | PN | N | PN | Low |
| 32875931 | 2020 | PN | N | PN | Low |
| 32699976 | 2020 | N | NI | N | Low |
| 33361337 | 2020 | PN | PN | N | Low |
| 33637626 | 2021 | PN | PN | PN | Low |
| 34455067 | 2021 | PN | PN | PN | Low |
| 34243078 | 2021 | N | N | N | Low |
| 34158360 | 2021 | N | N | N | Low |

Figure S1- Overall incidences of grade 5 adverse events according to treatment regimen.

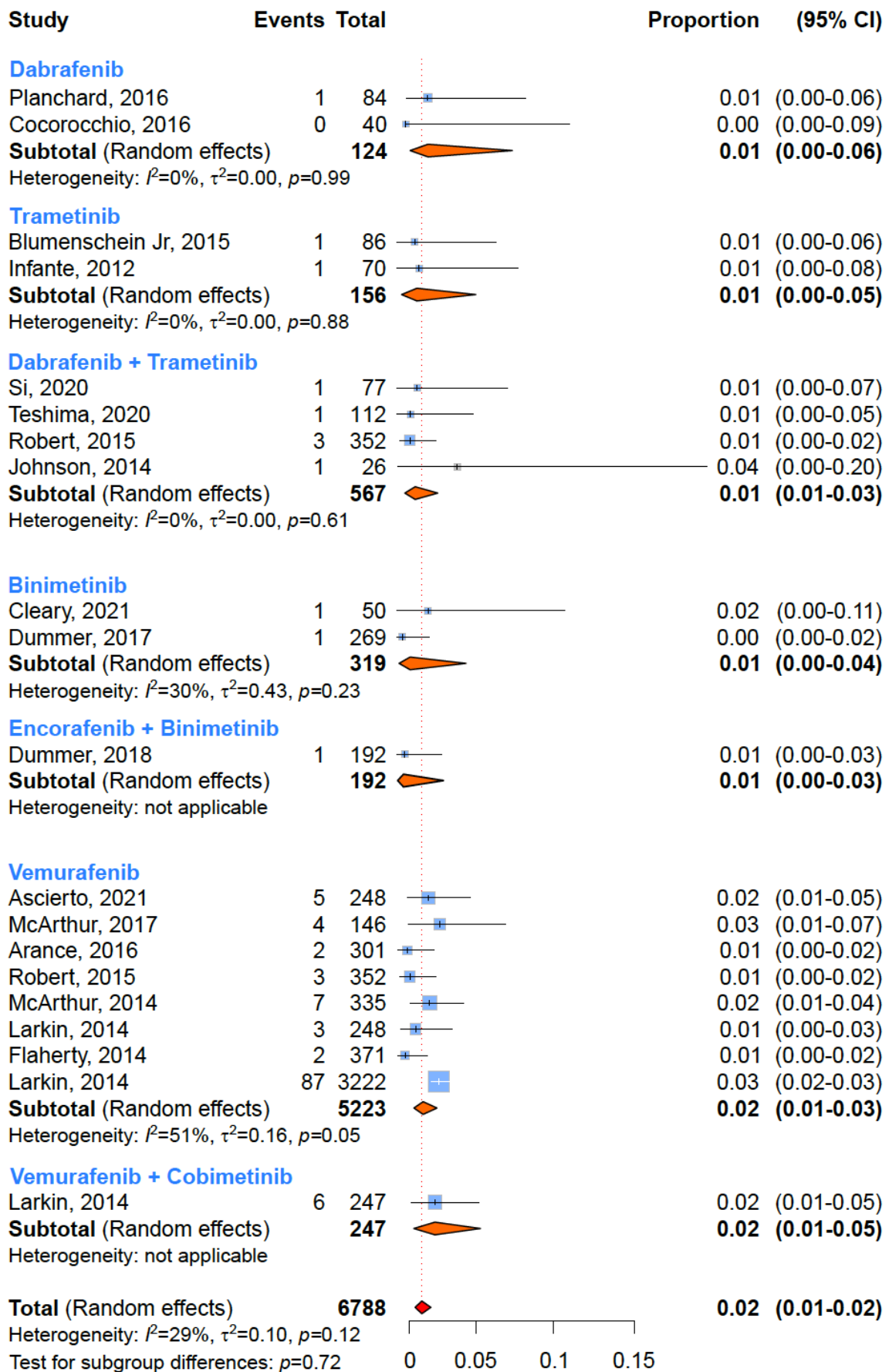


Table S3-Adverse events grade 5

| DRUG | ADVERSE EVENT | N |
|--|---------------------------------------|----------|
| Vemurafenib | Death | 12 |
| | General Physical Health Deterioration | 6 |
| | Cerebral Haemorrhage | 6 |
| | Cerebrovascular Accident | 5 |
| | Pneumonia | 5 |
| | Intracranial Tumour Haemorrhage | 5 |
| | Pulmonary Embolism | 5 |
| | Cardiac Arrest | 3 |
| | Multi-Organ Failure | 3 |
| | Sepsis | 3 |
| | Dyspnoea | 3 |
| | Cardiopulmonary Failure | 2 |
| | Myocardial Infarction | 2 |
| | Respiratory Tract Infection | 2 |
| | Completed Suicide | 2 |
| | Haemorrhagic Stroke | 2 |
| | Cerebral Ischemia | 1 |
| | Cardiac Failure | 1 |
| | Chronic Fatigue Syndrome | 1 |
| | Euthanasia | 1 |
| | Multi-Organ Disorder | 1 |
| | Sudden Cardiac Death | 1 |
| | Cerebral Haematoma | 1 |
| | Convulsion | 1 |
| | Dizziness | 1 |
| | Haemorrhage Intracranial | 1 |
| | Hydrocephalus | 1 |
| | Intracranial Pressure Increase | 1 |
| | Ischaemic Stroke | 1 |
| | Acute Respiratory Distress Syndrome | 1 |
| | Acute Respiratory Failure | 1 |
| | Chronic Obstructive Pulmonary Disease | 1 |
| | Pulmonary Oedema | 1 |
| | Pulmonary Toxicity | 1 |
| | Respiratory Failure | 1 |
| | Acute Myocardial Infarction | 1 |
| | Cardiogenic Stroke | 1 |
| | Coronary Artery Disease 2 | 1 |
| | Torsade De Pointes | 1 |
| | Escherichia Sepsis | 1 |
| | Septic Shock | 1 |
| Soft Tissue Infection | 1 | |
| Pneumocystis Jiroveci Pneumonia | 1 | |
| Anemia | 1 | |
| Agranulocytosis | 1 | |
| Disseminated Intravascular Coagulation | 1 | |
| Thrombocytopenia | 1 | |
| Fall | 1 | |

| | | |
|----------------------------------|--------------------------------------|---|
| | Injury | 1 |
| | Multiple Injuries | 1 |
| | Poisoning | 1 |
| | Diverticular Perforation | 1 |
| | Gastrointestinal Necrosis | 1 |
| | Intra-Abdominal Haemorrhage | 1 |
| | Circulatory Collapse | 1 |
| | Extremity Necrosis | 1 |
| | Atelectasis | 1 |
| | Renal Colic | 1 |
| | Toxic Epidermal Necrolysis | 1 |
| | Metastases To Central Nervous System | 1 |
| | Aortic Aneurysm Rupture | 1 |
| | Pleural Infection | 1 |
| | Glioma | 1 |
| | No information | 5 |
| Dabrafenib | Intracranial Haemorrhage | 1 |
| Trametinib | Sudden Death | 1 |
| | No Information | 1 |
| Binimetinib | Multi-Organ Failure | 1 |
| | No information | 1 |
| Vemurafenib + Cobimetinib | Cardiac Arrest | 1 |
| | Coma | 1 |
| | Clostridium Difficile Colitis | 1 |
| | Myocardial Infarction | 1 |
| | Pneumonia | 1 |
| | No information | 1 |
| Dabrafenib + Trametinib | Cerebral Haemorrhage | 2 |
| | Brain Stem Haemorrhage | 1 |
| | Pneumoperitoneum | 1 |
| | Disease Progression | 1 |
| | Hyponatremia | 1 |
| | Neurological decompensation | 1 |
| Encorafenib + Binimetinib | Suicide | 1 |