Efficacy and Safety of Remimazolam Versus Etomidate for Induction of General Anesthesia: Protocol for A Systematic Review and Meta-analysis

Li Zhao, Yiping Guo, Xuelei Zhou, Wei Mao, Linlin Chen, Ying Xie, Linji Li

Table of Contents

Efficacy and Safety of Remimazolam Versus Etomidate for Induction of General Anesthesia: Protocol for A Systematic Review and Meta-analysis

Li Zhao[1]; Yiping Guo[2, 3]; Xuelei Zhou[4]; Wei Mao[4]; Linlin Chen[4]; Ying Xie[4]; Linji Li[4]

[1]Department of Anesthesiology, The Second Clinical Medical College, North Sichuan Medical College, Nanchong Central Hospital, Nanchong, China CN

[2]School of Humanities and Management, Key Laboratory for Quality of Life and Psychological Assessment and Intervention, Guangdong Medical University, Dongguan, China, Dongguan, China, CN

[3]Nanchong Center for Disease Control and Prevention, Nanchong, China Nanchong, China CN

[4]Department of Anesthesiology, The Second Clinical Medical College, North Sichuan Medical College, Nanchong Central Hospital, Nanchong, China Nanchong, China CN

Corresponding Author:
Linji Li
Department of Anesthesiology, The Second Clinical Medical College, North Sichuan Medical College, Nanchong Central Hospital, Nanchong, China
Nanchong, China
Nanchong, China
CN

Abstract

Background: Post-induction hypotension (PIHO) is a hemodynamic abnormality commonly observed during the induction of general anesthesia. Previous studies have found that etomidate is considered a safer drug for the induction of anesthesia because it has only minor adverse effects on the cardiovascular and pulmonary systems. Remimazolam is a innovative benzodiazepine. Recent evidence found that remimazolam has minimal inhibitory effects on circulation and respiration. However, the efficacy and safety of remimazolam versus etomidate in the induction of anesthesia are unclear.

Objective: To compare the efficacy and safety of remimazolam versus etomidate for general anesthesia.

Methods: We plan to search the Web of Science, Cochrane Library, EMBASE, and PubMed from the date of their creation until December 31, 2023. The language limit is English only. The search terms that will be employed are "randomized controlled trials," "etomidate," and remimazolam." The incidence of PIHO was the primary outcome measure. Secondary outcomes included depth of anesthesia after induction, sedation success rate, time to loss of consciousness (LOC), hemodynamic profiles, recovery time, the incidence of injection pain, and postoperative nausea and vomiting. Reviews, meta-analyses, case studies, abstracts from conferences, and comments will not be accepted. The heterogeneity of the results will be evaluated by sensitivity and subgroup analysis. RevMan software and Stata software will be used for data analysis. We will evaluate the quality of included studies using the Cochrane Collaboration's risk of bias tool. The confidence of the evidence will be assessed through the Grading of Recommendations, Assessments, Developments, and Evaluations (GRADE).

Results: Our study will conclude which drug has more stable hemodynamics and lower incidence of PIHO by comparing the use of etomidate and remimazolam in the induction of general anesthesia. The results of this systematic review and meta-analysis will be publicly available and published in a peer-reviewed journal.

Conclusions: This is the first meta-analysis comparing remimazolam with etomidate for general anesthesia. The results of this study will provide data guidance for future anesthesia induction drugs. Clinical Trial: PROSPERO Registration Number: CRD42023463120.

Preprint Settings

1) Would you like to publish your submitted manuscript as preprint?
   Please make my preprint PDF available to anyone at any time (recommended).

Please make my preprint PDF available only to logged-in users; I understand that my title and abstract will remain visible to all users.
Only make the preprint title and abstract visible.

✔ **No, I do not wish to publish my submitted manuscript as a preprint.**

2) If accepted for publication in a JMIR journal, would you like the PDF to be visible to the public?

✔ **Yes, please make my accepted manuscript PDF available to anyone at any time (Recommended).**

Yes, but please make my accepted manuscript PDF available only to logged-in users; I understand that the title and abstract will remain v

Yes, but only make the title and abstract visible (see Important note, above). I understand that if I later pay to participate in <a href="http

Original Manuscript

Efficacy and Safety of Remimazolam Versus Etomidate for Induction of General Anesthesia: Protocol for A Systematic Review and Meta-analysis

Li Zhao[1#], Yiping Guo[2,3#], Xuelei Zhou[1], Wei Mao[1], Linlin Chen[1], Ying Xie[1], Linji Li[1*]

1. Department of Anesthesiology, The Second Clinical Medical College, North Sichuan Medical College, Nanchong Central Hospital, Nanchong, China

2. School of Humanities and Management, Key Laboratory for Quality of Life and Psychological Assessment and Intervention, Guangdong Medical University, Dongguan, China,

3. Nanchong Center for Disease Control and Prevention, Nanchong, China

#: Li Zhao and Yiping Guo contributed equally to this work.

*: Corresponding author

[Abstract] Background: Post-induction hypotension (PIHO) is a hemodynamic abnormality commonly observed during the induction of general anesthesia. Previous studies have found that etomidate is considered a safer drug for the induction of anesthesia because it has only minor adverse effects on the cardiovascular and pulmonary systems. Remimazolam is a innovative benzodiazepine. Recent evidence found that remimazolam has minimal inhibitory effects on circulation and respiration. However, the efficacy and safety of remimazolam versus etomidate in the induction of anesthesia are unclear. **Objective:** To further understand the potential of remimazolam, it is necessary to design a meta-analysis to evaluate remimazolam versus the classic safe anesthetic etomidate in the induction of general anesthesia. Our study will conclude which drug has more stable hemodynamics and lower incidence of PIHO. In addition our study will also yield data on sedation efficiency, time to loss of consciousness, time to awakening, incidence of injection pain and postoperative nausea and vomiting in both groups. **Methods:** We plan to search the Web of Science, Cochrane Library, Embase, PubMed, China National Knowledge Infrastructure, Wanfang Database, from the date of their creation until March 31, 2025. The language limit is English and Chinese. The search terms that will be employed are "randomized controlled trials", "etomidate", and remimazolam". The incidence of PIHO was the primary outcome measure. Secondary outcomes included depth of anesthesia after induction, sedation success rate, time to loss of consciousness, hemodynamic profiles, recovery time, the incidence of injection pain, and postoperative nausea and vomiting. Reviews, meta-analyses, case studies, abstracts from conferences, and comments will not be accepted. The heterogeneity of the results will be evaluated by sensitivity and subgroup analysis. RevMan software and Stata software will be used for data analysis. We will evaluate the quality of included studies using version 2 of the Cochrane risk-of-bias tool. The confidence of the evidence will be assessed through the Grading of Recommendations, Assessments, Developments, and Evaluations (GRADE). **Results:** The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) in November 2023. The review is expected to be completed in March 2025. We expect to be able to submit manuscripts for peer review by the end of June 2025. **Conclusion:** By synthesising the available evidence and comparing remazolam and etomidate, we hope to provide valuable insights into the selection of anaesthesia-inducing drugs to reduce the incidence of PIHO and improve patient prognosis. **PROSPERO registration number:** CRD42023463120.

Keywords: General Anesthesia; Anesthesia Induction; Post-induction hypotension; Remimazolam; Etomidate; Meta

Introduction:

As medical care advances worldwide, the number of patients undergoing surgery under general anesthesia has increased[1]. Post-induction hypotension (PIHO) is a hemodynamic abnormality commonly observed during induction of general anesthesia[2]. The hypotension occurring within 20 minutes after anesthesia

48 induction or before surgical incision is referred to as PIHO. Some studies have found that the incidence of
49 PIHO was as high as 45%~ 55%.[3-5]. Common PIHO risk factors include methods and dosages of
50 anesthesia, patient's poor baseline condition, hypovolemia, and poor cardiac function[6]. Because circulatory
51 reserves weaken with age, older patients are especially vulnerable to the development of PIHO[7]. Acute renal
52 damage[8], neurocognitive dysfunction[9], and perioperative cardiovascular events[10] are all linked to PIHO.
53 Increased mortality (8.8%), ICU stay (7.9%), and postoperative mechanical ventilation (20.7%) were
54 observed in PIHO patients[8, 11]. Therefore, it is important to find safer and more effective anesthesia-
55 inducing drugs to avoid PIHO.

56   Most intravenous anesthetics have a direct inhibitory effect on circulatory function[12]. Previous studies
57 have found that etomidate has minimal adverse effects on the cardiovascular and pulmonary systems[13-15].
58 Etomidate is thought to be a somewhat safer drug for the induction of anesthesia in patients having heart
59 surgery because of the reduced risk of hypotension[16, 17]. However, the etomidate's drawbacks, including
60 adrenocortical depression and myoclonus, have limited its usage[18].

61   Remimazolam is an innovative benzodiazepine[19]. Its effects began and ended more quickly than
62 with midazolam. Remimazolam can be continuously infused due to its ultra-short-acting profile[20].
63 Additionally, its clearance is not dependent on liver or renal function, because it's metabolized by
64 tissue esterase.[21, 22]. Recent research has shown that remimazolam and propofol have comparable
65 rates of sedative success but that remimazolam has less respiratory and circulatory depression[23-25].

66   However, the conclusions are controversial in comparing remimazolam and etomidate for
67 induction of general anesthesia. Huang et al. found that the remimazolam group had a higher
68 incidence of PIHO and a lower heart rate during induction than the etomidate group did[26].
69 However, some studies have found that low-dose remimazolam is hemodynamically more stable and
70 has fewer adverse effects than etomidate in noncardiac and cardiac surgery[27, 28].

71   Therefore, to further understand the potential of remimazolam, it is necessary to design a meta-
72 analysis to evaluate remimazolam versus the classic safe anesthetic etomidate in the induction of
73 general anesthesia. By comparing the use of etomidate and remimazolam in the induction of general
74 anesthesia, our study will conclude which drug has more stable hemodynamics and lower incidence
75 of PIHO. In addition our study will also yield data on sedation efficiency, time to loss of
76 consciousness, time to awakening, incidence of injection pain and postoperative nausea and vomiting
77 in both groups.

Methods:
 Study registration
 We have registered this meta-analysis in the International Prospective Registry of Systematic Reviews under
CRD42023463120. The Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols were
followed for reporting it[29]. This meta-analysis doesn't need ethical approval.

 Search strategy
  We plan to search the Web of Science, Cochrane Library, Embase, PubMed, China National Knowledge
Infrastructure, Wanfang Database, from the date of their creation until March 31, 2025. The language limit is
English and Chinese. We will look for more studies by looking through the references of related research and
the International Clinical Trials Registry Platform. Multimedia Appendix 1 displays the complete PubMed
search flowchart.

 Eligibility criteria
   Studies were considered eligible for inclusion using the following PICOS criteria: Patients aged 18 years or
older undergoing surgery under general anaesthesia (P); Remimazolam was used in the intervention group at
the induction of anaesthesia (I); The intervention group was induced with etomidate anaesthesia (C); The
primary outcome was the incidence of PIHO (O); Randomized controlled trials (S).

Study selection
   Two authors will independently determine which research is eligible by screening the title and abstract of
prospective eligible papers and then examining the entire texts of those publications. Arguments will be

101   settled through dialogue with a third author. Studies will be selected by using Preferred Reporting Items for
102   Systematic Reviews and Meta-Analyses.
103
104   **Data extraction**
105   Two authors will independently extract the following information from included studies: first author, year
106   of publication, patient characteristics, sample size, dosage of remimazolam, type of surgery, Incidence of
107   PIHO, time to loss of consciousness, and recovery time. We will attempt to contact the corresponding author
108   for raw data if the results were found by median with range. If there is no response, the median with range
109   will be converted to the mean with standard deviation according to the methods described by hozo et al[30].
110   Disagreements were solved through discussion with a third author.
111
112   **Risk of Bias Assessment**
113   We will evaluate the quality of included studies using version 2 of the Cochrane risk-of-bias tool[31]. The
114   judged domains were the randomisation process, deviations from intended interventions, missing outcome
115   data, measurement of the outcome, and selection of the reported results. Each domain was judged as high,
116   low, or some concern.
117
118   **Statistical Analysis**
119   Meta-analysis will be carried out using RevMan software and Stata software. For continuous data, we will
120   use the mean difference and 95% confidence interval (CI), and for dichotomous data, we will calculate the
121   risk ratio and 95% CI. The I^2 statistic will be used to analyze study heterogeneity. When there is insignificant
122   heterogeneity ($I^2 < 50\%$), a fixed-effects model will be used. Otherwise, a random-effects model will be used.
123   In addition, if high heterogeneity is encountered, sensitivity analysis or subgroup analysis will be conducted to
124   determine the reasons behind it. Methods for sensitivity analysis include, but are not limited to, single-study
125   exclusion method, meta-regression, etc. Subgroup analysis will be performed based on the final included
126   studies, focusing on patient age, gender, type of surgery, intervention dosage, etc. When more than ten studies
127   are included, publication bias will be assessed using Stata software for Egger's test or Begg's test[32]. For all
128   analyses, two-tailed tests with a significance level of $p < 0.05$ will be employed. The GRADE working group
129   approach will be used to assess the confidence of the evidence[33].
130
131   **Results**
132   The protocol was registered in the PROSPERO in November 2023. The review is expected to be completed
133   in March 2025. We expect to be able to submit manuscripts for peer review by the end of June 2025.
134
135   **Discussion**
136   Because of decreased vascular elasticity, autonomic nerve reflexes, and cardiac function reserve, PIHO is
137   more common in the elderly[34], and may have disastrous results such as myocardial ischemia, cerebral
138   infarction, kidney injury, neurocognitive impairment, death, and so on[35]. A recent large sample (409 cases)
139   multicentre randomised controlled trial found that induction of general anaesthesia with remimazolam
140   significantly reduced the incidence of PIHO and the use of vasoactive drugs compared with propofol. In
141   addition, the incidence of bradycardia was significantly lower in patients in the remimazolam group.
142   Although etomidate has a lesser effect on circulation, several recent studies have found a lower incidence of
143   PIHO with remimazolam than with etomidate[27, 28, 36]. However, these studies had small sample sizes
144   and were single-centre studies, and lacked meta-analysis studies. Therefore, meta-analysis is necessary to pool
145   the results of the current studies. Many anaesthetic drugs during induction of anaesthesia affect PIHO,
146   including opioids. Considering the impact of opioids on PIHO, we will avoid it in data extraction and analysis.
147   The effect of opioids on the primary outcome PIHO was reduced by ensuring that the same opioid medication
148   was used across studies or by using subgroup analyses.
149   This study also has some limitations. Firstly, only articles published in English and Chinese were searched
150   in this study. Second, due to the novelty of this topic, fewer studies are available for analysis in the results of
151   the current search. Despite this limitation, it is necessary to synthesise current studies on the incidence of
152   PIHO in the induction of general anaesthesia with remimazolam and etomidate to inform evidence-based
153   clinical decision-making and plan future studies.
154   **Conclusion:**

155   **By synthesising the available evidence and comparing remazolam and etomidate, we hope to provide**
156 **valuable insights into the selection of anaesthesia-inducing drugs to reduce the incidence of PIHO and**
157 **improve patient prognosis.**
158
159
160 **Abbreviations**
161 **CI: confidence interval.**
162 **GRADE:Grading of Recommendations, Assessments, Developments, and Evaluations.**
163 **PIHO: Post-induction hypotension.**
164 **PROSPERO: the International Prospective Register of Systematic Reviews.**
165

178
179 **Multimedia Appendix 1**
180 Search strategy for PubMed.
181
182 **Multimedia Appendix 2**
183 PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist

184

References:

185

186 [1].   Weiser, T.G., et al., Estimate of the global volume of surgery in 2012: an assessment supporting
187 improved health outcomes. Lancet (London, England), 2015. 385 Suppl 2: p. S11.

188 [2].   Lee, J., et al., Comparative Analysis on Machine Learning and Deep Learning to Predict Post-
189 Induction Hypotension.. 2020.

190 [3].   Purushothaman, S.S., et al., Ultrasound Measurement of Inferior Vena Cava Collapsibility as a
191 Tool to Predict Propofol-Induced Hypotension. Anesthesia, essays and researches, 2020. 14(2): p. 199-202.

192 [4].   Choi, M.H., et al., Pre-anaesthesia ultrasonography of the subclavian/infraclavicular axillary vein
193 for predicting hypotension after inducing general anaesthesia: A prospective observational study. European
194 journal of anaesthesiology, 2020. 37(6): p. 474-481.

195 [5].   Okamura, K., et al., Pre-anesthetic ultrasonographic assessment of the internal jugular vein for
196 prediction of hypotension during the induction of general anesthesia. Journal of anesthesia, 2019. 33(5): p.
197 612-619.

198 [6].   Golparvar, M., et al., Effect of ondansetron on prevention of post-induction hypotension in elderly
199 patients undergoing general anesthesia: A randomized, double-blind placebo-controlled clinical trial. Saudi
200 journal of anaesthesia, 2015. 9(4): p. 365-9.

201 [7].   Reich, D.L., et al., Predictors of hypotension after induction of general anesthesia. Anesthesia and
202 analgesia, 2005. 101(3): p. 622-628.

203 [8].   Maheshwari, K., et al., The association of hypotension during non-cardiac surgery, before and after
204 skin incision, with postoperative acute kidney injury: a retrospective cohort analysis. Anaesthesia, 2018.
205 73(10): p. 1223-1228.

206 [9].   Krzych, Ł.J., et al., Investigating Association between Intraoperative Hypotension and
207 Postoperative Neurocognitive Disorders in Non-Cardiac Surgery: A Comprehensive Review. Journal of
208 clinical medicine, 2020. 9(10).

209 [10].   Walsh, M., et al., Relationship between intraoperative mean arterial pressure and clinical outcomes
210 after noncardiac surgery: toward an empirical definition of hypotension. Anesthesiology, 2013. 119(3): p.
211 507-15.

212 [11].   Green, R.S. and M.B. Butler, Postintubation Hypotension in General Anesthesia: A Retrospective
213 Analysis. Journal of intensive care medicine, 2016. 31(10): p. 667-675.

214 [12].   Jor, O., et al., Hypotension after induction of general anesthesia: occurrence, risk factors, and
215 therapy. A prospective multicentre observational study. Journal of anesthesia, 2018. 32(5): p. 673-680.

216 [13].   Hong, J.T. and S. Park, Etomidate versus propofol for sedation in gastrointestinal endoscopy: A
217 systematic review and meta-analysis of outcomes. Medicine, 2023. 102(6): p. e32876.

218 [14].   Zhi, Y. and W. Li, Effects of total intravenous anesthesia with etomidate and propofol on
219 postoperative cognitive dysfunction. Physiological research, 2023. 72(2): p. 251-258.

220 [15].   Chen, L., et al., Safety and efficacy of combined use of propofol and etomidate for sedation during
221 gastroscopy: Systematic review and meta-analysis.. 2019. p. e15712.

222 [16].   Hannam, J.A., et al., Haemodynamic profiles of etomidate vs propofol for induction of
223 anaesthesia: a randomised controlled trial in patients undergoing cardiac surgery.. 2019. p. 198-205.

224   [17].   Dai, Z., et al., Etomidate vs propofol in coronary heart disease patients undergoing major
225   noncardiac surgery: A randomized clinical trial.. 2021. p. 1293-1303.

226   [18].   Lu, Z., et al., Effect of Etomidate vs Propofol for Total Intravenous Anesthesia on Major
227   Postoperative Complications in Older Patients: A Randomized Clinical Trial. JAMA surgery, 2022.
228   157(10): p. 888-895.

229   [19].   Borkett, K.M., et al., A Phase IIa, randomized, double-blind study of remimazolam (CNS 7056)
230   versus midazolam for sedation in upper gastrointestinal endoscopy.. 2015. p. 771-80.

231   [20].   Sneyd, J.R. and A.E. Rigby-Jones, Remimazolam for anaesthesia or sedation. Current opinion in
232   anaesthesiology, 2020. 33(4): p. 506-511.

233   [21].   Kilpatrick, G.J., Remimazolam: Non-Clinical and Clinical Profile of a New Sedative/Anesthetic
234   Agent. Frontiers in pharmacology, 2021. 12: p. 690875.

235   [22].   Oka, S., et al., Sedation outcomes for remimazolam, a new benzodiazepine. Journal of oral
236   science, 2021. 63(3): p. 209-211.

237   [23].   Wu, X., et al., Comparison of remimazolam and propofol about safety outcome indicators during
238   general anesthesia in surgical patients: a systematic review and meta-analysis. Minerva anestesiologica,
239   2023. 89(6): p. 553-564.

240   [24].   Tang, Y., et al., Remimazolam versus traditional sedatives for procedural sedation: a systematic
241   review and meta-analysis of efficacy and safety outcomes. Minerva anestesiologica, 2022. 88(11): p. 939-
242   949.

243   [25].   Dong, S., et al., A randomized, controlled clinical trial comparing remimazolam to propofol when
244   combined with alfentanil for sedation during ERCP procedures. Journal of clinical anesthesia, 2023. 86: p.
245   111077.

246   [26].   Huang, X., et al., The difference in mean arterial pressure induced by remimazolam compared to
247   etomidate in the presence of fentanyl at tracheal intubation: A randomized controlled trial. Frontiers in
248   pharmacology, 2023. 14: p. 1143784.

249   [27].   Chen, J., et al., Remimazolam vs Etomidate: Haemodynamic Effects in Hypertensive Elderly
250   Patients Undergoing Non-Cardiac Surgery.. 2023. p. 2943-2953.

251   [28].   Hu, B., et al., Comparison of Remimazolam Tosilate and Etomidate on Hemodynamics in Cardiac
252   Surgery: A Randomised Controlled Trial. Drug design, development and therapy, 2023. 17: p. 381-388.

253   [29].   Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015:
254   elaboration and explanation. BMJ (Clinical research ed.), 2016. 354: p. i4086.

255   [30].   Hozo, S.P., B. Djulbegovic and I. Hozo, Estimating the mean and variance from the median, range,
256   and the size of a sample. BMC medical research methodology, 2005. 5: p. 13.

257   [31].   Sterne, J.A.C., et al., RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ
258   (Clinical research ed.), 2019. 366: p. l4898.

259   [32].   Egger, M., et al., Bias in meta-analysis detected by a simple, graphical test. BMJ (Clinical research
260   ed.), 1997. 315(7109): p. 629-34.

261   [33].   .

262   [34].   Engel, D., et al., The impact of fluid optimisation before induction of anaesthesia on hypotension
263   after induction.. 2020. p. 1402.

264   [35].   Park, J., et al., Effect of pneumatic leg compression on post-induction hypotension in elderly

265   patients undergoing robot-assisted laparoscopic prostatectomy: a double-blind randomised controlled trial.
266   Anaesthesia, 2023. 78(6): p. 730-738.
267   [36].   Liu, X., et al., The Efficacy and Safety of Remimazolam Tosilate versus Etomidate-Propofol in
268   Elderly Outpatients Undergoing Colonoscopy: A Prospective, Randomized, Single-Blind, Non-Inferiority
269   Trial. Drug design, development and therapy, 2021. 15: p. 4675-4685.
270   X

271 Introduction to the research team

author	affiliations
Li Zhao	1. Department of Anesthesiology, The Second Clinical Medical College, North Sichuan Medical College, Nanchong Central Hospital, Nanchong, China
Yiping Guo	2.School of Humanities and Management, Key Laboratory for Quality of Life and Psychological Assessment and Intervention, Guangdong Medical University, Dongguan, China 3.Nanchong Center for Disease Control and Prevention, Nanchong, China
Xuelei Zhou	1.Department of Anesthesiology, The Second Clinical Medical College, North Sichuan Medical College, Nanchong Central Hospital, Nanchong, China
Wei Mao	1.Department of Anesthesiology, The Second Clinical Medical College, North Sichuan Medical College, Nanchong Central Hospital, Nanchong, China
Linlin Chen	1.Department of Anesthesiology, The Second Clinical Medical College, North Sichuan Medical College, Nanchong Central Hospital, Nanchong, China
Ying Xie	1.Department of Anesthesiology, The Second Clinical Medical College, North Sichuan Medical College, Nanchong Central Hospital, Nanchong, China
Linji Li	1.Department of Anesthesiology, The Second Clinical Medical College, North Sichuan Medical College, Nanchong Central Hospital, Nanchong, China

272 **corresponding author:** : Linji Li,

273 **full address:** No. 97 Renmin South Road, Shunqing District, Nanchong

274 City, Sichuan Province, China

275 **Email:** llj-stephen@163.com

276 **Phone:** +86 15583009555

277 **Fax:** none

278

Supplementary Files

Multimedia Appendixes

the complete PubMed search flowchart.
URL: http://asset.jmir.pub/assets/10120863ce8dda6f8e699cdb079c60eb.docx

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist.
URL: http://asset.jmir.pub/assets/2996bb85302fc6c374f4adbc1b94631b.doc

CONSORT (or other) checklists

Protocol.
URL: http://asset.jmir.pub/assets/f76e412dea047d36a63c9070b4cf034e.pdf