PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Opioid versus opioid-free analgesia after surgical discharge: protocol for a systematic review and meta-analysis
AUTHORS	El-Kefraoui, Charbel; Olleik, Ghadeer; Chay, Marc-Aurele; Kouyoumdjian, Araz; Nguyen-Powanda, Philip; Rajabiyazdi, Fateme; Do, Uyen; Derksen, Alexa; Landry, Tara; Amar-Zifkin, Alexandre; Ramanakumar, Agnihotram; Martel, Marc-Olivier; Baldini, Gabriele; Feldman, Liane; Fiore Jr, Julio

VERSION 1 - REVIEW

REVIEWER	Helene Beloeil University and teaching Hospital, Rennes, France
REVIEW RETURNED	21-Nov-2019

GENERAL COMMENTS	I would like to thank the authors for this analysis. As stated, data are missing on the subject. The manuscript is very well written and the objectives and methodology are clearly stated. My only comments are: - The type of anesthesia (ie. Opioid-free anesthesia or regional or opioid-based anesthesia) has an impact on postoperative pain and analgesic consumption. This will have to be taken into account in your analysis - Why did you decide to not include articles with IV administration of analgesics? According to your chart, Day 1 is between 13 and 24 hours after surgery; patients , specially after high risk surgery are stil receiving IV analgesics at that time. Moreover, by not including these studies (IV studies), you may miss some important articles on the subject. The route of administration does not really matter for your outcome, does it? If it is not too late, I would recommend to include articles with IV administration of analgesics. It would strenghten your message.

REVIEWER	Patrice Forget University of Aberdeen, UK Previously advisory board member for Grunenthal. Cochrane collaboration member. Editorial board member of the Eur J Anaesth and BMC Anesthesiology.
REVIEW RETURNED	12-Dec-2019

GENERAL COMMENTS	Dear authors, Thanks for submitting your work to the journal. You describe a protocol for a systematic review and meta-analysis addressing the question of the role of opioid vs. opioid-free analgesia after surgical discharge. The question is highly relevant as this may permit to influence the prescription behaviours, for instance by limiting, or not, the prescriptions of opioids after surgical discharge. At the moment, many patients receive opioid prescriptions, but this is highly dependent on the prescriptions pattern, and the variability is unacceptably high. The methods are well described and adequate. As pointed by the authors, the risk of a high heterogeneity may limit the interpretability of the results. This reviewer would like to point out the following complements that may improve the work and the usefulness of the results (for the interpretation and/or to improve the design of future studies): - Please consider the use of a network meta-analysis methodology. If not, please argue briefly why not. - Please consider the concomitant realisation of a Confidence in Meta-Analysis (i.e. using the CiNeMA software, available on cinema.ispm.unibe.ch) Minor comments: - Abstract.l.11 : As well pointed in the Introduction, this is well shown in North America, maybe present in the rest of the world but not that clear. Please add something like 'in North America'. - p.14.l.32. : As suggested in the introduction, why not to consider a potential effect of the country, or the continent in sensitivity analyses? - p.15.l.40. : Ethics and Dissemination: Please consider the involvement of Public/Patients organisations as this may have an impact on your timelines/use of resources. They could certainly be useful to enrich your dissemination plan.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1, Helene Beloeil:

Comment 1: The type of anesthesia (ie. Opioid-free anesthesia or regional or opioid-based anesthesia) has an impact on postoperative pain and analgesic consumption. This will have to be taken into account in your analysis.

Response: This is a very good point. As mentioned in our methods section (page 10, paragraph 2, line 10), we will extract data regarding type of anesthesia. As suggested by the reviewer, we will include a subgroup analysis to investigate the potential impact of anesthesia on the effect of opioid versus opioid-free analgesia post-discharge. The manuscript has been modified to include this analysis (page 14, paragraph 3, line 10-11).

Comment 2: Why did you decide to not include articles with IV administration of analgesics? According to your chart, Day 1 is between 13 and 24 hours after surgery; patients, specially after high risk surgery are still receiving IV analgesics at that time. Moreover, by not including these studies (IV studies), you may miss some important articles on the subject. The route of administration does not really matter for your outcome, does it?

If it is not too late, I would recommend to include articles with IV administration of analgesics. It would strengthen your message.

Response: Thank you for the opportunity to clarify this exclusion criterion. Our systematic review aims to summarize the evidence of postoperative analgesia regimens prescribed after surgical discharge. Since analgesic administration via invasive routes are usually prescribed during hospital stay and rarely prescribed for use at home after discharge, we decided to exclude these studies. The manuscript has been amended to clarify this point (page 8, paragraph 2, line 8). Similarly, Table 2 (page 18) has been changed to make it clear that we are looking at outcomes after surgical discharge.

Reviewer 2, Patrice Forget:

Comment 1: Please consider the use of a network meta-analysis methodology. If not, please argue briefly why not.

Response: Thank you for your suggestion. Conducting a network meta-analysis is beyond the scope of our work focused on the direct comparison between postoperative analgesia regimens including opioids versus opioid-free analgesia. Our findings may contribute venues for future research aimed to compare (directedly and indirectly) specific opioid versus non-opioid drugs, where a network meta-analysis approach may be extremely valuable.

Comment 2: Please consider the concomitant realisation of a Confidence in Meta-Analysis (i.e. using the CiNeMA software, available on cinema.ispm.unibe.ch)

Response: We appreciate this suggestion. CiNeMA is an important tool to grade evidence in network meta-analyses. Since we are conducting a pairwise meta-analysis, we will use GRADE to assess the quality of evidence for all the outcomes of interest in our review.

Comment 3: Abstract.l.11: As well pointed in the Introduction, this is well shown in North America, maybe present in the rest of the world but not that clear. Please add something like 'in North America'.

Response: The abstract introduction was revised according to this suggestion (page 3, paragraph 1, line 2).

Comment 4: p.14.l.32: As suggested in the introduction, why not to consider a potential effect of the country, or the continent in sensitivity analyses?

Response: Thank you for your suggestion. We will extract data regarding the location of the studies. As suggested by the reviewer, we will include a subgroup analysis to investigate the potential impact of study location on the effect of opioid versus opioid-free analgesia. The manuscript has been modified to include this analysis (page 14, paragraph 3, line 11).

Comment 5: p.15.l.40: Ethics and Dissemination: Please consider the involvement of Public/Patients organisations as this may have an impact on your timelines/use of resources. They could certainly be useful to enrich your dissemination plan.

Response: Thank you for bringing up this important point. We included further information about our knowledge dissemination plans, including via public and patient organizations (page 4, paragraph 1, line 2-4 and page 15, paragraph 2, line 1-9).

VERSION 2 – REVIEW

REVIEWER	helene beloeil CHU Rennes, Université Rennes, France
REVIEW RETURNED	02-Jan-2020

GENERAL COMMENTS	The reviewer completed the checklist but made no further comments.

REVIEWER	Patrice Forget University of Aberdeen, UK
REVIEW RETURNED	18-Dec-2019

GENERAL COMMENTS	The comments have been appropriately addressed.