## 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

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| **TITLE (PROVISIONAL)** | Comparing rates and characteristics of ambulance attendances related to extramedical use of pharmaceutical opioids in Australia: a protocol for a retrospective observational study |
| **AUTHORS** | Nielsen, Suzanne; Crossin, Rose; Middleton, Melissa; Martin, Catherine; Wilson, James; Lam, Tina; Scott, Debbie; Smith, Karen; Lubman, D |

## VERSION 1 – REVIEW

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| **REVIEWER** | Avik Chatterjee<br>Brigham and Women's Hospital, United States of America |
| **REVIEW RETURNED** | 29-Jan-2019 |

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| **GENERAL COMMENTS** | As outlined by the authors, this study will provide a comprehensive, nuanced view of opioid-related ambulance calls in multiple states in Australia. The protocol is clear, thoughtful, and comprehensive.<br><br>Specific comments:<br>1) age--I noticed that in the variable section there is a large age range of 12-54, then 55-65, then >65. I believe that an overdose in adolescence is much different than an adult in order adulthood (see for example Chatterjee et al in Drug and Alcohol Dependence, 2018). Consider justifying why the age groups are broken down that way, or, I might suggest different age categories with adolescents in their own group, perhaps dividing younger adults from older adults, etc.<br>2) The rubric suggests a checklist such as the STROBE checklist for a study like this. Perhaps this was a separate file I could not see? I think you cover all of the items, so I am not sure it is necessary to do explicitly, though this seems to be suggested by the journal.<br>3) I have not seen supply-adjusted overdose rates calculated in this way. I understand the stated justification, but is there a reference for using this method to assess supply-adjusted overdose rates, divided by sales, as you do here? |

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| **REVIEWER** | André Scherag<br>Jena University Hospital, Institute of Medical Statistics, Computer and Data Sciences, Germany |
| **REVIEW RETURNED** | 08-Feb-2019 |

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| **GENERAL COMMENTS** | In "Comparing rates and characteristics of ambulance attendances related to extramedical use of pharmaceutical opioids in Australia: a protocol for a retrospective observational study" Nielsen et al. describe a protocol of a planned and industry-funded |

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| | observational study using real world evidence (mainly ambulance data derived from electronic patient care records) on opioid-related harm. The study aims at answering three questions (Do the supply-adjusted rates of ambulance presentations differ by opioid potency?; Does the severity of presentation vary by opioid type? Are there differences in the context surrounding ambulance presentations related to extramedical use of oxycodone and tapentadol?).<br>This is an interesting project which will generate interesting complementary data to existing data sets. However, I have several recommendations which I would like to see addressed in a revised version of the manuscript. First of all, the authors should include a flow chart to depict how patients and data (at what time point) will enter the project (the process view of the project). Such a figure should provide a quick overview of the project and should contribute to a better understanding. Secondly, I recommend putting all variables and their detailed annotation (referring to international medial standards/codes to enable interoperability with other projects) in one or several table as "catalog of items" (maybe as a supplement). The authors have started this in Table 2. But such an extended table should also include the documentation source, potential intended data aggregations, transformations or quality control measures. In sum, this will make the data (and what to expect) more transparent, will allow future data sharing projects and will make parts of the manuscript (e.g. page 7 bottom) more readable. This table should ideally be related to the (process) figure and provide the details that cannot be displayed in the figure. Third, the authors should consider including one or several small validation study/studies to e.g. make sure that inter-coder extraction is reliable. |

**VERSION 1 – AUTHOR RESPONSE**

Reviewer(s)' Comments to Author:

Reviewer: 1
Reviewer Name: Avik Chatterjee

As outlined by the authors, this study will provide a comprehensive, nuanced view of opioid-related ambulance calls in multiple states in Australia. The protocol is clear, thoughtful, and comprehensive.

Specific comments:
1) age--I noticed that in the variable section there is a large age range of 12-54, then 55-65, then >65. I believe that an overdose in adolescence is much different than an adult in order adulthood (see for example Chatterjee et al in Drug and Alcohol Dependence, 2018). Consider justifying why the age groups are broken down that way, or, I might suggest different age categories with adolescents in their own group, perhaps dividing younger adults from older adults, etc.
Thank you for this suggestion. We note that, national data from the Australian Institute of Health and Welfare indicate that, in Australia, most overdoses are adults (peaking around 35-44 yo, with largest increases in older age groups). While adolescents are an interesting area to examine, in this dataset there would be insufficient cases in these younger age groups to enable analysis across opioid types (particularly noting the restriction on reporting cells of < 5). In response to the reviewers' suggestion, we have now divided the 12-54 age group into two groups (12-34 and 35-54) to allow a greater sense

the age distribution while not having age groups that will lead to censoring of the data due to small cell sizes. We have expanded our explanation of this in the supplementary material as suggested by reviewer 2.

2) The rubric suggests a checklist such as the STROBE checklist for a study like this. Perhaps this was a separate file I could not see? I think you cover all of the items, so I am not sure it is necessary to do explicitly, though this seems to be suggested by the journal.
We will report the findings according to the RECORD checklist (given that this study utilises routinely collected health data). This is noted on page 11. The RECORD checklist is based on the STROBE but includes additional measures that are relevant for when administrative data are used. This checklist is intended to be submitted as supplementary material with the outcomes papers but is not included here. We are happy to provide a checklist for the protocol if the editor prefers it, please let us know.

3) I have not seen supply-adjusted overdose rates calculated in this way. I understand the stated justification, but is there a reference for using this method to assess supply-adjusted overdose rates, divided by sales, as you do here?
Supply adjusted rates for prescription-related harm have been published by others (e.g. SAEs adjusted for opioid sales in Murphy et al 2018, and pharmaceutical opioid related mortality adjusted for opioid supply by Roxburgh et al 2017), full references below). To clarify, we are not adjusting by the number of sales, but are quantifying the total volume sold in kg. We now note these previous studies that have used this method in the text.

Murphy DL, Lebin JA, Severtson SG, Olsen HA, Dasgupta N, Dart RC. Comparative Rates of Mortality and Serious Adverse Effects Among Commonly Prescribed Opioid Analgesics. Drug Saf. 2018;41(8):787-95.
Roxburgh, A., et al. (2017). "Trends in heroin and pharmaceutical opioid overdose deaths in Australia." Drug & Alcohol Dependence 179: 192-198.

Revised text reads: ‘The total amount of each opioid will be calculated by jurisdiction in mg, converted into Oral Morphine Equivalents (OME) (24), and used to calculate a supply-adjusted rate of attendances, consistent with previous studies of pharmaceutical opioid related harm that have adjusted for supply using similar methods (8, 25).’

Reviewer: 2
Reviewer Name: André Scherag

Nielsen et al. describe a protocol of a planned and industry-funded observational study using real world evidence (mainly ambulance data derived from electronic patient care records) on opioid-related harm. The study aims at answering three questions (Do the supply-adjusted rates of ambulance presentations differ by opioid potency?; Does the severity of presentation vary by opioid type? Are there differences in the context surrounding ambulance presentations related to extramedical use of oxycodone and tapentadol?).
This is an interesting project which will generate interesting complementary data to existing data sets. However, I have several recommendations which I would like to see addressed in a revised version of the manuscript.

First of all, the authors should include a flow chart to depict how patients and data (at what time point) will enter the project (the process view of the project). Such a figure should provide a quick overview of the project and should contribute to a better understanding.
We have added a figure as suggested (See Figure 1).

Secondly, I recommend putting all variables and their detailed annotation (referring to international medial standards/codes to enable interoperability with other projects) in one or several table as "catalog of items" (maybe as a supplement). The authors have started this in Table 2. But such an extended table should also include the documentation source, potential intended data aggregations, transformations or quality control measures. In sum, this will make the data (and what to expect) more transparent, will allow future data sharing projects and will make parts of the manuscript (e.g. page 7 bottom) more readable. This table should ideally be related to the (process) figure and provide the details that cannot be displayed in the figure.
We have added a more detailed table as supplementary material as suggested (See Appendix B), and also have retained Table 2 in the main text as an overview of this information for the reader.

Third, the authors should consider including one or several small validation study/studies to e.g. make sure that inter-coder extraction is reliable.
Thank you for the chance to clarify this point. A strength of this data are the detailed steps to ensure it is as reliable as possible. There are a number of processes in place to ensure data are reliable. We have provide a detailed description in the supplementary material of the processes to maximise reliability of the data (Appendix A), and have made reference to this supplementary material in the main body of text (page 7). In brief, in the most recent audit to confirm interrater reliability there was 0.2% difference in coding between coders. Please see Appendix A in the supplementary material for a full description.

**VERSION 2 – REVIEW**

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| **REVIEWER** | André Scherag<br>Jena University Hospital, Institute of Medical Statistics, Computer and Data Sciences |
| **REVIEW RETURNED** | 21-Mar-2019 |

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| **GENERAL COMMENTS** | I thank the authors for addressing all my concerns - and all the best with the study! |