## PEER REVIEW HISTORY



## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | Protocol for a Mixed Methods Feasibility Study for the Surviving Opioid Overdose with Naloxone Education and Resuscitation (SOONER) Randomized Control Trial |
| **AUTHORS** | Orkin, Aaron; Campbell, Douglas; Handford, Curtis; Hopkins, Shaun; Klaiman, Michelle; Leece, Pamela; Parsons, Janet; Shahin, Rita; Strike, Carol; Thorpe, Kevin; Sellen, Kate; Milos, Geoffrey; Wright, Amy; Charles, Mercy; Sniderman, Ruby; Morrison, Laurie; SOONER Investigators, The |

## VERSION 1 – REVIEW

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| **REVIEWER** | Kristin Klemmetsby Solli<br>Akershus University Hospital and Centre for Addiction Researsch, University of Oslo, Norway |
| **REVIEW RETURNED** | 29-Apr-2019 |

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| **GENERAL COMMENTS** | This paper presents a protocol for a Mixed Methods Feasibility Study. The research group plan to conduct a randomized controlled trial and presents in detail how the trial will be performed. The paper deals with an important topic; improving the work with preventing opioid overdoses. Although the paper have merit, it also raises some questions I recommend the authors to clarify.<br>According to the title, the research group intends to conduct a RCT, but this is not properly reflected throughout the paper. The intervention arm is described in detail, but it is unclear what kind of measures the control group will receive. I understand that the measures varies between the different sites, but if the two arms are being compared, the readers need to know more details about what the controls are offered. A RCT sets high demands on the researchers if it is to be carried out in a proper and good manner (see e.g. CONSORT checklist). I recommend the authors to make sure that the different parts of their paper (e.g. interventions and outcomes) reflects that this is a RCT.<br>The paper is missing date for when the study is expected to be initiated.<br>The references should be thoroughly revised. Two references are duplicated (Festinger et al 2008 and Neset et al 2012) and different font size is used. |

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| **REVIEWER** | Marica Ferri<br>EMCDDA, Europe |
| **REVIEW RETURNED** | 24-May-2019 |

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| **GENERAL COMMENTS** | Dear authors,<br>Congratulations over this important initiative and paper.<br>Nowadays in the light of the severe opioid epidemics mainly in the US but not only, it is of extreme importance to study ways to improve Naloxone provision and overdose reversion. I have a couple of requests for clarifications. 1) How was the power of your study calculated (why did you choose to recruit 28 participants in 4 weeks)? How does this power relate to your target population (number of individuals you aim at recruiting in your trial and - most importantly - the number of Opioid overdose potential witnesses in your target community).<br>2) It is not clear if your inclusion criteria have to be all satisfied. If this is the case, why did you include only opioid users and not also relatives, partenrs and friends of opioid users? Can you explain how the inclusion/exclusion criteria relate to the epidemiology of opioid overdose in your reference community?<br>3) I think your background setion needs some epidemiological data on the number of cases you expect to reduce through the results of your study.<br>4) You may wish to add to your reference list some further publications:<br>Preventing fatal overdoses: a systematic review of the effectiveness of take-home naloxone<br>http://www.emcdda.europa.eu/system/files/publications/932/TDAU14009ENN.web_.pdf;<br>Community management of opioid overdose<br>https://www.who.int/substance_abuse/publications/management_opioid_overdose/en/ |

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| **REVIEWER** | Mimi Kim<br>Duke University, USA |
| **REVIEW RETURNED** | 30-May-2019 |

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| **GENERAL COMMENTS** | Please review tracked comments in PDF. Overall, my most significant concern is the lack of detail on this co-design frameowrk. The submission could also benefit from clearer attention to detail and clarity<br><br>The reviewer also provided a marked copy with additional comments. Please contact the publisher for ful details. |

**VERSION 1 – AUTHOR RESPONSE**

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| Reviewer 1 | |
| This paper presents a protocol for a Mixed Methods Feasibility Study. The research group plan to conduct a randomized controlled trial and presents in detail how the trial will be performed. The paper deals with an important topic; improving the work with preventing opioid overdoses. | Thank you. |
| Although the paper have merit, it also raises some questions I recommend the authors to clarify.<br><br>According to the title, the research group intends to conduct a<br><br>RCT, but this is not properly reflected throughout the paper. The | This is a protocol for a mixed methods feasibility study — it is not itself an RCT. A feasibility study is a piece of research done before the RCT to answer the question "Can the main RCT be done?" (see citation 19 in the manuscript.) Our primary feasibility study outcome is overall recruitment |
| intervention arm is described in detail, but it is unclear what kind of measures the control group will receive. I understand that the measures varies between the different sites, but if the two arms are being compared, the readers need to know more details about what the controls are offered. A RCT sets high demands on the researchers if it is to be carried out in a proper and good manner (see e.g. CONSORT checklist). I recommend the authors to make sure that the different parts of their paper (e.g. interventions and outcomes) reflects that this is a RCT. | and retention rate, as discussed in Section 3.5. This will be analysed in the proposed study. The outcomes of the underlying RCT are described in Section 3.6, but are not analysed or reported in the context of the feasibility study. This is stated in Section 3.6. Therefore, this study does not propose any comparison between the two arms.<br><br>To demonstrate that this protocol attends to all relevant elements of an RCT protocol (with appropriate modifications for a feasibility study), we included a SPIRIT checklist as a supplementary file. |
| The paper is missing date for when the study is expected to be initiated. | The expected date for the first recruitment has been added to Section 3.3. |
| The references should be thoroughly revised. Two references are duplicated (Festinger et al 2008 and Neset et al 2012) and different font size is used. | Revised accordingly (these changes are not tracked because tracking changes in the endnotes introduced formatting errors). |
| Reviewer 2 | |
| Congratulations over this important initiative and paper. Nowadays in the light of the severe opioid epidemics mainly in the US but not only, it is of extreme importance to study ways to improve Naloxone provision and overdose reversion. | Thank you. |

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| I have a couple of requests for clarifications. 1) How was the power of your study calculated (why did you choose to recruit 28 participants in 4 weeks)? How does this power relate to your target population (number of individuals you aim at recruiting in your trial and - most importantly - the number of Opioid overdose potential witnesses in your target community). | Section 3.3.c, Sample Size, has been revised thoroughly to address this question.<br><br>The sample size, recruitment rate and retention rates are chose to reflect logistical and budgetary constraints, the number of candidate participants presenting to the recruitment sites, and the scientific requirements of the underlying RCT. |
| 2) It is not clear if your inclusion criteria have to be all satisfied. If this is the case, why did you include only opioid users and not also relatives, partners and friends of opioid users? Can you explain how the inclusion/exclusion criteria relate to the epidemiology of opioid overdose in your reference community? | Table 1 states:<br><br>"Inclusion Criteria: Participants are eligible by meeting any one or more of the following: [list of inclusion criteria]" and<br><br>"Exclusion Criteria: Participants are ineligible by meeting any one or more of the following: [list of exclusion criteria].<br><br>Therefore, an eligible candidate must fulfil any one or more inclusion criteria, and may not fulfil any one or more exclusion criteria. |
| | One of the inclusion criteria is "Live with or is in frequent contact with others who use opioids or heroin." Therefore, partners and friends of opioid users are eligible for the study in addiction to opioid users.<br><br>The study inclusion criteria are adapted from the 2015 American Heart<br><br>Associated Guidelines on Cardiopulmonary Resuscitation in Special Circumstances, which includes criteria for populations that may benefit from OEND. Those guidelines draw on a global literature regarding populations at risk of fatal and non-fatal overdose, including in Canada (see especially citation 22 and 24 in this manuscript). |
| 3) I think your background section needs some epidemiological data on the number of cases you expect to reduce through the results of your study. | This is a protocol for a mixed methods feasibility study — it is not itself an RCT. A feasibility study is a piece of research done before the RCT to answer the question "Can the main RCT be done?" (see citation 19 in the manuscript.) Furthermore, we do not intend to design or power the underlying RCT to assess reductions in fatal or non-fatal opioid overdose cases, but rather to assess the training effectiveness of the novel OEND tool. Therefore, we have not attempted to compute or present the suggested epidemiological data. |

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| 4) You may wish to add to your reference list some further publications:<br><br>Preventing fatal overdoses: a systematic review of the effectiveness of take-home naloxone [pdf provided], Community management of opioid overdose [pdf provided] | Thank you for these references. We added both of them to the manuscript (see citation 3 and 23). |
| Reviewer 3 | |
| Please review tracked comments in PDF. | Abstract:<br><br>The reviewer has posed various questions at the level of the abstract that are answered in detail in the manuscript. We have clarified some details in the abstract. For example, we clarified that the simulation involves the participant as a responder with a mannequin. However, if the abstract is to remain brief, readers will need to refer to the full manuscript for comprehensive answers to some of the questions posed. For example, a full description of the recruitment and retention strategies and how they are relevant to the study population is found in the main text. Formatting: |
| | Font changes have been corrected throughout. |
| Overall, my most significant concern is the lack of detail on this co-design framework. The submission could also benefit from clearer attention to detail and clarity. | Community groups and individuals with lived experience have been involved in the project in two ways:<br><br>1) In Phase I of the SOONER Project, which was a co-design initiative to create a new overdose education and naloxone distribution tool. This is discussed in Section 4.1 of the manuscript. Please note that the feasibility trial described in the present manuscript is Phase II of the SOONER Project.<br>2) As ad hoc members of the SOONER Project Steering Committee, where they have been involved in study design and implementation. This is described in the new Patient and Public Involvement section (see section 4.2 of the manuscript). The abstract and manuscript has been reworked to make this clearer, especially with the addition of Section 3.2. |

**VERSION 2 – REVIEW**

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| **REVIEWER** | Kristin Klemmetsby Solli<br>Akershus University Hospital, Centre of Addiction Research<br>University of Oslo, Vestfold Hospital Trust |
| **REVIEW RETURNED** | 05-Jul-2019 |

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| **GENERAL COMMENTS** | My questions have been adequately addressed, and I recommend that the paper be accepted for publication. |