PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	The effect of synchronous remote-based interventions on suicidal behaviours: Protocol for a systematic review and meta-analysis
AUTHORS	Comendador, Laura; Jimenz Villamizar, Mara Paola; Losilla, Josep-Maria; Sanabria-Mazo, Juan; Mateo Canedo, Corel; Cebria, Ana Isabel; Sanz, Antoni; Palao, Diego

VERSION 1 – REVIEW

REVIEWER	McConnachie, Alex University of Glasgow, Robertson Centre for Biostatistics
REVIEW RETURNED	27-Jun-2023

GENERAL COMMENTS	This review looks at the paper by Comendador and colleagues, a protocol for a systematic review and meta-analysis of synchronous, remote interventions for suicidal behaviours. I am particularly interested in the statistical aspects of the paper. The writing needs a little work in places, particularly around the use of past and future tense. For example, the abstract state that the literature search will (future) cover the period to April 2022, which is over a year in the past, which suggests the review has been done. In other places, the writing appears to talk about what was done (in the past). Incidentally, I note that the section of the paper talking about the literature search says that it will be rerun if more than a year has passed since the initial search – is that now going to happen? Overall, I thought the paper was written quite well, giving a clear description of what will (or has been) done, and my comments are generally quite minor. In the introduction to the main paper, the first paragraph quotes suicide rates. I assume these rates are per year, but it could be clearer. Just after this, there is a statement that “increased risk of recidivism is directly related to a previous history of suicidal behaviour”, which seems hard to believe. Is it more likely that both reflect a common cause? In the section on “Types of outcome measures”, it says that assessments at baseline could be included. How would that work? To be an outcome, an assessment must come after the intervention, surely? It is stated that suicidal ideation may be measured by different

	outcomes, but gives only one example. Why not list all measurement tools that are known, perhaps in a table? Suicide attempts will be measured as a count, but what if a paper only reports this as a binary (any vs. none) outcome? The statistical section states that meta-analysis will be done if an outcome is reported by three or more studies. Since a standardised effect size is being used, does that mean different tools for measurement of suicidal ideation will be combined? I assume so, but this could be explicit. For subgroups analyses, are there plans to look at study type (RCT/observational) or quality in relation to between-study heterogeneity?

REVIEWER	Bridge, Jeffrey A. The Ohio State University College of Medicine, Research Institute at Nationwide Children's Hospital
REVIEW RETURNED	11-Jul-2023

GENERAL COMMENTS	The authors report on a protocol to conduct a systematic review and meta-analysis of the efficacy of suicide prevention interventions implemented via synchronous remote-based approaches. The authors are to be commended for proposing to undertake the proposed meta-analysis, which if successful could inform suicide prevention strategies. There are, however, several limitations that reduce enthusiasm. Specific suggestions: 1) The field has moved away from the term “completed suicide.” Please use “suicide death” or “suicide” instead of “completed suicide.” 2) Page 4, line 42: The authors state that the study will incorporate both quantitative and qualitative synthesis but there does not appear to be any discussion of how qualitative data will be analyzed. 3) Page 5, line 46: It would aid the reader to provide the country from which the suicide statistics are being presented. 4) Page 7, line 17: Please clarify whether there was overlap in studies included in the Milner and Noh meta-analyses. 5) Page 8, line 39: The terms “efficacy” and “effectiveness” are used interchangeably but these are different trial designs. Are both types of intervention trials included in the meta-analysis? If so, will sensitivity analyses be conducted to assess results in studies testing efficacy vs. effectiveness? 6) Page 8, line 53: It is unclear how results from various types of studies will be pooled for meta-analysis? Are RCTs weighted the same as quasi-experimental or case-control studies? 7) Page 9, line 53: The inclusion of studies using minimal in-person contact seems to run counter to the aim of examining remote-based interventions on future suicide risk. Please provide a rationale for this study inclusion criterion. 8) Page 10, line 46: It is unclear how the varying follow-up periods will be handled in the meta-analyses. Please clarify. 9) Page 12, line 17: It is unclear what sensitivity are specificity are referring to in the context of the literature search strategy. 10) Page 13, line 10: The “Data collection process” section is redundant with the “Selection process”. Please edit for brevity. 11) Page 14, line 19: The Data Synthesis section should be expanded upon to provide more specific details of the proposed

	analytic approaches. 12) Page 15, line 41: There are other measures to quantify publication bias that might also be considered that would complement the proposed methods (e.g., trim-and-fill approaches). 13) Page 17, line 7: It is unclear how results of this study will lead directly to better framing of targets for intervention and prevention of suicide.

VERSION 1 – AUTHOR RESPONSE

REVIEWER: 1 Prof. Alex McConnachie, University of Glasgow

This review looks at the paper by Comendador and colleagues, a protocol for a systematic review and meta-analysis of synchronous, remote interventions for suicidal behaviours. I am particularly interested in the statistical aspects of the paper.

Authors

- **Thank you very much for your comments and your particular interest in the statistical aspects of the present paper. We believe that the systematic review and meta-analysis will provide a new perspective on suicide prevention by examining synchronous remote-based interventions implemented in patients with suicidal behaviour.**

The writing needs a little work in places, particularly around the use of past and future tense. For example, the abstract state that the literature search will (future) cover the period to April 2022, which is over a year in the past, which suggests the review has been done. In other places, the writing appears to talk about what was done (in the past).

Authors

- **We fully agree that it was necessary to make some modifications in the use of the past and future tenses. For this reason, we have made modifications in the "Abstract" section (see adjustment on lines 11 to 14) and in the "Data collection and analysis" section (see adjustment on lines 192 to 218) to clarify which actions have been developed and which will be developed in the future. The authors hope to have provided solutions to any errors you may have found. Thank you very much for helping us correct the typographical and grammatical errors detected.**

Incidentally, I note that the section of the paper talking about the literature search says that it will be rerun if more than a year has passed since the initial search – is that now going to happen?

Authors

- **We made explicit that the literature search was re-run as more than a year has passed since the initial search (see adjustment on lines 215 to 218). Thank you very much for your comment.**

Overall, I thought the paper was written quite well, giving a clear description of what will (or has been) done, and my comments are generally quite minor.

Authors

- **Thank you very much for your encouraging comments. We appreciate the acknowledgement and the contribution of your suggestions to the improvement of the paper submitted.**

In the introduction to the main paper, the first paragraph quotes suicide rates. I assume these rates are per year, but it could be clearer.

Authors

- **We fully agree that it was necessary to clarify in the "Introduction" section the first paragraph quoting suicide rates. The way in which we originally described it could be confusing for the reader. We considered the suggestion to describe the annual suicide rates and made modifications on lines 40 to 53. Thank you very much for your suggestion.**

Just after this, there is a statement that "increased risk of recidivism is directly related to a previous history of suicidal behaviour", which seems hard to believe. Is it more likely that both reflect a common cause?

Authors

- **We consider the suggestion, and we fully agree that there was a need for further clarification of this statement. For this reason, we reconstruct the sentence to facilitate its understanding. The adjustments introduced in the manuscript are between lines 55 and 57.**

In the section on "Types of outcome measures", it says that assessments at baseline could be included. How would that work? To be an outcome, an assessment must come after the intervention, surely?

Authors

- **Thank you very much for your comment. We fully agree that to be an outcome, the assessment must come after the intervention. We have incorporated the review of baseline assessments both as a measure of comparison pre- *vs*. post-intervention and as a control for pre-Intervention differences among the conditions to be compared (intervention *vs.* control groups), although we recognise that reporting this in the "Types of outcome measures" section may be confusing for the reader. In addition, in measures of suicide deaths, it would not be relevant to report a baseline assessment, as patients who have committed suicide would not be eligible for study interventions. According to your recommendations, we have amended lines 181 and 182 of this section. Thank you very much for helping us clarify these possible confusions.**

It is stated that suicidal ideation may be measured by different outcomes, but gives only one example. Why not list all measurement tools that are known, perhaps in a table?

Authors

- **We consider the suggestion to list all known instruments for measuring suicidal ideation. The manuscript includes a description of the most common assessment instruments for suicidal ideation, according to a recent systematic review by Andreotti *et al.* [44]. The adjustments introduced in the manuscript are between lines 183 and 185. In addition, as requested, we have included a table in the manuscript reporting the most**

cited instruments in the literature to assess suicide risk (Table 1; see line 190). Thank you very much for your suggestion.

Suicide attempts will be measured as a count, but what if a paper only reports this as a binary (any vs. none) outcome?

Authors

- **We consider your comment relevant and have decided to incorporate it into the manuscript. Your contribution will help us describe this issue In the "Data synthesis" section more accurately. We agree that when conducting a meta-analysis, it is important to ensure that the data you are combining from different studies is comparable and can be appropriately synthesised. If we encounter a sitution where some studies report suicide attempts as a binary outcome while others report them as a count, we may need to make some data recoding to incorporate both types of data into the analysis. These adjustments could involve contacting study authors to request more detailed data (see lines 248-250); depending on the distribution of the data and the available information, we might consider transforming the binary outcome into a count; we could consider conducting sensitivity analyses to assess the impact of including or excluding studies that report the binary outcome; on the other hand, we could consider conducting separate subgroup analyses for each type of data if we have enough studies that report count data and studies that report binary outcomes; or adopting a narrative synthesis approach when a quantitative combination of studies is not feasible. For a more comprehensive understanding by the reader, this procedure is now described in detail in the manuscript (see adjustment on lines 275 to 284). Ultimately, the approach we take will depend on the available data and the research question we are addressing. Any data transformations or adjustments that are made will be documented in the manuscript, and the limitations introduced by differences in data reporting between studies should be acknowledged.**

The statistical section states that meta-analysis will be done if an outcome is reported by three or more studies. Since a standardised effect size is being used, does that mean different tools for measurement of suicidal ideation will be combined? I assume so, but this could be explicit.

Authors

- **We fully agree that it could be explicit that different tools will be combined for the measurement of suicidal ideation. For this reason, we have described it in the statistical section (see adjustment on lines 292 to 293). Thank you very much for helping us clarify these possible confusions.**

For subgroups analyses, are there plans to look at study type (RCT/observational) or quality in relation to between-study heterogeneity?

Authors

- **For subgroup analyses, we will consider the type and quality of studies in relation to between-study heterogeneity. The adjustments introduced in the manuscript are between lines 306 and 321 to 323. Thank you very much for your comments.**

REVIEWER: 2 Dr. Jeffrey A. Bridge, The Ohio State University College of Medicine, Research Institute at Nationwide Children's Hospital

Comments to the Author:

The authors report on a protocol to conduct a systematic review and meta-analysis of the efficacy of suicide prevention interventions implemented via synchronous remote-based approaches. The authors are to be commended for proposing to undertake the proposed meta-analysis, which if successful could inform suicide prevention strategies. There are, however, several limitations that reduce enthusiasm.

Authors

- **Thank you very much for your encouraging comments. We appreciate the acknowledgement of the contribution of the systematic review and meta-analysis to the evidence for suicide prevention interventions implemented via synchronous remote-based approaches. The authors expect that the systematic review and meta-analysis protocol, as well as the current peer review being conducted, will provide more transparency in the methods and processes involved, decrease the possibility of duplication, and reduce bias. We are aware of the limitations of the research and encourage further RCTs to demonstrate the clinical benefits, in particular the prevention of suicide attempts. We expect that our work will help advance this field of research and outline pathways for further research. We kindly hope that the suggestions raised will be addressed below. The authors thank you in advance for your comments.**

Specific suggestions:

1) The field has moved away from the term “completed suicide.” Please use “suicide death” or “suicide” instead of “completed suicide.”

Authors

- **Following your recommendations, we have revised the entire manuscript to replace the term “completed suicide” with “suicide death” or “suicide”. Thank you very much for your comments; they will also be considered in future research.**

2) Page 4, line 42: The authors state that the study will incorporate both quantitative and qualitative synthesis but there does not appear to be any discussion of how qualitative data will be analyzed.

Authors

- **The discussion of the analysis of qualitative and quantitative data is now reported in greater depth in the section “Data synthesis” (see lines 271-298). Also, we have replaced in the “Abstract” section the paragraph on how the quantitative and qualitative synthesis will be carried out (see amendment on lines 18 to 20). We hope that the current version of the manuscript clearly describes on how the qualitative data will be analysed.**

3) Page 5, line 46: It would aid the reader to provide the country from which the suicide statistics are being presented.

Authors

- **We fully agree with your suggestion. For this reason, after a careful review of this part, we made modifications on lines 40 to 53 to provide the country to which the presented suicide statistics are related. In addition, to aid the reader with further information on suicide statistics by country and region, we have expanded the evidence reported with two paragraphs to this section according to World Health Organisation (WHO) data [2, 3] (see changes on lines 42 to 46 and 47 to 49).**

4) Page 7, line 17: Please clarify whether there was overlap in studies included in the Milner and Noh meta-analyses.

Authors

- **As suggested, we have make It clear the existence of an overlap in studies included in the Milner *et al.* [32] and Noh *et al.* [33] meta-analyses (see adjustment on lines 95 to 96). Thank you for helping us to be more precise in the description of the studies included in the manuscript.**

5) Page 8, line 39: The terms "efficacy" and "effectiveness" are used interchangeably but these are different trial designs. Are both types of intervention trials included in the meta-analysis? If so, will sensitivity analyses be conducted to assess results in studies testing efficacy vs. effectiveness?

Authors

- **We fully agree that the terms "efficacy" and "effectiveness" are used for different trial designs. Both types of intervention trials will be included in the meta-analysis. For this reason, and in accordance with your recommendation, we clarified in the manuscript that sensitivity analyses will be conducted to assess results in studies testing efficacy vs. effectiveness (see line 300-302). Thank you very much for your comment.**

6) Page 8, line 53: It is unclear how results from various types of studies will be pooled for meta-analysis? Are RCTs weighted the same as quasi-experimental or case-control studies?

Authors

- **The authors are grateful for your interest in reducing possible confusion regarding this issue. We fully agree that in a meta-analysis, the process of pooling results from various types of studies involves several considerations, including the weighting of different study types such as RCTs, quasi-experimental studies, and case-control studies. The weighting of these study types in a meta-analysis depends on the methodological rigour and quality of each study, as well as the assumptions made about the similarity of their underlying effects. Sensitivity analyses (see lines 300 to 302) and subgroup and subset analyses (see lines 304 to 323) will be performed if feasible and warranted, to examine potential effect modifiers based on participants' socio-demographic characteristics, length, type of treatment, research design (RCTs, quasi-experimental trials, and observational case-control studies), and risk of bias assessment. In summary, while RCTs typically carry more weight due to their strong experimental design, the weighting of different study types in the meta-analysis will depend on their quality, methodology, and relevance to the research question.**

7) Page 9, line 53: The inclusion of studies using minimal in-person contact seems to run counter to the aim of examining remote-based interventions on future suicide risk. Please provide a rationale for this study inclusion criterion.

Authors

- **Thank you very much for your comment. We fully agree that further clarification is needed in the "Types of interventions" section. Remote-based interventions in suicide risk prevention occasionally conduct a pre-post face-to-face assessment or, on fewer occasions, an intervention session that is conducted through in-person contact. To avoid excluding from the systematic review**

and meta-analysis studies of telematic and synchronous interventions that employ, in a complementary way, minimal face-to-face contact (i.e., a maximum face-to-face contact of 1 session), this specification has been made in the inclusion criteria. Based on your request for a rationale for this study's inclusion criteria, we understand that the way this statement was originally described may be confusing for the reader. We have modified the formulation of this sentence (see adjustment on lines 156 to 159). Thank you very much for helping us clarify these possible confusions.

8) Page 10, line 46: It is unclear how the varying follow-up periods will be handled in the meta-analyses. Please clarify.

Authors

- **To the best of the authors' knowledge, no solid evidence for setting a standard for the follow-up period of suicide prevention interventions has been identified to date. Based on the evidence, more RCTs are required to determine which follow-up factors or mechanisms (e.g., greater engagement in care) may affect outcomes [1, 2]. For this reason, we have decided not to exclude studies based on the follow-up period. Instead, we have formulated the subgroup and subset analyses (see lines 318 to 320) based on the length of the contact period. We have also Included a sentence in the "Data synthesis" section (see lines 287 to 291) to clarify how we will approach this situation. We recognise that there could be varying follow-up periods. According to this statement and in connection with your comment, we have specified this possible limitation in the "Discussion" section (see lines 356 to 360). In addition, the authors will describe in the "Discussion" section of the systematic review and meta-analysis manuscript the possibility of significant variability in follow-up periods. This information may be useful for research groups seeking to explore the topic further.**

References

1. **Brown GK, Green KL. A review of evidence-based follow-up care for suicide prevention: where do we go from here? *Am J Prev Med*. 2014;47:S209-15. https://doi.org/10.1016/j.amepre.2014.06.006**
2. **Ghanbari B, Malakouti SK, Nojomi M, *et al*. Suicide Prevention and Follow-Up Services: A Narrative Review. *Glob J Health Sci*. 2015;8:145-53. https://doi.org/10.5539/gjhs.v8n5p145**

9) Page 12, line 17: It is unclear what sensitivity are specificity are referring to in the context of the literature search strategy.

Authors

- **We consider your comment relevant and proceed to clarify what sensitivity and specificity are referring to in the context of the literature search strategy. As you mentioned, the authors decided to achieve a higher degree of sensitivity (retrieval rate) than specificity (precision rate) with the literature search (see lines 222 to 224). The rationale for this decision was based on the researchers' commitment to avoid omitting possible significant studies, at the expense of greater precision in the search. This means that the authors aim to Identify all the information available relevant to the research question, so we prioritised a comprehensive search, using generic terms, synonyms, and few limits. We expect that this strategy will yield numerous articles, some of which will be relevant and some of which will not, the researchers will take the time to find the articles that are relevant to the research question. It is expected that a limited number of available articles meeting the inclusion criteria will be found, which has led the authors to conduct a sensitive search strategy. We fully agree that there was a need for further clarification. The way in which we originally described it could be confusing for the reader. For this reason, we have included two new references [46, 47] that we consider relevant to support this evidence-based**

decision and have rewritten this section to clarify what sensitivity and specificity refer to in the context of the literature search strategy (see adjustment on lines 222 to 224 and 355 to 356).

10) Page 13, line 10: The “Data collection process” section is redundant with the “Selection process”. Please edit for brevity.

Authors

- **Thank you very much for your suggestion. We edited for brevity the “Data collection process” section. We have deleted the redundant information on inter-rater agreement and the process to be followed with unresolved disagreements (see adjustment on lines 246 to 250).**

11) Page 14, line 19: The Data Synthesis section should be expanded upon to provide more specific details of the proposed analytic approaches.

Authors

- **Thank you very much for your comment. We have revised the “Data Synthesis” section to provide more specific details of the proposed analytic approaches (see adjustment on lines 271 to 298).**

12) Page 15, line 41: There are other measures to quantify publication bias that might also be considered that would complement the proposed methods (e.g., trim-and-fill approaches).

Authors

- **Thank you very much for your suggestion. We have included trim-and-fill approaches to complement the proposed methods for quantifying publication bias (see adjustment on lines 326 to 327).**

13) Page 17, line 7: It is unclear how results of this study will lead directly to better framing of targets for intervention and prevention of suicide.

Authors

- **We considered your comment: accordingly, we have rewritten the “Discussion” section to clarify how the results of this systematic review and meta-analysis would contribute to improve the strategies for suicide intervention and prevention. In addition, we explicitly state the advantages of developing a systematic review and meta-analysis study protocol. This information has been incorporated in lines 365 to 374 of the manuscript. Thank you very much for helping us better explicit the scope and implications of our study.**

VERSION 2 – REVIEW

REVIEWER	McConnachie, Alex University of Glasgow, Robertson Centre for Biostatistics
REVIEW RETURNED	23-Sep-2023

GENERAL COMMENTS	The main focus of this review is on the statistical aspects, which are generally appropriate. The authors plan to include an offset term when looking at the number of suicide attempts. Will papers report the total number of events and the total duration of follow-up by study group, or are they more likely to report the incidence rate ratio between groups? Perhaps more for the observational studies, but if a paper reports an adjusted comparison between groups, would that be used for meta-analysis, rather than using the raw data to extract an unadjusted comparison? I assume random effects models will be used. I don't think it is explicitly stated anywhere. Other than these minor comments, I think this is very good. Sensitivity and subgroup analyses are pre-specified. Risk of bias, publication bias, and quality grading will be done. I believe this protocol should lead to a robust study.

REVIEWER	Bridge, Jeffrey A. The Ohio State University College of Medicine, Research Institute at Nationwide Children's Hospital Dr. Bridge receives research grant funding from the National Institute of Mental Health, the Centers for Disease Control and Prevention, and the Patient-Centered Outcomes Research Institute; he is also a member of the Scientific Advisory Board of Clarigent Health.
REVIEW RETURNED	02-Oct-2023

GENERAL COMMENTS	The authors have been responsive to prior reviewer concerns, and as a result, the manuscript is improved.

VERSION 2 – AUTHOR RESPONSE

REVIEWER: 1 Prof. Alex McConnachie, University of Glasgow

Comments to the Authors:

The authors plan to include an offset term when looking at the number of suicide attempts. Will papers report the total number of events and the total duration of follow-up by study group, or are they more likely to report the incidence rate ratio between groups?

Authors:

- **We agree with the reviewer that in the literature both indicators can be found reported. Although in a preliminary analysis we have been able to verify that most eligible studies for our meta-analysis report the number of events, often accompanied by the follow-up duration, we have reconsidered the analysis as follow lines 285-292:**

"Three types of meta-analyses will be conducted according to the type of outcome measure: count (incidence rate ratio between groups of the number of suicide attempts), quantitative (standardised mean differences of suicidal ideation), and binary (odds ratio between groups of deaths by suicide). All outcomes will be analysed at different follow-up time intervals, as indicated below in the description of subgroup analyses."

Perhaps more for the observational studies, but if a paper reports an adjusted comparison between groups, would that be used for meta-analysis, rather than using the raw data to extract an unadjusted comparison?

Authors:

- **We greatly appreciate your observation. We have expanded the analysis description and have also modified the sensitivity and subgroup analysis sections accordingly (lines 290-292):**

  "Comparisons adjusted for confounders between groups will be included in meta-analyses when reported in studies, and the effect of these adjustments on the meta-analytic summary will be studied using sensitivity and subgroup analyses."
  We have also reflected the treatment of confounders adjustment in sensitivity analyses (line 303), and in the analysis of subgroups or subsets (lines 308 and 324).

I assume random effects models will be used. I don't think it is explicitly stated anywhere.

Authors:

- **Effectively a random effects model is planned, as described in previous version of the manuscript (line 274).**

Other than these minor comments, I think this is very good. Sensitivity and subgroup analyses are pre-specified. Risk of bias, publication bias, and quality grading will be done. I believe this protocol should lead to a robust study.

Authors:

- **We appreciate your good assessment of the manuscript, which has substantially improved in relation to the original version thanks to your constructive and opportune review.**

REVIEWER: 2 Dr. Jeffrey A. Bridge, The Ohio State University College of Medicine, Research Institute at Nationwide Children's Hospital

Comments to the Authors:

The authors have been responsive to prior reviewer concerns, and as a result, the manuscript is improved.

Authors:

- **Thank you very much for your assessment of the work done to improve the manuscript derived from your thorough review and timely suggestions.**