PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Smartphone-based Ecological Momentary Intervention for secondary prevention of Suicidal Thoughts and Behavior: protocol for the SmartCrisis 2.0 randomized clinical trial
AUTHORS	Barrigon, Maria; Porras-Segovia, Alejandro; Courtet, Philippe; Lopez-Castroman, Jorge; Berrouiguet, Sofian; Pérez-Rodríguez, María-Mercedes; Artes, Antonio; MEmind, Group; Baca-Garcia, Enrique

VERSION 1 – REVIEW

REVIEWER	Nuij, Chani Vrije universiteit amsterdam
REVIEW RETURNED	05-Jun-2021

GENERAL COMMENTS	Thank you for the opportunity to review this interesting study protocol of a RCT on smartphone-based EMI for secondary prevention of suicidal thoughts and behaviour. The aim of this study is to evaluate the feasibility and effectiveness of a smartphone-based EMI to prevent suicidal thoughts and behaviour by a RCT among patients with a history of suicidal behaviour. I think that this project will make a significant contribution to the field of suicide research and mobile heath more generally. In my opinion, there are several things for the authors to consider, as listed below. - I advise the authors to do some additional editing for spelling and grammar. - In the abstract, the apps MEmind and eB2 are mentioned under Ethics and dissemination, but they have not been introduced before. It is unclear what the apps are. - Can the authors explain why they do not use a cut-off score on a questionnaire (for example the CSSRS) as inclusion criteria for their RCT. - It is unclear what treatment the patients receive at one of the five locations when they are recruited for the research. - The procedure of the study is unclear. De assessments should be described in more detail, as it is currently unclear who will administer the questionnaires and how long such a session will last. - Can the authors explain the TAU in more detail? Is an active treatment given? - Is the SmartSafe app discussed/embedded in the treatment? Does the participant discuss the apps with a clinician, to keep the safety plan up to date and to monitor the intervention and EMA?

	- The authors state that each day, 2-4 random questions will be asked at random times. What is the EMA schedule, and why do the amount of questions vary per day? - Do the authors want to analyse the answers to the EMA questions, and if yes, how do they want to analyse the EMA data. - What do the authors want to assess in the two comparisons (before/after and between intervention and control group). - Which qualitative satisfaction survey will be used? - Why do the authors include the VR environment assessment and the IAT assessment, since it seems they have no research questions related to those assessments? In sum, I feel that this RCT will break new ground, but the current manuscript ought to be revised in order to clarify the study description.

REVIEWER	Han, Jin Black Dog Institute
REVIEW RETURNED	06-Jun-2021

GENERAL COMMENTS	The paper reports the protocol for a smartphone-based ecological momentary intervention for suicidal thoughts and behaviour (the SmartCrisis 2.0) amongst the patients with suicidal behaviour in France and Spain. Below listed a few comments that might help the authors improve their study. 1. P7 L6-11, could the authors please report the prevalence of suicidal thoughts and behaviour in the target population in the introduction (i.e., Spanish-speaking adults in France and Spain)? 2. P7 L20-22, could the authors please provide the definition of secondary prevention? 3. P10 L50-58, it would be helpful to indicate why a pilot study of 40 patients is needed in the current study and the supporting references for the indicated sample size. 4. P11 L26-29, the authors indicated that “psychiatrist will set up the SmartSafe intervention according to patient’s preferences”. Could the authors please clarify which parts of the SmartSafe intervention need to be set up manually? 5. P15 L19-24: could the authors please provide more details of the mental toolbox? For example, what relaxation techniques and behavioural activation exercises will be provided in the app? 6. P15 L26-29: please add the safety protocol/risk management strategies, randomisation procedure, reimbursement, missing data handling procedure, and detailed EMA protocol (e.g., time window of EMA prompts) to the protocol paper. 7. P15 L56-58: could the authors please provide the definitions of active and passive suicidal ideation, EMA-detected crises (P16 L2-5) and in the introduction? In general, the paper may benefit from a professional language editing service, especially the strengths and limitations of the study. This is an innovative and important piece of work in suicide prevention research. I am looking forward to reading the authors’ findings derived from the current study.

VERSION 1 – AUTHOR RESPONSE

Reviewers' Comments:

Reviewer: 1

Ms. Chani Nuij, Vrije universiteit amsterdam

Comments to the Author:

Thank you for the opportunity to review this interesting study protocol of a RCT on smartphone-based EMI for secondary prevention of suicidal thoughts and behaviour.

The aim of this study is to evaluate the feasibility and effectiveness of a smartphone-based EMI to prevent suicidal thoughts and behaviour by a RCT among patients with a history of suicidal behaviour. I think that this project will make a significant contribution to the field of suicide research and mobile heath more generally.

In my opinion, there are several things for the authors to consider, as listed below.

- I advise the authors to do some additional editing for spelling and grammar.

The manuscript was revised by an English native speaker, who corrected all spelling and grammar issues and increased readability.

- In the abstract, the apps MEmind and eB2 are mentioned under Ethics and dissemination, but they have not been introduced before. It is unclear what the apps are.

We have substituted the mention of the application for a different, more generic, sentence:

It is expected that, in the near future, our mobile health intervention and monitoring system can be implemented in routine clinical practice.

- Can the authors explain why they do not use a cut-off score on a questionnaire (for example the CSSRS) as inclusion criteria for their RCT.

This is a detail we had omitted from the protocol. We have now included a further explanation of this inclusion criteria in the Methods section:

Inclusion criteria:

1. Being 18 years of age or older.

2. Presenting with a SA or an emergency referral for SI in the past month. At the time of evaluation in the ER, the attending psychiatrist will administer the Columbia Suicide Severity Rating Scale (CSSRS)[35] to determine eligibility —see details on Procedures section.

(...)

Procedure

At inclusion (i.e., at the index event), the attending psychiatrist will check the patients' eligibility by checking inclusion criteria and by administering the CSSRS[35]. We will consider that patients meet the criteria for SI if they score ≥ 4 —active SI with some intent to act— in the CSSRS SI subscale. We will consider a suicide attempt has occurred when the patient meets the criteria for "actual suicide attempt" in the CSSRS suicidal behavior subscale. Additionally, the CSSRS will be administered at every follow-up visit.

- It is unclear what treatment the patients receive at one of the five locations when they are recruited for the research.

We have included a clarification in the inclusion criteria section:

We will accept participants with any diagnosis and any kind of previous treatment (including no treatment).

- The procedure of the study is unclear. De assessments should be described in more detail, as it is currently unclear who will administer the questionnaires and how long such a session will last.

The Procedure section has been expanded:

Procedure

At inclusion (i.e., at the index event), the attending psychiatrist will check the patients' eligibility by checking inclusion criteria and by administering the CSSRS[35]. We will consider that patients meet the criteria for SI if they score ≥ 4 —active SI with some intent to act— in the CSSRS SI subscale. We will consider a suicide attempt has occurred when the patient meets the criteria for "actual suicide attempt" in the CSSRS suicidal behavior subscale. Additionally, the CSSRS will be administered at every follow-up visit.

After checking the patients' eligibility, the attending psychiatrist will explain the project in detail and invite patients to participate. If patients agree to participate, they will be asked to sign the informed consent, after which they will be randomly assigned to the intervention group (EMI + EMA + TAU) or the control group (EMA + TAU) using a mixed block randomization scheme generated with NQuery software. Allocation ratio will be 1:1.

After enrollment, participants will undergo a baseline interview, which will be divided into two parts: the first part will be carried out by attending psychiatrist who will further assess the characteristics of the suicide attempt using the Brief Suicide Questionnaire[38], and set up the MEmind application — which administers EMI and EMA— with the participant. One of the interventions —the digital safety plan— is fully customizable. It will be set up by the clinicians following the patients' preferences, and patients will be able to further customize the plan at home if they wish to do so. The second part of the interview will be performed by a trained research assistant, blind to the patient's assigned arm, who will install the eB2 application and administer the standardized questionnaires described in the "non-digital measures" section and in Table 2.

Patients will be followed up for one year, with face-to-face research visits —carried out by the research assistant— at 6 months and at the end of the study, and phone follow-ups —also by the research assistant— at 3 months and 9 months. All questionnaires will be completed through the MEmind website.

We also have included information about who will perform each of the questionnaires:

The Brief Suicide Questionnaire (BSQ)[37] will be administered by the attending psychiatrist to characterize the index event that motivated inclusion in the study (suicide attempt or emergency referral for SI). It includes questions on lethality, method and surrounding circumstances of the attempt, and lifetime history of suicidal behaviour.

The CSSRS scale[35] will be administered by the attending psychiatrist at inclusion. to determine eligibility. Additionally, the CSSRS will be administered by the research assistant at every follow-up visit to detect the occurrence of a new suicidal event.

The research assistant will also verify suicide attempts and deaths by suicide through digital medical records, which integrates information on ER visits, hospitalizations, and visits to specialist consultations. If a patient cannot be located, and there is no information in their record, we will contact the patient's family telephone number. We will also request access to the Spanish register of deaths and causes of death of the "Instituto Nacional de Estadística" [National Statistics Institute] and its French counterpart, the "Institut national de la statistique et des études économiques" [National Institute of Statistics and Economic Studies].

We have also included a new column in Table 2 informing about who will oversee each of the questionnaires:

Table 2. Summary of SmartCrisis 2.0 questionnaires

Domain	Questionnaire	Overseen by	Index event	Baseline interview	3 months	6 months	9 months	12 months
Sociodemographics	Age, sex, employment, marital status, educational level	RA	x					
Suicidal behavior	Brief Suicide Questionnaire[35]	AP	x					
Suicidal thoughts & behavior	Columbia Suicide Severity Rating Scale (CSSRS)[34]	AP & RA	x	x	x	x	x	x
Diagnosis	Mini International Neuropsychiatric Interview (MINI) 7.0.2[45]	RA		x				
Depression	Inventory of Depressive Symptomatology-30 (IDSC-30)[46]	RA		x		x		x
Anxiety	Generalised Anxiety Disorder-7 (GAD-7)[47]	RA		x		x		x
Mania	Young Mania Rating Scale (YMRS)[48]	RA		x		x		x
Psychosis	The Positive and Negative Syndrome Scale (PANSS)[49]	RA		x		x		x
Functionality	World Health Organization disability assessment schedule 2.0 (WHODAS 2.0)[50]	RA		x		x		x
Life traumatic events	The List of Threatening Experiences (LTE) of Brugha & Cragg[51]	RA		x				
Quality of life	Satisfaction with Life Domains Scale[52]	RA		x		x		x
Social adversity	Tool for Health and Resilience in Vulnerable Environments (THRIVE)[53]	RA		x	x			
Alcohol use	Alcohol Use Disorders Identification Test (AUDIT)[54]	RA		x		x		x
Tobacco use	Fagerström test for Nicotine Dependence (FTND)[55]	RA		x		x		x
Illegal drugs use	Drug Abuse Screening Test[56]	RA		x		x		x
Impulsivity	Barrat Impulsiveness Scale-11[57]	RA		x				
Personality	Millon Clinical Multiaxial Inventory-IV[58]	RA		x				
Neuropsychological assessment	Spheres & Shield Maze Task (Virtual Reality assessment)[42]	RA		x				
Satisfaction	Qualitative and qualitative surveys[59]	RA						x

AP=Attending Psychiatrist; RA=Research Assisstant

- Can the authors explain the TAU in more detail? Is an active treatment given?

We have created a new section titled “Non-digital intervention” to explain the TAU:

Non-digital intervention

All patients, regardless of their group —Intervention or Control— will receive TAU, consisting of a scheduled mental health follow-up at an Outpatient Mental Health Clinic. TAU will consist of scheduled clinical reviews based on BIC recommendations adapted to a follow-up of 12 months instead of the original 18 months (1, 2, 4, 7 and 11 weeks, and 4, 6, 9 and 12 months)[34]. The BIC intervention has shown to significantly lower the odds for suicide (OR = 0.20, 95% CI 0.09–0.42)[63]. The need for psychopharmacological treatment and the treatment chosen in each case will be decided by the attending psychiatrist based on the individual needs of each patient.

- Is the SmartSafe app discussed/embedded in the treatment? Does the participant discuss the apps with a clinician, to keep the safety plan up to date and to monitor the intervention and EMA?

We have added a comment on this at the end of the Digital Intervention section:

During the scheduled appointments, patients will have the opportunity to discuss the safety plan with the attending psychiatrist, who will assist them in performing further customizations and keeping the plan up to date.

- The authors state that each day, 2-4 random questions will be asked at random times. What is the EMA schedule, and why do the amount of questions vary per day?

The amount of questions vary in order to perform a more exhaustive monitoring during the first two months, when there might be greater risk of suicide:
Each day, a prompt will appear containing 2-4 random questions —4 questions during the first two months, as this is the period with the higher risk of suicide re-attempt[56]; 2 questions afterwards—

- Do the authors want to analyse the answers to the EMA questions, and if yes, how do they want to analyse the EMA data.

We have clarified this in the Statistical analysis section:

In addition to the traditional analyses, with the Signal Theory Department of the Carlos III University's support, unsupervised analyses will be carried out using machine learning techniques to create behavioral models and patient activity profiles from data collected through active and passive EMA.

- What do the authors want to assess in the two comparisons (before/after and between intervention and control group).

We have clarified this in the Outcomes section:

Two comparisons will be made after the intervention: before/after comparison, and comparison between the intervention group and the control group, regarding the primary and secondary outcomes mentioned below.

- Which qualitative satisfaction survey will be used?

This has been clarified in the “Non-digital measures” section:

patients will complete a previously used qualitative satisfaction survey[36] referring to each of the applications used
The satisfaction surveys are referenced in Table 2:

Quantitative and qualitative surveys[39]
39. Migoya-Borja M, Delgado-Gómez D, Carmona-Camacho R, Porras-Segovia A, López-Moriñigo JD, Sánchez-Alonso M, Albarracín García L, Guerra N, Barrigón ML, Alegría M, Baca-García E. Feasibility of a Virtual Reality-Based Psychoeducational Tool (VRight) for Depressive Patients. Cyberpsychol Behav Soc Netw. 2020 Apr;23(4):246-252. doi: 10.1089/cyber.2019.0497. Epub 2020 Mar 24. PMID: 32207997.

- Why do the authors include the VR environment assessment and the IAT assessment, since it seems they have no research questions related to those assessments?

These are parallel projects that will be used on the same sample. Upon reflection, we decided to exclude them from the protocol.

In sum, I feel that this RCT will break new ground, but the current manuscript ought to be revised in order to clarify the study description.

We want to thank the reviewer for the time and attention expended at revising our manuscript.

Reviewer: 2

Dr. J Han, Black Dog Institute

Comments to the Author:

The paper reports the protocol for a smartphone-based ecological momentary intervention for suicidal thoughts and behaviour (the SmartCrisis 2.0) amongst the patients with suicidal behaviour in France and Spain. Below listed a few comments that might help the authors improve their study.

1. P7 L6-11, could the authors please report the prevalence of suicidal thoughts and behaviour in the target population in the introduction (i.e., Spanish-speaking adults in France and Spain)?

This information has been included in the Introduction section:

In Spain has a yearly suicide rate of 7.9 per 100,000 inhabitants[3], while France has a suicide rate of 12.1 per 100,000 inhabitants[4].

2. P7 L20-22, could the authors please provide the definition of secondary prevention?

Definition of secondary prevention was included in the Introduction section:

A key aspect to prevent death by suicide is implementing secondary prevention strategies. Secondary prevention consists of acting in the early stages of a disease to prevent its progression; in this case, focusing on people with a history of suicidal ideation or behaviour with the aim of preventing death by suicide.

3. P10 L50-58, it would be helpful to indicate why a pilot study of 40 patients is needed in the current study and the supporting references for the indicated sample size.

A comment about this was included in the Methods section:

The aim of this pilot is to detect any technical or human failure in time, as well as to know what our patients think of the intervention, to optimise it as much as possible before the start of the clinical trial. This kind of studies have been performed with other EMIs, such as Crisis Care, EMMA or MyPlan, with sample sizes ranging from 14 to 40 patients[37]

4. P11 L26-29, the authors indicated that "psychiatrist will set up the SmartSafe intervention according to patient's preferences". Could the authors please clarify which parts of the SmartSafe intervention need to be set up manually?

We have clarified this in the Procedure subsection, stating that the customizable part of the intervention is the safety plan:

One of the interventions —the digital safety plan— is fully customizable. It will be set up by the clinicians following the patients' preferences, and patients will be able to further customize the plan at home if they wish to do so.
We have also expanded our explanation of the safety plan in the Digital Intervention subsection:

The safety plan has the following elements, all of which are customizable:

1) Warning signs. This is a list of symptoms of signs that may alert the patient that a suicidal crisis is about to take place. For instance: insomnia in the past few days.

2) Internal coping strategies. What can I do on my own to get better? For instance: a video with relaxation techniques.

3) External coping strategies. These are distraction strategies, such as going for a stroll or going to watch a movie.

4) Personal contacts. Family or friends who can help us. Phone contacts can be imported and directly accessed through the app.

5) Professional contacts. Institutions and professionals that can provide help. Phones or web links can be imported. Also, a link to a Maps application showing the fastest route to the nearest Emergency Room or Mental Health Clinic can be uploaded to the app.

6) Safe environment. Tips for keeping the environment free of lethal means.

7) Reasons for living. The most important reason for staying alive. Here, the patient can, for instance, upload the photo of a loved one.

5. P15 L19-24: could the authors please provide more details of the mental toolbox? For example, what relaxation techniques and behavioural activation exercises will be provided in the app?

This information has been added to the Digital intervention subsection:

relaxation techniques —deep breathing and meditation—, behavioral activation exercises —self-monitoring of activities, and activity scheduling and structuring—,

6. P15 L26-29: please add the safety protocol/risk management strategies, randomisation procedure, reimbursement, missing data handling procedure, and detailed EMA protocol (e.g., time window of EMA prompts) to the protocol paper.

Safety protocol subsection included in the Methods section:

Safety protocol

To safeguard the well-being of our patients, we will implement a suicide risk safety protocol: the CSSRS will be administered to all patients at every measurement point. Upon detecting an alarming level of SI severity (threshold established at CSSRS score ≥ 4), their attending psychiatrist will be informed, and patients will be offered to go to the emergency room. Also, as part of the EMI intervention, extreme values of SI detected by EMA will activate the safety plan contained in the application, which will implement different strategies to contain suicide risk, as explained in the section ‘Digital Intervention’.

Explanation of randomisation procedure was expaneded in the Procedure subsection:

If patients agree to participate, they will be asked to sign the informed consent, after which they will be randomly assigned to the intervention group (EMI + EMA + TAU) or the control group (EMA + TAU) using a mixed block randomization scheme generated with NQuery software. Allocation ratio will be 1:1.

Information on Reimbursment was included in the Study approval subsection:

There is no cost or financial compensation for participating in this study.
Information on Missing data handling procedure was included

in the Sample size calculation subsection:

We assumed a dropout rate of 20%

and in the Strengths and Limitations sections:

Sample size calculation has been performed taking into account missing data.
Information on the number and time window of the EMA prompts was included in the digital monitoring subsection:

Each day, a prompt will appear containing 2-4 random questions —4 questions during the first two months, as this is the period with the higher risk of suicide re-attempt[56]; 2 questions afterwards— will be asked at random times (respecting sleep hours: from 9 a.m. to 9 p.m.) from the pool of 34 questions that make up the questionnaire,

7. P15 L56-58: could the authors please provide the definitions of active and passive suicidal ideation, EMA-detected crises (P16 L2-5) and in the introduction?

Active and passive suicidal ideation:

Reduction of EMA-measured active SI —thoughts about taking one's life— and passive SI —i.e., wish to die.

EMA-detected crises:

Correlation between clinically observed suicidal events and active and passive EMA-detected crises. For active EMA, crisis will be defined as extreme scores in the SI questions. For passive EMA, crisis will be defined as changes in the previously detected usual behavioral patterns —sleep, physical activity, and smartphone use— for each patients —15 days of use are required to determine such patterns.

In general, the paper may benefit from a professional language editing service, especially the strengths and limitations of the study. This is an innovative and important piece of work in suicide prevention research. I am looking forward to reading the authors' findings derived from the current study.

The manuscript was revised by an English native speaker, who corrected all spelling and grammar issues and increased readability.

We want to thank the reviewer for the time and attention expended at revising our manuscript.

VERSION 2 – REVIEW

REVIEWER	Nuij, Chani Vrije universiteit amsterdam
REVIEW RETURNED	08-Jan-2022

GENERAL COMMENTS	Thank you for the opportunity to re-review this manuscript. The previous comments have been well processed. I have no other comments. Good luck with the study, and I am looking forward to the results.

REVIEWER	Han, Jin Black Dog Institute
REVIEW RETURNED	29-Dec-2021

GENERAL COMMENTS	Thanks for the authors' efforts in addressing the comments. A few minor suggestions have been listed below: 1. p3 L33-34: references are not needed for the abstract. 2. p6 L2: please remove "traditional(ly)". 3. p6 L20-24: references are missing. 4. p7 L48-53: the sentence is hard to follow. Could the authors please edit it? 5. p9 L32: what does "human failure" refer to? In addition, could the authors please specify what will be asked in the focus group for the pilot study? 6. p10 L31-54, please format these paragraphs.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 2
Dr. Jin Han, Black Dog Institute
Comments to the Author:
Thanks for the authors' efforts in addressing the comments. A few minor suggestions have been listed below:
1. p3 L33-34: references are not needed for the abstract.

Reference was erased:

recommendations (1, 2, 4, 7 and 11 weeks, and 4, 6, 9 and 12 months).

2. p6 L2: please remove "traditional(ly)".

Sentence changed:

. Active EMA involves asking...

3. p6 L20-24: references are missing.

Reference added:

EMIs can be a useful add-on to traditional treatment, thanks to their 24-hour availability, low cost, and the possibility of continuing follow-up in a non-presential manner[25].

4. p7 L48-53: the sentence is hard to follow. Could the authors please edit it?

We have rephrased the sentences:

Another possibility is to combine these two modalities offered by mobile technology: monitoring -EMA- and intervention -EMI-. In this way, systems could monitor suicide risk and automatically launch an EMI if a high risk is detected. To our knowledge, a case series[31] and a clinical trial protocol[32] have considered the combination of EMA with EMI.

5. p9 L32: what does "human failure" refer to?

Human failure refers to errors made by the staff in contrast with technical/software errors. This was explained:

The aim of this pilot is to detect any technical —software, hardware, servers, etc.— or human failure —i.e., errors made by the staff— in time,

In addition, could the authors please specify what will be asked in the focus group for the pilot study?

Info added:

Patients will be asked what they found most useful, what improvements they would make to the application, and to what extent they would be willing to recommend it to their family or friends.

6. p10 L31-54, please format these paragraphs.

Line spacing was adjusted

Reviewer: 1
Ms. Chani Nuij, Vrije universiteit amsterdam
Comments to the Author:
Thank you for the opportunity to re-review this manuscript.
The previous comments have been well processed. I have no other comments.

Good luck with the study, and I am looking forward to the results.

Reviewer: 2
Competing interests of Reviewer: No

Reviewer: 1
Competing interests of Reviewer: None