



The WIRED Trial - Wii Sports™ as a virtual Reality Exercise Experience to improve Depression in healthcare workers during the COVID-19 Pandemic: A Multicenter, Prospective, Randomized, Controlled, Superiority Phase II Trial.

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Abstract:

Background: Due to the coronavirus pandemic, the number of hospitalized individuals increased exponentially. The sudden increase in workload, the social isolation, and the fear of COVID-19 contributed to a remarkable increase of depression cases (from 20.9% to 43.2%) among healthcare workers. Although many treatments are available for depression, including pharmacotherapy, exercise, and virtual reality, response varies widely, from complete recovery to non-responders and relapsing cases. In this sense, Wii Sports™ may serve as an alternative to improve response to standard first-line therapy, since it provides an interactive environment, physical activity and incorporates playfulness.

Objective: Evaluate the effect of Wii Sports™ in treating mild and moderate cases of major depressive disorder in healthcare professionals who developed depression during the COVID-19 pandemic.

Methods: The WIRED trial is a phase II, multicenter, randomized, active-controlled, single-blinded, superiority trial with two parallel groups. The intervention group will be composed of Wii Sports™ in addition to a first-line antidepressant, while the control group will be composed of Wii™ games that do not involve physical activity in addition to a first-line antidepressant. The primary outcome is to detect a group mean difference in the 17-item Hamilton Depression Rating Scale (HAM-D17) at week twelve, while secondary outcomes include participant adherence and comparison of HAM-D17 scores at different time points.

Conclusion: To our knowledge, there is no previous literature published that targets the same population, tests the same intervention, and evaluates the same outcomes, highlighting the possible impact of the study on the psychological and psychiatric fields, regardless of its results.

Keywords: Coronavirus, COVID-19, depression, Major Depression Disorder, Wii Sports™, virtual reality, exercise.

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Abbreviations

COVID-19: acute respiratory illness in humans caused by a coronavirus.
 HAM-D17: Hamilton Depression Rating Scale
 HCW: healthcare workers
 MDD: Major Depressive Disorder
 PHQ-9: Patient Health Questionnaire
 VR: virtual reality

INTRODUCTION

The outbreak of a new coronavirus disease, COVID-19, was declared by the World Health Organization (WHO) as a public health emergency of international concern (WHO, 2020). The persistence of the crisis has burdened healthcare workers (HCW) with greater psychological stressors, such as anxiety and depression symptoms (Hassannia, 2020), which was already high previously (20.9% - 43.2%) among young HCW (Mata, 2015). Diagnostic criteria of major depressive disorder are met when one pervasively experiences five or more depression symptoms, including depressed mood or anhedonia, for a period of at least two weeks as defined by the Diagnostic and Statistical Manual of Mental Disorders - Fifth Edition (DSM-5) criteria; and diagnosis of mild and moderate depression is defined by Patient Health Questionnaire (PHQ-9) (**Figure A.1 - Appendix**) score between 10 to 19.

HCW are exposed to excess workload and have a high risk of infection. Mental problems were detected in medical and nursing staff working in Wuhan, where the pandemic started: 36.9% subthreshold mental health disturbances and 34.4% mild, 22.4% moderate, and 6.2% severe disturbances in the immediate wake of the viral epidemic (Kang-a, 2020). Mental health problems can debilitate HCW's abilities such as attention, understanding, and decision-making, including preventing them from combatting the virus (Kang-b, 2020). In light of the continued devastating consequences of this deadly viral disease on the physical and mental wellbeing of healthcare workers, new strategies to combat such conditions are vital.

Many treatments are available for Major Depressive Disorder (MDD) including pharmacotherapy, meditation, cognitive behavioral therapy (Berk, 2013), and exercise (Brenes, 2007; Craft, 2004). The most innovative approach is virtual reality exercise or exergaming. Virtual reality (VR) is a computer-generated, interactive environment. It can be either immersive, which provides the sensation of physically being in the environment, or non-immersive,

which creates only a simulation of physical presence in virtual reality (Radianti, 2020; Piccione, 2019). Exergames are a gaming experience that requires physical effort from the player (Mestre, 2011; Plante, 2003). Wii Sports™ is one type of non-immersive exergame, which can detect the players' movements.

Some of the mechanisms by which the Wii™ platform can improve depressive disorder are its ability to stimulate moderate physical activity, to create an artificial entertaining environment and social gathering, and to improve depressed mood (Lindner et al., 2019; Maples-Keller et al., 2017, Li J et al., 2016). Although there is established evidence of VR exercise as part of the treatment of depression (Li J et al., 2016); (Segura-Ortí E et al., 2019), little information is known about the effect of Wii Sports™ in healthcare providers diagnosed with depression.

Therefore, the primary aim of this study is to evaluate the superiority of Wii Sports™ in addition to standard pharmacotherapy in decreasing symptoms of mild and moderate major depression in Brazilian HCW frontliners during the COVID-19 pandemic, when compared to standard pharmacotherapy plus Wii™ games not involving physical activity. The intervention period will be of twelve weeks duration with a subsequent four-week follow-up. Our hypothesis is the symptoms of depression, measured as the mean group score of the Hamilton Depression Rating Scale (HAM-D17) (**Figure A.2 - Appendix**), will be reduced by at least three points in the intervention group compared with the control group.

METHODS**Trial Design**

The WIRED trial is a phase II, multicenter, randomized, active-controlled, open-label, superiority trial with two parallel groups. The intervention group will be assigned to Wii Sports™ in addition to standard pharmacological therapy. The control group will be assigned to Wii™ games, that do not involve physical activity (Mario Kart, Guitar Hero, Punch Out and Monopoly) in addition to standard pharmacological therapy. The primary endpoint is the mean change in HAM-D-17 score at week twelve.

Study Setting

Brazilian cities with a high incidence rate of COVID-19 and high annual incidence of depression will be included. In a study conducted in Brazil (2010 to 2011) it was reported that the prevalence of depressive

symptoms among healthcare workers was 36.3%, and of probable major depression up to 18% in community health workers (da Silva, 2016). We will recruit physicians and nurses who cared for hospitalized COVID-19 patients, regardless of the time of exposure.

Randomization

Participants will be randomly assigned to control or experimental groups in a 1:1 ratio. To secure allocation concealment, web-based randomization (REDCap) will be performed using random block sizes of 4, 6, and 8. This strategy was selected to guarantee balanced group allocation over time, considering the possibility of fluctuation of the pandemic burden.

Details of the process, including the allocation sequence, will be unavailable to researchers and psychiatrists responsible for enrolling participants and assigning the intervention. To avoid selection bias, only data handlers will have access to the password-secured allocation sequence list.

Blinding

This trial will be conducted as an open-label study: clinicians (psychiatrists and psychologists) and subjects (HCW) will not be blinded to the assigned groups because the nature of the intervention renders their blinding unfeasible. Clinicians will monitor patients throughout the Wii sessions, thus, they cannot be blinded. Outcome assessors and statisticians will be blinded to the randomization sequence.

Appointments with healthcare providers and outcome assessors will take place on the same day but in independent settings to avoid additional subject burden. Subjects will be educated to not disclose their assigned group to assessors.

Blinding will be evaluated once 50% of enrollment has been reached. Bang's Blinding Index (BI) method will be used, which can be seen as a two-sided test of blinding since it can evaluate the "direction" of the unblinding. Assessors will rate their guesses regarding participants' allocation: "active", "control" and "do not know". Values between 0 and 1 indicate correct guesses (failure in blinding above random guessing), while values between -1 and 0 indicate incorrect guesses (Kolahi et al, 2009). Zero indicates no confidence at all in guessing and, thus, successful blinding.

If unblinding is identified, assessors will be interviewed to identify potential factors influencing blinding, which will be further addressed. Unblinded personnel will be replaced. Emergency unblinding is unnecessary due to the open-label design of the trial.

Eligibility Criteria

Inclusion Criteria:

- Physicians and nurses of any age, working in public hospitals, responsible for caring for patients with COVID-19, regardless of the time of exposure;
- Diagnosis of Major Depressive Disorder as defined by the Diagnostic and Statistical Manual of Mental Disorders - Fifth Edition (DSM-5) criteria;
- Diagnosis of mild and moderate depression as defined by Patient Health Questionnaire (PHQ-9) (**Figure A.2 - Appendix**) score between 10 to 19.

Exclusion Criteria:

- Participants younger than 18 years old;
- Severe depression, defined by a Patient Health Questionnaire-9 (PHQ-9) score higher than 19;
- Severe depressive episode, suicidal ideation and/or psychosis;
- Current use of antidepressant medication and/or active engagement in psychotherapy;
- Unwillingness to receive pharmacological treatment;
- History of failure to respond to antidepressant therapy;
- Depression related to medical conditions, medications, or substance use;
- Regular traditional exercise (greater or equal to three times per week);
- Participants who meet DSM-V criteria for any other psychiatric illness other than major depression (e.g., bipolar disorder, schizophrenia);
- Medical conditions that contraindicate physical activity (e.g. severe cardiac and pulmonary diseases, bone/joint disorders, neurological diseases, or significant vision/hearing impairment) or which might prevent the safe practice of WiiSports;
- Pregnancy;
- No participation in the learning session or are unable to use the devices of Wii™ Platform;
- Participants who play Wii Sports™ and/or Wii™ games regularly (at least three times per week).

Ethical aspects

All research methods will be submitted to Institutional Review Boards (IRB) approval. Eligible participants will provide informed consent after receiving a complete explanation of study procedures and a detailed information paper sheet. Subjects will be aware that they may leave the study at any time.

Participants willing to join the study but scoring more than 19 on PHQ-9 (severe MDD), will be referred

to the psychiatric department for further evaluation. The same will happen to participants after the trial is over, regardless of their improvement during the study. The continuation of games and pharmacological treatments will then be evaluated by the patient together with a psychiatrist, taking into consideration the study results.

In case of protocol amendments, the main investigator will be responsible for communicating with the relevant parties (IRBs, participants and sponsors) by email, with the need for an acknowledgment of receipt. Study data will be stored electronically and protected by a password, to enhance confidentiality.

Recruitment Strategy

Pamphlets and brochures will be distributed in the selected hospitals for all the recruitment periods. Additionally, researchers will partner with institutional human resources departments to acquire telephone numbers and e-mail addresses to contact employees. Each center will have a principal investigator in charge of monitoring and coordinating the recruitment process and data registration.

Individuals expressing interest in participating will be asked to complete the consent form. An online screening for depression using the Patient Health Questionnaire (PHQ-9) will be administered within one week from initial contact with study personnel. Those who have not completed the screening within the week will receive one telephone call and one email reminder to complete the questionnaire, and 2 extra days will be given to fulfill the questionnaire. Not filling the PHQ-9 after these 9 days implies the exclusion from the study.

Having done the screening (PHQ-9 10-19), the subject will have an appointment with a psychiatrist scheduled. Selection of the pharmacological therapy will be restricted to drugs approved by APA (American Psychological Association) Guidelines. A specific pharmacological class of drug for treating depression was not determined, considering the recommendations of APA that the initial treatment modality should be influenced by depression severity and patient preference, among other clinical features.

A two-month enrollment period is planned, however, it might be extended until the desired sample size is achieved. The minimum number of recruited participants per site is 30, to respect the assumption of the Central Limit Theorem for normality.

Adherence

Healthy and trustworthy relationships with subjects will be encouraged. Self-report questionnaires, assessing adverse effects and the need for further guidance, will be obtained at weeks six and twelve. Weekly messages and email reminders will be sent to subjects one day before their appointments to encourage compliance. Participants who miss appointments will receive a phone call to discern the reason for non-compliance and will be given an opportunity to reschedule appointments.

Also, care will be taken to inform subjects about psychological support availability. However, since it is unethical to advise against psychotherapy, those who desire to schedule appointments as part of their treatment and those who are unwilling to receive antidepressants will be excluded from the trial. The same reasoning will be applied to exercise. All

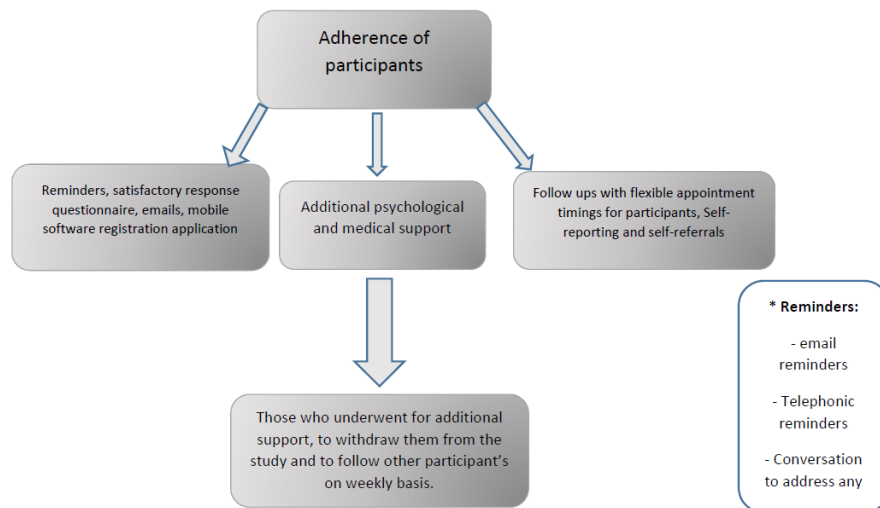


Figure 1. Adherence Strategies

participants practicing physical exercise on a regular basis will be excluded from the sample, regardless of whether they started it before or during the trial.

Adherence to VR exercise will be measured by the register of subjects' assistance and participation. Successful adherence is defined as the completion of two-thirds or more of the prescribed sessions (at least 24 sessions) (Hawley-Hague et al. 2016). Therefore, dropout is determined as missing at least one-third of the sessions and/or the final HAM-D17 score assessment at week 12.

Adherence to pharmacological treatment will be assessed by the 8-item Morisky Medication Adherence Scale (MMAS - 8), one of the most accepted and validated self-report measures for adherence to medication (Lam, W. Y. and Fresco, P. 2015) (De Oliveira-Filho et al. 2014). Successful adherence is defined by MMAS-8 equal to or higher than 6 points. In addition, medication pick-up/refill rates will be monitored according to pharmacy dispensing records. To maintain adherence in the four-week follow-up period, weekly reminders will continue via emails and/or text messages (depending on participant preference). We will also offer flexibility in the appointment scheduling to accommodate participant availability (Figure 1).

Timeline

After obtainment of the informed consent, filing of PHQ-9, and collection of medical history, subjects who screen positive for mild to moderate depression (PHQ-9 between 10 and 19) will be referred for psychiatric evaluation to decide the pharmacological treatment. If warranted, and the subject agrees to treatment with antidepressants, they will complete the baseline Hamilton Depression Rating Scale (HAM-D17).

At this time, eligible subjects will be randomized to either control or intervention group: non-exertional Wii™ games with standard antidepressant treatment or exertional Wii Sports™ with standard antidepressant treatment. A learning session will be provided to all participants to promote adaptation to Wii™ devices (Figure 2). The intervention period will be of twelve weeks duration with a subsequent four-week follow-up. Subjects will complete the HAM-D17 at baseline, and at weeks two, six, twelve, and sixteen.

Interventions

All sessions will be conducted in a lab specifically designed for the intervention within the designated hospitals. Sessions can be conducted from 6 am to 8 pm Brasilia Time. Subjects will be constantly monitored by clinicians throughout the sessions.

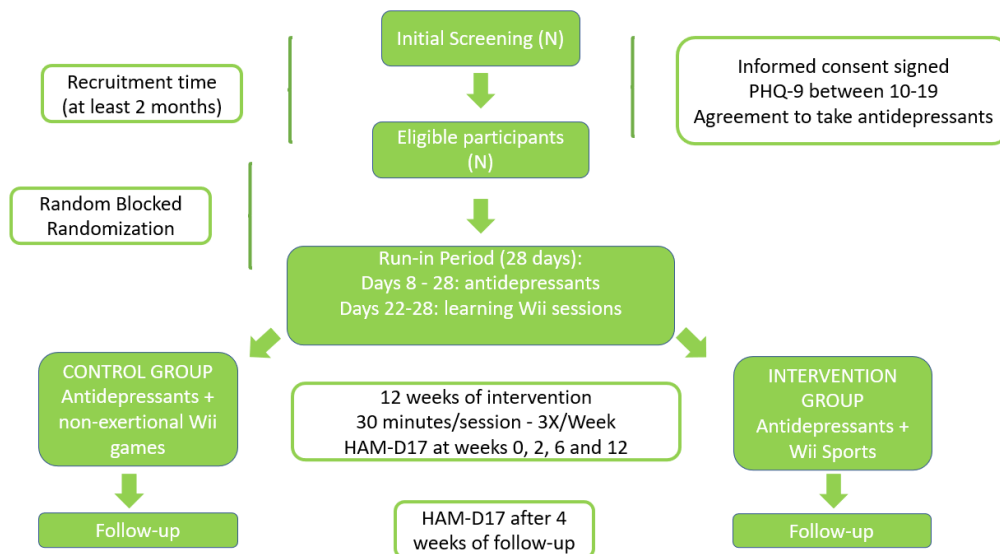


Figure 2. A proposed timeline of study procedures is outlined in the following. Day 0: subject recruited and consented for participation. Day 1-7: Participants will complete online depression screening, PHQ-9, and medical screening. If the subject screens positive for depression, he/she will see a psychiatrist. If diagnosis warrants and the participant agrees to treatment with antidepressants, will be enrolled and randomized to group assignment. Patients will complete baseline HAM-D17 at this time. Day 8: start of medication. Day 8-28: 3-week-medication run-in period and subject completes Wii™ training session. Day 29: subject begins Wii™ activities (intervention or control). Day 43 (+/- 3 days): 2-week HAM-D17 assessment. Day 71 (+/- 3 days): 6-week HAM-D17 assessment; adverse events questionnaire application. Day 113 (+/- 3 days): 12-week HAM-D assessment. End of intervention. Satisfaction and adverse events questionnaire application. Day 141 (+/- 3 days): 4-week follow-up assessment. HAM-D17 assessment.

After randomization, a learning session will be offered to all participants commensurate with their group assignment, to promote adaptation to Wii™ devices and games. Subjects unable to use the devices, determined by the clinician's evaluation, will be excluded.

These learning sessions will occur during the medication run-in period before the Wii™ intervention begins, and they will mimic every aspect of the intervention. A clinician will be evaluating participants at all times. Each participant can have only one individual learning session, in which he/she must play all the games offered in the platform, according to their assigned group. These sessions may last up to thirty minutes, depending on the participant's dexterity and level of familiarity with the device.

The intervention group will play Wii Sports™: boxing, bowling, golf, and tennis. The control group will play Wii™ games: Mario Kart, Punch Out, Monopoly, and Guitar Hero. Participants can select a different game during sessions, as long as they finish the game "championship". Additional time will not be allowed despite brief disruptions associated with game selection.

Each game has an approximate ten-minute duration. In each session, participants will play three sets of their preferred games in their preferred order for a total of thirty minutes of participation. Intervention group participants will be supervised in three, thirty-minute aerobic exercise sessions each week for twelve weeks (Perraton et al. 2013). Control group participants will be supervised playing non-exertional games during three, thirty-minute sessions each week for twelve weeks.

Thereby, study groups will be under pharmacological standard therapy, differing only on the VR exercise. We decided not to include traditional exercise in the control arm because systematic reviews and meta-analyses evaluating traditional exercise in depression showed non-significant effects (Krogh et al. 2017). In addition, the study design is in accordance with the study hypothesis, which is not to test for the superiority of VR exercise compared to traditional exercise but to analyze if VR exercise has a positive effect add-on to standard pharmacological therapy.

Pharmacological standard therapy refers to all antidepressants included in APA (American Psychological Association) Guideline of treatment of patients with Major Depressive Disorder (APA, 2019). Selection of the initial treatment modality will be influenced by clinical features (severity of symptoms,

presence of co-occurring disorders, and prior treatments), patient's preference, and clinician's expertise, as per APA Guideline. Participants will be given prescriptions so they can acquire the proper medication by SUS defrayal (Unified Health Brazilian System) or on their own.

Modification/discontinuation

In the event of any unexpected problem with the devices, additional session time will be offered to the participants to conclude the sets of games per session. The session will be rescheduled if the delay exceeds fifteen minutes.

Discontinuation may take place if strategies to avoid the adverse effects and bothersome symptoms are unsuccessful. Strategies include eye drops for dry eyes; adequate medication 15 minutes prior to the intervention to avoid headaches and motion sickness; change in brightness of the TV and Lab Room to avoid decreased visual acuity and dizziness; and changing game modality in case of fatigue or orthopedic concerns. Also, participants may withdraw from the study voluntarily or by a psychiatrist diagnosis of worsening of depression symptoms or in case of severe adverse events from the intervention or antidepressant therapy. The trial will be discontinued if evidence emerges demonstrating significant safety concerns associated with the proposed intervention.

Outcomes

The primary outcome is to detect a group mean difference in the 17-item Hamilton Depression Rating Scale (HAM-D17) at week twelve. An equal to or greater than the three-point mean difference (NICE, 2004) is a minimal clinically important difference (MCID). HAM-D17 was considered as a continuous variable to preserve study power.

HAM-D17 is the most used scale to assess outcomes in MDD clinical trials (Dunlop et al., 2019) and it also has good internal validity, strong psychometric properties, coverage of the depressive symptoms, and ability to measure change over time (Bobo et al. 2016).

For the secondary outcome, the HAM-D17 scores at baseline, at weeks 2, 6, 12, and at the 4th week of the follow-up period will be compared between groups. Success is defined if the 4-week follow-up HAM-D17 score is equal to or lower than the immediate post-treatment HAM-D17 score.

Other secondary outcomes include treatment adherence of participants and the evaluation of the percentage of subjects achieving a marked

improvement, defined as a reduction ratio of 50% or more in the HAM-D17 score.

Data Management and Monitoring

Psychiatrists evaluating the questionnaires (PHQ-9 and HAM-D17) will be trained with example scenarios, to improve their skills, ensuring data quality.

For data management, the REDCap system will be used. All data will be recorded in electronic format. All patient evaluations will be entered only by a data handler into REDCap System (REDCap Survey).

A medical coding dictionary for regulatory activities (MedDRA) and World Health Organization-drug dictionary (WHO-DDE) will be used for coding adverse events and drugs. Only one researcher per site will be responsible for entering the data. This is a short-term study assessing participants' initial response to treatment for depression associated with a pandemic condition, thus, there is no need for data monitoring.

Sample Size Calculation

Previous studies point to a mean of 21.2 in the HAMD-17 in untreated patients and an SD of 5.9 and 6.0 in the control and intervention groups, respectively (Bobo et al. 2016). Assuming that a minimal clinically significant difference is 3 (Montgomery et al. 2009, NICE 2009), we calculated a sample size of 202 with an alpha of 0.05 and power of 0.09, and 20% drop out (Cooney et al. 2013). A high dropout rate is expected due to the intervention's nature and population characteristics. We increased power to 0.9, given that previous trials on VR and depression have failed to find significant results.

Statistical Analysis for Primary and Secondary Outcomes

Baseline characteristics as HAM-D17 scores, age, gender, body mass index, vital signs, socioeconomics, medications, and comorbidities will be measured at the beginning of the trial for each group. All baseline variables will be presented using descriptive statistics: mean and standard deviation (SD) for normally distributed continuous data, median and interquartile range (IQR) for non-normally distributed continuous data, and proportions and frequencies for categorical data.

The primary analysis will compare intervention and control groups on their mean difference in HAM-D17 scores at week twelve by unpaired T-Test, since data is normally distributed. The estimated difference in mean values and the corresponding 95% confidence

interval (CI) will be presented. P-values will be reported to three decimal places with p-values less than 0.001 reported as $p < 0.001$. For all tests, we will use 2-sided p-values with alpha < 0.05 level of significance.

In the secondary analysis, the mean difference in HAM-D17 scores at baseline, weeks two, six, twelve, and sixteen (four weeks of follow-up) will be compared using linear mixed models with a random intercept for participants and an interaction between group and time.

Adherence and marked improvement are categorical data and will be analyzed by the Chi-Square test. Report of adverse events will be analyzed by Fisher's exact test. All calculations will be performed in STATA 16.1.

Missing Data

Possible reasons for missing data in studies assessing psychological status include: (1) the skepticism by some participants regarding the intervention, (2) lack of time and motivation to participate, and (3) delay in symptom improvement.

To prevent missing data, the appointment scheduling will be flexible. If a participant withdraws from study procedures, he/she may complete scheduled HAM-D17 assessments for the remainder of the study period and data will be analyzed to identify trends regarding the intervention and subsequent subject response without study procedures. Skepticism, lack of motivation, and delay in symptom improvement are intended to be reduced by education of participants regarding the nature of the intervention and the pathophysiology of the disease, and also by having open and trustworthy communication between patients and research staff.

We will assume that data will be missing at random (MAR) relating to observed aspects of the intervention or characteristics of subjects. Missing data can be ignored if dropout rates are less than 5%. However, because higher rates are expected, Intention to Treat analysis (ITT) will be applied. A multiple imputation method will be utilized, which estimates missing values based on repeated imputations from several datasets. It allows missingness to be addressed more accurately, as values are imputed based on participants' baseline covariates. Additionally, scatter plots will be generated to assess the effects of observed variables. Sensitivity analysis is also going to be performed to evaluate the robustness of the trial regarding the missing values.

DISCUSSION

Depression is a prevalent condition with a significant impact on multiple domains of individual and social functioning. Not only does it have a varying response to standard pharmacological therapy (Cuijpers et al. 2014; Kolovos et al. 2017), but it also had an exponential increase in its prevalence during COVID-19 pandemic, which justifies trials searching for interventions to improve response. Healthcare workers are especially susceptible to develop depressive symptoms due to multiple psychological stressors they have been facing during the current pandemic outbreak.

The knowledge gap that will be addressed by the study is whether non-immersive virtual reality provided by Wii Sports™ can serve as a useful add-on intervention to standard pharmacotherapy in health workers with mild and moderate Major Depressive Disorder. Wii Sports™ is a distraction provider with a large playfulness component that is easily accessible.

The study was designed to prove the intervention's superiority over the control, however, we may not find statistically significant results. Even though, this study would still be relevant because it would add evidence regarding additional interventions for the treatment of depression, a highly variable response condition (Khan et al. 2012).

On the other hand, positive results may be due to subjects being unblinded to their assigned group, which can introduce ascertainment and response biases due to the Hawthorne Effect, which are exceedingly difficult to detect. Furthermore, depending on the statistical analysis, results could suggest the intervention could be beneficial in a specific subgroup, such as those with higher baseline scores in the HAMD-17. In this case, further trials focusing solely on a specific subgroup could be designed and pursued.

The study may have limited external validity due to the narrow study population and to the fact that the study only addresses mild and moderate depression severity. Finally, the trial's long duration may jeopardize recruitment and adherence.

Despite these limitations, the study was carefully designed to address all possible ethical concerns regarding the safety of the subjects. For instance, subjects are going to be aware of the possibility of scheduling a psychiatric or psychological appointment. Physical activity is also going to be recommended. Due to the design of the study, however, subjects will be withdrawn from the trial. Outcome assessors and data analysts will be blinded to minimize observer and rater bias. Finally, the trial design was delicately planned

regarding our aim to assess the “pure effect” of the intervention.

In light of what was already known, this study design is feasible and relevant to our current COVID-19 pandemic outbreak. A positive result indicates that this intervention can serve as an alternative add-on to standard therapy in depression, promoting symptom recovery and reducing the burden of such a prevalent disease. To our knowledge, there is no previous literature published that targets the same population, tests the same intervention, and evaluates the same outcomes, highlighting the possible impact this study will have in the psychological and psychiatric fields, regardless of the results.

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Conflict of Interest

None.

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