Clinical Trial Protocol

Title: Effects of Open-label Placebos Administered Through Telehealth on COVID-related Stress, Anxiety, and Depression

Brief Title: Effects of Open-label Placebos on COVID-related Psychological Health

Study Sponsor: Michigan State University

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HRP-503 - Template – Protocol

MICHIGAN STATE UNIVERSITY HUMAN RESEARCH PROTECTION PROGRAM

- Complete this template for new exempt, expedited, or full board studies.
  - Complete Section I for ALL studies (exempt, expedited, full board)
  - Complete Section II ONLY if your study does not qualify for exemption and requires an expedited or full board review. Contact the IRB office if you have any questions.
- CLICK™ IRB:
  - Include the template with a New Study Submission.
  - Upload the completed template to the Basic Information SmartForm page, Question 10.
  - When uploading documents to Click (e.g. consent documents, instrument), provide distinct file names.
- See the Click Quick Guides and the HRPP Manual for more information, available at hrpp.msu.edu

Study Title:	Leveraging non-deceptive placebos administered through telehealth to manage stress and anxiety related to COVID-19
Click Study ID (if known):	STUDY00004435
Sponsor (if applicable):	Dr. Jason Moser
Sponsor ID (if applicable):	jmoser

Section I. IRB Protocol for <u>All</u> Studies

Section I is completed for ***all studies*** and includes questions to determine whether the study qualifies for exemption. Section II is <u>only</u> completed if the study does not qualify for exemption.

1. Hypothesis / Objective / Goals / Aims.

Briefly describe the study's hypothesis / objectives / goals / aims.

Placebo interventions offer a cost-effective and scalable tool in helping people manage a host of psychological and physical conditions. However, the prevalent idea that people need to be deceived into believing they are taking an active treatment in order for placebos to work prevents their widespread use. Fortunately, accumulating research suggests that placebos can still produce beneficial effects even when administered without deception (i.e., non-deceptive placebos) by communicating to people what placebos are, explaining the science behind how the work, and highlighting how they can still be effective even if people know they are taking them.

Goal:
Building on this research, the goal of this project is to harness the beneficial effects of placebos administered without deception by testing the efficacy of a cost-effective, easily implementable, and scalable telehealth interventions for helping people manage their stress and anxiety related to the COVID-19 pandemic. The intervention involves participants watching an informational video on the beneficial effects of placebos without deception, remotely interacting with an experimenter, and taking open-label placebo pills (NDP Video + Experimenter). The intervention will be compared to a no treatment, assessment only control group.

Prediction:
We expect those in the NDP Video + Experimenter group to experience less over all stress and anxiety related to COVID-19 compared to the NT Control group.

2. Subject Population.

2A. Study purposefully includes the following subject population(s) (select all that apply):

- ☐ Cognitively impaired adults
- ☐ Minors (children) (view information about the definition of a child)
- ☐ Minors who are wards of the state
- ☐ Pregnant women, fetuses, or neonates
- ☐ Prisoners
- ☒ Students

2B. Study involves (select all that apply):

- ☐ Funding, support, or other requirement to comply with U.S. Department of Justice regulations
- ☒ Incomplete disclosure or attempted deception of subjects

CLICK IRB: Upload the debriefing script, document, etc. to the Consent Forms and Recruitment Materials SmartForm page, Question 1.

3. Estimated Study Duration.

Provide the time estimated to complete all human subject research, including analysis of the subjects' identifiable private information.

This study will take an estimated three years including data collection and analysis.

4. Reasonably Foreseeable Risks.

4A. There are (select one of the following):

- ☐ No reasonably foreseeable risks to subjects
- ☒ Reasonably foreseeable risks to subjects

4B. Explain the selection. *If you selected that there are reasonably foreseeable risks to subjects, describe the risks, considering physical, psychological, social, legal and economic risks.*

We expect the risk to subjects to be minimal. There is a small risk of psychological distress from replying to questions regarding their psychological and physical health within the COVID-19 pandemic context. Participants in the intervention conditions who are not accustomed to taking pills may also experience distress from taking inactive placebo pills

4C. If you selected that there are reasonably foreseeable risks, describe the procedures for protecting against or minimizing potential risks and provide an assessment of their likely effectiveness.

In order to protect subjects from the risk of psychological distress from replying to questions regardng their psychological and physical health within the COVID-19 pandemic context, participants will have the option to skip any questions or withdraw from the study at anytime. Participants in the intervention conditions will be asked if they are willing to take placebo pills, and those who are not comfortable or wishes not to do so will not be able asked to participate in the study. Moreover, participants will receive resources, which can provide additional support and counseling if needed.

5. Conflict of Interest.

Do any investigators or research staff have a financial interest related to the research that has not otherwise been disclosed elsewhere in this submission? ☒ No ☐ Yes

6. Exemption Criteria. ☐ Not Applicable

A study may qualify for exemption when the only involvement of human subjects will be in one or more of the following categories (please view full exemption category / description here: https://hrpp.msu.edu/help/required/exempt-categories.html). ***(If the study does not qualify for the exemption criteria, do not complete this question and proceed to Section II.)***

6A. Exemption Categories.

6A1. Select the category(ies) applicable to the study if the only involvement of human subjects in this study will be in one or more of the categories. Studies involving prisoners cannot be exempt UNLESS the research is aimed at involving a broader subject population that only incidentally includes prisoners *If your study is subject to U.S. Department of Justice requirements, do not complete this section; complete 6A2 below.*

☐ ***Exempt 1.*** Research conducted in established or commonly accepted educational settings, involving normal educational practices that are not likely to adversely impact students' opportunity to learn required educational content or the assessment of educators who provide instruction. ***IF YOU SELECTED THIS CATEGORY, EXPLAIN WHY THE RESEARCH WILL NOT LIKELY ADVERSELY IMPACT STUDENTS' OPPORTUNITY TO LEARN REQUIRED EDUCATIONAL CONTENT OR THE ASSESSEMENT OF EDUCATORS WHO PROVIDE INSTRUCTION.***

☐ ***Exempt 2.*** Research that only includes interactions involving educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior. ***IF YOU SELECTED THIS CATEGORY, SELECT THE APPROPRIATE OPTION(S) BELOW.***

- ☐ (i) Information obtained is recorded by investigator in manner that identity of subjects cannot readily be ascertained, directly or through identifiers linked to subjects
- ☐ (ii) Any disclosure of subjects' responses outside research would not reasonably place subjects at risk of criminal or civil liability or be damaging to subjects' financial standing, employability, educational advancement, or reputation.
- ☐ ***(iii)*** **LIMITED IRB REVIEW REQUIRED**. Information obtained is recorded by investigator in manner that identity of subjects can readily be ascertained, directly or through identifiers linked to subjects, and responses could reasonable place subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation ***(LIMITED IRB REVIEW IS REQUIRED; YOU MUST ALSO COMPLETE QUESTION 6E TO DESCRIBE PRIVACY AND CONFIDENTIALITY SAFEGUARDS.)***

☐ ***Exempt 3.*** Research involving benign behavioral interventions in conjunction with the collection of information from an adult subject through verbal or written responses (including data entry) or audiovisual recording if the subject prospectively agrees to the intervention and information collection. ***IF YOU SELECTED THIS CATEGORY, SELECT THE APPROPRIATE OPTION(S) BELOW.***

- ☐ (i) Information obtained is recorded by investigator in manner that identity of subjects cannot readily be ascertained, directly or through identifiers linked to subjects.
- ☐ (ii) Any disclosure of subjects' responses outside research would not reasonably place subjects at risk of criminal or civil liability or be damaging to subjects' financial standing, employability, educational advancement, or reputation
- ☐ ***(iii)*** **LIMITED IRB REVIEW REQUIRED**. Information obtained is recorded by investigator in manner that identity of subjects can readily be ascertained, directly or through identifiers linked to subjects, and responses could reasonable place subjects at risk of criminal or civil liability or be damaging to subjects' financial standing, employability, educational advancement, or reputation ***(LIMITED IRB REVIEW IS REQUIRED; YOU MUST ALSO COMPLETE QUESTIONS 6E TO DESCRIBE PRIVACY AND CONFIDENTIALITY SAFEGUARDS.)***

☐ ***Exempt 4.*** Secondary research uses of identifiable private information or identifiable biospecimens. ***IF YOU SELECTED THIS CATEGORY, SELECT THE APPROPRIATE OPTION(S) BELOW.***

- ☐ Identifiable private information or identifiable biospecimens are publicly available.
- ☐ Information, which may include information about biospecimens, is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained directly or through identifiers linked to the subjects, the investigator does not contact the subjects, and the investigator will not re-identify subjects. ***IF YOU SELECTED THIS CATEGORY, CONFIRM THE FOLLOWING:***
  - ☐ Investigator and research team will not contact the subjects
  - ☐ Investigator and research team will not re-identify the subjects
- ☐ The research involves only information collection and analysis involving the investigator's use of identifiable health information when that use is regulated under the Health Insurance Portability and Accountability Act (HIPAA) 45 CFR parts 160 and 164.
- ☐ The research is conducted by, or on behalf of, a Federal department or agency using government-generated or government-collected information obtained for nonresearch activities, if the research generates identifiable private information that is or will be maintained on information technology that is subject to and in compliance with specific federal privacy standards.

☐ ***Exempt 5.*** Federal demonstration projects.

☐ ***Exempt 6.*** Taste and food quality evaluation and consumer acceptance studies.

☐ ***Exempt 97***. ONLY applicable to research NOT FUNDED by a federal department or agency: Research involving the study of previously collected identifiable data (please view additional exclusions before selecting this category).

By checking the boxes below, you are confirming that the study will not include any of the following exclusions for the study's duration:

- ☐ Federal funding or federal training grants
- ☐ FDA regulated
- ☐ Sponsor or other contractual restrictions
- ☐ Clinical interventions (including clinical behavioral interventions)
- ☐ Receipt of an NIH issued certificate of confidentiality to protect identifiable research data
- ☐ Multi-site collaborative research study where another institution plans to rely or is relying upon MSU's IRB review

☐ ***Exempt 98.*** ONLY applicable to research NOT FUNDED by a federal department or agency: Prospective data collection with adults through verbal or written responses involving a benign intervention (please view additional exclusions before selecting this category).

By checking the boxes below, you are confirming that the study will not include any of the following exclusions for the study's duration:

- ☐ Federal funding or federal training grants
- ☐ FDA regulated
- ☐ Sponsor or other contractual restrictions
- ☐ Clinical interventions (including clinical behavioral interventions)
- ☐ Receipt of an NIH issued certificate of confidentiality to protect identifiable research data
- ☐ Multi-site collaborative research study where another institution plans to rely or is relying upon MSU's IRB review
- ☐ Children as research subjects

6A2. DEPARTMENT OF JUSTICE Exemption Categories. Complete this section ONLY if the research is subject to Department of Justice requirements.

6A2i. Select the category(ies) applicable to the study if the only involvement of human subjects in this study will be in one or more of the categories. Studies involving prisoners cannot be exempt.

☐ ***Exempt 1.*** Research conducted in established or commonly accepted educational settings, involving normal educational practices.

☐ ***Exempt 2.*** Educational tests, survey procedures, interview procedures, observation of public behavior unless data is recorded in a manner such that subjects are identifiable and the responses could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation (research cannot involve children, except for educational tests or observation of public behavior where the investigator does not interact with the child).

☐ ***Exempt 3.*** Educational tests, survey procedures, interview procedures, or observation of public behavior not otherwise exempt that involves public officials or federal statute.

☐ ***Exempt 4.*** Collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens if publicly available or information is recorded by investigator in a manner that subjects cannot be identified.

☐ ***Exempt 5.*** Federal demonstration projects.

☐ ***Exempt 6.*** Taste and food quality evaluation and consumer acceptance studies.

6A2ii. Explain why the study presents minimal risk to subjects.

6B. By checking the boxes below, you are confirming that the following are true and will remain true for the study's duration:

☒ Selection of subjects is equitable (considering the purposes of the research, setting in which research will be conducted, any vulnerable populations).

☒ If there is recording of identifiable information, there are adequate provisions to maintain the confidentiality of the data.

☒ There are adequate provisions to maintain the privacy interests of subjects.

☒ Safeguards are or will be put in place to protect against any coercion or undue influence if you or members of your study team are or may be associated with the subjects at any point in the study (e.g. students, employees, colleagues, patients).

6C. Consent

6Ci. There will be a consent process for the study's duration that will disclose information such as that the activity involves research, a description of the procedures, that participation is voluntary and withdrawal is without penalty, and the name and contact information for the researcher (select appropriate option below):

☒ For All Subjects
☐ For Some Subjects
☐ For None of the Subjects (consent will not be obtained)

CLICK IRB: Upload the consent document to the Consent Forms and Recruitment Materials SmartForm page.

6Cii. Please explain your selection.

6D. Please acknowledge that you may not begin the research at non-MSU institutions (regardless of engagement), until you receive the appropriate approvals/permissions from the sites (e.g. IRB review/exempt determination from non-MSU sites, data use or research agreements, other regulatory approvals). An MSU exempt determination does not provide approval/permission for a non-MSU site, including sites with reliance agreements with MSU. Please note that non-MSU sites may have requirements that differ from MSU for exempt research. Note that this also applies to sites added after the MSU exempt determination.

☒ Acknowledged

6E. LIMITED IRB REVIEW. If the exemption(s) require limited IRB review (if you selected Exemption 2(iii) or 3(i)(C) in Question 6A), complete questions 1 and 2 to describe privacy and confidentiality.

6E1. Privacy of Subjects.

How will subjects' privacy be protected? Consider the number of individuals interacting with the subject or subject's records, location of consent process and study, presence of individuals not associated with the study, sensitivity of the research.

6E2. Confidentiality of Data.

6E2i. Select the appropriate option:

☐ Identifying or coded information will not be stored with the information and/or biospecimen(s)

☐ Identifying or coded information will be stored with the information and/or biospecimen(s)

6E2ii. Please explain your selection. If you are storing identifying or coded information with the information and/or biospecimen(s), explain why identifiable or coded information and/or biospecimen(s) needs to be maintained and how long it will be necessary to maintain it.

6E2iii. Describe the procedures and safeguards you will use to secure the information and/or biospecimen(s), including during transport of information and/or biospecimen(s).

Other Click IRB Documents to Upload As Appropriate (Applicable to All Studies)
• *Upload this completed protocol to the Basic Information SmartForm page, Question 10.* • *Upload any funding materials not accessible in Kuali Coeus in the Supporting Documents SmartForm page.* • *Upload the HRP-537 - Template - Use of Protected Health Information Application to the MSU Additional Study Information SmartForm page.* • *Upload the HRP-538 - Template - MSU Authorization to Use or Disclose Health Information for Researchers to the MSU Additional Study Information SmartForm page.*

IF THE STUDY MAY QUALIFY FOR AN EXEMPTION (INCLUDING THOSE THAT MAY REQUIRE LIMITED IRB REVIEW), STOP HERE AND DO NOT COMPLETE SECTION II.

CONTINUE ONLY IF THE STUDY DOES NOT QUALIFY FOR AN EXEMPTION.

COMPLETE QUESTIONS 7-23 FOR AN EXPEDITED OR FULL BOARD STUDY.

Section II. Additional Questions for an Expedited or Full Board Study

Not all questions or sections are applicable to every study. If the question or section is not applicable, check the "Not Applicable" box. All other questions are required.

7. Expedited Categories.

7A. Please select the Expedited category(ies) and sub-categories as applicable to the study if the only involvement of human subjects in this study will be in one or more of the categories. If the study involves more than minimal risk or none apply, select "The study involves more than minimal risk OR none of the expedited category(ies) apply."

☐ ***The study involves more than minimal risk OR none of the expedited categories apply. IF THIS OPTION IS SELECTED, DO NOT SELECT ANY OF THE EXPEDITED CATEGORY(IES).***

☐ ***Expedited 1.*** Clinical studies of drugs and medical devices only when condition (a) or (b) is met. ***IF YOU SELECTED THIS CATEGORY, SELECT THE APPROPRIATE OPTION(S) BELOW.***

- ☐ (a) Research on drugs for which an investigational new drug application (21 CFR Part 312) is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)
- ☐ (b) Research on medical devices for which (i) an investigational device exemption application (21 CFR Part 812) is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.

☐ ***Expedited 2.*** Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture. ***IF YOU SELECTED THIS CATEGORY, SELECT THE APPROPRIATE OPTION(S) BELOW.***

- ☐ (a) from healthy, nonpregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; or
- ☐ (b) from other adults and children [2], considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week

☐ ***Expedited 3***. Prospective collection of biological specimens for research purposes by noninvasive means.

☒ ***Expedited 4***. Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.)

☐ ***Expedited 5***. Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis).

☐ ***Expedited 6***. Collection of data from voice, video, digital, or image recordings made for research purposes.

☐ ***Expedited 7***. Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.

7B. **For Studies Regulated by the U.S. Food and Drug Administration or the U.S. Department of Justice**. If you selected an expedited category, explain why the study presents minimal risk to subjects.

8. **More than Minimal Risk Research.** *Complete the following question if you selected "The study involves more than minimal risk OR none of the expedited categories apply" in Question 7A (Expedited Categories).*

8A. Describe the relevant prior experience and gaps in current knowledge, relevant preliminary data, if any, and the scholarly background for, and significance of, the research based on existing literature and how it will add to existing knowledge.

8B. Sample Size.

8Bi. Total number of subjects who will be approached (including screen failures, controls and subject withdrawals) to reach enrollment numbers for the lifetime of the study at this investigator's sites.

8Bii. Total number of subjects who will be enrolled in the study at this investigator's site.

8Biii. Describe the statistical justification or rationale for the proposed sample size. Considerations for sample size may include the acceptable level of significance, power of the study, expected effect size, underlying event rate in the population, standard deviation in the population, saturation of themes, and/or have a theoretical basis.

9. **Minimal Risk Research.** *Complete the following question if you selected an expedited category in Question 7A.*

9A. Briefly describe the background for conducting the research. (1-2 sentences)

Placebos without deception (non-deceptive placebos) offer a relatively cost-effective, minimally invasive, and powerful way to facilitate reductions in stress and anxiety related to COVID-19. Although there is a predominant belief that deception is necessary in order to harness the beneficial effects of placebos, new research shows that non-deceptive placebos can still be effective in managing a host of physical and psychological conditions (Charlesworth et al., 2017; Kaptchuk et al., 2010). For example, non-deceptive placebos are effective in managing negative emotions (Guevarra et al., 2020) and overall emotional distress (El Brihi, Horne, & Faasse, 2019). Moreover, theoretical and empirical work suggest that placebos may provide their beneficial effects with minimal cognitive resources (Braunstein et al., 2017; Buhle et al., 2012). As such, non-deceptive placebos potentially offer a relatively cost-effective, easily implementable, and scalable way to help manage stress and anxiety related to COVID-19.

Despite their efficacy, non-deceptive placebo studies are typically done in person to help facilitate beneficial effects. Moreover, placebo research suggests that an in-person interaction with an authority figure in the form of a medical doctor or experimenter may be an important ingredient in order to maximize placebo effects (Kaptchuk et al., 2008). Nevertheless, positive expectations and beliefs in the efficacy of treatment are powerful ingredients of placebos that can be leveraged online, as research indicates that expectations and beliefs can be effectively changed remotely and thus lead to the intended beneficial effects (Geers et al., 2019; Kaptchuk et al., 2010; Yeager et al., 2019).

In this project, we will test the efficacy of a cost-effective and scalable telehealth interventions. Participants will be randomly assigned to one of two conditions: 1) a no-treatment,

assessment only control (NT Control) and 2) a non-deceptive placebo intervention administered through an informational video and remote interaction with an experimenter (NDP Video + Experimenter). The informational video will consist of a brief explanation of placebos and the placebo effect, how placebos provide beneficial effects for many different conditions, how placebos can affect behavior and biology, and how placebos can still work even when people know they are taking one. In the NDP Video + Experimenter intervention, participants will remotely interact with an experimenter who will reiterate and emphasize the placebo information and provide instructions on how to take the open-label placebo pills. Participants in the NDP Video + Experimenter intervention will be instructed to take open-label placebo pills on a daily basis for two weeks.

9B. Sample Size.

9Bi. Provide an estimated sample size for the lifetime of the study at this investigator's sites.

100 to 400

9Bii. Describe the basis for that estimate.

We plan to screen as many as participants as possible that would allow us to enroll a minimum of 100 participants in a two-arm randomized controlled trial. Each arm will require a minimum of 50 participants. We determined this sample size in a few ways. One, the typical sample size for a between-subjects study comparing non-deceptive placebos to a control group ranges from 30 to 50 per condition (Kaptchuk et al., 2010; El Brihi et al., 2019; Locher et al., 2017). Two, from a more practical standpoint, we only have the financial resources to run approximately 50 in each condition. We are applying for additional funding, but for now, we only have a budget for 50 in each condition. Three, we determined 50 participants in each arm by hypothesizing a d effect size of .60 between the control group and each of the treatment arms with a power of .80 at an alpha level of .05. Non-deceptive placebo studies have typically used an ANOVA model followed up by pairwise comparisons. These effect sizes are calculated from these pairwise comparisons.

Our assumption of a d effect size of .60 is a liberal assumption based on the literature in which the d effect size between a non-deceptive placebo and a no treatment control ranges from .30 to 1.00. The most relevant non-deceptive placebo study is El Brihi et al. (2019) in which they tested the effects of non-deceptive placebos on emotional distress and positive mental well-being. Comparing two types of non-deceptive placebos versus a control showed a non-deceptive placebo effect that ranges from a Cohen's d of .78 to 1.01 on emotional distress. Comparing two types of non-deceptive placebos versus a control showed a non-deceptive plaebo effect that ranges from a Cohen's d of .55 to .93 for psychological well-being. As such, we estimate that a d effect size of .60 between a control group and our non-deceptive placebo group because our primary outcomes is also emotional distress and psychological well-being. A .60 d effect size is within a reasonable range of what is expected regarding a non-deceptive placebo effect on emotional distress. This will allow us to run approximately 50 in each condition, which is more than the sample size of the El Brihi et al. (2019) study in which they had n = 29 in the control condition and n = 30 and n = 31 in each of the non-deceptive placebo condition.

For our primary outcomes, we plan to run a 2 (Group) by 3 (Time: Time 2, Time 3) mixed factorial ANOVA (while controlling for baseline levels) followed by independent pairwise comparisons at each of time point. When possible, we plan to use multiple imputation methods to account for missing data. If a participant is missing data from 2 or more time points for our primary outcome, they will be removed for analyses. If a person is unresponsive for 5 days, we will consider them a dropout. We will send a final letter indicating that we apologize for their drop

and that they can contact us if they need anything and provide them resources if they require it. If participants wants to drop out, we can inquire why and offer them resources and contact information for future studies.

Again, we also only have a budget to run 50 participants in each condition. We plan to apply for further funding but for now, this is our limit. We want the option to test more than 50 in each condition because it will increase our confidence in any effect we find. If we receive funding, we will run more than 50 in each condition, but we will not enroll more than 200 participants in each arm. The 200 in each arm maximum will allow us to detect a d effect size of .30 with some room for error such as participants dropping out or not filling out all of our measures.

10. Benefits.

Describe any potential direct benefit(s) to subjects in this study, if any and the importance of the knowledge that may reasonably be expected to result. Within the description, do not include payment to subjects as a benefit.

The intervention group will develop a better understanding of placebos and placebo effects. There is a possibility that this understanding may lead those in the intervention group to feel less stress and anxiety related to COVID-19 compared to the control group. In terms of societal benefits, there is a possibility that we may provide support for a cost-effective and scalable intervention to help people manage their stress and anxiety related to COVID-19.

11. Screening, Recruitment, and Determining Eligibility.

11A. Describe how subjects will be identified and recruited, including who will perform the recruitment.

Broadly, our target sample is any Michigan resident that fits our eligiblity criteria. Participants will be between 18 and 30, English as their primary language, do not have a self-reported history of severe mental illness, do not have a current diagnosis of COVID-19, no major health problems such as heart and lung diseases, and is able and willing to participate in a longitudinal study spanning 17 to 20 days. In order to ensure people's identity, people will be required to show their ID in a HIPPA compliant Zoom call. In order to ensure that our sample is currently experiencing a moderate amount of stress and anxiety related to COVID-19, we will also only enroll participants who score a 35 or higher on the COVID Stress Scale.

For those in the intervention condition, we will have additional criteria asking if they would be willing to provide an address where we can send them a bottle of placebo pills and if they are willing to take placebo pills 2 weeks. People in the intervention group will also indicate that they are willing to take pills for 2 weeks and not be allergic to common ingredients found in pills such as microcyrstaline cellulose, silica, gelatin, titanium dioxide, Red # 3, and Blue #1.

Participants will be recruited from the MSU student population and broader Michigan community. Since the study is online, we are not restricted by East Lansing geopgraphy. We plan to recruit online through cragslist, facebook, and other research online platforms such as ResearchMatch.

We will also recruit through the Paid Subject Pool from the Communication Arts and Sciences Department that is managed by Dr. Anna McAlister.

We are also partnering with a collaborator from University of Michigan to help with recruitment, and we plan to use their health research participant pool. The collaborator will not interact or intervent with subjects for research purposes, they will not collect data or obtained consent or study or analyze any of the data with identifiable information. The University of Michigan IRB will

not be conducting their own review. They agreed that MSU IRB will oversee this study. University of Michigan IRB is waiting for MSU IRB approval in order to file a "Requesting Review by a Non-UM IRB" application.

Recruitment and eligiblity follow-up will be performed by trained research assistants and personnel.

CLICK IRB: Upload the recruitment materials to the Consent Forms and Recruitment Materials SmartForm page, Question 2.

11B. The study team will obtain for the purpose of screening, recruiting, or determining the eligibility of prospective subjects (please select the appropriate option(s)): ☐ Not Applicable

☒ Information through oral or written communication with the prospective subject or legally authorized representative. Before the information is obtained for the purpose of screening, recruiting, or determining eligibility, consent: ☒ will be obtained. ☐ will not be obtained. *Please describe screening consent procedures in Question 12.*

☐ Identifiable private information or identifiable biospecimens by accessing records or stored identifiable biospecimens. Before the information is obtained for the purpose of screening, recruiting, or determining eligibility, consent: ☐ will be obtained. ☐ will not be obtained. *Please describe screening consent procedures in Question 12.*

Note: The revised Common Rule permits an exception from informed consent for screening, recruiting, or determining eligibility when certain criteria are met; this exception does not apply to studies subject to the Pre-2018 Common Rule Requirements and/or studies regulated by the U.S. Food and Drug Administration (FDA).

11B1. Please explain your selection(s).

We need to collect information in order to screen for major psychological and physical health problems as well as other criteria such as age, capabilities and willingness to participate in a longitudinal study, willingness to show ID over HIPPA compliant zoom, no COVID-19 diagnosis, English as their primary language, and experiencing moderate amount of COVID-19 related stress and anxiety.

12. Consent Process.

12A. If the study involves adults, consent will be obtained from (select appropriate option(s)): ☐ Not Applicable

☒ All subjects
☐ Some subjects
☐ No subjects (consent will not be obtained)

CLICK IRB: Upload the consent document, script, etc. (including translations) to the Consent Forms and Recruitment Materials SmartForm page, Question 1.

12B. If the study involves children, parental permission will be obtained from (select appropriate option(s)): ☒ Not Applicable

☐ Both parents or guardians (unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child)
☐ One parent or guardian
☐ Will not be obtained

CLICK IRB: Upload the parental permission forms to the Consent Forms and Recruitment Materials SmartForm page, Question 1.

12C. If the study involves children, child assent will be obtained from (select appropriate option): ☐ Not Applicable

☐ All children
☐ Some children
☐ Will not be obtained

CLICK IRB: Upload the child assent form to the Consent Forms and Recruitment Materials SmartForm page, Question 1.

12D. Describe the consent process, including an explanation of your selection(s) above. If the study involves screening activities, please describe whether consent will be obtained and if consent will not be obtained, explain how the screening data will be used. If only some subjects will provide consent, explain who will or will not provide consent. If only some children will provide assent, explain which children will and will not provide assent.

The consent process will happen two times. First, consent will be obtained before the prescreening questionnaire is administered. The prescreening questions will be administered via an online survey through the Qualtrics platform. Once potential participants complete the survey, trained research assistants and personnel will determine if participants are eligible to be part of the study. Those who are not eligible will be sent an email thanking them for their participant. Those who are eligible will be contacted in order to set up a meeting for a potential enrollment.

For those who are eligible, participants will be provided with more details regarding the study to determine if they wish to participate. The consent process will involve a detailed description of the study, study expectations, and study payment. Participants will be told that they can withdraw from the study at anytime. A research assistant will walk participants through the consent process over the phone to ensure that they understand what the study entails. They will indicate consent through an online platform.

12E. If consent will not be obtained, explain why. Describe why the research could not be practicably carried out if consent was required. If the research involves identifiable private information or identifiable biospecimens, describe why the research could not practicably be carried out without using such information or biospecimens in an identifiable format. ☒ Not Applicable

12F. If your study involves use of a consent form, complete i, ii, and iii. ☐ Not Applicable

12Fi. Select the appropriate option(s) below for the documentation of consent.

☐ Will use a written consent document signed by subjects
☐ Will use a short form written consent document signed by subjects
☐ Will not obtain a signed consent document for some subjects
☐ Will not obtain a signed consent document for all subjects

12Fii. Describe when and how the subject will receive a copy of the consent form.

We will send a pdf copy of the consent form through email. We will also send them a link online in order for them to click yes or no.

12Fiii. If subjects will not be signing the consent document, please explain why. If some subjects will not sign the consent document, explain who will and will not sign the consent. ☐ Not Applicable

Due to COVID-19, this study will be conducted online. As such, to ease participant burden, we will not obtain physical signatures from our participants. They will indicate consent by clicking yes on a digital version of the consent form.

12G. If the study involves cognitively impaired adults, explain the process to determine whether a subject is capable of consent, use of any legally authorized representative(s), and any assent process. ☒ Not Applicable

CLICK IRB: Upload any assessment tools to the Supporting Documents SmartForm page.

13. Coercion or Undue Influence.

13A. If some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons, describe additional safeguards that have been included in the study. ☒ Not Applicable

13B. If you or your study team are associated with the subjects (e.g. your students, employees, colleagues, patients), explain the nature of any association and measures taken to protect subjects' rights, including safeguards against any coercion or undue influence (e.g. pressure a subject might feel to participate based on the association). ☒ Not Applicable

14. Privacy.

How will subjects' privacy be protected? Consider the number of individuals interacting with the subject or subject's records, location of consent process and study, presence of individuals not associated with the study, sensitivity of the research.

Participant demographic information and name will be stored in a password-protected electornic document in a password protected computer. The data collected will not be stored with identifying information. We will assign a unique subject ID to label the study data and the key that links this unique ID to identifying information will be kept separately and securely from the data. It will be stord in a password-protected document.

The survey will only be accessed with a username and password by trained personnel. We will keep this data until after the full research period is over (5 years), after which it will be deleted. The consent process and the entirety of the experiment will take place online via phone call and for one condition, via an encrypted, password protected Zoom call.

Only the primary investigator, trained lab coordinators, graduate students, post-docs, and trained undergraduate research assistants will interact with the participant.

Each participant will be enrolled by one trained lab member.

15. Withdrawal of Subjects. ☐ Not Applicable

If there are any anticipated circumstances where the researcher will withdraw subjects from the study regardless of the subject's wishes, describe the circumstances and the procedures when subjects are withdrawn from the study.

The participant will take a total of 4 surveys spanning 17 to 20 days. It is very important that participants take the first two surveys and the last survey (First, Second, and Fourth) or they will not be able to proceed with the study. The first two surveys help us establish baseline psychological and physical health and if they do not take it, we will not be able to do anything meaningful with the rest of their data. They really can only miss the Third Survey.

16. Monitoring Plan to Assess Data to Ensure Safety of Subjects.

16A. Is there a monitoring plan to periodically assess the data to ensure the safety of subjects or to ensure negative outcomes do not occur?

☒ No
☒ Yes

Explain your answer. If you answered Yes, describe the monitoring plan.

Yes. Darwin Guevarra will oversee the collect and storage of data and supervise authorize personnel. Data will be reviewed on a weekly basis until data collection is completed. The following conditions will necessitate termination from the study: 1) participant indicates that they are experiencing a significant amount of stress and wishes to pursue a different treatment and 2) participants no longer wish to participate for any reason.

CLICK IRB: Upload any data safety monitoring plans to the Supporting Documents SmartForm pages.

16B. If there is a data safety monitoring committee or board, describe the composition and frequency of meetings.

☐ Not Applicable

17. Results and Data Sharing.

17A. Could this research generate any results that could be clinically relevant, including individual research results, or general, or aggregate research findings?

☒ No
☐ Yes, clinically relevant individual research results
☐ Yes, clinically relevant general or aggregate research findings

17A1. If yes, explain what clinically relevant research results will be generated, whether they will be disclosed to subjects or others (e.g. subject's primary care physician), and if so, under what conditions. Address individual research results and/or general or aggregate research findings, as appropriate. *This also needs to be explained in the consent document.*

17B. For other research results, select all that apply:

☒ Not Applicable

☐ Overall study results will be shared directly with subjects
☐ Individual results or incidental findings of individual subjects will be shared with subjects or others
☐ Data will be submitted to a repository or database as part of data sharing agreement (e.g. genomic data sharing)

17B1. Explain your selection(s), including how the data or results will be shared and with who (e.g. subject's primary care physician, data repository).

18. Local Context and Multi-Site Study.

18A. Describe the locations of where the study team will obtain information or biospecimens through intervention or interaction with the subject or obtain the subjects' private identifiable information.

All aspects of the study will take place online Enrollment will take place via Zoom. All survey instances will also be administered through Zoom. For the intervention group, the study will be conducted online via a private encrypted, password protected Zoom video call.

18B. If the study will engage employees or agents of non-MSU organizations (e.g. performance sites), explain how the employees or agents will be engaged (e.g. will they perform research procedures, will they obtain informed consent from subjects). ☒ Not Applicable

18C. If the study involves multiple performance sites, describe the methods for communicating with engaged sites related to the protection of human subjects (e.g. any potential unanticipated problems that may involve risks to subjects others). ☒ Not Applicable

18D. If there are any cultural or local contexts or requirements that may impact the protection of human subjects or present additional risks to subjects that have not otherwise been described, please describe. If research is conducted outside the state of Michigan, this could include additional state or international requirements or laws. ☒ Not Applicable

18E. If translations to a language other than English will be provided to subjects, describe the translation process. ☒ Not Applicable

CLICK IRB: Upload translated documents to the appropriate SmartForm page(s).

19. Resources and Financial Compensation and Costs.

19A. If someone will receive a payment for recruiting the subjects, explain the amount of payment, who pays it, who receives it, and why they are being paid. ☒ Not Applicable

19B. If subjects will incur additional financial costs as a result of their participation in this study, explain the additional costs. ☒ Not Applicable

19C. Describe any resources not otherwise described elsewhere in the submission (e.g. internal funding) for the protection of human subjects. ☒ Not Applicable

CLICK IRB: Upload any funding materials not accessible in Kuali Coeus in the Supporting Documents SmartForm page.

19D. If subject's biospecimens (even if identifiers are removed) may be used for commercial profit, describe whether the subject will or will not share in the commercial profit. *This also needs to be explained in the consent document.*

☒ Not Applicable

20. Information and/or Biospecimen(s) Management and Confidentiality.

20A. Select the appropriate option:

☒ Identifying or coded information will not be stored with the information and/or biospecimen(s)
☐ Identifying or coded information will be stored with the information and/or biospecimen(s)

20B. Please explain your selection. If you are storing identifying or coded information with the information and/or biospecimen(s), explain why identifiable or coded information and/or biospecimen(s) needs to be maintained and how long it will be necessary to maintain it.

Identifying information from the initial survey will not be stored with other information from the study.

20C. Describe the procedures and safeguards you will use to secure the information and/or biospecimen(s), including during transport of information and/or biospecimen(s).

Only the project investigators and trained research assistants will be interacting with study participants or their data. When enrolling subjects, each subject will be assigned an identification number. The data itself will only be identified by these code numbers, making it impossible for anyone to link data to a person's name or any other identifying information. All de-identified data will be stored separately, away from identifiable forms (e.g., consent forms). Any electronic data files will be password-encrypted and stored on a password-protected computer.

21. Drug and/or Device Storage, Handling, and Administration. ☒ Not Applicable

Describe the procedure and plan for storage, handling, and administration of the drug and/or device so that they will be used only on enrolled subjects and be used only by authorized study personnel.

22. Future Research.

If the research involves the collection of identifiable private information or identifiable biospecimens, select the appropriate option: ☐ Not Applicable

☒ The subject's information or biospecimens, even if identifiers are removed, could be used for future research studies or distributed to another investigator for future research studies
☐ The subject's information or biospecimens, even if identifiers are removed, will NOT be used or distributed for future research studies

Please be sure to carefully consider the appropriate option, as this needs to be explained in the informed consent and can limit what is done or used for future research.

23. MSU Additional Information. ☒ Not Applicable

Identify if your study involves any of the following: (check all that apply)

☐ Use of human stem cells
☐ Research with biospecimens will (if known) or might include whole genome sequencing (i.e., sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen). *If so, this needs to be explained in the consent document.*

Other Click IRB Document Uploads As Appropriate (Applicable to Expedited or Full Board Studies)
• *Upload list of external study team members (non-MSU individuals) to the Study Team Members SmartForm page, Question 2.* • *Upload other institution(s) approval letter(s), if submitted to other IRB(s) or ethics committees, to the Supporting Documents SmartForm page.* • *Upload FDA communications, package inserts, FDA form 1572, or other information related to drugs or devices to the appropriate Drug or Device SmartForm pages.* • *Upload the HRP-540 - Template - ICH-GCP - For Investigator to the MSU Additional Study Information SmartForm page.* • *Upload HRP-541 - Template - Involvement of Prisoners in a Research Project to the MSU Additional Study Information SmartForm page.* • *Upload the investigator brochure to the Supporting Documents SmartForm page* • *Upload the MRI Screening Form – Women to the Supporting Documents SmartForm page.* • *Upload the translation of instrument(s) provided to non-English speaking subjects to the Supporting Documents SmartForm page.* • *Upload the curriculum vitae(s) when research is more than minimum risk to the Supporting Documents SmartForm page.* • *Upload case report forms to the Supporting Documents SmartForm page.* • *Upload the Non-MSU Employee Conflict of Interest Disclosure Form to the Supporting Documents SmartForm page.* • *Upload any other pertinent documents related to the proposed research study to the Supporting Documents SmartForm page*