Woebot for Substance Use Disorders Phase 2 RCT: Digitally Delivered Intervention for Reducing Problematic Substance Use

NCT ID: 04925570

March 17, 2023

Title : Woebot for Substance Use Disorders Phase 2 RCT: Digitally Delivered Intervention for Reducing Problematic Substance Use (SU sIRB) Short name: Anchor Study

Approval Period: 03/17/2023 - 05/11/2023

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Modification

1. Summarize your proposed changes.

(a) This modification will assist with addressing the issue report # IRB-58725-1.
1) Updated message templates. Changes are tracked.
2) Updated screening questionnaire to include email verification within the survey platform. Changes are tracked.
3) DOB will also be asked at each follow up survey to verify identity.
[redacted]
6) 2/22/23: Added updated templates to Protocol Information section 16: Phone script, Resources, Automated emails.

(b) To date: 122 have completed ICF, and 111 have been randomized.

(c) Temporarily closed to enrollment until this modification is approved.

(d) None. Consent form has not changed. Protocol Information sections 13 and 15 has been updated to include the Qualtrics platform for the screening consent.

(e) N/A.

2. Indicate Level of Risk

No Change

3. Update the Conflict of Interest (COI) section if any changes in COI have been made since the last protocol submission.

N Is there a change in the conflicting interest status for any existing personnel on this protocol?

Protocol Director

Name		Degree (Program/year if student)		Position, e.g. Assistant Professor, Resident, etc.
[redacted]		[redacted]		[redacted]
Department		**Phone**		**E-mail**
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CITI Training current	[redacted]			

Admin Contact

Name		Degree (Program/year if student)		Position, e.g. Assistant Professor, Resident, etc.
[redacted]		[redacted]		[redacted]
Department		**Phone**		**E-mail**
[redacted]	[redacted]	[redacted]		[redacted]

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[redacted]				
CITI Training current				[redacted]

Investigator

Name		**Degree (Program/year if student)**		**Position, e.g. Assistant Professor, Resident, etc.**
Department		**Phone**		**E-mail**
CITI Training current				

Other Contact

Name [redacted]		**Degree (Program/year if student)** [redacted]		**Position, e.g. Assistant Professor, Resident, etc.** [redacted]
Department [redacted]	[redacted]	**Phone** [redacted]		**E-mail** [redacted]
CITI Training current				[redacted]

Academic Sponsor

Name		**Degree (Program/year if student)**		**Position, e.g. Assistant Professor, Resident, etc.**
Department		**Phone**		**E-mail**
CITI Training current				

Other Personnel

Name [redacted]		**Degree (Program/year if student)** [redacted]		**Position, e.g. Assistant Professor, Resident, etc.** [redacted]
Department		**Phone**		**E-mail** [redacted]
CITI Training current				[redacted]

Name [redacted]		**Degree (Program/year if student)**		**Position, e.g. Assistant Professor, Resident, etc.**
Department [redacted]		**Phone**		**E-mail** [redacted]
CITI Training current				[redacted]

Participant Population(s) Checklist **Yes/No**

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• Children (under 18)	N
• Pregnant Women and Fetuses	N
• Neonates (0 - 28 days)	N
• Abortuses	N
• Impaired Decision Making Capacity	N
• Cancer Subjects	N
• Laboratory Personnel	N
• Healthy Volunteers	N
• Students	N
• Employees	N
• Prisoners	N
• Other (i.e., any population that is not specified above)	Y
• International Participants	N

Please enter the countries separated by comma

Study Location(s) Checklist

	Yes/No
• Stanford University	Y
• Clinical & Translational Research Unit (CTRU)	
• Stanford Hospital and Clinics	
• Lucile Packard Children's Hospital (LPCH)	
• VAPAHCS (Specify PI at VA)	
• Other (Click ADD to specify details)	

General Checklist

Multi-site

	Yes/No
• Is this a multi-site study? A multi-site study is generally a study that involves one or more medical or research institutions in which one site takes a lead role.(e.g., multi-site clinical trial)	N

Collaborating Institution(s)

	Yes/No
• Are there any collaborating institution(s)? A collaborating institution is generally an institution that collaborates equally on a research endeavor with one or more institutions.	Y

Institution Name	Contact Name	Contact Phone	Contact Email	Permission?	Engaged?
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Cancer Institute	**Yes/No**
• Cancer-Related Studies (studies with cancer endpoints), Cancer Subjects (e.g., clinical trials, behavior/prevention) or Cancer Specimens (e.g., blood, tissue, cells, body fluids with a scientific hypothesis stated in the protocol).	N

Clinical Trials	**Yes/No**
• Investigational drugs, biologics, reagents, or chemicals?	N
• Commercially available drugs, reagents, or other chemicals administered to subjects (even if they are not being studied)?	N
• Investigational Device / Commercial Device used off-label?	Y
• IDE Exempt Device (Commercial Device used according to label, Investigational In Vitro Device or Assay, or Consumer Preference/Modifications/Combinations of Approved Devices)	N
• Will this study be registered on? clinicaltrials.gov? (See Stanford decision tree)	Y
• Who will register for ClinicalTrials.gov? NCT#	N

Tissues and Specimens	**Yes/No**
• Human blood, cells, tissues, or body fluids (tissues)?	N
• Tissues to be stored for future research projects?	N
• Tissues to be sent out of this institution as part of a research agreement? For guidelines, please see https://sites.stanford.edu/ico/mtas	N

Biosafety (APB)	**Yes/No**
• Are you submitting a Human Gene Transfer investigation using a biological agent or recombinant DNA vector? If yes, please complete the Gene Transfer Protocol Application Supplemental Questions and upload in Attachments section.	N
• Are you submitting a Human study using biohazardous/infectious agents? If yes, refer to the Administrative Panel on BioSafety website prior to performing studies.	N
• Are you submitting a Human study using samples from subjects that are known or likely to contain biohazardous/infectious agents? If yes, refer to the Administrative Panel on BioSafety website prior to performing studies.	N

Human Embryos or Stem Cells	**Yes/No**
• Human Embryos or Gametes?	N
• Human Stem Cells (including hESC, iPSC, cancer stem cells, progenitor cells)	N

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Veterans Affairs (VA)	**Yes/No**
• The research recruits participants at the Veterans Affairs Palo Alto Health Care System(VAPAHCS).	N
• The research involves the use of VAPAHCS non-public information to identify or contact human research participants or prospective subjects or to use such data for research purposes.	N
• The research is sponsored (i.e., funded) by VAPAHCS.	N
• The research is conducted by or under the direction of any employee or agent of VAPAHCS (full-time, part-time, intermittent, consultant, without compensation (WOC), on-station fee-basis, on-station contract, or on-station sharing agreement basis) in connection with her/his VAPAHCS responsibilities.	N
• The research is conducted using any property or facility of VAPAHCS.	N

Equipment	**Yes/No**
• Use of Patient related equipment? If Yes, equipment must meet the standards established by Biomedical Engineering (BME) (650-725-5000)	N
• Medical equipment used for human patients/subjects also used on animals?	N
• Radioisotopes/radiation-producing machines, even if standard of care? http://www.stanford.edu/dept/EHS/prod/researchlab/radlaser/Human_use_guide.pdf More Info	N

Payment	**Yes/No**
• Subjects will be paid/reimbursed for participation? See payment considerations.	Y

Funding	**Yes/No**
• Training Grant?	N
• Program Project Grant?	N
• Federally Sponsored Project?	Y
• https://doresearch.stanford.edu/policies/research-policy-handbook/definitions-and-types-agreements/specialized-categories-sponsored-p Industry Sponsored Clinical Trial?	N

Funding

Funding - Grants/Contracts

Funding Administered By : [redacted]
SPO # (if available) : [redacted]
Grant # (if available) :
Funded By (include pending) : [redacted]
Principal Investigator : [redacted]

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Grant/Contract Title if different from Protocol Title :

RCT of Woebot for Treating Substance Use Disorders

Y For Federal projects, are contents of this protocol consistent with the Federal proposal?
N Is this a Multiple Project Protocol (MPP)?
N Is this protocol under a MPP?

Funding - Fellowships

Gift Funding

Dept. Funding

Other Funding

Resources :

a) Qualified staff.

Please state and justify the number and qualifications of your study staff.

[redacted]

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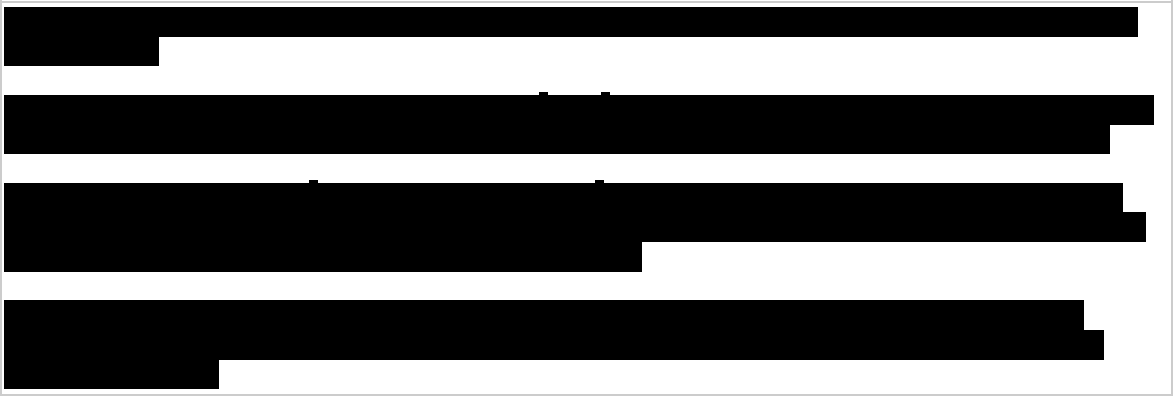

b) Training.

Describe the training you will provide to ensure that all persons assisting with the research are informed about the protocol and their research-related duties and functions.

All study staff maintain up-to-date CITI certification and current knowledge of the research literature on use of digital health technologies for health behavior change.

c) Facilities.

Please describe and justify.

Dr. Prochaska has a faculty office at Stanford University in the Medical School Office Building with full computing resources needed for the trial.

All study data are gathered on a HIPAA compliant web platform that resides behind Stanford security firewalls and has been tried and tested by the University for several years, thus actual risk from data breach for study data is low.

d) Sufficient time.

Explain whether you will have sufficient time to conduct and complete the research. Include how much time is required.

Dr. Prochaska's faculty time is 100% devoted to research and this is one of her funded projects to which she dedicates her time.

e) Access to target population.

Explain and justify whether you will have access to a population that will allow recruitment of the required number of participants.

This NIDA-funded project is a collaboration with Woebot, a technology start up that is using artificial intelligence (AI) in a bot to deliver tailored messaging to improve mental health.

Participants will be recruited through a wide variety of strategies including but not limited to paid online advertising (e.g., sidebar Gmail and Yahoo advertisements); third party vendors such as Qualtrics panels, Clara Health, Map & Story, Splash Clinical; flyers; social media; free online and email advertising (e.g., Dr Prochaska's laboratory webpage, email listservs of digital health companies and the Stanford University student, faculty, and staff community); participants from previous studies who have interest in other studies; and national outpatient clinics with substance abuse programming including Stanford's Department of Psychiatry and Behavioral Sciences' Dual Diagnosis Clinic.

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Dr. Prochaska's team has extensive experience in recruiting research participants who use substances, including for online studies and has published on best practices.

f) Access to resources if needed as a consequence of the research.

State whether you have medical or psychological resources available that participants might require as a consequence of the research when applicable. Please describe these resources.

Foreseeable risks to subjects include the possibility that some assessment questions and/or treatment procedures may be upsetting to subjects. Experience at Stanford with similar populations has indicated that the risk of emotional upset during the assessments is low and if it occurred, the upset would likely not be serious in nature and temporary. Such risks will be minimized by the thoughtful selection of questionnaires. Potential participants will also be informed that they may drop out of the study at any time and if requested, appropriate treatment referrals would then be given.

g) Lead Investigator or Coordinating Institution in Multi-site Study.

Please explain (i) your role in coordinating the studies, (ii) procedures for routine communication with other sites, (iii) documentation of routine communications with other sites, (iv) planned management of communication of adverse outcomes, unexpected problems involving risk to participants or others, protocol modifications or interim findings.

1. Purpose

a) In layperson's language state the purpose of the study in 3-5 sentences.

This study aims to validate W-SUDs as a digitally-delivered substance use disorder program through a fully-powered randomized control trial that will test the comparative efficacy of the mobile-app based substance use disorder program to reduce substance use relative to an education-only control condition, which has no cognitive behavioral therapy and the content is not delivered through a conversational user interface.

b) State what the Investigator(s) hope to learn from the study. Include an assessment of the importance of this new knowledge.

The COVID-19 pandemic introduced significant, unprecedented, and immediate psychological challenges to all, including individuals with substance use disorders (SUDs). The impact upon individuals with SUDs will be multifaceted and far reaching. In terms of physical health, experts postulate that individuals with SUDs may be at greater risk of mortality from COVID-19 given the variety of pre-existing physical health conditions this group has traditionally faced (i.e., COPD, cardiovascular disease, general poor respiratory health). In addition, the pandemic will beget significant emotional and psychiatric disruption from the multifaceted impact of the illness. Such responses may include large-scale grief, loneliness, fear, loss of life experiences, constrained

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or frank inability to work, financial instability, risk of contagion, overwhelmed hospitals, limited access to recovery programs and reduced or significantly changed mental health service provision from clinics.

[redacted] Woebot for Substance Use Disorders (W-SUDs) is a 2 phase SBIR industry-academic partnership between Woebot Labs Inc. and Stanford University that aims to develop and evaluate the evidence of the novel digital therapeutic, delivered by an artificial intelligence (AI)-powered, automated conversational agent named Woebot which is embedded in the therapeutic W-SUDs.

Milestones for Phase I included the development (e.g., content and engineering) of W-SUDs and piloting its preliminary efficacy, feasibility and acceptability among n=101 individuals with SUD.

Phase I (N=101) has concluded and a manuscript is in submission. In this study, W-SUDs was feasible to deliver, engaging, and acceptable; and associated with significant improvements in substance use, confidence, cravings, depression, and anxiety. Study attrition was high.

The supplemental study (W-C19) is a randomized control trial with a wait-list control condition. This study aimed to expand understanding of W-SUDs' performance among users experiencing SUDs whilst contributing to our overall understanding of COVID-19's impact upon this population. The intervention had concluded with N=180 participants enrolled. Experiencing worsened mental health symptoms during COVID-19 was associated with more substance use problems and depression and anxiety symptoms. Pandemic disruptions may exacerbate preexisting substance use problems.

Phase II will evaluate the efficacy of W-SUDs in a large scale RCT relative to an education-only control condition. Primary outcomes will be measures of the quantity and frequency of substance use including, number of substance use occasions, heavy drinking days (if applicable), percent days abstinent. Additionally, phase II will evaluate whether W-SUDs results in a greater reduction in substance-related problems than Education Only control and explore: Does engagement with W-SUDs, relative to education-only control (a) improve symptoms of depression and anxiety (b) improve work productivity (i.e. reduce presenteeism/absenteeism), (c) reduce cravings, (d) improve situational confidence. Phase II will also allow the team to learn more about the population interested in digitally delivered interventions.

Impact
Immediate access to a digital therapeutic in a resource constrained, social distance healthcare ecosystem amidst growing psychological challenges in this already vulnerable and underserved population. Elements of our W-C19 program have already been integrated into W-SUDs because we felt that it was timely and appropriate to address users' concerns about the pandemic and demonstrated that Woebot was 'intelligent' to the current crisis.

c) Explain why human subjects must be used for this project. (i.e. purpose of study is to test efficacy of investigational device in individuals with specific condition; purpose of study is to examine specific behavioral traits in humans in classroom or other environment)

The purpose of this study is to test the efficacy of a mobile-application delivered substance use disorder intervention compared to an education only control group.

2. Study Procedures

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a) Please SUMMARIZE the research procedures, screening through closeout, which the human subject will undergo. Refer to sections in the protocol attached in section 16, BUT do not copy the clinical protocol. Be clear on what is to be done for research and what is part of standard of care.

Updated consent forms and HIPAA authorization will be uploaded before the start of recruitment. Ads, questionnaires, etc. will be uploaded for review before recruitment begins.

Recruitment will be a joint effort by Stanford University and Woebot Labs. Woebot may communicate the research opportunity through social media channels, and third party recruitment groups (e.g. Splash Clinical, Map & Story, Clara Health). The Stanford team may recruit through Qualtrics panels, ResearchMatch, listservs, and contact participants from previous research studies who are interested in future studies. Working with Dr. Prochaska's research team at Stanford, the Woebot team will take part in mapping out message development for the intervention and Woebot's IT team will lead the app programming (including build and quality control/de-bugging). Woebot will collect user data via the Woebot app (automatic process), which will be provided to the Stanford team. The Woebot team will participate in disseminating the study findings via publications and presentations.

Participants from recruitment channels will go through and screening consent and eligibility screener, and if eligible, will be asked to participate in their randomized group for 8 weeks and answer questionnaires administered at the beginning, mid-intervention (4-week), end of intervention (8-week), and post intervention (12-week). Informed consent form will appear after screening eligible, and must be signed before the baseline survey can be accessed. Computer randomization will occur after the baseline survey, and instructions for their group will be sent out. Woebot will rely on Stanford University IRB for review of this study.

The Stanford team will lead the study evaluations including the study measures, data collection (baseline and follow-ups at the 4-week, 8-week, and 12-week/30 days post treatment marks), data analyses, and writing up of study findings for dissemination. Participants will be randomized to condition via the online assessment platform, which has the functionality to allow randomization to one of two groups. Those randomized to W-SUDs (group 1) or education control (group 2) will see a private, email or study-only page pertaining to their group. To minimize bias and maximize study validity, group blinding will be in place; Participants should not know what the other intervention involves. Instructions will be provided for each group. A study debrief regarding group blinding will be provided to participants after the final survey. If the final survey is not completed, the debrief will be provided a month after the final survey was due.

Woebot is responsible for app management, study payments (e.g. purchasing Amazon e-gift cards for participant compensation). Participant management is on the Stanford side, including sending out the compensation, kits, etc. If the participant ends up contacting Woebot about the app or for a study related question, that message is passed on to the Stanford team or answered by the Woebot team if they have the answers.

In order to better understand what specific W-SUDs content the participants like, Lesson Completion Rates and Content Rating Metrics will be analyzed. Descriptive statistics will be used for the following scales: Usage Rating Profile Intervention (UPRI)-Acceptability, Usage Rating Profile Intervention (UPRI)-Feasibility, and Client Satisfaction Questionnaire (CSQ-8). Such descriptive statistics will provide a summary index of how likable the content and program was overall. Tests involving statistical significance will be used to assess the intervention's impact from baseline to EOT.

Utilizing study results as described above, the research team will learn the efficacy of a digital substance use therapeutic compared to an education only control group. The intent is to utilize and leverage what was learned in this study to provide an intervention in a time where in person services are discouraged and to see if the intervention is more beneficial than a nonactive

treatment condition.

Data flow:
Participants provide data by completing surveys. The Stanford team is the recipient of this data. Emails are shared with the Woebot team for the interventions, payment, and cross-checking for intervention contamination (i.e. commercial Woebot app use, WSUDs program use but are supposed to be in Education only group). Intervention contamination information will be shared by Woebot to Stanford. Participants also provide data by interacting with the Woebot app. Woebot Labs will share user data with the Stanford team, who will link the data to survey responses. The Stanford team will analyze the data and then share analyzed data with the Woebot team.

Quality checks (IRB modification 8/26/2022):
Protection against bot responses:
A question to detect bot activity will be in the screening questionnaire. This question will be a hidden survey field (i.e. human respondents will not be able to see the question), but a bot can pick up this question and answer. If there is an answer, the study team will consider the survey response to be from a bot and thus ineligible for participation. Set up procedures for REDCap Cloud are attached in Protocol Information section 16.

Protection against international respondents:
[redacted] the study team will implement a check on IP Address using https://IPhub.info to: 1) Prevent responses from international IP addresses, which indicate a respondent from outside the U.S. (exclusion criteria); and 2) Block respondents from using a virtual private network (VPN) to take the survey, as the use of a VPN allows for concealment of international IP addresses. This IP address check will apply to all who screen for eligibility. Attached in Protocol Information section 16 is an updated version of survey, with a new message to let respondents know about the IP address check. No changes are needed to the screening consent form, as it includes collection of IP address.

Rationale for the IP address check: This study is completely remote and will be using social media recruitment methods, where other studies have encountered survey responses from spammers and bots. Fraudulent survey responses to online surveys have been problematic, as highlighted in the manuscript found on DOI: 10.1017/psrm.2020.6
Implementation of the VPN check is based on the guidelines presented in the following manuscript on https://ssrn.com/abstract=3327274

The IP address check can be done manually by study staff by uploading a CSV file of IP addresses onto IPhub.info. The study team proposes to check IP addresses on IPhub.info after a potential respondent passes the screening questionnaire, before the ICF is sent out. Respondents who do not pass this check will not be considered eligible for the study and will not receive an invite to the ICF.

The screening questionnaire will include a message about this check after the screening consent, and if screened eligible, a reminder that the IP address will be checked.

Protection against spamming:
Respondents who passed the screening questionnaire, but share an IP address with one or more respondents who passed screening, may be the same respondent using different emails. These respondents will not receive an invite to the ICF.

Protection against duplicates:
Respondents with the same email or phone number will not receive an invite to the ICF.

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Quality check before randomization:
If 20% or more of the responses answered in the baseline survey are "Prefer to not respond/Prefer to not answer", these respondents are not providing informative data for the study and can be removed from participation.

b) Explain how the above research procedures are the least risky that can be performed consistent with sound research design.

Given that the research aims to enroll a low-treatment seeking population, we do not envisage that participation in the study will be associated with elevated risk.

However, some risk is always present in studies that involve human participants.

Such risk may include the following:
Risk from breach of protected health information.
Possibly the greatest risk is from a leak of health information. All study data are gathered on a HIPAA compliant web platform that resides behind Stanford security firewalls and has been tried and tested by the University for several years, thus actual risk from data breach for study data is low. In addition, the Woebot application encrypts all message data exchanged between service users and Woebot, and collects minimal protected health information. Emails are hashed and not kept along side message data so that they are not easily associated with each other. [redacted]

Risk from answering questions that may be emotionally upsetting.
Experience at Stanford with similar populations has indicated that the risk of emotional upset during the assessments is low and if it occurred, the upset would likely not be serious in nature and temporary. Such risks will be minimized by the thoughtful selection of questionnaires. Potential participants will also be informed that they may drop out of the study at any time and if requested, appropriate treatment referrals would then be given.

Risk of treatment avoidance due to engagement with either of the randomized interventions. In both interventions it is explicitly stated in the consent form that the service should not be used in place of traditional treatment. In the case of the W-SUDs intervention, Woebot is designed to hold individuals accountable for pursuing additional options in conditions of unchanged symptoms for a prolonged amount of time (4 weeks). In addition, Woebot will invite the user to consider what seeking additional services would look like.

c) State if deception will be used. If so, provide the rationale and describe debriefing procedures. Since you will not be fully informing the participant in your consent process and form, complete an alteration of consent (in section 13). Submit a debriefing script (in section 16).

There will be intervention group blinding to maximize validity and minimize bias (i.e. reducing factors may affect the study outcomes). The research team does not know if W-SUDs is more effective than an education only control group. Group blinding minimizes preconceived expectations for each group and behaviors as a result of those expectations. To keep the group blinding effective, the groups are not fully described in the consent form, and full details of the group intervention a participant is randomized to will

be provided after randomization.

A debrief document is attached in Section 16 and will be provided to participants after their study period. For those who complete the final survey, it'll be provided by email soon after. For those who do not complete the final survey, the information will be provided by email a month after the final survey (at 12-weeks) is due. This is to allow sufficient opportunity for the final survey to be completed before the timing of the final survey is considered "late". No participant will be given the debrief after the intervention period at 8-weeks since the study will also be observing sustained change post-intervention (between 8-weeks and 12-weeks).

d) State if audio or video recording will occur. Describe what will become of the recording after use, e.g., shown at scientific meetings, erased. Describe the final disposition of the recordings.

No audio or video recordings will occur.

e) Describe alternative procedures or courses of treatment, if any, that might be advantageous to the participant. Describe potential risks and benefits associated with these. Any standard treatment that is being withheld must be disclosed in the consent process and form. (i.e. standard-of-care drug, different interventional procedure, no procedure or treatment, palliative care, other research studies).

Alternative Treatments for SUDSs include in-person individual and group forms of psychotherapy as well as Alcoholics Anonymous and Narcotics Anonymous.

All alternative options will be provided if she/he/they wishes to engage in an alternative treatment rather than the proposed study. However, given that previous Woebot study results are promising, the proposed line of treatments would appear to be appropriate and acceptable interventions for SUDs.

No standard treatment is being withheld.

f) Will it be possible to continue the more (most) appropriate therapy for the participant(s) after the conclusion of the study?

Yes

g) Study Endpoint. What are the guidelines or end points by which you can evaluate the different treatments (i.e. study drug, device, procedure) during the study? If one proves to be clearly more effective than another (or others) during the course of a study, will the study be terminated before the projected total participant population has been enrolled? When will the study end if no important differences are detected?

The endpoint will be the follow-up 30 days after end-of-treatment. This will end their study participation and study staff will do analysis.

3. Background

a) Describe past experimental and/or clinical findings leading to the formulation of the study.

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[redacted]

W-SUDs Pilot for the phase II RCT (IRB 62053): Preliminary data from this study shows that there are feasibility issues with the study including time demand on personnel, complications introduced with the Adobe Sign process (multiple emails to each participant, difficulty with the secure email process, varying delays between screening to consent to baseline survey), MINI interviewing scheduling challenges, and delays between baseline completion and randomization. Based on recruitment data so far, over 1574 screening attempts were made (responses at 0% do not get recorded in Qualtrics), with 128 respondents passing the screening. Of those that have passed, 23 (18% of the 128) have signed informed consent, and 18 have completed the baseline survey. 1 respondent was removed due to no use of substances in the past 30 days. 12 (71% of the 17 completing baseline survey) have completed the MINI interview.

The W-SUDs phase II study will evaluate the efficacy of W-SUDs in a large scale RCT relative to an education-only control condition, where there is no active treatment. To diversify the sample, we will utilize Qualtrics panels and set quotas. We'll utilize retention strategies in the W-C19 study to improve retention.

b) Describe any animal experimentation and findings leading to the formulation of the study.

N/A

[redacted]

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[redacted]

5. Devices

a) Please list in the table below all Investigational Devices (including Commercial Devices used off-label) to be used on participants.

5. 1 Device Name : Woebot

Describe the device to be used.

Woebot, a Conversational Agent (CA) instantaneously available 24 hours per day, 7 days per week, 'checks in' with users. Using conversational tones, it encourages mood tracking and delivers general psychoeducation as well as tailored empathy, cognitive behavior therapy (CBT)-based behavior change tools, and behavioral pattern insight. Woebot's app-based platform and user-centered design philosophy makes it an optimal modality for Substance Use Disorders (SUD) treatment delivery; it offers immediate, evidence-based tailored support in the patient's peak moment of craving.

Manufacturer : **Woebot Labs**

Risk : **Non-significant**

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Y I confirm the above are true.

Rationale for the device being non-significant risk:

The research aims to enroll a low-treatment seeking population, and employ randomization to two low-risk interventions, we do not envisage that participation in the study will be associated with elevated risk.

Sponsor of Project

Indicate who is responsible for submitting safety reports to the FDA:

Y The sponsor is the device manufacturer.

Ordering, Storage and Control

To prevent the device being used by a person other than the investigator, and in someone other than a research participant: Confirm that the device will be handled according to the SHC/LPCH policy for Investigational New Devices or as appropriate. If no, please provide an explanation. :

Y Confirm?

b) Please list in the table below all IDE Exempt Devices (Commercial Device used according to label, Investigational In Vitro Device or Assay, or Consumer Preference/Modifications/Combinations of Approved Devices) to be used on participants.

6. Drugs, Reagents, or Chemicals and Devices

a) Please list in the table below all investigational drugs, reagents or chemicals to be administered to participants.

b) Please list in the table below all commercial drugs, reagents or chemicals to be administered to participants.

7. Medical Equipment for Human Subjects and Laboratory Animals

If medical equipment used for human patients/participants is also used on animals, describe such equipment and disinfection procedures.

N/A

8. Participant Population

a) State the following: (i) the number of participants expected to be enrolled at Stanford-affiliated site(s); (ii)the total number of participants expected to enroll at all sites; (iii) the type of participants (i.e. students, patients with certain cancer, patients with certain cardiac condition) and the reasons for using such participants.

N=400 (nationally) will be invited to participate in this study and entered into the study on a rolling basis. Inclusion criteria include: all genders aged 18-65 years, meet CAGEAID score of 2+ (WSUDs is designed for substance use); access to the apps on smartphone, be available and committed to engage with app and complete assessments, be willing to provide working email address (to distribute incentives), working

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telephone number (for interview portion and follow ups), and be literate in English (as educational materials and W-SUDs conversational and video materials will be in English). Exclusion criteria include: pregnancy (as W-SUDs will not be specifically developed to address the unique needs of this population), history of severe drug/alcohol use, opioid misuse without medication-assisted treatment, and suicide attempt or opioid overdose within the past year.

b) State the age range, gender, and ethnic background of the participant population being recruited.

Recruitment efforts will seek to enroll a demographically diverse sample age 18-65. Substance disorders are prevalent in individuals of all genders, therefore all genders will be recruited as participants in the proposed study.

c) State the number and rationale for involvement of potentially vulnerable subjects in the study (including children, pregnant women, economically and educationally disadvantaged, decisionally impaired, homeless people, employees and students). Specify the measures being taken to minimize the risks and the chance of harm to the potentially vulnerable subjects and the additional safeguards that have been included in the protocol to protect their rights and welfare.

These populations are not being targeted but are also not excluded from the study. Exception: Pregnant women and children will be screened out.

d) If women, minorities, or children are not included, a clear compelling rationale must be provided (e.g., disease does not occur in children, drug or device would interfere with normal growth and development, etc.).

Exclusion of Pregnant Women: Pregnancy (as W-SUDs will not be specifically developed to address the unique needs of this population). Exclusion of Children. The proposed study will include individuals between 18-65 years of age. Persons younger than 18 will not be included in the study, as the proposed substance disorder treatments were not designed for nor tested among youth and the characterization of SUD in youth differs in meaningful ways from that in adults. Given that Woebot has not yet been tested among youth, the proposed research is focused on those aged 18 and older.

e) State the number, if any, of participants who are laboratory personnel, employees, and/or students. They should render the same written informed consent. If payment is allowed, they should also receive it. Please see Stanford University policy.

0

f) State the number, if any, of participants who are healthy volunteers. Provide rationale for the inclusion of healthy volunteers in this study. Specify any risks to which participants may possibly be exposed. Specify the measures being taken to minimize the risks and the chance of harm to the volunteers and the additional safeguards that have been included in the protocol to protect their rights and welfare.

0 healthy volunteers. 400 volunteers for the main trial will have endorsed a substance use concern for problematic use and screened out if pregnant during recruitment. Other than these health implications, participants will otherwise be healthy volunteers and will not be exposed to health risks through their participation.

g) How will you identify and recruit potential participants about the research study? (E.g., by: Honest Broker or other https://researchcompliance.stanford.edu/participantengagement Research Participation services; chart review; treating physician; ads). All final or revised recruitment materials, flyers, etc. must be submitted to the IRB for review and approval before use. You may not contact potential participants prior to IRB approval. See Advertisements: Appropriate Language for Recruitment Material.

Recruitment: For this study, Woebot Labs' may post study advertisements and recruit via their already active internet channels including Twitter (over 2,000 followers), LinkedIn (over 400 followers), and Facebook (over 16,500 followers). To supplement recruiment, Woebot Labs' may post on Craigslist, Nextdoor, Google Ads, and on Reddit through relevant subreddits with written permission from the subreddits' moderators. Woebot may email clinics. Woebot may also post physical flyers and the Stanford team may post on the Stanford Staffers listserv. The Stanford team may recruit from the WELL cohort via

newsletter, with permission. Stanford staff may post in other listservs with permission. The Stanford team may recruit participants from other studies who have indicated interest in other studies. The team may use Qualtrics panels, ResearchMatch (online health research tool funded by NIH to match volunteers with studies), the Stanford COVID-19 directory to recruit, and other third party recruitment vendors (e.g. Splash Clinical, Map & Story, Clara Health). [redacted] In regards to their specific substance use behaviors over the previous month, 22% of users reported having 5 or more alcoholic drinks in a row within a couple of hours (i.e., binge use), and 5% endorsed using non-prescription drugs. Woebot Labs has used these channels for previous research participation invitations with success.

Minor editing changes may be made to recruitment materials to enhance clarity.

Participants will be asked for their age during the screener. If ineligible, they will be not be able to participate in the study. We will ask for date of birth in the questionnaire after the signed consent to confirm that the participant is not underage. This is standard best practice for use of the program and for other online research studies.

IRB modification 8/26/2022: Quality checks will be implemented prior to the ICF and before randomization. These quality checks include protection against bots, international respondents, spamming,and duplicates. Baseline survey respondents with 20% or more "Prefer not to answer" responses will not be randomized.

IRB modification 12/19/2022: DOB will be asked at each survey to verify identity.

h) Inclusion and Exclusion Criteria.

Identify inclusion criteria.

Inclusion Criteria:
Eligible participants for this trial must:
1. Have a smartphone
2. Endorse a substance use concern
3. Be between 18 and 65 years of age
4. Be available and committed to engage with the Woebot app
5. Be literate in English.(This is required for inclusion because all materials will be in English).

Identify exclusion criteria.

Exclusion Criteria:
1. Pregnancy (as W-SUDs will not be specifically developed to address the unique needs of this population)
2. Suicide attempt within the past year (12 months)
3. Symptoms of severe drug/alcohol history: History of delirium tremens; Experiencing hypertension, drenching sweats, seizures or confusion after stopping alcohol or drugs; Liver trouble (cirrhosis or hepatitis); Convulsions or GI bleeding due to drug/alcohol use
4. Opioid overdose within the past year (12 months)
5. Opioid misuse without medication-assisted treatment
6. Not residing in the U.S.
7. Ever used Woebot

i) Describe your screening procedures, including how qualifying laboratory values will be obtained. If you are collecting personal health information prior to enrollment (e.g., telephone screening), please request a waiver of authorization for recruitment (in section 15).

Screening
IRB modification 3.3.23: There will be a brief internet delivered (via Qualtrics or REDCap Cloud) screener that will ascertain if individuals who express interest in participating in the study meet inclusion criteria. The screener-battery will include the CAGE Questions Adapted to Include Drug Use (CAGE-AID); The sum of these 4 items creates a score that is used to determine eligibility based on level of problematic use.

Please note that these items refer to alcohol or drug use and do not specify illicit drug use. The following measures will not be used in full, just a few selected items from these valid and reliable scales: Drug Abuse Screening Test (DAST-10), Michigan Alcohol Screening Test (MAST), Psychosis Screening Questionnaire (PSQ), and relevant demographic questions (i.e., age, pregnancy status, suicide or overdose within the past year). The study team will ask about alcohol and drug use broadly. Illicit drug use will not be specifically asked. The more sensitive items (such as suicide attempt and psychosis) will be be grouped in a larger list of ineligibility criteria. Those who do not meet criteria will be welcomed to begin using the generic (non-SUD focused) Woebot and the website without restriction but will not be enrolled into the study. In addition, additional substance treatment resources will be provided.

j) Describe how you will be cognizant of other protocols in which participants might be enrolled. Please explain if participants will be enrolled in more than one study.

Consent form will ask whether the participant is currently enrolled in any additional studies.

k) Payment/reimbursement. Explain the amount and schedule of payment or reimbursement, if any, that will be paid for participation in the study. Substantiate that proposed payments are reasonable and commensurate with the expected contributions of participants and that they do not constitute undue pressure on participants to volunteer for the research study. Include provisions for prorating payment. See payment considerations

Phase II funding approved. For each of the 400 participants: $25 for completing the baseline survey; $25 for 4-week survey completion; $25 for EOT (8-week) assessment completion; $25 for the 12-week (30 days post EOT) assessment completion. Total amount possible per participant is $100.

l) Costs. Please explain any costs that will be charged to the participant.

There will be no cost to participants.

m) Estimate the probable duration of the entire study. Also estimate the total time per participant for: (i) screening of participant; (ii) active participation in study; (iii) analysis of participant data.

Total duration for the research team is estimated to be 11 months. Content development is ready. Recruitment for about 5 months. Participation in the study is estimated to be 3 months. Estimated time for screening is around 5 minutes; Each survey estimated to be 15-30min. Study intervention is 8-weeks/2 months. Active participation is 3 months with follow up surveys at the 4- week, 8- week, and 12-week marks.
Data analysis is estimated to be 3 months.

9. Risks

a) For the following categories include a scientific estimate of the frequency, severity, and reversibility of potential risks. Wherever possible, include statistical incidence of complications and the mortality rate of proposed procedures. Where there has been insufficient time to accumulate significant data on risk, a statement to this effect should be included. (In describing these risks in the consent form to the participant it is helpful to use comparisons which are meaningful to persons unfamiliar with medical terminology.)

The risks of the Investigational devices.

N/A

The risks of the Investigational drugs. Information about risks can often be found in the Investigator's brochure.

N/A

The risks of the Commercially available drugs, reagents or chemicals. Information about risks can often be found in the package insert.

N/A

The risks of the Procedures to be performed. Include all investigational, non-investigational and non-invasive procedures (e.g., surgery, blood draws, treadmill tests).

N/A

The risks of the Radioisotopes/radiation-producing machines (e.g., X-rays, CT scans, fluoroscopy) and associated risks.

N/A

The risks of the Physical well-being.

N/A

The risks of the Psychological well-being.

Potential Upset due to Survey Questions: Foreseeable risks to subjects include the possibility that some assessment questions and/or treatment procedures may be upsetting to subjects. Experience at Stanford with similar populations has indicated that the risk of emotional upset during the assessments is low and if it occurred, the upset would likely not be serious in nature and temporary. Such risks will be minimized by the thoughtful selection of questionnaires. Potential participants will also be informed that they may drop out of the study at any time and if requested, appropriate treatment referrals would then be given.

There is possible risk of discomfort from losing access to the study intervention at the end of the 8-week period.

Possible risks of Woebot: Woebot is not intended to replace standard of care and should not be used in place of standard treatment.

Neither of the intervention groups are crisis services.

The risks of the Economic well-being.

N/A

The risks of the Social well-being.

Potential loss of confidentiality.

Overall evaluation of Risk.

Low - innocuous procedures such as phlebotomy, urine or stool collection, no therapeutic agent, or safe therapeutic agent such as the use of an FDA approved drug or device.

b) If you are conducting international research, describe the qualifications/preparations that enable you to both estimate and minimize risks to participants. Provide an explanation as to why the research must be completed at this location and complete the [LINKFORINTERNATIONALREASEARCHFORM] International Research Form. If not applicable, enter N/A.

N/A

c) Describe the planned procedures for protecting against and minimizing all potential risks. Include the means for monitoring to detect hazards to the participant (and/or to a potential fetus if applicable). Include steps to minimize risks to the confidentiality of identifiable information.

Given that the research aims to enroll a low-treatment seeking population, we do not envisage that participation in the study will be associated with elevated risk. We are not assessing suicidal ideation in our questionnaires. During the eligibility screener, those who have had a suicide attempt within the past year will be excluded from the study. It is not feasible to confirm the responses by participants to the questionnaires in real time. However, some risk is always present in studies that involve human participants. Such risk may include the following:

1. (IRB Modification 12/19/2022) Data Protection and Privacy: All study data are gathered on a HIPAA compliant web platform that resides behind Stanford security firewalls and has been tried and tested by the University for several years, thus actual risk from data breach for study data is low. All assessments,

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including the screening and four assessment batteries will be administered via a HIPAA compliant survey administration tool commonly used by Stanford University in its clinical trials (Qualtrics, REDCap Cloud). REDCap Cloud has all the capabilities of REDCap and is 21 CFR 11 compliant (https://uit.stanford.edu/guide/riskclassifications). Given the high data protection safeguards embedded within the HIPAA compliant survey administration tool, there is little risk to the subject associated in regards to their privacy and/or confidentiality.
Research material obtained from human subjects will involve behavioral and psychological assessments including self-report questionnaires. All data will be obtained specifically for purposes of this research project. Data that is obtained from the assessments will be stored and protected within REDCap Cloud. Data that is obtained via Woebot will be encrypted and stored on Amazon Web Services (AWS); Woebot Labs data gathering and storage procedures are compliant with both the Health Insurance Portability and Accountability Act (HIPAA) [redacted]. Only members of the research team (PI, Co-PIs, biostatistician, research assistant) will have access to the data.

2. Potential Upset due to Survey Questions: Foreseeable risks to subjects include the possibility that some assessment questions and/or treatment procedures may be upsetting to subjects. Experience at Stanford with similar populations has indicated that the risk of emotional upset during the assessments is low and if it occurred, the upset would likely not be serious in nature and temporary. Such risks will be minimized by the thoughtful selection of questionnaires. Potential participants will also be informed that they may drop out of the study at any time and if requested, appropriate treatment referrals would then be given.

3. Risk of treatment avoidance due to engagement with either of the randomized interventions. In both interventions it is explicitly stated that the service should not be used in place of traditional treatment. [redacted]

4. Risk of suicide: Woebot informs the participant that it is not designed for crisis service. [redacted] Additionally, if anyone is developing or indicating serious thoughts about suicide or harming themselves, it is best practice to call 9-1-1 and/or go to the nearest ER.

d) Explain the point at which the experiment will terminate. If appropriate, include the standards for the termination of the participation of the individual participant Also discuss plans for ensuring necessary medical or professional intervention in the event of adverse effects to the participants.

IRB Modification 12/19/2022: The study will terminate once the 3-month period with all 400 eligible participants has been completed and the analyses run and submitted for publication.

Participants can refuse to participate at any time.

When we learn of a participant's adverse event, the team will report the adverse event and may follow up with the participant for additional information. Resources will be offered. The EOT and 12-week surveys includes questions that assess for SAEs. More details about adverse events are in section e.

e) Data Safety and Monitoring Plan (DSMP). See guidance on Data Safety and Monitoring.

A Data and Safety Monitoring Plan (DSMP) is required for studies that present Medium or High risk to participants. (See Overall Evaluation of Risk above). If Low Risk, a DSMP may not be necessary. Multi-site Phase III clinical trials funded by NIH require the DSM Plan to have a Data Safety

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Monitoring Board or Committee (DSMC or DSMB). The FDA recommends that all multi-site clinical trials that involve interventions that have potential for greater than minimal risk to study participants also have a DSMB or DSMC.

The role of the DSMC or DSMB is to ensure the safety of participants by analyzing pooled data from all sites, and to oversee the validity and integrity of the data. Depending on the degree of risk and the complexity of the protocol, monitoring may be performed by an independent committee, a board (DSMC/DSMB), a sponsor's Data Safety Committee (DSC), a Medical Monitor, a sponsor's safety officer, or by the Protocol Director (PD).

Describe the following:

What type of data and/or events will be reviewed under the monitoring plan, e.g. adverse events, protocol deviations, aggregate data?

The Data Safety and Monitoring Plan will include Woebot's standard safety net protocol as well as a Data Safety and Monitoring Board overseen by Stanford University. Woebot's Safety Net Procedures Study informed consent will state that Woebot is not a crisis program designed to address active suicidal ideation or overdose. [redacted] To make sure that we do not miss any cases, we over detect, rather than under detect. In addition, we periodically check the data for true/false positive rates. Adverse Events We do not anticipate that the use of the interventions will increase risk as outlined above. In addition, there is a limited capacity to detect adverse events (such as overdose, suicide attempt or hospitalization related to substance use or other) unless explicitly voluntarily reported by the participant. In the case Stanford University and / or Woebot Labs becomes aware of an adverse event, the appropriate protocol, approved by the DSMB and Stanford University's Institutional Review Board, will be immediately implemented. This includes immediate notification of the IRB, DSMB, and NIH, and an immediate convening of the DSMB to discuss requisite follow-up steps.

Identify who will be responsible for Data and Safety Monitoring for this study, e.g. Stanford Cancer Institute DSMC, an independent monitoring committee, the sponsor, Stanford investigators independent of the study, the PD, or other person(s).

To ensure the data protection and safety of research participants, Stanford University will serve as the Data Coordinating Center for the study under the coordination of Drs. Biaocchi and Prochaska. They will convene a group of three to serve as an oversight board with professional expertise in the area of the study. Dr. Prochaska is an expert in the field of addiction and substance use, and Dr. Biaocchi has experience in managing data protections in the context of randomized clinical trials.

Provide the scope and composition of the monitoring board, committee, or safety monitor, e.g., information about each member's relevant experience or area of expertise. If the Monitor is the Stanford Cancer Center DSMC or the PD, enter N/A.

DSMB's specific goals: • Review new or modifications to existing risk management protocols • Review procedures for maintaining confidentiality, data collection, management, and analyses • Review progress towards meeting enrollment goals • Recommend continuation, discontinuation, modification, or termination of a study based on emerging data (from the study and from the literature) and evaluation of risk/benefit ratios • Conduct annual reviews to determine whether patient safety has been adequately safeguarded • Review progress reports

Confirm that you will report Serious Adverse Events (SAEs), Suspected Unexpected Serious Adverse Reactions (SUSARs), or Unanticipated Problems (UPs) to the person or committee

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monitoring the study in accordance with Sponsor requirements and FDA regulations.

Yes.

If applicable, how frequently will the Monitoring Committee meet? Will the Monitoring Committee provide written recommendations about continuing the study to the Sponsor and IRB?

Dr. Prochaska will coordinate the meetings by assisting in setting the agenda and ensuring that the necessary materials are provided for each meeting. The initial meeting of the Board will take place during the first three months of the study, i.e., before entry into the second Phase of the research, to allow for the consideration of the protocol from the viewpoint of data safety and participant confidentiality. Subsequent meetings will be held at 6-month intervals, with the possibility for either an interim meeting or telephone conversation conference call should the necessity arise. At the first meeting, Dr. Prochaska will brief the board on the study design and procedures. The Board will then provide feedback on the data that they will wish to review at their subsequent meetings.

Specify triggers or stopping rules that will dictate when the study will end, or when some action is required. If you specified this in Section 2g [Study Endpoints], earlier in this application enter 'See 2g'.

Endpoints will be indicated by the cessation of W-SUDs and educational intervention delivery at 8-weeks, the 12-week mark for WSUDs group (content will no longer be accessible), data analysis and interpretation, refinement of W-SUDs, and the end of the 3 month period (ending mark of the study).

Indicate to whom the data and safety monitoring person, board, or committee will disseminate the outcome of the review(s), e.g., to the IRB, the study sponsor, the investigator, or other officials, as appropriate.

The proposed study has a dissemination plan that encapsulates two important arenas: 1) ClinicalTrials.gov compliance and 2) Dissemination. ClinicalTrials.gov Compliance If the proposal is successfully awarded, the applicant will ensure that the the trial's registration and results reporting procedures are thoroughly managed. The trial will be registered promptly upon receipt of the award and before the recruitment of human subjects. All informed consent documents will include specific and thorough statements referring to the posting on ClinicalTrials.gov. At the conclusion of the study and following analysis of the results, results will be reported as well, in compliance with the ClinicalTrials.gov procedures. Woebot Labs has a protocol in place outlining the importance and details of ensuring the ClinicalTrials.gov procedures are up to date. Dissemination of Research Both Stanford University and Woebot Labs will facilitate with the dissemination of research. They will collaborate on manuscript preparation and submission, as well as abstract submission and presentations at national and international scientific and technology-oriented conferences.

Select One:

The Protocol Director will be the only monitoring entity for this study.

Y This protocol will utilize a board, committee, or safety monitor as identified in question #2 above.

10. Benefits

a) Describe the potential benefit(s) to be gained by the participants or by the acquisition of important knowledge which may benefit future participants, etc.

When evaluating the risks and benefits of the proposed study, it is believed that risks are relatively minimal when compared to the potential therapeutic benefits that subjects are likely to receive. The benefits of receiving W-SUDs include potentially reducing substance abuse, acquiring practical psychotherapeutic skills (from cognitive behavioral therapy, motivational interviewing, dialectical behavior therapy, and mindfulness), and receiving psychoeducation about substance abuse. Participants who reduce substance

abuse may derive additional benefits should reduction in substance abuse be associated with other psychological improvements such as interpersonal or occupational functioning. Study of the effectiveness of this intervention will also benefit society more generally by providing
data on the efficacy, utility, and cost-benefits of a W-SUDs, the first SUDs-focused digital therapeutic delivered by an artificial intelligence (AI)-powered conversational agent.

The study allows the opportunity to expand understanding of W-SUDs' performance among this population and will offer those in the WSUDs group immediate access to a digital therapeutic in a resource constrained, socially distanced healthcare ecosystem to an already vulnerable and underserved population, who are likely faced with readily growing psychological challenges.

11. Privacy and Confidentiality

Privacy Protections

a) Describe how the conditions under which interactions will occur are adequate to protect the privacy interests of participants (e.g., privacy of physical setting for interviews or data collection, protections for follow-up interactions such as telephone, email and mail communications).

All assessments, including the screening and the four assessment
batteries, will be administered via a HIPAA compliant survey administration tool commonly used by Stanford University in its clinical trials (REDCap Cloud). Given the high data protection safeguards embedded within REDCap Cloud, there is little risk to the subject associated in regards to their privacy and/or confidentiality.

Informed consent will utilize Stanford's Adobe Sign platform and procedures for part 11 compliance.

Research material obtained from human subjects will involve
behavioral and psychological assessments (including self-report
questionnaires). All data will be obtained specifically for purposes of this research project. Data that is obtained from the REDCap Cloud assessments will be stored and protected within REDCap Cloud. Data that is obtained via Woebot will be encrypted and stored on Amazon Web Services (AWS); Woebot Labs data gathering and storage procedures are compliant with both the Health Insurance Portability and Accountability Act (HIPAA) [redacted] compliant. [redacted]

Confidentiality Protections

b) Specify PHI (Protected Health Information). PHI is health information linked to HIPAA identifiers (see above). List BOTH health information AND HIPAA identifiers. If you are using STARR, use the Data Privacy Attestation to ensure that your request will match your IRB-approved protocol. Be consistent with information entered in section 15a.

Individual names, email addresses, mailing addresses, phone numbers, dates of birth, demographic information (gender, biological sex,race/ethnicity, disability status), IP addresses, geo location, survey, drug use.

Drug Use Psychopathology
1. The Drug Abuse Screening Test 10 (DAST-10), a brief, 10-item
self-report measure adapted from the 28-item DAST, assesses
consequences related to drug abuse, excluding alcohol and tobacco. A
score of 3 or higher indicates significant problems related to drug
abuse. The DAST-10 demonstrated discriminate validity between
individuals (i) with lifetime drug use disorders and those without and
(ii) who are current abusers and those who are former abusers. It also

has moderate level of test-retest and reliability as well as sensitivity and specificity.

2. The Drug Abstinence Self-Efficacy Scale (DASE) is a 12-item self-report scale, reflecting Bandura's (1986) cognitive-behavioral self-efficacy theory, and is a shortened version of the original 20-item scale. The 20-item scale has shown to be a reliable and valid measure of self-efficacy for drug use. The scale will be adapted to refer to use of both drugs and alcohol, by including that language in the item stem.

3. The CAGE Adapted to Include Drug USE (CAGE-AID) was developed by the John Hopkins Dept of Medicine. It's a brief instrument to measure problematic drug use. The CAGE-AID is designed to be an easy yet effective way for primary care providers to determine if substance abuse exists and needs to be addressed.

4. The Michigan Alcohol Screening Test (MAST), revised is a 22 question instrument to measure problematic alcohol use. One of the most widely used measures for assessing alcohol abuse, the MAST is a questionnaire designed to provide a rapid and effective screening for lifetime alcohol-related problems and alcoholism. The MAST has been productively used in a variety of settings with varied populations.

5. The Short Inventory of Problems- Alcohol and Drugs (SIP-AD) is a clinically tested 15-item measure developed by NIH funded research that assesses severity of problematic drinking and drug usage.

6. The Quick Drinking Screen (QDS) by Sobell & Sobell (2003), is a brief and reliable measure of drinking. Compared with the Timeline Followback (TLFB), the QDS collected similar aggregate drinking data for four drinking variables in a clinical sample of alcohol abusers.

General Psychopathology

9. The Patient Health Questionnaire (PHQ-8) is a brief 8-item scale used to determine the severity of depression in medical populations. The PHQ-8 has high reliability across populations.

10. The Generalized Anxiety Disorder (GAD-7) is a brief self-report scale that identifies the degree to which an individual may have generalized anxiety disorder. This scale has good internal consistency, convergent validity with depression, stress, and anxiety, and is a valid and efficient tool for GAD screening in clinical and general populations.
Employee Health

11. The Stanford Presenteeism Scale is (SPS-6) a six item measure derived from a 34 item measure of workforce productivity impacted by health status. The 6-item scale has excellent psychometric properties and has been validated.

12. The CAIR Pandemic Impact Questionnaire (C-PIQ) and the International COVID-19 Awareness and Evaluation Study questions were developed for measuring the impact of COVID-19. These include questions about COVID-19 in relation to their health, work, and lifestyle changes.

c) You are required to comply with University Policy that states that ALL electronic devices: computers (laptops and desktops; OFFICE or HOME); smart phones; tablets; external hard disks, USB drives, etc. that may hold identifiable participant data will be password protected, backed up, and encrypted. See http://med.stanford.edu/datasecurity/ for more information on the Data Security Policy and links to encrypt your devices.

Provide any additional information on ALL data security measures you are taking. You must use secure databases such as https://researchcompliance.stanford.edu/panels/hs/redcap RedCap. If you are unsure of the security of the system, check with your Department IT representative. Please see

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http://med.stanford.edu/irt/security/ for more information on IRT Information Security Services and http://www.stanford.edu/group/security/securecomputing/mobile_devices.html for more information for securing mobile computing devices. Additionally,any PHI data on paper must be secured in an locked environment.

By checking this box, You affirm the aforementioned. Y

IRB Modification 12/19/2022: All assessments, including the screening and three assessment batteries, will be administered via a HIPAA compliant survey administration tool commonly used by Stanford University in its clinical trials (Qualtrics and REDCap Cloud). Given the high data protection safeguards embedded within Qualtrics and REDCap Cloud, there is little risk to the subject associated in regards to their privacy and/or confidentiality.

IRB Modification 12/19/2022: Research material obtained from human subjects will involve behavioral and psychological assessments including self-report questionnaires. All data will be obtained specifically for purposes of this research project. Data that is obtained from Qualtrics and the REDCap Cloud assessments will be stored and protected within the electronic data capture platform, and on Stanford Medicine Box. Data that is obtained via Woebot will be encrypted and stored on Amazon Web Services (AWS); Woebot Labs data gathering and storage procedures are compliant with both the Health Insurance Portability and Accountability Act (HIPAA) [redacted] compliant. [redacted]

The Stanford research team will use Stanford encrypted, password protected, and backed up electronic devices (laptops, mobile devices) for this project.

d) Describe how data or specimens will be labeled (e.g. name, medical record number, study number, linked coding system) or de-identified. If you are de-identifying data or specimens, who will be responsible for the de-identification? If x-rays or other digital images are used, explain how and by whom the images will be de-identified.

Each participant will be assigned a unique study ID number that will take the place of any identifying information. Surveys will be done online with individual survey URLs matched to study ID provided to participants. All data therefore will be coded for the large dataset.

No names will be attached to surveys or biomarker tests. Study staff is responsible for the coding.

Woebot user data provided to Stanford will be de-identified and linked via study ID to the study assessments we collect via RedCap Cloud and the data will not be shared outside of the Woebot and Stanford teams.

e) Indicate who will have access to the data or specimens (e.g., research team, sponsors, consultants) and describe levels of access control (e.g., restricted access for certain persons or groups, access to linked data or specimens).

The PD and co-investigator and the research team will have access to the study data. All data will be locked or password-protected or both.

f) If data or specimens will be coded, describe the method in which they will be coded so that study participants' identities cannot be readily ascertained from the code.

Each participant will be assigned a unique participant ID number, starting with 001 through 1000, to code data.

g) If data or specimens will be coded, indicate who will maintain the key to the code and describe how it will be protected against unauthorized access.

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IRB Modification 12/19/2022: The codes of names and ID numbers will be accessed by the research team only, stored securely in Qualtrics, REDCap Cloud, and/or a password protected file.

h) If you will be sharing data with others, describe how data will be transferred (e.g., courier, mail) or transmitted (e.g., file transfer software, file sharing, email). If transmitted via electronic networks, describe how you will secure the data while in transit.See http://www.stanford.edu/group/security/securecomputing/ http://www.stanford.edu/group/security/securecomputing/. Additionally, if you will be using or sharing PHI see https://uit.stanford.edu/security/hipaa https://uit.stanford.edu/security/hipaa.

Coded data may be sent by secure email settings provided by Stanford, or through Stanford Medicine Box.

IRB Modification 12/19/2022: Woebot user data provided to Stanford will be coded and linked via study ID to the study assessments we collect via Qualtrics and REDCap Cloud, and the data will not be shared outside of the Woebot and Stanford teams.

i) How will you educate research staff to ensure they take appropriate measures to protect the privacy of participants and the confidentiality of data or specimens collected (e.g. conscious of oral and written communications, conducting insurance billing, and maintaining paper and electronic data)?

The research staff will all be HIPAA and CITI trained and compliant
and supervised by Dr. Prochaska.

12. Potential Conflict of Interest

Investigators are required to disclose any financial interests that " https://researchcompliance.stanford.edu/eprotocol-coi" target="_blank" reasonably appear to be related/li to this protocol.

Financial Interest Tasks

Investigators	Role	Potential COI?	Date Financial Interest Answered	Date OPACS Disclosure Submitted	COI Review Determination
[redacted]	[redacted]	[redacted]	[redacted]		[redacted]
[redacted]	[redacted]	[redacted]	[redacted]		[redacted]

13. Consent Background

13. 1 Waiver of Documentation Screening Consent

Check if VA related

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a) Describe the informed consent process. Include the following.

i) Who is obtaining consent? (The person obtaining consent must be knowledgeable about the study.)

ii) When and where will consent be obtained?

iii) How much time will be devoted to consent discussion?

iv) Will these periods provide sufficient opportunity for the participant to consider whether or not to participate and sign the written consent?

v) What steps are you taking to minimize the possibility of coercion and undue influence?

vi) If consent relates to children and if you have a reason for only one parent signing, provide that rationale for IRB consideration.

(i)IRB Modification 3/10/23: Study staff will be obtaining the screening consent via online platform (Qualtrics). The screening questionnaire consent page requests that the potential participant save a copy of the screening consent form. Study contact information is on the consent should any questions come up. (ii)IRB Modification 3/10/2023: This consent will be at the beginning of the screening questionnaire (via Qualtrics). Since consent is obtained online, it can be obtained at any location of potential participants' choosing. If the potential participant is not a US resident, they will be screened out on this question in the screening. Potential participants would be able to rescreen as long as they sign they screening consent each time. (iii)IRB Modification 3/10/23: There is no time limit- each respondent can take much time as they want to read through the consent. Reading the screening consent is anticipated to not take more than five minutes. Contact information is available on the consent form if any questions come up. The screening consent forms can be obtained via download on the Qualtrics . Qualtrics can store data securely. (iv)Since consent is obtained online, the participant may take as much time as they wish to consider whether or not to participate and proceed with the screener. Study staff will not be with the potential participant and there will be no possibility of coercion or undue influence. (v)No incentive or form of coercion is present for the screening process. The study is voluntary; Potential participants are informed that they can withdraw or choose not to participate at any time. There is no payment for going through the screener. (vi)N/A. If under 18 years of age, the respondent will be screened out on the age question.

b) What is the Procedure to assess understanding of the information contained in the consent? How will the information be provided to participants if they do not understand English or if they have a hearing impairment? See HRPP Chapter12.2 for guidance.

We are not recruiting participants who cannot understand English.

c) What steps are you taking to determine that potential participants are competent to participate in the decision-making process? If your study may enroll adults who are unable to consent, describe (i) how you will assess the capacity to consent, (ii) what provisions will be taken if the participant regains the capacity to consent,(iii) who will be used as a legally authorized representative, and (iv) what provisions will be made for the assent of the participant.

Participants will be reading the consent form before beginning the screener. Participants must be English literate to participate as the questionnaires, consent forms, communications, and Woebot app are only available in English. The participant will have to sign the screening consent form to participate in the study. Contact information is also provided during consent for the participant to use if they have questions about the study.

Select ALL applicable regulatory criteria for a Waiver of Documentation and provide a protocol-specific justification:

1)		**45 CFR 46.117(c)(1)(i)., that the only record linking the participants and the research would be the consent document, and the principal risk would be potential harm resulting from a breach of confidentiality; each participant (or legally authorized representative) will be asked whether he/she wants documentation linking the participant with the research, and the participant's wishes govern.**
2)	Y	**45 CFR 46.117(c)(1)(ii)., that the research presents no more than minimal risk of harm to participants and involves no procedures for which written consent is normally required outside of the research context.**
3)		**45 CFR 46.117(c)(1)(iii)., if participants or legally authorized representatives (LAR) are members of a distinct cultural group in which signing forms is not the norm, the research presents no more than minimal risk and there is an appropriate alternative mechanism for documenting that informed consent was obtained.**
4)	Y	**21 CFR 56.109(c)(1)., presents no more than minimal risk of harm to participants and involves no procedures for which written consent is normally required outside of the research context.**

Rationale for above selection:

This consent is for eligibility to participate in the study. The screening questionnaire has been

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updated to meet waiver of documentation criteria. To meet the criteria for a waiver of documentation (i.e., minimal risk of harm), we have grouped assessment of sensitive (e.g., opioid use) with nonsensitive items (e.g., pregnancy) with a single yes/no assessment to determine eligibility and to avoid having sensitive information on participants. The screening questionnaire includes a few select items from valid and reliable scales, not the full measures except for the CAGE-AID. To help with obtaining a diverse sample, the screening questionnaire includes questions on race/ethnicity, with an option to select Prefer not to Answer if respondents are not comfortable with providing a response. Contact information will be asked if screened eligible. [redacted]

13. 2 Alteration of Consent — Phase 2 ICF - Alteration of Consent

Check if VA related

a) Describe the informed consent process. Include the following.

i) Who is obtaining consent? (The person obtaining consent must be knowledgeable about the study.)

ii) When and where will consent be obtained?

iii) How much time will be devoted to consent discussion?

iv) Will these periods provide sufficient opportunity for the participant to consider whether or not to participate and sign the written consent?

v) What steps are you taking to minimize the possibility of coercion and undue influence?

vi) If consent relates to children and if you have a reason for only one parent signing, provide that rationale for IRB consideration.

(i) Consent will be obtained via REDCap Cloud. Once the informed consent form is fully signed, the potential participant will be notified by email that their consent form is fully signed, and they can go onto REDCap Cloud to download a copy of the fully signed consent form. Each potential participant going through consent will receive an invite from REDCap Cloud via email to create a REDCap account, make a password, and then would be able to read and sign consent. The person obtaining consent will receive an email ping that the consent form is ready to be reviewed and signed. The person obtaining consent can access the form on REDCap Cloud, then review and sign the form. (ii) The online consent can be obtained at anytime and place the potential participant would like. If the respondent is not a US resident, they will be screened out on this question in the screening. For reconsenting, the study team will reach out to the participant about this, and a new consent form invitation from REDCap Cloud will be sent. (iii) Potential participants may take as long as they like to read through the consent form. Estimated time is 5min. Informed consent form will be accessed on REDCap Cloud. The study team's contact information is within the consent form if any questions come up. Fully signed consent forms can be obtained via download on the REDCap Cloud platform. REDCap Cloud can store signed consent forms and data securely. A copy of the signed consents may also be stored on Stanford Medicine Box. Study staff can send fully signed consent forms via secure email upon request. (iv) Yes. (v) Study staff will not be with the potential participant and there will be no possibility of coercion or undue influence. (vi) If under 18 years of age, the respondent is screened out before the consent form appears. Additionally, birth date is asked in the baseline survey.

b) What is the Procedure to assess understanding of the information contained in the consent? How will the information be provided to participants if they do not understand English or if they have a hearing impairment? See HRPP Chapter12.2 for guidance.

Only English fluent participants will be recruited. The Consent form will be readable and those with a hearing impairment will still be able to access the consent form.

c) What steps are you taking to determine that potential participants are competent to participate in the decision-making process? If your study may enroll adults who are unable to consent, describe (i) how you will assess the capacity to consent, (ii) what provisions will be taken if the participant regains the capacity to consent,(iii) who will be used as a legally authorized representative, and (iv) what provisions will be made for the assent of the participant.

The consent form will only be accessible to those who can meet screening criteria. Participation will only include those competent to consent in the low risk study.

Address the following regulatory criteria for a waiver of consent and provide protocol-specific justification for each:

1) Y **The research/clinical investigation involves no more than minimal risk (as defined in 45 CFR 46.102(j), 21 CFR 50.3(k), or 21 CFR 56.102(i)) to the participants. [45 CFR 46.116(f)(3)(i) and/or 2017 FDA Guidance IV.1]**

The study is a RCT with group blinding to test whether WSUDs is more effective in reducing problematic substance use than an education only control. The study will involve four questionnaires

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about physical and mental health, and substance use. Participation information will be coded and stored on compliant platforms (Stanford Medicine Box) and on encrypted, password protected computers. App data is protected with Woebot's security measures.

2) Y **The waiver or alteration will not adversely affect the rights and welfare of the participants. [45 CFR 46.116(f)(3)(iv) and/or 2017 FDA Guidance IV.2]**

Confidentiality and HIPAA practices will still be in place. Data is stored on compliant platforms (e.g. Qualtrics, Stanford Medicine Box) and on encrypted password protected computers.

3a) Y **The research/clinical investigation could not practicably be carried out without the requested waiver or alteration. [45 CFR 46.116(f)(3)(ii) and/or 2017 FDA Guidance IV.3]**

3b) Y **For research using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format. [45 CFR 46.116(f)(3)(iii)]**

There will be intervention group blinding to maximize validity and minimize bias. To keep the group blinding effective, the groups are not fully described in the consent form, and full details of the group intervention a participant is randomized to will be provided after randomization. A debrief will be provided to participants after the 12-week assessment period.

4) Y **Whenever appropriate, the participants or legally authorized representatives will be provided with additional pertinent information after participation. [45 CFR 46.116(f)(3)(v) and/or 2017 FDA Guidance IV.4)]**

Participants will be provided with a debrief of group blinding at the end of their study participation. This will be provided by email either be after completion of the final survey or a month after the final survey was due (for those who don't complete the final survey).

14. Assent Background (less than 18 years of age)

15. HIPAA Background

15. 1 Alteration of Authorization screening consent-alteration of authorization

a) **Describe the Protected Health Information (PHI) needed to conduct the research. PHI is health information linked to HIPAA identifiers. List BOTH health information AND HIPAA identifiers. If you are using STRIDE, use the Data Privacy Attestation to ensure that your request will match your IRB-approved protocol.**

For the screening: Alcohol and drug use, and related events Demographics (e.g. age, sex, race/ethnicity) Past year suicide attempt or psychosis Name (consent process) Signature (consent process) Email (if eligible) Phone (if eligible)

b) Please Answer:

Y **Do you certify that the use or disclosure of protected health information involves no more than a minimal risk to the privacy of individuals?**

Y **Do you certify that the research could not practically be conducted with out the waiver?**

Y **Do you certify that you have adequate written assurances that the protected health information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research project, or for other research for which the use or disclosure of protected health information would be permitted?**

Y **Do you certify that the research could not practically be conducted with out access to and use of the**

[redacted]

[redacted]

protected health information?

c) Please describe an adequate plan to protect any identifiers from improper use and disclosure.

In the screening questionnaire, the study team will ask questions on alcohol and drug use (broadly), questions on demographics, and questions to ensure respondents are not high risk (e.g. past 12-month suicide attempt, psychosis). More sensitive questions will be grouped with less sensitive questions (e.g. high risk type questions will be in the same question group as pregnancy status).

d) Please describe an adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law.

Identifiers will be destroyed on December 31, 2045 or when the research project ends, whichever is earlier. This can be accomplished by deleting identifiers from the data set. If the data is coded, the codebook for identifiers is destroyed.

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Obligations

The Protocol Director agrees to:

- Adhere to principles of sound scientific research designed to yield valid results
- Conduct the study according to the protocol approved by the IRB
- Be appropriately qualified to conduct the research and be trained in Human Research protection, ethical principles, regulations, policies and procedures
- Ensure all Stanford research personnel are adequately trained and supervised

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- Ensure that the rights and welfare of participants are protected including privacy and confidentiality of data
- Ensure that, when de-identified materials are obtained for research purposes, no attempt will be made to re-identify them.
- Disclose to the appropriate entities any potential conflict of interest
- Report promptly any new information, modification, or unanticipated problems that raise risks to participants or others
- Apply relevant professional standards.

Any change in the research protocol must be submitted to the IRB for review prior to the implementation of such change. Any complications in participants or evidence of increase in the original estimate of risk should be reported at once to the IRB before continuing with the project. Inasmuch as the Institutional Review Board (IRB) includes faculty, staff, legal counsel, public members, and students, protocols should be written in language that can be understood by all Panel members. The investigators must inform the participants of any significant new knowledge obtained during the course of the research.

IRB approval of any project is for a maximum period of one year. For continuing projects and activities, it is the responsibility of the investigator(s) to resubmit the project to the IRB for review and re-approval prior to the end of the approval period. A Notice to Renew Protocol is sent to the Protocol Director 7 weeks prior to the expiration date of the protocol.

https://stanfordmedicine.box.com/shared/static/qbsi8u8h47qsotxhdpuzz50xlrqa0sgo.pdf Report promptly any new information, complaints, possibly serious and/or continuing noncompliance, or unanticipated problems involving risks to participants or others.

All data including signed consent form documents must be retained for a minimum of three years past the completion of the research. Additional requirements may be imposed by your funding agency, your department, or other entities. (Policy on Retention of and Access to Research Data, Research Policy Handbook,
http://doresearch.stanford.edu/policies/research-policy-handbook/conduct-research/retention-and-access-research-data)

APPROVAL LETTER/NOTICE NOTE: List all items (verbatim) that you want to be included in your approval letter (e.g., Amendment date, Investigator's Brochure version, consent form(s) version(s), advertisement name, etc.) in the box below.

1) Updated message templates
2) DOB will be asked at each follow up survey
3) Screening consent and questionnaire will be on Qualtrics

Y By checking this box, I verify that I, as the Protocol Director (PD) responsible for this research protocol, have read and agree to abide by the above obligations, or that I have been delegated authority by the PD to certify that the PD has read and agrees to abide by the above obligations.