Trial Protocol

A Randomized Controlled Trial Of a culturally-adapted version of Thrive, a computerized cognitive behavior therapy program, for rural Montanans

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1. Background

Montana's high rates of poor mental health combined with low rates of access to care [1] indicate a pressing urgency for alternative methods to meet the mental health needs of Montanans. Mental health service deficits in rural and frontier Montana communities, compared to more urban areas are even more substantial [2] where higher poverty, lower educational attainment, and lower employment rates occur [3]. Montana ranks last among all states in population density with 55 of 56 counties defined as rural or frontier [4].

Computer-administered CBT (cCBT) programs have generally shown similar efficacy as clinician-administered CBT [5] with positive impacts in rural communities outside the U.S. [6]. *Thrive* is an interactive version of cCBT with a heavy emphasis on video rather than text content that appears to improve participant engagement, a shortcoming seen in prior cCBT programs [7]. *Thrive* users proceed at their own pace and receive personalized treatment sequences based on assessment responses by each patient. *Thrive* provides safeguards and guidance if the program is not working effectively.

Thrive's developmental history reflects changes in accessible technology. Across all developmental versions, it has been shown to be efficacious in reducing depressive symptoms. First developed and studied as a desk top computer terminal administered program in a RCT compared with clinician CBT and wait-list control (WLC), it's early promise was reflected in effect sizes of 1.37 and 1.26 for computer treated and therapist treated groups, respectively, compared with WLC [8]. A substantially modified version called COPE was administered by telephone via interactive voice response [9]. COPE was subsequently converted for administration on the Internet and improved by reducing text and implementing use of videos, making the program more engaging and effective for individuals with lower literacy. It has since been designed to operate on smartphone and tablet devices in addition to computers. To provide a gold-standard test of efficacy of cCBT in rural U.S. communities, RCTs are needed. Given the high stigmatization of mental illness in remote rural communities [10], cCBT programs such as *Thrive* offer an accessible and confidential way to help people experiencing depressive symptoms, syndromes, and disorders in rural communities. Our project addresses this need.

Preliminary evidence on Thrive. Among commercially insured patients, *Thrive* resulted in an average reduction of 39% in depression severity as measured by the Patient Health Questionnaire-9 (PHQ-9) [11], from pre- to post-assessment (see Table). These uncontrolled trials indicate improvements in depression symptoms across all levels of baseline depression severity with marked improvements among those with moderate to severe depression.

Thrive Outcomes Among Commercially Insured Patients (N = 297)

	Baseline PHQ-9 Score Range*					
	0-4	**5-9**	**10-14**	**15-19**	**20-27**	**Total**
	None	**Mild**	**Moderate**	**Mod Severe**	**Severe**	
Number of Enrollees with	88	104	68	29	8	297

PHQ-9 Score of ≥2						
Mean Baseline Score	2.4	7.0	11.5	16.8	21.9	8.0
Mean Endpoint Score	2.0	4.6	6.5	8.7	12.0	4.9
Change in Mean Score	-0.4	-2.4	-5.1	-8.1	-9.9	-3.2
% Improvement in Score	**17%**	**34%**	**44%**	**48%**	**45%**	**39%**
Effect Size	0.22	1.12	1.82	2.30	2.35	0.67

*PHQ-9 score range based on 9 items with a 4-point response scale of 0 to 3

2. Research Objectives

This is a fully randomized trial of cCBT care for depression versus care as usual. The quantitative evaluation will be completed to achieve the following aims:

1. To determine the relative effectiveness of the *Thrive* program to decrease depressive symptomatology and improve overall quality of life compared to usual care.
2. To determine the long-term effectiveness of the *Thrive* program to decrease depressive symptomatology and improve overall quality of life

3. Methods

3.1 Design

This study uses a randomized wait-list controlled design, whereby participants will be assigned either to receive the *Thrive* program immediately upon enrollment for 8 weeks or wait 8 weeks following enrollment to receive the *Thrive* program. Subjects will be followed for a total of one year following delivery of *Thrive* to provide an exploratory evaluation of its long-term impact. During the RCT period, those randomized to the control group will receive basic information about depression from the National Institute of Mental Health [21], and will subsequently be provided access to the *Thrive* program at the end of the initial eight-weeks of the study trial.

3.2 Inclusion/Exclusion Criteria

3.2.1 Inclusion Criteria: Particpants must be aged 18 year or older; have residency in Montana, have reglar access to broadband internet, and have a score of 5 or greater on the Patient Health Questionnaire-9.

3.2.2 Exclusion Criteria: We will exclude persons aged 17 year or younger, non-residents of Montana, those who do not have access to broadband internet, and have a score of 4 or lower on the Patient Health Questionnaire-9.

3.3 Recruitment and Randomization

Community members will be recruited for participation in the RCT via channels identified from key informant interviews and focus group sessions. Example channels include

state Extension agents, Facebook, identified organization email listservs, and community flyers. A study enrollment and assessment portal will randomly assign each participant to either the intervention or wait-list control (WLC) groups.

3.4 Measures and data collection

Primary Outcome Measure: Patient Health Questionnaire nine-item scale (PHQ-9) [11], is a valid assessments of depression severity

Secondary Outcome Measures: Generalized Anxiety Disorder seven-item scale (GAD-7) [12]; Connor-Davidson Resilience ten-item Scale (CDRS-10) [13]; and, the Work and Social Adjustment Scale (WSAS) [14].

Data are collected by self-report online and will be uploaded and de-identified through the *Thrive* database and made accessible to the PI for monitoring and analysis. Participants randomized to the intervention group are assessed at baseline, 4 and 8 weeks, and 6 and 12 months from enrollment. Participants randomized to the waitlist control group are assessed at baseline, 4, 8, 12, and 16 weeks, and 8 and 14 months from enrollment.

3.5 Statistical Analysis Plan: Analyses will use an intent-to-treat approach to examine difference in mean scores between intervention and control groups. Depressive symptomatology (PHQ-9 scores) from baseline and weeks 4 and 8 will be the primary continuous outcome measure. Anxiety, Resilience, and Functional Impairment scores from baseline and weeks 4 and 8 will be secondary continuous outcome measures. For the primary and secondary outcomes, the change over time in each outcome will be compared between the intervention and WLC groups using a linear mixed model analysis of repeated measures. A separate mixed model will be conducted on each outcome measure. Each mixed model will contain fixed effects terms for treatment (intervention vs. WLC), time, treatment × time interaction, and respective baseline measure (prior to the intervention) as a covariate. Other relevant covariates will also be considered for inclusion in the mixed model. The correlation of any naturally-occurring paired participants (e.g., parent/child, siblings, husband/wife, and partners) will be accounted for in the mixed model analysis. Least squares (LS) means (adjusted treatment means) will be estimated as part of the mixed model so as to interpret the omnibus treatment effect (LS mean difference between treatments). Statistical analyses will be performed using SAS software, version 9.4 (SAS Institute, Inc., Cary, NC). The PROC MIXED procedures (mixed model approach in SAS) will make use of all available data from all participants from the efficacy analysis set, and provide a robust mechanism for handling data that are assumed missing at random [15-17]. The level of significance for all tests will be set at $\alpha = .05$ (two-tailed). Statistical expertise will be built into the budget for Years 1 and 2.

To evaluate the long-term effects of *Thrive*, in an exploratory analysis, a completely within-subjects linear mixed model analysis of repeated measures will be used to examine the change in each of the primary and secondary outcomes over the 12 months following delivery of *Thrive* by combining data from both treatment groups (intervention+WLC). In the case of the group randomized to *Thrive*, data will include assessments at baseline, 4 and 8 weeks, and 6 and 12 months. For the WLC group, baseline for this combined-group analysis will be 8

weeks after randomization (i.e., immediately prior to starting *Thrive*) and then 4 and 8 weeks, and 6 and 12 months after starting Thrive.

3.6 Sample Size Estimation and Power Analysis for the Primary Outcome of the Study: Effect sizes from the preliminary analysis of the 4 uncontrolled studies of *Thrive* as it relates to the primary continuous outcome (depressive symptomatology, as assessed by the PHQ-9) were consistently very large (d > 1.0). Using a conservative estimate of effect size (d~0.30), an a priori sample size estimation and power analysis was performed for the repeated measures design/analysis in the proposed controlled study. The results suggest that a sample size of 117 per group (N = 234) achieves 80% power to detect a conservative effect size of 0.30 (Cohen's *d*--standardized group mean difference) in a 2 (between-subjects) group design with 3 (within-subjects) repeated measurements having a compound symmetry covariance structure when the assumed within-subject correlation is 0.50, and the alpha level is 0.05 (two-tailed), with a normal distribution for the test statistic. We anticipate some dropouts [~49% within the first 4 weeks (the period designating an evaluable subject) after enrollment, based on treatment discontinuation results from *Thrive*]. Thus, 459 participants will be enrolled to allow for this expected rate of attrition with the intent of capturing a range of evaluable data for 234 participants. The Power Analysis and Sample Size (PASS) 2015 software, version 14.02, was used to carry out the sample size and power analysis [18].

4. Human Subjects Protections

4.1 Risks and anticipated benefits for trial participants

Risk posed to participants will be minimal. Cognitive Behavioral Therapy modules are developed to provide supportive positive messages and examples for participants to work through. It is possible that participants will feel discomfort or stress in processing material and applying skills outside the program. Wait-list control group participants will receive standard National Institute of Mental Health information about depression while waiting 8 weeks for their access to *Thrive*.

4.2 Informing potential participants of possible benefit and known risks

Study recruitment flyers and the informed consent forms notify potential participants of any possible benefits and risks. Participants are provided the contact information of the university's Institutional Review Board director and the study PI.

4.3 Obtaining informed consent from participants

Potential participants will see the electronic informed consent, which details the information about study participation, on the study portal webpage. They must provide an electronic signature to confirm their understanding of study obligations.

4.4 Trial documentation

Electronic data will be stored on secure encrypted servers and accessible only to the PI and study coordinator. Personal identifiable data are kept separate from health data. Paper records will be secured in locked file cabinets and offices. Data records will be retained for 7 years

upon study completion.

4.5 Monitoring and reporting adverse events

The PI will regularly monitor the data and indications of adverse events related to participation in the trial. If any adverse events are known to occur, the PI will promptly notify the university's Instiutional Review Board to determine its relevance to the trial continuation. The *Thrive* program and the study assessment portal has prompts to help users who indicate suicidal ideation how to receive immediate help (see Appendix).

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Appendix: Safety Measures in Thrive

In this document:

- Messaging about the appropriate use of Thrive
- The Patient Health Questionnaire (PHQ-9) in Thrive
- Feedback for users with high PHQ-9 scores

Messaging about the Appropriate Use of Thrive

Before a study subject can start the Thrive curriculum, Thrive presents an "Important Information" page describing, in text written at the 5th grade reading level, the appropriate use of Thrive. The user cannot continue in Thrive without agreeing with the information on this page. See next page for a text of the Important Information page.

The main points on the Important Information page are:

- Thrive does not provide psychological advice, medical advice, diagnosis, or treatment
- The user may continue to see his/her doctor

Below: an Important Information page is the first page a study subject sees after enrolling in Thrive. The subject cannot continue in Thrive without agreeing with this information.

During your participation in the *Thrive* study, you may continue seeing your doctor.

People all over the world have troubles with low mood. There is help, but no method is right for everyone.

Thrive may help you feel better, but it does not replace your doctor. Thrive does not give psychological or medical advice. If you want a diagnosis or treatment for any condition, or if you are not improving, please see your doctor.

Thrive is a computer program. Instructions you get in Thrive are not given by a person. It is your duty to ensure that they are right for you. When you give information to Thrive, **no one will review it.** Videos in Thrive of Dr. Greist may not give the only or best information or instructions. Instead, they give his general opinion. They may not be right for you. If you have questions about anything in Thrive, please see your doctor.

If you think you might hurt yourself or kill yourself, do one or more of these things right away:

- **Call 911 or your doctor or other healthcare provider right away**
- **Go to an Emergency Room, or**
- **Call the National Suicide Prevention Hotline at 1-800-273-TALK (8255)**
- **Text 'Matters' to 741741 to start a text chat with the Crisis Text Line, or**
- **Visit NowMattersNow.org to learn skills for dealing with thoughts of suicide"**

You may also continue using Thrive, but Thrive is not a substitute for the 5 actions above.

Starting Thrive is a great step, but you should continue in Thrive only if you agree with the information on this page.

(BOX) Check this box if you agree with the information on this page.

The PHQ-9 in Thrive

Thrive administers the PHQ-9 at baseline and subsequently every 10 days during user access to Thrive. The study subject can see his/her PHQ-9 score in a chart after completing each PHQ-9 on the Dashboard.

After the user completes a PHQ-9, Thrive evaluates the following items to determine which feedback to provide:

- Number of times he/she has completed the PHQ-9
- The user's most recent PHQ-9 score
- The user's previous PHQ-9 score (if this is not the user's first PHQ-9 score in Thrive)
- The user's level of activity in Thrive