STUDY PROTOCOL & STATISTICAL ANALYSIS PLAN

Official Title:	HYPERTHERMIA AS AN ADDITIONAL TREATMENT FOR THE BIOLOGY AND EXPERIENCE OF DEPRESSION: THE HEATBED STUDY
Clinicaltrials.gov #	NCT05708976
Date	25 September 2025
Development Phase:	Feasibility & Acceptability
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BACKGROUND

Depression recovery is not uniformly linear; people who recover from depression often experience acute improvements, termed 'sudden gains,' early in treatment. Data suggest that participants with clinical depression who receive whole body heating (Hanusch et al., 2013; Janssen et al., 2016) and participants who receive cognitive behavioral therapy (CBT) treatment (Aderka et al., 2012; Tang et al., 1999) show sudden gains. Ascertaining if a treatment comprising both sauna sessions and CBT sessions is feasible and tolerable will allow for further research of this integrative mind-body treatment as a potentially effective and disseminable treatment for clinical depression.

Prior work has demonstrated that whole body heating to an internal temperature of 38.5 °C (101.3 °F) using a head out infrared heating device is tolerable by healthy adults and is associated with significant reductions in clinical depression (Hanusch et al., 2013; Janssen et al., 2016) that characterize sudden gains. This prior work administered a single sauna session in a Heckel heating device, a medical hyperthermia device, and reported improvements in depression symptoms within 1 week of this session. This prior work did not ascertain if additional sauna sessions led to further decreases in depression; a dose-escalation study has not yet been performed. Our earlier pilot project established (in N=25 participants) that a readily accessible, commercially available sauna, which the UCSF IRB granted NSR designation, can achieve a core temperature of 101.3 °F without serious adverse events.

In addition to the body-based approach of using sauna as a possible treatment for depression symptoms, we will provide the current gold standard psychotherapy intervention, cognitive behavioral therapy (CBT) to participants. Cognitive behavioral therapy (CBT) is an efficacious, highly disseminable evidence-based treatment for depression. Many therapy modalities can elicit sudden gains; however, *sudden gains in cognitive behavioral therapy (CBT) are more frequent and durable* than those observed in non-CBT therapies (Aderka et al., 2012). Meta-analytic data suggest that the effects of sudden gains on depression symptoms in the context of CBT treatment are larger (Hedges's g=0.74) and longer lasting than those occurring in the context of non-CBT treatment (Hedges's g=0.23; Aderka et al., 2012). The conceptual framework of sudden gains suggests that such gains can lead to cognitive changes that then lead to further symptom reduction, sparking a positive feedback loop termed an "upward spiral" (Tang & DeRubeis, 1999). Sudden gains in CBT generally follow from "critical" therapy sessions characterized by substantial cognitive change. CBT is an effective manualized psychotherapy that a diverse range of mental health clinicians, including marriage and family therapists (MFTs) and clinical social workers (CSWs), can provide. In many areas, MFTs and CSWs are more readily available and affordable than clinical psychologists. Hence, optimizing an intervention that includes a psychotherapy modality that a range of mental health clinicians can provide strengthens the potential for dissemination.

References:

- Aderka IM, Nickerson A, Bøe HJ, Hofmann SG. Sudden gains during psychological treatments of anxiety and depression: A meta-analysis. *J Consult Clin Psychol*. 2012;80(1):93.
- Hanusch, K.-U., Janssen, C. H., Billheimer, D., Jenkins, I., Spurgeon, E., Lowry, C. A., & Raison, C. L. (2013). Whole-body hyperthermia for the treatment of major depression: Associations with thermoregulatory cooling. *American Journal of Psychiatry*, *170*(7), 802–804.
- Janssen, C. W., Lowry, C. A., Mehl, M. R., Allen, J. J. B., Kelly, K. L., Gartner, D. E., ... Raison, C. L. (2016). Whole-Body Hyperthermia for the Treatment of Major Depressive Disorder: A Randomized Clinical Trial. *JAMA Psychiatry*, *73*(8), 789–795.
- Tang TZ, DeRubeis RJ. Sudden gains and critical sessions in cognitive-behavioral therapy for depression. *J Consult Clin Psychol*. 1999;67(6):894

TITLE	**EXAMINING THE FEASIBILITY AND ACCEPTABILITY OF SAUNA SESSIONS AND COGNITIVE BEHAVIORAL THERAPY (CBT) FOR PARTICIPANTS WITH CLINICAL DEPRESSION**
SPONSOR	Ashley E. Mason, PhD
CO-SPONSOR	Frederick M. Hecht, MD
NUMBER OF SITES	1
RATIONALE	Depression recovery is not uniformly linear; people who recover from depression often experience acute improvements, termed 'sudden gains,' early in treatment. Data suggest that participants with clinical depression who receive whole body heating (Hanusch et al., 2013; Janssen et al., 2016) and participants who receive cognitive behavioral therapy (CBT) treatment (Aderka et al., 2012; Tang et al., 1999) show sudden gains. Ascertaining if a treatment comprising both sauna sessions and CBT sessions is feasible and tolerable will allow for further research of this integrative mind-body treatment as a potentially effective and disseminable treatment for clinical depression.
STUDY DESIGN	Randomized, blinded pilot trial

PRIMARY OBJECTIVE	Pilot RCT procedures: We will conduct a pilot trial (*N*=30) to test the feasibility and acceptability of recruitment, retention, and randomization procedures in preparation for a larger efficacy trial of WBH+CBT. We will randomize participants with clinical depression to receive 8 weekly CBT + 4 biweekly active sauna sessions (refined during Aim 1) or 8 weekly CBT + 4 biweekly sham sauna sessions. After the first half of enrollment (*n*=15) is complete, we will use participant and staff feedback to refine procedures for the remaining enrollment (we will submit any refinements or changes to the treatment to the UCSF IRB approval before implementing them).
SECONDARY OBJECTIVES	To pilot test the feasibility of all assessment procedures in anticipation of a larger trial.
NUMBER OF PARTICIPANTS	30
PARTICIPANT SELECTION CRITERIA	<u>Inclusion Criteria:</u> 1. Age of at least 18 years old 2. Current major depressive episode of at least 2 weeks duration as assessed by the Structured Clinical Interview for DSM-5 (SCID) and a Beck Depression Inventory-II (BDI-II) score ≥ 21 at screening 3. Able to understand the nature of the study and able to provide written informed consent prior to conduct of any study procedures 4. Must have smartphone onto which they can download an app from Apple App or Google Play stores 5. Ability to lie supine (on back) for 2 hours (required for sauna sessions) 6. Must be fully vaccinated against COVID-19 <u>Exclusion Criteria:</u> 1. >30% reduction in BDI-II score between Screen #1 and Screen #2 (conducted ~1 week after Screen #1). 2. Suicide attempt in the past 12 months defined using the SAMHSA suicidality question during the clinician-administered interview or active suicidal ideation as indexed by a score of 3 on the BDI-II suicidality item during the clinician-administered interview. 3. Any of the following medical conditions: cardiovascular disease (other than controlled hypertension), seizure disorder, history of cerebrovascular accident (CVA) or other serious neurological condition (e.g. Parkinson's disease, multiple sclerosis, or dementia), current neoplasia, any active enclosed infection (e.g. dental abscess, joint infection), hemophilia or other cause for excessive bleeding (e.g. platelet disorder), or other medical

	condition that in the opinion of investigators may increase the risk of WBH 4. Comorbid psychiatric conditions or history of comorbid psychiatric conditions that might better explain depressive symptoms, including schizophrenia, schizoaffective disorder, Bipolar Disorder I, Obsessive Compulsive Disorder, Anorexia Nervosa, Bulimia Nervosa, Alcohol Dependence, or Drug Dependence 5. Known hypersensitivity to hyperthermia and/or infrared exposure 6. Inability to fit into the sauna device 7. Breast implants 8. Pregnancy, active lactation or intention to become pregnant during the study period 9. Use of any medication that might impact thermoregulatory capacity, including: • diuretics, barbiturates • beta-blockers • antipsychotic agents • anti-cholinergic agents or chronic use of antihistamines • aspirin (other than low-dose ASA for prophylactic purposes) • medication prescribed for the treatment of depression (antidepressant medication [ADM]) including but not limited to: selective serotonin reuptake inhibitors [SSRIs], Serotonin and norepinephrine reuptake inhibitors [SNRIs], Monoamine oxidase inhibitors [MAOIs], Tricyclics [TCAs], and atypical antipsychotic and antidepressant medications (participants must have been free of these medications for at least 4 weeks) • antibiotics (past 14 days), pain medication (opioids) due to procedure, e.g., dental procedure (past 14 days), Emergency contraception pill (past 14 days) • any other medication that in the judgment of the PI would increase risk of study participation or introduce excessive variance into physiological or behavioral responses to WBH • recent use (multiple consecutive doses) of: non-steroidal anti-inflammatory drugs (NSAIDs), systemic corticosteroids, cytokine antagonists 10. Regular use of any nicotine products, including cigarettes, vapes, chewing tobacco, or other forms of nicotine (if use is not regular, must be willing to refrain for 24 hours before and 24 hours after sauna session) 11. Unwilling to refrain from using marijuana products and alcohol for the 24 hours before and 24 hours after sauna sessions

	12. Unwilling to refrain from heavy exercise on the day of sauna sessions 13. Unwilling to refrain from engaging with sauna, hot yoga, cold plunges, cryotherapy, and hot tub/jacuzzi outside of study (prospective participant must not have engaged with any of these activities for 30 days prior to their baseline study visit). 14. Has begun new psychotherapy treatment in the prior 6 weeks *Note: All medications reported by potential subjects will be reviewed by medical monitor Frederick Hecht, MD. If the medication is determined to not have meaningful impacts on bodily thermoregulatory processes and to not interact with whole body heating, the subject may participate.
TEST PRODUCT, DOSE, AND ROUTE OF ADMINISTRATION	Portable Sauna Dome – One Person Supine sauna device, head out, body inside of sauna Sauna session approx. 80 – 140 minutes, maximum 140 minutes Manufactured by Clearlight Infrared
CONTROL PRODUCT, DOSE AND ROUTE OF ADMINISTRATION	All participants receive cognitive behavioral therapy (CBT), and 50% of participants receive active sauna sessions while 50% receive sham sauna sessions (the test product treatment listed above, Portable Sauna Dome)

DURATION OF PARTICIPANT PARTICIPATION AND DURATION OF STUDY	This is a single-center, two-arm, randomized experimental study that will include 30 participants. Participants will be in the study for approximately 10 weeks. Total time involved will be approximately ~34 hours:
	• E-Screen: Web-based eligibility screen for self-report eligibility criteria
	  o ~10 minutes
	• Phone Screen: Phone call to review eligibility, verify shipping address for Oura ring sizing kit and schedule baseline study visits
	  o ~25 minutes
	• In-Person Screen / Baseline Visit: Participant to complete screening procedures, provide informed written consent and receive bill of rights, download Oura ring app, complete self-report questionnaires, anthropometric assessments, schedule study visits. Randomization to receive either active sauna sessions or sham sauna sessions.
	  o ~220 minutes
	• Weekly depression survey: Web-based surveys assessing depression symptoms on Mondays.
	  o ~ 10 minutes each

	• Sauna Visits 1-4: In-person visits, participant (if female) to complete pregnancy screen if the participant thinks there is a possibility of pregnancy, COVID-19 rapid test, complete questionnaires (all sauna visits), provide saliva samples (Sauna Visits 1 and 4) and blood samples (Sauna Visit 1, Sauna Visit 4 if the participant chooses), and complete sauna session
	  o ~220-240 minutes each
	• Cognitive Behavioral Therapy (CBT) Visits 1-8: In-person visits, participant to receive 50-minute CBT session and complete self-report measures
	  o ~65 minutes each
	• Closeout Visit: In-person visit, participant to complete questionnaires, complete clinician-administered assessment, provide blood and saliva samples, and return Oura ring.
	  o ~60 minutes

CONCOMMITANT MEDICATIONS	<u>Allowed:</u> • All medications reported by potential participants will be reviewed by medical monitor Frederick Hecht, MD. If the medication is determined to not have meaningful impacts on bodily thermoregulatory processes and to not interact with whole body heating, the participant may participate. <u>Prohibited:</u> 1. Use of any medication that might impact thermoregulatory capacity, including: diuretics, barbiturates, beta-blockers, antipsychotic agents, anti-cholinergic agents or chronic use of antihistamines, cytokine antagonists 2. Current antidepressant medications (all classes) or use within the past 30 days 3. Recent use (multiple consecutive doses) of systemic corticosteroids 4. Needing to use antihistamines, aspirin (other than low-dose ASA for prophylactic purposes), non-steroidal anti-inflammatory drugs (NSAIDs), or systemic corticosteroids, on Study Visit days 5. Use of any other medication that in the judgment of the PI would increase risk of study participation or introduce excessive variance into physiological or behavioral responses to WBH 6. Regular use of any nicotine products, including cigarettes, vapes, chewing tobacco, or other forms of nicotine 7. The following medications in these timeframes: Antibiotics (past 14 days), Pain medication (opioids) due to procedure, e.g., dental procedure (past 14 days), Emergency contraception pill (past 14 days)

EFFICACY EVALUATIONS	See below for primary and secondary endpoints.
PRIMARY ENDPOINT	*Primary outcomes.* The primary endpoint is study acceptability, as indexed by participant-reported net-promoter scores, which will range from 0 (*would not recommend*) to 10 (*would definitely recommend*).
SECONDARY ENDPOINTS	*Secondary outcomes.* We will assess pre-post intervention changes in: Beck Depression Inventory (BDI-II), Patient-Reported Outcome Measurement System (PROMIS) Depression, PROMIS Anxiety, and the Hamilton Depression Rating Scale (HAMD-6).
OTHER EVALUATIONS	N/A
SAFETY EVALUATIONS	Incidence of unexpected adverse events. We will monitor participants for unexpected adverse events and serious adverse events during and following the sauna sessions.
PLANNED INTERIM ANALYSES	Due to the current study design and safety profile of this test product (portable sauna dome – one person) and cognitive behavioral therapy (CBT; a standard depression psychotherapy treatment), we do not plan any interim analyses.
STATISTICS Primary Analysis Plan	Primary outcome: We assessed study acceptability by computing means and standard deviations of participant-reported net-promoter scores, which will range from 0 (*would not recommend*) to 10 (*would definitely recommend*). *Note on Original Primary Outcome*: Although we collected and reported this outcome, participants noted that they may not have recommended the study as highly to others because antidepressant medication use was an exclusion criteria, and many participants knew that their friends or family members used these medications. Because that awareness may have biased net promotor scores downward, we report an additional acceptability measure. *Revised Additional Primary Outcome:* A second study acceptability measure asked participants how likely they would be to enroll in the study given their experience in the study, on a scale from 1 (*extremely unlikely to enroll*) to 5 (*extremely likely to enroll*). We reported the score mean and standard deviation. Secondary outcomes: We assessed change in scores on the Beck Depression Inventory (BDI-II), Patient-Reported Outcomes Measurement Information Systems (PROMIS) measures, and Hamilton Depression Rating Scale (HAMD-6), using T-Tests, and report the mean changes and associated standard errors. Units for PROMIS measures are T-Score points.
Rationale for Number of Participants	The primary endpoint is participant-reported net-promoter scores, which will range from 0 (*would not recommend*) to 10 (*would definitely recommend*). If 25 of 30 Aim 2 participants rate the study experience > 7 (83%), the 95% CI will be 70% to 97% (normal approximation to the binomial), which we also believe will provide

	adequate precision for feasibility/acceptability testing.