Title: Bright Start Study Protocol

NCT number: NCT05356130

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1. **Protocol**

Protocol Title: Feasibility pilot in preparation for large pragmatic encouragement trial of Bright Light Therapy (BLT) for depression
Abbreviated Title: BLT Pilot
Participant Facing Name: Bright Start Study

Principal Investigator: Greg Clarke, PhD

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2. **Objectives**

Primary Objective (or Aim)

Our primary objective is to examine benefit of a deployment-ready BLT approach when delivered to complex real-world patients in an active health care system setting, against a background of other usual care. This trial will evaluate BLT effectiveness with little of the "scaffolding" typical of highly controlled efficacy trials. This R34 pilot will prepare for a future, fully powered effectiveness trial. Our focus will be on how participants in the condition with the most assistance (Arm 3: TAU + Enhanced BLT Encouragement + Adherence Promotion + MI) benefit in terms of BLT initiation, continued use, and depression outcomes compared to those participants enrolled in the other two arms (Control Arm 1: TAU control with no BLT assistance; and Minimal Assistance Arm 2: TAU + brief written BLT Educational material but no phone coaching).

Secondary Objectives (or Aim)

The secondary objectives are to:

- Conduct analyses that mirror those planned for a future, fully-powered trial. Key analytic contrasts are (a) active Arms 2 + 3 vs. control Arm 1; (b) each active Arm (2, 3) separately vs. control Arm 1; and (c) Minimal Arm 2 vs. Enhanced Arm 3. For each contrast we will initially examine differences between study arms in pre-post change in proposed mediators in BLT and MI effects; followed by examination of differences in pre-post change in the primary (PHQ-9) and key secondary outcomes.
- Examine candidate mediators (improved sleep, normalized circadian rhythm, increased physical activity, readiness for change) for mediating BLT and MI effects on depression. We will also examine moderation of BLT effects and subgroup outcome variation (e.g., receiving vs. not receiving TAU ADs).
- Examine cost data and conduct economic analyses.
- Collect pilot feasibility data that will facilitate rapid launch of a future trial: estimated recruitment, retention, and adherence with BLT protocol and compensation program for light box purchase; and a cautious estimate (with wide confidence intervals) of BLT effectiveness.

3. **Background Information and Rationale**

Depressive disorder is associated with significant adverse impacts on mental and physical health, reduced attainment of life milestones including employment and education, and lower psychosocial functioning. In the United States, it affects millions of people: in 2017, an estimated 17M adults (7.1%) had major depression. Effective, accessible treatment for depression is a major public health priority. The most common evidence-based treatments (EBTs) are pharmacotherapy such as SSRI

antidepressants (ADs), and psychosocial therapies such as cognitive behavioral therapy (CBT). However, even when delivered under ideal conditions these have moderate benefit. Treatment effectiveness is further reduced in real-world patients by low levels of initiation and adherence, and/or high levels of discontinuation. Patient reluctance to fully engage with these EBTs is fueled by high costs, limited availability of trained providers, concerns about side effects, and stigma.

While promising research is underway to improve engagement/adherence to existing depression EBTs and to develop new treatments, other approaches should be considered. One of these is an existing EBT with a strong research pedigree but has low adoption in clinical care: bright light therapy (BLT), most often administered via a "light box." BLT was developed out of basic science regarding seasonal affective disorder (SAD). For many years, BLT has been viewed as an appropriate treatment for SAD but not for non-SAD depression. However, recent trials and meta-analyses reveal that BLT yields medium to high clinical benefit for non-SAD depression as well as SAD, as both monotherapy or as an adjunct to ADs. BLT has several advantages over existing pharmacotherapy or psychotherapy. First, at a typical light box purchase price of $70 to $110 it is relatively affordable, and many insurance plans reimburse patients for the purchase cost. Second, BLT is hypothesized to work via a different mechanism than pharmacotherapy or psychotherapies, and evidence points to additional benefit when BLT augments other EBTs. Third, properly educated and motivated patients can self-administer BLT at home, alleviating barriers of travel burden and limited access to care—telehealth issues that have been highlighted during the present pandemic. Finally, contraindications are minimal (e.g., skin/eye photosensitivity), side effects are typically minor/transient, and antidepressant action is rapid (within 1-2 weeks). Despite these advantages adoption/promotion of BLT is low, even when patients are not engaged in other depression EBT. This represents a care gap that may be addressed in part with BLT.

Given that BLT has established medium-large efficacy, what is the next step? A large pragmatic effectiveness trial is a logical progression of research: to examine benefit of a deployment-ready BLT approach when delivered to complex real-world patients in an active health care system setting, against a background of other usual care. This trial will evaluate BLT effectiveness with little of the "scaffolding" typical of highly controlled efficacy trials. This R34 pilot will prepare for a future, fully-powered effectiveness trial.

4. Study Design

This is a three-arm randomized controlled trial (RCT), with treatment as usual (TAU; i.e., usual care) underlying all study arms. Following a 2-stage eligibility screening and baseline assessment, patients will be randomly assigned to:

- Arm 1: Treatment as Usual (TAU) control: A "usual care" control group (e.g., antidepressants, watchful waiting, psychosocial therapy, or no treatment, all determined by the participant in consultation with their TAU providers). All TAU will be recorded for all participants in all study conditions; or
- Arm 2: TAU + Minimal BLT Encouragement: TAU plus two minimal communications (mailed letter, secure EHR message, email, or text) identifying BLT as a promising treatment and outlining steps for participants to self-initiate. Arm 2 will not include any phone coaching or adherence promotion.
- Arm 3: TAU + Enhanced BLT Encouragement + Adherence Promotion + MI: TAU plus 2-6 brief calls to encourage BLT use, advise on purchase of a light box (LB) that meets all ideal technical

standards, assist with obtaining compensation for LB purchase, educate for correct LB use, and provide motivational interviewing (MI) as needed to promote adherence.

Outcomes will be assessed at baseline, 2, 4, and 6 months. The acute intervention period will be for 2 months. The primary outcome will be scores on the Patient Health Questionnaire-9 (PHQ-9), selected as representative of how depression is assessed in many usual care settings, consistent with effectiveness research principles.

5. Study Population

a. Number of Subjects

We will enroll 90 to 100 participants.

b. Inclusion and Exclusion Criteria

Potentially eligible individuals will be screened at two points in the recruitment phase: 1) preliminary identification of likely participants via a search of KPNW electronic health record (EHR) and 2) phone or online screening survey.

EHR inclusion criteria:

- Age 18-69 years, inclusive, and
- New episode of unipolar depression within the last month, defined as: New ICD-10 diagnosis of SAD or unipolar depression (i.e., major depression, minor depression, depression not otherwise specified, and/or adjustment disorder with depressed mood) AND usual care administration of the PHQ-9 depression scale in the last 30 days, with a total score of 10 or higher, and
- Participant must have a kp.org MyChart account, with evidence of use in the last 12 months.

EHR exclusion criteria:

- Chronic depression: ICD-10 diagnosis of SAD or unipolar depression in the 6 months prior to case-identification;
- Elevated PHQ-9 (score of 10 or higher) in the 6 months prior to case identification.
- Active EHR diagnoses and prescriptions representing any of the following contraindications for BLT: Conditions that might render skin or eyes more vulnerable to phototoxicity (e.g., ophthalmic disorders such as cataract, macular degeneration, glaucoma, retinitis pigmentosa; disorders affecting the retina such as retinopathy, diabetes, herpes); or photosensitive skin; or if they are taking a photosensitizing medication or herb (e.g., St. John's wort or a psoralen).
- EHR-recorded diagnoses of bipolar disorder I or II.

Screening inclusion criteria:

- Elevated PHQ-9 (score of 10 or higher);
- Able and willing to conduct study assessments and phone coaching in English;
- Phone and internet access.

Screening exclusion criteria:

- Participation barriers (e.g., terminal end-stage cancer, moving out of the region, no locator information);

- Contraindicated diagnoses or medications (see EHR exclusion criteria above) in case these are known to patients but are not EHR-recorded (e.g., if they were diagnosed with a contraindicated condition before becoming a KP member and have not yet sought care for it);
- Contraindicated diagnoses or medications (see EHR exclusion criteria) newly reported that were not captured in the EHR;
- Emergent bipolar, manic, mixed symptoms that may not have been formally diagnosed yet (e.g., significant mood swings, excessive increases in energy, dramatically less need for sleep).

In the event of a screen failure, or when a potential participant is contacted but declines participation, minimal demographic data collected (such as age, sex, race, ethnicity), and reason for declining will be retained for review. This data may help inform future study design.

c. Vulnerable Populations

Vulnerable Populations (VPs)	Include/Exclude	Rationale
Pregnant women	Include	Pregnancy has no known vulnerabilities for BLT. Further, BLT may be a valuable alternative treatment for pregnant women who might be hesitant to take antidepressants.
Children	Exclude	N/A
Neonates of uncertain viability or nonviable neonates	Exclude	N/A
Prisoners	Exclude	N/A

d. Setting

This study will be conducted by study staff at Center for Health Research (CHR), among the KPNW adult membership. Participants will be able to conduct all study activities from home.

e. Recruitment Methods

EHR Identification of Potential Recruitment Pool. We will run an EHR case-finding program as needed for the projected 16-month recruitment period to generate an initial outreach list of potentially eligible individuals. After each recruitment list is generated, we will send a secure EHR message to each individual's primary care provider (PCP) and mental health specialist (e.g., psychiatrist) if applicable. In this message, we will state our intent to reach out to the patient unless we hear from the provider within three business days that it would be unwarranted (e.g., due to more acute condition for which other health care should be primary).

Once an individual has been identified once by this EHR search program, they will be excluded from subsequent runs of the program to avoid multiple waves of contact.

Recruitment Mailing, Emailing, Online Screening, and Calls. For patients not opted out by clinician(s), we will mail/email a recruitment packet containing the recruitment letter, recruitment flyer, and a copy of the consent information sheet. Interested patients have the option to complete the screening survey online. For those who screen eligible online, study staff will follow up by phone to obtain verbal informed consent as described in Section F. Patients also have the option to opt out online.

If the screening survey is not completed online, study assessment staff will begin making recruitment calls to those who have not preemptively declined at least two calendar days after the recruitment packet is sent. If a potential participant did not receive the recruitment packet, upon request, we will email the recruitment packet to the individual. The consent and the recruitment flyer will also be available as downloadable PDF documents on the public access study recruitment website (no account needed). We will use IRB-approved email templates and will follow CHR guidelines in emails sent to potential participants regarding this study.

During the recruitment call, study staff will explain the study and answer questions. For those individuals who are interested, study staff will complete the screening survey. Individuals who pass the screening survey will be invited to complete the baseline survey after study staff obtains verbal informed consent as described in Section F.

Recruitment Contact Methods and Frequency. Study assessment staff will make multiple telephone attempts to contact potentially eligible individuals, not to exceed 3 attempted calls unless otherwise requested by the individual. The study may also employ recruitment text messages and emails to potential participant cell phones and email addresses (if listed in HealthConnect member contact data), sending a maximum of 2 recruitment text messages and emails. Pending KPNW regional permission granted to use this system, we may also send secure messages via the MyChart function in HealthConnect, which offers a password-protected, more secure messaging system than typical email or text.

Staffing. All participant recruitment and assessment contacts will be conducted by CHR mental health interviewers, occasionally with backup from SPD study project management staff. All intervention delivery will be conducted by BAC department staff or other CHR staff with the previous requisite training and licensure.

f. Consent

Informed Consent Process

Potentially eligible individuals will be sent a copy of the consent information sheet in the recruitment packet as described previously. For individuals who screen eligible, study staff will use the recruitment script to obtain verbal informed consent via phone. Verbal consent will be documented in the study tracking system.

We ensure the language in the consent and recruitment script is appropriate for an adult population. They will be reminded that participation is completely voluntary and there will be no penalty

for opting out – refusal to participate will not influence their ability to receive care and they are free to withdraw at any time. Procedures for ensuring confidentiality and a statement of potential risks are included in the informed consent form.

We take the following steps to minimize the possibility of coercion or undue influence:

- Gift certificate values that are not so high that they unduly influence decisions to take part (see Compensation to Participants section);
- Assessment and intervention staff will mention, especially during highly sensitive interview/questionnaire topics, that participants have the right to not answer any questions, although if they refuse to answer key outcome questions we may elect to administratively withdraw them from the study;
- Participants may withdraw from the study at any time.

Waiver or Alteration of Informed Consent or Signed Informed Consent

The Application for Waiver or Alteration of Consent or Authorization has been filled out and is included in the submission.

- Waiver of Informed Consent: We are requesting a waiver of informed consent for the preliminary EHR case-finding program and the eligibility screen. Participants who pass the screen will be asked for verbal consent and authorization for study participation as described above.
- Waiver of Signed Informed Consent for Participant Assessments: The study cannot practicably be conducted without a waiver of signed informed consent because we will only be contacting participants by phone, and requesting a return mailed consent form would increase burden to participants and study staff. The consent information sheet will be mailed to potential participants prior to the recruitment call. During the recruitment call the elements of informed consent will be read and verbal consent will be obtained and documented.
- Waiver of Signed Informed Consent for Provider Surveys: We are also requesting a waiver of signed informed consent, as the provider survey will be administered online and we do not plan to obtain written consent from participating providers. The Consent Information Sheet will be displayed for the provider to review on the REDCap "page" prior to the survey questions.

Non-English-Speaking Subjects

Not applicable.

Assent of Children and Parent Permission

Not applicable.

Adults Unable to Consent/Decisionally Impaired

Not applicable.

g. HIPAA Authorization – if study will use or disclose Protected Health Information (PHI)

HIPAA authorization will be combined into the informed consent information sheet and verbal consent will be obtained and documented during the recruitment phone call.

Waiver or Alteration of HIPAA Privacy Rule Authorization

Alteration of Authorization is requested to allow for a waiver of the signature and date requirement for HIPAA authorization. This research will be conducting a HIPAA privacy rule authorization procedure, but without signed documentation. We believe the study cannot practicably be conducted without a waiver of signed authorization because eligible participants are only being contacted by phone.

A request for Waiver of Authorization is also requested for recruitment. During the first stage of the screening process, we will run an EHR case-finding program to generate an initial outreach list of potentially eligible individuals. This initial case finding algorithm does not itself qualify individuals for the study, but merely generates a likely pool within which further screening is merited.

This waiver allows study staff to approach (via letter, email/the EHR patient portal, and subsequent phone call) likely interested and eligible individuals and offer them the study opportunity. The study could not complete the research without access to and use of PHI because it is not practical to recruit eligible individuals without pre-identifying using medical record information and contact information. It would be too costly and would un-duly burden the KP membership to receive invitations to every study. Only the minimum amount of PHI will be accessed to identify participants who are likely to meet the study eligibility criteria.

6. Study Procedures

Recruitment

Recruitment procedures are described in the earlier Recruitment Methods section.

Randomization

Participants will be randomized 1:1:1 to three conditions, stratified by gender (male vs. female + all non-CIS gender identities), age (median split; estimated as <46yrs vs >= 47yrs), and minority status (white non-Hispanic vs. all other races/ethnicities).

Monitoring for Safety

The target condition is depression, and the most likely emergent risks (and how we will monitor for these) are:

- Worsening depression, evaluated at each assessment with the PHQ-9 depression measure.
- Intentional self-harm, including suicidal thoughts and behavior. This will be evaluated at each assessment with the Columbia Suicide Severity Rating Scale (C-SSRS).
- Emergent bipolar disorder symptoms (a possible risk of triggered symptoms from lightbox use). This will be assessed at each follow up assessment with the 5-item Altman Self-Rating Mania Scale (ASRM).

Any increased risk evident from any of these measures, or other unexpected increased in other less common safety issues (e.g., threats to harm others) will be reviewed between the interviewing staff and Dr. Clarke, with a review of the relevant usual health care the individual is already receiving.

We will also send EHR messages to TAU providers of Arm 2 and 3 participants stating that they are being encouraged to self-administer BLT, so that they can coordinate other depression care as needed, or if some new condition or situation arises that might impact BLT; e.g., emergent bipolar disorder.

Depending on the level of risk revealed through the monitoring procedures above, possible risk amelioration actions include: recommendation that the participant meet with their primary care provider and/or specialist provider(s) to seek new care; research staff share the risk information with these providers or others; and in the most extreme risk cases initiate a 'warm handoff' to the KPNW Emergency Psychiatric Service 24/7 call line for immediate, additional evaluation of risk.

Drugs and Devices

No drugs will be used in this research. Participants in study Arms 2 and 3 will be encouraged to use light boxes designed to treat depression. The specific devices recommended by the study will be those that meet the ideal light therapy criteria, but they are available to the general public to purchase "over the counter" (e.g., via Amazon or Best Buy) and are not considered regulated or approved devices.

Source records that will be used to collect data about subjects

- HealthConnect Electronic Health Record (EHR) case-finding data program, identifying highly likely individuals who meet preliminary indicators of study inclusion criteria and did not meet exclusion criteria
- Recruitment Script: Includes recruitment voicemail, call script, screening survey, and verbal consent script;
- Baseline and Follow-Up Assessments: Scripts and measures for the randomization phone call and all assessments are incorporated into one document titled "Scripts and Measures_All Assessments_Randomization" (see Survey Measures section below for a description of the measures);
- Intervention Contact Form (Arm 3 only): Used by phone coach to capture details of intervention contacts with participants;
- We will obtain data from the EHR to describe TAU in all study arms for 12 months prior to enrollment and up to 12 months post-enrollment.

Study Conditions

Arm 1: TAU control condition. The control condition is non-research treatment as usual (TAU), most of which is delivered in the KPNW HMO. TAU also underlies the active intervention Arms 2 and 3.

Arm 2: TAU + Minimal BLT promotion. Participants will receive 2 brief communications (mailed letter, secure EHR message, email, and/or text) identifying BLT as a promising treatment with few side effects, and steps for participants to self-initiate. The educational and background information from the 2 communications will also be made available as PDFs or webpages on the secure study website. If requested, participants will be provided with a copy of these materials by email. Arm 2 has no phone coaching, adherence promotion or MI.

Arm 3: TAU + BLT encouragement + adherence promotion. BLT promotion coaches will follow a four-

step approach in engaging with Arm 3 participants: (a) provide encouragement to consider using BLT; (b) provide guidance regarding light box purchase and compensation; (c) educate participants about ideal BLT use to obtain maximum benefit; and (d) provide ongoing brief telephonic adherence promotion and motivational interviewing (MI) where warranted to maximize persistent and appropriate BLT use. The educational and instructional information for these 4 steps will also be made available as PDFs or webpages on the secure study website. If requested, participants will be provided with a copy of these materials by email.

Encouragement. Coaches will encourage participants to consider BLT during the first post-randomization contact, in most cases by telephone. Coaches will address the reason for the call (BLT promotion) and advantages of BLT. They will also gauge interest in using BLT; for ambivalent participants they will offer a brief motivational interviewing (MI) exercise.

Compensation for BLT purchase. In Arms 2 + 3 interested participants will receive written guidance on purchasing a light box (LB) that meets minimum study requirements. Arm 3 coaches guide participants to purchase LBs and obtain compensation (up to $80 in Fred Meyer gift cards) for this cost through the study. This compensation process is modeled to simulate the KP durable medical equipment (DME) benefit, which does not currently cover LBs. Arm 2 offers the same written information about LB purchase and compensation, but no coach assistance.

Education. Participants in both Arms 2 and 3 will receive written information about how to obtain the greatest BLT benefit, including recommended day/time usage, session duration, eye distance from light box, the length of time to continue using, and the small risk of emergent mania or BD and how to recognize this. Written best practices for ideal BLT will be provided in both Arms 2 and 3 via secure EHR message, email, and/or USPS. PDFs of best practices for BLT will also be available for download on our study website. Arm 3 participants will also review this material with coaches in the initial phone session. They will also address common patient concerns and reactions, respond to reported barriers to usage and provide possible solutions, and offer suggestions for maintaining the correct use of BLT. In Arm 3 coaches will review and emphasize the ideal BLT protocol as needed in subsequent adherence promotion calls.

Duration of BLT. Both Arms 2 and 3 materials will recommend a minimum 4-weeks of acute daily BLT sessions to achieve and consolidate maximum benefit. If by week 4 an acute response of at least 2 weeks with few or no depressive symptoms has not been achieved, participants will be encouraged to continue with daily sessions with the goal of maximizing a tolerable but still therapeutic level of BLT exposure. Beyond the written best practices for both Arms 2 and 3, phone coaches will work with Arm 3 participants to explore possible contributing factors and possible solutions. For example, if incomplete BLT adherence is identified, coaches will work with participants to address barriers (discomfort, scheduling, competing demands, low motivation) to maximize adherence to the ideal protocol. Once depression response is obtained and sustained for at least 2 weeks, written materials (and coaches in Arm 3) will encourage participants to continue with a longer-term but less intense maintenance period to sustain BLT benefits, in which the duration and/or frequency of light exposures can be reduced. Written materials (and coaches in Arm 3) encourage participants to monitor for a return of depressive symptoms, and to take steps should that occur; e.g., restart or increase frequency of BLT.

Adherence promotion (AP) + Motivational Interviewing (MI). This Arm 3 component will focus on monitoring appropriate light box use and guiding participants back to this protocol when there is drift. Ideally, coaches will make an initial check-in phone contact within 72 hours of enrollment, encourage purchase of light box, assist with compensation for light box purchase, and review educational material about the ideal use of BLT. Coaches will make additional AP+MI contacts by phone after 1 week of BLT use. For adherent participants who are using BLT consistent with the ideal protocol, coaches will make one more call in week 3 or 4 to confirm ongoing adherence and to assist participants with the shift to the maintenance phase. For participants who are only partially or weakly adherent, coaches will make up to 6 additional brief contacts to assist, promote use, and help overcome barriers or low motivation to use BLT according to the ideal protocol. In all cases, coaches will employ standardized problem-solving techniques to identify the issue(s), barriers, and facilitators for ideal BLT use, and assist participants in brainstorming possible solutions. Coaches will also monitor for relapse to depression episode, with plan to restart BLT or increase session duration/frequency as needed.

If motivation to adhere to the BLT protocol is lacking, coaches will employ brief MI. Many of our behavioral health and assessment (BAC) staff have delivered MI and adherence promotion protocols similar to this for previous trials. While BAC staff have prior MI experience, they will also attend MI workshops offered by KPNW and will then be trained by senior staff to address MI specifically for BLT use. We have engaged a MI fidelity expert, Dr. Ernst to rate training cases and ongoing calls to confirm initial and ongoing coach MI fidelity. During start-up each coach will conduct several simulated BLT coaching calls; Dr Ernst will rate audio recordings of these simulations for MI quality/adherence. Staff who are rated 4 or higher on four global components of MI quality/adherence for these initial simulations will be cleared to conduct study MI with enrolled participants. We will also conduct ongoing MI fidelity ratings for study Arm 3 phone coach contacts. Dr. Ernst will conduct MI fidelity reviews of a random 10% selection of these Arm 3 coaching calls (blocked by coach, and by early/late session). Additionally, as Dr. Ernst reviews MI sessions she will also complete fidelity checklists (to be created and submitted in a subsequent modification) of BLT health education review/practice and problem solving that coaches may deliver to promote ideal BLT sessions (e.g., did coach review whether daily BLT sessions occurred? If not, were barriers identified and possible solutions explored?). Dr Ernst's MI fidelity and BLT education ratings will be used as process variables, but also to provide feedback to coaches during supervision meetings.

Based on prior coaching experiences, ~10% of individuals randomized to Arm 3 will likely not engage with coaches, despite indicating a previous willingness to do so. Coaches attempt to reach all Arm 3 participants, but after 3 failed outreach attempts coaches will send a final "contact us if you wish" email or letter.

<u>Assessments</u>

We will ask participants to complete baseline and follow-up surveys using the REDCap online survey system; those who do not complete the online surveys after 3 prompts will be called by interviewers and verbally administered the same scales. Assessments consist of the baseline assessment; a post-acute treatment assessment at 2 months after enrollment; and follow-up assessments at month 4 and month 6, for a total of 4 data points over the course of six months. Interviewers will be blinded to study condition.

Demographics data will be collected on all potential participants during the screening process and/or baseline assessment and will include race, ethnicity, sex assigned at birth, gender identity, relationship status, employment status, and education and income information.

Survey Measures

All measures will be administered at the baseline assessment and all follow-up assessments unless otherwise indicated. The surveys will include questions from the following measures, either in part or in their entirety: ***Patient Health Questionnaire–9 (PHQ-9); Seasonal Pattern Assessment Questionnaire (SPAQ); Quick Inventory of Depressive Symptomatology, self-report (QIDS-SR); Geriatric Depression Scale (GDS);*** the abbreviated ***self-report Columbia Suicide Severity Rating Scale (C-SSRS); Altman Self-Rating Mania Scale (ASRM); Generalized Anxiety Disorder-7 (GAD-7); Brief Medication Questionnaire (BMQ); Short Form 6 Dimension (SF-6D); Pittsburgh Sleep Quality Index (PSQI); Reduced Version of the Morningness-Eveningness Questionnaire (rMEQ); Split Week Self-Assessment of Sleep Survey (SASS-Y); Readiness Ruler (RR);***

Non-Standardized Measures to be collected include:

Alternative depression treatments. We will ask participants whether they are currently using, or intend to use, any "alternative" treatments for depression such as BLT (including whether light box purchase was new or had existing), yoga, Tai Chi, mood-enhancing diets (e.g., Mediterranean Diet), exercise, omega-3 fatty acids, St John's wort, and others.

Satisfaction and Feedback. At the 2-month follow-up assessment, we will ask participants in Arms 2 and 3 about their experience as a participant in this study.

Actigraphy

Following the baseline and 2-month follow-up assessments, participants will be mailed an actigraphy device to wear for 10 days or until the battery dies and then return in supplied postage-paid envelope. We will download/score actigraphy data for sleep and physical activity using ActiLife software, then reset the actigraphy device and reuse it again with additional participants.

Ecological Momentary Assessment (EMA)

Up to 4 days per week during the 9-week acute intervention phase (baseline to 2-month follow-up), and twice weekly thereafter to 6 months, all participants will be sent text and/or email links to a brief EMA REDCap survey about mood and sleep in the last 24 hours. For participants in Arms 2 and 3, the EMA survey will also include brief questions about BLT adherence.

Electronic Health Record (EHR) Data Abstraction

EHR-Derived Comorbidity Index (EHR-CI). Medical comorbidity is a risk factor for mental health disorders. We will use an EHR calculated CI using medical diagnoses and prescription dispensing data.

TAU health care utilization. We will extract health care utilization data from the EHR to examine other outcomes (e.g., antidepressant prescription fills, ED visits). Another moderator category will be clinical/demographic EHR factors (e.g., comorbidities; age, ethnicity/race, sex; pharmacotherapy use).

Formative Qualitative Exit Interviews

We will not conduct *formal* qualitative interviews and analysis, but we will conduct *formative qualitative interviews* with a subset of participants who represent several 'types:' those who (a) were consistently adherent with study tasks such as surveys; (b) rapidly dropped out of study tasks or withdrew from the study; and among participants in active intervention Arms 2 and 3, (c) those who reported difficulties with BLT such as side effects, low motivation, and/or lack of benefit; and (d) those who appeared to tolerate BLT well and had high adherence to the ideal protocol. We aim to conduct interviews with 3 to 4 participants of each type, for a total of 12 to 16 qualitative interviews. These brief interviews will include questions about the participant's experiences in the study, pros and cons, feedback on how to improve the study and the BLT protocol, ease of use or barriers, and any unanticipated problems or benefits.

We will also conduct surveys with 6 to 10 representative healthcare providers whose patients enrolled in the study, asking about positive and negative impacts of BLT use, coordination with other treatments, and burden on providers.

Formative Qualitative Interview Recruitment. Participants will be selected for qualitative interview recruitment based on their pattern of survey completion, survey responses, and/or interactions with study staff. These participants will be sent the "Qualitative Interview Email" and/or will be invited to participate in the qualitative interview during contact with study staff for other study activities. After the initial email outreach, study staff will make a maximum of two follow up contact attempts by phone, text, or email, unless otherwise requested by participants. For participants wishing to withdraw or already withdrawn, any communication regarding the qualitative interview will include acknowledgement of study withdrawal and emphasize that participants are not being asked to join the study again. Participants who withdrew their HIPAA authorization or who expressed a desire to not be contacted again about this study will not be contacted/recruited for these formative qualitative interviews.

Several Kaiser Permanente healthcare providers whose patients enroll in the study will be invited to complete a brief survey via HealthConnect. The survey invitation will include a link to the provider survey instrument in REDCap. No incentive will be provided for this survey.

The estimated date for study completion is May 2024.

Participant Withdrawal

Participation in this study is purely voluntary. Participants are free to withdraw from this study at any time and will be removed from the study if requested. Participants who wish to withdraw will be offered the option to withdraw from intervention but continue with the follow up assessments. Subsequent contact with those who elect to continue with the follow up assessments will be for assessment purposes only. Participants will also be informed that should they choose not to continue to participate that their Kaiser Permanente healthcare will not be jeopardized.

Participants may be formally withdrawn from the study by the PI and study team if they (a) develop a condition that meets criteria for exclusion (e.g., psychosis) or (b) show evidence of functional deterioration that clinically indicates alternate services incompatible with continued participation (e.g., inpatient hospitalization). If a participant is withdrawn from the study, they will be provided information

on access to Kaiser Permanente resources at the appropriate level of care for their clinical presentation. Participants who are removed will be encouraged to continue participating in the remainder of the follow-up assessments as is compatible with their clinical status.

In the event of a potential study-initiated termination, the PI and the relevant study team members will consult. If merited, we will seek consultation with the IRB. The individual circumstances for termination may be variable and unique, so we are not pre-specifying the possible triggers and outcomes. After consultation with the IRB, the study team, and other inputs as needed (e.g., the participant's KP care team), the PI will decide final termination and write a corresponding justification. The terminated participant will be contacted to explain the outcomes and reasons for it. No further study procedures or events will be scheduled or delivered for that participant.

a. Data Analysis

Preliminary data evaluation. Before any analyses, we will conduct procedures to assess data quality and completeness and will evaluate missing data patterns. To maximize analytic team efficiency, we will audit data from the initiation of data collection. Careful descriptive analyses (e.g., mean, SD, range, skewness) will be conducted for all study variables of interest. We will evaluate distributions to ensure that they meet the assumptions of planned analyses (below), including the detection of outliers (another potential indicator of entry error).

Management of missing data. To carry out the planned ITT analyses, we use multiple imputation methodology to account for missing data. These methods preserve the correlational structure among the study measures and incorporates the uncertainty inherent in replacing missing values, and as with other imputation procedures, they assume data are “missing at random” (MAR). We will create 10 imputed datasets, repeating outcome analyses across each replicate, and will use Rubin’s rules to produce adjusted estimates and statistics from which inferences will be drawn.

Analysis of primary outcome. For our PHQ-9 primary outcome, we will test whether there are differences in score trajectories across time between arms with two-level hierarchical linear models (HLMs) in a growth curve framework. The first level of the model will include time as a predictor, modeling within-person variation. The second level will include a dummy variable for arm (e.g., 1=TAU+BLT+AP or TAU+BLT, 0=TAU) as the predictor variable for both the random effects of the intercept and slope for time. A significant coefficient for arm on the time slope would indicate that there are different trajectories across time for BLT arms versus TAU.

We will probe any significant arm x time interactions by graphing the simple-effects equations to determine whether the observed pattern is consistent with hypotheses.

Moderation and mediation. In addition to primary outcome analyses we will conduct exploratory analyses of moderation using variables identified through previous research and clinical expertise, specifically indication of pharmacotherapy use (1=yes, 0=no), age (continuous), gender (1=female, 0=male), race and ethnicity (1=racial/ethnic minority, 0=non-Hispanic white), baseline PHQ-9 (1=clinically elevated, 0=below clinical range), and EHR indication of mental health comorbidities such as eating disorders, anxiety (1=comorbidity, 0=no comorbidity). Moderation will be indicated by a significant time x arm x moderator interaction in HLM.

We will conduct exploratory analyses of the BLT mediation pathway as the extent to which the relation between BLT and outcomes is mediated by changes in participants' 1) sleep (SASS-Y and actigraphy, and PSQI subjective sleep quality), 2) total physical activity, and 3) circadian timing and chronotype. For example, to evaluate the mediating effect of PSQI sleep quality we will regress post-acute treatment PSQI on baseline PSQI and a randomization condition indicator; and we will regress follow-up PHQ-9 at post-acute treatment PSQI and a randomization condition indicator. Using the product coefficients mediation approach, we will use the resulting regression coefficients and standard errors (SEs) to estimate the indirect effect. Because SEs of the products of regression coefficients are not normal, we will use bias-corrected bootstrapping to estimate the SEs for the indirect effect. We will use a similar approach for the MI pathway to test the mediating effect of participants' increased readiness to change on BLT adherence.

Analysis of secondary outcomes. Continuous measures over time will be modeled with HLM methods described above. Health service use can be categorized into binary (e.g., met threshold for medication possession ratio, had > 1 hospitalization) and count outcomes (e.g., N of ED visits, primary care visits). Binary outcomes will be modeled with multivariable logistic regression, and the coefficient of study arm membership (e.g, 0=TAU, 1= TAU+BLT+AP & TAU+BLT) is the coefficient of primary interest. Count outcomes are modeled with either multivariable Poisson or negative binomial regression depending on which yields optional fit.

BLT process outcomes. To examine the effects of adherence and MI elements, we will contrast Arms 2 vs. 3 across months 2, 4, and 6, comparing: (a) % cumulative light box purchase; (b) % cumulative compensation for light box purchase; and (c) mean EMA-adherence (aka, dose). We will conduct these analyses using methods similar to those for secondary outcomes; however, the analysis sample will be restricted to Arms 2 and 3. We will describe similar metrics in the TAU condition (Arm 1).

Economic analysis. The future full trial will conduct a cost-effectiveness analysis (CEA) of the BLT intervention relative to TAU to inform the merits and costs of implementing such a program. In this pilot we will conduct both the relevant data collection and the economic analyses to prepare for this. Two major CEA cost components include 1) TAU costs related underlie all study arms, and 2) costs of the BLT intervention, including the equipment but also phone coach staff time. This pilot study provides the opportunity for our research team to hone the data collection process and measurement of these cost components, building on our several previous economic analyses conducted in concert with our mental health RCTs. While this pilot is underpowered to detect significant difference in costs between study conditions, we will be able to richly describe and categorize TAU services underlying each condition. In addition, Dr. Dickerson will lead efforts to estimate the total cost of the intervention by developing a data collection tool for phone coaches and research staff to track time used to the deliver the interventions. He will also periodically meet with those who are providing data to assess whether the tools are meeting their needs and if the data are truly capturing the resource intensity needed to deliver the protocol. This tool will be submitted in a subsequent modification.

Power analysis, sample size. The R34 pilot funding cap limits us to a feasibility sample that is insufficient for an adequately powered test of the hypothesis. Nonetheless, we provide an estimate of the statistical power obtained from this sample of a minimum of 90 participants (up to 100 ppts if recruitment success

allows). Meta-analyses suggest an overall effect size for BLT of d=0.84. We conservatively estimate the effect size likely to be obtained in this pilot trial as lower than reported in meta-analyses because this is a real-world effectiveness population; even with Arm 3 adherence promotion BLT adherence is likely to be lower than in efficacy trials, leading to lower clinical benefit. Assuming a retained sample size of N=81 at the final 6-month assessment, we conducted power analysis for the HLM of the primary outcome (using SAS version 9.4) to determine the minimum detectable effect size. At a two-tailed alpha level of 0.05 and conservatively assuming an autocorrelation of 0.70, we would have 80% power to detect a Cohen's d for the time by arm effect as small as 0.39 for the contrast between active intervention arms (Arms 2 and 3) and TAU, and as small as 0.55 for contrasts between individual arms; both estimates are medium effects. This pilot study is not powered to evaluate mediation, but we will conduct mediation analyses as if this were the full-powered R01 confirmatory trial to test feasibility of the analytic methods and to provide informative estimates of potential mediators. We estimate that we will have 80% power using a 95% bias-corrected confidence interval to identify effect sizes of 0.43 or larger for the pathways between randomization status to mediator, and mediator to outcome (BLT adherence for MI pathway, and PHQ-9 for BLT pathway); and we will be able to identify direct and indirect effects of 0.19 or larger, which correspond to a small-medium effect.

Use of pilot results to estimate power for the future full trial. Regardless of the between-condition effect size that we observe in this pilot, we will heed the cautions that have been raised about using pilot study results to estimate effect for full trial power/sample calculations. We will consider between-condition effect size (ES) results highly tentative given the small pilot sample and will use it only with wide confidence intervals when employing it to estimate power for the future full pragmatic trial. For example, if we obtain an effect size of d=0.45, we will generate a power/sample size matrix with estimated effects of 0.35, 0.40, 0.45, 0.50—all ranging around the observed effect from this pilot, but trending to somewhat smaller and more conservative effects.

b. Sharing of Results with Subjects
Immediate, individual level results will not be shared with participants. However, approximately 6 months after the study end we will send a brief summary of the results to participants via email and/or US post.

c. Data and/or Specimen Banking
Data collected for this research will not be used for future unspecific research. No specimens are collected in this study.

7. Privacy, Confidentiality and Data Security

Additional Information about Sensitive Data

As described previously, mental health diagnoses and/or records will be collected (e.g., prescription dispensing data and health care utilization). These data are necessary to identify potentially eligible participants in the recruitment phase and to examine possible moderators of effects during analysis.

Describe the plan for storage of data and/or specimens.

Data collected for all participants will be kept strictly confidential, except as may be required in the case of a psychiatric or medical crisis (reporting abuse, imminent danger to self or others). All research files

are kept on a secure server that uses multiple layers of data protection, and all research personnel sign a confidentiality agreement and receive human subjects protection training. These data are only used for the purpose of recruitment and for contacting study participants during the course of the study.

Data from participants who do not qualify for participation will be collected, including the reasons why participants did not qualify, and basic demographics from the EHR that are associated with the case-finding program (e.g., age, gender, gender minority status, race, ethnicity). This data will be used to enhance recruitment efforts in planned randomized control trial proposals, by permitting us to understand whether our study and/or recruitment methods may be less often acceptable to certain demographic groups. The data will be retained no longer than three years.

A unique study identifier will be assigned to each study participant and used to code the data.

Paper Data: We do not plan to utilize any hard copies of data. However, if it is necessary to collect hard copies (e.g., REDCap is unavailable), hard copies of data will be kept in a locked office at KP CHR to which only research staff has access. Hard copies of paper data will be stored at any location where staff are working remotely. Data for all participants will be kept strictly confidential, except as mandated by law. All research files are kept in locked file cabinets or in a locked file room.

Collection of data from subjects electronically

Electronic data will either be (a) stored on the study file service, which is accessible only to study staff who have been given access by the project manager or the principal investigator, or (b) stored in REDCap. Assessment and intervention data will be collected via REDCap. An email containing a unique survey link will be sent to participants or data will be directly entered into REDCap by study assessment staff. Within REDCap data collection forms, participants will be identified by a study ID only.

Recordings: Recordings of intervention contacts with participants will be stored on a secure file server at CHR, using the study ID for identification. These recordings will be used for training and quality assurance purposes only. A select sample of the recordings will be securely transferred to our research collaborator, Dr. Denise Ernst, via the SFT site for quality assurance purposes. Dr. Ernst will access the SFT website through a uniquely assigned account and download the files to a secure location on their network.

Destruction of Identifiers: Once the study is completed, identifiable information will be removed from the study tracking system and stored in the CHR secure electronic data storage system until such time that the PI no longer needs the data. At that time, the data will be professionally erased following standard procedures in place at that time. Identifiable information in paper form will be stored in the secure off site storage area until the PI no longer needs the data at which time it will be returned to the CHR and sent to be shredded.

Does this study involve the disclosure of PHI to a collaborator?

Dr. Denise Ernst. A select sample of phone coaching call recordings will be securely transferred to our research collaborator, Dr. Ernst, via Secure File Transfer for quality assurance purposes. Dr. Ernst will access the SFT website through a uniquely assigned account and download the files to a secure location on their network. While the recording files will be labeled with study ID and study staff will not solicit PHI, it is always possible that a participant will share a name or other unique identifier during a recorded phone coaching call.

National Database for Autism Research (NDAR). This study is subject to NIH policies on data banking with NDAR. We will submit data on study participants to NDAR via the National Institute of Mental Health Data Archive system. Data will be de-identified prior to upload to the NDA. However, there remains the possibility of deductive disclosure of participants with unusual characteristics.

Data Commitments (data and specimen sharing)
FROM KPNW

Recipient and Description of Materials	**Identifiers*** (note w/an X)	**Health Information**** (note w/an X)	**HIPAA Documentation** (see policy NWRC.PRIV.04)
Dr. Denise Ernst Phone coaching call recordings labeled with study ID will be shared via SFT. Study staff will not solicit PHI during recordings, but it is possible that a participant will share a name or other unique identifier during a recording.	__Fully Identifiable __Limited Data Set X__De-Identified __Aggregate	__Yes _X_No	__Signed Authorization __Waiver of Authorization __Limited Data Set only (DUA Required) __De-Identified or Aggregate Data _X_N/A, No Health Information
National Database for Autism Research (NDAR) We will share de-identified participant data with the National Institute of Mental Health Data Archive (NDA) as required by the NOA.	__Fully Identifiable __Limited Data Set _X_De-Identified __Aggregate	__Yes X__No	__Signed Authorization __Waiver of Authorization __Limited Data Set only (DUA Required) __De-Identified or Aggregate Data X__N/A, No Health Information

8. Provisions to Monitor Data to Ensure the Safety of Subjects

Dr. Clarke will assume responsibility for and oversee patient safety on the overall project. Drs. Clarke and Dickerson will liaise with a data safety monitoring board (DSMB), which will have overall review responsibility for patient safety and serve as a reporting body to the NIMH and study IRB. The DSMB will consist of 3 TBN members: a community mental health advocate, a biostatistician, and another clinical or research mental health expert.

The DSMB will conduct twice-yearly reviews to determine whether patient safety has been adequately safeguarded. The DSMB members, in consultation with Dr. Clarke, are empowered to take whatever immediate action is necessary to safeguard the welfare of individual patients. The DSMB group will also examine adverse events (AEs) annually, and serious adverse events (SAEs) as they occur (see reporting times below). Safety information will be collected at each assessment timepoint as described previously in section 6 under "Monitoring for Safety".

Dr. Dickerson will generate quarterly interim reports for the DSMB as well as summary 6-month reports. These interim analyses will be conducted for safety outcomes (suicidal behavior, other crises, study terminations, all AEs, SAEs, other events) and data quality indicators (recruitment, retention, instrument reliability, intervention fidelity), but not routinely for clinical effectiveness or economic outcomes. Study conditions will be masked (e.g., Red, Green, Blue arms) in these safety and data quality reports but the DSMB can request unblinding at its discretion should a safety or data quality concern arise.

The study team will notify the IRB and the DSMB (and as required, the NIMH Project Officer) of any clinically significant new emergent issues detected in this study, even if seemingly unrelated to the study, BLT or procedures (e.g., new diagnosis of cancer). We will follow KPNW IRB reporting dates for DSMB notification. In many cases, because the study does not routinely assess participants for new emergent issues that are not anticipated as a possible risk (see list of expected clinical issues in section 6 under "Monitoring for Safety"), these incidental diagnoses/conditions will be detected either through spontaneous patient report or review of the electronic health record (EHR). Given that all participants are members of the Kaiser Permanente health organization, in the case of new EHR-recorded diagnoses/conditions this means that the usual care health providers (primary care providers, mental health and other specialists) will already know about and will be addressing these conditions/diagnoses.

Given the enrolled population will have been pre-identified by virtue of EHR depression clinical diagnosis or elevated PHQ-9, none of the clinical events summarized previously (worsening depression, suicide/self-harm, new comorbidity, Bipolar Disorder) are considered 'unexpected.' In other words, they are not unusual given the high comorbidity of depression with other mental disorders generally. Suicide, self-harm, anxiety, substance misuse and BD are particularly possible given the case-selection for active depression disorder and/or symptomatology. In this study, the most likely anticipated event possibly related to research would be the precipitation of BD and any variant on exposure to BLT. We will make appropriate clinical referrals to emergency or non-emergency services, and/or communicate with TAU providers as warranted – and as summarized previously.

9. Risks and Benefits

a. Risks to Subjects

The assessments and treatments in this study pose no greater risk than standard treatment or therapy, or clinical interviews. These risks include:

1. The potential for an unintended breach of confidentiality. We will be in touch with participants by email and text message to schedule study events or to remind them about surveys. Any confidential information sent through the Internet or by text message has a small risk of being read by someone other than the person it was sent to. As described in the data handling section above, we will store all information in locked cabinets, on password protected servers, or within REDCap (a HIPAA-compliant, web-based application for data capture).
2. The possibility of distress in association with addressing emotional difficulties during the completion of surveys or study activities. Participants are free to refuse to answer any questions and will be reminded of this prior to addressing sensitive subjects.
3. Engaging in bright light therapy may have risks for individuals with vulnerability to phototoxicity, photosensitive skin, or who are taking a photosensitizing medication or herb. Our EHR case-finding program will exclude patients with active EHR diagnoses and prescriptions representing any of the few contraindications for BLT. We will also ask about these diagnoses and conditions during the screening survey to further exclude those with these potential contraindications.
4. There is a small risk of manic activation from BLT light exposure. This risk is inherent in the general population and could occur whether or not individuals were enrolled in the study. Our EHR case-finding program will exclude patients with any variation of bipolar disorder recorded in the EHR. We will also screen for emerging symptoms of mania during the screening survey and follow-ups. We will inform the TAU providers of our participants that their patients are participating in this study, which may involve self-administration of BLT.

If study staff suspects a participant is in danger or unsafe, they will immediately report this to a licensed study team member and discuss possible strategies for responding (see DSMP section for more details).

Some participants may become pregnant during the study. However, nothing in the study procedures or interventions is expected to have any adverse impact on the mother or child.

b. Potential Benefits to Subjects

The study treatment participants may utilize as a result of participating in this study may help improve their well-being and functioning and reduce mental health problems. Additionally, participants often feel good that participating in research may help other people.

10. Economic Burden to Subjects

There are no costs to participants for study assessments or study phone coaching activities. However, participants may incur the following costs during participation:

- Usual care underlies all three arms of the study, and some of that usual care may be directed at depression. Participants may incur costs for usual care; e.g., co-pays; paying for treatment, therapies, or other interventions. However, the delivery of these usual care services will be at the discretion of the KP providers, or community providers for usual care services participants may receive outside of KP.
- Participants in study arms 2 and 3 will be encouraged, but not required, to purchase a light box with an estimated cost of $70 to $200 depending on the model. All of these participants will be provided with written information about obtaining compensation (up to $80 in Fred Meyer gift

cards) for this purchase through the study. In Arm 3, a study coach will guide participants to obtain compensation. Participants will be responsible for any purchase price greater than $80. The study light box compensation process is modeled to simulate the KP durable medical equipment (DME) benefit, which does not currently cover LBs for non-SAD depression. Preliminary conversations with the DME decision group seem to indicate willingness to cover LBs for non-SAD depression when a published meta-analysis determines that there is sufficient evidence of LB benefit for non-SAD depression. While there are individual studies showing LB benefit for non-SAD depression, this evidence does not quite meet the threshold for changing the DME benefit.

Participants will be informed of these potential costs in the consent information form and during the recruitment call with our staff.

11. Compensation to Participants

Participants will be provided with Amazon gift certificate incentives for participating in each assessment ($25 for baseline, $25 for 2-month follow up, $30 for 4-month follow up, $40 for 6-month follow up). Participants are compensated for completing each assessment, even if the participant chooses to not finish all portions of the surveys. Participants who complete the qualitative interview will be provided with a $20 Amazon gift certificate. Participants will be notified of the compensation details in the consent information sheet and during the recruitment call with our staff.

12. Resources Available

Not applicable.

13. Additional Approvals

Not applicable.

14. Drugs or Devices

a. Drug Studies
Not applicable.

b. Device Studies:
Not applicable.

15. Multi-Site Research

N/A

16. Community-Based Participatory Research

N/A