Clinical Trials Cover Page

Official Title: Morning Light Treatment at Home to Improve Glucose Metabolism in People at Increased Risk for Type 2 Diabetes

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PROTOCOL TITLE:
Morning Light Treatment at Home to Improve Glucose Metabolism in People at Increased Risk for Type 2 Diabetes

PRINCIPAL INVESTIGATOR:
Kristen Knutson
Department of Neurology
312-503-1526
kristen.knutson@northwestern.edu

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OBJECTIVES:
The primary purpose of this pilot study is to test a novel head worn light device (Re-Timer®) as an intervention to improve glucose metabolism in people with prediabetes. The hypothesis is that morning light treatment will improve glucose metabolism. This is a pilot study and the data from this project will be used to develop a larger clinical trial.

BACKGROUND:
Circadian Misalignment Impacts Risk for Type 2 Diabetes
The central circadian clock, which regulates many circadian rhythms, is located in the suprachiasmatic nuclei (SCN, [1]). In humans, central circadian timing is most reliably estimated from the onset of melatonin secretion in dim light (DLMO [2,3]), which occurs ~2-3 h before habitual bedtime [4]. Melatonin must be measured in dim light because it is suppressed by light [5,6]. In most humans (>70%), the endogenous period of the central circadian clock is greater than 24 h [7,8], resulting in an endogenous tendency to drift later each day (phase delay). Such drift can result in a mismatch between behavioral cycles (sleep-wake and meal times) and internal biological time, known as “circadian misalignment”. There is evidence indicating that circadian misalignment is associated with increased diabetes risk and worse diabetic outcomes. Later sleep timing or self-reported eveningness (suggestive of circadian misalignment) is positively associated with obesity [9-12], and T2DM (OR 1.73-2.5, [13,14]), and predictive of future increases in BMI [15], even after adjusting for potentially confounding variables such as age, sex, race, SES, physical activity and sleep duration. Later sleep timing is also associated with reduced glycemic control (higher HbA1c) in patients with T2DM [16], even after adjusting for age, sex, race, BMI, insulin use, depression, sleep debt and diabetes complications.

Laboratory studies have also investigated the effects of circadian misalignment on diabetes risk in healthy humans. In one study, circadian misalignment resulted in an overall 6% increase in 28 h levels of glucose, despite a 22% increase in insulin, and 3 out of 8 subjects exhibited 2-h postprandial glucose responses >140- <210 mg/dl (prediabetic or diabetic levels) [17]. In a second study, circadian misalignment resulted in an 8% increase in glucose but 12% decrease in insulin (fasting), and a 14% increase in glucose but 27% decrease in insulin (postprandial) [18]. However, in these studies circadian misalignment also disrupted sleep, and disrupted sleep can impair glucose metabolism [19]. A third study examined less severe circadian misalignment (2 x 2 daytime sleep episodes interspersed with night-time sleep) and controlled for sleep by

comparing to a control condition with equivalent sleep loss [20]. They found that circadian misalignment, independent of sleep loss, resulted in an additional 26% reduction in insulin sensitivity in men, with no compensatory increases in insulin release, reflecting a significant increased risk of T2DM. The authors concluded "this provides evidence in support of an intrinsic adverse effect of circadian misalignment on glucose metabolism." (p1868, [20]).

The precise mechanism(s) by which changes in circadian timing could affect metabolism remain to be determined, but may include: (1) direct impact of SCN activity on glucose regulation via multisynaptic projections from the SCN to the liver and pancreas [21-23], (2) suppressed melatonin levels (light exposure during night), which is independently associated with increased insulin resistance in nondiabetics [24] and the development of T2DM [25]. Indeed, the melatonin receptors on pancreatic beta-cells [26] preserve beta-cell function by preventing "functional overcharge" [27,28], (3) circadian misalignment results in peripheral molecular dysfunction [29], which downstream in the pancreas and liver can adversely impact diabetes risk [30-32]. Thus, "dysregulation of circadian secretion may be a key to the increase of T2DM" (p829, [33]).

The Effect of Morning Light Treatment on Glucose Metabolism Remains to be Investigated

Light is the strongest environmental signal that can alter circadian timing. Light is captured by the 5 retinal photoreceptors (rods, 3 cones, and the intrinsically photosensitive retinal ganglion cells [ipRGCs] [34,35]). The ipRGCs are the primary circadian photoreceptor as they transmit the light signal directly to the SCN [34,36]. The ipRGCs are most sensitive to short (~480 nm) wavelengths of light. Evening light shifts circadian timing later (phase delays) and can exacerbate the endogenous tendency towards circadian misalignment [37,38]. By reducing exposure to evening light, there is potential to phase advance circadian timing [39,40]. Conversely, morning light shifts the clock earlier (phase advance), and helps to realign circadian timing to more closely match the external environment, and reduce circadian misalignment [37,38]. Thus, morning light is the most important light most humans receive every day.

Given the associations between later sleep/circadian timing and risk for T2DM, one would expect morning light to be associated with a reduction in risk for T2DM. Four studies have examined these relationships. The first reported that the addition of daily morning light (1 h, 5,000 lux) to a 6 week exercise program in 17 overweight/obese people led to a significant reduction in body fat that did not occur with exercise alone [41]. A second study reported that daily morning light (45 mins, 1300 lux) for 3 weeks significantly reduced body fat and appetite in 34 overweight women [42]. The reduction in body fat was seen after 2 weeks of morning light treatment [42]. A third study reported that a single dose of morning light (2 h, 60 lux) changed appetite regulating hormones (leptin, ghrelin) in a direction that would reduce hunger in 11 sleep deprived subjects [43]. Last year, a study of healthy individuals reported that brighter light exposure (>500 lux) earlier in the day independently predicted a lower BMI, even after adjusting for age, sex, season, activity and sleep duration [44]. All these studies point to the high potential for morning light treatment to reduce risk for T2DM, and highlight that many of the effects of morning light were observed in small sample sizes. Indeed, as others have recently stated: (1) "prescribed light exposure needs to be tested for its ability to restore the physiological dialogue between circadian mechanisms and metabolic pathways" (p7, [45]) and (2) "interventional studies assessing the role of manipulating the master clock in the treatment of T2D are needed…the master clock can be manipulated by light therapy" (p326, [46]).

Preliminary Data

Later Circadian Timing is Associated with Increased Risk for Type 2 Diabetes

Drs. Knutson and Burgess collaborate on an ongoing R01 project to examine the cross-sectional association between sleep/circadian timing and diabetes risk in persons without

diabetes. We examined the associations between the timing of sleep based on 1-week of actigraphy (average midpoint of sleep) and circadian timing (gold standard circadian phase marker in humans, DLMO), and fasting glucose levels in the first 20 subjects with data (Figure 1). Results indicate that later sleep/circadian timing is significantly associated with higher fasting glucose even in those who do not currently have diabetes. These data are entirely consistent with the literature and represent the first data examining the relationship between the DLMO and fasting glucose.

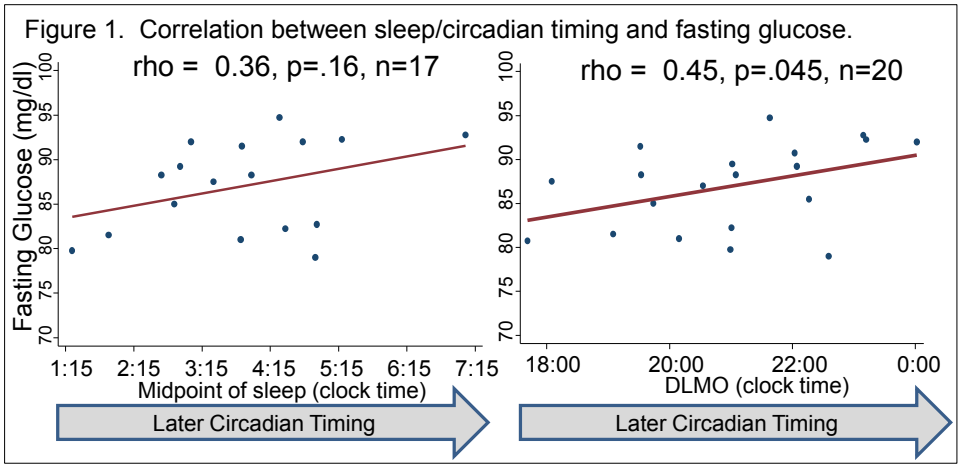


Figure 1. Correlation between sleep/circadian timing and fasting glucose.

Creating a Placebo Light Treatment

We now plan to test an active Re-timer® versus a placebo Re-timer®. We first considered creating a placebo Retimer® by retrofitting the Re-timer® with red LEDs (~660 nm), as this wavelength is further from the maximum sensitivity of the ipRGCs [34,36]. However, this would have required additional ocular and electrical safety testing. Furthermore, subjects would have quickly discovered the red Re-timers® were not standard treatment, as we find many subjects look up their light devices on the internet. Thus, it appeared likely that subject expectations would have differed significantly between the standard versus red Re-timer®. Therefore, we enlisted the help of Dr. Dingcai Cao from Rush University (consultant on this grant), who used neutral density filters to markedly reduce the light intensity of the Re-timers® to a level that will not shift circadian timing. There are no safety concerns because the light from the already safety approved Re-timer® has simply been dimmed. Dr. Cao's spectroradiometer recordings confirm that irradiance in these dimmed Re-timers® is reduced from 230 $\mu W/m^2$ to 3 $\mu W/m^2$, and lux reduced from 500 lux to 7 lux (Figure 2). Importantly, the placebo (dimmed) Re-timers® appear identical to those featured on the Re-timer® website and so are a highly believable placebo that should lead to similar expectations between treatment groups.

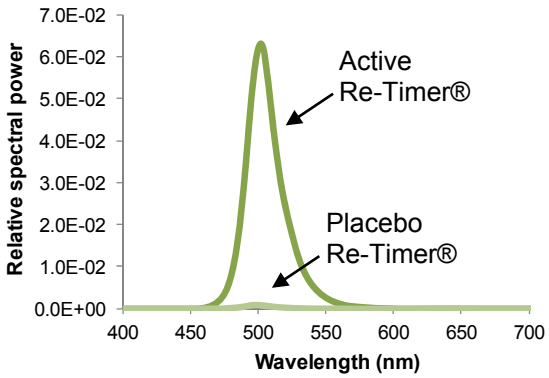


Figure 2. Spectral power distribution of the active vs. placebo Re-Timer® measured with a PR670 spectroradiometer with a 2nm resolution.

Measures of Compliance to Light Treatment

Dr. Burgess (Rush University PI) developed a measure of compliance to the Re-timer®, as none exists. By securing an Actiwatch Spectrum to the inside of the Re-timer® (does not unbalance frame), she can examine (1) green light to determine active Re-timer® on/off times and (2) activity to confirm both placebo and active Re-timers® are worn at the assigned times.

INCLUSION AND EXCLUSION CRITERIA:

We will enroll 34 subjects (50% female, age 35-70 y) with prediabetes to complete the study. Laboratory sessions will occur during women's follicular phase or women will be postmenopausal (≥6 months since last menses). These subjects will: (1) be overweight or obese (BMI≥25 kg/m^2), (2) have prediabetes (HbA1c 5.7% to <6.5%), and (3) be free of severe obstructive sleep apnea (apnea-hypopnea index<30). The laboratory sessions will occur during women's follicular phase or women will be postmenopausal (≥6 months since last menses). Women on oral contraceptives or hormone replacement therapy will be excluded (alters OGTT [48,49] and melatonin [4]). We will also exclude women who are pregnant, planning on becoming pregnant, or are breastfeeding. We will exclude men and women who have a child at home that does not sleep through the night. Adults unable to consent, individuals who are not yet adults (infants, children, teenagers), pregnant women, and prisoners are also excluded.

Additional exclusion criteria include: history of type 1 or type 2 diabetes, use of diabetes medications, age outside 35-70 years (we will not enroll anyone older than 70 years because of a reduced response to light [50]), smokers, shift workers, failing urine drug test (drugs of abuse, nicotine), eye disease, photosensitizing medications, regular hypnotic use (≥3 nights/week), , daily beta-blocker, NSAID or melatonin use (confounds DLMO), history of the following psychiatric disorders (confounds effect of light treatment, per relevant items from Mood Disorder, Psychotic Screening and Substance Use Disorders Modules of the Structured Clinical Interview for DSM-IV Axis I Disorders - Non-Patient Edition (SCID-IV/NP; [51]): schizophrenia, bipolar depression, substance abuse, suicidal ideation, or obsessive compulsive disorder, PTSD). At screening subjects who score >20 on the Center for Epidemiologic Studies – Depression (CES-D) scale[52] will also be excluded. Additional exclusion criteria include irregular menses, history of cardiovascular disease (excluding hypertension), endocrine, kidney, gastrointestinal or liver disorder, seizures, and cancer. Subjects will be scheduled to participate ≥ 1 month from travel outside the central time zone, and during a time with minimal special events.

STUDY-WIDE NUMBER OF PARTICIPANTS:
N/A Northwestern University is the only site where recruitment and participation in study will occur.

STUDY-WIDE RECRUITMENT METHODS:
N/A Northwestern University is the only site where recruitment and participation in study will occur.

MULTI-SITE RESEARCH:
N/A Northwestern University is the only site where recruitment and participation in study will occur.

STUDY TIMELINES:
The protocol will last 6-10 weeks depending on how soon after consent the subject can participate. We aim to complete recruitment by 05/31/2018 and primary data analysis by 05/31/2019.

STUDY ENDPOINTS:

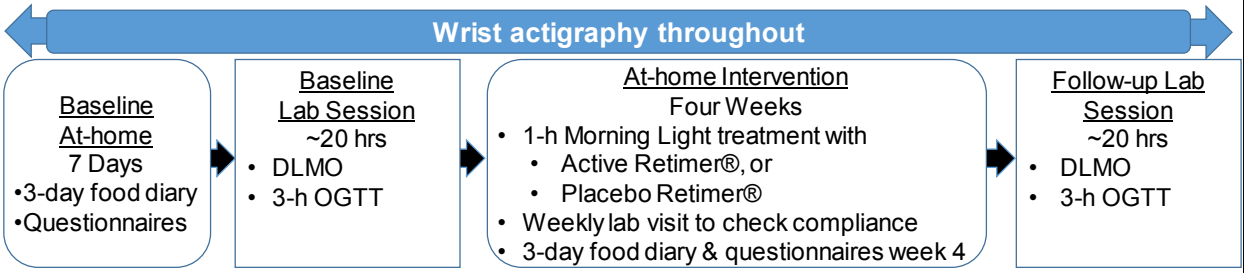
The goal of this research project is to test a novel behavioral intervention, morning light treatment, to see if it can improve glucose metabolism in people with prediabetes.

Primary Outcomes:
Outcome 1: We will determine the effect of active versus placebo morning light treatment on glucose metabolism in individuals with prediabetes.

Outcome 2: We will determine the extent to which circadian phase advances in the DLMO are related to improvements in glucose metabolism in individuals with prediabetes.

PROCEDURES INVOLVED:
Figure 3 presents an overview of the 5 week protocol. After screening for eligibility (see below) and informed consent, subjects will wear a wrist actigraph throughout the study. Subjects will complete a daily sleep and medication log, a questionnaire packet, and a 3-day food diary at the end of the baseline week and week 4. After the baseline week, there will be an overnight stay at the Northwestern University Clinical Research Center. Questionnaires and food diaries will be reviewed and body fat via bioimpedance will be measured. The DLMO will be assessed. Subjects will be given dinner 4 h before bedtime and consumed 3 hours prior to bedtime to ensure duration of fasting is at least 8 h and does not exceed 14 h. In the morning, a 3 hour oral glucose tolerance test (OGTT) will be performed in the Clinical Research Unit (CRU) 2 h after wake. Subjects will then begin a 4 week morning light treatment (see details below). The first 10 subjects will be assigned active (bright), and the following 5 will be assigned placebo (dim) Re-timer®. If more subjects are enrolled in the study, the next 10 will be placed on active (bright) treatment. Subjects will receive feedback on their compliance at weekly visits. Subjects will be paid $95 in cash at each visit to increase likelihood of participation and retention. In the final week, subjects will complete questionnaires and food diaries again. After the 4 week treatment, subjects will repeat the laboratory session for reassessment of the DLMO and OGTT.

Figure 3. Protocol Overview



Subjects and Screening. As a first step in testing morning light treatment to improve glucose metabolism, we will enroll a sample of 34 subjects (50% female, ages 35-75 years), who are most likely to benefit from morning light. These subjects will: (1) be obese (BMI≥25 kg/m^2), (2) have prediabetes (HbA1c 5.7% to <6.5%), and (4) be free of severe obstructive sleep apnea (apnea-hypopnea index<30). Subjects will be screened initially over the phone or by completing the screening survey online via RedCap, and be asked to begin recording their bed times and wake times to determine the schedule for their light treatment. If potentially eligible, they will be invited to a pre-study screening visit, during which height and weight and HbA1c (finger stick of blood) will be assessed. Subjects will also need to pass a urine drug screen. Dr. Aleppo, a board-certified endocrinologist (co-investigator), will refer any subjects who are identified as having diabetes, for treatment. Any subjects identified as having prediabetes will also be

referred to treatment, but also invited to participate in the final home screen for obstructive sleep apnea. Note that subjects who begin prediabetes treatment prior to the end of the study will be dropped, however, due to common delays in seeing a physician (over a month), this is unlikely to affect many subjects (as part of intent-to-treat analysis the last observation will be carried over). Subjects will be instructed in the use of the WatchPAT™ device (Itamar Medical Ltd.) to screen for obstructive sleep apnea. WatchPAT utilizes Peripheral Arterial Tone (PAT), a physiological signal that mirrors changes in the autonomic nervous system caused by respiratory disturbances during sleep. The automatic algorithm of WatchPAT analyzes the PAT signal amplitude along with heart rate and oxygen saturation to identify respiratory events and provide AHI. Dr. Park, who is board certified in sleep medicine and a consultant on this grant, will oversee the interpretation of the home sleep screen. Any subject with an apnea-hypopnea index≥15 will be informed of the result by study investigators and offered referral to a nearby sleep center for treatment and excluded from study participation.

Laboratory sessions will occur during women's follicular phase or women will be postmenopausal (≥6 months since last menses). Women on oral contraceptives or hormone replacement therapy will be excluded (alters OGTT [48,49] and melatonin [4]). Additional exclusion criteria include: history of any form of diabetes, smokers, shift workers, eye disease, photosensitizing medications, regular hypnotic use (≥ 3 nights/week) daily beta-blocker, NSAID or melatonin use (confounds DLMO), history of psychiatric disorders (confounds light treatment), pregnancy/breastfeeding, irregular menses, history of cardiovascular disease (excluding hypertension), endocrine, kidney, GI or liver disorder, seizures, cancer. Recruitment will include advertising the study to current diabetes patients to recruit family members who may meet eligibility criteria. Dr. Aleppo sees over 350 diabetes patients each year. Recruitment will also include posting fliers, brochures, newspaper advertisements, and advertisements around Chicago, online, at various clinics in the Chicago area (as permitted by the local staff and healthcare providers) and attending community events. Note that recruitment at various clinics will involve only distributing flyers and brochures, but will not include sharing of patient information directly with us. Thus, the initial contact will be made by the volunteer.

Light Treatment. The 1 h daily morning light treatment will start within a few minutes after each subject's average wake time, as determined from the baseline week of actigraphy. The light treatment may start up to 1 h earlier to accommodate the subject's usual morning schedule (work, child care) if required [53,54]. Subjects are provided with an alarm set to the start of the morning treatment. A light log to note light on/off times and any interruptions to the light treatment will be provided. Subjects will be instructed to maintain their baseline sleep duration throughout the light treatment. Daily bed and wake time phone calls to a time-stamped voice mail will be reviewed daily with phone calls to subjects if required to ensure compliance. Wrist actigraphy data will be reviewed weekly in the presence of the subject. Importantly, the Re-timer® light device is commercially available. The adjustable nose pad on each Re-timer® (whether active or placebo) will be individually fit to each subject to optimize the light treatment (Appendix). After the introduction to the Re-timer® (whether active or placebo), subjects will complete a treatment expectation item of 0 "expect no change" to 10 "expect to be healthier". In between weekly visits, subjects will be encouraged to call research staff 24/7 with any questions about the light treatment. At the start of the second laboratory session, subjects will complete a treatment satisfaction item of 0 "not at all satisfied" to 10 "extremely satisfied".

Measures

Oral Glucose Tolerance Test. During each laboratory session, a 3-h 75 gm OGTT will be performed in the CRC. After an overnight fast, a blood sample for fasting glucose and insulin will be obtained at -15 mins and 0 mins immediately followed by the oral administration of 75g of

dextrose. Plasma glucose and insulin blood samples will be collected at 30, 60, 90, 120, 150 and 180 min after glucose ingestion. The primary outcome measure will be fasting glucose levels, a commonly used clinical marker. Fasting glucose levels are significantly correlated with HbA1c [55], which is a marker of glycemic control over 3 months that the ADA now recommends health care providers use to assess treatment effects [56]. We will not measure HbA1c as an outcome measure in this pilot study because our 4 week intervention is unlikely to affect a measure of the 3-month average of plasma glucose levels. Secondary outcomes will be the 2-h glucose level and the Matsuda index (MI) of insulin sensitivity [57]. These measures will allow us to ascertain whether there was an improvement in glucose metabolism. The CRC regularly performs these tests and Drs. Knutson and Aleppo are experienced in their interpretation. As noted above, subjects who are identified as having T2DM [56] at the screening visit will be notified, excluded from study participation, and referred to a physician/clinic. Subjects who are identified as having prediabetes [56] at the screening visit will be notified, included in study participation if they meet all other inclusion criteria, and referred to a physician/clinic. Dr. Aleppo will oversee these referrals. Subjects who begin diabetes treatment prior to the end of the study will be dropped, however, due to common delays in seeing a physician (over one month), this is unlikely to affect many subjects. If the original HbA1c screen suggested prediabetes but the fasting and/or 2-h glucose suggest diabetes, the subject will be retained in the study, but Dr. Aleppo will discuss the results with the subject.

Dim Light Melatonin Onset. Subjects will be prompted by phone calls to refrain from NSAID use 72 h, and alcohol/caffeine 24 h, before each laboratory session and will be breathalyzed on arrival. Lights in the collection room are dimmed (<5 lux) beginning 6.5 h before and up to the subject's habitual bedtime as determined from the baseline week of actigraphy. After 30 mins in dim light, saliva samples via salivettes will be collected every 30 mins according to standard procedures [58-61]. Saliva samples are frozen until delivery to Rush where they are thawed, centrifuged, refrozen and shipped in dry ice to Solidphase, Inc. (ME) who performs direct RIA assay using standard commercially available ALPCO kits [8,62]. Dr. Burgess will calculate the DLMOs and a trained research assistant will confirm accuracy before results are unblinded. We will calculate DLMO threshold as the mean of 3 low daytime points plus 2 times the SD of the 3 points as per consensus report [63]. The morning light treatment will phase advance the DLMO by ~1-2 h [37,53,54].

Wrist Actigraphy. Sleep timing and duration at baseline and during the intervention will be assessed continuously using wrist actigraphy (Actiwatch Spectrum, Philips, Inc.). Due to the unobtrusive nature of this device, habitual sleep behavior can be measured over weeks. Dr. Knutson has extensive experience working with actigraphy data [64-66]. Actiwatch monitors feature digital integration, which is the most accurate measure of both movement level and intensity. Each subject will also complete a short sleep log every day, and call a time-stamped voice mail when they go to bed each night and when they wake up each morning [58,67].

Food Diary. Subjects will complete a 3-day food diary for the last 3 days of the baseline week and week 4. The food diary will ask for the amount and types of food eaten and the time of meals and snacks. Diet analysis will be performed using ESHA Food Processor version 10.7, which calculates the overall calorie intake and estimated calories obtained from each nutritional component. Dr. Knutson has experience with this method and software and is using them in a current R01 project.

Questionnaires. Sociodemographic information will be collected only once and will include age, sex, education, employment status and the MacArthur Socioeconomic Questionnaire [68]. Subjects will complete several questionnaires at both baseline and week 4 of the intervention, including, an assessment of physical activity (International Physical Activity Questionnaire –

Short Version), and health factors (self-rated health [69], Physical Health Questionnaire [70]) in case of significant changes in health during the study. We will also include several sleep and circadian questionnaires: circadian preference based on the Horne-Ostberg Morningness-Eveningness ("owl-lark") questionnaire [71], Munich Chronotype Questionnaire, Pittsburgh Sleep Quality Index, and Epworth Sleepiness Scale. We will also administer Cohen's Perceived Stress Scale [72], and the Center for Epidemiologic Studies - Depression Scale [52]. Finally, we will include questionnaires to assess frequency of caffeinated beverage, alcohol and tobacco consumption. The Systematic Assessment for Treatment Emergent Effects questionnaire (SAFTEE) will be administered weekly to assess potential side effects of intervention. Questionnaire responses will be entered into the password-protected REDCap database and saved according to confidential study ID number.

DATA AND SPECIMEN BANKING:
N/A No data or specimen banking will occur.

DATA AND SPECIMEN MANAGEMENT:
Sample Size and Power Analysis
We plan to enroll 34 subjects (50% female, age 35-70 y) with prediabetes. We conservatively estimate a 17% attrition rate (final n=28) which includes dropouts and noncompliance (noncompliance defined as <25% of morning light treatment, as per [77]). This attrition rate is based on Dr. Burgess' light treatment trials (5% such attrition), and the work of others (4 week bright light treatment group 6% attrition [77], 12 week bright light treatment group 19% attrition [78]). Note that subjects who obtain only 25% of the prescribed active light (e.g. 15 min/day) are likely to obtain some benefit, as even only 15-20 mins of morning light can be clinically effective [79,80], and only a 12 min pulse can shift the DLMO [81].

A primary goal of this project is to determine the effect sizes associated with morning light treatment to develop a larger RCT. However, for this pilot project we also estimated the required sample size to detect a clinically meaningful change in our primary outcome measure, fasting glucose level. We will also measure 2-h glucose and MI from the OGTT but have kept fasting glucose level as our primary outcome measure as it is a commonly used clinical measure. To estimate sample size for fasting glucose, we used a standard deviation (SD) of 9.0 mg/dl, which is the mean SD in a large sample of men and women with prediabetes [82]. Using these values for a two-tailed independent t-test, with a total of 14 subjects per group, we will have 81% power (α=.05) to detect a change of 10 mg/dl, which is a clinically meaningful change and similar to that observed in a 2-week drug study [83]. Thus we are well powered with an anticipated final sample size of n=28 to detect a clinically meaningful change in fasting glucose.

Data Analysis
Aim 1: For our primary analyses, we will examine the effect sizes in active treatment group. The analysis will use two-sided statistical tests and a nominal significance of 5%. Our primary analysis will focus on the pre-post measurements in the active group. As a descriptive analysis, we will estimate the mean outcome measures at each time point for each subject and test time-specific differences using non-parametric tests. If we recruit sufficient subjects for the placebo condition, we will compare the effects in the two groups.

Aim 2: To determine the extent to which circadian phase advances in the DLMO are related to improvements in glucose metabolism, we will first examine if the DLMO has changed significantly in the active light treatment group (and compared to placebo if possible), and then

examining if these differences are correlated with changes in glucose metabolism measures.

Exploratory Aim: In a similar analysis to Aim 2, we will examine possible alternative mediators (body fat, activity, total caloric intake, and sleep fragmentation [wrist actigraphy]) through which morning light treatment may impact glucose metabolism (fasting glucose, 2-h glucose, MI). We will measure body fat because it was reduced in two previous light studies (reviewed in A.2.). We will measure physical activity because light treatment has an energizing effect [84]. We will assess total caloric intake, as differences in circadian timing can impact diet [85]. We do not expect changes in sleep duration as subjects will be instructed to maintain their habitual sleep duration during the treatment. However, a shift in circadian timing can impact sleep consolidation [86] so we will assess sleep fragmentation from wrist actigraphy.

Confidentiality
Study records will be kept confidential and data and records will be stored in locked cabinets in private offices. Electronic data files will be stored on password-protected computers. Data files and documents (with the exception of the consent form) will be stripped of identifying information and subjects will be identified only by a unique study ID code. All saliva samples will be deidentified using only the study ID code.

Specimen Handling
The saliva specimens will be stored in -20C freezers and then transported in insulated travel packs to Rush University by study coordinators. Once assayed they will be destroyed. They will be destroyed appropriately according to procedures regarding handling of biological specimens.

PROVISIONS TO MONITOR THE DATA TO ENSURE THE SAFETY OF PARTICIPANTS:
This study will recruit volunteers with prediabetes and study them for 5 weeks. Subjects will be assigned to one of two intervention groups: (1) *active* morning light treatment with a commercially available Re-timer® or (2) *placebo morning light treatment with dimmed Re-timer®*. This project is considered to be “minimal risk” because the probability and magnitude of harm or discomfort anticipated in the research are not greater than those ordinarily encountered in daily life or during the performance of routine physical and psychological examinations or tests.

All adverse events, serious and non-serious, occurring during the course of the study will be collected, fully documented, and reported to the Northwestern University Internal Review Board (IRB) by the Principal Investigator, Dr. Knutson. For each adverse event, the investigator will provide the onset, duration, intensity and treatment required, outcome and action taken. In addition to adverse event reporting, the investigators will report a summary of the protocol findings, subject recruitment, drop-outs, and events to the IRB annually. The physiological studies will be conducted in the Northwestern CRU, and as such, will be overseen by the CRU Data Safety Monitoring Board. All data will be kept confidential and in a locked cabinet. Only approved study personnel will have access to study related documents.

WITHDRAWAL OF PARTICIPANTS:
Participants are free to choose to stop participation in the study at any time. They will be explicitly told that choosing not to be in this study or to stop being in this study will not result in any penalty to them or loss of benefit to which they are entitled. Specifically, the choice to withdraw will not negatively affect the right to any present or future medical treatment to which

they are otherwise entitled. If participants withdraw, the procedure will immediately stop, they will be asked to fill out paperwork regarding monetary compensation for the completed portion of the study. Compensation will be prorated on the number of visits completed as described in the consent form. We will ask for the reason for withdrawal, but participants are not obligated to provide one. Their data will be included in analyses as appropriate.

Participants may be taken off the study without consent if:

- They are unable to meet the requirements of the study;
- If they begin treatment for prediabetes before completion of study;
- Their medical condition changes;
- If the study is stopped.

RISKS TO PARTICIPANTS:

One potential risk is that subjects may experience some distress when sharing personal information during the two telephone screening calls and while completing questionnaires for the study. To reduce distress about public disclosure, the meaning of confidentiality will be explained. Subjects will be explicitly instructed that revealing deeply personal information, by exploring the past or confiding to the investigators about personal secrets, is not considered part of the protocol and if revealed, will not be shared, recorded or disclosed to anyone.

The clinical procedures involve some discomfort associated with the finger stick screen for HbA1c and later venipuncture associated with the OGTT assessment. There might be slight bruising at the site, which will recover in a short period of time. There is also slight risk of inflammation of the vein or infection. However, the research assistant who will conduct the finger stick and our nurses who perform the OGTT procedures will be highly trained and thus these risks are minimal. The amount of blood withdrawn is minimized to prevent significant blood loss. Furthermore, a study physician (Dr. Aleppo) will be available should any medical concerns arise. There is also the potential of discomfort from the equipment placement of the wireless WatchPAT™ device used for the home sleep apnea screen. Efforts will be made to minimize this discomfort, with the research assistant first demonstrating the correct application of the WatchPAT™ device on themselves, followed by the subject doing a test application in front of the research assistant, before the subject applies the device at home later that night (the screening visit will be scheduled to occur on a day in which the subject is available to do the home sleep apnea screen that night if they pass the screening visit).

Subjects will receive a 1 hour morning light treatment for 4 weeks. Morning light treatment is already used in clinical practice, such as for winter depression [87-90] and circadian rhythm sleep disorders [91,92]. Morning light treatment is considered safer than sunlight because there are no UV rays, and indeed no changes in extensive ophthalmologic examination were observed after up to 6 years of daily light treatment (in fall and winter) [93]. Morning light treatment is associated with some side effects, the most common being headache, eyestrain, nausea and agitation [90], but often these side effects spontaneously remit [90,94], and patients rarely discontinue due to side effects [94]. A rare but serious side effect is mania in bipolar patients who overexpose themselves to the light [90,94] but bipolar depressives are excluded from this study and all subjects will be provided with strict instructions to limit their light treatment to 1 hour/day. Additionally, the Re-timer® device automatically turns off after 1 hour of use. Further, all subjects will be instructed to not permit family/friends to play with the Re-timers®, and to only turn the Re-timers® on during the scheduled time. Note that mania in response to morning light treatment is so rare that light treatment has even been clinically tested in bipolar patients and found to be safe [95]. The active light treatment will result in light intensities greater than most indoor light, but much dimmer than sunlight on a bright day (about 100,000 lux). The active Re-timer® used in this

study is commercially available and already in use in the general population. The Re-timer® meets international ultraviolet and blue light hazard safety standards (standard ICNIRP 7/99 and CIE S009/E: 2002, also known as international standard IEC 62471/Ed. 1 published in 2006), and is safe (no UV light, no power in wavelengths <400nm). The placebo Re-timer® is also safe as the light has simply been dimmed. Finally, the circadian phase shifts (~1-2 hours) resulting from the active morning light treatment may lead to transient symptoms akin to jet lag after crossing 1-2 time zones, including transient sleepiness, fatigue and headache. These symptoms are similar to those experienced on a Monday morning after a late weekend. However, such 'jet lag' will be very short lived as the circadian phase shifts will likely complete within the first few days of morning light treatment.

There is the risk of loss of confidentiality, but as described below, procedures are in place to minimize this risk. There are no other known risks involved in any of the other measurement procedures. Participation is voluntary and subjects may withdraw from the study at any time.

POTENTIAL BENEFITS TO PARTICIPANTS:

All subjects will receive the results of the finger stick HbA1c at screening and Dr. Aleppo will discuss the results with each subject as soon as possible. All subjects will receive the results from the home sleep apnea screen within 5 business days, and Dr. Park will discuss the results with each subject as soon as possible. Anyone who seeks treatment for OSA, even if AHI<15, will be excluded from the study (as part of intent-to-treat analysis the last observation will be carried over). If the original HbA1c screen suggested prediabetes but the fasting and/or 2-h glucose suggest diabetes, the subject will be retained in the study, but Dr. Aleppo will discuss the results with the subject. The information gained from this study will help to develop a larger randomized clinical trial to test a novel intervention, morning light treatment, to reduce risk of developing T2DM. The risks are only minimal and the risk-to-benefit ratio is very small. Subjects have the option of dropping out of the study at any time.

Metabolic disorders such as diabetes and prediabetes are highly prevalent in the U.S. The primary goal of this study is to test whether morning light treatment may be an effective and feasible intervention to reduce risk for T2DM. If our hypotheses are correct, morning light treatment could be a feasible, effective, safe and non-pharmacological intervention to reduce diabetes risk in millions of Americans.

VULNERABLE POPULATIONS:

N/A. No vulnerable populations.

COMMUNITY-BASED PARTICIPATORY RESEARCH:

N/A. No community-based participatory research.

SETTING:

Research activities will take place in the Circadian Rhythms & Sleep Research Laboratory (NU Chicago campus) located at 710 N. Lake Shore Dr., Suite 500 and at Northwestern Memorial Hospital in the Clinical Research Unit. Study measurements will also be collected in the person's home (actigraphy, light, WatchPAT).

RESOURCES AVAILABLE:
Experienced research staff, knowledgeable of the protocol and trained in the devices and procedures outlined in the protocol, are already present and any new study personnel will be trained by senior researchers. All equipment required to conduct this research is already owned by the PI. A sleep laboratory is already in place.

Participants will be recruited from the general public. Dr. Aleppo will recommend the study to her patients identified as prediabetic.

PRIOR APPROVALS:
University of Chicago IRB- see supporting documents.

RECRUITMENT METHODS:
Potential subjects will be recruited via digital and print advertising (e.g., flyers, poster, Doctor-to-Patient Letter).Potential subjects may also be recruited online through Research Match and health registries (e.g., Women's Health registry, NUCATS registry, and NMEDW) including but not limited to sites for professionals who see patients with early diabetes (prediabetes) or related conditions. Research Match is a secure online, national recruitment tool that is maintained by Vanderbilt University. ResearchMatch.org allows researchers to conduct feasibility or recruit potential study participants. Participants who are interested and released their contact information to the study team will be contacted via telephone or email. If participants cannot be reached via telephone the Research Match follow-up email will be sent to them via email.

The Illinois Women's Health Registry was established and overseen by Northwestern University's Women's Health Research Institute at the Feinberg School of Medicine to encourage investigator-initiated research targeting women's health. The role of the Registry is to facilitate the recruitment and identification of women who may be eligible to participate in IRB approved research being conducted at Northwestern University and other research institutions across the state of Illinois.

The General Research Registry, overseen by NUCATS, includes people who are interested in participating in research at Northwestern and have consented to be contacted about research studies for which they may be eligible. These potential participants will first be contacted via phone or email, provided detailed study information, and if interested in participating, encouraged to complete a pre-screening questionnaire to confirm if they meet study inclusion criteria. The Enterprise Data Warehouse (EDW) is also overseen by Northwestern Medicine. It consists of a comprehensive database of clinical and research data. Data requests from EDW can yield potentially eligible subjects, to whom the research team can reach out.

Recruitment will also include advertising the study to current diabetes patients in order to recruit their potentially eligible family members. Dr. Aleppo, a co-investigator on this project, is an endocrinologist who has been treating diabetes patients for over 15 years and who sees over 350 patients with diabetes each year at the Northwestern Hospitals. She will provide patients with a flyer with more information and tell them to have any interested family members to contact us. Recruitment will also include posting flyers, newspaper advertisements and advertisements around Chicago and online, and attending community events. Thus, the initial contact will be made by the volunteer.

For participating in this study the subjects will receive a total amount of $485 for completing the entire study. They will receive $10 in cash for completing the finger stick at screening. If they also complete the home sleep apnea screen, but do not continue the study, they will receive $40 in cash. Those that complete at least one week of the full study will receive a check at the end of the study totaling $95 for each week completed. Subjects who drop out prior to completing will be paid for the number of weeks completed.

- $95 for the first ambulatory week of actigraphy plus laboratory session
- $95 for week 1 of intervention (Week 2 of study)
- $95 for week 2 of intervention (Week 3 of study)
- $95 for week 3 of intervention (Week 4 of study)
- $95 for week 4 of intervention plus laboratory session (Week 5 of study)

NUMBER OF LOCAL PARTICIPANTS:
We will enroll 34 subjects (50% female, age 35-70 y) with prediabetes to complete the study. We conservatively estimate a 17% attrition rate (final n=28) which includes dropouts and noncompliance (noncompliance defined as <25% of morning light treatment, as per [77]).

CONFIDENTIALITY:
To minimize loss of confidentiality, study records will be kept confidential and data and records will be stored in locked cabinets in private offices. Electronic data files will be stored on password-protected computers. Data files and documents (with the exception of the consent form) will be stripped of identifying information and subjects will be identified only by a study ID code. Only one file will have the name and contact information linked to the study code, and this information will be linked for the duration of the study. After this time, the linked information will be destroyed.

PROVISIONS TO PROTECT THE PRIVACY INTERESTS OF PARTICIPANTS:
Study records will be kept confidential and data and records will be stored in locked cabinets in private offices. Electronic data files will be stored on password-protected computers. Data files and documents (with the exception of the consent form) will be stripped of identifying information and subjects will be identified only by a study ID code. Only one file will have the name and contact information linked to the study code, and this information will be linked for the duration of the study (2 years). After this time, the linked information will be destroyed.

Note this protocol involves collaboration with Dr. Helen Burgess from Rush University. Her expertise in assessing DLMO at home is required. She will initially be part of the research team that meets with subjects to explain the at-home procedures and answer questions. After the research team has had sufficient training from her, these meetings will occur without her presence. Finally, she will assist with data analysis of melatonin to identify DLMO, but the data will all be de-identified before being shared. This protocol will also be reviewed by the IRB at Rush University.

COMPENSATION FOR RESEARCH-RELATED INJURY:
N/A. Research only includes minimal risk.

ECONOMIC BURDEN TO PARTICIPANTS:
Participation is at no cost to subjects.

CONSENT PROCESS:
Interested subjects will call the study phone number on the flyer/ad, and the assigned research staff will discuss the study with the volunteer over the phone and ascertain potential eligibility. If the volunteer appears eligible and remains interested, the research staff will obtain verbal consent to request that the subjects record their bed times and wake times beginning that night and continuing until meeting for informed consent. This information is later used to prepare a schedule for their light treatment. The study coordinator will also set up a screening visit to explain the study in detail and obtain informed consent before the screening assessments are conducted. Thus, the initial contact will be made by the volunteer. Verbal consent will be given by the subject over the phone to begin recording bed time and wake times before coming into the screening visit and written informed consent will be obtained after all details of the study have been explained by one of the study personnel and the subject has received satisfactory answers to all of his/her questions. In the Consent Form, it will be emphasized that subjects may discontinue participating at any time and still receive prorated compensation for any procedures they have completed. The study coordinator will inform potential subjects that participation is completely voluntary, and they may withdraw at any time without penalty or running the risk of jeopardizing current and future treatment at Northwestern Hospitals or Rush University Medical Center.

PROCESS TO DOCUMENT CONSENT IN WRITING:
An IRB approved consent form will be signed by each participant.

DRUGS OR DEVICES:

Device	Manufacturer	IDE Class
Actiwatch Spectrum Pro	Philips Respironics	Non-significant Risk
ReTimer	SMR Automotive Australia	Non-significant Risk
WatchPAT	Itamar Medical Ltd	Non-significant Risk

Actiwatches, ReTimers, and the WatchPAT will be stored in dry, temperature-controlled, locked offices accessible only to Circadian Rhythms & Sleep Research Laboratory staff. Subjects are given an actiwatch, WatchPAT, and ReTimer for wear at home after adequate training and are required to return the devices upon finishing the screen or the full study. All devices will be cleaned, updated, and calibrated as per manufacture requirements.

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Permission to Take Part in a Human Research Study

Do not sign this consent if today's date is later than the stated expiration date above.

Title of Research Study: Light Treatment to improve Diabetes Risk: A Pilot Study

Investigator: Kristen L. Knutson, PhD Phone: (312) 503-1526

Supported By: This research is supported by the NIH, Northwestern University, and Rush University.

Key Information:

The first few pages of this document include a summary of this study to help you decide whether or not to participate. Detailed information is provided after the summary.

Why am I being asked to take part in this research study?

We are asking you to take part in this research study because you are a healthy adult between the ages of 40-65*.*

What should I know about a research study?

- Someone will explain this research study to you.
- Whether or not you take part is up to you.
- You can choose not to take part.
- You can agree to take part and later change your mind.
- Your decision will not be held against you.
- You can ask all the questions you want before you decide.

Why is this research being done?

The purpose of this study is to determine if a morning light device can help to improve blood sugar levels in people with an early form of diabetes ("prediabetes").

How long will the research last and what will I need to do?

We think you will be in the study for about 6 weeks, including the screening period.

You will participate in a brief screening session which will include: a urine drug test, drawing a small amount of blood from your finger, wearing a device for 1 night on your hand/wrist to measure your sleep at home, and a single page sleep log to track your bed and wake times.

You will be asked to wear a wristwatch device at home for one week to measure your typical sleep patterns. You will be asked to complete questionnaires and food and sleep diaries.

You will also spend 2 overnight visits 4 weeks apart in our clinic. We will collect saliva and blood samples. We will measure your body fat by attaching sensors to your foot and hand. You will also have an "oral glucose tolerance test," which measures how your body uses sugar. An IV will be inserted into one arm and blood will be sampled every 30 minutes for 3 hours, totaling about 5 tablespoons of blood.

You will be given a light device to wear for 1 hour after waking up, everyday for 4 weeks. The device is worn on your head and delivers light to your eyes. It looks like large glasses, and can be worn over your eyeglasses if you wear them. It is easy to put on and to go about your daily morning activities while wearing it. You will continue to wear the wristwatch device to measure sleep during this time and complete sleep and food diaries.

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More detailed information about the study procedures can be found under the section **What happens if I say "Yes, I want to be in this research"?**

Is there any way being in this study could be bad for me?

The study may include the following risks. There is a potential risk of experiencing skin pain or irritation from the IV blood draw. It is possible that information that we collect be visible to persons who are not part of the research team, but we will treat the information that we collect using the professional standards of confidentiality.

More detailed information about the risks of this study can be found under **"Is there any way being in this study could be bad for me? (Detailed Risks)"**

Detailed Information:
The rest of this document includes detailed information about this study (in addition to the information listed above).

Who can I talk to?

If you have questions, concerns, or complaints, or think the research has hurt you, talk to the research team at (312) 503-4965 or Dr. Kristen Knutson at (312) 503-1526

This research has been reviewed and approved by an Institutional Review Board (IRB). You may talk to them at (312) 503-9338 or irb@northwestern.edu if:

- Your questions, concerns, or complaints are not being answered by the research team.
- You cannot reach the research team.
- You want to talk to someone besides the research team.
- You have questions about your rights as a research participant.

You want to get information or provide input about this research.

How many people will be studied?

Up to 34 people may participate in this study at Northwestern University.

What happens if I say "*Yes, I want to be in this research*"?

After reviewing this consent form and discussing the details of the study with study personnel, there will be a brief screening session where we will take some blood and measure sleep (see "Screening" on the next page). After screening, the rest of the study will last 5 weeks and includes 6 separate, weekly visits to the laboratory (not counting this one). Two of these visits are overnight stays in our sleep laboratory. For the last 4 weeks of the study you will be asked to wear a light device on your head (ReTimer ®) for one hour each morning.

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Pre-screening
You have already completed pre-screening over the telephone or in person, which included asking about previously diagnosed conditions, such as diabetes. We also had you complete two questionnaires that screen for sleep apnea (the Berlin and the STOP-BANG). People with sleep apnea are not eligible for this study.

You provided verbal consent over the phone to record your bed times and wake times before coming in for the screening visit.

Screening:
You will have the following tests and procedures today to see if you can be in the study:

- You will be asked to provide a urine sample which will be tested for recreational drug use. Recreational drugs interfere with the laboratory tests used to process saliva and blood samples and are strictly prohibited for participation in this study.
- We will stick your finger to draw a small amount of blood to see if you have an early form of diabetes and to see if you are healthy enough to give more blood in the study. If you do not have an early form of diabetes, called pre-diabetes, you will not be able to be in this study.
- You will be asked to wear a device overnight on your wrist and hand to measure your sleep at home for one night. You will be given instructions about how to do this.
- You will be given a single page sleep log to continue tracking your bed times and wake times until you come in to pick up equipment at the start of week 1, the Start-up visit, after which you will be filling out sleep diaries to record this information.

If the results of these tests match what is needed for this study you will be allowed to participate. You will then be scheduled for the full study.

Start-up visit:
We will review the sleep recording done at home and if you qualify we will provide you with the equipment and materials necessary for week 1. At this visit, you will be given a wrist activity monitor (similar to a wristwatch called an "Actiwatch"), sleep diaries, and food diaries.

Week 1:
During this week, you will wear the wrist monitor all day and night and complete sleep diaries each morning. The activity monitor is water resistant. It can be worn while showering, but not to be kept underwater for long periods of time (over 30 minutes). Please do not wear while swimming.

In addition, you will complete several questionnaires and on the last 3 days of this week, you will complete a 3-day food diary that asks for both the amount and types of food eaten and the time of your meals and snacks.

Laboratory visit #1:
At the end of the week, you will spend approximately 20-24 hours in our laboratory. We will tell you the specific time to arrive, but it will be early afternoon. Dinner will be provided. Saliva (spit) samples will be collected every half hour in the late afternoon and evening until bedtime. You will continue to wear the wrist activity monitor.

In the morning, body fat will be measured by attaching sensors to your foot and to your hand. Then, you will have an "oral glucose tolerance test" (OGTT), which measures how well your

body uses sugar. An IV will be inserted into one arm. Two blood samples will be taken 15 minute apart and then you will drink a sugar solution within 5 minutes. After that you will remain seated and blood will be sampled every 30 minutes through the IV. The last sample will be taken 3 hours after you drank the sugar solution. The total amount of blood drawn will be approximately 5 tablespoons.
After the OGTT, you will get lunch and a member of the research team will meet with you to discuss the next part of the study. At this point you will be randomly assigned to receive either a low light level or a high light level. We will tell you at the end of the study which level you received. We will then give you instructions on how and when to use the light device each morning. The light device is worn on your head and delivers light to your eyes. It looks like very large eye glasses, and can be worn over your eye glasses if you wear any. You will only wear it for an hour after waking up, every day over four weeks. It is easy to put on and to conduct your daily morning activities as you are undergoing treatment. After we have gone over the light device and associated questionnaires, you are free to leave. You will receive phone call reminders around the scheduled light treatment time for the first three days of wearing the light device, and text message reminders for the remainder of the study duration.

Week 2:
At this visit, we will give you the specific times and how we would like you to use the light device. You will continue to wear the wrist activity monitor and complete sleep diaries. At the end of this week, you will visit our laboratory and get a new wrist activity monitor to wear the following week. We will also discuss how the use of the light device is going and how often you used it. We will again discuss the rest of the study and the times to use the light device.

Week 3:
You will continue to follow the instructions we give you about the light device. You will continue to wear the wrist activity monitor and complete sleep diaries. At the end of this week, you will visit our laboratory and get a new wrist activity monitor to wear the following week. We will also discuss how the use of the light device is going and how often you used it. We will again discuss the rest of the study and the times to use the light device.

Week 4:
You will continue to follow the instructions we give you about the light device. You will continue to wear the wrist activity monitor and complete sleep diaries. At the end of this week, you will visit our laboratory and get a new wrist activity monitor to wear the following week. We will also discuss how the use of the light device is going and how often you used it. We will again discuss the rest of the study and the times to use the light device.

Week 5:
You will continue to follow the instructions we give you about the light device. You will continue to wear the wrist activity monitor throughout the study and complete sleep diaries. In addition, you will complete the questionnaires and a 3-day food diary at the end of this week that asks for both the amount and types of food eaten and time of meals and snacks. At the end of this week you will spend another day in the laboratory.

Laboratory visit #2:
At the end of Week 5, you will spend approximately 20-24 hours in our laboratory. We will tell you the specific time to arrive, but it will be early afternoon. Dinner will be provided. This session will be the same as the first laboratory session. Saliva (spit) samples will be collected every half hour in the late afternoon and evening until bedtime. You will continue to wear the wrist activity monitor. In the morning, body fat will be measured by attaching sensors to your foot and to your hand. Then, you will have another "oral glucose tolerance test" (OGTT), which

will include 8 blood samples taken through an IV every 10-30 minutes over 3 hours. Total amount of blood withdrawn will be approximately 5 tablespoons. After the OGTT you will get lunch. Afterwards, you are free to leave.

The blood and saliva samples that we collect from you will be frozen and stored indefinitely for potential future research. These samples will be stored using a unique code and not your name.

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Day by Day Outline of the Full Study

Week 1	
Day 1	**Start-up Visit** Pick up equipment, sleep diaries, food diary and instructions Starting wearing wrist activity monitor
Days 2 – 4	Continue to wear wrist actigraphy Complete sleep diary
Days 5 – 7	Continue to wear wrist actigraphy Complete sleep diary Complete food diary
Day 7	Arrive at laboratory at specified time (afternoon). Bring in sleep and food diaries. **Overnight laboratory session** begins Dinner will be provided Saliva sampling every 30 minutes until bedtime Continue to wear wrist actigraphy
Day 8	Body fat will be measured in morning 3-hour oral glucose tolerance test (involves IV insertion for taking blood) Lunch will be provided Discuss remainder of study and light treatment with research team. Leave in the afternoon.
Week 2	
Day 8	Begin to use light device at specified times that we gave you Continue to wear wrist activity monitor
Days 9 - 14	Continue to use light device at specified times that we gave you Complete sleep diary each day Continue to wear wrist activity monitor
Day 14	**Visit to our laboratory (approximately 1 hour)** Bring in sleep diaries and light device Discuss use of light device Get new wrist activity monitor & diaries
Week 3	
Days 15-20	Continue to use light device at specified times that we gave you Continue to wear wrist activity monitor Complete sleep diary each day
Day 21	**Visit to our laboratory (approximately 1 hour)** Bring in sleep and food diaries and light device Discuss use of light device Get new wrist activity monitor & diaries

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Week 4	
Day 22-28	Continue to use light device at specified times that we gave you Continue to wear wrist activity monitor Complete sleep diary each day
Day 28	**Visit to our laboratory (approximately 1 hour)** Bring in sleep diaries and light device Discuss use of light device Get new wrist activity monitor & diaries
Week 5	
Days 29-31	Continue to use light device at specified times that we gave you Continue to wear wrist activity monitor Complete sleep diary each day
Days 32-34	Continue to use light device at specified times that we gave you Continue to wear wrist activity monitor Complete sleep diary each day Complete food diary each day
Day 35	Arrive at laboratory in early afternoon. Bring in sleep and food diaries and light device. **Overnight laboratory session** begins Dinner will be provided Saliva sampling every 30 minutes until bedtime Continue to wear wrist actigraphy
Day 36	Body fat will be measured in morning 3-hour Oral glucose tolerance test (involves IV insertion for taking blood) Lunch will be provided Leave in the afternoon.

During this study, Dr. Kristen Knutson and her research team will collect information about you for the purposes of this research. This information includes the following: height, weight, measure of body fat, hormone response to a sugar load, and some hormone levels. We also collect sleep data, wrist activity monitoring data, and questionnaires about sleep, behavior, and appetite and alertness, food diaries, dates, e-mail address, names, telephone numbers, medical record number, and social security number (for payment purposes).

What are my responsibilities if I take part in this research?

If you take part in this research, you will be responsible for completing the procedures, assessments, and visits stated above. You are also responsible for communicating with the study coordinator or investigator when you are unable to or unwilling to continue to study.

What happens if I say "Yes", but I change my mind later?

You can leave the research at any time it will not be held against you. If you decide to leave the research, contact the study coordinator or investigator so that they can cancel scheduled visits and assess the payment you qualify for according to the breakdown detailed later in this document.

Choosing not to be in this study or to stop being in this study will not result in any penalty to you or loss of benefit to which you are entitled. Specifically, your choice not to be in this study will not negatively affect your right to any present or future medical treatment, your class standing (for students enrolled in a class at NU), or your present or future employment (for employees at NU or its affiliates). If you withdraw from the study before you finish, we will still include your

data in our analyses. We will ask you for the reason you are withdrawing, but you are not required to provide one. Once you withdraw from the study, no more data will be collected.

Detailed Risks: Is there any way being in this study could be bad for me?

IV Insertion and Blood Draw Risks

- Temporary pain
- Bleeding
- Slight bruising
- Possible inflammation
- Possible fainting
- Possible infection
- Care will be taken to avoid these complications. An experienced research nurse will insert the IV under sterile conditions.

Confidentiality Risks

- It is possible that information that we collect may be visible to persons who are not a part of the research team.
- We will treat the information that we collect using the professional standards of confidentiality. Please see specific information about this in the "Confidentiality" section on page 7 of this consent form.

Other:

- If your answers during the screening interview show that you have depression and may be at risk of hurting yourself or others we will take you to the Emergency Department (ED) and will disclose that information to the ED physicians and nurses.

There may be other risks that could arise which are not reasonably foreseeable. If new information becomes available which could influence your willingness to continue, this new information will be discussed with you.

This study involves the use of your identifiable, personal information and there is a chance that a loss of confidentiality could occur. The researchers have procedures in place to lessen the possibility of this happening. See the section below titled: "What happens to the information collected for the research?".

Will it cost me anything to participate in this research study?

There will be no costs to you or your insurance company resulting from your participation in this research study. However, you or your insurance company will be responsible for costs related to your usual medical care.

Will being in this study help me in any way?

If you agree to take part in this study there may or may not be direct medical benefit to you. We hope the information learned from this study will help us further understand whether the use of a light device like the Re-Timer can help treat or prevent diabetes.

What happens to the information collected for the research?

Study records that identify you will be kept confidential. Study records will be kept in a locked office and are only accessible by members of the research team. Data will be coded so that you are not identified and will not contain information that can identify you. The data collected in this study will be used for the purpose described in the form. Data from this study may be used in medical publications or presentations. Your name and other identifying information will be

removed before this data is used. If we wish to use identifying information in publications, we will ask for your approval at that time.

Efforts will be made to limit the use and disclosure of your personal information, including research study and medical records, to people who have a need to review this information. We cannot promise complete secrecy. Organizations that may inspect and copy your information include the IRB and other representatives of this institution. The research team includes the individuals listed on this consent form and other personnel involved in this study at the Northwestern University and Rush University. As part of the study, Dr. Knutson and her research team may report the results of your study-related procedures and tests explained above to the National Institutes of Health (NIH). These include the information from the wrist activity monitor, the sleep recording and the questionnaires, as well as your age, sex, ethnicity, height and weight. The information being sent will not contain any information that identifies you.

All samples will be deidentified using only the study ID code. After the saliva specimens collected in lab are assayed they will be destroyed at Rush University. In this study, you will be asked about illegal activities or highly personal behavior. We have obtained a Certificate of Confidentiality from the federal government. However, we may still be required under certain circumstances to release your information.

The sponsor, monitors, auditors, the IRB, the Northwestern University Office for Research Integrity, the US Office of Research Integrity (ORI), the US Office for the Protection of Human Research Protections (OHRP), the US Food and Drug Administration (FDA) may be granted direct access to your medical records to conduct and oversee the research. By signing this document you are authorizing this access. We may publish the results of this research. However, we will keep your name and other identifying information confidential.

Data Sharing

De-identified data from this study may be shared with the research community at large to advance science and health. We will remove or code any personal information that could identify you before files are shared with other researchers to ensure that, by current scientific standards and known methods, no one will be able to identify you from the information we share. Despite these measures, we cannot guarantee anonymity of your personal data.

Can I be removed from the research without my OK?

Dr. Knutson may decide to take you off of the study without your consent if:

- You do not follow the instructions about light treatment;
- You are unable to meet the requirements of the study;
- Your medical condition changes;
- If the study is stopped.

What else do I need to know?

If you become ill or get injured as a result of this study (medications, devices or procedures), you should seek medical treatment through your doctor or treatment center of choice. You should promptly tell the study doctor about any illness or injury.

The hospital [university, researchers] will not pay for medical care required because of a bad outcome resulting from your participation in this research study. This does not keep you from seeking to be paid back for care required because of a bad outcome.

<u>Payment</u>

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For participation in this study you will receive a check at the end of the study for each week completed, as detailed below. Northwestern University requires that you complete a receipt after receiving any cash, which involves simply printing and signing your name. You will receive $10 in cash for screening blood test, and only if you do not qualify for the rest of the study, $40 in cash for the home sleep test.

- $95 for Week 1, including laboratory session
- $95 for week 2
- $95 for week 3
- $95 for week 4
- $95 for week 5, including laboratory session

HIPAA Authorization

We are committed to respect your privacy and to keep your personal information confidential. When choosing to take part in this study, you are giving us the permission to use your personal health information that includes health information in your medical records and information that can identify you. For example, personal health information may include your name, address, phone number or social security number. Your health information we may collect and use for this research includes:

- All information in a medical record
- Results of physical examinations
- Medical history including an mental health diagnosis
- Lab tests, or certain health information indicating or relating to a particular condition as well diaries and questionnaires
- History of substance or alcohol abuse
- History of mental health disorders (e.g. depression, anxiety) including prescribed medications, doses, and length of use.

During this study you may be coming to a Northwestern Memorial Healthcare Corporation entity (for example, Northwestern Memorial Hospital, Prentice Women's Hospital) for research appointments or to get clinical services, such as lab tests, needed for the study. When that happens, you will be scheduled for these services through the NMHC computer system. When a clinical exam or lab is done by NMHC or one of its employees for the purpose of this research study, that information will be kept in both NMHC's clinical records and in the study records.

The following clinical providers may give the researchers information about you: all current and previous health care providers, including but not limited to the Rehabilitation Institute of Chicago (RIC), Northwestern Medical Group (NMG), Northwestern Memorial Hospital (NMH), Northwestern Lake Forest Hospital (NLFH).

Once we have the health information listed above, we may share some of this information with the following offices or entities outside of Northwestern University and its clinical partners (or affiliates): the Northwestern University Institutional Review Board Office and Office for Research Integrity; the US Office of Research Integrity; the US Office for Human Research Protections; the US Food and Drug Administration.

Any research information shared with outside entities will not contain your name, address, telephone or social security number or any other personal identifier unless disclosure of the identifier is necessary for review by such parties or is required by law or University policy [except that such information may be viewed by the Study sponsor and its partners or contractors at the Principal Investigator's office].

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- Authorized members of the Northwestern University workforce, who may need to see your information, such as administrative staff members from the Office for Research, Office for Research Integrity and members of the Institutional Review Board.
- Clinical affiliates, including but not limited the Rehabilitation Institute of Chicago (RIC), Northwestern Medical Group (NMG), Northwestern Memorial Hospital (NMH), Northwestern Lake Forest Hospital (NLFH), and the Ann & Robert H. Lurie Children's Hospital of Chicago (Lurie Children's). Your participation in this clinical trial may be tracked in an electronic database and may be seen by investigators running other trials that you are enrolled in and by your healthcare providers.
- Clinical affiliates, including but not limited to Northwestern Medical Group (NMG), Northwestern Memorial Hospital (NMH), and Northwestern Lake Forest Hospital (NLFH), for purposes including, but not limited to, the affiliate's provision of care to you and/or the affiliate's scheduling of appointments and/or billing activities.
- Other University research centers and University contractors who are also working on the study,
- Study monitors and auditors who make sure that the study is being done properly,
- Government agencies and public health authorities, such as the Food and Drug Administration (FDA) and the Department of Health and Human Services (DHHS).

Those persons who get your health information may not be required by Federal privacy laws (such as the Privacy Rule) to protect it. Some of those persons may be able to share your information with others without your separate permission.However, Illinois law does not allow the re-release of HIV/AIDS, genetic testing, mental health and developmental disabilities information by the recievers of the information except in precise situations allowed by law.

Also, Federal Confidentiality Rules, 42 CFR Part 2, prohibit making any further disclosure of substance use disorder information unless further disclosure of this information is expressly permitted by written consent of the person to whom it pertains or as otherwise permitted by 42 CFR Part 2.

The results of this study may also be used for teaching, publications, or for presentation at scientific meetings.

Unless you revoke your consent, it will expire at the end of the research study.

Although you may revoke consent to participation in this research at any time and in any format, you must revoke authorization for use or disclosure of your health information in writing. To revoke your authorization, write to:

Kristen L. Knutson, PhD
Center for Circadian and Sleep Medicine
Department of Neurology
Northwestern University Feinberg School of Medicine
710 N Lakeshore Drive, Room 523
Chicago, IL 60611

You do not have to authorize the use or disclosure of your health information; however, you will not be allowed to take part in this research study. If you do not authorize the use or disclosure of your health information, it will not affect your treatment by health care providers, or the payment or enrollment in any health plans, or affect your eligibility for benefits.

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A copy of this signed consent document, information about this study, and the results of any test or procedure done may be included in your medical records and may be seen by your insurance company.

Optional Elements:

The following research activities are optional, meaning that you do not have to agree to them in order to participate in the research study. Please indicate your willingness to participate in these optional activities by placing your initials next to each activity.

I agree	I disagree	
_____	_____	The researcher may contact me after I have finished participating in the study to clarify and ask questions about my responses to questionnaires and my performance on study activities.
_____	_____	The researcher may contact me in the future to see whether I am interested in participating in other research studies by the Principal Investigator of this study.
_____	_____	The researcher may retain any leftover blood or tissue samples taken during the study. These samples may be used for other research not related to this study. These samples will be retained in non-identifiable form, meaning that there will be no information associated with the blood or samples that will allow anyone to readily ascertain my identity.

Your signature documents your permission to take part in this research. You will be provided a copy of this signed document.

_____ _____

Signature of Participant Date

_____

Printed Name of Participant

_____ _____

Signature of Person Obtaining Consent Date

_____

Printed Name of Person Obtaining Consent