AWARD NUMBER: W81XWH-19-1-0558

TITLE: Using Early Time-Restricted Feeding and Timed Light Therapy to Improve Glycemic Control in Adults with Type 2 Diabetes

PRINCIPAL INVESTIGATOR: Courtney M. Peterson, Ph.D.

CONTRACTING ORGANIZATION: University of Alabama, Birmingham, AL

REPORT DATE: October 2021

TYPE OF REPORT: Annual Report

PREPARED FOR: U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Department of Defense, Washington Headquarters Services, Directorate for Information Operations and Reports (0704-0188), 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. **PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.**

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
October 2021	Annual Report	01Sep2020 – 31Aug2021

4. TITLE AND SUBTITLE
Using Early Time-Restricted Feeding and Timed Light Therapy to Improve Glycemic Control in Adults with Type 2 Diabetes

5a. CONTRACT NUMBER
W81XWH-19-1-0558

5b. GRANT NUMBER
GRANT12715627

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Courtney Peterson, Ph.D.; Rachel Benz, M.S.N., R.N.; Kimberly Armstead, B.S.

E-Mail: cpeterso@uab.edu

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
University of Alabama at Birmingham
UAB
701 S 20TH ST
BIRMINGHAM, AL 35294-0001

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT
In this clinical trial, we will test whether two circadian-based therapies--a form of meal timing called early time-restricted eating (eTRE) and timed light therapy--can improve blood sugar control in adults with type 2 diabetes. Approximately 344 adults with type 2 diabetes will be randomized to the following 2 x 2 study design: (1) control group, (2) eTRF, (3) timed light therapy, and (4) eTRF and timed light therapy. Participants will follow their assigned lifestyle intervention for 16 weeks and be followed for a total of one year. In addition, we will determine whether the two circadian therapies can improve circadian rhythms, sleep quality, weight loss, cardiovascular health, quality of life, and psychological health. We will also determine which patients benefit the most from these therapies. At the start of year 2, our facilities were still shut down due to the COVID-19 pandemic. Thereafter, they re-opened, and we resumed research. We finished setting up the clinical trial and completed the renovation and expansion of inpatient testing rooms in the hospital. We began recruiting and enrolling participants. Our first participant has completed the 16-week intervention. The delivery of the intervention is going well, and retention is very high. We are currently preparing larger advertising campaigns to enroll more people.

15. SUBJECT TERMS
Early Time-Restricted Feeding, Bright Light Therapy, Circadian Rhythms, Intermittent Fasting

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	16	19b. TELEPHONE NUMBER *(include area code)*

TABLE OF CONTENTS

- **INTRODUCTION**

  This clinical trial will investigate whether two circadian-based therapies can improve blood sugar control, reduce diabetes complications, explain some of the heterogeneity of type 2 diabetes, and improve several other aspects of health. In this clinical trial, we will test for the first time whether a form of meal timing called early time-restricted feeding (eTRF) and/or timed light therapy can improve blood sugar control in adults with type 2 diabetes. Approximately 344 adults with type 2 diabetes will be randomized to the following 2 x 2 study design: (1) control group, (2) eTRF, (3) timed light therapy, and (4) eTRF and timed light therapy. Participants will follow their assigned lifestyle intervention for 16 weeks and be followed for a total of one year. In addition, we will determine whether the two circadian therapies can improve circadian rhythms, sleep quality, weight loss, cardiovascular health, quality of life, and psychological health. We will also determine which patients benefit the most from these therapies.

- **KEYWORDS**

  Type 2 Diabetes, Early Time-Restricted Eating, Bright Light Therapy, Circadian Rhythms, Chronobiology, Intermittent Fasting, Veterans

- **ACCOMPLISHMENTS:**

  - **What were the major goals of the project?**

TASKS	MONTHS	PROGRESS
TASK 1: SET-UP CLINICAL TRIAL		
Advertise, interview, and hire a research coordinator with prior experience in managing clinical trials at UAB	*2 months prior to start date*	*Complete.*
Refine the protocol and informed consent	1-2	Complete
Develop recruiting materials and screening forms, and refine the screening process	1-3	Complete
Set-up recruiting processes at the Birmingham VA Medical Center and UAB Hospital	1-4	Complete
Order supplies and equipment	1-4	Complete
Review the recent literature on bright light exposure protocols, finalize the bright light exposure protocol, and write a review article	1-4	Literature review complete. Manuscript is being drafted.
Develop procedure manuals for the lifestyle interventions and for behavioral counseling	2-3	Complete
Set-up a material transfer agreement with Brigham and Women's Hospital (BWH) to analyze sleep data (Aim 3)	2-3	Complete
Finalize the study protocol and informed consent	2-3	Complete
Set-up the study database and questionnaires in REDCap	2-4	Complete
Develop procedure manuals for all study procedures	2-4	Complete
Train nursing staff in the operation of PSG equipment	2-4	Complete
Set-up the rooms for inpatient testing	2-5	Complete
Develop data collection forms for nurses to use during the 38-hour inpatient testing	3-5	Complete
Train behavioral counselor	4-5	Complete
Train nurses to perform 38-hour inpatient tests and study procedures	4-5	Complete
Rehearse screening process and procedures	5	Complete
Milestone achieved: IRB & HRPO approval	5	Complete
Milestone achieved: All project-related staff trained	5	Complete

Milestone achieved: Study is set-up and ready to recruit participants	5	Complete
Milestone achieved: Submit review article on recent bright light therapy protocols and their effects on the circadian system and cardiometabolic health	5	In process. Revised target is month 8 of the next fiscal year.
TASK 2: CONDUCT CLINICAL TRIAL		
Recruit, consent, screen, and enroll potential participants	6-38	Ongoing
Milestone achieved: First participant enrolled	6	Complete
Participants follow their assigned intervention for 16 weeks	6-42	Ongoing
Perform behavioral counseling every 2 weeks	6-42	Ongoing
Aim 1: Perform procedures related to glycemic control	6-42	Ongoing
・Three 3-hour meal tolerance tests		
・24-hour measurement of glucose, insulin, and C-peptide		
・HbA1c		
Aim 2: Perform procedures related to the circadian system	6-42	Ongoing
・24-hour measurement of melatonin and cortisol		
・Constant glucose infusion procedure		
Aim 3 (Sleep): Perform polysomnography (PSG) and administer sleep questionnaires	6-42	Ongoing
Aim 3 (Body Weight): Measure weight and body fat (DXA)	6-42	Ongoing
Aim 3 (Cardiovascular): Measure blood pressure and heart rate and draw blood to measure lipids and inflammatory markers	6-42	Ongoing
Aim 3 (Quality of Life and Psychological Health): Administer questionnaires and perform semi-structured interview	6-42	Ongoing
Aims 1, 2, and 3: Perform assays of glucose, insulin, C-peptide, HbA1c, cortisol, melatonin, lipids, and inflammatory markers	6-42	Ongoing
Collect other outcome data: daily survey, Actiwatch data, food records, accelerometry, physical activity questionnaire, appetite questionnaire, and resting metabolic rate	6-42	Ongoing
Monitor intervention adherence and daily surveys	6-42	Ongoing
Monitor participant safety	6-end	Ongoing
Follow-up with participants to recollect any missing data	6-end	Ongoing
Monitor data validity and integrity	6-end	Ongoing
・Glycemic data (Aim 1 and glucose infusion data from Aim 2)		
・24-hour measurement of melatonin and cortisol (rest of Aim 2)		
・Sleep data (part of Aim 3)		
・Cardiovascular data (part of Aim 3)		
・Semi-structured interview (part of Aim 3)		
・Electronic questionnaires and study database in REDCap		
・All other outcomes		
Collect 8-month and 12-month follow-up data	14-end	Not started
Write and submit a manuscript on the study protocol	20-24	Not started. Will complete this coming fiscal year.
Accrual and adherence meetings	Twice a month	Ongoing
Monthly progress meetings	Monthly	Ongoing
Data and safety monitoring meetings	Quarterly	Ongoing
Submit quarterly reports to the DoD	Quarterly	Ongoing
Submit protocol amendments, adverse events, and protocol deviations to IRB and HRPO	As needed	Complete and ongoing

Submit annual reports for continuing review to IRB and HRPO	Annually	Complete and ongoing
Milestone achieved: Last participant enrolled	38	Not started
Milestone achieved: Last participant completes the intervention	42	Not started
TASK 3. ANALYZE DATA AND REPORT STUDY OUTCOMES		
Aim 3: Analyze sleep (PSG) data	6-42	Ongoing
Analyze food intake and Actiwatch data	6-42	Ongoing
Analyze physical activity data from accelerometers	6-42	Ongoing
Final quality check of entire study database and study closeout	36-43	Not started
Analyze, write, and submit a manuscript on the baseline data	35-40	Not started
Aims 1-3: Perform statistical analyses on all data	38-46	Not started
Aim 1: Mathematically model data from meal tolerance tests to calculate insulin sensitivity and secretion	40-43	Not started
Aim 1: Mathematically model 24-hour glucose, insulin, and C-peptide data to extract key glycemic endpoints	40-43	Not started
Aim 2: Mathematically model the 24-hour melatonin and cortisol data to determine rhythms of the central clock	40-43	Not started
Aim 2: Mathematically model data from the constant glucose infusion procedure to determine rhythms of the peripheral clocks	40-43	Not started
Aim 3: Analyze quality of life and psychological health data	40-45	Not started
Aim 3: Mathematically model the 24-hour blood pressure data to extract blood pressure endpoints	44-45	Not started
Write and submit manuscripts on the study results and disseminate findings	42-48	Not started
Milestone achieved: All manuscripts submitted	48	Not started

- **What was accomplished under these goals?**

COVID-19
Because of the COVID-19 pandemic, we were unable to enroll participants until the middle of Year 2. In the meantime, we pre-screened applicants by phone. Our kitchen re-opened in January, and we hired and trained nurses and sleep technicians between January - April. We finally received the Actiwatch equipment in late February and the PSG (sleep) equipment the first week of April. We began screening in-person on March 29, 2021. Our university resumed normal business operations in May 2021.

Recruitment
This past year, we began recruiting participants.

In the **second quarter** of Year 2 (December 2020 - February 2021), we started recruiting by posting a recruitment ad in the university's electronic newsletter (December 21, 2020). Shortly thereafter (January 12, 2021), we advertised the study on a local TV station, resulting in a wave of applicants. In total, we pre-screened 178 applicants in the second quarter. Of the 178 applicants, 33 were eligible to screen in-person. We expected that most of the 33 people on our waiting list would want to enroll in the study once our facilities re-opened, so we slowed down recruitment efforts for the rest of the quarter to avoid creating a further backlog. (Unfortunately, once all our facilities re-opened in late March, we later found out that a majority of people on the waiting list were no longer interested in participating. We found that there is a "recency" effect, meaning that people lose interest if they remain on the waiting list too long.)

In the **third quarter** of Year 2 (March - May 2021), we began a mass recruitment campaign. We posted flyers and posters on campus. In late April, we started mailing postcards to potentially eligible patients who were identified using electronic medical records at the UAB Hospital. During the third quarter, we sent out two batches of 350 postcards (~700 postcards in total), separated by a couple of weeks. The response rate to the postcards was lower than we expected. To determine why the postcard campaign was not more successful, we reached out to four UAB researchers who have used electronic medical records to recruit patients with type 2 diabetes. We found out that researchers who

had success using electronic medical records to recruit patients were typically sending out batches of 1,000-2,000 postcards at a time—much larger batches than what we initially tried. Second, we learned that those researchers who were more successful sent "personalized" letters and often followed up with a phone call. As of a couple years ago, our IRB no longer allows "personalized" mail to be sent, unless the patient's physician is part of the research study. So, unfortunately, the latter method is not an option for us. After learning all this, for the fourth quarter of Year 2, we planned to send out larger batches of postcards and set a goal of sending out about ~10,000 postcards in the fourth quarter. Finally, we reached out to Internal and Family Practice physicians and disseminated our flyers and information to them.

In the **fourth quarter** of Year 2 (June - August 2021), we began sending out postcards at a rate of about ~1,000 per week during most weeks. During this quarter, we also began recruiting patients using electronic medical records from our local VA medical center (BVAMC). (There was a delay in getting access to the list of potentially eligible patients due to issues in logistics within the BVAMC itself.) In total, we sent out about ~9,000 postcards. The response rate was about ~1%, which is lower than we expected. On June 29, 2021, we ran a second TV ad on the same local TV station, which resulted in a wave of about 105 applicants. Unfortunately, nearly all applicants from the TV ad were ineligible due to having good blood sugar control (HbA1c < 7%). We also note that July and August were particularly slow months, which we suspect was due to a combination of reasons, including vacation, the start of the school year, and the delta variant.

Overall, recruitment has been slower than expected, largely due to the COVID-19 pandemic. One big challenge we have faced is that the number of people who fail to show up for their screening appointment ("no-shows") is much higher than it used to be before the pandemic. Moving forward, we will have to work even harder to recruit at the same rate we used to recruit before the pandemic. We will do the following in Year 3:

- Launch a major digital advertising campaign on Facebook, Google, Instagram, and Twitter, by working with the company TrialFacts (www.trialfacts.com). One of our colleagues has had fantastic success working with a similar company to recruit similar patients for his clinical trials. In only 10 weeks, his trial received more than 800 applicants from digital advertising. Therefore, we expect that digital advertising will become our primary recruitment method in the long term and will significantly improve our enrollment.
- Launch a major radio advertising campaign on a popular radio station via "I Heart Radio."
- Mail out postcards at an even higher rate of 1,000-2,000 per week.
- Obtain earned media spots to advertise the study by working with the UAB Media Relations Office.
- Reach out to the Chair of the Department of Endocrinology, Diabetes, and Metabolism at UAB Hospital to increase the number of physician referrals.

See "*What do you plan to do during the next reporting period to accomplish the goals?"* for more details on each of these approaches.

Screening and Enrollment

To date, we have pre-screened 442 applicants by phone or online. Of these, 67 were eligible for Screening Visit 1. As mentioned previously, due to the COVID-19 pandemic, we have a much higher than expected no-show rate. Thus, of the 67 who were eligible, only 24 showed up for their Screening Visit 1 appointment. (We note that UAB Hospital's no-show rate for doctor's appointments is also much higher during the pandemic.) About 8 were brought in for Screening Visit 2, and 6 have been enrolled. The main reasons that applicants did not qualify were:

- HbA1c outside of 7-10% (n=97)
- Exclusionary disease, medication, or medical procedure (n=67)
- Eats an early dinner (n=39)
- Unable or unwilling to follow the study protocol (n=28)
- On insulin (n=23)
- Spends more than 1.5 hours/day outdoors (n=23)
- Already practicing some form of intermittent fasting (n=20)

We enrolled our first participant in May, and the first participant recently completed the 16-week intervention. In addition, there are 23 individuals who may be eligible in the future who we will recontact.

Importantly, in the first month of the new year, we have already seen a great improvement in enrollment, and we have enrolled an additional 6 participants (1.5 per week) in September. This is much closer to our desired target of ~2.3 per week. This is even though the digital marking campaign and radio ads have not yet launched, which should greatly improve enrollment.

Retention and Adherence
To date, retention has been outstanding (100%), and no participants have dropped out of the study. All participants enrolled in the study and who are actively participating in the intervention have been very adherent to their assigned interventions, adhering at least 5-6 days/week. All our enrolled participants have been very dedicated and committed, so adherence has been excellent and on track with what we hoped.

Data Collection
Data collection has gone well overall, with only a couple of minor issues that we are further refining. Minor issues include the ambulatory blood pressure monitor occasionally missing some time points (known issue; part of Aim 3) and the YSI machine missing some time points (part of Aim 2). These issues are minor. All other aspects of data collection have gone very well. In addition, we have begun analyzing multiple types of data on an ongoing basis (see Milestones Table for more details).

Adverse Events & Safety
There have been no serious or unexpected adverse events. To date, we have had less than a dozen adverse events, all of which are minor. Adverse events reported include fatigue, sleepiness, and increased thirst, most of which occurred during the inpatient testing.

To reduce the risks of contracting COVID-19 during the pandemic, we met with the study physicians and developed a modified plan to monitor participants' safety during the COVID-19 pandemic in the comfort of their own homes. Both glucose and blood pressure are being checked at the same frequency as in the original grant proposal, but now participants perform these safety checks at home to reduce the risk of transmission of COVID-19. This has been going very well.

To date, we have had two safety and progress meetings with our independent safety monitors (Dr. Holly Wyatt and Stewart Frank) to evaluate patient safety (once per quarter). The monitors made a couple suggestions to improve recruiting during the COVID-19 pandemic, both of which we are pursuing. Also, of note, Dr. Wyatt has asked us to consult with a renal doctor to see if there is any way to further optimize saline/supporting fluid infusions to reduce participant fatigue/sleepiness and optimize hydration during the inpatient testing. We are currently in the process of completing this task.

Regulatory & Subcontracts
We submitted continuing reviews to all regulatory bodies and have received approval from the UAB IRB [September 16, 2020 and August 30, 2021], BVAMC IRB [October 22, 2020 and pending review currently], and HRPO [November 30, 2020, pending review currently]). Additionally, our co-investigator Dr. Sarah-Jeanne Salvy received IRB approval at Cedars-Sinai in 2020 and 2021. All sub-awards were also completed for Year 2.

Staffing and Training
Dr. Peterson worked on and set up a staffing plan for nurses, phlebotomists, biospecimen-processing technicians, and sleep technicians through frequent meetings with the UAB Center for Clinical and Translational Science and UAB Hospital.

- **Nurses**. In the second and third quarters, we hired and trained four nurses. (This process had been delayed by three months due to an expected death in the financial operations office.) The nurses work in the Center for Clinical and Translational Science and perform the inpatient testing for this protocol. One nurse recently left (due to a conflict with completing her schooling), and we currently have three nurses. We are in the process of replacing the fourth nurse and will be conducting interviews in the next quarter.
- **Biospecimen-Processing Technicians.** In the third and fourth quarters, we collaborated with the UAB Center for Clinical and Translational Science and used a hybrid staffing model to process biospecimens during the inpatient testing. Dr. Peterson has also finalized the associated research billing processes for these staff. Staffing to support biospecimen processing has been working well.

- **Sleep Technicians.** As reported previously, we had to shift our staffing plan for the PSG (sleep) testing. During the second quarter, we assembled a pool of seven already-trained sleep technicians to perform the PSG tests through collaboration with the UAB Sleep/Wake Disorders Center. This was a two-month process that involved contracts and negotiations with the UAB Sleep/Wake Disorders Center and UAB central administration. The PSG installation and training was completed on April 5, 2021, and all sleep technicians were trained in its use in April 2021.
- **Student Workers.** We hired and trained a couple student workers to assist with mailing postcards and processing biospecimens this summer.
- **Behavioral Counselor**. Dr. Felicia Steger, who was our lead dietitian and a postdoctoral fellow, accepted a faculty position at Kansas University Medical Center with a start date of September 7, 2021. We recruited a replacement for her. In the fourth quarter, we hired and trained Ms. Sara Hannum, a behavioral counselor with more than 20 years of experience in doing lifestyle counseling for research studies. Ms. Hannum is fully trained and took over from Dr. Steger at the end of the fourth quarter.
- **Research Coordinator**. Ms. Kim Armstead, who was serving as a research coordinator on this trial, has been promoted from a coordinator I to a coordinator II position within Dr. Peterson's laboratory. She is now taking on a new clinical trial. Ms. Errin Jessie, a new Coordinator I in the laboratory, will be replacing her. Ms. Jessie will be trained in month 1 of the next quarter. Ms. Armstead will serve as a backup counselor for this clinical trial.

All study staff were retrained in all relevant BVAMC privacy and security measures, and WOC appointments are still active.

Finalizing and Rehearsing the Protocol

In the first half of Year 2, while waiting for operations to return to normal, we rehearsed and finalized the protocol. After running into some minor hiccups in getting the IV extension tubing to work, we finally got it to work (with tips from a collaborator), and we rehearsed and finalized the frequent blood sampling protocol. (These rehearsals had been put on hold during the first few months of the COVID-19 pandemic.) We then completed the SOPs for blood sampling and the polysomnography (PSG). Thereafter, we rehearsed the entire 38-hour inpatient testing protocol in the second and beginning of the third quarters of Year 2. Also, as we refined the protocol, we made minor changes in the questionnaires used and the light therapy intervention. (Minor protocol revisions were completed in the second quarter of this award prior to submission to HRPO.) We conducted the final run-through of the 38-hour inpatient testing protocol with the newly installed PSG equipment on April 10-11, 2021. We also assembled the policy and procedure (P&P) manual for the study and finalized all data collection forms and the extensive REDCap database. To help us track participants and ensure data quality, we created several data validity reports and automated forms to track participants. Lastly, we finalized the behavioral counseling scripts and the exit interviews. Our statistician is still in the process of finalizing software code in R to regularly check for missing data.

Facilities

Over several months, we negotiated with UAB hospital to procure four rooms within the hospital to conduct the inpatient testing protocol in weekends. This required over two dozen meetings over a several-month period and was ultimately approved by the Chief Compliance Officer and the Associate Vice President of Regulatory Services for the UAB Hospital. As reported previously, we outfitted these rooms, including by developing a system of blackout curtains and doors; testing the light levels in the rooms; purchasing new equipment and supplies; and configuring the rooms. We also acquired and outfitted a new room in the Webb building as a backup room and purchased new furniture for it (i.e., a bed, cabinet, recliner, trays, etc.).

Dr. Peterson also regularly met with the UAB Center for Clinical and Translational Science and contractors to work on the renovation of two additional inpatient testing rooms to use on weekdays. The construction was delayed several by the COVID-19 pandemic and was completed in June 2021. We also procured new hospital beds, all equipment, a system of blackout curtains and doors, etc., for the room.

The acquisition and renovation of rooms were a major undertaking.

Other Activities

- Monthly meetings were set up with Co-Investigators including the following people:
    - The study statistician Dr. Joshua Richman
    - Co-investigator and circadian expert Dr. Karen Gamble
    - Co-study physicians Drs. Tim Garvey and Dr. T. Brooks Vaughan
    - Co-investigator Dr. Sarah-Jeanne Salvy
    - Paid independent consultant Dr. Frank Scheer (BWH).
- This year, we sourced and ordered all of the remaining equipment and supplies, including the YSI 2500 analyzer to measure glucose, the polysomnography (PSG) equipment, the ambulatory blood pressure monitors, the glucometers, test strips, at-home blood pressure units, IV extension tubing, and accelerometers. We also ordered two hospital beds; blackout curtains, and a range of hospital supplies to outfit the new inpatient testing rooms.
- We reviewed the literature on bright light therapy for the treatment of cardiometabolic disease. This allowed us to refine the delivery of the light therapy intervention. In particular, we will allow participants to either use a light box or light therapy glasses (there are now light therapy glasses on the market). Due to the COVID-19 pandemic, we temporarily de-prioritized writing the review article and planned to resume once the study is up and running at full capacity. We resumed working on the review article in August 2021.

- **What opportunities for training and professional development has the project provided?**
  Nothing to Report

- **How were the results disseminated to communities of interest?**
  Nothing to Report

- **What do you plan to do during the next reporting period to accomplish the goals?**

Due to the COVID-19 pandemic, recruitment has been much slower than expected.

Fortunately, in the first month of the new year, we have already seen a large improvement in enrollment, and we have enrolled an additional 6 participants (1.5 per week) in September. This is much closer to our desired target of ~2.3 per week.

We will do the following in the next quarter:

1. **Social Media Advertising**. We will launch a major digital advertising campaign to recruit patients with type 2 diabetes on Facebook, Google, Instagram, and Twitter. We will work with the company Trialfacts, one of the leading clinical trial advertising companies in the world. In the fourth quarter, we worked hard to finalize an extensive set of digital ads and accompanying content (see 100+ page document). We initiated the contract and are currently waiting on our institutions' IT approval process. We expect to launch the campaign sometime in the first quarter of the next year. We expect that digital advertising will become our primary recruitment method in the long term and will significantly improve our enrollment. Encouragingly, one of our colleagues has had fantastic success working a very similar approach: in only 10 weeks, his trial received more than 800 applicants from digital advertising.

2. **Radio Advertising**. We will launch a major radio advertising campaign on a popular radio station via "I Heart Radio." The contract was just approved by UAB's contracts office on September 30th, and the ads will air starting in October.

3. **Mailing Postcards**. We will mail out postcards at an even higher rate of 1,000-2,000 per week. Postcards will be mailed to patients with type 2 diabetes identified via electronic medical records at the UAB Hospital and the BVAMC. We reworded some of the recruitment materials, particularly the postcards, to include language related to intermittent fasting. We believe that this will entice more people to apply to participate.

4. **Earned Media**. We will work with the university's press relations office to get earned spots on TV shows and radio to talk about and advertise the study. We appeared on the local TV station WBRC on September 23rd. We are currently reaching out to *Good Morning Alabama* and other local media outlets.

5. **Flyers at UAB Hospital**. We will put up dozens of laminated flyers in the UAB Hospital, including in plastic mounts in high-traffic areas such as the pharmacy and waiting rooms. (This was indeed started in month 1 of the next year.)

6. **Physician Referrals**. We will try to forge a partnership with the Chair of the Division of Endocrinology, Diabetes, and Metabolism at UAB to encourage physicians to refer more patients to our clinical trial. We are meeting with the Chair on October 15th.

As mentioned, our enrollment rate this past month has improved to 1.5 per week, a large improvement. For the remainder of the upcoming quarter, we will target enrolling 2.3 participants per week (as planned in the original grant). We aim to achieve this benchmark by the end of the next quarter.

- **IMPACT:**

  - **What was the impact on the development of the principal discipline(s) of the project?**
    We finalized participant handouts and instructions for the lifestyle interventions. These materials are now being used and adapted in two other large clinical trials on intermittent fasting. There will be additional impacts once the study is finished and the results are reported.

  - **What was the impact on other disciplines?**
    Nothing to Report

  - **What was the impact on technology transfer?**
    Nothing to Report

  - **What was the impact on society beyond science and technology?**
    Nothing to Report

- **CHANGES/PROBLEMS:**

  - **Changes in approach and reasons for change**
    We modified our eligibility criteria to enroll more participants. We originally excluded individuals taking sulfonylureas (a diabetes drug), as we were concerned that there may be an increased risk of hypoglycemia arising from intermittent fasting. Our trial now includes individuals taking sulfonylureas under the conditions that they 1) have been taking them for longer than 2 years and 2) have an HbA1c of 8-10%. The rationale for this change is that we were excluding many people who would otherwise qualify and, as long as these two conditions are met, the risks of hypoglycemia are likely remote.

  - **Actual or anticipated problems or delays and actions or plans to resolve them**

    We experienced delays for three primary reasons:

    1. **COVID-19 Pandemic**

       a. **Facilities Temporarily Shut Down**. We experienced a one-year delay due to the COVID-19 pandemic temporarily shutting down our clinical trial and our research facilities and also impacting our operations. This has been resolved, and our facilities have all re-opened.

       b. **Supply Shortages**. There continue to be supply shortages for many medical supplies and other items used in this trial. To mitigate these delays, we have been pro-actively ordering supplies earlier and using those supplies conservatively.

       c. **Slower Recruitment and More No-Shows**. We have had an unprecedented number of no-shows for screening appointments, and fewer people than normal are participating in research studies. For instance, during a two-week period in mid-August, we had a ~65% no-show rate across two of our studies. Our hospital system is similarly seeing a large increase in their no-show rate during the pandemic. This indicates that there is still a lot of

fear in the community about COVID-19, particularly with the delta variant. As a result, recruitment has been much slower than expected. July and August were particularly slow months, but enrollment has started to pick up again in September (presumably also because the school year has started and people are no longer on vacation). To resolve these issues with recruitment during the pandemic, we will do the following:

i. To mitigate the higher no-show rate for appointments, we will screen more people than needed, knowing that some individuals will not show up to their appointment.
ii. Launch several major advertising campaigns (see *"What do you plan to do during the next reporting period to accomplish the goals?"*)
iii. Continue sending out 1,000-2,000 postcards per week
iv. Try to forge a partnership with the Chair of the Division of Endocrinology, Diabetes, and Metabolism at UAB to directly enroll more patients.

2. **Inpatient Testing Facilities**. The renovation and construction of the two additional inpatient testing rooms were delayed several months due to space issues within the hospital, regulatory and compliance issues, and the COVID-19 pandemic. Construction began two quarters ago and was completed in July 2021. This issue is now completely resolved.

3. **Staffing Issues**. Because this grant was funded as an alternate, we experienced an initial delay in recruiting, hiring, and training project staff in Year 1. In Year 2, we had a vacant coordinator position on another study, so to prevent that study from collapsing (given that there were participants actively participating in the intervention), we had to pull some effort from personnel involved in this study to the other study, which temporarily reduced our staff capacity. This issue is now resolved. More recently, one of our nurses can no longer work for our study, so we are currently in the process of trying to find a replacement. We expect to resolve this issue within the next 2-3 months.

- **Changes that had a significant impact on expenditures**
  Due to the COVID-19 pandemic, our institution shut down all in-person clinical research (except for life-saving research) in March 2020 and we were not able to begin enrollment until several months later in Year 2. We have a large balance that we will need to carry forward, which we will spend in future years to conduct the trial as originally planned.

- **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**
  Nothing to Report

- **Significant changes in use or care of human subjects**
  Nothing to Report

- **Significant changes in use or care of vertebrate animals.**
  Not Applicable

- **Significant changes in use of biohazards and/or select agents**
  Not Applicable

- **PRODUCTS**

  - **Publications, conference papers, and presentations**

    - **Journal publications**
      Nothing to Report. Two publications are planned for the coming fiscal year, to catch up with the original timeline.

    - **Books or other non-periodical, one-time publications**
      Nothing to Report

- **Other publications, conference papers, and presentations**
  Nothing to Report

- **Website(s) or other Internet site(s)**
  This past quarter, we drafted new digital ads to recruit participants via ads on Facebook, Instagram, Twitter, and Google. Potential applicants who click on the ads will be brought to a webpage to apply for the study. The recruitment webpages will go live in the next quarter, once all IT approvals are complete and the contract is approved. See Appendix for the digital materials.

- **Technologies or techniques**
  Nothing to Report

- **Inventions, patent applications, and/or licenses**
  Nothing to Report

- **Other Products**

  - **Data or Databases**. We have developed an extensive REDCap database to collect participant data and information, including responses to questionnaires.

  - **Clinical interventions**. We optimized the light therapy intervention and its mode of delivery by reviewing the most recent literature and speaking to other leading researchers. We changed the light therapy intervention to allow participants to use either a light therapy box (original plan) and/or light therapy glasses (new addition based on evolving technology). We also tested out several light therapy glasses and selected the best product. We expect that this change will increase participant adherence, and it has already given our participants a more customizable and enjoyable experience.

  - **Educational aids or curricula**. We finalized participant handouts and instructions for the lifestyle interventions. These materials are now being used and adapted in two other large clinical trials on intermittent fasting.

- **PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS**

  - **What individuals have worked on the project?**

Name	Courtney Peterson, Ph.D.
Project Role	Principal Investigator
Researcher Identification (ORCID #)	0000-0002-4845-6782
Nearest Person Month Worked	5
Contribution to the Project	Dr. Peterson is serving as the study PI. She oversees all aspects and operations of the clinical trial (except where noted below). She also is reviewing study data on an ongoing basis to ensure data validity.
Funding Support	
Name	Sarah-Jeanne Salvy, Ph.D.
Project Role	Co-Investigator and Clinical Psychologist
Researcher Identification (ORCID #)	0000-0002-8202182X
Nearest Person Month Worked	1
Contribution to the Project	Dr. Salvy designed the behavioral aspects of the intervention and crafted behavioral SOPs. She currently oversees the behavioral counseling and is responsible for ensuring quality control.

Funding Support	
Name	Joshua Richman, M.D., Ph.D.
Project Role	Co-Investigator and Statistician
Researcher Identification (ORCID #)	0000-0002-6166-7488
Nearest Person Month Worked	1
Contribution to the Project	Dr. Richman assisted with designing the study database in REDCap and created the statistical and data validity protocols for the trial, using software programming. He also created the randomization code. He is overseeing data management and the study database on an ongoing basis.
Funding Support	
Name	Karen Gamble, Ph.D.
Project Role	Co-Investigator
Researcher Identification (ORCID #)	0000-0003-3813-8577
Nearest Person Month Worked	1
Contribution to the Project	Dr. Gamble has provided important guidance on the light therapy intervention, protocol, and circadian rhythms measurements. She also helped negotiate for and set up the inpatient testing rooms. Dr. Gamble is currently overseeing the collection of circadian data.
Funding Support	
Name	Felicia Steger, Ph.D., R.D.
Project Role	Postdoctoral Scholar
Researcher Identification (ORCID #)	0000-0002-8117-4082
Nearest Person Month Worked	12
Contribution to the Project	Dr. Steger has assisted Dr. Peterson in her role as PI by helping to refine the protocol; develop and select data collection instruments; build the study database in REDCap; refine the clinical intervention; and co-design the behavioral counseling. Dr. Steger is currently delivering the behavioral counseling, assisting with screening visits, and leading the writing of manuscripts.
Funding Support	
Name	Rachel Benz, M.S.N., R.N.
Project Role	Research Nurse Manager
Researcher Identification (ORCID #)	0000-0001-6211-7771
Nearest Person Month Worked	12
Contribution to the Project	Lead research coordinator and nurse manager
Funding Support	
Name	Kimberly Armstead, B.S.
Project Role	Research Coordinator
Researcher Identification (ORCID #)	N/A
Nearest Person Month Worked	10
Contribution to the Project	Research coordinator, with a focus on recruiting, screening, and consenting participants.
Funding Support	
Name	Shelby Leverett, B.S.N.
Project Role	Research Nurse

Researcher Identification (ORCID #)	N/A
Nearest Person Month Worked	6
Contribution to the Project	Perform nursing and collect research data during the 38-hour inpatient tests. Also assist with phlebotomy and screening visits.
Funding Support	
Name	Haley Hulsey, B.S.N
Project Role	Research Nurse
Researcher Identification (ORCID #)	N/A
Nearest Person Month Worked	8
Contribution to the Project	Perform nursing and collect research data during the 38-hour inpatient tests. Also assist with phlebotomy and screening visits.
Funding Support	
Name	Cynthia Venton, B.S.N.
Project Role	Research Coordinator
Researcher Identification (ORCID #)	N/A
Nearest Person Month Worked	9
Contribution to the Project	Perform nursing and collect research data during the 38-hour inpatient tests. Also assist with phlebotomy and screening visits.
Funding Support	
Name	Elizabeth Cochran, B.S.N., R.N.
Project Role	Research Nurse
Researcher Identification (ORCID #)	N/A
Nearest Person Month Worked	2
Contribution to the Project	Perform nursing and collect research data during the 38-hour inpatient tests. Also assist with phlebotomy and screening visits.
Funding Support	

- **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**

Dr. Peterson (PI) and Dr. Salvy (co-Investigator) both received another grant as MPIs from the NIH. Both will devote 15% effort (1.8 calendar months).

R01 CA258222 (Peterson, Figueiredo, and Salvy) 6/15/2021 – 5/31/2026 1.80 Calendar
NIH/NCI
Time-Restricted Eating and Cancer: Clinical Outcomes, Mechanisms, and Moderators
This clinical trial aims to determine whether a form of intermittent fasting called time-restricted eating improves clinical cancer outcomes, including treatment-related toxicity, quality of life, and pathological complete response rates among rectal cancer patients. This grant will also test whether these improvements are mediated through the IGF-1 pathway according to the Differential Stress Sensitization hypothesis and how time-restricted eating affects daily functioning and behaviors.
Role: MPI

Dr. Gamble (co-investigator) has had three changes: she has received one grant and is no longer supported by two grants.

New Support
R01 AG061785-01A1 (Roberson and Gamble) 09/15/2021-05/31/2026 3.0 calendar
NIH/NIA
Circadian Changes Network Excitability and Alzheimer Disease Pathogenesis

The major goals of this project will test the hypothesis that dysregulation of the molecular clock and resulting changes in PV+ interneuron gene expression and activity contribute to Alzheimer's Disease-related neuronal hyperexcitability.

Moved to Past Support
R01 DK112934 (Habegger) 04/01/2017 – 02/28/2022 0.5 calendar
NIH/NIDDK
Glucagon Mediated Potentiation of Insulin Sensitivity in Glucose Metabolism
The goal of this project is to elucidate the underlying molecular mechanism/s of glucagon-mediated improvements in insulin action, especially in light of glucagon's diabetogenic program.
Role: Co-Investigator

P01 HL136267 (Pollock) 09/09/2019 – 03/31/2021 0.6 calendar
NIH/NHLBI
AD Supplement: Salt-Dependent Hypertension and the Central Clock
The purpose of the current one-year administrative supplement is to establish that high salt diets diminish Bmal1 rhythms in SCN neurons (via ET-1/ETB), impairing the primary neural output of the central clock.

All three investigators still remain under the maximum effort allowed. There have been no other changes in active support among key personnel.

- **What other organizations were involved as partners?**
  Organization Name: Cedars-Sinai Medical Center
  - **Location of Organization:** Los Angeles, CA
  - **Partner's contribution to the project**
    - **Collaboration**
      Co-investigator Dr. Sarah-Jeanne Salvy assisted in the development of the behavioral aspects of the research protocol, including the design of behavioral counseling, behavioral interviews, psychological questionnaires, and the corresponding SOPs**.** She is currently overseeing all behavioral counseling and is responsible for ensuring quality control of the behavioral aspects of the intervention.

  Organization Name: Brigham and Women's Hospital
  - **Location of Organization:** Boston, MA
  - **Partner's contribution to the project**
    - **Collaboration**
      The project's consultant, Dr. Frank Scheer, provided detailed feedback on the study protocol and timed light therapy intervention. He continues to attend the monthly co-investigator meetings and provide suggestions.

- **SPECIAL REPORTING REQUIREMENTS**

  - **Collaborative Awards**
    Not Applicable

  - **Quad Charts**
    See Next Page

- **APPENDICES**

  See attached for new recruitment materials. We included the most important 18 out of 100+ pages of images and text.