

AUGUST 24, 2023

CONDUCTING RESEARCH 101

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Director | Research Outcomes for Children's Surgery



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TODAY'S TAKEAWAYS



How to Write a
Winning Grant
Proposal



How to Complete
the Grant when
Awarded



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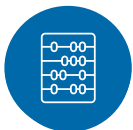


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STEPS TO WRITING A WINNING GRANT PROPOSAL



DEVELOP A SYSTEM



ASK FOR FUNDED GRANTS



LEARN ABOUT YOUR FUNDER



WIN THEM OVER ON FIRST PAGE
-AIMS PAGE-



NOTE ALL POTENTIAL PROBLEMS & SOLUTIONS



PAY ATTENTION TO DETAILS



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DEVELOP A SYSTEM

1. To obtain grant funding, commit to the game
 - 5-10% of proposals are funded
 - Create a plan to submit the same proposal to multiple funding sources
2. Develop a strategic plan for submissions
 - Year 1: Document preliminary data
 - Year 2-3: Apply for pilot funding
 - Year 4-5: Submit a large proposal



GAME PLAN: YEAR 1

1. Preliminary Studies

Feasibility of recruitment: Recruiting adolescents with inadequate sleep (< 7 hours per night) is feasible as most adolescents report chronic exposure to short sleep, well below the recommended 8-10 hours per night,^{7,8} consistent with our local data collected on sleep duration by co-Is, Drs. Simon, Cree-Green and Nadeau. Per an Epic query performed on 8/14/2018: In the last 12 months, 131 unique patients were seen by lifestyle medicine between the ages of 13-18 years who were obese and had pre-diabetes, thus, providing an ample sample from which to recruit for this feasibility study.

Feasibility of delivering intervention: Our multidisciplinary team has a strong cumulative background in sleep extension interventions in children and adolescents and conducting behavioral interventions in both adolescent and adult populations with multiple federal funded RCTs. This team has four (2 NIH R01 & 2 ADA/JDRF) RCTs (PI: Catanacci, Nadeau), one NIH K23 sleep extension intervention (PI: Simon), and a NIH U01 multi-center RCT in obese adolescents with prediabetes/T2D (PI: Nadeau).

Feasibility of performing metabolomics measures: Dr. Cree-Green's study examined metabolites associated with IR in 21 obese girls with and without polycystic ovarian syndrome (PCOS). In fasting state, 125 metabolites were identified as different. Higher valine (BCAA) was associated with worse IR ($p=0.006$). FFAs and AC were also significantly different ($p<0.01$) suggesting that obese girls with PCOS have a distinct metabolic signature from obese girls without PCOS.

Preliminary data on effect of sleep extension on metabolic and metabolomic measures: Utilizing data from Drs. Simon and Cree-Green, their combined samples of 41 overweight/obese (mean BMI percentile of 97.1) adolescents, aged 14-19 (mean 15.9 years), 49% had insufficient sleep (< 7 hours/night). Total sleep time ranged from 4.63 – 6.97 hours per night in those with insufficient sleep and 7.01-8.33 hours per night in those with adequate sleep. Adolescents with insufficient sleep had significantly worse HOMA-IR compared to those in the sufficient group (4.19 vs 3.16; $p=0.03$).



GAME PLAN: YEARS 2-3

No studies have used a behavioral intervention in short sleeping adolescents to improve sleep duration and examine these metabolites as potential mediators of alterations in insulin sensitivity. Understanding energy metabolism in adolescents, under conditions of adequate versus insufficient sleep, may be an essential key to provide insights for future development of interventions to improve IR. This proposal will take the first step towards filling this research gap by testing the feasibility of a sleep extension protocol in research setting among overweight and obese adolescents diagnosed with prediabetes.

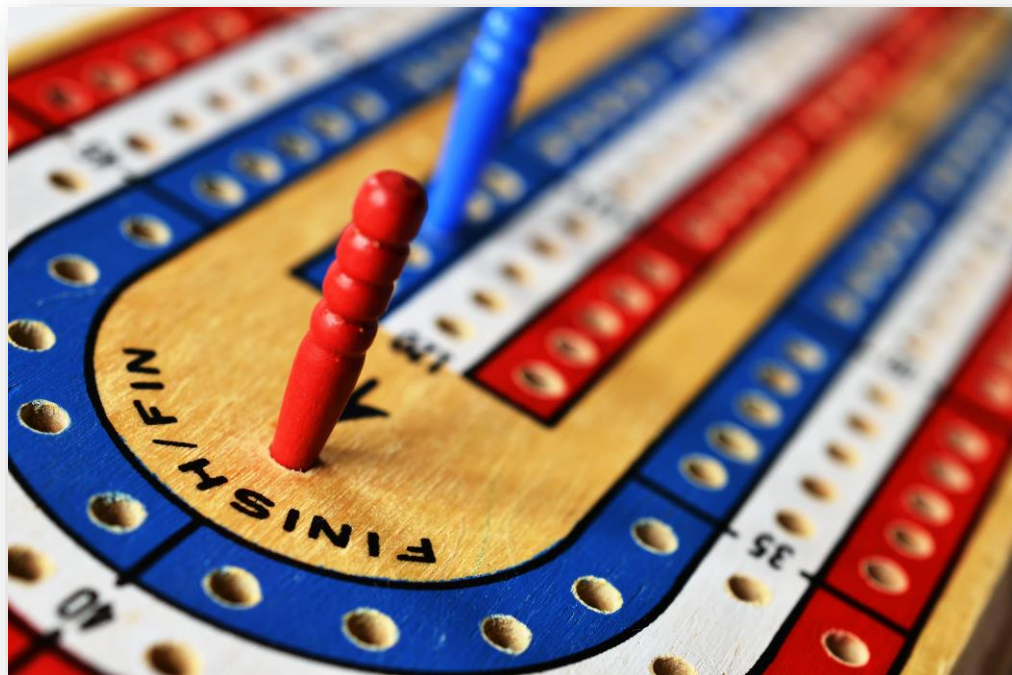
The specific aims of this **feasibility study** are:

1. To examine the feasibility of recruitment and retention of adolescents with overweight/obesity, pre-diabetes, and inadequate sleep into a sleep extension intervention.
2. To assess adherence to and initial pre-post sleep outcomes of a sleep extension intervention to increase total sleep time in adolescents with overweight/obesity, pre-diabetes, and inadequate sleep.
3. To determine estimates of the mean and variability of potential intervention outcomes, including metabolomics, body composition, and substrate oxidation.

Impact: The results of this feasibility study will be used to inform recruitment methodology, intervention development, and sample size estimates for a pilot RCT to be submitted as an NIH R34 application to NHLBI PAR-18-463 in October 2019.



GAME PLAN: YEARS 4-5



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ASK COLLEAGUES FOR FUNDED GRANTS

Ask for “funded” research proposals from colleagues that are more senior to you or if at your level and have secured the funding you want

Ultimate goal, an example of successful proposal formatted exactly for where it is going (i.e., NIH R01/R21, American Heart Association Scientist Development Grant, etc)



REVIEW THE FUNDED GRANT & FIND THE STRATEGY



How did this grant align with the funders' mission?



How many aims did they have? Are aims mechanistic, behavioral, RCT, etc?



Is there preliminary data? Do you have similar data you can use?



How is the grant formatted? Are there sections that surprise you or that you aren't prepared for and need more data?



LEARN ABOUT YOUR FUNDER

Research Grants on Improving the Use of Research Evidence

We welcome studies that pursue one of three aims:

Building, identifying, or testing ways to improve the use of existing research evidence

Building, identifying, or testing ways to facilitate the production of new research evidence that responds to decision-makers' needs

Testing whether and under what conditions using research evidence improves decision-making and youth outcomes

The online application is now open. The next deadline for applications is August 3, 2022 at 3pm ET.



LEARN ABOUT YOUR FUNDER

Do you need to submit a letter of intent?

Is there a note that speaking to the program officer (PO) is strongly encouraged?

Will you be able to submit the proposal, or do you have to go through your office of grants and contracts (OGC)?

What other forms or documents are needed for submission?



STEPS TO WRITING A WINNING GRANT PROPOSAL



DEVELOP A SYSTEM



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GRANT PROPOSALS

The “Aims” Page



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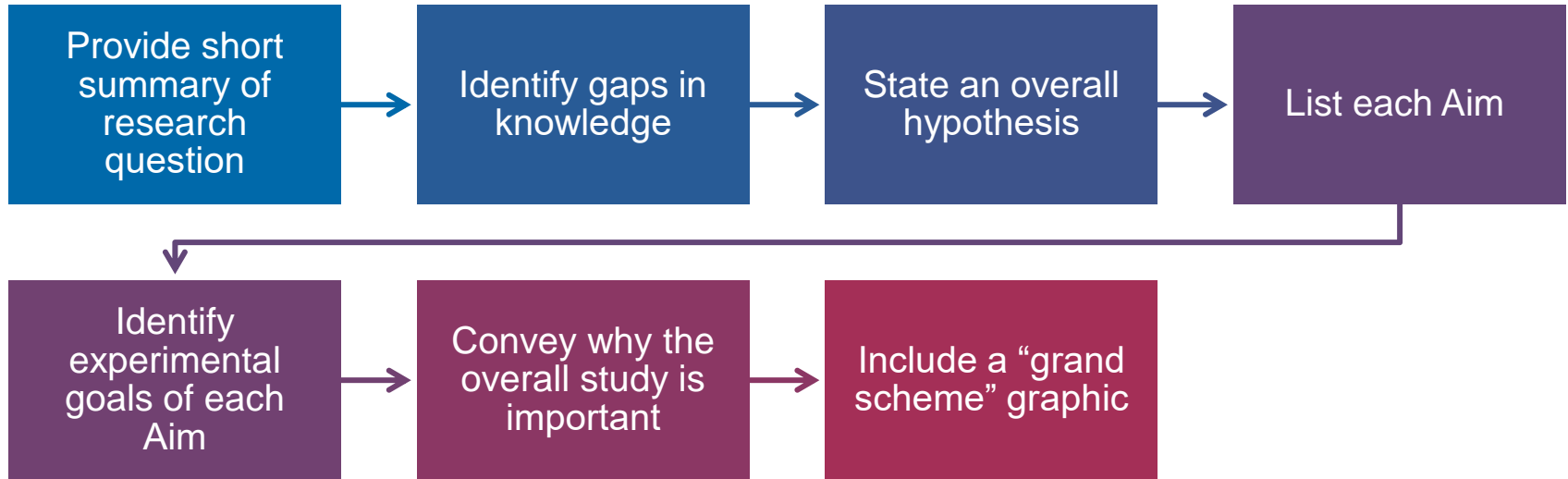


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SPECIFIC AIMS: The most crucial part of the application, do in sequence

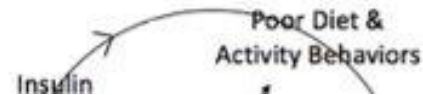


EXAMINE THE HIDDEN FORMULA

SPECIFIC AIMS

Obesity affects over one-third of US adolescents and related comorbidities, including type 2 diabetes (T2D), are increasingly prevalent in youth.^{1,2} Youth-onset T2D is associated with insulin resistance (IR) and increased mortality. Over half of youth with T2D in the TODAY and RISE randomized controlled trials (RCT) failed primary therapy by 3-years, which is almost 4 times faster than seen in similar studies of adults.^{3,4} It is thus imperative to focus on treating IR prior to the development of T2D as early intervention may offer a critical window for prevention prior to development of these long-lasting health consequences.

Obesity-associated IR is an early mediator of T2D.⁵ Numerous health behaviors have been individually associated with obesity-associated IR, including excessive-poor quality energy intake, physical inactivity and insufficient sleep, all of which are common in adolescence. However, interventions targeting IR to-date in teens have focused on diet & physical activity behaviors alone, with and without medications (i.e., metformin) but have largely been ineffective.^{4,6} No lifestyle interventions to-date in adolescents have comprehensively addressed healthy lifestyles by intervening on all relevant behaviors (i.e., diet, activity, and sleep) simultaneously, nor have studies included sleep extension as a major component of the intervention.⁶ To design more effective obesity interventions in adolescents, an understanding of the impact of sleep on the underlying pathophysiology of IR is needed (Figure 1). This is a major goal of my research program, of which this proposed feasibility study addresses a critical first step.



OPENING SENTENCE

Obesity affects over one-third of US adolescents and related comorbidities, including type 2 diabetes (T2D), are increasingly prevalent in youth.^{1,2} Youth-onset T2D is associated with insulin resistance (IR) and increased

Need to immediately capture the reviewer's attention by highlighting the relevance of your topic

- Consider the mission of the funder and include key words that highlight that mission



CURRENT KNOWLEDGE

increasingly prevalent in youth.^{1,2} Youth-onset T2D is associated with insulin resistance (IR) and increased mortality. Over half of youth with T2D in the TODAY and RISE randomized controlled trials (RCT) failed primary therapy by 3-years, which is almost 4 times faster than seen in similar studies of adults.^{3,4} It is thus imperative to focus on treating IR prior to the development of T2D as early intervention may offer a critical window for prevention prior to development of these long-lasting health consequences.

In 3-4 sentences what is known on the subject

- Keep in mind you are setting up the reviewer for the “gap in knowledge” you are proposing to fill with your proposal



RESEARCH GAP

have focused on diet & physical activity behaviors alone, with and without medications (i.e., metformin) but have largely been ineffective.^{4,6} No lifestyle interventions to-date in adolescents have comprehensively addressed healthy lifestyles by intervening on all relevant behaviors (i.e., diet, activity, and sleep) simultaneously, nor have studies included sleep extension as a major component of the intervention.⁶ To design more effective obesity interventions in adolescents, an understanding of the impact of sleep on the underlying pathophysiology of IR is

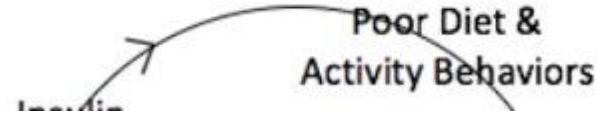
Define the subject of your proposal

- Keep it simple, direct, and relate it to the preceding sentences



LONG-TERM GOAL

studies included sleep extension as a major component of the intervention.⁶ To design more effective obesity interventions in adolescents, an understanding of the impact of sleep on the underlying pathophysiology of IR is needed (Figure 1). This is a major goal of my research program, of which this proposed feasibility study addresses a critical first step.



State to the reviewers where this project will go next

- They want to see that the results from this project will continue into the next logical step



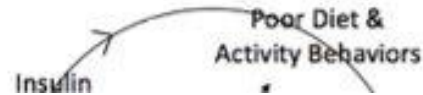
PART 1: IMPORTANCE

Identify the Gap in Literature

SPECIFIC AIMS

Obesity affects over one-third of US adolescents and related comorbidities, including type 2 diabetes (T2D), are increasingly prevalent in youth.^{1,2} Youth-onset T2D is associated with insulin resistance (IR) and increased mortality. Over half of youth with T2D in the TODAY and RISE randomized controlled trials (RCT) failed primary therapy by 3-years, which is almost 4 times faster than seen in similar studies of adults.^{3,4} It is thus imperative to focus on treating IR prior to the development of T2D as early intervention may offer a critical window for prevention prior to development of these long-lasting health consequences.

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PART 2: PRELIMINARY DATA

Most adolescents report chronic exposure to short sleep, well below the recommended 8-10 hours per night.^{7,8} Current literature in adolescents demonstrates a clear association between short sleep and IR.⁶ Insufficient sleep may shift metabolism towards utilization of protein rather than fat for energy generation, processes which are associated with IR and metabolic disease in numerous conditions other than obesity. This association is potentially explained by the contribution of the circadian sleep-wake cycle to important metabolic pathways. In animal and adult experimental studies, chronic sleep restriction has been shown to induce IR as well as significantly disrupt serum metabolomic patterns reflective of underlying macronutrient metabolism (specifically in *branched chain amino acids (BCAA)* and *acylcarnitines (AC) metabolites*).⁹⁻¹² Obese adolescents are different physiologically from adults in that they experience puberty- and obesity related-IR and have a shifted circadian rhythm both of which demand separate studies as underlying mechanisms related to IR have been shown to differ.^{4,13,14}

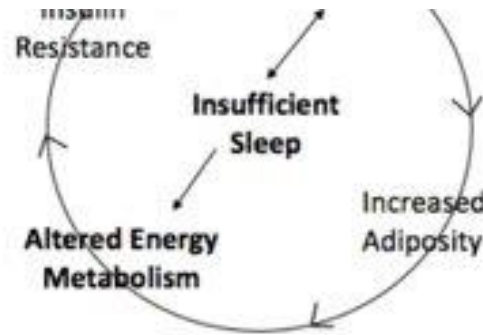


Figure 1. Cyclic Relationship of Insufficient Sleep



THE TERMS

PRELIMINARY DATA

&

PILOT DATA

CAN'T BE USED INTERCHANGEABLY.



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PART 3: RATIONALE, AIMS, & HYPOTHESIS

Appropriate Aims for PILOT STUDY

No studies have used a behavioral intervention in short sleeping adolescents to improve sleep duration and examine these metabolites as potential mediators of alterations in insulin sensitivity. Understanding energy metabolism in adolescents, under conditions of adequate versus insufficient sleep, may be an essential key to provide insights for future development of interventions to improve IR. This proposal will take the first step towards filling this research gap by testing the feasibility of a sleep extension protocol in a research setting among overweight and obese adolescents diagnosed with prediabetes.

The specific aims of this **feasibility study** are:

1. **To examine the feasibility** of recruitment and retention of adolescents with overweight/obesity, pre-diabetes, and inadequate sleep into a sleep extension intervention.
2. **To assess adherence to** and initial pre-post sleep outcomes of a sleep extension intervention to increase total sleep time in adolescents with overweight/obesity, pre-diabetes, and inadequate sleep.
3. **To determine estimates** of the mean and variability of potential intervention outcomes, including metabolomics, body composition, and substrate oxidation.

Impact: The results of this feasibility study will be used to inform recruitment methodology, intervention development, and sample size estimates for a pilot RCT to be submitted as an NIH R34 application to NHLBI PAR-18-463 in October 2019. |



BIOSKETCH



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PERFECTLY ALIGNED

A. Personal Statement

My research examines the pathway towards establishing health behaviors (i.e., sleep, diet, physical activity, screen time) early in life. As a maternal and child health epidemiologist, I have studied how maternal factors and behaviors during pregnancy influence offspring health behaviors and ultimately impact pediatric risk for obesity and other cardiometabolic disease states (insulin resistance, type 2 diabetes, cardiovascular disease). I use observational methods to first identify key associations with health behaviors and disease risk, and then use these findings to guide intervention strategies with potential for widespread dissemination and implementation.

Through this Research Institute Pilot Study Award, I will be 1) extending my methodology expertise by utilizing the tool of metabolomics and 2) establishing a multi-disciplinary team of collaborators with unique expertise that will move forward together in applying for federal funding. This proposal will use advanced tools in metabolomics research to identify biomarkers involved in pathways that may be modified by health behavior change. Prior metabolomics research has identified unique patterns of metabolites between individuals with obesity, insulin resistance, and type 2 diabetes. No studies have used these advances in metabolomics to examine early improvements in metabolites that may result from improved health behaviors prior to seeing the improvements in clinical outcomes such as absolute fat percent or weight loss.

My fifteen years of experience in human subject research has me well-positioned to serve as PI on this project and contribute expertise in health behavior change, chronic disease risk in pediatric populations, and development of behavioral intervention strategies. This proposal presents an outstanding opportunity to enhance my leadership skills as I work closely with my multi-disciplinary team of co-investigators to accomplish the aims of this intervention study. The results of this feasibility study will be used as preliminary data for an NIH R34 application to NHLBI PAR-18-463 in October 2019.



STUDY DESIGN



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HOW TO CHOOSE STUDY DESIGN

GOAL:

- Valid and precise information
- Association between exposure and disease
- Using minimum resources

EXPERIMENTAL:

- Research question involves a prevention or treatment
- Small effect expected
- Ethical and feasible
- Money is available

OBSERVATIONAL:

- Research question involves a prevention, treatment, or causal factor
- Moderate or large effect expected
- Trial not ethical or feasible
- Trial too expensive

COHORT:

- Little known about exposure
- Evaluate many effects of an exposure
- Exposure is rare
- Underlying population is fixed

CASE-CONTROL:

- Little known about disease
- Evaluate many exposures
- Disease is rare
- Disease has long induction and latent period
- Exposure and data are expensive
- Underlying population is dynamic

PROSPECTIVE:

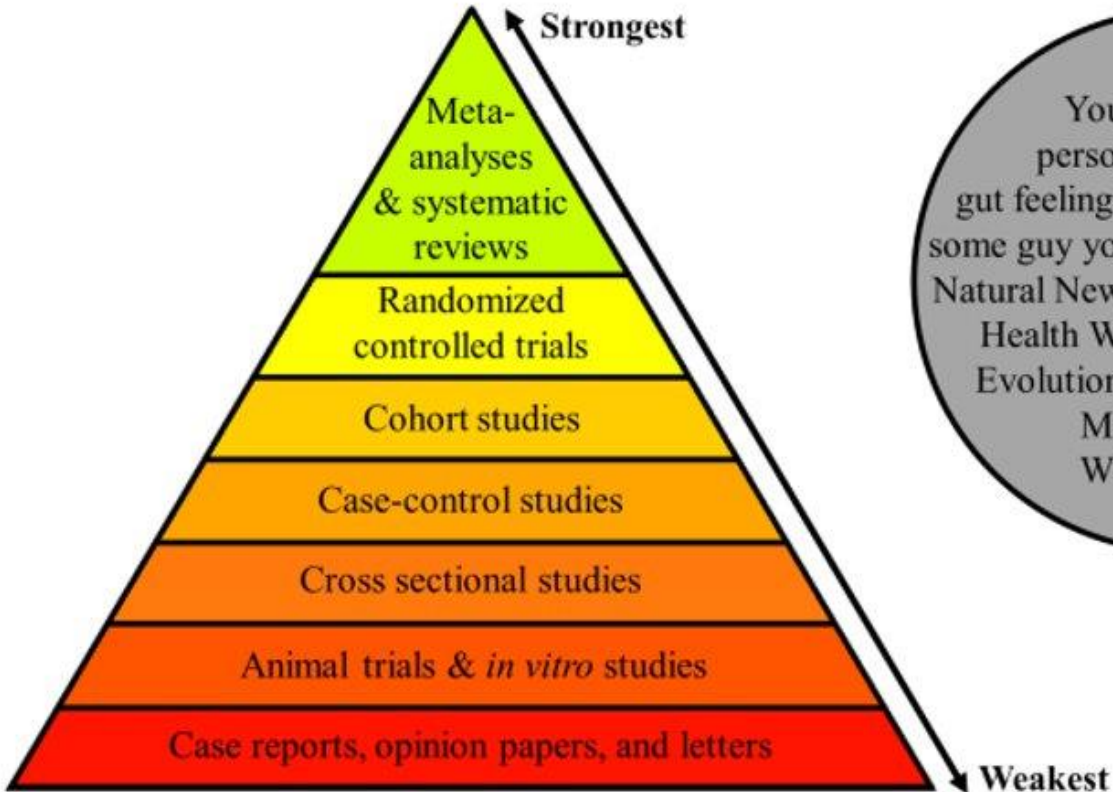
- Disease has short induction and latent period
- Current exposure
- Want high-quality data

RETROSPECTIVE:

- Disease has long induction and latent period
- Historical exposure
- Want to save time and money



Hierarchy of Scientific Evidence



Not Scientific Evidence

Youtube videos, personal anecdotes, gut feelings, parental instincts, some guy you know, websites like Natural News, Info Wars, Natural Health Warriors, Collective Evolution, Green Med Info, Mercola.com, Whale.to, etc.

thelogicofscience.com



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STUDY DESIGN CHEAT SHEET

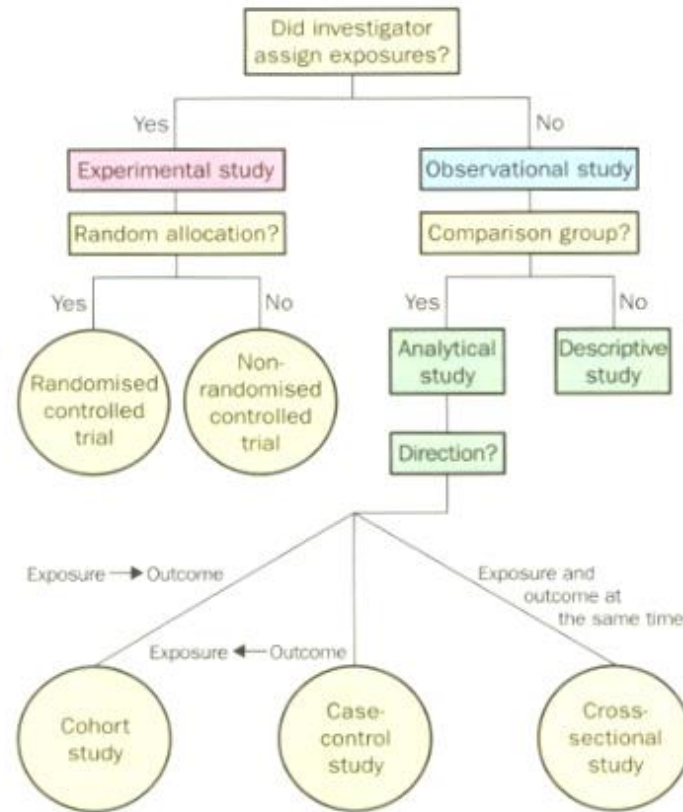


Figure 1: Algorithm for classification of types of clinical research



STEPS TO WRITING A WINNING GRANT PROPOSAL



DEVELOP A SYSTEM



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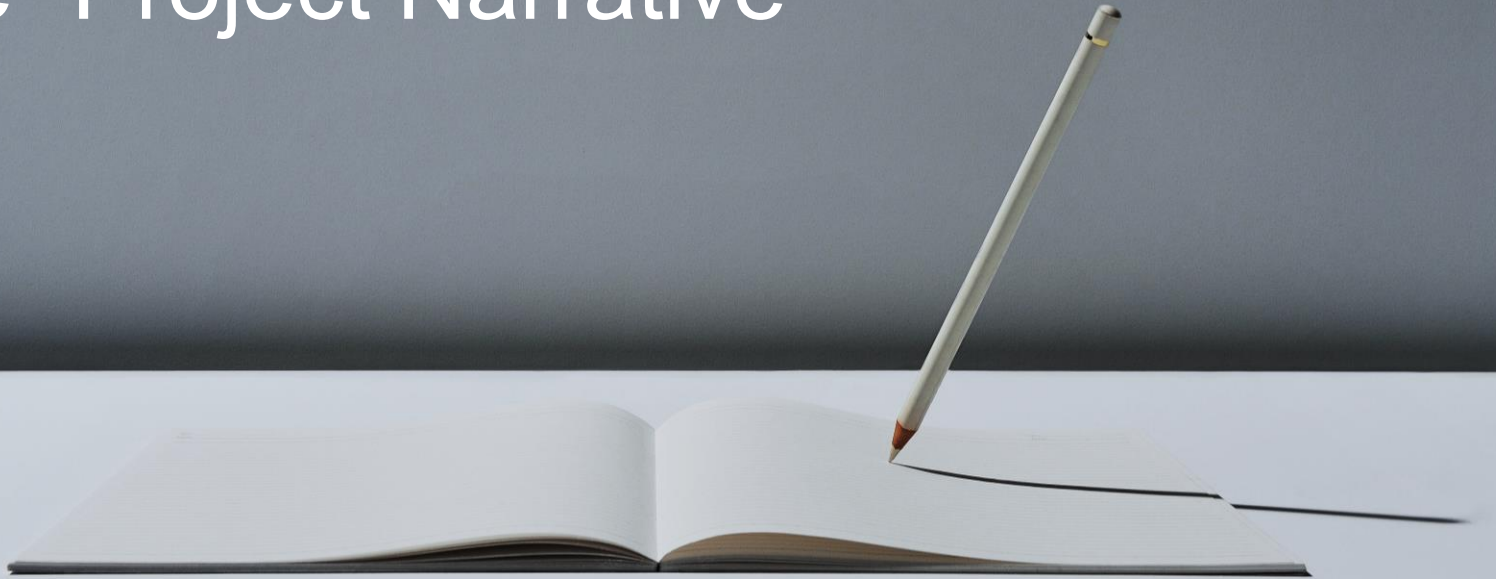


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GRANT PROPOSALS

The “Project Narrative”



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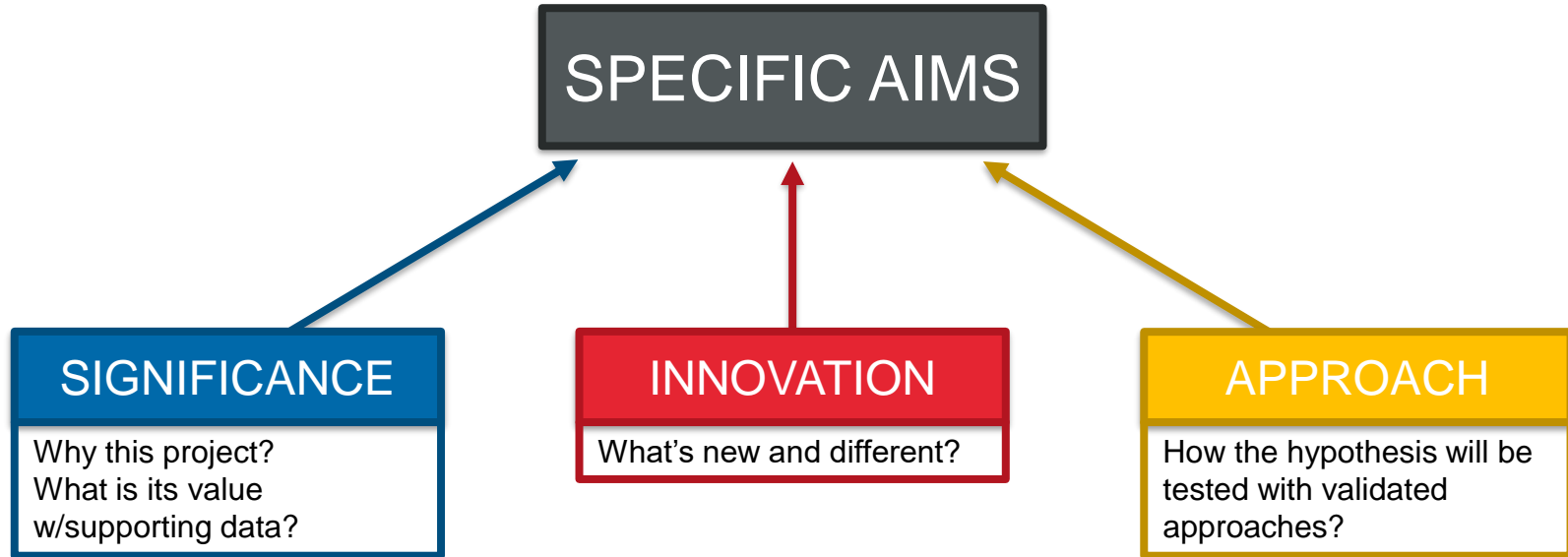
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ADDRESS THE W'S

- **Who** is your audience? Understand the focus of the granting agency
- **What** is the question you are addressing?
 - ✓ Is the biological/physiological/pathophysiological importance of the question?
 - ✓ Tools will be used to address the question?
 - ✓ Deliverables will be obtained?
- **Where** will the research lead (i.e., future directions)?
- **Why** is now the time to address your question?
 - ✓ Are you the person to perform the research?



STRATEGIC PLAN



FORMAT, FORMAT, AND FORMAT...

Does the funder recommend section headings, a specific format, page limits, font size, font style, etc?

Research Strategy

Significance
Scientific Premise
Research Gap
Innovation

Approach

Preliminary Studies
Study Design
Study Procedure
Assessments
Analytical Plan
Project Timeline
Future Directions

- Summary of Proposed Work (100 words)
- Project Significance & Potential Impact
- Research Hypothesize and Study Aims
- Research Design: Data and Study Methods
- Key Personnel
- Anticipated Products and Target Audience
- Prior/Ongoing Research Directly Related to the Proposed Work

Significance
Research Plan
Personnel
Resources



TIPS AND TRICKS

Assume

Assume reviewers don't know anything about the topic of your work

Use

Use text from the funding announcement that highlights how your work will address one of their needs/focus areas

Consider

Consider framing your work using a theory of change or mechanism of action



COMMON PROBLEMS

The project you plan to do is not clearly defined

The significance of the project doesn't match the research you propose to do

Lack of information regarding the setting, population, and outcomes



LIST POTENTIAL PROBLEMS WITH SOLUTIONS

Roadblocks and Alternatives, Rigor and Reproducibility, and Future Directions

Potential Roadblocks and Alternatives. Challenges with in-school intervention delivery: It is possible that in some schools or with some teachers, students will not be released from class on schedule to attend intervention sessions. If this occurs, we will build on our 3 years of experience partnering with schools to engage relevant school stakeholders (e.g., administrators, teachers, and staff) to identify acceptable routines and schedules to enable students to participate in the intervention. Loss to follow-up at one-year assessment: Similarly, we will work closely with our school partners to identify improved methods for assessments (e.g., scheduled grade-wide assessments administered by ALLY facilitators). However, if these occur, these roadblocks relate directly to the implementation factors and outcomes under investigation; thus, encountering these problems and exploring their causes (e.g., lack of adoption, low satisfaction, low fidelity) will inform our Aim 3 analyses and conclusions and allow us to identify strategies to improve future implementation of ALLY in a wide range of school settings. Lastly, in the circumstance that our hypothesized effect is not observed in Aim 1, associations of potential mediators with negative affectivity (Aim 2) will still be examined to inform future interventions.



POWER ANALYSIS

Sample size determination and power analysis: We will recruit up to $n=26$ to conservatively account for up to 20% attrition, for a final sample size of $n=20$. We will make every effort to minimize attrition from the study by frequent contacts in person and by phone. This is a feasibility study where most study aims will be evaluated using descriptive statistics. The sample size of 20 will be sufficient to address study feasibility, such as alerting the research team to non-rare adverse events and establishing procedures for recruitment and retention (Aim 1). The sample size will also provide stable estimates of the mean and variability of the proposed intervention outcomes (Aim 3). Formal power analyses were conducted for detecting changes in sleep from pretest to posttest (Aim 2). Assuming two-sided alpha of 0.05, the sample size of $n=20$ will provide 80% power to detect an effect size of Cohen's $d = 0.66$ for change in total sleep time. Although this is a large effect, it is reasonable based on research demonstrating sleep improvements of 71 minutes ($t = 12.52$, $p < .001$) in 18 adolescents following a sleep extension protocol.⁵⁰



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ADVICE FROM COLLEAGUES



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AIMS PAGE: CRITICAL COMPONENT

Spend 80% of time writing the grant on the aims page

Share the aims page with people in and outside the field

Most often this is the only page reviewers (2nd-3rd) will review and your score will be a result of this page only



GENERAL ETIQUETTE AND TIMELINE

Etiquette

- Draft letters of support
 - This will give you an opportunity to document the key items you need from each person
- Email colleagues early and provide due date and draft
 - Give them due date 7-10 business days before your deadline

Takes Time

- Give yourself 4-6 months of dedicated time to process ideas, get feedback, and rewrite
- Writing proposal is not something you do in your “free time”
- Schedule 2-3 hour blocks of time to write – consider your best “creative” time



REVIEWER'S PERSPECTIVE

Reviewers are asked to review many grants, and in a short amount of time

Most reviewers will skim read

- Make points clear and simple
- Use tables and bullets to summarize key elements

Read the reviewer criteria to ensure you are addressing each of the criteria very clearly

- In other words, hand them what they need and don't make them have to work to find it
- Bold and underline this specific language so the reviewers see it immediately

Don't assume

- Reviewers may know nothing about you and your field
- The only information they know is written in your proposal



SUMMARY



BE PATIENT



STAY FOCUSED



COLLABORATE



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HOW TO COMPLETE A FUNDED PROJECT



PROTOCOL &
IRB APPLICATION



DATA
COLLECTION



DATA ENTRY
& CLEANING



ANALYZE &
INTERPRETATION
OF RESULTS



PUBLICATIONS



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PROTOCOL COMPONENTS

Hypothesis and Specific Aims

Background and Significance

Preliminary Studies/Progress Report

Research Methods

- Outcome Measures
- Description of Population to be Enrolled
- Study Design and Research Methods
- Description, Risks, and Justification of Procedures & Data Collection Tools
- Potential Scientific Problems
- Data Analysis Plan
- Summarize Knowledge to be Gained
- References



HYPOTHESIS AND SPECIFIC AIMS

I. Hypotheses and Specific Aims:

The specific aims of this **pilot and feasibility study** are:

1. To examine the feasibility of recruitment and retention of adolescents with overweight/obesity, pre-diabetes, and inadequate sleep into a sleep extension intervention.
2. To assess adherence to and initial pre-post sleep outcomes of a sleep extension intervention to increase total sleep time in adolescents with overweight/obesity, pre-diabetes, and inadequate sleep.
3. To determine estimates of the mean and variability of potential intervention outcomes, including metabolomics, body composition, and substrate oxidation.



BACKGROUND & SIGNIFICANCE

II. Background and Significance:

Obesity affects over one-third of US adolescents and related comorbidities, including type 2 diabetes (T2D), are increasingly prevalent in youth with higher rates of T2D documented in adolescents.^{1,2} Insulin resistance (IR) is a critical contributor to the link between obesity and cardiometabolic diseases, such as T2D and cardiovascular disease (CVD).³ More than half of youth with T2D in the TODAY RCT failed primary metformin and metformin/rosiglitazone therapy by 3-years, a rate that is almost 4 times faster than seen in similar studies of adults.^{4,5} In the RISE study, pancreatic β -cell function continued to decline despite interventions effective at preventing decline in adults. Taken together, emerging data suggests that T2D in youth has a more aggressive phenotype than in adults. Focusing on the pathways underlying the relationships among poor health behaviors, obesity, and IR in adolescents is vital to improve their long-term health.



PRELIMINARY STUDIES / PROGRESS REPORT

III. Preliminary Studies/Progress Report:

Feasibility of recruitment: Recruiting adolescents with inadequate sleep (< 7 hours per night) is feasible, as most adolescents report chronic exposure to short sleep, well below the recommended 8-10 hours per night,^{21,22} consistent with our local data collected on sleep duration by co-Investigators, Drs. Simon, Cree-Green, and Nadeau. According to electronic medical record query performed on 8/14/2018, in the last 12 months, 131 unique patients were seen by lifestyle medicine between the ages of 13-18 years who were obese and had pre-diabetes, thus, providing an ample sample from which to recruit.

Feasibility of delivering a behavioral intervention: Our multidisciplinary team has a strong cumulative background in sleep extension interventions in children and adolescents and conducting behavioral interventions in both adolescent and adult populations with multiple federal funded RCTs. This team has participated in four (2 NIH R01 & 2 ADA/JDRF) RCTs (PI: Catanacci, Nadeau), one NIH K23 sleep extension intervention (PI: Simon), and a NIH U01 multi-center RCT in obese adolescents with prediabetes/T2D (PI: Nadeau).



RESEARCH METHODS

IV. Research Methods

A. Outcome Measure(s):

Primary Outcome Measures: Feasibility of recruitment and retention of adolescents with overweight/obesity, pre-diabetes, and inadequate sleep into a sleep extension intervention. Adherence to and initial pre-post sleep outcomes of a sleep extension intervention to increase total sleep time in adolescents with overweight/obesity, pre-diabetes, and inadequate sleep.

Secondary Outcome Measures: Estimates of the mean and variability of potential intervention outcomes, including metabolomics, body composition, and substrate oxidation.



DESCRIPTION OF POPULATION TO BE ENROLLED

B. Description of Population to be Enrolled:

Participants: This study will allow for data collection on 20 adolescents. Total enrollment will be up to 26 participants to allow for screen failures and dropouts. We will conduct a chart review to determine eligible patients and approach them during their clinic visit. After providing written informed consent, participants will undergo an in-person screening interview to confirm eligibility.

Inclusion Criteria:

- 1) High school students between the age of 13-19 years
- 2) BMI >85th percentile for age and sex
- 3) Prediabetes defined as a HbA1c 5.7-6.4%
- 4) Tanner Stage 4-5 (based on breast development for girls and testicular size for boys)

Exclusion Criteria:

- 1) Any medications that affect insulin resistance or sleep (e.g., metformin, stimulants, atypical antipsychotics, current use of oral steroids)
- 2) Regular use of melatonin or other sleep aids
- 3) A prior diagnosis of a sleep disorder (e.g., insomnia, delayed sleep phase syndrome, obstructive sleep apnea) or abnormal scores on sleep disorders screening measures
- 4) Type 2 diabetes (HbA1c \geq 6.5%)
- 5) IQ<70 or severe mental illness that may impact sleep or ability to consent/assent (e.g., schizophrenia, psychotic episodes), verified through chart review
- 6) Teens not enrolled in a traditional high school academic program (e.g., home school students)
- 7) Schedules that would preclude participants from adhering to the sleep extension protocol (e.g., night shift employment)
- 8) Travel across more than two time zones in the 2 weeks prior to the study



RECRUITMENT AND CONSENT

Recruitment: Adolescents will be recruited from the Children's Hospital Colorado Lifestyle Medicine Clinics.

Informed Consent Plan: Appropriately qualified and informed personnel who have completed the COMIRB and HIPAA course requirements will fully explain the study protocol and consent form to the subject and guardian verbally in the language they understand. The explanation will be conducted in a quiet environment with adequate time given for the participant and guardian to review the study procedure before the commencement of the study. Asking the participant to explain the study in their own words will assess the participants' understanding. If non-English speaking participants are enrolled in the study, the investigators will adhere to Section 10C of the COMIRB Instructions for Clinical Investigators regarding the consent of these subjects. The qualified personnel mentioned above will then obtain written consent from the guardian and assent from the participant, co-signed on the consent form, or in participants who are 18 years or older, direct consent. The PI will make a good faith effort to obtain both parent signatures. The subject and guardian will be provided a copy of the consent form for better understanding and record purposes.

Consent/Assent Plan: Consent will be obtained from all participants in the study. Following explanation, all participants below 18 years old will co-sign the consent form in addition to the parents signing the consent form. All participants age 18 or older will sign the standard consent form.

Compensation, Incentives & Rewards: Participants will be compensated with Greenphire debit card payments at study visits. Participants will be compensated for each completed visit; maximum of \$150 for study participation.



STUDY DESIGN AND RESEARCH METHODS

C. Study Design and Research Methods

We propose a 4-week sleep extension intervention to evaluate feasibility of the protocol and obtain preliminary data on intra-individual changes in metabolic parameters induced by sleep extension for the design of future longer studies. See **Table 1** for a summary of the measurements and research visits.

Study Procedures. Participants will receive a Standard Care Diet and Physical Activity Education Intervention (SC) and an Extended Sleep Intervention (ES). For the SC, participants will have their diet, physical activity, and screen time assessed by study interventionist. Prescribed goals will be determined collaboratively through discussion with

Table 1. Summary of Measurements at Clinical (CV) & Research Visits (RV)

	CV Pre-RCT	RV 1 Baseline	Phone Week 1	RV 2 Week 2	Phone Week 3	RV 3 Post-RCT	CV Week 12
Recruitment							
Screening	X						
Consent	X						
Intervention							
Intervention Delivery		X	X	X	X		
Education/Goal Setting		X	X	X	X		
Free-Living Measurements							
Sleep (actigraphy)	X	X	X	X	X		X
Physical Activity (actigraphy)		X	X	X	X		
Diet Assessment (FFQ)		X				X	
Clinical Visit Measurements							
Body Composition (BMI, WC)		X				X	X
Clinical Markers of CVD Risk		X				X	X
Indirect Calorimetry		X				X	
Fasting Labs & Metabolomics		X				X	
Insulin Resistance (OGTT)		X				X	



ASSESSMENTS

Assessments.

Sleep Disorders Screening: The Adolescent Sleep Wake Scale (ASWS)²³ & Sleep Disorders Inventory for Students-Adolescent (SDIS-A)²⁴ will be completed at the first clinic visit to evaluate sleep disorders.

Sleep duration & timing: An actigraphy watch (AW Spectrum Plus, Phillips Respironics, Bend, OR) will be worn on the non-dominant wrist to monitor sleep patterns continuously throughout study. Average sleep start and end time, duration, mid-sleep time, and efficiency will be calculated with Actiware Sleep v6 software.²⁵ The actigraphy devices are well-tolerated by adolescents with good adherence in our previous studies.²⁶

Physical Activity (PA): A triaxial thigh-worn ActivPal (PAL Technologies, UK) will be used to measure sedentary, upright, and ambulatory activities.²⁷ The data will be downloaded and the device recharged at the second research visit after 2 weeks of continuous wear and then replaced for the last two weeks of the study.

Energy and Macronutrient Intake: The SEARCH Food Frequency Questionnaire will be used to assess energy intake (EI) and compare intra-individual changes in EI.²⁸ We recognize the limitations of self-reported measures of EI.²⁹

Feasibility & Acceptability: Participants will complete a modified Feasibility Acceptability Questionnaire (FAQ³⁰) following the intervention. Information will be used to further develop the intervention for testing our pilot study.



RISKS OF PROCEDURES

D. Description, Risks and Justification of Procedures and Data Collection Tools:

Participants will be encouraged to report any discomforts during testing and any illness or change in wellbeing immediately to the PI or study coordinator at any time during the study. This is a healthy participant population; therefore, no adverse events are expected. Any serious and unexpected adverse events will be reported to the IRB immediately. Total time to complete study measures (research visit 1 and 3) will be approximately 5-6 hours.

Blood Sampling (including metabolomics)

Description: Blood will be drawn prior to the start of the OGTT and include glucose, insulin, c-peptide, free-fatty acids, and triglycerides.

Risk: Minimal. Risk of pain, bruising at site of blood draw, excessive amount of blood.

Justification/Minimization: The routine guidelines in our Pediatric CTSC are 2.5ml/kg for a single draw and no more than 5 ml/kg over a 4-week period. Our baseline OGTT visit includes up to 15 ml of blood and our Post-RCT OGTT, which will occur 4 weeks after the intervention, also includes up to 15ml of blood. Thus, our OGTT visits are within Children's Hospital Colorado's institutional guidelines of 5 ml/kg. In addition, our CTSC has a system to track other studies subjects might enroll in, and we ask during our consent process if the subject has been involved in any other studies in the past 6 weeks to avoid excessive blood drawing.

Questionnaires

Description: Participants will complete questionnaires regarding their sleep and feasibility & acceptability of the intervention.

Risk: There is a small possibility that participants will be uncomfortable answering a particular question.

Justification/Minimization: The questionnaires used in the study are widely used in both research and clinical practice and are not of a particularly sensitive nature. Participants will be able to skip any items that they find uncomfortable. None of the items assess for suicidality.

Violation of Privacy and Loss of Confidentiality

Description: These are both risks to which research participants are exposed. The possibility of these risks increases when protected health information is collected. Every effort will be made to decrease this risk by limiting access to protected health information, storing this information in a password protected database, and identifying subjects only by a unique identifier that is kept in a separate location in a locked container, traceable only by study personnel. All of the tests involve the risk of identifying asymptomatic abnormalities. The study may include risks that are unknown at this time.

Justification/Minimization: Every effort will be made to decrease the risk of loss of confidentiality by limiting access to protected health information, storing this information in a password protected database, and de-identifying study specimens.



POTENTIAL SCIENTIFIC PROBLEMS

D. Potential Scientific Problems:

Plans for Optimal Recruitment

Investigative team have previously been successful at recruiting/retaining adolescents for similarly demanding protocols, including overnight admissions, and have established relationships with local pediatric practices for successful participant recruitment. Additionally, the investigative team has successfully extended sleep in adolescents in previous protocols.

Plans for Robust and Unbiased Results

Gold-standard techniques (objective sleep, physical activity, and metabolomic measurement) are proposed over surrogate or self-report. Measurements are performed in the AM fasting, in the early follicular phase where possible for menstruating females, preceded by 3 days of no strenuous physical activity and standardized weight-maintenance meals (breakfast, lunch, dinner, and snack) the day before the OGTT (as in Dr. Nadeau and Cree-Green's previous studies) as variations in diet, activity, and menstrual cycle affect insulin resistance.^{50,51} Season, school attendance, and time-zone affect sleep timing and circadian rhythm and thus will be documented.



DATA ANALYSIS PLAN

F. Data Analysis Plan:

Power analyses were conducted for detecting changes in sleep from pre- to posttest (Aim 2). Assuming two-sided α of 0.05, $n=20$ will provide 80% power to detect an effect size of Cohen's $d=0.66$ for change in total sleep time. This effect is reasonable based on research demonstrating sleep improvements of 71 minutes ($t=12.52$, $p<0.001$) in 18 adolescents following a sleep extension protocol.³⁵ Conservatively estimating 20% attrition, we will recruit 26 adolescents. The sample size of 20 will be sufficient to address study feasibility, such as alerting the research team to non-rare adverse events and establishing procedures for recruitment and retention (Aim 1). The sample size will also provide stable estimates of the mean and variability of the proposed intervention outcomes (Aim 3).

Statistical analysis will be performed using SAS v9.3. All data will be entered and managed using REDCap. Descriptive statistics will be presented using means and standard deviations for continuous variables and frequencies for categorical variables. Independent t-test and Cochran Mantel-Haenzel tests will be used to assess differences in continuous and categorical variables, respectively. Measures include (see Table 2 for further details):

Aim 1: Recruitment (rate of recruitment and proportion of consented participants with insufficient sleep measured by actigraphy) and retention (attrition, missing data, completed in-person versus phone call visits).

Criteria for feasibility: We anticipate that we will be able to recruit 5 participants per month and that 80% of these will be deemed eligible based on objectively measured insufficient sleep. We anticipate a 20% attrition rate; hence will recruit 26 participants in order to obtain complete data on 20 individuals.



SUMMARIZE KNOWLEDGE TO BE GAINED

G. Summarize Knowledge to be Gained:

In this pilot and feasibility study we expect to establish a recruitment and retention protocol that can be used in a larger proposal (Aim 1). In Aim 2, we expect to increase total sleep time using our sleep extension protocol. Finally, the data collected in Aim 3 will assist us in better understanding and quantifying the mean and variability of potential intervention outcomes we propose to use in a larger proposal. Examining changes in metabolomics, insulin resistance, substrate oxidation, etc in a sample of adolescents with insufficient and sufficient sleep has not been documented to date; hence, this proposed pilot data will be the first to document such clinically relevant markers. Together these results will be prepared and presented at relevant national conferences and submitted to peer review journals for wider dissemination.



HOW TO COMPLETE A FUNDED PROJECT



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DATA ENTRY
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DATA COLLECTION



Log In



Only IRB-approved protocol data should be stored in REDCap, unless you have received prior approval for an exception. Contact redcap@ucdenver.edu if you have any questions.

For information on obtaining a UCD REDCap account, policies and procedures, and to watch our tutorial videos, please visit [our REDCap Info Site](#).

Please log in with your user name and password. If you are having trouble logging in, please contact [REDCap Admin](#).

Username:

Password:

Log In

[Forgot your password?](#)



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BUILDING A DATA DICTIONARY

Variable / Field Name	Form Name	Field Type	Field Label	Choices, Calculations, OR Slider Labels
study_id	demographic	text	Study ID	
dob	demographic	Y-M-D	Date of birth	
Sex	demographic	Checkbox	Sex	Female, 1 Male, 0
race	demographic	checkbox	Race	1, Caucasian 2, African American 3, Asian 4, Pacific Islander 5, American Indian or Alaska Native 6, Other 7, Not Reported
ethnicity	demographic	checkbox	Ethnicity	0 Non-Hispanic 1 Hispanic
age_dx	pmh	Text	Age at diagnosis	number verification
date_dx	pmh	Y-M-D	Date of diagnosis	
height_dx	pmh	text	Height at diagnosis	number verification
weight_dx	pmh	text	Weight at diagnosis	number verification
bmi_dx	pmh	calc	BMI at diagnosis	$[\text{weight_dx}] * 10000 / ([\text{height_dx}] * [\text{height_dx}])$
bcell_lineage	pmh	checkbox	B-Cell Lineage	1, Yes 0, No
tcell_lineage	pmh	checkbox	T-Cell Lineage	1, Yes 0, No
wbc_dx	pmh	Text	WBC at diagnosis	1, <50 x 10 ⁹ /L 2, >=50 x 10 ⁹ /L
cns_status	pmh	Text	CNS status	1, CNS-1 2, CNS-2 3, CNS-3 0, Traumatic lumbar puncture w/blast cells
treatment_type	pmh	checkbox	Type of treatment	1, Chemotherapy 2, Bone Marrow Transplant
date_1st_treat	pmh	Y-M-D	Date of 1st treatment	
age_1st_treat	pmh	calc	Age at 1st treatment	$\text{datediff}([\text{dob}][\text{date_1st_treat}])^y$

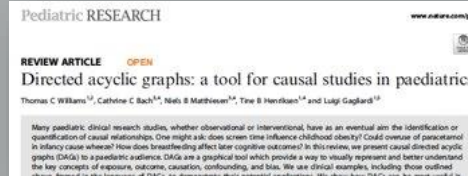
pid	dob	sex	race	ethnicity	income	w1bedtime	w2bedtime	w3bedtime	d1bedtime	d2bedtime	d3bedtime
1401	3/24/15	1	2	2	3	20:32	22:24	20:30	20:53	21:51	21:13

Female	[0, Male 1, Female]	
Hispanic	[0, Non-Hispanic 1, Hispanic]	
LowIncome	[0, No 1, LowIncome]	
T2D	[0, No 1, T2D]	



BIostatistician

- Everyone needs one
- Involve them early
- Meet with them regularly
- Learn their language



Toward a Better Understanding of the Influences on Physical Activity
The Role of Determinants, Correlates, Causal Variables, Mediators, Moderators, and Confounders

Adrian E. Bauman, PhD, James F. Sallis, PhD, David A. Hovell, PhD, Neville Owen, PhD

Biostatistics: A Review
Tony Gerlach, Pharm.D, BCPS

USMLE Epidemiology and Biostatistics

Meta-Analysis: pools data from several studies (greater power), limited by quality/bias of individual studies
Clinical Trial: compares two groups in which one variable is manipulated and its effects measured
Cohort (relative risk): compares group with risk factor to a group without - asks "what will happen"
Case Control (odds ratio): compares group with disease to group without disease - asks "what happened"
Issues with confounding and inability to prove causation
Case Series: good for rare diseases, describe clinical presentation of certain disease
Cross-Sectional: data from a group to assess disease prevalence at a particular point in time - asks "what is going on now?"

Sensitivity (rule out - screening): proportion of people with disease who test positive: $TP / (TP + FN) = 1 \cdot FN$. If 100%, then all negative tests are TN.
Specificity (rule in - confirmatory): proportion of people without disease who test negative: $TN / (TN + FP) = 1 \cdot FP$. If 100%, then all positive tests are TP.

Population: entire collection of objects or individuals about which information is desired
 → easier to take a sample
 • Sample: part of the population that is selected for analysis
 • Wards out bias
 • Limited sample size that might not be representative of population
 • Simple Random Sampling: Every possible sample of a certain size has the same chance of being selected

Observational Study: there can always be lurking variables affecting results
 • Is a strong positive association between shoe size and intelligence for boys?
 • "Should never show causation"

Experimental Study: lurking variables can be controlled, can give good evidence for causation

Descriptive Statistics Part I
 → Summary Measures

Mean: arithmetic average of data values
 • "Highly susceptible to extreme values (outliers). Goes towards extreme values"
 • Mean could never be larger or smaller than maximum value but could be for the minimum value

Median: in an ordered array, the median is the middle number
 • "Not affected by extreme values"

Quartiles: split the ranked data into 4 equal groups
 • Use and Whisker Plot

Standard Deviation: shows variation about the mean
 $s = \sqrt{\frac{\sum(x_i - \bar{x})^2}{n-1}}$
 • Highly affected by outliers
 • Use same units as original data
 • Inverse = terrible measure of risk (stomach example)

Descriptive Statistics Part II
 Linear Transformations

The Statistics Tutor's Quick Guide to Commonly Used Statistical Tests

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DATA ANALYSIS AND INTERPRETATIONS



List the main findings



Plan how to best communicate the findings



Create a plan to disseminate the results



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PUBLICATION STRATEGY



SUBMIT ABSTRACT



DRAFT MANUSCRIPT



CLOSER TO CONFERENCE
DATE – SUBMIT MANUSCRIPT



LIST POTENTIAL JOURNALS



<http://jane.biosemantics.org/>

5

Journal Metrics

3.739 2018 Impact Factor	9th of 123 Rank in Thomson ISIs Pediatrics category	2.9 Weeks to First Decision
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THANK YOU!

Questions?



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