This document is provided as a sample application. Some pages and text have been redacted.

PI: **Allen, Alicia M**	Title: Hormonal Response to Infant Caregiving: A Novel Strategy to Break the Opioid Relapse Cycle during the Postpartum Period	
Received: 08/22/2019	Opportunity: RFA-RM-19-006 Clinical Trial:Optional	Council: 05/2020
Competition ID: FORMS-E	FOA Title: NIH Directors New Innovator Award Program (DP2 Clinical Trial Optional)	
1DP2HD105541-01	Dual: OD,RM,DA	Accession Number: 4340471
IPF: 490201	Organization: UNIVERSITY OF ARIZONA	
Former Number: 1DP2OD028874-01	Department: Family and Community Medicine	
IRG/SRG: ZRG1 MOSS-R (70)R	AIDS: N	Expedited: N
Subtotal Direct Costs (excludes consortium F&A) Year 1: [redacted]	Animals: N Humans: Y Clinical Trial: N Current HS Code: 30 HESC: N	New Investigator: Y Early Stage Investigator: Y
Senior/Key Personnel:	*Organization:*	*Role Category:*
Alicia Allen Ph.D	University of Arizona	PD/PI

APPLICATION FOR FEDERAL ASSISTANCE
SF 424 (R&R)

3. DATE RECEIVED BY STATE	State Application Identifier

1. TYPE OF SUBMISSION*

○ Pre-application ● Application ○ Changed/Corrected Application

4.a. Federal Identifier

b. Agency Routing Number
1 BSS; 3 CTR

2. DATE SUBMITTED | **Application Identifier**

c. Previous Grants.gov Tracking Number

5. APPLICANT INFORMATION **Organizational DUNS*:**

Legal Name*: Arizona Board of Regents, University of Arizona
Department: [redacted]
Division: [redacted]
Street1*: [redacted]
Street2: [redacted]
City*: [redacted]
County: [redacted]
State*: [redacted]
Province:
Country*: [redacted]
ZIP / Postal Code*: [redacted]

Person to be contacted on matters involving this application
Prefix: First Name*: [redacted] Middle Name: Last Name*: [redacted] Suffix:
Position/Title: Director, Post Award Services
Street1*: [redacted]
Street2:
City*: [redacted]
County: [redacted]
State*: [redacted]
Province:
Country*: [redacted]
ZIP / Postal Code*: [redacted]
Phone Number*: [redacted] Fax Number: Email: [redacted]

6. EMPLOYER IDENTIFICATION NUMBER *(EIN) or (TIN)** [redacted]

7. TYPE OF APPLICANT* H: Public/State Controlled Institution of Higher Education

Other (Specify):
Small Business Organization Type ○ Women Owned ○ Socially and Economically Disadvantaged

8. TYPE OF APPLICATION*

● New ○ Resubmission
○ Renewal ○ Continuation ○ Revision

If Revision, mark appropriate box(es).
○ A. Increase Award ○ B. Decrease Award ○ C. Increase Duration
○ D. Decrease Duration ○ E. Other *(specify)* :

Is this application being submitted to other agencies?* ○Yes ●No What other Agencies?

9. NAME OF FEDERAL AGENCY*
National Institutes of Health

10. CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER
TITLE:

11. DESCRIPTIVE TITLE OF APPLICANT'S PROJECT*
Hormonal Response to Infant Caregiving: A Novel Strategy to Break the Opioid Relapse Cycle during the Postpartum Period

12. PROPOSED PROJECT
Start Date* Ending Date*
08/15/2020 06/30/2025

13. CONGRESSIONAL DISTRICTS OF APPLICANT
[redacted]

[redacted]

SF 424 (R&R) APPLICATION FOR FEDERAL ASSISTANCE

14. PROJECT DIRECTOR/PRINCIPAL INVESTIGATOR CONTACT INFORMATION

Prefix: First Name*: Alicia Middle Name: Last Name*: Allen Suffix: Ph.D

Position/Title: Assistant Professor

Organization Name*: University of Arizona

Department: [redacted]

Division: [redacted]

Street1*: [redacted]

Street2:

City*: [redacted]

County: [redacted]

State*: [redacted]

Province:

Country*: [redacted]

ZIP / Postal Code*: [redacted]

Phone Number*: [redacted] Fax Number: Email*: [redacted]

15. ESTIMATED PROJECT FUNDING

a. Total Federal Funds Requested*	[redacted]
b. Total Non-Federal Funds*	$0.00
c. Total Federal & Non-Federal Funds*	[redacted]
d. Estimated Program Income*	$0.00

16.IS APPLICATION SUBJECT TO REVIEW BY STATE EXECUTIVE ORDER 12372 PROCESS?*

a. YES ○ THIS PREAPPLICATION/APPLICATION WAS MADE AVAILABLE TO THE STATE EXECUTIVE ORDER 12372 PROCESS FOR REVIEW ON:

DATE:

b. NO ● PROGRAM IS NOT COVERED BY E.O. 12372; OR

○ PROGRAM HAS NOT BEEN SELECTED BY STATE FOR REVIEW

17. By signing this application, I certify (1) to the statements contained in the list of certifications* and (2) that the statements herein are true, complete and accurate to the best of my knowledge. I also provide the required assurances * and agree to comply with any resulting terms if I accept an award. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. (U.S. Code, Title 18, Section 1001)

● I agree*

** The list of certifications and assurances, or an Internet site where you may obtain this list, is contained in the announcement or agency specific instructions.*

18. SFLLL or OTHER EXPLANATORY DOCUMENTATION File Name:

19. AUTHORIZED REPRESENTATIVE

Prefix: First Name*: [redacted] Middle Name: L. Last Name*: [redacted] Suffix: Ph.D

Position/Title*: [redacted]

Organization Name*: [redacted]

Department:

Division: [redacted]

Street1*: [redacted]

Street2:

City*: [redacted]

County: [redacted]

State*: [redacted]

Province:

Country*: [redacted]

ZIP / Postal Code*: [redacted]

Phone Number*: [redacted] Fax Number: Email*: [redacted]

Signature of Authorized Representative*

[redacted]

Date Signed*

08/22/2019

20. PRE-APPLICATION File Name:

21. COVER LETTER ATTACHMENT File Name:

OMB Number: 4040-0001
Expiration Date: 10/31/2019

RESEARCH & RELATED Other Project Information

1. Are Human Subjects Involved?* ● **Yes** ○ **No**

1.a. If YES to Human Subjects

Is the Project Exempt from Federal regulations? ○ Yes ● No

If YES, check appropriate exemption number: _ 1 _ 2 _ 3 _ 4 _ 5 _ 6 _ 7 _ 8

If NO, is the IRB review Pending? ● **Yes** ○ **No**

IRB Approval Date:

Human Subject Assurance Number 00004218

2. Are Vertebrate Animals Used?* ○ **Yes** ● **No**

2.a. If YES to Vertebrate Animals

Is the IACUC review Pending? ○ Yes ○ No

IACUC Approval Date:

Animal Welfare Assurance Number

3. Is proprietary/privileged information included in the application?* ○ **Yes** ● **No**

4.a. Does this project have an actual or potential impact - positive or negative - on the environment?* ○ **Yes** ● **No**

4.b. If yes, please explain:

4.c. If this project has an actual or potential impact on the environment, has an exemption been authorized or an environmental assessment (EA) or environmental impact statement (EIS) been performed? ○ Yes ○ No

4.d. If yes, please explain:

5. Is the research performance site designated, or eligible to be designated, as a historic place?* ○ **Yes** ● **No**

5.a. If yes, please explain:

6. Does this project involve activities outside the United States or partnership with international collaborators?* ○ **Yes** ● **No**

6.a. If yes, identify countries:

6.b. Optional Explanation:

	Filename
7. Project Summary/Abstract*	Allen_NIH-DP2_ProjectSummary.pdf
8. Project Narrative*	Allen_NIH-DP2_ProjectNarrative.pdf
9. Bibliography & References Cited	
10.Facilities & Other Resources	Allen_NIH-DP2_Facilities.pdf
11.Equipment	

Funding Opportunity Number: RFA-RM-19-006. Received Date: 2019-08-22T15:21:46.000-04:00

PROJECT SUMMARY/ABSTRACT

The prevalence of opioid use disorder (OUD) during pregnancy has increased by nearly 500% over the past 15 years. While pregnancy presents a strong motivation for seeking and complying with OUD treatment, the postpartum period is associated with a high risk for relapse. Indeed, up to 80% of women with OUD relapse to illicit opioid use within six months of delivery. Relapse leads to a wide range of negative health and social outcomes for both the infant, mother, and entire family, such as physical (e.g., fatal and non-fatal overdose, increased risk of substance use disorders in children), emotional (e.g., anxiety, depression), and social (e.g., foster care placement, poor academic achievement) consequences. Unfortunately, little research is available on how to prevent postpartum opioid relapse. A wide-range of hormones (e.g., cortisol, progesterone, oxytocin) have been linked to substance use disorders and infant caregiving activities. While hormones have the potential to significantly reduce the risk for postpartum relapse, methodological limitations (e.g., single hormone assessment, limited time assessment), content limitations (e.g., opioid use, polysubstance use), and a lack of dissemination of knowledge across disciplines are all limiting this use of this potentially highly impactful approach. Therefore, my overall goal is to use new technologies and methodologies to directly address the current limitations and enhance the cross-discipline dissemination of knowledge to utilize hormonal level(s)/pattern(s) to protect against opioid relapse during the high-risk postpartum period. To achieve this goal, this New Innovator Award will address four objectives: (1) measure hormones, infant caregiving activities, relapse risk factors, and OUD-related outcomes during the postpartum period using a prospective cohort study design, (2) identify hormonal level(s)/pattern(s) that are predictive of postpartum opioid use via with data-driven predictive analytics, (3) examine methods to elicit/identify targeted hormone level(s)/pattern(s) using specific infant caregiving activities, exogenous hormone delivery, and/or continuous/frequent hormone monitoring, and (4) preliminarily assess the link between the identified hormonal level(s)/pattern(s) and OUD-related outcomes. Upon completion of this high-risk/high-reward project, I will either (a) be able to rule out a hormonally-based intervention as an element of a comprehensive behavioral-psycho-social approach to prevent postpartum opioid relapse, *or* (b) have strong preliminary evidence for the use of hormone level(s)/pattern(s) to prevent postpartum opioid relapse. Further, this work will be ripe for expansion to other substances of abuse (e.g., cannabis), as well as application to other postpartum health issues (e.g., depression, anxiety).

PROJECT NARRATIVE

Among women who had been compliant with OUD treatment during pregnancy, up to 80% relapse to illicit opioid use within six months of childbirth. This project will examine how the hormonal response to infant caregiving influences postpartum opioid relapse and whether these hormones could be modulated as a preventative strategy.

FACILITIES AND OTHER RESOURCES

Overall Environment

The University of Arizona (UA), founded in 1885, is the leading public research university in the American Southwest. A land-grant, state university governed by the Arizona Board of Regents, the UA produces more than $687 million in research activity annually, ranking in the top 25 public universities.

The University of Arizona Health Sciences (UAHS) is part of the UA, comprising the Colleges of Medicine, Nursing, Pharmacy and Public Health, and 11 other specialty centers. UAHS has eleven major buildings and three Banner Health-UA affiliated hospitals (Banner-University Medical Center, Banner-University Medical Center South, and Banner Children's at the Diamond Children's Medical Center) on a 48-acre site situated in the northeast quadrant of the UA campus. In FY2017, UAHS research expenditures totaled $193 million (including clinical trials, research and training grants). Of these expenditures, NIH funding totaled $88.1 million.

College of Medicine (COM) is part of UAHS with campuses in Tucson and Phoenix. It is the only MD degree-granting college in the state, dedicated to its mission of continually improving health care through education, research, and clinical care. In FY2017, the COM received more than $86 million in research awards.

Department of Family & Community Medicine (DFCM), housed within the COM, is one of the top-ranking family medicine programs in the country, known for outstanding pre-doctoral and post-doctoral education, groundbreaking research, and innovative community outreach programs designed to improve the health of individuals, families and communities. The faculty is comprised of 53 core members that include leaders in the areas of substance use, mobile technologies, serious mental illness, community participatory research, and work with underserved and minority populations. In FY2018, DFCM grants and contracts totaled $5.2 million.

Research Space and Resources (UA)

The Collaboratory features over 12,000 square feet of contiguous space in the Herbert K. Abrams Public Health Center. This 4-story building includes 189,000 square feet of space and a Family Medicine Clinic and a Women-Infants-Children (WIC) Clinic located on the entry floor. The location of the Collaboratory puts clinicians and scientists together (and in close proximity to the Banner-University hospital – South) fostering collaborative research and enhanced educational opportunities. This space will be used for ongoing data collection efforts by Dr. Allen and her staff.

REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture and storage for research studies, providing an intuitive interface for validated data entry; audit trails for tracking data manipulation and export procedures; automated export procedures for seamless data downloads to common statistical packages; and procedures for importing data from external sources. The UA is an institutional REDCap member with a Bioinformatics Manager in the CaTS Research Center who is responsible for development and maintenance. This application will be used to collect and manage data.

Laboratory for the Evolutionary Endocrinology of Primates (LEEP) is housed in the UA School of Anthropology. Facilities include two vented fume hoods, cold storage (two -20ºC, one -80ºC, one +8ºC), two centrifuges, Biotek spectrophotometer, multi-mode microplate reader, and plate washer, a balance, an incubator, Barnstead water system, pH meter, water bath, nitrogen evaporation bath, centrifugal concentrator (speedvac), lyophilizer, two manifolds for conducting solid phase extraction, and a manifold for column chromatography. LEEP provides sufficient (modular) bench space for training, storage space for samples, and temperature monitors on the refrigerator and freezers. This space will be used to analyze biological samples for hormones under the direction of LEEP's director, [redacted].

Model-Based Design Laboratory (MBDL) occupies approximately 1,000 square feet of space in the UA Electrical & Computer Engineering building. It includes seven desktop PCs, two MacPro quad-core computers, two laser printers (one black and white, one color), a 42" presentation monitor with conference table and chairs, and electronic test and development equipment. The lab accommodates individual work areas for ten students. For parallel processing, MBDL offers a small private cluster of 6 servers connected by gigabit networking. This space will be used to conduct the predictive analytics under the direction of [redacted].

Institutional Commitment to the Early-Stage Investigators

As an early-stage investigator, Dr. Allen qualifies for substantial internal support, such as programs/training (e.g., "New Faculty Mentoring Program"), intellectual/collaborative resources (e.g., access to key collaborators/information on wearable technology via BIO5 Institute), and funding assistance (e.g., "New Faculty Seed Grants" and assistance with proposal development via Research Discovery and Innovation's development services).

OMB Number: 4040-0001
Expiration Date: 10/31/2019

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Project Director/Principal Investigator

Prefix: First Name*: Alicia Middle Name Last Name*: Allen Suffix: Ph.D

Position/Title*: Assistant Professor
Organization Name*: University of Arizona
Department: [redacted]
Division: [redacted]
Street1*: [redacted]
Street2:
City*: [redacted]
County:
State*: [redacted]
Province:
Country*: [redacted]
Zip / Postal Code*: [redacted]

Phone Number*: [redacted] Fax Number:

E-Mail*: [redacted]

Credential, e.g., agency login: [redacted]

Project Role*: PD/PI Other Project Role Category:

Degree Type: PhD Degree Year: 2012

Attach Biographical Sketch*: File Name: Allen_NIH-DP2_Biosketch.pdf

Attach Current & Pending Support: File Name: Allen_NIH-DP2_OtherSupport.pdf

Tracking Number: GRANT12923549 Funding Opportunity Number: RFA-RM-19-006 . Received Date: 2019-08-22T15:21:46.000-04:00

OMB No. 0925-0001 and 0925-0002 (Rev. 09/17 Approved Through 03/31/2020)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contr butors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Allen, Alicia

eRA COMMONS USER NAME (credential, e.g., agency login): [redacted]

POSITION TITLE: Assistant Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Minnesota, Minneapolis, MN	B.S.	08/2003	Health & Wellness
University of Minnesota, Minneapolis, MN	M.P.H.	05/2006	Community Health Education
Associations of Schools of Public Health, Atlanta, GA	Fellow	09/2007	Centers for Disease Control & Prevention Prenatal Smoking Fellow
University of Minnesota, Minneapolis, MN	Certificate	05/2009	Addiction Studies
University of Minnesota, Minneapolis, MN	Ph.D.	11/2012	Social & Behavioral Epidemiology
University of Minnesota, Minneapolis, MN	NIH Training Grant	11/2016	Building Interdisciplinary Research Careers in Women's Health (BIRCWH) K12 Training Program

A. Personal Statement

While growing up in rural Minnesota, I witnessed the vicious cycle of addiction first-hand within my family and circle of friends. These observations lead me to pursue my long-term research program goals to design, develop, and disseminate effective interventions to prevent and/or treat substance use disorder specifically designed to the unique needs of women. Thus, the goal of the proposed project – to harness the effect of hormonal response to infant caregiving to reduce postpartum opioid relapse – aligns strongly with my long-term interests. In addition to being eligible for the New Innovator Award as an early-stage investigator, I also embody many of the qualities the New Innovator Award values. First, my training as a behavioral epidemiologist provides me with the ability to be adaptable as this line of research develops. It is highly possible that our observations may lead us down an unexpected path. Should that occur, the rigor and reproducibility of the subsequent examination will not be compromised as my expertise is in methodology rather than a specific scientific area. Second, I have a history of making bold and creative choices, including changing the direction of research projects when necessary. My K12 training serves as an example. Initially, I sought to examine the link between allopregnanolone and stress-response within a lab-based setting. Our preliminary observations were not promising. So, I changed directions to a focus on hormonal contraceptives. My decision to do this was three-fold. (1) The potential for major impact: based on previous studies over the years, I had excluded nearly half of all interested women due hormonal contraceptive use. Clearly these women also needed assistance with tobacco cessation, (2) The potential to advance science: the literature was extremely sparse on the link between hormonal contraceptives and smoking, despite substantial research on hormonal contraceptives and risk factors for smoking/relapse (e.g., negative mood, weight gain), signaling a major gap that needed to be addressed, and (3) The potential for ease of dissemination: I recognized that use of hormonal contraceptives was something that any healthcare provider could easily assess and apply to their recommendations for smoking cessation pharmacotherapies. Indeed, this shift in focus proved sound as since that time (five years ago), I have received three additional grants and have had five peer-reviewed papers published, including one that was selected as for the Editor's Choice Award at a top journal. Currently, I have an additional three manuscripts in progress. Next, I have a proven history of successfully implementing projects and disseminating the results. I have received internal funding (e.g., Academic Health Center Seed Grant), external funding by local non-profits (e.g., ClearWay Minnesota) and

national non-profits (e.g. American Cancer Society), and federal awards (e.g., R21 via NIDA). I currently have nearly 40 peer-reviewed publications (29 as first author) and have made over 80 presentations at international, national, regional, and local conferences. Finally, I have a lengthy and highly productive history of collaborating with a wide range of experts. In this case, I have strong community ties with healthcare and other services providers (e.g., substance use treatment) for the population at risk. As a result of these values and skills, I am confident that this high risk project has a strong potential to be of high impact by breaking the addiction-relapse and generational cycle of opioid use disorder in women during the postpartum period.

Related Publications

1. **Allen AM**, Prince CB, Dietz PM. Postpartum depressive symptoms and smoking relapse. Am J Prev Med. 2009 Jan;36(1):9-12. PubMed PMID: 19095161
2. **Allen AM**, Tosun N, Carlson S, Allen SS. Postpartum Changes in Mood and Smoking-Related Symptomatology: An Ecological Momentary Assessment Investigation. Nicotine Tob Res. In Press. PMCID: PMC5934674
3. Allen SS, **Allen AM**, Lunos S, Tosun N. Progesterone and Postpartum Smoking Relapse: A Pilot Double-Blind Placebo-Controlled Randomized Trial. Nicotine Tob Res. 2016 Nov;18(11):2145-2153. PMCID: PMC5055745
4. **Allen AM**, Jung AM, Lemieux AM, Alexander AC, Allen SS, Ward KD, al'Absi M. Stressful life events are associated with perinatal cigarette smoking. 2019. Preventive Medicine; 118: 264-271. PMID: 20468790

B. Positions and Honors

Positions and Employment

2002 - 2006 Clinical Research Study Coordinator, University of Minnesota, Minneapolis, MN
2007 - 2013 Clinical Research Project Manager, University of Minnesota, Minneapolis, MN
2012 - 2014 Adjunct Faculty, University of Saint Thomas, Saint Paul, MN
2013 - 2016 Assistant Professor, Department of Family Medicine and Community Health, University of Minnesota, Minneapolis, MN
2016 - Tenure-Track Assistant Professor, Department of Family & Community Medicine (Primary) and Epidemiology and Biostatistics (Joint), University of Arizona, Tucson, AZ

Other Experience and Professional Memberships

2004 - Member, Society for Research on Nicotine and Tobacco
2013 - Associate Member, College of Problems on Drug Dependence
2016 - Affiliate Member, Cancer Prevention and Control Program, University of Arizona Cancer Center
2017 - 2019 Editorial Fellow, Journal of Addiction Medicine
2017 - Member, American Academy of Pediatrics, Tobacco Consortium
2018 - Associate Editor, Nicotine and Tobacco Research
2018- Clinical Research Committee, College of Problems on Drug Dependence
2018 - Clinical Director, Society for Research on Nicotine and Tobacco University (SRNT-U)
2019- Steering Committee Member, Women in Academic Medicine
2019- Member, Substance Exposed Newborns, Arizona State Task Force
2019- Steering Committee Member, Polysubstance Abuse in Pregnancy and Newborns, Southern Arizona Task Force

Honors

2005 J.B. Hawley Award, School of Public Health, University of Minnesota
2005 Women & Gender Junior Investigator Award, College of Problems on Drug Dependence, National Institute of Drug Abuse
2007 Oral Abstract Award – Second Place, Maternal and Child Health Epidemiology Annual Conference, Centers for Disease Control and Prevention
2009 American Psychological Association Travel Award, National Institute of Drug Abuse and National Institute of Alcohol Abuse & Alcoholism
2009 Women and Sex/Gender Junior Investigator Award, College of Problems on Drug Dependence, National Institute of Drug Abuse
2011 J.B. Hawley Award, School of Public Health, University of Minnesota
2012 Dean's PhD Scholar Award, School of Public Health, University of Minnesota
2012 Best Abstract Award, 9th Annual Women's Health Research Conference

2012 J.B. Hawley Award, School of Public Health, University of Minnesota
2014 Outstanding Junior Mentor Award, Clinical and Translational Science Institute, University of Minnesota
2019 Editor's Choice Award, Nicotine and Tobacco Research, "Oral Contraceptives and Cigarette Smoking: A Review of the Literature and Future Directions"

C. Contributions to Science

1. Endogenous Sex Hormones and Smoking Behavior: A large portion of my work has focused on the role of menstrual phase as a proxy for sex hormones in smoking cessation and related symptomatology. This work has demonstrated that the luteal phase (e.g., high progesterone, moderate estradiol) is associated with the following: improved quit outcomes during self-selected quit attempts, decreased nicotine absorption among non-depressed women smokers, and less predictability of craving on smoking relapse. Further, my prior research has demonstrated variations in alloprenanolone and cortisol in response to nicotine by menstrual phase variation in smoking-related symptomatology during abstinence.
    a. Allen SS, **Allen AM**, Lunos S, Hatsukami DK. Patterns of self-selected smoking cessation attempts and relapse by menstrual phase. Addict Behav. 2009 Nov;34(11):928-31. PMCID: PMC2766357
    b. **Allen AM**, al'Absi M, Lando H, Allen SS. Allopregnanolone association with psychophysiological and cognitive functions during acute smoking abstinence in premenopausal women. Exp Clin Psychopharmacol. 2015 Feb;23(1):22-8. PMCID: PMC4394732
    c. **Allen AM**, Lunos S, Heishman SJ, al'Absi M, Hatsukami D, Allen SS. Subjective response to nicotine by menstrual phase. Addict Behav. 2015 Apr;43:50-3. PMCID: PMC4304933
    d. Carlson S, **Allen AM**, Allen SS, al'Absi M. Differences in Mood and Cortisol by Menstrual Phase during Acute Smoking Abstinence: A Within-Subject Comparison. 2017. Experimental and Clinical Psychopharmacology; 25: 338-345. PMCID: PMC5687826

2. Hormonal Contraceptives and Smoking Behavior. Hormonal contraceptives (e.g., oral contraceptives, hormonal intrauterine device) blunt the menstrual phase variation in endogenous sex hormones. Consequently, I hypothesize that hormonal contraceptive use influences addictive behaviors, such as cigarette smoking cessation. My work to-date suggests that hormonal contraceptive users differ from naturally-cycling women in terms of smoking-related symptomatology and smoking motives.
    a. Hinderaker K, **Allen AM**, Tosun N, al'Absi M, Hatsukami D, Allen SS. The effect of combination oral contraceptives on smoking-related symptomatology during short-term smoking abstinence. Addict Behav. 2015 Feb;41:148-51. PMCID: PMC4314472
    b. **Allen AM**, Lundeen K, Eberly LE, Allen SS, al'Absi M, Muramoto M, Hatsukami D. Hormonal contraceptive use in smokers: Prevalence of use and associations with smoking motives. (2018). Addictive Behaviors; 77: 187-192. PMCID: PMC5701821
    c. **Allen AM**, Carlson S, Eberly LE, Hatsukami D, Piper ME. Use of Hormonal Contraceptives and Smoking Cessation: A Preliminary Report. (2018). Addict Behav; 76: 236-242. PMCID: PMC5614855
    d. **Allen AM**, Weinberger AH, Wetherill RR, Howe CL, McKee SA. Oral Contraceptive and Cigarette Smoking: A Review of the Literature and Future Directions. (2019). Nic Tob Res; 21: 592-601. PMCID: PMC6468133

3. Smoking Relapse Risk Factors in Women: Women face many barriers to smoking cessation including depressive symptoms, concerns about weight gain and stress. Much of my work has focused on elucidating the relationship between these barriers and cessation outcomes. These studies have documented differences greater gender differences occur in nondaily smokers, neither gender responded well to snus as a harm reduction approach, and women were less likely to quit smoking and less likely to utilize state quit line services.
    a. **Allen AM**, Oncken C, Hatsukami D. Women and Smoking: The Effect of Gender on the Epidemiology, Health Effects and Cessation of Smoking. Current addiction reports. 2014; 1:53. PMCID: PMC4871621
    b. **Allen AM**, Scheuermann TS, Nollen N, Hatsukami D, Ahluwalia JS. Gender differences in smoking behaviors and dependence motives among daily and nondaily smokers. Nicotine Tob Res. 2016: 18: 1408-1413. PMID: 26136526.

c. **Allen AM**, Vogel RI, Meier E, Anderson A, Jensen H, Severson HH, Hatsukami D. Gender differences in snus versus nicotine gum for cigarette avoidance among a sample of US smokers. Drug Alcohol Depend. 2016: 168: 8-12. PMID: 27610935.
d. **Allen AM**, Yuan NP, Wertheim BC, Krupski L, Bell ML, Nair U. Gender differences in utilization of services and tobacco cessation outcomes at a state quitline. (2018). Translational Behavioral Medicine. [Epub ahead of print]. PMID: 3099557

4. Methodological Advancements: As an epidemiologist, one of my primary interests is to reduce bias and error in clinical research. As such, I have published papers that aim to improve the methodology around menstrual phase identification, remote verification of smoking status, and measurement of physical activity in a smoking-related trial.
   a. **Allen AM**, McRae-Clark AL, Carlson S, Saladin ME, Gray KM, Wetherington CL, McKee SA, Allen SS. Determine menstrual phase in human biobehavioral research: A review with recommendations. Exp Clin Psychopharmacol; 24: 1-11.
   b. **Allen AM**, Carlson SC, Bosch TA, Eberly LE, Okuyemi K, Nair U, Gordon JS. High-intensity interval training and continuous aerobic exercise interventions to promote self-initiated quit attempts in young adults who smoke: Feasibility, acceptability, and lessons learned form a randomized pilot trials. (2018). J Addict Med; 12: 343-380. PMID: 29762196.
   c. **Allen AM**, Lundeen K, Murphy SE, Spector L, Harlow BL. Web-Delivered Multimedia Training Materials for the Self-Collection of Dried Blood Spots: A Formative Project. (2018). JMIR Form Res; 2: e11025. PMID: 30684406.

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/myncbi/browse/collection/44908510

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

001269 Allen (PI) 07/2019-06/2020
Research Advancement Grants, University of Arizona
Development of an Adjunctive Behavioral Treatment for Opioid Use Disorder during the Postpartum Period
The goal of this formative research project is to conduct focus groups and key informant interviews with healthcare providers, Arizona Department of Child Safety caseworkers, new mothers with opioid use disorders, and their self-identified social support persons to identify gaps and barriers to OUD treatment during the postpartum period. This information will inform the development of a new behavioral intervention for OUD that is an adjunctive to medication assisted therapy and specific to the postpartum period.
Role: Principal Investigator

CK635 Allen (Site PI) 07/2018-06/2020
Sonoran Prevention Works
Advocating Health Equity in Addressing the Opioid Epidemic
This proposal will work to change statute to decriminalize syringe access programs and address three major elements of healthy communities: access to health care and coverage, social and cultural cohesion, and social justice. This proposal seeks to change basic state policy that is fundamental in beginning to address these inequities for high-risk opioid users.
Role: Site Principal Investigator

R21DA046604 Allen/Nair (MPI) 06/2018-05/2020
NIH/NIDA
Testing the Feasibility of a Novel Smoking Cessation Intervention by Timing Quit Dates to Menstrual Phase in a Quitline Setting
This project aims to test the feasibility, acceptability and preliminary evidence for timing quit dates to the follicular menstrual phase within a standard nicotine replacement therapy and behavioral counseling cessation intervention delivered by the Arizona Smokers' Helpline.
Role: Multiple Principal Investigator

ADHS16-162520 Muramoto (PI) 03/2017-02/2020
Arizona Biomedical Research Commission Investigator Award

Tobacco Cessation Brief Intervention Training for Behavioral Health
The overall goal of this research is to adapt the existing Helpers tobacco cessation-training program to prepare behavioral health professionals and peer mental health mentors to motivate their clients to engage in evidence-based tobacco cessation treatment and to implement clinical practice changes to support cessation.
Role: Co-Investigator

Completed Research Support

127849-IRG-16-124-34-IRG Allen (PI) 01/2018-12/2018
American Cancer Society – Institutional Research Grant
Hormonal Contraceptives and Menstrual Cycle Variability in Smoking-Related Symptoms
This project prospectively examined the variability of smoking-related symptoms (e.g., craving) during a six-week period among premenopausal smokers who do not use any hormonal contraceptives or who use either depot medroxyprogesterone acetate or monophasic oral contraceptives.
Role: Principal Investigator

L30 DA038337-02 Allen (PI) 09/2016-08/2017
NIH/NIDA
Sex and Sex Hormones in the Maintenance of Nicotine Addiction
The loan repayment award supported work to characterize the effect of sex and sex hormones on nicotine addiction.
Role: Principal Investigator

K12HD055887 Allen (PI) 01/2013-11/2016
NIH
University of Minnesota, Building Interdisciplinary Research Careers in Women's Health (BIRCWH) Program
Differences in Smoking Behavior by Gender and Use of Hormonal Contraceptives
The objective of this research project, supported by a training grant, was to identify differences in smoking behaviors by gender and the use of hormonal contraceptives as self-reported via an online, anonymous survey. Role: Principal Investigator

Grant #: - Allen (PI) 06/2015-10/2016
ClearWay Minnesota
Exercise to Promote Quit Attempts in Young Adults
This pilot study compared participants randomized to a high-intensity interval training intervention to those assigned to a moderate intensity exercise intervention to a delayed control group in terms of self-initiation of a quit attempt.
Role: Principal Investigator

Grant #: - Allen (PI) 06/2015-06/2016
University of Minnesota Foundation
Feasibility of Self-Collection of Dried Blood Spots
This project developed, pilot-tested and validated materials that instruct study participants how to self-collect and mail in dried blood spots.
Role: Principal Investigator

L30 DA038337-01 Allen (PI) 09/2014-08/2016
NIH/NIDA
Menstrual Phase and Stress-Induced Allopregnanolone Response in Smokers
The loan repayment award supported work to characterize the effect of smoking on stress-induced allopregnanolone response in women by menstrual phase.
Role: Principal Investigator

P50 DA033942-01 Carroll (PI) 08/2012-11/2016
NIH/NIDA
Sex Differences and Progesterone Effects on Impulsivity, Smoking and Cocaine
The overall goal of this project was to investigate the impact of exogenous progesterone on smoking and cocaine cessation outcomes in men and women attempting to stop.
Role: Science and Education Core Co-Director

PHS 398 Cover Page Supplement

OMB Number: 0925-0001

Expiration Date: 03/31/2020

1. Vertebrate Animals Section

Are vertebrate animals euthanized? ○ Yes ● No

If "Yes" to euthanasia

Is the method consistent with American Veterinary Medical Association (AVMA) guidelines?

○ Yes ○ No

If "No" to AVMA guidelines, describe method and provide scientific justification

2. *Program Income Section

*Is program income anticipated during the periods for which the grant support is requested?

○ Yes ● No

If you checked "yes" above (indicating that program income is anticipated), then use the format below to reflect the amount and source(s). Otherwise, leave this section blank.

*Budget Period	*Anticipated Amount ($)	*Source(s)

Tracking Number: GRANT12923549

Funding Opportunity Number: RFA-RM-19-006 . Received Date: 2019-08-22T15:21:46.000-04:00

PHS 398 Cover Page Supplement

3. Human Embryonic Stem Cells Section

*Does the proposed project involve human embryonic stem cells? ○ Yes ● No

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s) from the following list: http://grants.nih.gov/stem_cells/registry/current.htm. Or, if a specific stem cell line cannot be referenced at this time, check the box indicating that one from the registry will be used:

❑ Specific stem cell line cannot be referenced at this time. One from the registry will be used.

Cell Line(s) (Example: 0004):

4. Inventions and Patents Section (Renewal applications)

*Inventions and Patents: ○ Yes ○ No

If the answer is "Yes" then please answer the following:

*Previously Reported: ○ Yes ○ No

5. Change of Investigator/Change of Institution Section

❑ Change of Project Director/Principal Investigator

Name of former Project Director/Principal Investigator

Prefix:

*First Name:

Middle Name:

*Last Name:

Suffix:

❑ Change of Grantee Institution

*Name of former institution:

PHS 398 Research Plan

OMB Number: 0925-0001
Expiration Date: 03/31/2020

Introduction	
1. Introduction to Application (for Resubmission and Revision applications)	
Research Plan Section	
2. Specific Aims	
3. Research Strategy*	Allen_NIH-DP2_Essay.pdf
4. Progress Report Publication List	
Other Research Plan Section	
5. Vertebrate Animals	
6. Select Agent Research	
7. Multiple PD/PI Leadership Plan	
8. Consortium/Contractual Arrangements	
9. Letters of Support	
10. Resource Sharing Plan(s)	
11. Authentication of Key Biological and/or Chemical Resources	
Appendix	
12. Appendix	

Tracking Number: GRANT12923549
Funding Opportunity Number: RFA-RM-19-006. Received Date: 2019-08-22T15:21:46.000-04:00

A. Project Science Areas

1 BSS, 3 CTR

B. Project Description

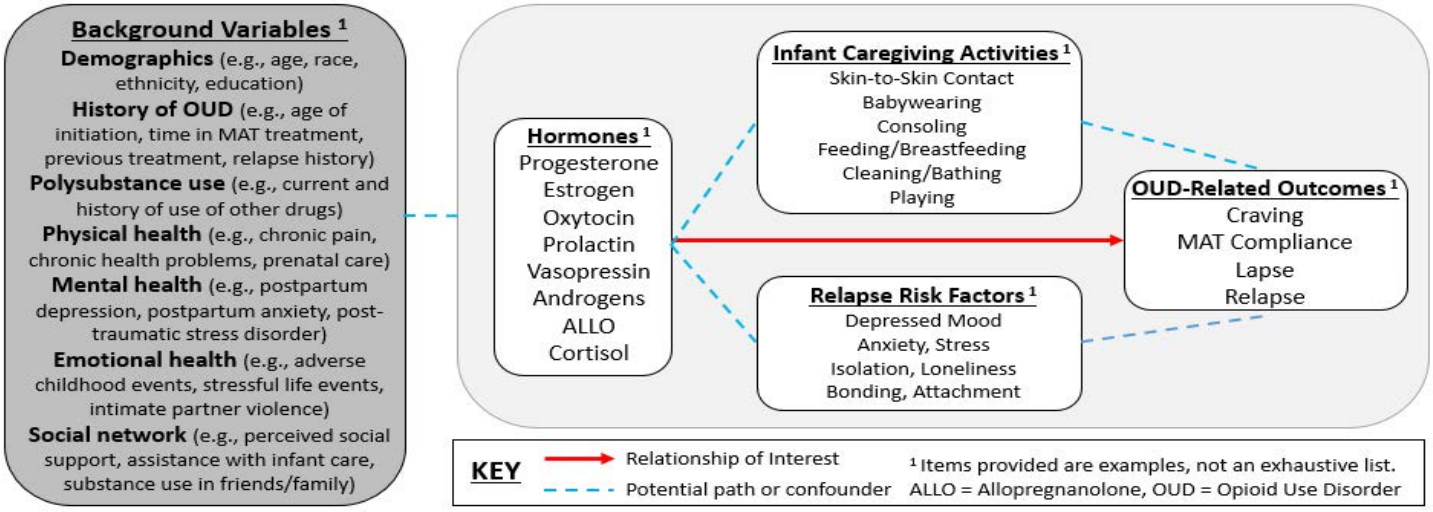
> *"There is a magic window during pregnancy… It's a time when the desire to be a good mother and raise a healthy, happy child creates motivation to overcome incredible obstacles …"* – David Olds, PhD

B.1. Overview of the Scientific Opportunity

The prevalence of opioid use disorder (OUD) during pregnancy has increased by nearly 500% over the past 15 years.[1] While pregnancy presents a strong motivation to seek and comply with OUD treatment, up to 80% of women relapse to illicit opioid use within six months of childbirth.[2] This relapse leads to a wide range of negative outcomes for the infant, mother, and the rest of the family, such as physical (e.g., fatal and non-fatal overdose), emotional (e.g., anxiety, depression), and social (e.g., foster care placement, poor academic achievement) consequences.[3] Thus, preventing postpartum opioid relapse would have dramatic and far-reaching effects that may extend for generations. Effective postpartum opioid relapse prevention interventions need to include components that address each of the bio-psycho-social elements. While my colleagues and I, as well as others, have ongoing research in the development of psycho-social components, less research has focused on the biological components.

A wide-range of hormones (e.g., progesterone, oxytocin) have been linked to substance use disorders and infant caregiving activities. While hormones have the potential to prevent postpartum opioid relapse, methodological limitations (e.g., assessment of single hormone and/or time point), content limitations (e.g., opioid use, prolactin), and a lack of knowledge dissemination across scientific disciplines are all limiting the use of this potentially high-impact approach. Thus, my overall goal is to use new technologies and methodologies to directly address the current limitations and enhance the cross-discipline dissemination of knowledge to utilize hormonal level(s)/pattern(s) to protect against opioid relapse during the high-risk postpartum period (**Figure 1**). To achieve this goal, this New Innovator Award will address four objectives: (1) measure hormones, infant caregiving activities, relapse risk factors, and OUD-related outcomes during the postpartum period using a prospective cohort study design, (2) identify hormonal level(s)/pattern(s) that are predictive of postpartum opioid use via with data-driven predictive analytics, (3) examine methods to elicit/identify targeted hormone level(s)/pattern(s) using specific infant caregiving activities, exogenous hormone delivery, and/or continuous/frequent hormone monitoring, and (4) preliminarily assess the link between the identified hormonal level(s)/pattern(s) and OUD-related outcomes. Upon completion of this high-risk/high-reward project, I will either (a) be able to rule out a hormonally-based intervention as an useful biological element of a comprehensive bio-psycho-social approach to prevent postpartum opioid relapse, or (b) have strong preliminary evidence for the use of hormone level(s)/pattern(s) to prevent postpartum opioid relapse. *The latter high-reward option would yield a high-impact via the identification of an effective postpartum opioid relapse prevention intervention and provide greater opportunities for the mother, infant and family to achieve numerous favorable long-term outcomes*.

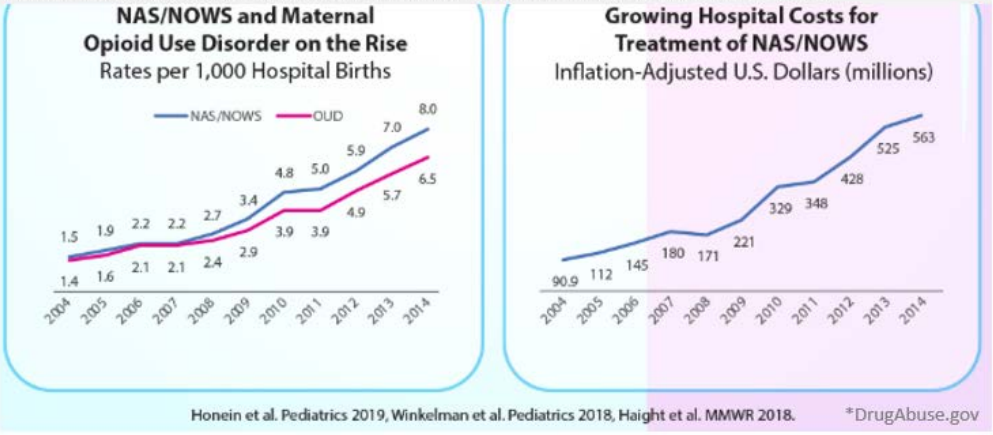
Figure 1. Conceptual Diagram



B.2. Significance and Potential Impact

While the prevalence of other substance use disorders during pregnancy has remained fairly stable, the prevalence of OUD during pregnancy has increased by nearly 500% over the past 15 years (**Figure 2**).[1] During the postpartum period, the risk for OUD relapse is two to four times greater than it is during pregnancy.[2] It is estimated that within six months of delivery, up to 80% of women with OUD relapse to illicit use.[2] Unfortunately, effective postpartum opioid relapse interventions are virtually nonexistent. This critical and missing public health intervention is having a substantial and negative impact on infants, mothers, and families. Postpartum opioid relapse leads to a wide range of negative health and social outcomes such as physical (e.g., increased risk of fatal and non-fatal overdose, intimate partner violence), emotional (e.g., increased risk of anxiety, depression, attention deficit disorder), and social (e.g., increased risk of unstable housing or homelessness, poor academic achievement, foster care placement) consequences.[3] *Ultimately, the identification of an effective postpartum opioid relapse prevention intervention will allow mothers, infants, and families opportunities to achieve better long-term outcomes that may extend into the next generations.*

Figure 2. Rates and Costs of Neonatal Abstinence Syndrome (NAS), Neonatal Opioid Withdrawal Syndrome (NOWS), and Opioid Use Disorder (OUD) in 2004-2014*



B.3. Background and Rationale

B.3.i. Hormones in Substance Use Disorders. There is ample preclinical evidence demonstrating that females are at greater risk at all stages of substance use disorder development, from initiation to dependence and relapse.[4] This may be related to the effect of ovarian hormones (e.g., progesterone, estradiol) and related metabolites (e.g., allopregnanolone), as well as other steroid hormones (e.g., cortisol) on the development and maintenance of substance use disorders.[4] This hormonal influence on substance use behaviors may be amplified during the perinatal period when hormones change by up to 300-fold during pregnancy, a dramatic decline early postpartum and then continued variation due to lactation.[5] Moreover, the natural hormonal patterns that occurs during the perinatal period directly mirror changes in substance use risk, which declines during pregnancy and increases in the postpartum, especially among those who do not breastfeed.[6]

While these observations are intriguing and hold promise for future prevention/intervention development, they contain at least *four major limitations*. First, the vast majority of this research has examined the effect of a single hormone in isolation. Emerging research has demonstrated that hormone levels relative to each other may be more important than single hormone levels, as they are often interdependent. For example, the ratio of progesterone to estradiol has been indicated as one of the best predictors of cigarette smoking behavior in women.[7] Further, analyses of hormonal ratios are limited due to a lack of consideration of the statistical approaches and limitations.[8] Future research should consider alternative approaches, such as data-driven predictive analytics. Second, few studies have examined temporal patterns of hormones beyond two time points and/or outside acute effects in lab-based settings. For example, changes in the ratio of progesterone to estradiol from one time point to a second time point is more predictive of smoking behavior than a single time point effect.[7] Hormones are continuously in flux, especially during the perinatal period, and variations occur as a result of many factors, such as breastfeeding and stress.[5] Given that hormones have a significant effect on several aspects of neurobiology, including reward response and stress response, assessing effects at one or two time points is insufficient.[5] Third, despite a strong biological premise,[4] the link between hormones and opioid use is a relatively unexplored area. Fourth, the vast majority of research on the relationship between hormones and substance use is focused on a single substance, even though polysubstance use is the norm.[9] Understanding how hormones influence behaviors related to substance use within a polysubstance use context is necessary to produce effectiveness interventions. *In sum, while hormones may a major impact on postpartum opioid relapse risk, methodological limitations (e.g., single hormone assessment, limited time assessment) and content limitations (e.g., opioid use, polysubstance use) are limiting their potential.*

B.3.ii. Hormones in Infant Caregiving. Ample evidence also demonstrates that a link between infant caregiving activities and neuroendocrine systems. For instance, changes in hormones and neuropeptides (e.g., prolactin, androgens, oxytocin, and arginine-vasopressin) in new mothers[10] and are thought to facilitate infant care.[11] Indeed, *a dose-response relationship has been identified indicating that more involved parental care is linked to greater hormonal response*.[12] The neuropeptide oxytocin has been shown to increase in response to bonding and infant caregiving activities such as synchronizing with and exposure to infants.[13–15] For example, oxytocin increases with affection and during skin-to-skin contact with infants in women.[16] It is hypothesized to be stimulated by touch, as to encourage attention towards particular stimuli while associating memory with reward and its activation of the reward centers of the brain may therefore maintain nurturing behaviors.[17] Oxytocin is linked to a vast number of favorable effects on mood (e.g., increased feelings of trust and empathy, and decreased feelings of isolation and depressive symptoms).[18] It is also likely a key mechanism by which social support protects health.[19] Changes in oxytocin over time are common (e.g., from early postpartum to six months postpartum) and may be linked to changes in social behavior such as development of social and passive coping strategies for stress management.[18,20] Oxytocin also appears to reduce pain perception and the memory of pain, and encourages bonding after traumatic events,[20] playing a pivotal role during the perinatal period, with effects on birth, breastfeeding, and bonding. Prolactin increases in female animal models in response to interactions with newborns.[12] It is possible that the effects of prolactin on caregiving actions may occur via effects on mood such as through reducing anxiety and/or negative affect.[11] In contrast, androgens decrease after parturition, but research on individual variation is lacking. Finally, arginine-vasopressin has similar effects as oxytocin on behavior.[21] Arginine-vasopressin is linked to feelings of attachment, but it is also associated with maternal aggression, anxiety, and sleep. Like oxytocin, dysregulation of the arginine-vasopressin system can adversely impact health, causing stress and anxiety disorders.[22]

Similar to the link between hormones and substance use disorders (see Section B.3.i), measuring hormones in relation to caregiving is promising but contains at least four important limitations. First, experimental results of exogenous administration of hormones to achieve specific behaviors have been null.[11] This may be because observations in the link between hormones and caregiving activities vary by species.[11] Thus, translation from one species to another may not be as straightforward as in other research areas. Further, caregiving-hormone relationships have been studied almost exclusively under lab conditions, where individuals are subject to unnatural selection pressures. Experimental manipulations have produced mixed effects on paternal care behavior, in part because altering hormone levels outside the normal physiological range can actually disrupt paternal responsiveness.[23] Thus, real-world implications of hormonal level(s)/pattern(s) is questionable. Second, and similarly, hormonal effects on caregiving are often studied by analyzing hormones in isolation, rather than in concert with each other. Endogenous hormones do not exist in isolation; thus, studying their effect in isolation limits the application of findings, and can help explain equivocal findings in experimental studies. Third and also similarly, hormonal effects on caregiving are often studied using one or two time points, or with changes over an acute period of time (e.g., minutes/hours). Hormonal patterns over longer time spans may be a more significant influence on behavior and feelings than single or acute time point absolute level effects. Fourth, studies of the hormonal effects of caregiving are largely conducted on a very limited set of captive, rodent and monkey species, and studies of humans often rely on personal, retrospective reports of past caregiving or brief interactions with their children in experimental settings. This limits the generalizability to real-world settings. *In brief, infant caregiving activities have a significant and wide-range of effects on hormones. Unfortunately, these observations contain critical limitations. Further, very little of this knowledge has been translated to the field of substance use disorders research; severely limiting the potential for scientific advancements.*

B.3.iii. Data-Driven Predictive Analytics in Hormonal Response Research. As detailed above, there are numerous intriguing observations linking hormonal level(s)/pattern(s), infant caregiving activities, and substance use related outcomes (**Figure 1**). However, the application of these observations to improve substance use related outcomes has been sparse. For instance, I have examined the delivery of exogenous progesterone to prevent postpartum cigarette smoking and for smoking cessation in men and women,.[24,25] While the results have shown promise, they were underwhelming; underscoring the importance of the existing limitations detailed above (Sections B.3.i and B.3.ii). To address these major field limitations, I will collaborate with colleagues in engineering to capitalize on their innovative approaches to synthesize meaningful data patterns overtime in large datasets. Specifically, we will leverage techniques from data science and machine learning to characterize the trends in the hormone samples collected from study participants over time. *Advances in data science and engineering allow for a novel approach to advance this area of work. Specifically, these analytical techniques*

will allow for an examination of hormonal effects in context of other hormones and over time in relation to risk of postpartum opioid relapse.

B.4. Project Goals and Objectives

My overall goal is to use new technologies and methodologies to directly address the current limitations and enhance the cross-discipline dissemination of knowledge to utilize hormonal level(s)/pattern(s) to protect against opioid relapse during the high-risk postpartum period (**Figure 1**).). To achieve this goal, I will work with a variety of collaborators to address the following four objectives in this five-year grant period: Objective 1: measure hormones, infant caregiving activities, relapse risk factors, and OUD-related outcomes during the postpartum period using a prospective cohort study design; Objective 2: identify hormonal level(s)/pattern(s) that are predictive of postpartum opioid use via with data-driven predictive analytics; Objective 3: examine methods to elicit/identify targeted hormone level(s)/pattern(s) using specific infant caregiving activities, exogenous hormone delivery, and/or continuous/frequent hormone monitoring, and Objective 4: preliminarily assess the link between the identified hormonal level(s)/pattern(s) and OUD-related outcomes. This overall goal and corresponding objectives directly responds to NIH/NIDA's 2016-2020 priority focus areas (i.e., understanding how substance use is mediated by biological factors, accelerating the development of treatments, and advancing bidirectional translation) and addresses several cross-cutting themes (i.e., increasing scientific rigor and reproducibility, leveraging technology, driving innovation, prompting collaboration and multidisciplinary workforces, and increasing real-world relevance of research).

Note: In order to comply with the instructions included in the Funding Opportunity Announcement, a detailed research plan and extensive preliminary data are *not* provided.

B.5. Objective 1 (Year 1-2): Measure hormones, infant caregiving activities, relapse risk factors, and OUD-related outcomes during the postpartum period using a prospective cohort study design

B.5.i. Study Participants & Recruitment. We will enroll an estimated 50 pregnant women with OUD ("OUD group"), as well as 25 pregnant women without OUD ("controls") into this prospective observational cohort study to ensure a final sample size of 40 in the OUD group and 20 controls. Eligibility criteria selected to ensure safety of participants/infants and address confounding (see "Human Subjects and Clinical Trials" document). We will work with our community partners to recruit from local hospitals, clinics, and task forces where we expect to have access to approximately 275 pregnant women with OUD per year (see "Recruitment and Retention" document). *Feasibility of Recruitment*: While recruitment during perinatal period can pose challenges, I have experience recruiting and retaining participants during this time. For example, similar to the proposed methods here, I have enrolled approximately 28 pregnant women with OUD between gestational weeks 30-35 for an ongoing quality improvement project with a local hospital to be conducted over a two-year period (~2 participants recruited per month).[26] Therefore, I am confident in our ability to recruit a similar study sample.

B.5.ii. Methods. Using methods I have had success with, we will complete eligibility interviews over the phone followed by an in-person enrollment visit (which may occur at our clinic, the participants' home or a community-based location [e.g., private room in a library or place of worship], per their preference) at gestational weeks 30-35. At this enrollment visit, participants will each provide informed consent, complete baseline assessments, complete a release of information for partner hospitals and clinics (OUD group only), receive training on study-related procedures, and schedule upcoming appointments. At gestational week 36, participants will commence data collection procedures through postpartum month 9. At weekly and biweekly visits, participants will be compensated with $20 and a pack of diapers with additional bonuses at primary study time points; for a total possible compensation of $890 and an additional estimated $500 in diapers. We recognize that this is considerable compensation for a vulnerable group, but we also want to ensure adequate compensation for data collection efforts that may be burdensome during the postpartum period while caring for a high-needs infant and prior research indicates cash is used in a responsible and safe manner in similar populations.[27] *Feasibility of Approach*: Data collection and retention during the perinatal period can be difficult. However, I have experience conducting research during this challenging time. For example, I worked on a project focused on preventing postpartum cigarette smoking relapse which successfully met with 98% (45/46) of participants with within three days of childbirth, > 72% of the daily assessments were completed for a 16 week period, and 87% were followed through postpartum week 12.[28] We have also developed a contingency plan that may be implemented if necessary (see "Recruitment and Retention" document).

B.5.ii. Measures. As depicted in **Figure 1**, we will collected four types of data. First, the baseline surveys will be collected upon study enrollment via a self-administered survey housed on the REDCap[29] website, which is designed for research purposes and includes a high-level of security to protect data and study participants. Second, participants will report on current infant caregiving activities (such as parent/infant engagement[30]), relapse risk factors (such as perceived stress[31]), and OUD-related outcomes (such as craving[32]) at each time point via self-administered REDCap surveys. We will also collect biological (saliva, urine, dried blood spots) samples at each meeting to measure hormones (progesterone, estrogen, oxytocin, prolactin, vasopressin, testosterone, allopregnanolone, and cortisol). Specific collection protocols will vary by hormone to account for known influences (e.g., diurnal changes, interaction with offspring) following prior recommendations, which we have previously utilized.[33–36] For instance, outside of study visits, participants will collect a series of five saliva samples to measure cortisol and account for the typical diurnal pattern of cortisol. These samples will be collected at 8 pm and bedtime on the day before the study visit, and at waking, 30 minutes after waking, and 60 minutes after waking on the day of the study visit. All hormone samples will be analyzed using commercial enzyme immunoassay kits from Arbor Assays, using established protocols by my collaborators [redacted] (UA's School of Anthropology) and [redacted] (University of Minnesota's Department of Family Medicine and BioBehavioral Health). *Feasibility of Approach*: I have utilized these collection and analysis methods and self-administered surveys via REDCap in a wide range of study participants including women of reproductive age, pregnant women, and pregnant women with OUD. These efforts have had a high-level of compliance.

B.6. Objective 2 (Years 2-3): Identify hormonal level(s)/pattern(s) that are predictive of postpartum opioid use via with data-driven predictive analytics

In collaboration with my colleagues [redacted] and [redacted] (UA's College of Engineering), the following approaches will be pursued to identify the link between hormonal level(s)/pattern(s) and OUD relapse:

B.6.i Identification of Hormonal Level(s)/Pattern(s). Utilizing data collected in Objective 1, we are estimating a total of between 9,000 to 100,000 data points to discover underlying trends. We will leverage single and multivariate change detection methods on each participant's data to identify hormonal level(s)/pattern(s). We will experiment with both parametric and nonparametric change detection methods since we may not be able to assume the form of the distribution.[37] We will use the KS and Lillifore's tests for determining if a parametric method can be employed to model the distribution of the data.[38] In the case that we cannot assume the distribution of the data, then we will use a nonparametric estimator for the distribution of the data. The change detection will be performed at multiple levels. First, we will implement change detection on each of the study participants. Such a study will allow us to understand changes that are specific to each individual. Second, we will then perform change detection across the study sample to understand the general changes in the target population (e.g., women with OUD). Using data from the control group for comparison, we can identify the hormonal level(s)/pattern(s) specific to our target population.

B.6.ii Forecasting High Risk of Relapse. Identifying risk of relapse is an essential outcome of this research. Techniques from machine learning, and data science will be used to achieve this inference. We will build a forecasting model using machine learning to predict the probability that a women would relapse based on historical hormone measurements from study participants (i.e., a sequence of hormone measurements will be used, not a single measurement). We will investigate LSTM neural networks to forecast this probability. These types of neural networks have shown state-of-the-art performances in many tasks of sequential prediction.[39] In order to be able to achieve this goal, we will need to collect data that represent individuals who have relapsed. Based on the baseline risk of 80%,[2] we are estimating approximately 8-10 of our OUD group participants remain abstinent and 32-40 of OUR group participants will relapse. Therefore, upon completion of this objective, we will be able to estimate when the sequential hormone measurement levels are outside of the normal for the trend in a control population, as well as differing trends among OUD participants by relapse status.

B.6.iii. Translating Observations to Objective 3. As we move into Objective 3, our goal will be to identify hormonal level(s)/pattern(s) unique to the participants with OUD who remain abstinent that can be elicited ideally by infant caregiving activities or, less ideally, via exogenous hormone administration. As a third option, if we are unable to identify hormonal level(s)/pattern(s) that could be elicited, we will identify hormonal level(s)/pattern(s) that we could capture via continuous/frequent hormonal monitoring. We will also explore additional secondary outcomes including: craving for opioids, MAT compliance, and lapse. Thus, should we not find any links between hormonal level(s)/pattern(s) and relapse, we can explore these the prevention of these secondary outcomes via

targeted a hormonal level(s)/pattern(s) as an approach to prevent postpartum opioid relapse. Thus, the are at least 12 possible combinations of hormonal level(s)/pattern(s) and OUD-related outcomes that provide a pathfor us to advance to Objective 3.

B.7. Objective 3 (Year 3): Examine methods to elicit/identify targeted hormone level(s)/pattern(s) using specific infant caregiving activities, exogenous hormone delivery, and/or continuous/frequent hormone monitoring

We will explore at least three approaches to eliciting or identifying the targeted hormone level(s)/pattern(s) based on the observations made in Objective 2 by (in order of preference):

- Specific Caregiving Activities: As described in Section B.3.ii, caregiving can elicit a wide range of hormonal responses. One such example may be the use of skin-to-skin contact which results in an increase in oxytocin. In collaboration with [redacted] (UA's School of Anthropology) and [redacted] (Arizona State University's School of Social Work), we will explore the use of specific caregiving activities to elicit the targeted hormonal response.
- Exogenous Hormone Delivery: Targeted hormones may either directly or indirectly achieved be administration of exogenous hormones. For example, natural progesterone is commercially available as Prometrium®. We have used this form of exogenous hormone in prior research.[25,28] Allopregnanolone is a metabolite of progesterone.[40] Thus, it may be possible to target favorable allopregnanolone levels via delivery of exogenous progesterone and/or allopregnanolone indirectly.[40] In collaboration with [redacted] (UA's College of Pharmacy), [redacted] (Yale School of Medicine) and [redacted] (Colorado State University's College of Veterinary Medicine & Biomedical Sciences) to identify the available options for exogenous administration.
- Continuous/Frequent Hormone Monitoring: Similar to continuous glucose monitoring,[41] we could develop technology and methodology to continuously or frequently monitor hormones. This novel approach may be especially useful in the event we identify a hormonal signal that we cannot replicate with caregiving activities and/or exogenous hormones. For example, if an increase in a hormone level is linked to an increase risk of relapse, continuous monitoring could preemptively identify this risk and, for example, a counselor or peer support person could proactively reach out in response to the hormonal signal. I will work with [redacted] (UA's College of Medicine) and [redacted] (UA's College of Engineering), as well as our internal BIO5 Institute, to pursue the development of this technology/methodology to pursue this approach.

It is highly likely that we may pursue a combination of these approaches and/or additional approaches as the field continues to evolve. Thus, these approaches are only some of the possible options.

B.8. Objective 4 (Years 4-5): Preliminarily assess the link between the identified hormonal level(s)/pattern(s) and OUD-related outcomes.

The details of this last objective are highly dependent on the results of the prior objectives. However, in brief, I also anticipate conducting a pilot randomized trial with conditions yet to be determine, though recruiting and data collection methods will likely be similar to previous methods (see Sections B.5.i and B.5.ii). Our primary outcomes for this objective will observe current recommendations for conducting preliminary pilot trials (e.g., recruitment and retention rate, intervention compliance, successful hormonal level(s)/pattern(s) replication)[42] and the potential efficacy of hormonal level(s)/pattern(s) by including the OUD-related outcomes (see Section B.5.iii.). The specific number of participants we recruit will be dependent on the anticipated effect size based on Objectives 2 and 3. However, it is also important to note that the goal of this objective is not to complete a fully-powered effectiveness trial. Rather, we are exploring feasibility and acceptability outcomes, in addition to preliminary estimates. It is likely that we will not be properly powered to determine efficacy, which is appropriate for a pilot/preliminary study.[42]

B.9. Anticipated Challenges and Alternative Approaches

As with any research, challenges are likely to occur at some point. We have identified alternative approaches to at least four possible challenges and alternative approaches. First, we may experience difficulties with recruitment and/or retention. We have established contingency plans. See the "Recruitment and Retention" document for additional details. Second, it is possible that we will not identify useful hormonal level(s)/pattern(s) in Objective 2 and/or be unable to replicate the favorable levels in Objective 3. If this occurs, we will change the course of the project to revert to Objective 1 with the intent of exploring other hormones or, possibly, other

variables that may be linked to substance use relapse. However, we feel this is an unlikely outcome given the signals identified to date used limited methods, as well as the numerous endpoints available (e.g., opioid relapse, craving, MAT compliance). Lastly, given there are a number of new collaborations on this project that cross diverse fields of study (e.g., engineering, endocrinology), it is possible that we may face communication or collaboration difficulties. If this challenge occurs, we will request additional engagement with mentors and/or utilize resources at the University of Arizona (e.g., the BIO5 Institute whose goal is to encourage and support working across disciplines). It is possible additional, unanticipated challenges may occur. Our team members, who have decades of applicable experience, are confident we can address any problems if they arise.

B.10. Timeline

Table 1 provides details of timing of major activities associated with each objective.

Table 1. Timing of Objective/Procedures

	Year 1				Year 2				Year 3				Year 4				Year 5			
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Objective 1 (Measurement)	X	X	X	X	X	X	X													
- Finalize Measures/Databases	X																			
- Gain Regulatory Approvals	X																			
- Recruit		X	X	X	X															
- Data Collection		X	X	X	X	X														
- Analyze hormonal samples							X													
Objective 2 (Identify)								X	X	X	X									
- Transfer Datasets								X												
- Analyses								X	X	X	X									
Objective 3 (Replicate)										X	X	X								
- Collaborative Brainstorming										X	X	X								
- Trial/Error Method Testing											X	X								
Objective 4 (Prelim Testing)													X	X	X	X	X	X	X	X
- Finalize Measures/Databases													X							
- Gain Regulatory Approvals													X							
- Recruit														X	X	X	X			
- Data Collection														X	X	X	X	X		
- Statistical Analyses																		X	X	
Dissemination of Results							X				X								X	X

B.11. Payoffs and Future Directions

Should our observations show promise, we will immediately pursue R01-type funding to conduct a fully-powered efficacy trial in which we randomize participants to our newly developed intervention versus standard of care (or similar) and examine the effect on risk of postpartum opioid relapse. Shortly thereafter, we will also pursue R01-type funding to conduct a prospective cohort trial in which we follow the infants who participate in the efficacy trial. By following the infants, we will be able to examine the effect of the infants' exposure to the hormones, related behavior changes, and, additional ancillary effects (e.g., intact family). While outside the scope of this current project, this will be of interest given prior research has demonstrated that infancy exposure to hormones (e.g., oxytocin) leads to improved adaptability of children in later life. This may ultimately override the in utero exposure to opioids, which is linked to poorer long-term physical and cognitive development. Additionally, future research beyond our planned grants may explore the effects of our intervention on the use of other substances (e.g., cannabis, tobacco/nicotine) and with/without existing evidence-based interventions (e.g., behavioral counseling, pharmacotherapies, state quit lines). Ultimately, this intervention is likely *easily translatable* to a wide-range of clinical practices as caregiving activities given there is likely no adverse effects, training could be executed in the hospital or clinics by a wide range of licensed and non-licensed providers. The other options (exogenous hormone administration and/or continuous hormone monitoring) would also be translatable to clinical practice though likely with directly implementation and oversite with licensed healthcare providers. Any of these interventions would likely have substantially less cost than the cost associated with opioid relapse. Regardless of the results, this project will advance our knowledge on how hormones respond to caregiving activities, as well as influence substance use outcomes in women during the postpartum period. This knowledge can be applied to a wide range of behavioral change interventions during the postpartum period (e.g., postpartum weight loss or depression, breastfeeding), as well as within the context of substance use disorders (e.g., cannabis, opioids), or other addictive behaviors (e.g., eating disorders). Therefore, the application of this work sustaining a power influence on future research and clinical care is highly likely.

C. Innovativeness

This project features several highly innovative premises that build on the rigor of prior research by directly responding to the current limitations to the fields (Sections B.3.i and B.3.ii) and address new unexplored areas.

1. *Focus on the treatment of OUD as a neurobiological disease*. Broadly speaking, most OUD treatments focus on two aspects: (1) pharmacological treatment to alter the response to rewards, pain, and/or substances

and/or the reduction of withdrawal symptoms, and/or (2) behavioral treatment to identify or develop applicable skills, support, knowledge, and other behavioral responses to cues, triggers, and opportunities for use. While both of these aspects are important to maintain treatment and/or sobriety, *neither of these elements address the underlying neurobiological causes of this disease*. In contrast, hormones not only have direct impact on neurobiological reward response to rewards, pain, and/or substances (like the pharmacological treatments), but they also directly alter a wide variety of substance use risk factors such as mood, stress, cue-response, and sleep. The altering of hormones during the postpartum and infant care stage of life offers a unique and powerful opportunity to overcome OUD.

2. *Assessment of temporal patterns of hormones in context with other hormones.* The vast majority of research on substance use behaviors and hormones has relied on exploring the effect of a single hormone at one or two time points. We will use data science approaches to explore the effect of hormones in concert with each other and over time.
3. *Investigation into the link between hormones and OUD*. A wide range of hormones (e.g., oxytocin, vasopressin) have known and significant effects on behaviors that are risk factors for substance use (e.g., stress response). Furthermore, these hormones exhibit substantial changes during the perinatal period, a time that is known for increased risk of substance use. Thus, a critical opportunity exists to examine hormone-OUD relationships that have yet to be evaluated. This will be the first to link these hormones, along with previously identified hormones, to opioid relapse during the perinatal period.
4. *Targeting the postpartum period for intervention development*. There are multiple points throughout pregnancy (e.g., prenatal, childbirth, postpartum), where mothers have interactions with the healthcare system. In the cases of infants exposed to substances while in utero, this healthcare interaction often commences with a lengthy hospital stay for the infant. While this is a highly stressful time for the mother, opportunities exist through further engagement with the healthcare system and department of child series. Therefore, given these frequent touchpoints and heightened risk, postpartum is an ideal time to intervene. For example, should we identify specific caregiving activities that elicit protective hormonal response, perhaps this could be included in a training by hospital staff (e.g., nurses, aides) while infant is admitted and/or caseworkers upon discharge. Therefore, rather than viewing this as a stressful, troubled time, we will treat this unique opportunity for further engagement, intervention and support.

D. Investigator Qualifications

D.1. Principal Investigator Qualifications. As early stage and independent researcher seeking to have profound and positive impact families affected by OUD, my exceptional training, applicable expertise, and outstanding qualifications make me the ideal applicant for this award. To demonstrate, I provide the following four points.

1. I have a *history of making bold research and methodological choices* that advance the field. For example, I pioneered a line of research focusing on the effects of hormonal contraceptives on cigarette smoking. For nearly 40 years, research on ovarian hormone effects on cigarette smoking consistently excluded women who used exogenous hormones, including hormonal contraceptives, which severely limited the generalizability of the results. One of my first projects in my K12 training grant was to launch a line of research in this area. My research has demonstrated that about half of women who smoke also use hormonal contraceptives and preliminarily found that women who use hormonal contraceptives have a different smoking behavior, withdrawal symptoms, and, perhaps, cessation outcomes. I have also advanced the field similarly in terms of methodology by developing and promoting the use of systematic methods to identify menstrual phase and capitalizing on dried blood spot technology to reduce participant burden while increasing the incoming data pool. These actions demonstrate my willingness to take bold moves, even when it is against the norms of the field.
2. I have more than *15 years of experience at all levels of substance use related research*. In 2001, I serendipitously accepted my first undergraduate research assistant position on a study that immediately captured my interest and, unbeknownst to me at the time, was the start of my career in substance use research. Since that time, I have stayed actively engaged in this content area, and have sought to expand my expertise in all aspects of my projects by taking on roles including recruiter, screener, community outreach worker, counselor, data manager, data analyst, project manager, director, co-investigator and principal investigator. I am knowledgeable and competent in the execution all aspects of substance use research. Thus, despite any challenges we may face, I am confident I have the insight and skills to overcome them (including knowing when to reach out to my mentors, colleagues, and collaborators for assistance).

3. I am *trained as a behavioral epidemiologist*. So, I am well-versed in a wide-range of methodologies, measurement of errors/bias, estimation of and, when applicable, correction for confounding, and assessment of causality. Therefore, regardless of where this path takes us, I am skilled and confident in the use of appropriate methodologies to assess the research question at hand. Ultimately, this will not only make the rigor of the present work stronger, but it will allow for reproducibility beyond our research.
4. I am a strong believer in *collaborations and diversity*. As I learned and witnessed while a BIRCWH (Building Interdisciplinary Research Careers in Women's Health) scholar, different perspectives provide new insights to the same problem. This is extremely advantageous to the advancement of science. I have had success in this area leading collaborative efforts with national groups (e.g., a review paper published on oral contraceptives and smoking behavior won the journal's editor choice award and led to several subsequent invitations to present at national venues). Consequently, I have internal and external collaborators, as well as community partners, who have eagerly and graciously agreed to participate in this project, as needed.

D.2. Collaborators and Community Partnerships. [redacted] I have formed a strong and diverse team collaborators to augment my own expertise. Further, as detailed in the "Recruitment and Retention" document, I have strong and ongoing partnerships with numerous community partners, including local hospitals, clinics, treatment facilities, governmental agencies, and tasks forces.

E. Suitability for the New Innovator Award

In addition to the highly innovative features (described in Section C), the high potential for great impact (described in Section B.2), and the investigator fit (described in Section D), this proposed project is an ideal fit for the New Innovator Award given the following additional features:

- High-Risk Features: (1) We do not have preliminary data to support an R01-type application. Without this necessary preliminary evidence, an R01-type application would not be well-received and the timeframe for the proposed activities are too ambitious for an R21-type award. (2) Despite the high potential for targeting hormones as a treatment for OUD, it is possible that we will not identify a useful signal.
- High-Reward Features: (3) OUD is a pressing public health crisis that needs immediate attention and action. Targeting women during the postpartum period has higher potential to profoundly impact substance use disorders than current strategies. (4) This could also break the treatment-relapse cycle in the woman, overcome the negative effects of *in utero* substance use exposure, and extend effects into the next generation by reducing the negative effects (e.g., foster care placement, risk of substance use) in the children. (5) By leveraging my expertise with my collaborations skills, we will be able to advance the science via fast dissemination and immediate application across transdisciplinary disciplines via my multi-disciplinary collaborations.

The flexibility of the new innovator award is ideal for this project as it allows for certain aspects of the protocol to be developed as the knowledge develops. For example, in Objective 3, we will be able to choose a path (e.g., caregiving activities, exogenous hormone administration, and/or continuous hormone monitoring) in response to our conclusions in Objective 2 become known.

F. Statement of Research Effort Commitment

I will commit a minimum of three person-months (25% effort) of my research effort to this project for all five years of the New Innovator Award.

G. References

(1) Haight SC, et al. Opioid Use Disorder Documented at Delivery Hospitalization — United States, 1999–2014. *MMWR Morb Mortal Wkly Rep*. 2018;67(31):845-849. **(2)** Schiff DM, et al. Fatal and Nonfatal Overdose Among Pregnant and Postpartum Women in Massachusetts. *Obstet Gynecol*. 2018;132(2):466-474. **(3)** Reddy UM, et al. Opioid Use in Pregnancy, Neonatal Abstinence Syndrome, and Childhood Outcomes. *Obstet Gynecol*. 2017;130(1):10-28. **(4)** Anker J, et al. Females Are More Vulnerable to Drug Abuse than Males: Evidence from Preclinical Studies and the Role of Ovarian Hormones. In: *Current Topics in Behavioral Neurosciences*. Vol 8. ; 2010:73-96. **(5)** Mishell DR. *Reprod. Endocrinology*. 3rd ed. Philadelphia: Current Medicine, Inc.; 1999. **(6)** Forray A, et al. Perinatal substance use: A prospective evaluation of abstinence and relapse. *Drug Alcohol Depend*. 2015;150:147-155. **(7)** Schiller CE, et al. Association between ovarian hormones and smoking behavior in women. *Exp Clin Psychopharmacol*. 2012;20(4):251-257. **(8)** Sollberger S, et al. How to use and interpret hormone ratios. *Psychoneuroendocrinology*. 2016. **(9)** Jarlenski M, et al. Polysubstance Use Among US Women of Reproductive Age Who Use Opioids for Nonmedical Reasons. *Am J Public Health*. 2017;107(8):1308-1310. **(10)** Ziegler TE. Hormones associated with non-maternal infant care: a review of mammalian and avian studies. *Folia Primatol (Basel)*. 71(1-2):6-21. **(11)** Saltzman W, et al. Functional significance of hormonal changes in mammalian fathers. *J Neuroendocrinol*. 2014;26(10):685-696. **(12)** Storey AE, et al. Primate paternal care: Interactions between biology and social experience. *Horm Behav*. 2016;77:260-271. **(13)** Zeki S. The neurobiology of love. *FEBS Lett*. 2007;581(14):2575-2579. **(14)** Carter CS. Neuroendocrine perspectives on social attachment and love. *Psychoneuroendocrinology*. 1998. **(15)** Kenkel WM, et al. Neuroendocrine and Behavioural Responses to Exposure to an Infant in Male Prairie Voles. *J Neuroendocrinol*. 2012. **(16)** Feldman R, et al. Natural variations in maternal and paternal care are associated with systematic changes in oxytocin following parent-infant contact. *Psychoneuroendocrinology*. 2010;35(8):1133-1141. **(17)** Bartz JA, et al. Effects of oxytocin on recollections of maternal care and closeness. *Proc Natl Acad Sci*. 2010. **(18)** Carter CS. Oxytocin pathways and the evolution of human behavior. *Annu Rev Psychol*. 2014;65:17-39. **(19)** Heinrichs M, et al. Common oxytocin receptor gene (OXTR) polymorphism and social support interact to reduce stress in humans. *Proc Natl Acad Sci*. 2011. **(20)** Gordon I, et al. Oxytocin and the development of parenting in humans. *Biol Psychiatry*. 2010;68(4):377-382. **(21)** Insel TR, et al. Neuropeptides and the evolution of social behavior. *Curr Opin Neurobiol*. 2000;10(6):784-789. **(22)** Cochran DM, et al. The role of oxytocin in psychiatric disorders: a review of biological and therapeutic research findings. *Harv Rev Psychiatry*. 21(5):219-247. **(23)** Ziegler TE, et al. Prolactin's mediative role in male parenting in parentally experienced marmosets (Callithrix jacchus). *Horm Behav*. 2009. **(24)** Allen SS, et al. Progesterone and Postpartum Smoking Relapse: A Pilot Double-Blind Placebo-Controlled Randomized Trial. *Nicotine Tob Res*. August 2016. **(25)** Tosun NL, et al. Exogenous progesterone for smoking cessation in men and women: a pilot double-blind, placebo-controlled randomized clinical trial. *Addiction*. May 2019. **(26)** Allen A, et al. Eat-sleep-console as a treatment for infants with neonatal abstinence syndrome. In: *Mommy and Me: Perinatal*. San Antonio: College of Problems on Drug Dependence; 2019. https://cpdd.org/wp-content/uploads/2019/07/abstracts_2019.pdf. **(27)** Festinger DS, et al. Paying substance abusers in research studies: Where does the money go? *Am J Drug Alcohol Abuse*. 2012;38(1):43-48. **(28)** Allen SS,et al. Progesterone and postpartum smoking relapse: A pilot double-blind placebo-controlled randomized trial. *Nicotine Tob Res*. 2016;18(11). **(29)** Harris PA, et al. Research electronic data capture (REDCap)—A metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009;42:377-381. **(30)** Samra HA, et al. The NICU parent risk evaluation and engagement model and instrument (PREEMI) for neonates in intensive care units. *JOGNN - J Obstet Gynecol Neonatal Nurs*. 2015. **(31)** Park ER, et al. Development of a Postpartum Stressor Measure. *Matern Child Health J*. 2015;19(10):2094-2101. **(32)** McHugh RK, et al. Assessing craving and its relationship to subsequent prescription opioid use among treatment-seeking prescription opioid dependent patients. *Drug Alcohol Depend*. 2014. **(33)** Carlson SC, et al. Differences in mood and cortisol by menstrual phase during acute smoking abstinence: A within-subject comparison. *Exp Clin Psychopharmacol*. 2017;25(5). **(34)** Allen AM, et al. Web-Delivered Multimedia Training Materials for the Self-Collection of Dried Blood Spots: A Formative Project. *JMIR Form Res*. 2018;2:e11025. **(35)** de Jong TR, et al. Salivary oxytocin concentrations in response to running, sexual self-stimulation, breastfeeding and the TSST: The Regensburg Oxytocin Challenge (ROC) study. *Psychoneuroendocrinology*. 2015. **(36)** Gettler LT, et al. Prolactin, fatherhood, and reproductive behavior in human males. *Am J Phys Anthropol*. 2012;148(3):362-370. **(37)** Ditzler G,et al. Learning in Nonstationary Environments: A Survey. *IEEE Comput Intell Mag*. 2015;10:12-25. **(38)** Lilliefors HW. On the Kolmogorov-Smirnov Test for Normality with Mean and Variance Unknown. *J Am Stat Assoc*. 1967;62(318):399-402. **(39)** Guo J, et al. Nonlinear Brain Tumor Model Estimation with Long Short-Term Memory Neural Networks. In: *Proceedings of the International Joint Conference on Neural Networks*. Vol 2018-July. Institute of Electrical and Electronics Engineers Inc.; 2018. **(40)** Allen AM. Allopregnanolone during Short-Term Smoking Abstinence: Associations with depressive symptoms, smoking-related symptomatology and nicotine response. 2012. **(41)** Chen C, et al. Current and Emerging Technology for Continuous Glucose Monitoring. *Sensors (Basel)*. 2017;17. **(42)** Thabane L, et al. A tutorial on pilot studies: the what, why and how. *BMC Med Res Methodol*. 2010;10:1.

PHS Human Subjects and Clinical Trials Information

OMB Number: 0925-0001 and 0925-0002

Expiration Date: 03/31/2020

Are Human Subjects Involved	● Yes ○ No
Is the Project Exempt from Federal regulations?	○ Yes ● No
Exemption Number	❑ 1 ❑ 2 ❑ 3 ❑ 4 ❑ 5 ❑ 6 ❑ 7 ❑ 8
Other Requested Information	

Human Subject Studies

Study#	Study Title	Clinical Trial?
1	Hormonal Response to Infant Caregiving: A Novel Strategy to Break the Opioid Relapse Cycle during the Postpartum Period - Objectives 1 and 2	No

Section 1 - Basic Information (Study 1)

OMB Number: 0925-0001 and 0925-0002

Expiration Date: 03/31/2020

1.1. Study Title *

Hormonal Response to Infant Caregiving: A Novel Strategy to Break the Opioid Relapse Cycle during the Postpartum Period - Objectives 1 and 2

1.2. Is this study exempt from Federal Regulations * ○ Yes ● No

1.3. Exemption Number ❑ 1 ❑ 2 ❑ 3 ❑ 4 ❑ 5 ❑ 6 ❑ 7 ❑ 8

1.4. Clinical Trial Questionnaire *

1.4.a. Does the study involve human participants?	● Yes	○ No
1.4.b. Are the participants prospectively assigned to an intervention?	○ Yes	● No
1.4.c. Is the study designed to evaluate the effect of the intervention on the participants?	○ Yes	● No
1.4.d. Is the effect that will be evaluated a health-related biomedical or behavioral outcome?	○ Yes	● No

1.5. Provide the ClinicalTrials.gov Identifier (e.g. NCT87654321) for this trial, if applicable

Section 2 - Study Population Characteristics (Study 1)

2.1. Conditions or Focus of Study

- n/a

2.2. Eligibility Criteria

Inclusion criteria for the OUD group includes: (1) an uncompleted pregnancy at gestational week 30-35, (2) self-report or toxicology tests indicating infant has been exposed to opioids in utero, (3) motivated to maintain compliance with medication assisted treatment (MAT) and/or maintain sobriety after childbirth (as indicated by a score of 7 or greater on a 10-point Likert-type scale), (4) self-reported expectation to have custody of infant, (5) fluent in English, (6) willing/able to comply with study procedures, and (7) willing/able to provide informed consent. Inclusion criteria for the control group includes: (1) an uncompleted pregnancy at gestational week 30-35, (2) self-reported expectation to have custody of infant, (3) fluent in English, (4) willing/able to comply with study procedures, and (5) willing/able to provide informed consent.

2.3. Age Limits	Min Age: 18 Years	Max Age: 45 Years
2.4. Inclusion of Women, Minorities, and Children	Allen_NIH-DP2_Inclusion.pdf	
2.5. Recruitment and Retention Plan	Allen_NIH-DP2_RecruitmentPlan.pdf	
2.6. Recruitment Status	Not yet recruiting	
2.7. Study Timeline	Allen_NIH-DP2_StudyTimeline.pdf	
2.8. Enrollment of First Subject	11/15/2020	Anticipated

INCLUSION OF WOMEN, MINORITIES AND CHILDREN

1. Inclusion of Women and Minorities

This study will only be recruiting pregnant women because the study question addressed is focused on the hormonal changes that occur during the postpartum period. We will recruit women locally from Tucson, Arizona. Based on the demographics of women who participated in the “Family-Centered Neonatal Abstinence Care Program” (an unfunded and ongoing quality improvement study run by Dr. Allen with Banner University Medical Center, Diamond Children’s Medical Center’s Neonatal Intensive Care Unit), we are estimating that our sample will include 70% White, 15% American Indian/Alaskan Native, 3% Black, 2% Asian, and, and 10% more than one race. We expect that approximately 70% will be non-Hispanic and 30% will be Hispanic. If minority women do not respond to the advertisements, we will make special efforts to solicit their participation by focused advertising efforts on social media, as well as advertising in local neighborhood newspapers with high minority readership. Finally, we will identify churches, other health centers, and community centers with high minority participation disseminating information regarding the study opportunity.

2. Inclusion of Children

Children (under 18 years old) are not included since pregnancy and OUD are less common. However, future work could target this especially vulnerable population. Young women (aged 18-20 years) will be recruited for participation in our study using the same methods as adult recruitment

RECRUITMENT AND RETENTION PLAN

Recruitment

To achieve Objective 1, we will utilize an approximate 12-month recruitment period to enroll 50 participants. This equates to about 4-5 participants per month. We have experience recruiting a similar population in an unfunded study at a rate of two participants per month without any staff support. Thus, with this project that includes a full-time post-doctoral research associate, as well as a part-time undergraduate research assistant, we are confident we can achieve our goal of 50 participants.

To recruit this sample, we will pursue the following methods:

1. Community partnerships across multiple organizations, including:
    - Hospitals: Tucson Medical Center and Banner University Medical Center
    - Clinics/Treatment Facilities: CODAC, Community Health Services, The Haven, and the Banner Obstetrics and Gynecology Clinic
    - Departments of Child Safety: Arizona State, Maricopa County, and Pima County
    - Polysubstance Abuse in Pregnancy and Newborns Southern Arizona Task Force
    - Substance Exposed Newborns Arizona State Task Force
2. Social media advertisements (i.e., Facebook, Instagram, Reddit)
3. Mass media advertisements (i.e., TV, radio ,and newspaper)
4. Earned media via partnership with the Office of Public Affairs at the University of Arizona
5. ResearchMatch.org

We anticipate that our community partnerships will be the most fruitful of the methods listed above given we have strong and ongoing relationships with numerous community partners. First, we will work closely with the two largest *hospitals* in the Tucson, Arizona metro area – *Tucson Medical Center* (TMC) and *Banner University Medical Center* (BUMC). Together these hospitals deliver approximately 85% of babies born to mothers with OUD in the Tucson metro area, including an estimated 120 babies annually born with neonatal abstinence syndrome (NAS). Notably, these two hospitals have very different approaches to treating infants with NAS. TMC uses a pharmacological treatment (i.e., morphine) as a first-line approach whereas BUMC utilizes a non-pharmacological method (i.e., eat-sleep-console) as a first line approach. This difference is important as it will allow for a wide range of caregiving activities in our sample. Second, we will work with at least four *clinics/treatment facilities* in the Tucson area – CODAC, Community Health Services, The Haven, and the Banner Obstetrics and Gynecology Clinic. Together these four facilities treat an average of 1,500 women with OUD per year, including an estimated 275 pregnant women per year. Third, we will also work with the Arizona State and Pima County *Departments of Health Services (DHS)*. Specifically, DHS has a program titled Substance Exposed Newborn Safe Environment (SENSE) which has approximately 50 caseworkers visiting the homes of these newborns up to five times per week for three months. Partnering with the SENSE program during data collection efforts will likely increase our retention rates. Finally, we will also recruit and continue to expand our community partnerships in Arizona primarily via two local professional networks – *Substance Exposed Newborns* (SEN; state-wide) and *Polysubstance Abuse in Pregnancy and Newborns* (PAPN; regional). The PI is on the steering committee of the local Poly Substance Abuse in Pregnancy and Newborns (PAPN) Task Force. Twice a year the PAPN Task Force hosts a meeting of approximately 200-300 healthcare providers, social workers, and community resource workers to network and share resources. Thus, this will be an ideal opportunity for the study team to disseminate the need for referrals for the study.

We will work with our community partners to approach recruiting efforts in three ways: (1) all the community partners have agreed to post flyers and study brochures in their waiting and exam rooms, and/or distribute recruitment materials to clients/patients during home visits; (2) we will host informational sessions and/or tabling events onsite to allow for onsite recruitment by study staff; and (3) we will review records for potentially eligible participants and meet with them at scheduled appoints to allow for onsite recruitment by study staff. All of these efforts will only be completed upon IRB approval.

Second to community partners, we anticipate social media advertising will be the second most productive method based on our previous experiences. To do this, we will place IRB-approved advertisements on popular social media websites expressing our need for study volunteers. If a potentially interested individual clicks our ad, she will be routed to the REDCap website where a description of our study will be displayed and the individual may enter her contact information for additional information and to complete the telephone screening interview. We have had prior success with these methods. For example, in an eight-month time period our advertisements on

Facebook resulted in over 16,000 visits (5,000/week) to our website, an estimated 152 phone calls with 84 callers meeting eligibility criteria (~10-11 eligible callers/month) and an enrollment of 45 participants (~6 participants/month). While this was for a postpartum cigarette smoking cessation trial, given over 80% of young adults regularly use social media, with even higher rates observed in women and during pregnancy, we still anticipate this to be a fruitful venue for recruitment.

Contingency Plan: If we have not enrolled at least 10 participants by the third month of recruitment, we will also initiate a proactive recruitment plan. This will include: (a) direct fax referrals from our community partners, (b) direct mailings to clinic patients who may, based on medical records, meet our eligibility criteria, (c) tabling at local clinics, and (d) hosting informational sessions at community centers, and/or community events. If we have not enrolled at least 15 participants by the fourth month of recruitment, we will expand our efforts to the Phoenix area (as noted above) via our partnerships with Maricopa County Department of Child Safety, Substance Exposed Newborns Task Force and Dr. Maria Manriquez-Sanchez's clinical practice.

Retention

Our goal is to retain 40 (80%) participants until the end of the nine month follow-up period. To improve retention we are employing the following strategies based on previously published recommendations:

- Location flexibility. We will complete all meetings between study staff and study participants at the participants' preferred location. This could be done at their home, at our clinic, at a neutral meeting location (e.g. local library meeting room), and/or, at their regular health clinic.
- Time flexibility. Offer flexibility in scheduling dates/times to include weekends and evenings.
- Cash payments. We will provide participants with cash at the end of each meeting.
- Gift. We will provide participants with diapers at the end of each meeting.
- Bonus payments. In addition to regular compensation, participants will be paid bonuses for attending key clinic visits including $50 at month 3, $100 at month 6, and $150 at month 9.
- Reminders. We will send reminder texts/emails to participants and offer rescheduling if the participant needs to do so.
- Encouragement and communication. We will continuously encourage continued participation regardless of their substance use.
- Medical record data abstraction. At enrollment, participants will complete a release of medical information that will allow us to pull data from their electronic medical records at their clinic and hospitals (among our partnering clinics and hospitals). Therefore, if a participant becomes loss to follow-up, we will still be able to access their treatment compliance for their medication assisted therapy. We will be able to assume that those who become loss to follow-up and also discontinue their medication assisted therapy are considered in treatment relapse. This will allow us to assess our primary study outcome without direct participant input.

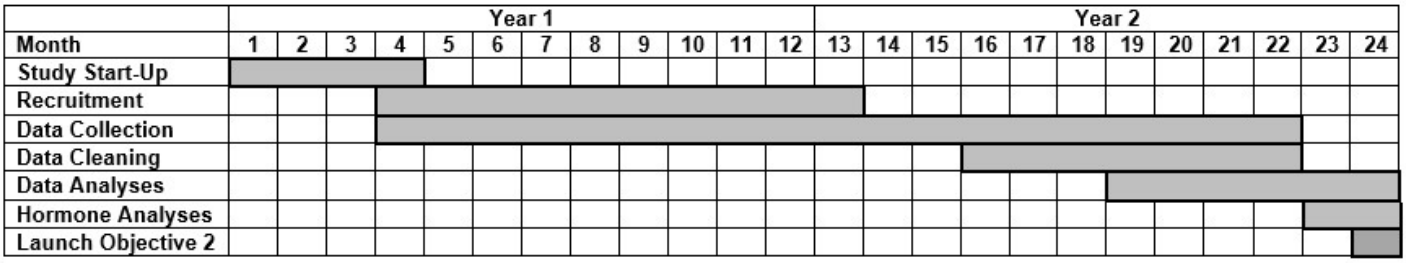
Contingency Plan: If we have not retrained at least 70% of the first 10 participants (n<8), we will consider the following in an effort to increase retention: (a) reduced frequency of meetings (e.g., perhaps monthly visits will suffice instead of bimonthly), (b) reduce length of meetings (e.g., participants may be willing/able to complete surveys prior to arrival, which may reduce length of meetings), (c) increase compensation, (d) increase gifts, and (e) reduce number of assessments/samples at each visit.

Should these efforts not increase retention and we fail to retain at least 70% of the first 20 participants (n<15), then we will consider augmenting our protocol such that we will reduce the data collection periods for participants and will also recruit additional participants. For example, we could recruit 50 participants to complete Month 1-3 data collection, and an additional 100 participants to complete Months 3-6 (n=50) and 6-9 (n=50). This will limit the overall burden on any individual participants and also provide us with the necessary data to complete the first step of this line of research. This may also introduce some selection bias/error as there may be differences among those who are willing/able to collect data during this finite periods. Thus, additional work may be necessary to address these errors.

Overall, we appreciate the challenges involved with recruiting and retaining study participants with OUD. However, we are confident that with the plans outlined above, together with our successful prior experience, that we will be able to meet our recruitment and retention goals for this study.

Study Timeline

We developed a timeline for Objectives 1 and 2 to facilitate timely achievement of our major milestones, which will ensure a timely completion of these objectives. The results are these objectives must be known prior to the pursuit of Objectives 3 and 4.



Major Milestones

Objective 1: Measure hormones, infant caregiving activities, relapse risk factors, and OUD-related outcomes during the postpartum period using a prospective cohort study design

- Milestone 1 – Regulatory approvals complete (finalized by Month 3).
- Milestone 2 – All data collection materials and databases developed and pilot tested (finalized by Month 4).
- Milestone 3 – All staff trained (finalized by Month 4).
- Milestone 4 – Advertising and other recruitment efforts launched (initiated end of Month 4).
- Milestone 5 – First participant enrolled (by end of Month 4).
- Milestone 6 – Begin monthly assessment of recruitment goals (initiated in Month 5).
- Milestone 7 – Initiate recruitment contingency plan, if applicable (decision made in Month 7).
- Milestone 6 – Begin monthly assessment of retention goals (initiated in Month 7).
- Milestone 8 – Initiate retention contingency plan, if applicable (decision made in Month 10).
- Milestone 9 – Last participant enrolled (by Month 13).
- Milestone 10 – Initiate data cleaning and preparation procedures (by Month 16).
- Milestone 11 – Initiate descriptive data analyses (by Month 19).
- Milestone 12 – Final participant completed (by Month 22).
- Milestone 13 – Send biological samples for analyses (by Month 23).

Objective 2 - Identify hormonal level(s)/pattern(s) that are predictive of postpartum opioid use via with data-driven predictive analytics

- Milestone 14 – Send database to engineering colleagues (by Month 24).
- Milestone 15 – Begin weekly meetings with engineering colleagues (by Month 24)
- Milestone 16 – Identify targeted hormonal level(s)/pattern(s) and begin exploring ways to elicit or identify (by Month 30; not shown on timeline).
- Milestone 17 – Submit primary results manuscript for publication (by Month 30; not shown on timeline).

Inclusion Enrollment Reports

IER ID#	Enrollment Location Type	Enrollment Location
Study 1, IER 1	Domestic	Hospitals, Clinic/Treatment Facilities, Departments of Child Safety, Polysubstance Abuse in Pregnancy and Newborns Southern Arizona Task Force, Substance Exposed Newborns Arizona State Task Force

Inclusion Enrollment Report 1

Using an Existing Dataset or Resource* : ○ Yes ● No

Enrollment Location Type* : ● Domestic ○ Foreign

Enrollment Country(ies): USA: UNITED STATES

Enrollment Location(s): Hospitals, Clinic/Treatment Facilities, Departments of Child Safety, Polysubstance Abuse in Pregnancy and Newborns Southern Arizona Task Force, Substance Exposed Newborns Arizona State Task Force

Comments:

Planned

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	9	0	2	0	11
Asian	2	0	0	0	2
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	2	0	1	0	3
White	35	0	18	0	53
More than One Race	3	0	3	0	6
Total	51	0	24	0	75

Cumulative (Actual)

Racial Categories	Ethnic Categories									Total
	Not Hispanic or Latino			Hispanic or Latino			Unknown/Not Reported Ethnicity			
	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	
American Indian/ Alaska Native	0	0	0	0	0	0	0	0	0	0
Asian	0	0	0	0	0	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0	0	0	0	0
Black or African American	0	0	0	0	0	0	0	0	0	0
White	0	0	0	0	0	0	0	0	0	0
More than One Race	0	0	0	0	0	0	0	0	0	0
Unknown or Not Reported	0	0	0	0	0	0	0	0	0	0
Total	0	0	0	0	0	0	0	0	0	0

Section 3 - Protection and Monitoring Plans (Study 1)

3.1. Protection of Human Subjects	Allen_NIH-DP2_ProtectionHuman.pdf
3.2. Is this a multi-site study that will use the same protocol to conduct non-exempt human subjects research at more than one domestic site?	○ Yes ● No ○ N/A
If yes, describe the single IRB plan	
3.3. Data and Safety Monitoring Plan	
3.4. Will a Data and Safety Monitoring Board be appointed for this study?	○ Yes ○ No
3.5. Overall structure of the study team	

PROTECTION OF HUMAN SUBJECTS

This project includes four objectives. This document covers objective one and two. Objectives three and four are pending given they are dependent on the results of the first two objectives.

1. Risks to Human Subjects

1.1 Human Subjects Involvement, Characteristics, and Design

1.1.1 Involvement of Human Subjects. We will recruit pregnant women with opioid use disorder (OUD group) and without ("controls"). In brief, our participants will complete five tasks. First, they will complete enrollment procedures when includes a telephone interview, in-person assessment, and completion of self-administered validated questionnaires to assess eligibility criteria and collect baseline information. This will be completed between gestational week 30-36. Second, at the baseline visit the participants will also complete a realse of information form applicable to their OB clinic, anticipated hospital of delivery, and MAT clinic (OUD group only). This will allow us to directly collect information regarding childbirth outcomes and MAT compliance. Third, they will complete a series of biological samples including saliva, urine, and dried blood spots. These will be collected on a weekly basis for the first approximately four months (starting at gestational week 36 and continuing until postpartum month 3) followed by biweekly for the next six months (from postpartum month 3 to postpartum month 9). At east time point five saliva samples (at 8pm, bedtime, upon waking, 30 minutes after waking, and 60 minutes after waking) will be collected in order to capture the diurnal pattern of cortisol. The urine sample and dried blood spot samples will be collected once (upon waking) at each time point to measure the remaining hormones. Fourth, they will complete a series of self-administered validated questionnaires to measure their infant caregiving activities, OUD-related outcomes, and other relevant variables (e.g., confounding). These questionnaires will also be completed on a weekly and biweekly basis during the same time periods. Lastly, they will complete in-person visits with study staff. These meetings will occur during the same weekly (gestational week 36 to postpartum month 3) and biweekly (from postpartum month 3 to postpartum month 9) time points to correspond with the collection of the biological samples and completion of the validated questionnaires. These visits are anticipated to last approximately 30 minutes and may occur at our clinic, the participant's home, or a community-based location (e.g., library or faith-based meeting room). For these activities, participants will earn up $20 cash plus a package of diapers at each meeting. They will also earn bonuses of $25 at Month 1, $50 at Month 2, $75 at Month 3, $100 at Month 6 and $150 at Month 9. Depending on gestational week at birth, the estimated total possible compensation if $890 plus approximately $500 in diapers.

1.1.2 Characteristics and Eligibility Criteria of Human Subjects. We will enroll 50 women into the OUD group and 25 women into the control group.

Inclusion criteria for the OUD group includes: (1) an uncompleted pregnancy at gestational week 30-35, (2) self-report or toxicology tests indicating infant has been exposed to opioids in utero, (3) motivated to maintain compliance with medication assisted treatment (MAT) and/or maintain sobriety after childbirth (as indicated by a score of 7 or greater on a 10-point Likert-type scale), (4) self-reported expectation to have custody of infant, (5) fluent in English, (6) willing/able to comply with study procedures, and (7) willing/able to provide informed consent.

Inclusion criteria for the control group includes: (1) an uncompleted pregnancy at gestational week 30-35, (3) self-reported expectation to have custody of infant, (4) fluent in English, (5) willing/able to comply with study procedures, and (6) willing/able to provide informed consent.

1.1.3 Recruitment and Enrollment. We will be recruiting primarily via our community partners, which includes a variety of local hospitals, clinics, treatment facilities, government agencies, and task forces (see "Recruitment and Retention" for additional details). Specific activities are likely to include posting and distribution of recruitment materials (e.g., flyers, brochures), meeting with potentially eligible participants at clinic visits, tabling at events, hosting informational sessions, etc. Additional recruiting efforts will include advertising on social and mass media, earned media, posting on ResearchMatch.org, and similar.

Individuals who express interest in participating in the study will complete a telephone interview to confirm eligibility and learn more about the study. This interview will also include a description of the study's purpose, procedures, schedule and compensation. If the potential participant meets eligibility criteria and is interested in participating, an enrollment visit will be scheduled. This visit will be held at the location of the potential participant's preference including our clinic, their home, or a community-based location (e.g., library or faith-based meeting room). At this visit, informed consent will be obtained, eligibility will be confirmed, baseline data

will be collected, and the participant will receive training on how to complete data collection procedures.

1.1.4 Rationale for Involvement of Special Vulnerable Populations. We are including pregnant women in this project given the nature of the research is focused on hormonal level(s)/pattern(s) that occur during the postpartum period.

1.1.5 Collaborating Sites. Not applicable.

1.2. Sources of Material

1.2.1 Materials Obtained from Human Subjects. Participants will provide salvia, urine, and dried blood spot samples. All samples will be self-collected by the participant after trained by study staff. All samples will be labeled with a unique alphanumeric code to protect the participant's identify. All samples will be collected at each study meeting and stored in a -80ºC freezer until analyses.

1.2.2 Data Recorded from Human Subjects. Data recorded from participants includes the following: (a) baseline data including demographics, substance use history, physical health history, mental health history, emotional health history, social network information, (b) caregiving activities such as skin-to-skin contact, baby wearing, consoling, feeding, cleaning and playing, (c) relapse related risk factors including mood, stress, isolation, bonding, attachment, partner use, and (d) OUD-related outcomes including craving, MAT compliance, lapse, and relapse (OUD group only).

1.2.3 Who has Access to Private Health Information (PHI). Study staff will have access to PHI during the study. PHI will be kept on a secured survey in a password-protected file. Upon completion of the study, PHI will be destroyed.

1.2.4 Collection and Storage of Data. All data will be stored on REDCap servers, which are HIPAA-compliant. All study-related data will be labeled with an alphanumeric code unique to each participant but unlink-able to participants without the code. PHI, codes, and contact information will be accessible only through authorized research team members. Only research team members will be allowed to view or export the data collected. No names or identifying information will be included in research reports and presentations. Participants' names do not appear on questionnaires or components of the intervention. The investigators control access by assigned user roles.

1.3 Potential Risks

There are very few risks associated with participation in the study. In some cases, questionnaires may elicit emotional distress; however, the study staff will trained to provide support and problem solve issues in a manner that minimizes the likelihood and degree of distress a participant might experience. Participants may face a risk of minimal privacy violation as they will be self-administering validated questionnaires via REDCap. All data, as mentioned above, will use stored in s secure manner. Only the PIs and the study staff will have access to the data. There may be the potential for privacy violation while the participant completes these tasks in their own environment and, thus, others may see what they enter into the surveys.

Although the collection of urine and saliva samples do not present risks to participants, dried blood spots pose minimal risk. These risks include momentary pain and/or discomfort due to the prick of the micro lancet. Further, some participants may feel uncomfortable at the sight of blood. To minimize the risk of dried blood spot collection, we will counsel participants to use multiple collection sites and to complete the collection process while sitting. There are a total of 12 collection sites (right and left side of the pointer, middle and ring finger on both hands) and a rotation of the sites will minimize soreness. Further, participants will practice the self-collection technique at their enrollment visit. Any errors in collection will be corrected immediately.

2. Adequacy of Protection Against Risks

2.1 Recruitment and Informed Consent

Participants recruited in-person via community partners will be given a blank informed consent form at the initial point of contact. This will allow her to review in detail at her leisure and then, if she's interested, contact study staff for more information and to assess eligibility. Participants who are recruited via social media will be able to access the consent form online so that they can also review in detail at their leisure and then call study staff if they so choose. At the telephone interview, each potential participant will be told about the study, have

an opportunity to ask questions, and will then be screened by telephone interview for eligibility. If the participant is determined eligible, she will be scheduled for an enrollment meeting with study staff. Prior to this meeting she will be mailed a reminder letter, along with a blank informed consent form to allow for additional time to review. At the enrollment visit, the study staff will be provide with a detailed explanation of the study purpose and procedures (including risk involved), answer any questions a participant may have, ask participants to answer questions to assess their understanding of the study, and informed consent will be obtained before any study procedures are implemented.

2.2 Protections Against Risk

Participants will be told the potential risks involved in this study. As noted above, the following actions will be taken to minimize these risks.

All adverse events (AEs) occurring during the study must be collected, documented, and reported to the PIs. Each week the PIs will review the AE forms from the previous week for events that were reported as new or continuing. The study investigators will follow all AEs to the point of a satisfactory resolution. A study participant may be withdrawn from the study if the PIs decide it is best in order to protect the safety of the participant. All AEs will be assessed to determine if they meet criteria for an SAE.

While we do not anticipate any serious adverse events (SAEs) arising from the study, any SAE, whether or not related to participation in the study, will be reported to the IRB and NIH. Serious AEs will be verbally reported to the local IRB and to NIH within the three days of our receipt of information regarding the event and written reports will be submitted within ten days. If a participant either withdraws from the study or the investigator decides to discontinue a participant due to a SAE, the participant will have appropriate follow-up medical monitoring. Monitoring will continue until the problem requiring hospitalization was resolved or stabilized with no further change expected. Outcome of SAEs will be periodically reported to NIH. A summary of the SAEs that occurred during the previous year will be included in the annual progress report to NIH.

There may be risk to confidentiality and privacy of study data. To minimize this risk, participants will be assigned unique six-digit alpha-numeric identifiers. The questionnaires and biological samples will retain only the unique identifier. These numbers will be linked to the participant's identifier information in a database separate from other data collected. The database requires at least two levels of security (i.e., passwords), which will allow only authorized research team members to access the information.

Participants will be trained on proper procedures for the collection of dried blood spots, including thorough handwashing prior to collection, collecting at a clean surface, and use of sterile micro-lancets and other equipment. Further, participants will be encouraged to rotate between the 12 potential collection sites to limit soreness, as well as to collect samples while sitting to limit dizziness.

3. Potential Benefits of the Proposed Research to Human Subjects and Others

Whereas no assurance can be made to an individual participant that they will personally benefit from such research, the experience should be favorable one. In the future, society, and new mothers with OUD in particular, may benefit from a better understanding of how to prevent opioid relapse during the postpartum period. The risks in relation to the potential benefits are minimal to the individual research participant.

4. Importance of the Knowledge to be Gained

Postpartum opioid relapse rates are high and can pose significant health risks to the woman, infant, other children, and the family. While this study is primarily aimed at collecting informative data, in the long run we are optimistic that these data can be used to inform comprehensive postpartum relapse prevention strategies.

Section 4 - Protocol Synopsis (Study 1)

4.1. Brief Summary

4.2. Study Design

4.2.a. Narrative Study Description

4.2.b. Primary Purpose

4.2.c. Interventions

Type	Name	Description

4.2.d. Study Phase

Is this an NIH-defined Phase III Clinical Trial? ❍ Yes ❍ No

4.2.e. Intervention Model

4.2.f. Masking ❍ Yes ❍ No

❑ Participant ❑ Care Provider ❑ Investigator ❑ Outcomes Assessor

4.2.g. Allocation

4.3. Outcome Measures

Type	Name	Time Frame	Brief Description

4.4. Statistical Design and Power

4.5. Subject Participation Duration

4.6. Will the study use an FDA-regulated intervention? ❍ Yes ❍ No

4.6.a. If yes, describe the availability of Investigational Product (IP) and Investigational New Drug (IND)/ Investigational Device Exemption (IDE) status

4.7. Dissemination Plan

Delayed Onset Studies

Delayed Onset Study#	Study Title	Anticipated Clinical Trial?	Justification
The form does not have any delayed onset studies			